The Association Between Early Mobilization Intervention and the Development of Pressure Injuries in the Intensive Care Unit

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ABSTRACT

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Critically ill patients in ICU settings have a higher rate of PIs than other patients. These patients are at increased risk due to severe physiological instability and immobility. Immobility is one of the major risk factors of PI development. Mobilizing patients out of bed could be one way of preventing the development of PIs.

This dissertation studied the association between PI development and mobilizing patients out of bed within the first seven days of ICU admission. Three chapters provided a comprehensive exploration of the association between EM and PI development.

Chapter 2 presented detailed background information about EM, as well as a meta-analysis of the effects of EM on critically ill patients. The meta-analysis showed that mobilizing critically ill patients reduces their ICU and hospital LOS. Moreover, the EM group experienced better QoL six months after discharge. There were no significant effects of EM on mechanical ventilator days, the number of ventilator free days, vasopressors, sedation, delirium, or patient physical function.

Chapter 3 provided a systematic review of the PI risk factors in critically ill patients in ICU settings , reviewed the pathophysiology of PI development, There is limited evidence concerning the association between EM interventions and PI development, so this chapter presented a conceptual framework exploring how EM could mitigate PI development. The framework introduced conceptual links between EM and PI development using Braden and Bergstrom's conceptual scheme and demonstrates that immobility, shear, and friction are factors that can be mediated directly when ICU patients are mobilized out of bed.

Finally, *Chapter 4* reported a study that examined the relationship between EM and PI development in ICU patients. The study was comprised of a retrospective chart review of PI and EM events. Two sub-study designs, which did not and did control for other PI risk factors, were used to examine this association. The first phase used a cohort design that compared PI events before EM, during EM, and during hospital expansion. This phase found that there was no significant increase in PI events between these three periods. The second phase used a case control design that compared PI patients (cases) to non-PI patients (controls). When comparing the characteristics of the cases to the controls, we found that the cases had a significantly higher risk of PI development, higher APACHE II scores, a higher use of hemodialysis, a higher use of MV, and lower hemoglobin levels compared to the control group. The univariate logistic regression revealed that the following risk factors were significant predictors of PI development: total Braden score, Braden subscale scores (sensory,, activity, moisture, and friction), hemoglobin level, APACHE II score, hemodialysis, MV usage, EM received within 72 hours and EM received within seven days, , dangling, sitting, standing, ambulating, and EM sessions count. The multivariate logistic regression included two models. Model one used EM within 72 hours and model two used EM within 7 days as the main risk factors in the second block of the logistic analysis. Model one showed four significant variables: total Braden score, Braden moisture, Braden friction, and receiving EM within 72 hours. Model two revealed five significant

risk factors: Braden score, Braden moisture, Braden friction, BMI, and receiving EM within 7 days.

There is a gap in the knowledge about the relationship between PI and EM. The systematic review and studies presented as a part of this dissertation expand the body of science and our knowledge of this relationship and the additional benefit of EM.

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DEDICATION

To my loving parents, Siblings and to Dr. Bridges, without whom this dissertation would not be possible

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CHAPTER 1

Introduction

Pressure injuries (PIs) are a global hospital-acquired health issue. The treatment of PIs places a substantial financial burden on health-care organizations,[1] costing between $9.1 billion to $11.6 billion per year in the US alone.[2] Approximately 2.5 million patients are treated for PIs each year.[2] As a result, PI prevention is an important action that needs to be undertaken by health-care organizations. The development of PIs is a very complex phenomenon, starting at the internal cellular level (intrinsic factors) and extending to the environmental level (external factors).[3-5] PIs cause pain, an increased risk of inflammation and infection, longer hospitalization, an increased likelihood of readmission, and higher mortality rates.[6-11]

Critically ill patients in intensive care units (ICUs) are at a higher risk of acquiring PIs than other patients.[12,13] A national cross-sectional cohort study found that the prevalence of PIs is highest in ICUs, ranging from 9.2% in general cardiac ICUs to 12.1% in medical ICUs in 2008, and from 8.8% in general ICUs to 10.3% in surgical ICUs in 2009.[14] Patients are usually admitted to ICU settings with life-threatening conditions. They exhibit severe physiologic instability that challenges health-care providers to save these patients' lives while preventing PI development. Due to physiologic instability, critically ill patients may be immobile for extended periods of time.[6,11] For example, ICU patients may be mechanically ventilated (MV) and sedated for periods of time, resulting in continuous bed rest.

Immobility is considered one of the major risk factors for the development of PIs.[11,15] When immobile for an extended period, the weight of the patient exerts mechanical load pressure on the soft tissue located between the bony area and the surface they are in contact with, such as a mattress or a chair, and this may impair circulation and create a tissue injury. Moreover, immobilized patients are at a higher risk for two further mechanical factors that

increase PI development, namely, friction and shear. Friction is defined as the force that is created when two different surfaces rub against each other.[15,16] Friction is evident when critically ill patients are lifted or dragged to change positions. Shear is the perpendicular force created by gravity and leads to changes in the deeper tissues through the angulation and deformation of the vascular bed that passes the deep vesical and superficial fascia.[15,17,18] Shear is commonly seen in ICU settings, especially when MV patients are in an elevated-head of bed position to prevent ventilator-associated pneumonia. Interventions are needed to relieve pressure, friction, and shear. Mobilizing patients out of bed may be a solution to reduce the risk associated with these factors.

Early mobilization (EM) is an intervention that is applied in some of ICU settings[19]. It was introduced to prevent immobility complications such as deep venous thrombosis, physical impairment, and respiratory muscle atrophy. Several studies have shown that EM reduces short-term physical impairment, prevents bed-rest complications, decreases the number of ventilator days, and shortens the length of stay (LOS) in ICU or hospital,[20-24] thus indirectly reducing the cost of care. EM is defined as activities, exercises, or rehabilitation that are administered during the early stages of treatment (within 7 days of ICU admission).[20,25-30] The interventions may include active range-of-motion exercises, resistive exercises, mobilization activities, and walking, as delivered by a team of care providers There is an association between patient participation in an EM program in the ICU and their ability to continue activities of daily living after hospital discharge; thus, early mobilization may improve patients' quality of life (QoL).[27,31]

There is a gap in our knowledge about the relationship between EM and PI development: we do not know whether EM implementation decreases or increases PI development. The occurrence of PIs has been measured as one of many outcomes in studies that compared patients who received EM to patients who did not receive EM. However, to date, no study has addressed the association between PI and EM implementation in detail. This

dissertation therefore examines in-depth the association between EM implementation and PI development. The following chapters provide comprehensive information about the association between EM and PI development.

Chapter 2. Meta-analysis of the effects of early mobilization on critically ill patients

To close the knowledge gap regarding EM implementation and PI development, we first need to understand what an EM intervention is and how it affects critically ill patients. This chapter provides background information to explain why EM is implemented for critically ill patients in the ICU, as well as a systematic review and meta-analysis of randomized clinical trials on EM. The systematic review and meta-analysis focuses on analyzing the effects of EM on patient and hospital outcomes in medical and surgical ICU settings. The hospital outcomes studied include hospital and ICU LOS, mechanical ventilation duration (MVD), ventilator-free days (VFD), vasopressor days, sedation days, and mortality rate (MR), while the patient outcomes include muscle strength, physical function, and QoL.

Chapter 3. Systematic review: how early mobilization mediates the risk factors for pressure injury development in intensive care populations

The third chapter addresses the PI development process by providing a systematic review of the literature over the past decade to identify the intrinsic and extrinsic risk factors for PIs in ICU populations. Moreover, the systematic review is supplemented by a second literature review that illuminates the pathophysiology of PI and EM outcomes in ICU populations and discusses how EM can be used to intervene in PI development. This chapter provides a conceptual framework for how EM may mitigate PI development.

Chapter 4. The association between early mobilization interventions and the development of pressure injuries in the intensive care unit

Informed by evidence presented in the previous chapters, this chapter presents a study that assesses the association between EM and PI development. This study aimed to examine the relationship between EM and PI using an approach that employed two different study designs. The first was a cohort design that sought to determine the association between EM and PIs without controlling for any risk factors. The second phase used a case control design to assess the same association while controlling for PI risk factors. The cohort design compared the difference in the rate of PIs in critically ill patients before and after EM interventions at the University of Washington Medical Center (UWMC) from 2011 to 2016, while the case control design tested the association of EM exposure with PI development. In addition, for the patients who received EM, the differences in the dose, intensity, and duration of the EM interventions between the PI group and the non-PI group were examined. Finally, the differences in PI occurrence (location on body and severity of PI) in patients who did and did not receive EM were compared.

Chapter 5. Conclusions and recommendations

This chapter provides a summary of all the previous chapters and discusses the results relative to existing literature. The chapter concludes with recommendations for future research.

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CHAPTER 2

Meta-Analysis of the Effects of Early Mobilization on Critically Ill Patients

Background

Inactivity, nutrient imbalance, neuropathological changes, and side effects of pharmacological agents are strong risk factors for ICU-acquired neuromuscular weakness. [1-5] Muscle wasting occurs quickly in the ICU and is highest in the first two or three weeks of an ICU stay. [6,7] Patients with muscle atrophy are difficult to wean from mechanical ventilation; their ventilation treatment is about eight- thirteen days longer than normal. [8,9] Muscle atrophy is associated with a longer ICU/hospital length of stay (LOS), [8,9] a higher mortality rate, [10-15] decreased physical condition, [10] and low quality-of-life care. [9,10]

Recently, early mobilization (EM) or rehabilitation has been advocated to prevent muscle weakening. [16-20] Early mobilization of critically ill patients in the ICU is associated with reductions in short-term physical impairment, the number of ventilation days, and the length of stay in the ICU and hospital [21-25]; thus, it also indirectly reduces the cost of care. [17] The purpose of this paper is to analyze the effect of early mobilization on patients' and hospitals' outcomes in medical and surgical ICU settings. The hospital outcomes studied included hospital and ICU LOS, mechanical ventilation duration (MVD), ventilator-free days (VFD), vasopressor days, sedation days, and mortality rate (MR). Patients' outcomes included muscle strength, physical function, and quality of life (QoL).

Research Methods

A comprehensive electronic search of the PubMed, CINAHL, and EMBASE databases was undertaken using the following as MeSHD terms or as terms within the title and abstract: *early physical therapy*, *early mobilization*, *early ambulation*, *mechanical ventilation*, *acute*

respiratory failure, and *critically ill patients*. The operators *OR* and *AND* were used while searching for articles, and the publication years ranged from 1983–2017.

The search was limited to reports of randomized controlled trials (RCTs) that were written in English only. The search found 488 articles: 420 from PubMed, seven from CINAHL, and 61 from the EMBASE database. After reviewing the titles and abstracts and removing duplicates, there were 25 articles with the potential for inclusion in a meta-analysis. Of these, eight studies fulfilled the inclusion criteria (Figure 1).

The inclusion criteria for the meta-analysis were: 1) studies that delivered early mobilization or early physical therapy to critically ill patients or mechanically ventilated patients of ages 18–65 year-old in either medical or surgical intensive care settings in North America, Europe, and Australia; and 2) studies that investigated muscle strength, physical function, QoL, FVD, MVD, ICU and hospital LOS, and MR.

The exclusion criteria were: 1) studies that investigated passive therapy or functional electrical muscle stimulation (EMS) as the sole rehabilitation; and 2) studies that combined an intervention of mobilization with cognitive therapy and compared it to the standard of care. In this paper, *intervention* was defined as early activities, exercise, or rehabilitation that were administered within two to seven days of ICU admission. The interventions included active range-of-motion exercises, resistive exercises, active ergometry, mobilization activities, and walking.

Analysis

The Comprehensive Meta-Analysis Program, version three, was used to perform the meta-analysis. A random effect model was used because there were large variations in the type, duration, frequency, and intensity of the EM interventions among the studies.

Results

Demographics. The sample sizes and the patients' severity of illness, overall mean age and age range in years, and gender percentages are presented in Table 1. The total sample size for all eight studies was n = 1041 (early mobilization group [EMG]: n = 522; standard of care group [SCG]: n = 519), with a range of 50 to 300 patients. The overall mean age in the trials was 59.8 year old for the EMG and 57.6 year old for the SCG. The overall percentage of females in all studies was 44% for the EMG and 42.6% for the SCG. The patients were recruited from mixed ICUs in three studies, [26-28] general ICUs in two studies, [29,30] medical ICUs in two studies, [21,31] and a surgical ICU in 1 study. [32] The trials were performed in different countries: three trials in the USA, [21,29,31] two trials in Australia, [28,30] one trial in Belgium, [27] and two trials in multiple countries. [26,32]

EMG *vs.* SCG. The early mobilization interventions reported in the RCT included a wide range of techniques, because the studies varied in the type, duration, frequency, and intensity of physical therapy. In some of the trials, patients in the EMG received physical therapy that progressed gradually from passive range of motion (PROM) to active range of motion (AROM) to resistive exercise to ambulation. [21,27,29,30,32] The study by Kayambu et al. included electrical stimulation in the intervention.[30] The rest of the studies progressed from active range of motion to ambulation without including passive range of motion. [26,28,31]

Similarly, patients in the SCG received a wide range of standards of care, because each setting had its own local protocol. Only one study did not provide any physical therapy for patients in the first two weeks of the ICU stay [21]; one study provided only PROM, [33] one study provided PROM and AROM,[29] and five studies provided different ranges of PROM and AROM and some mobilization (Table 2). [21,28,31,34]

Length of Stay. The ICU LOS, measured in number of days following the ICU EM intervention, was examined in seven studies, [26,27,29,31,34] using pooled data in a random effect model (Q = 7.51, P = .28, I^2 = 20.10). There was a significant reduction in ICU LOS with early

mobilization for mechanically ventilated patients in the ICU (pooled Hedges's g = -0.19; 95% CI: -0.35, -0.04; P = .015; Table 3).

The hospital LOS, measured in number days following the ICU EM intervention, was assessed in six studies, [21,26,27,29,30,34] using pooled data (Q = 4.56, P = .47, I^2 = 0.00). The meta-analysis showed that there was a significant reduction in the hospital LOS for critically ill patients post-ICU (pooled Hedges's g = -0.21; 95% CI: -0.35, -0.07; P = .003; Table 3).

Mechanical Ventilation Duration and Ventilator-Free Days. The effect of EM intervention on the MVD, assessed in four studies, [21,26,35,36] was shown by the number of days that patients were on breathing assistance (Q = 9.52, P = .02, I^2 = 68.49). There was no significant overall effect on the MVD (pooled Hedges's g = -0.19; 95% CI: -0.59, 0.22; P = .369; Table 3). Also, five studies assessed the effect of EM on the FVD, shown by the number of days the patient was alive and breathing without assistance during hospitalization (Q = 4.91, P = .30, I^2 = 18.49). [21,26,29,30,34] There was no effect of EM on the FVD (pooled Hedges's g = 0.093; 95% CI: -0.08, 0.27; P = .286; Table 3).

Number of Days of Vasopressors, Sedation, and Delirium. Two studies reported the vasopressor outcome as the number of days that patients were on vasopressors (Q = 1.66, P = .20, I^2 = 39.58). [29,34] The overall effect size was small with no significant result (pooled Hedges's g = 0.09; 95% CI: -0.14, 0.32; P = .447; Table 3). Also, three studies reported the sedation outcome as the number of days that patients received sedation (Q = 6.62, P = .04, I^2 = 69.78). There was no significant effect of EM on the number of days that patients were sedated (pooled Hedges's g = -0.002; 95% CI: -0.33, -0.32; P = .99; Table 3). Two studies reported the number of days that patients exhibited delirium (Q = 10.01, P = .001, I^2 = 90.08); there was no difference between the EMG and the SCG in the number days of being delirious (pooled Hedges's g = -0.031; 95% CI: -0.79, 0.73; P = .94; Table 3).

Mortality. MR was measured at different time points. Two studies measured the mortality in the ICU, [26,30] four at hospital discharge, [21,26,31,34] two at three months post-discharge,

[30,34] and two at one year post-discharge [27,28]. In the pooled analysis, no significant difference was found between the EMG and SCG in MR at any time point.

Muscle Strength and Physical Function. The effect of EM on patients' muscle strength was measured in four studies using the Medical Research Council tool (MRC) at hospital discharge *(Q* = 2.99, *P* = .39, I^2 = 0.00). The meta-analysis showed that there was no significant difference between the people who received EM and those who received SC (pooled Hedges's *g* = 0.15; 95% CI: -0.05, 0.35; *P* = .13; Table 3). Physical function was measured in three studies using the physical function ICU test (PFIT) at ICU discharge (*Q* = 4.91, *P* = .30, I^2 = 0.00). There was no difference between the EM and SC groups in the level of physical function (pooled Hedges's *g* = -0.08; 95% CI: -0.35, 0.19; *P* = .13; Table 3).

Quality of life. The SF-36 physical function domain tool was used to measure the patient's quality of life at different time points (Table 3). Two studies measured the QoL at hospital discharge, two studies at three months, and three studies at six months. There was a significant difference between the groups at six months post-discharge (pooled Hedges's *g* = -7.29; 95% CI: -11.99, -2.59, *P* = .002).

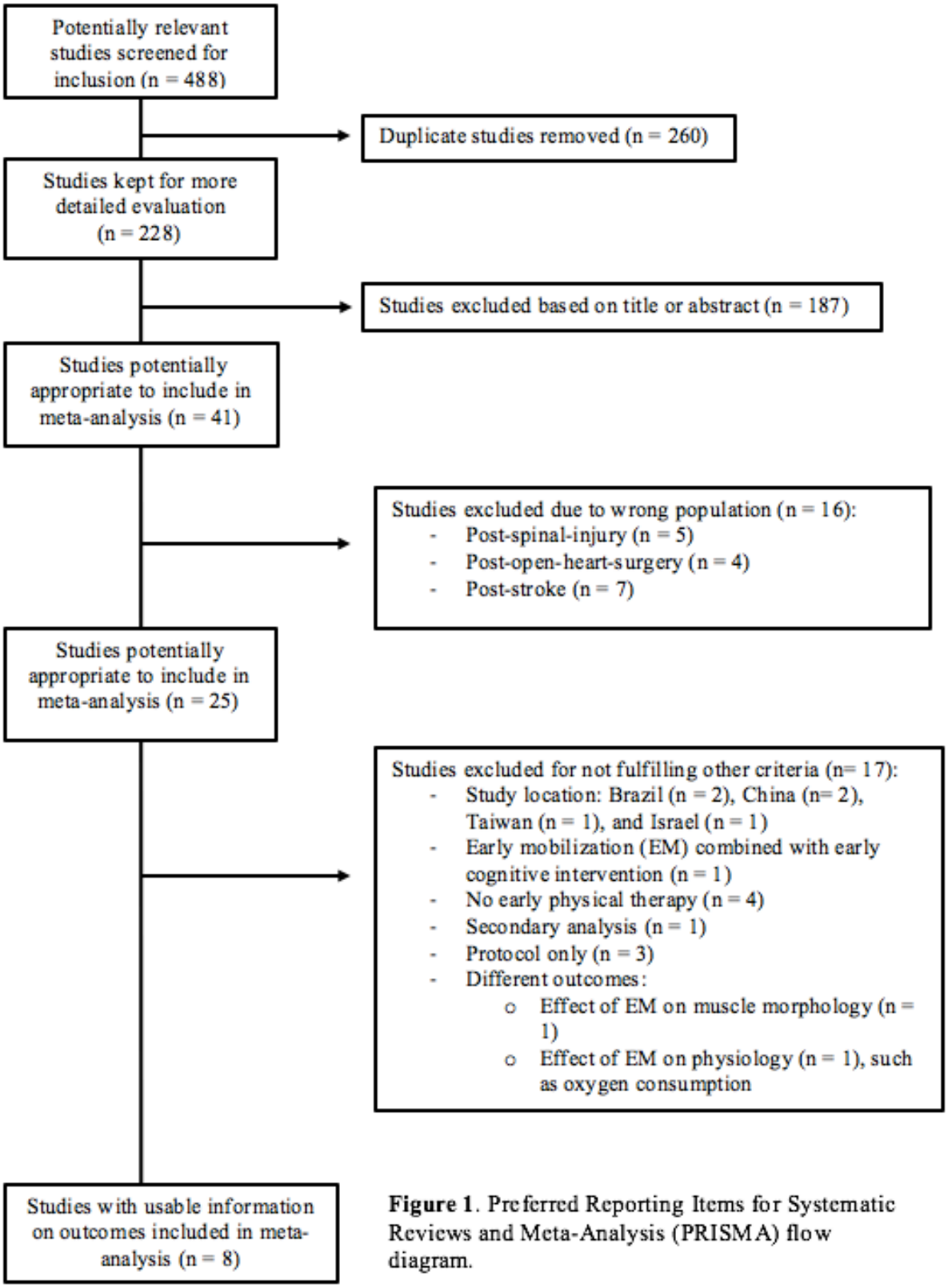


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

Table 1. Demographics of Studies Included in the Meta-Analysis

Study	Design	Country	Settings	Sample Size	APACHE II* Mean (±SD or Range)		Age, yr Mean (±SD or Range)		Number Female n (%)	
				Total (EMG/SCG)	EMG	SCG	EMG	SCG	EMG	SCG
Burtin et al [27].	RCT	Belgium	MICU, SICU	90 (31/36)	26 (±6)	25 (±4)	56 (±16)	57 (±17)	9 (29%)	10 (27.7%)
Denehy et al.[28]	RCT, Phase 2	Australia	MICU, SICU	150 (74/76)	19 (±6)	20.7 (±7.7)	61.4 (±15.9)	60.1 (±15.8)	31 (41.9%)	24 (31.6%)
Hodgson et al.[26]	Pilot RCT	Australia New Zealand	5 ICUs, MICU, SICU, Trauma	50 (29/21)	19.8 (±9.8)	15.9 (±6.9)	64 (±12)	53 (±15)	8 (38%)	12 (41%)
Kayambu et al. [30]	Double Blinded RCT	Australia	General ICU	50 (26/24)	28 (±7.6)	27 (±6.8)	62.5 (30–83)	65.5 (37–85)	8 (16%)	10 (20%)
Moriss et al.[29]	RCT, Single Center	USA	General ICU	300 (150/150)	APACHE III 76 (±26)	75 (± 27)	55 (±17)	58 (±14)	84 (56%)	82 (54.7%)
Moss et al.[31]	RCT	USA	MICU	120 (59/61)	17.9 (± 6.2)	17.4 (± 5.6)	56 (±14)	49 (±15)	23 (39%)	26 (43%)
Schaller et al.[34]	RCT, Multi-Center	Austria Germany USA	5 SICUs	200 (104/96)	16 (12–22)	17 (11–22)	66 (48–73)	64 (45–76)	39 (38%)	34 (36%)
Schweickert et al.[21]	RCT	USA	MICU	104 (49/55)	20 (15.8–24)	19 (13.3–23)	57.7 (36.3–69.1)	54.4 (46.5–66.4)	29 (59%)	23 (42%)

*APACHE II: Acute Physiology and Chronic Health Evaluation II

Table 2. Summary of RCTs Investigating ICU Early Mobilization Therapy in the Critically Ill

Study	Population	EM *vs.* SC	Starting Point of EM	Significant Outcomes
Burtin et al [27].	– ≥17 years old – Critically ill patients – ICU LOS ≥ 7 days	**EM:** SC plus cycling exercise at six levels of increasing resistance **Dosage:** 5 days/week for 20 minutes **SC:** PROM, AROM, and ambulation **Dosage:** 5 days/week	Day 5 of ICU admission	– ↑ 6MWD at Hos-D (P < .05) – ↑ SF-36 [PF] at Hos-D – (P < .01) – ↑ Isometric quadriceps force at ICU-D (P < .01). – 6MWD was correlated with quadriceps force (P < .01). – Quadriceps force and SF-36 [PF] were correlated (P < .001).
Denehy et al. [28]	– ≥18 years old – ICU LOS ≥ 5 days	**EM:** PROM, AROM, sitting, sit-to-stand exercise, walking **Dosage:** MV patients: 15 min/day; Weaned patients: 2×15 min/day; intensity based on BBS **SC:** Active bed exercise and mobility **Dosage:** Treatment was encouraged.	Day 5 of ICU admission	- Significant difference in 6MWT at ICU-D. EMG walked significantly shorter distance than SCG.
Hodgson et al. [26]	– ≥18 years old – MV <48 hours – Require MV ≥24 hours	**EM:** Active functional activities (e.g., sitting and walking); started with the highest level of patients' IMS and worked down to	Between Days 2 and 4	– ↑ Activity level of IMS scores (P = .01) – ↑ Activity duration (P = .002) – EMG able to stand more than SCG (P = .02)

		maximize level **Dosage:** depended on IMS level **SC**: PROM only **Dosage:** 5–10 min/day		– EMG able to walk more than SCG (*P* = .05)
Kayambu et al. [30]	- ≥18 years old - MV ≥48 hours - Diagnosed with sepsis within 48 hours of admission	**EM:** PROM, AROM, resistive exercises, EMS, and ambulation **Dosage:** 30 min, 1–2 times/day **SC:** Simple mobilization activities (sitting out of bed or ambulation) **Dosage:** ND	Within 24 hours of diagnosis of sepsis	– ↑ SF-36 of physical function and physical role domain (*P* = .04, *P* = .005)
Moriss et al. [29]	– ≥18 years old – MV<3 days – Hospitalized <1 week.	**EM:** PROM, AROM, progressive resistance exercise (e.g., sitting), pre-gait standing activities, and ambulation **Dosage:** 3 separate sessions/day for 7 days/week **SC:** routine PT, no rehabilitation intervention **Dosage:** NM	From the enrollment day	– ↑ SPPB at 2 and 6 months (*P* = .5, *P* = 0.04) – ↑ FPI at 6 months (*P* = .02) but not at 2 and 4 months – ↑ SF-36 [PFS] at 6 moths (*P* = .001) – ↑ SF-36 [PHS] at 6 months (*P* = .05)

Moss et al.[31]	- Age ≥18 years - Required MV for > 5 days	**EM:** Breathing technique during exercise, AROM, strengthening exercise, functional mobility retraining exercise **Dosage:** 30 min for 7 days/week in the ICU, 60 min for 3 days/week at home until Day 28 **SC:** ROM, positioning, and functional mobility retraining **Dosage:** 3 days/week	At Days 6 and 8 of ICU admission	- No difference between groups in CS-PFP-10 Scores at 1, 3, and 6 months. However, the CS-PFP-10 increased significantly from 3 months to 6 months in both groups ($P < .01$).
Schaller et al.[34]	– ≥18 years old – MV <48 hours – Required MV ≥24 hours	**EM:** combination of daily early directed goal mobilization and inter-professional closed loop communication. The intervention uses SOMS algorithm (no mobilization, PROM, sitting, standing, and walking). **Dosage:** ND **SC:** local protocol **Dosage:** NM	No later than 1 day after trial enrollment	– Significant ↑ SOSM level ($P < .001$). The SOMS level 4 (ambulating) was higher in the EMG (52% *vs.* 25 %) – ↓ SICU LOS ($P = .0054$) – Significant ↑ mmFIM score at ICU and Hos-D ($P = .009$, $P < .001$) – ↓ Hospital LOS ($P = .011$) – ↓ Delirium days

Schweickert et al.[21]	– ≥18 years old – MV <72 hours – Required MV ≥24 hours	**EM:** PROM, AROM, bed activity mobility (e.g., transferring to upright), ADLS, and walking. **Dosage:** daily PT, but duration not mentioned **SC:** no PT for MV <2 weeks **Dosage:** NM	Day of enrollment	– ↑ independent functional status at Hos-D (*P* = .02) – ↑ Barthel index score in EMG (*P* = 0.05) at Hos-D – ↓ Delirium days (*P* = .03, *P* = .02) – ↓ VFD (*P* = 0.05) – ↓ MVD (*P* = 0.02) – ↑ walk distance at Hos-D (*P* = 0.004)

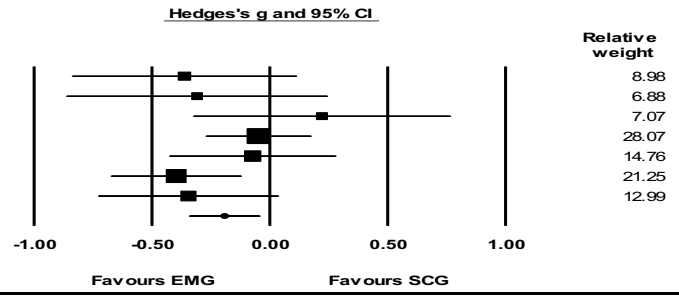
6MWD: *6-minute walk distance,* ***6MWT:*** *6-minute walk test,* ***ACIF:*** *Acute care index of function,* ***ADL:*** *Activity of daily living,* ***AE:*** *Adverse events,* ***AROM:*** *Active range of motion,* ***BBS:*** *Berg balance scale ,* ***CS-PFP-10:*** *Continuous scale physical functional performance test,* ***EMG:*** *Early mobilization group,* ***EMS:*** *Electrical muscle stimulation,* ***FPI:*** *Functional performance inventory,* ***FSS-ICU:*** *Functional status score for the ICU,* ***HADS:*** *Hospital anxiety and depression scale,* ***Hos-D:*** *Hospital discharge,* ***ICU-D****: Intensive care unit discharge,* ***IMS:*** *ICU mobility scale,* ***LOS:*** *Length of stay,* ***MMSE:*** *Mini-mental state examination score,* ***MR:*** *Mortality rate,* ***MRC:*** *Medical Research Council,* ***MV:*** *Mechanically ventilated,* ***MVD:*** *Mechanical ventilation days,* ***ND:*** *No difference,* ***NM:*** *Not mentioned,* ***PFIT:*** *Physical functional ICU test,* ***PROM:*** *Passive range of motion,* ***PT:*** *Physical therapy,* ***SCG:*** *Standard of care group,* ***SF-36 [MHS]:*** *Mental health system,* ***SF-36 [PHS]:*** *Physical health system,* ***SOMS:*** *Surgical optimal mobilization score,* ***SPPB:*** *Short performance physical battery,* ***TUG:*** *Timed up and go,* ***VFD:*** *Ventilator-free days*

Table 3: Patient and Hospital Outcomes

Continuous Outcomes

Intensive Care Unit Length of Stay

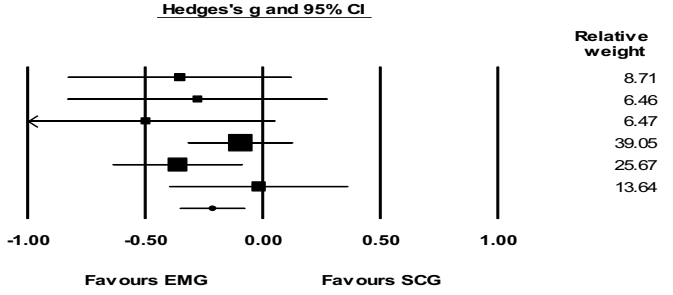
Study name	Hedges's g	Lower limit	Upper limit	p-Value	Relative weight
Burtin, 2009	-0.362	-0.840	0.117	0.138	8.98
Hodgson, 2016	-0.308	-0.864	0.248	0.277	6.88
Kayambu, 2015	0.222	-0.326	0.770	0.428	7.07
Morriss, 2016	-0.048	-0.273	0.178	0.680	28.07
Moss, 2016	-0.073	-0.428	0.283	0.689	14.76
Schaller, 2016	-0.397	-0.676	-0.118	0.005	21.25
Schweickert, 2009	-0.345	-0.730	0.040	0.079	12.99
	-0.191	-0.345	-0.038	0.015	



Q = *7.51,* P = *.28,* I^2 = *20.10*

Hospital Length of Stay

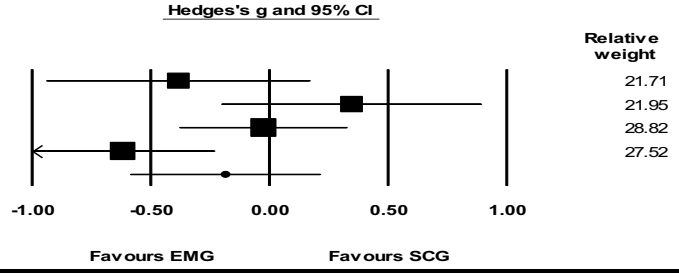
Study name	Hedges's g	Lower limit	Upper limit	p-Value	Relative weight
Burtin, 2009	-0.353	-0.831	0.126	0.148	8.71
Hodgson, 2016	-0.278	-0.833	0.278	0.327	6.46
Kayambu, 2015	-0.498	-1.053	0.056	0.078	6.47
Morris, 2016	-0.095	-0.321	0.131	0.410	39.05
Schaller, 2016	-0.362	-0.641	-0.083	0.011	25.67
Schweickert, 2009	-0.017	-0.399	0.365	0.930	13.64
	-0.213	-0.354	-0.072	0.003	



Q = *4.56,* P = *.47,* I^2 = *0*

Mechanical Ventilation Duration

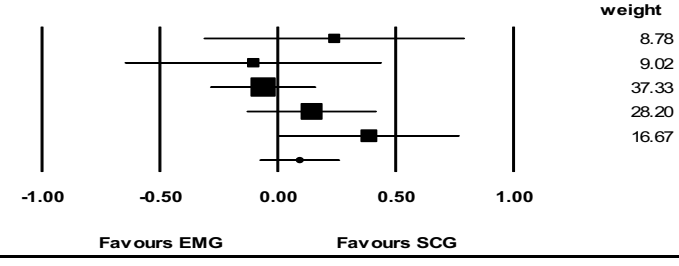
Study name	Hedges's g	Lower limit	Upper limit	p-Value	Relative weight
Hodgson, 2016	-0.384	-0.942	0.174	0.178	21.71
Kayambu, 2015	0.346	-0.204	0.897	0.217	21.95
Moss, 2016	-0.025	-0.381	0.330	0.890	28.82
Schweickert, 2009	-0.619	-1.010	-0.227	0.002	27.52
	-0.185	-0.588	0.218	0.369	



Q = *9.52,* P = *.02,* I^2 = *68.49*

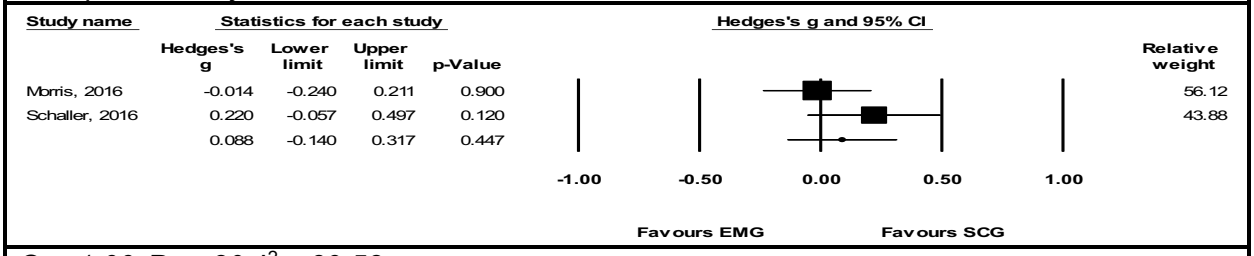
Ventilator-Free Days

Study name	Hedges's g	Lower limit	Upper limit	p-Value	Relative weight
Hodgson, 2016	0.239	-0.315	0.794	0.397	8.78
Kayambu, 2015	-0.104	-0.651	0.442	0.709	9.02
Morries, 2016	-0.062	-0.288	0.164	0.590	37.33
Schaller, 2016	0.144	-0.133	0.420	0.309	28.20
Schweickert, 2009	0.387	0.001	0.773	0.049	16.67
	0.093	-0.078	0.265	0.286	



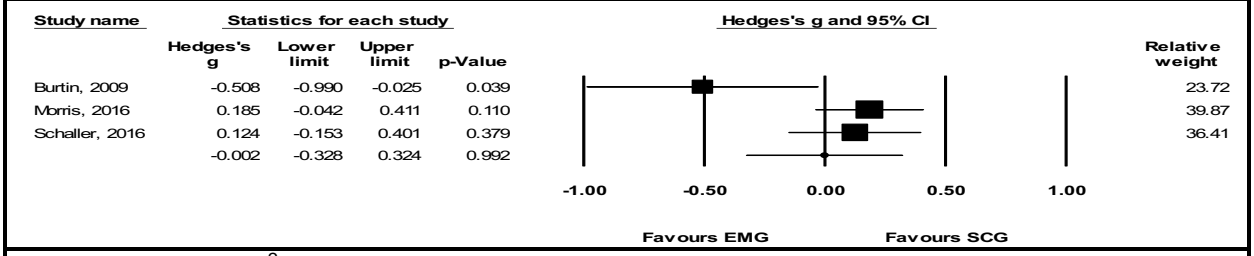
Q = *4.91,* P = *.30,* I^2 = *18.49*

Vasopressor Days



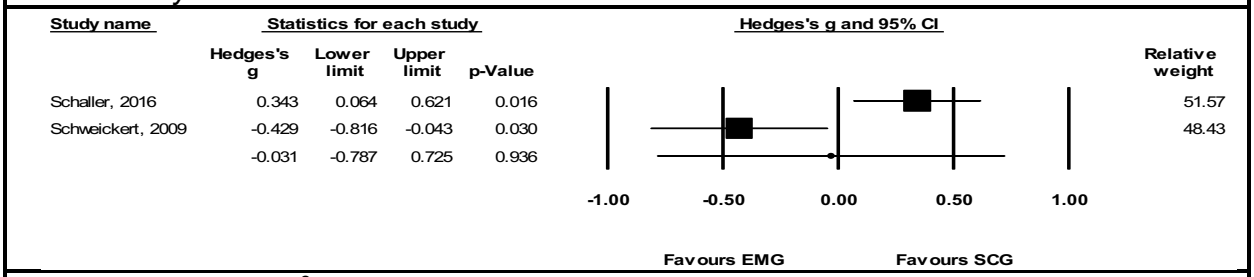
Q = *1.66,* P = *.20,* I^2 = *39.58*

Sedation Days



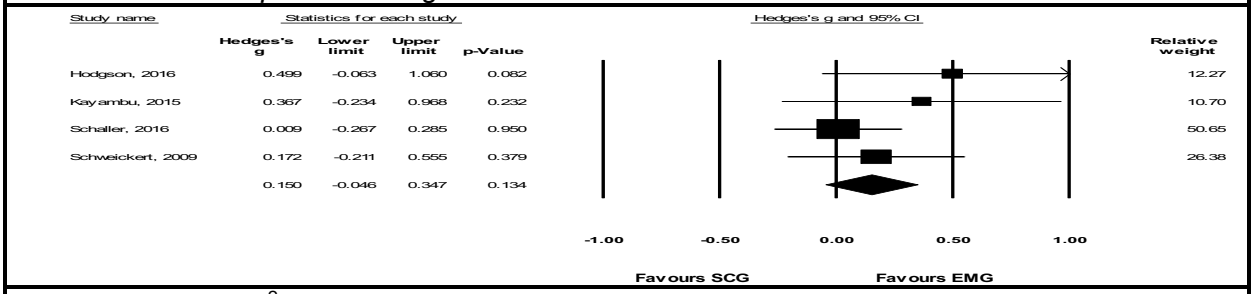
Q = *6.62,* P = *.04,* I^2 = *69.78*

Delirium Days



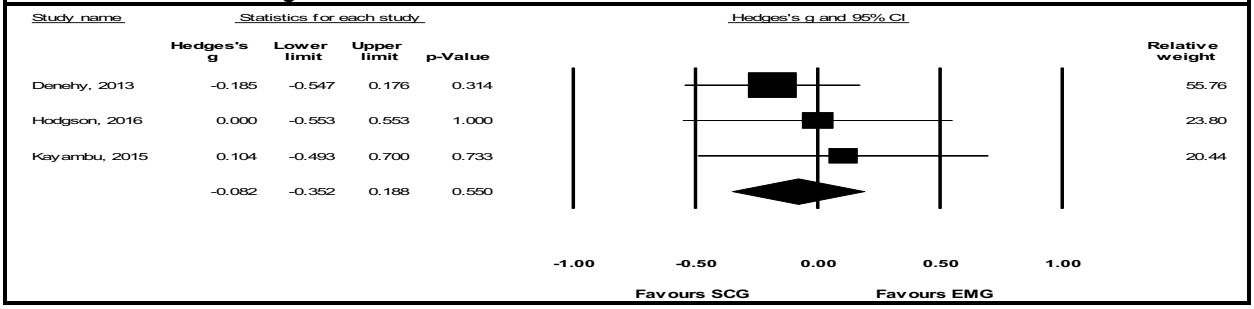
Q = *10.01,* P = *.001,* I^2 = *90.08*

MRC Scale at Hospital Discharge



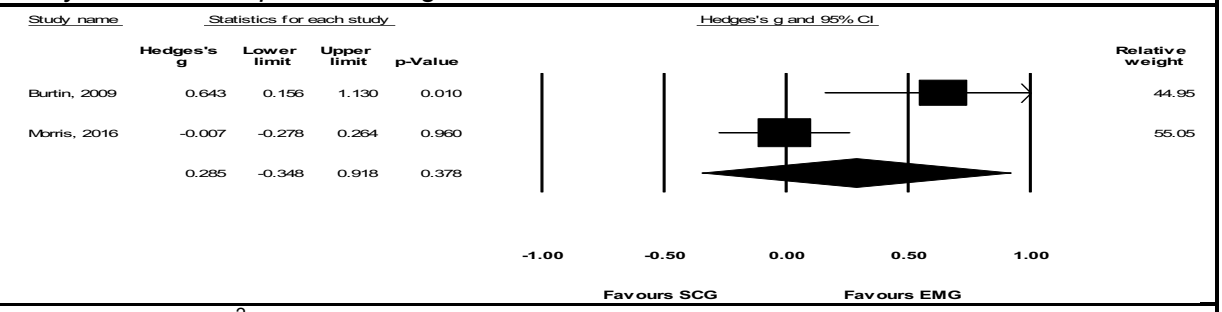
Q = *2.99,* P = *.39,* I^2 = *0*

PFIT at ICU Discharge



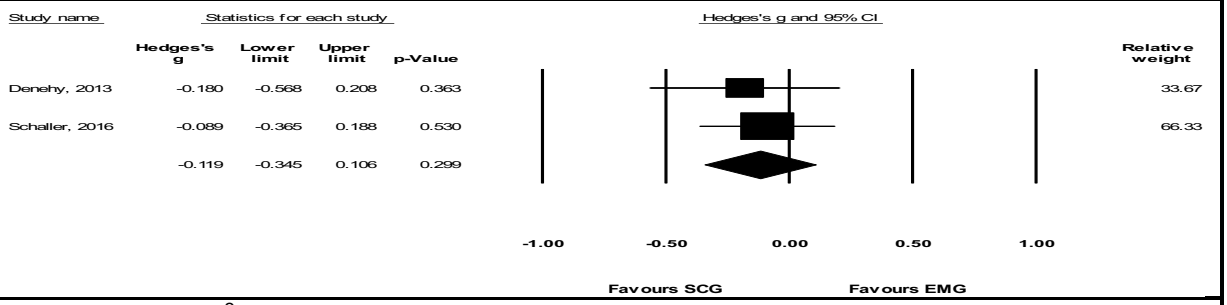
Q = *4.91*, P = *.30*, I^2 = *0*

Quality of Life at Hospital Discharge



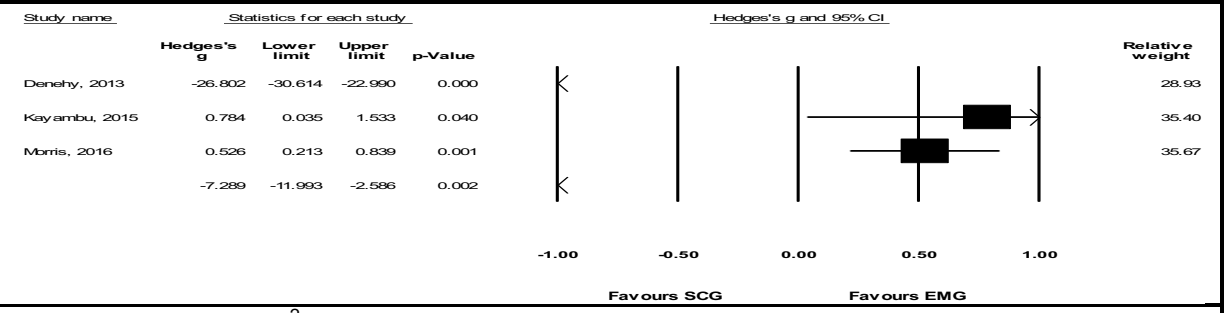
Q = *5.22*, P = *.02*, I^2 = *80.84*

Quality of Life at 3 Months



Q = *.14*, P = *.71*, I^2 = *0*

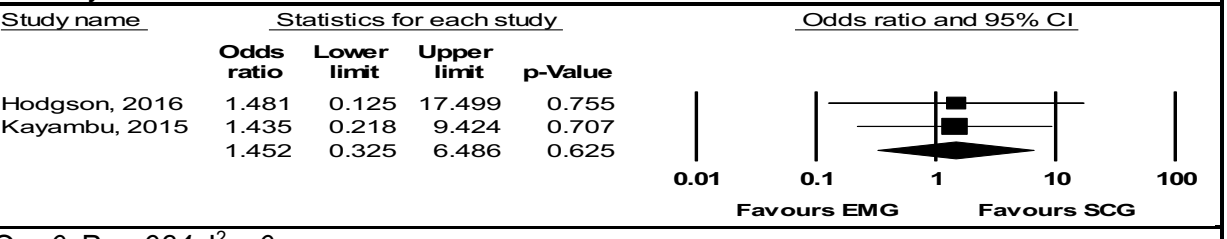
Quality of Life at 6 Months



Q = *197.26*, P < *.001*, I^2 = *98.99*

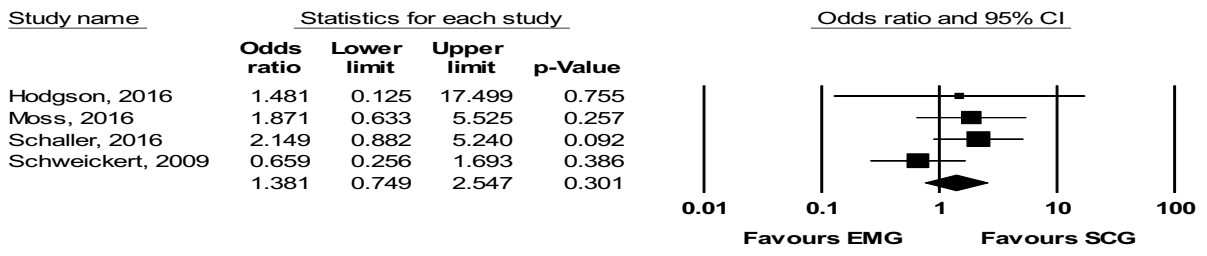
Binary Outcomes

Mortality at ICU



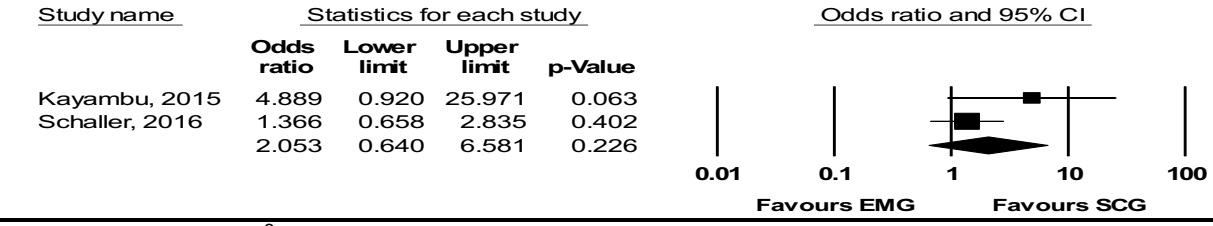
Q = *0*, P = *.984*, I^2 = *0*

Mortality at Hospital



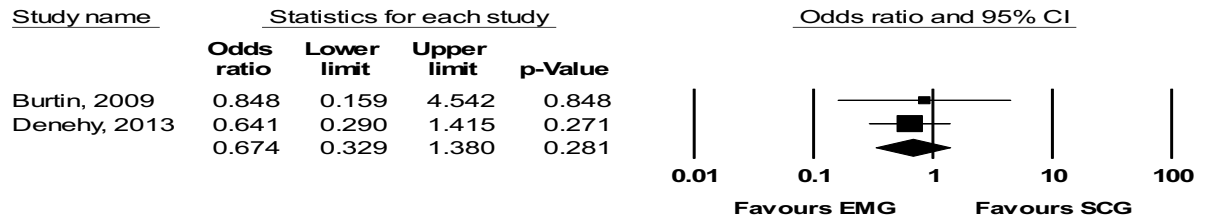
Q = *3.61,* P = *.306,* I^2 = *16.96*

Mortality at 3 Months



Q = *1.88,* P = *.170,* I^2 = *46.80*

Mortality at 1-Year



Q = *.088,* P = *.767,* I^2 = *0*

Discussion

This meta-analysis found that EM of ICU patients decreased their lengths of stay in the ICU and hospital. In addition, patients' quality of life six months after hospital discharge improved. However, this result should be interpreted cautiously, because the huge variations might have led to significant difference between the two groups such as level of sickness of both groups. Moreover, the measures of many outcomes, such as MVD, QoL at Hos-D, sedation days, delirium days, and MR at Hos-D and six months' post-discharge, vary across studies. These inconsistencies across trials may be caused by variations in intervention technique, duration, intensity, sedation protocol, or staff. It is difficult to demonstrate the overall effect of the EM on patients' physical performance and muscle strength. The meta-analysis did not indicate an improvement in the patients' physical function and muscle strength, but seven out of

eight trials indicated significant improvement in patients' physical function. However, each study used distinct measurements and tools to measure physical function, which makes measuring the overall effect on physical function difficult. Only three studies in this meta-analysis used the PFIT to measure physical function. [5,26,28] Similarly, four studies used the MRC to measure muscle strength [21,26,30,34] while others either used different tools or did not measure muscle strength. Those studies were not enough to show the overall effect of the intervention on muscle strength. Similarly, meta-analysis of Castro-Avila et al. reported that the intervention did not show an improvement on muscle strength.[37] The Castro-Avila et al.'s study also supports the finding that non-uniform measurement instruments make assessing the overall effect of EM on physical function and muscle strength impossible.[37]

Moreover, this meta-analysis demonstrates that EM or rehabilitation in the ICU has no effect on mortality rates. [21,26-28,30,31,34] Thus, interventions are safe, as they do not increase the mortality rates in patients who receive EM. Similarly, the Kayambu [38] reports that the early rehabilitation in the ICU did not show a significant effect on MR. To show the effect of this intervention on MR, more longitudinal studies with larger sample sizes to follow patients at hospital discharge and a year after discharge are required.

Two previous meta-analysis reviews differ from this current meta-analysis. Both studies included multiple types of intervention; both studies included EMS as the sole intervention, though EMS was excluded in this meta-analysis, [37,38] as this study focuses on the effect of EM on ICU patients. In addition, Castro-Avila's meta-analysis [37] includes both early and late rehabilitation in the ICU and focused only on functional outcomes, while this meta-analysis included only studies that delivered the intervention within a week of admission and included a wider range of outcomes. Further, Kayambu's meta-analysis includes studies completed in Asian countries such as China which this meta-analysis excluded. [30]

Limitations

Because of the limited number of studies covering this intervention, this meta-analysis included RCTs either in pilot phase or in phase two with small sample sizes (n = 50) [26,30]. Also, definitions of EM and SC differed in each study, which reflected on different types of interventions, techniques, durations, and intensities. Some studies did not include PT for SC, while others provide PT and some type of mobilization less intense than EM.

Future research

Future studies should carefully choose the instruments used to measure outcomes. It was difficult to draw conclusions about the effect of EM on physical function and muscle strength because each study under meta-analysis used different instruments. Studies should also provide more detailed information about EM and SC, which would help researchers draw conclusions about the appropriate dose of EM for ICU patients. Finally, larger, well-designed studies of EM delivered in multicenter locations are needed to provide careful consideration to the subject and to unify the SC between ICUs, because variations in the SC might affect results of the EM on ICU patients.

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CHAPTER 3

Systematic Review: How Early Mobilization Mediates Pressure Injury Development Risk Factors in Intensive Care Populations

Background

Patients in intensive care units (ICUs) are at higher risk of developing pressure injuries (PIs) than patients elsewhere.[1-6] Preventing PIs in the ICU is not always the foremost concern of health-care providers,[7] because ICU patients often exhibit severe physiological instability that requires therapies to stabilize and support them. However, these same patients are at risk for PIs because of lack of mobility. Approximately 2.5 million hospitalized patients per year are treated for PIs, according to the Agency for Healthcare Research and Quality (AHRQ).[8] Studies showed variation in PIs. Within last five years, studies found PI incidence is highest in ICUs, ranging from 5.6% to 31%. [9-13]

PIs not only lead to negative patient outcomes, but also place an additional burden on health-care systems. PIs are associated with discomfort, pain, infection, depression, longer hospitalization, a higher mortality rate, and an increased likelihood of readmission.[14-20] In 2014, the AHRQ stated that the treatment of PIs costs between $9.1 and $11.6 billion per year.[8]

In 2007–2008, the Center for Medicare and Medicaid Services changed its system of reimbursement for patients with PIs, paying nothing for patients with healthcare acquired stage III and IV PIs.[21] The development of PIs is considered a sign of low-quality care because it is a preventable condition.[20] Consequently, health organizations and health-care providers are focusing more on preventing PIs, both to prevent negative outcomes for patients and because the occurrence of PIs is a proxy for the general quality of care.

ICU patients, and mechanically-ventilated (MV) patients in particular, are usually immobilized for long periods, which is a main factor in PI development.[15,20,22] Researchers have

recommended mobilizing ICU patients to prevent PIs.[9,11] Recently, a new technique known as early mobilization (EM) has been introduced in ICUs, which helps decrease complications due to immobility.[15] Early mobilization has been shown to decrease muscle weakening[23-27] and is associated with reductions in short-term physical impairment, the number of ventilator days, and the length of stay (LOS) in the ICU and hospital;[28-32] thus, it also indirectly reduces the cost of care.[24] Despite the promise of EM, no researchers have explored the effects of EM on PIs development. To clarify the connection between EM intervention and PIs, this paper provides a systematic review of the literature over the past decade to identify PIs risk factors in ICU populations. The review is supplemented by another literature review that illuminates PI pathophysiology and EM outcomes in ICU populations and shows how EM could intervene in PI development.

Research Methods

A comprehensive electronic search of the PubMed, CINAHL, and EMBASE databases was undertaken using the following as MeSH terms or as terms within the title and abstract: *pressure ulcers, bedsores, decubitus ulcers, intensive care unit, risk factors.* The operators *OR* and *AND* were used while searching for articles. The search was limited to studies written in English and published between 2007 and 2017. There were 119 articles with the potential for inclusion in the systematic review. Of these, 19 studies fulfilled the inclusion criteria (Figure 1). The inclusion criteria were the following: 1) primary research, 2) adult ICU populations, and 3) specific study designs including prospective cohort, retrospective/prospective record review, descriptive, cross-sectional, observational studies, and randomized control trials. The exclusion criteria were the following: 1) PI treatment studies, 2) PI screening tool development, reliability, and validity studies, 3) device-related Pi studies, 4) prevalence-only studies, 5) PI prevention protocols, and 6) spinal cord injury studies.

Results

Studies and patients' characteristics

These 19 included 10 prospective studies (4 cohorts, 4 descriptive, and 2 cross-sectional designs) and 9 retrospective studies (2 cohort, 4 chart reviews, and 3 cross-sectional designs). The studies were carried out in eight countries (United States of America, Turkey, Brazil, China, Japan, Germany, Italy, and Belgium) and in different ICU settings. A summary of the included studies is detailed in Table 1.

The 19 studies included a total of 11,141 patients in ICUs. The mean age of the patients was 61.8 years (range 50.4–70 years). The median occurrence of PIs was 16.35% (range 5.6%–34.4%). The sacrum (range 14%–58%) and heel (range 5%–39.6%) were the most common PI sites. Most of the PIs appeared in less than 14 days (range 2–23 days). Eleven studies reported stage-1 PIs (incidence range 2.7%–74%); 9 studies reported PIs of stages 2, 3, and 4 (range 5.2%–57%, 0%–55.6%, and 0%–16.2%, respectively); 5 studies reported unstageable PIs (range 0%–56%); and 4 studies reported suspected deep-tissue injuries (range 20.7%–56%).

PI risk factors

Two major statistical concepts were mentioned to analyze the risk factors in most of studies. The first analytical concept focused on identifying the factors that were different between the patients with PIs and those without (15 studies[9-13,18,20,33-40]). The significant factors were age (4 studies[10,20,33,38]), severity of illness (6 studies[9,10,18,20,35,36]), diabetes mellitus (DM) or uncontrolled blood glucose level (5 studies[9-13,18,20,33-40]), nutrition (3 studies [10,20,36]), albumin (3 studies[12,20,40]), cardiovascular disease (CVD; 2 studies[9,10]), diastolic blood pressure (DBP) less than 60 mmHg (4 studies[10,12,20,39]), systolic BP (SBP) less than 90 mmHg (2 studies[10,12]), mean arterial pressure (MAP) less than 60 mmHg (4 studies[9,10,12,20]), vasopressors (5 studies[9-11,20,40]), and hospital LOS (4 studies[9,20,33,35]).

The second type of analytical concept focused on assessing the relationships between the risk factors and PI development (17 studies[9-13,18,33-39,41-44]). Age and gender were non-modifiable risk factors. Age (9 studies[10,11,18,33-35,38,42,45]) and gender (3 studies[35,45,46]) were significantly associated with PI development, as were severity of illness (3 studies [18,35,43]).

This systematic review also identified 5 factors that affect the loading pressure applied to the skin that were significantly associated with PI development: mobility (2 studies[10,41]), activity (1 study[37]), friction/shear (4 studies[10,12,41,42]), repositioning (3 studies[13,41,43]), and sedation (1 study[43]). In addition, there are many factors that affect the skin perfusion system: vasopressors (5 studies [9,10,12,33,43]), SBP less than 90 mmHg (1 study[12]), MAP less than 60 mmHg (1 study[9]), continuous venous hemofiltration (1 study[43]), edema (1 study[43]), MV (3 studies[9,39,43]), DM (3 studies[11,38,44]), CVD (4 studies[9,10,43,44]), pulmonary disease (1 study[12]), and albumin (1 study[44]). Moreover, two studies reported moisture as a factor associated strongly with PIs development.[18,38] Finally, 6 studies reported that ICU LOS is significantly associated with PI.[10,18,34,35,37,45]

Finally, the scores of different PI scales were different between the patients with PIs and without PIs (8 studies[9,10,13,18,20,35,37,38]), Also, those scales scores were significantly associated with PI development (4 studies[18,38,42,43]).

Discussion

The risk factors that emerged from this review accord well with the Braden and Bergstrom conceptual scheme.[22] Fundamentally, PIs are caused by increased external pressure and decreased tissue tolerance.[6,15,22,36] Mobility, activity, friction/shear, repositioning, and sedation are risk factors that affect the pressure exerted on the skin. Exposure to a continuous loading pressure for long periods of time is the most important factor in the development of PIs.[6] Three elements contribute to the close relationship between pressure and PIs: low sensory perception of pain, immobility, and inactivity.[15,22] Patients with decreased sensory perception are not able to protect themselves from continuous pressure because they are not able to sense

discomfort and change position to distribute the pressure.[6,15,22] Decreased sensory perception is particularly common in sedated patients (those who are unconscious) or patients with spinal cord injury (those who have impaired cutaneous sensation).[15,22] Immobile patients may lose the ability to move and change their position when they experience pressure.[6,22] Also, inactivity puts pressure on vulnerable areas of the skin and contributes to PI development. Exposure to pressure increases interstitial pressure, leading to capillary leakage that can cause edema.[6,15] Therefore, adjusting the patient's position to redistribute pressure is important for preventing ischemia and lacerations.[47]

Tissue tolerance

Tissue tolerance to ischemia plays an important role in the development of PIs. Many factors may cause skin tissue to lose tolerance. These can be divided into extrinsic risk factors (moisture, friction, and shear) and intrinsic risk factors (nutrition, age, circulation, and tissue perfusion).

Moisture does not cause PIs, but it can exacerbate the generation of chronic wounds.[6] Perspiration, urine, stool, and drainage from a fistula or wound are all sources of moisture for ICU patients.[15,22] The constant exposure of the skin to moisture softens the upper layer of the skin and changes the acid-alkaline balance of the skin, which leads to excoriation and maceration.[6,48]

Friction and shear are the main mechanical factors involved in producing PIs.[20] Friction is the force that is created when two surfaces move against each other, such as when bedridden patients are lifted or dragged to change positon.[15,22,49] Friction creates wounds in the epidermal and dermal layers of the skin, leading to the development of rashes or cellulitis.[22,49] Shear is a force created by the interplay of gravity and friction that leads to changes in deeper tissues through the angulation and deformation of the vascular bed that passes the deep vesical and superficial fascia.[2,22,44,49-51] Shear causes a decrease in the blood perfusion through and

oxygen supply to skin tissue.[52] Shear often occurs in the ICU when MV patients are kept in an elevated-head bed position in order to prevent ventilator-associated pneumonia.

Nutritional deficiencies cause hypoproteinemia and anemia, which alter the ability of the skin to tolerate long exposure to pressure.[49] Albumin maintains oncotic pressure, which influences tissue tolerance.[44,53] Hypoalbuminemia decreases oncotic pressure inside the blood vessels, which causes edema and can lead to low oxygen and nutrient perfusion in the skin tissue.[51,54]

Delayed or decreased blood flow increases the risk of PI development.[51,55] There are many factors that decrease blood flow, including vasopressor use and comorbidities. Vasopressor medications cause generalized vasoconstriction, which decreases the oxygen supply to the skin tissue.[10] Some of the comorbidities affecting patients' circulation include diabetes mellitus, cardiovascular disease, and high blood pressure. Diabetes mellitus causes a thickening of the capillary membranes and reduces the function of the sympathetic nervous system, which slows blood flow to the skin and alters tissue perfusion.[51,55] Cardiovascular and respiratory diseases affect the oxygen concentration in the capillaries, which also changes perfusion.[6,55]

Early Mobilization

One intervention that may decrease the occurrence of PI is early mobilization. Early Mobilization reduces MV days and LOS, thus significantly reducing the cost of care. Morris et al.'s (2008) study showed that early mobility led to cost savings of general overall cost more than $500,000, compared to standard of care.[29]Therefore, EM might be an effective intervention because it may reduce the incidence of PIs, even though the implementation of EM does not cost any more than the usual care.

There is a lack of evidence concerning the association between EM intervention and PI development. To show conceptually how EM might mediate PI development, links were introduced between EM and PI development in the Braden and Bergstrom conceptual scheme.

[22] This conceptual scheme explains how various risk factors are related to PI development. Immobility, inactivity, shear, and friction are factors that can be mediated directly when patients are mobilized from the supine position to the edge of the bed, to a chair, and finally, up and ambulating. The main concern is the constant loading pressure, which affects circulation and can lead to ischemia. A particularly high risk group for PI are ICU patients who are intubated. The mechanically ventilated patients are usually immobilized over long periods due to sedation. Those patients lost their sensory perception to pain and they are unable to change their position to relieve and distribute the constant pressure over their bony prominence areas. Notably, the implementation of EM was associated in a reduction in sedative usage.[56,57] Also, EM increases both the activity level and the physical functioning of MV patients in ICUs.[57-63] MV patients, who received the EM, have walked 200 feet at ICU discharge more than usual group.[28]Thus, early mobilization affects factors associated with pressure injury development. A study of the direct relationship between EM and pressure injury development in ICU patients, and the modifying effects on risk factors is needed.

Table 1: Summary of Pressure Injury Risk Factor Studies in ICU Populations						
Author(s)	**Study Design**	**Country**	**Setting(s)**	**Sample Size (*N*)**	**Population**	**Significant Results**
Alderden et al.[33]	Retrospective chart review	USA	89% ICU pts; 10% not admitted to ICU	87	- age ≥ 18 years - critically ill and trauma pts - accepted pts w/o PI	**Multivariate analysis:** - Age (*P* = 0.009) - Creatinine (*P* = 0.04) - Hospital LOS (*P* = 0.02) - Vasopressor infusion (*P* < 0.01) **LRA:** - Vasopressors (*P* = 0.005) - Spinal cord injury (*P* = 0.02) - Age ≥ 40 years (*P* = 0.001)
Bly et al.[12]	Retrospective chart review	USA	MICU, CICU	345	- age ≥ 18 years - No PI on admission	**1st LRA, all *P* < 0.05:** 1. Any transport off unit 2. Number of days to bed change 3. Systolic blood pressure < 90 mmHg 4. Use of > 1 vasopressor 5. History of pulmonary disease **2nd LRA, all *P* < 0.0:** 1. Any transport off unit 2. Number of days to bed change 3. Feeding tube 4. Systolic blood pressure < 90 mmHg 5. Use of > 1 vasopressor
Campanil et al.[34]	Prospective cohort study	Brazil	CICU	360	- age ≥ 18 years - No PI on admission - ICU stay < 24 hrs - BSS ≤ 18	**Statistical difference between the PI and N-PI:** - ICU LOS (*P* < 0.001) - Extracorporeal circulation time (*P* = 0.030) - DM (*P* = 0.004) - Presence of supporting surface (*P* < 0.001) **Classification and regression tree, *P* < 0.05:** - ICU LOS - Age ≥ 45 years

						- Race = Caucasian (White)
Cox[10]	Retrospective correlational design	USA	MICU, SICU, CICU	306	- age > 18 years - ICU stay > 24 hrs. - Pts received vasopressors	**Statistically difference between the PI and N-PI:** - Norepinephrine (*P* = 0.04) - Vasopressin (*P* < 0.001) **Multivariate analysis:** Vasopressin was the only significant predictor. **LRA:** - Cardiac arrest (*P* = 0.05) - MV > 72 hrs. (*P* < 0.001) - MAP < 60 mmHg (*P* = 0.01) - Vasopressin (*P* = 0.004) Cardiac diagnosis on ICU admission (*P* = 0.03)
Cox[9]	Retrospective descriptive correlational design	USA	MSICU	347	- age ≥ 18 years - ICU stay ≥ 24 hrs. - No PI on admission	**1st LRA:** - Mobility score (*P* = 0.04) - Age (*P* = 0.03) - ICU LOS (*P* < 0.001) - Cardiovascular disease (*P* = 0.007) **2nd LRA, excluding all pt. with Stage 1 PI:** - Friction/shear scores (*P* = 0.01) - ICU LOS (*P* < 0.001) - Norepinephrine (*P* = 0.04) - Cardiovascular disease (*P* = 0.02)
Frankel et al.[11]	Retrospective chart review	USA	SICU	820	Stage 2 of PI or greater during or after SICU stay	**Stepwise LRA:** - DM (*P* = 0.023) - Creatinine > 3 mg/dl (*P* = 0.019) - Spinal cord injury (*P* = 0.021)
Gremasco et al.[35]	Prospective descriptive study	Brazil	3 ICUs	160	- age ≥ 18 years - No PI on admission - ICU stay < 24 hrs.	**Statistical difference between the PI and N-PI:** - Hos LOS (*P* = 0.025) - ICU LOS (*P* < 0.001) - BSS (*P* < 0.001) - SAPS II (*P* = 0.002) **Multivariate linear regression**: - Nursing activity score (*P* < 0.001) - SAPS II (*P* = 0.002) - Age (*P* = 0.042) **Multivariate LRA:**

						- Gender (P = 0.014) - ICU LOS (P = 0.002) - Nursing activity score (P = 0.011) - SAPS II (P = 0.035)
He et al.[18]	Prospective cohort study	China	SICU	102	- Adult pts - No PI on admission - Not malnourished	**<u>Bivariate correlational analysis</u>** **Weak positive correlations:** - BSS and moisture content (P < 0.01) - APACHE IV and age (P = 0.01) - APACHE IV score and moisture content (P < 0.01) **Moderate positive correlations:** - BSS and APACHE IV (P < 0.01) - Moisture content and skin surface pH (P < 0.01) **Strong positive correlations:** - LOS and moisture content (P < 0.01) - LOS and skin surface pH (P = 0.03)
Hyun et al.[13]	Retrospective cohort study	USA	SICU, MICU	2632	- age ≥ 18 years - ICU stay > 3 days - No PI on admission	**Univariate analysis:** BMI and incidence of PI were related in the ICU. **Multiple LRA:** - Underweight vs. obese (P < 0.001) - Obese vs. extremely obese (P < 0.001)
Kaitani et al.[36]	Prospective cohort study	Japan	GICU, HCU	98	- age ≥ 20 years - ICU stay > 24 hrs. - No PI on admission	PIs were not associated with APACHE II score or any medications that affected skin integrity. **LRA:** - Emergency admission to ICU/HICU (P = 0.037) - Schedule ICU/HCU patients (P = 0.010) - Frequent turning (P = 0.040) - Edema (P < 0.05) -

Lahmann et al.[45]	Repeated cross-sectional survey	Germany	SICU, MICU, orthopedic interdisciplinary unit	2237	Comparison between ward patients' and ICU patients' risk factors	**All 7 RFs were significant in the LRA (*P* < 0.001)** - Male - >79 years old - Repositioning - Pressure redistribution device - Friction and shear - Impaired mobility - Intensive care unit
Sayar et al.[37]	Prospective descriptive analysis	Turkey	SICU, MICU	140	Adult critically ill patients in the ICU	**Statistical difference between the PI and N-PI (*P* < 0.05):** - ICU LOS - WSS - Creatinine - Consciousness - Cooperation **Multiple stepwise LR:** - LOS (*P* < 0.01) - Activity level (*P* = 0.05)
Senturan et al.[39]	Prospective descriptive observational study	Turkey	ICU	30	- age ≥ 18 years - Pts on MV > 24 hrs. - Pts w/o COPD or DM - No PI on admission	**Mann-Whitney *U* test:** - Diastolic BP (*P* = 0.057) - Blood glucose level (*P* = 0.028)
Serra et al.[46]	Retrospective cohort study	Italy	MSICU	610	- age ≥ 18 years - ICU stay ≥ 24 hrs. - No PI on admission	**Receiver operating characteristic curve:** - Close association between serum albumin and PI **Male:** - Hypoalbuminemia (*P* < 0.001) - DM (*P* = 0.002) - Congestive heart failure (*P* = 0.018) - Malnutrition (*P* = 0.01) **Female:** - Hypoalbuminemia (*P* < 0.001) - DM (*P* = 0.047)

						- Congestive heart failure (P = 0.005) - Obesity (P = 0.018) - Malnutrition (P = 0.04)
Shahin et al.[38]	Prospective cross-sectional study	Germany	SICU, MICU, interdisciplinary ICU	1760	Adult pts	**LRA:** - Bowel incontinence (P = 0.010) - Age (P = 0.022) - BSS (P = 0.010)
Slowikowski and Funk[42]	Prospective descriptive cross-sectional study (two phases)	USA	SICU	369	Adult pts in SICU	**LRA:** - BSS (P < 0.001) - Age ≥ 70 (P = 0.04)
Smit et al.[40]	Retrospective chart review	USA	MICU	76	Critically ill pts	**Chi-square and Kruskal-Wallis tests:** - Vasopressors (P = 0.016) - Days from admission to PI development (P = 0.021)
Terekeci et al.[20]	Prospective cohort study	Turkey	ICU	142	- Adult pts - Pts with or without PI on admission - Critically ill pts	**<u>Fisher's exact test</u>** **On admission:** - Nutritional risk screening (NRS-2002) (P < 0.05) - NSS (P < 0.05) - Albumin (P < 0.05) - APACHE II (P = 0.016) - Nutritional risk screening (NRS-200) (P = 0.001) - MAP and hemoglobin levels were not different (P > 0.05) **On discharge:** - Nutritional risk screening (NRS-200) (P < 0.05) - NSS (P > 0.05) - Albumin (P < 0.05) - MAP (P < 0.05) - APACHE-II score (P<0.05] - Hospitalization period (P < 0.05) - Two or more comorbidities (P < 0.05) - Infections (P < 0.05) - Medications (P < 0.05)

Nijs et al.[43]	Prospective descriptive design	Belgium	SICU	520	- age ≥ 16 years - ICU stay ≥ 24 hrs. - accepted pts with PI	**Multivariate LRA 44 hours before the occurrence of PI (grades 2–4):** - MV (*P* = 0.003) - History of vascular disease (*P* = 0.001) - IHD or CVVH (*P* = 0.001) - Turning≥ 6 times/day (*P* < 0.001) - Floating heels (*P* < 0.002) - Sedation (*P* = 0.004) **Multivariate LRA 24 hours before the occurrence PI (grades 2–4):** - Dopamine ≤ 5 microgram g/kilo gram /min (*P* = 0.003) - Medical history of cardiovascular disease (*P* = 0.045) - IHD/CVVH (*P* = 0.045) - Turning ≥ 6 times/day (*P* < 0.001) - Sedation (*P* = 0.006) - Body temperature ≥ 38.5°C (*P* = 0.029) - Sitting on chair (*P* < 0.001)
BP: *blood pressure;* ***CICU:*** *Cardiac intensive care unit;* ***COPD:*** *chronic obstructive pulmonary disease;* ***CVH:*** *continuous venovenous hemodialysis;* ***CVVH:*** *Continuous venovenous haemofiltration;* ***DM:*** *diabetes mellitus;* ***FiO_2:*** *inspired oxygen concentration;* ***HCU:*** *high care unit;* ***GICU:*** *General ICU;* ***ICU:*** *intensive care unit;* ***IHD:*** *intermittent hemodialysis;* ***LOS:*** *length of stay;* ***LRA:*** *logistic regression analysis;* ***MAP:*** *mean arterial pressure;* ***MV:*** *mechanical ventilation;* ***MICU:*** *Medical intensive care unit;* ***MSICU:*** *Medical surgical intensive care unit;* ***N-PI****: No pressure ulcer;* ***OR:*** *operating room;* ***PEEP:*** *positive end-expiratory pressure;* ***PI:*** *Pressure ulcer;* ***Pt(s):*** *patient(s);* ***RFs:*** *risk factors;* ***SICU:*** *Surgical intensive care unit;* ***$ScvO_2$:*** *central venous oxygen saturation;* ***SpO_2:*** *oxygen saturation as shown by pulse oximetry;* ***SvO_2:*** *venous oxygen saturation;* ***W/O:*** *without*					**Tools or Scales:** **APACHE II:** Acute physiology and chronic health evaluation II **BSS:** Braden Scale score **NSS:** Norton Scale score **SAPS II:** simplified acute physiology score II **WSS:** Waterlow Scale score

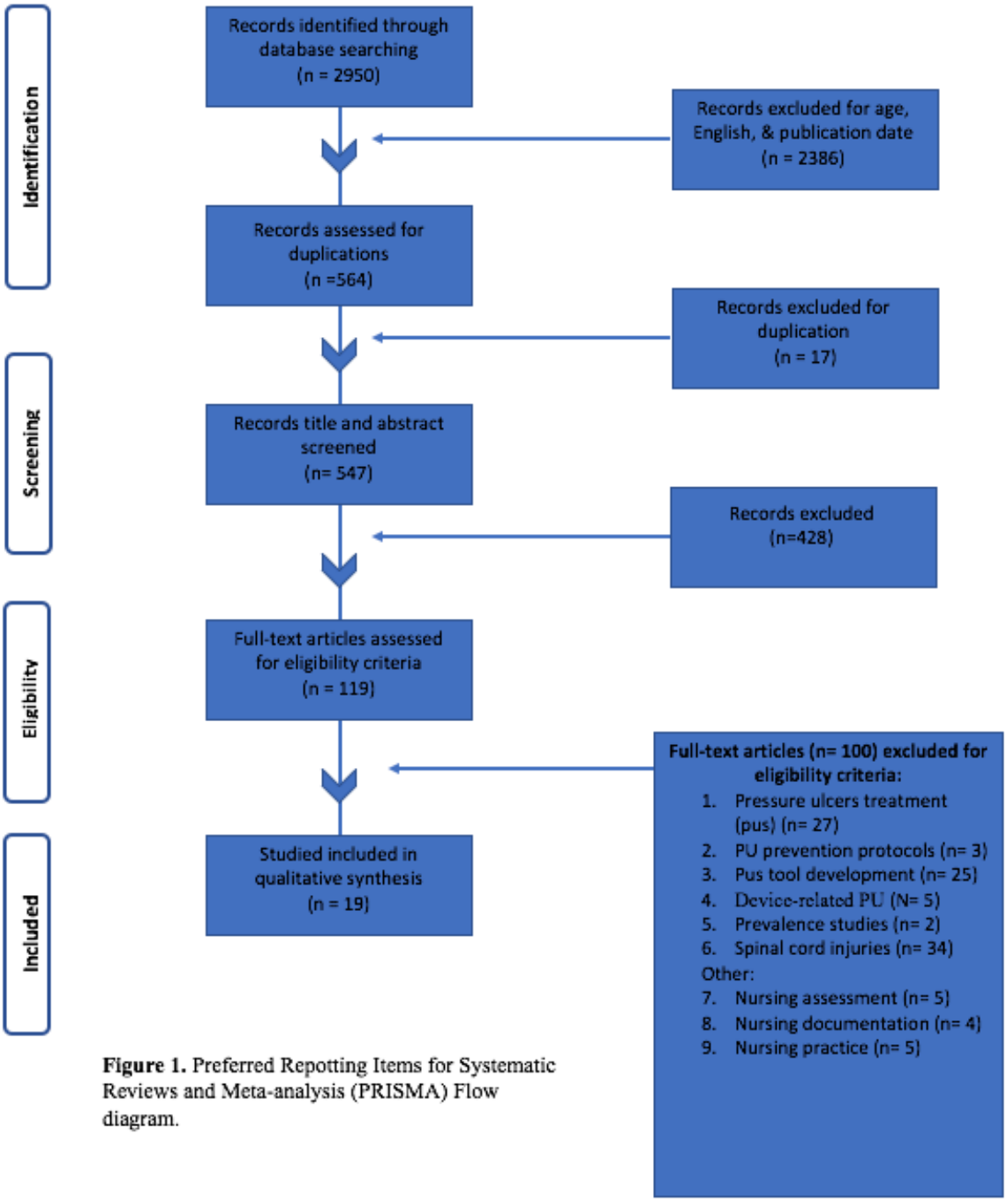

Figure 1. Preferred Repotting Items for Systematic Reviews and Meta-analysis (PRISMA) Flow diagram.

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CHAPTER 4

The Association Between Early Mobilization Intervention and the Development of Pressure Injuries in the Intensive Care Unit

Background

Pressure injury (PI) prevention is one of major challenges that health care providers consistently face. PI development is a complex, multifactorial problem with contributing factors that range from the patient's cellular level to the environmental level of health care settings. Critically ill patients in intensive care units (ICUs) are a challenging population to care for because of their physiological instability. As a consequence, it is challenging for health care providers to prevent PI while simultaneously trying to save a patient's life.

Patients in ICU settings have a higher rate of PI incidence compared to patients in other departments.[1,2] The PI incidence rate in ICU settings ranges widely from 5% to 34%.[3-17] The Agency for Healthcare Research and Quality reported that PIs cost from $9.1 to $11.6 billion per year in the US.[18] and the cost of care for PIs for each individual ranges from $20,900 to $151,700.[18,19] Moreover, in 2008, the Medicare and Medicaid program changed their reimbursement policy for several conditions. One change was that any patient who acquired a stage 3 or stage 4 PI during hospitalization would not be reimbursed for the cost of care for those two stages.[20] PI is a multifactorial process, and immobility is one of the most important factors that contribute to PI.[21]

Critically ill patients in the ICU may be confined to a bed for extended periods of time because of their condition.[22,21] Movement and positioning in bed produce pressure, friction, and shear. Those three factors exert high pressure that may damage the skin, displace tissues, and impede tissue blood flow, which may lead to tissue injury.[23,24] Mobilization of patients out of bed may relieve or reduce these risk factors.

An early mobilization (EM) intervention was introduced in the ICUs of the US to prevent muscle atrophy and respiratory dependence on mechanical ventilation (MV). EM has been reported to reduce muscle weakness,[25-33] shorten ICU and hospital length of stay,[30,31,34,35] reduce the number of days spent on a ventilator,[30] and reduce the number of days spent in delirium.[30,31] Moreover, it was estimated that the EM of ventilated patients within 72 hours of admission and 48 hours of mechanical ventilation was associated with a cost savings of more than $500,000 compared with the standard of care.[36] EM decreased immobility and ICU complications and reduced ICU lengths of stay, which indirectly reduced the cost of care.[35] The goal of EM is to mobilize critically ill patients and gradually get them out of bed within 7 days from ICU admission.[30-33,37-40]

Given the high cost and risk of PIs and the beneficial effects of EM, it would be valuable to assess whether this intervention could also help us to reduce the occurrence of PIs. The aim of this study was to assess the association between EM, risk factors, and PI development. Also, this study explored whether EM changes the characteristics of PIs, such their locations and stages.

Methods

Design

This study utilized a retrospective chart review design to explore the relationship between EM and the occurrence of PIs in the ICU. Patient data were collected from patients' electronic medical records (EMRs) at an academic medical center in the Pacific Northwest. All patients admitted to the medical-surgical ICU (MS-ICU) and cardiothoracic ICU (CT-ICU) from 2011 to 2016 were included in the study. The outcome of interest was PI events, and the exposure of interest was the EM intervention.

The study utilized two different designs. The first component used a cohort design to compare PI rates in MS-ICU and CT-ICU during three different periods between 2011 and 2016. The first period was between 2011 and 2012, prior to implementing EM. The second period was

between 2013 and 2015 when the EM intervention was adopted and administered consistently. The third period was in 2016 when the rate of delivering EM was reduced due to hospital expansion (HE). The ICUs' staffing level was affected during expansion and EM was not consistently performed, with a resultant temporary decrease in EM performance rate. Therefore, the experimental conditions occurred naturally, which provided an opportunity to compare PI rates pre- and post-EM implementation, as well as during HE.

The second component used a case-control design, which addressed the association between EM and the development of PIs in greater detail. EM-related variables (i.e., the dose, duration, intensity, and number hours elapsed between ICU admission and receiving EM) were assessed using a case group (PI) and a control group (No PI). PI-related variables (i.e., body-sites and severity of the PI) were also assessed among patients in the case group who received or did not receive the EM intervention. The case-control component focused on patients who were admitted between 2013 and 2015, which was when the EM intervention was introduced to the MS-ICU and CT-ICU.

Early mobilization intervention

Patients were eligible to receive the EM intervention after they were physiologically stabilized. In this study, ventilated and non-ventilated patients who received the EM protocol within 3-7 days of their ICU admission were included. The EM protocol focuses on motivating ventilated patients to ambulate at least two times per day and non-ventilated patients to ambulate three times per day, with a goal of standing for at least 10 minutes by the time the patient is discharged from ICU. The goal of EM is to enable patients to perform activities of daily living and ambulate for at least 100 feet prior to ICU discharge or as ordered by the provider.

The EM intervention has five levels. For the first level, the patient receives passive range of motion (PROM), active range of motion (AROM), and on-the-bed activities. For the second level, the patient dangles his or her legs over the side of the bed, with or without support. The third level involves helping the patient move from the bed and into a chair. The fourth level is

standing, with or without support. The fifth level is walking, with the patient being helped to walk slowly, with or without support. However, in this study PROM, AROM, and on-the-bed activities were not included because the aim was to test the association between mobilizing the patient out of bed and the rate of PI occurrence.

Sample

The cohort section included all patients who developed a PI from 24 hours after ICU admission through ICU discharge in the MS-ICU or CT-ICU from 2011 to 2016. The case-control section included all patients who developed a PI during their ICU stay between 2013 and 2015 (i.e., the case group). The EM review focused on the first 15 days after ICU admission for patients who developed a PI. As mentioned, EM is typically delivered within three to seven days of ICU admission, and the main aim of this study was to test the association between receiving EM and the development of PIs. It is known that most PI events occur during the first two weeks after admission to the ICU. The investigator, therefore, decided to follow patients for only two weeks, as this would ensure that any increase or decrease in the occurrence of PIs would be associated with the implementation of EM in the ICU setting. Therefore, the investigator controlled for one of the major risk factors for developing PIs, which is an extended ICU stay.

From 2011 to 2015, the MS-ICU and CT-ICU each functioned as a single unit. Then, in 2016, the MS-ICU was split into a surgical ICU (S-ICU) and a medical oncology ICU (Med/Onc ICU), while the CT-ICU was split into a medical cardiac care unit (M-CCU) and a surgical cardiothoracic ICU (SCT-ICU). The investigator, therefore, decided to count PI events that occurred in the S-ICU or Med/Onc ICU and considered them a single unit, namely, the MS-ICU. Similarly, all PI events occurring in the M-CCU and SCT-ICU were considered as being from one unit, namely, the CT-ICU to allow for consistency across study periods.

The control group included patients who were admitted to the same ICU setting within the same year. These patients did not have any PI events during the first 15 days after their ICU

admission. For each case, there were three controls matched on the following variables: unit of admission, age,[5,13,21,41,42] gender,[6,10,13,22] major comorbidities (i.e., diabetes mellitus,[1,3-5,8,9,43,44] cardiac disease,[1,4,5,43] and cardiopulmonary disease[3]), mechanical ventilation usage,[1,4] undergoing surgery,[1] and vasopressor usage.[1,3-5,21,45] These variables are all well-known risk factors associated with the development of PIs. The focus of this study was on determining whether EM was associated with an increase or decrease in PI events after controlling for the most important risk factors.

The inclusion criteria were as follows: patients aged 18 years or older who did not have a PI upon admission and stayed in the ICU for longer than one week. The exclusion criteria included patients who had a brain injury, spinal cord injury, or a history of immobility, such as missing limbs. Moreover, this study excluded any PI event that had occurred before ICU admission or during the first 24 hours of the ICU stay, any medical device-related PI, and PI events that were not clearly documented regarding the site or cause.

Study variables

The main interest was to test EM as the main variable of the study relative to other variables (i.e., well-known risk factors). All the variables and their definitions are listed in Table 1.

Data analysis

The data were analyzed using T-test and Chi-Square to compare the characteristics of patients with a PI event (i.e., the case group) and without a PI event (i.e., the control group). A logistic regression analysis with sequential entries was used to assess the association between EM and other ICU variables in the development of PIs. IBM-SPSS version 25 software was used to perform the statistical analysis.

Case-control

Data were collected from the EMRs of a total of 1,756 patients who were admitted to the ICU from 2013 to 2015. Data were collected for 861 patients who had a PI event and 895 patients who did not. Of the 1,756 patients, 1,107 met the inclusion and exclusion criteria. After matching the cases and their controls using propensity score matching in SPPS, there were 181 patients who had experienced a PI event during their hospitalization (i.e., the case group) and 572 patients who had not (i.e., the control group). The case and control patients were matched on all variables mentioned previously, except for their use of mechanical ventilation (MV). When we included this variable, we lost almost all the PI patients and were left with only 50 patients with PI events. Therefore, it was decided to exclude the mechanical ventilation variable from the matching process, and this variable was included later in the logistic regression analysis.

Multiple imputation (MI) was used for any missing data. A large number of values were missing for laboratory blood work. The missing percentages of blood work values were lactate (93%), pre-albumin (92%), creatinine (88%), albumin (31%), and hemoglobin (8%). Hence, lactate, pre-albumin, and creatinine were not included in the multiple imputation process. Albumin was included through a logistic regression without imputation, and it was not significant in the model after controlling for the other factors. MI was then performed five times using SPSS. Pooled data from MI were used in the logistic regression analysis, and albumin was still not significant in the model after controlling for other factors. Therefore, albumin was dropped from the analysis in the final model, and the MI data were not needed in the final analysis.

Univariate and multivariate logistic regression was used to assess the relationships between the ICU variables and the EM variable. All ICU variables were entered into the first block, and EM variables were entered into the second block. Two multivariate logistic regression analyses were performed. The first model entered EM within 72 hours in the second block, without controlling for outliers. The second model entered EM within 7 days in the second block, without control for outliers. Ninety-two patients were considered outliers because their z-scores

were higher than 3.29 on the standard deviation. The outliers in the analysis was considered because, in most ICUs, there are patients with extreme physiologic variability (i.e., outliers) who can disturb the association between the ICU variables and the EM variables in terms of PI development. Outliers included patients who were either less sick or far sicker than the rest of the sample. For example, some patients had more mobilization events than others because they were not as sick as the rest of the sample, conversely some patients experienced more episodes of hypotension than the average patient in the sample.

Finally, the study variables were checked for multicollinearity. Hemoglobin levels at ICU admission and 48 hours prior to PI development were collinear. Therefore, we decided to use the hemoglobin reading at 48 hours prior to PI development because it was closer to the PI event.

Results

Cohort results. There were 1,692 patients who had PI events (a total of 2,977 PI events) during their ICU hospitalization. Of these, 115 patients were excluded due to being paralyzed or having a brain injury. Another 552 PI events were excluded because the site and cause were unknown, the PI event was present upon admission, or the PI event was related to the use of a medical device. An additional 1,085 PI events that occurred within 24 hours of ICU admission were excluded, which resulted in including a total of 1,224 PI events for 766 patients in the analysis. The sample included 490 males (64%) and 276 females (36%). The mean age of the patients was 60 ± 15 years. The MS-ICU contributed 393 patients (51%) and the CT-ICU 373 patients (49%).

During the three periods, 372 PI events occurred before the introduction of EM (2011–2012), 644 events occurred during EM implementation (2013–2015), and 208 events occurred during the hospital expansion period (2016). Because the census data before 2015 could not be obtained to calculate the rate of PI events for each unit/year; we decided to compare PI events

for 2012, 2014, and 2016 with each other. The comparison of the number of PI events for each year showed no significant differences among these three years (Table 2).

Case-control results. There were 181 patients in the case group and 571 patients in the control group, for a total of 753 patients. The average age of the patients was 58 ± 15 years. There were 279 female patients (37%) and 474 male patients (63%). Of the patients, 341 (45%) were admitted to the MS-ICU, and 412 (55%) were admitted to the CT-ICU (Table 3). The 181 cases had 213 PI events during the first 15 days of ICU admission. Most PIs occurred within the first week after ICU admission (69%), and of these events, 19% appeared within the first three days after ICU admission. The most common PI sites were the coccyx/sacrum (38%), buttock (17%), thigh (7%), heel (7%), occipital area (5%), and the back (4 %). Of the cases, stage II was the most common level of injury (54%), and there were no deep tissue injuries (Table 4).

Comparing all study variables in the case and control groups (Table 5) revealed that there were significant differences between the case and control groups on total Braden scale scores and all sub-scale scores. The case group had a significantly higher risk of PI development (lower total Braden score) than the control group. The case group had a higher APACHE II score and a lower hemoglobin than the control group. The case group also had a higher use of dialysis (21.5%) in the first 15 ICU days, compared to 13.5% of the control. Similarly, more patients in the case group received MV (88%), compared to 75% in the control group. There were no significant differences between cases and controls in vital signs, BMI, cardiac arrest history, or cardiopulmonary assistive device usage

When the EM variables were analyzed, significant differences were found between the cases and controls who received EM within 72 hours and within 7 days, as well as the level of EM and the total number of EM sessions. The case group had fewer patients who received EM within 72 hours and within 7 days compared to the control group. Similarly, the cases had fewer EM sessions and lower levels of EM compared to the controls (Table 6). Finally, a comparison

of the PI stages and sites in PI patients (the case group) who received or did not receive EM showed that the only significant difference was in PI stage 2 (Table7).

Logistic regression analyses. All variables were entered in a univariate logistic regression to assess the association between each variable with PI development. The following risk factors were the significant predictors of PI development: total Braden score, sensory score, activity score, moisture score, friction score, hemoglobin level, APACHE II score, received hemodialysis, MV usage, received EM within 7 days, received EM within 72 hours, dangling, sitting, standing, ambulating, and EM sessions count. However, vital signs, cardiac arrest history, cardiopulmonary device, and BMI were not significant in the univariate logistic regression (Table 8).

Multiple logistic regression with a sequential predictor entry was used to predict PI development using a sample of N = 753 with no control for outliers. The *first model* used EM within 72 hours in the second block. The first block, which contained all the ICU variables, was found to have a significantly better fit than the null model with no predictors ($X^2[16] = 120.213$, $p < 0.001$). The approximate variance in the development of PI status accounted for 0.24 using the Nagelkerke formula, and the hit rate of this model (80%) was slightly better than the null model's hit rate (78%). When EM within 72 hours was entered into the second block, the model had a better fit than the model with all the ICU variables ($X^2[17] = 124.524$, $p < 0.001$). The full model's Nagelkerke pseudo-R2 was 0.26, and the overall hit rate was 80.4%. The intercept was significantly different from zero, which means that the log-odds of PI development across the sample while holding all predictors constant was B = -1.271 (S.E. = 0.338), Wald (1) = 14.119, $p < 0.001$. There were four significant variables in this logistic analysis model: total Braden Score, Braden-moisture, Braden-friction, and receiving EM within 72 hours. However, there were no significant associations between PI occurrence and Braden sensory, Braden activity, vital signs, APACHE II score, BMI, cardiac arrest, cardiopulmonary device usage, hemodialysis, MV usage, and hemoglobin reading at 48 hours prior to PI occurrence.

The *second model* used EM within 7 days in the second block without controlling for outliers. The first block, which included all of the ICU variables except EM, was found to have a significantly better fit than the null model with no predictors ($X^2[16] = 120.213$, $p < 0.001$). The approximate variance accounted for in PI development status was 0.25 using the Nagelkerke formula, and the hit rate of this model (80.4 %) was better than the null model's hit rate (78%). Then, when EM within 7 days was entered into the second block, the model became a better fit than the model with all the ICU variables alone ($X^2[17] = 135.909$, $p < 0.001$). The full model's Nagelkerke pseudo-R2 was 0.28, and the overall hit rate was 81.6%. The intercept was significantly different from zero, which means the log-odds of PI development across the sample while holding all predictors constant was B = -0.798 (S.E. = 0.362), Wald (1) = 4.874, p = 0.027. The significant variables in this second model were total Braden score, Braden moisture, Braden friction, BMI, and receiving EM within 7 days (Table 9). Finally, there were no significant associations between PI occurrence and Braden sensory, Braden activity, vital signs, APACHE II score, cardiac arrest, cardiopulmonary device usage, hemodialysis, MV usage, and hemoglobin readings at 48 hours prior to PI occurrence.

Discussion

The cohort section of the study compared PI occurrence before implementation of EM, during EM, and during hospital expansion when there was less EM delivery, without controlling for any risk factors. There was no significant difference between the three periods. Floyd's study also found no significant differences using a matched pair design in CT-ICU to compare a non-EM group (n=30) and EM group (n=30), including several outcomes such as PI development, ICU and hospital length of stay.[46] In contrast, three studies showed significant differences in PI occurrence between a non-EM group and an EM group. Azuh and colleagues' prospective case series study was a quality improvement project that focused on MICU patients.[47] The PI incidence in 2011 (before EM) was 9.2%, and the incidence in 2013 (during EM) was 6.2%, a significant reduction. A study by Klein and colleagues was a prospective comparative design

involving neurological ICU patients,[48] in which the EM group showed a significantly lower number of PIs compared to the non-EM group,. Similarly, in a retrospective longitudinal study by Fraser and colleagues that randomly assigned critically ill patients in MICU, SICU, CICU to either EM intervention (n=66) or to routine care (n=66),[49] the EM group showed a significantly lower PI rate than the routine care group ($P < 0.001$).

However, these four studies had PI events as one of many outcomes.[46-49] There was no detailed information on what kind of PIs were included. For example, we do not know whether these studies included device-related PI or how they dealt with PIs that were not related to the ICU stay, such as PIs upon ICU admission or appearing less than 24 hours after ICU admission. Moreover, these four studies included PROM and AROM within the EM intervention for bedridden patients, while this study excluded PROM and AROM. Klein and colleagues included paralyzed and brain injury patients, while the other studies and this study excluded such patients. However, our study controlled for these factors given that our main interest was to assess the association of mobilizing patients out of bed and PI occurrence.

The literature shows that most PIs appear in the first week of ICU hospitalization.[3-5,8,10,22] The case-control part of this study showed that 69% of PIs appeared in the first week of ICU hospitalization, which is similar to the incidence reported in the literature. Sixty percent of the cases did not receive EM within 72 hours of the ICU stay, and Chi-Square test showed significant difference in receiving EM within the case and control group. Cases had higher APACHE II score (more sick) than other controls. Being sick and not being able to receive the EM could exacerbate why most cases appeared in the first week of the ICU stay. The PI incidence may have been different if all eligible patients were mobilized within 72 hours.

The most common PI location sites in the literature included the scapula,[13,15] the coccyx/sacrum,[3-5,13,41,42] the buttock,[4,5,41] and the heel. [4,5,42] This study found that the coccyx/sacrum (38%) and buttock (17%) were the most common sites for PI appearance. Of note, the PI group received more sitting sessions than other types of sessions, which might

exacerbate the PI development in those body areas. Therefore, health care providers should consider the type of chairs used, the length of time sitting and use of pressure reducing strategies in the chairs.

This study used the Braden total score, and the scores from the sensory, activity, moisture, and friction subscales. The Braden total score and subscale scores were significant in comparison analysis between the control group and the case control group. The case group had a lower Braden total score and subscale scores than the control group. Univariate logistic regression analysis showed a significant association between PI development and all the Braden subscale scores and the total scores. Multivariate logistic regression showed that the total Braden score, moisture and friction scores were significant while accounting for all other factors. The case group had a significantly higher APACHE II score than the control group. Most of the case group (88%) were mechanically ventilated and were confined to bed until their condition become stabilized.

The four studies discussed above focused on assessing the differences in PI development between an EM group and a non-EM group.[46-49] PI occurrence was one of many outcomes; however, this study looked at the PI as the main outcome. No study tested the association of EM with PI development while controlling for other well-known risk factors (by matching) and accounting for other risk factors using logistic regression analysis. Univariate and multivariate logistic regression showed that the odds of patients being exposed to EM were higher among the controls than the cases. There was significant negative association between PI development and receiving EM within 72 hours or within 7 days. This finding may indicate that exposure to EM among patients is a protective factor for PI development.

This study used two different study designs to assess the association of EM to PI development. In the case-control section, we controlled for well-known risk factors by matching and accounted for other risk factors in logistic regression. This design showed a significant association between EM and PI. However, when we tested the PI rate in three different periods,

while not controlling for any differences in risk factors, there was no significant difference. As a result, the EM intervention was not robust enough to show difference between groups while not controlling and accounting for any risk factors.

Study strengths and limitations

The strength of this study was the natural experiment, which enabled us to compare the PI occurrence rate in three periods (before and during implementing EM, and during hospital expansion). Even though there was no significant difference in PI incidence between the three periods, this informed us that implementing EM was not associated with increasing PI. The cohort and case control design helped us consider EM and PI association in a holistic view. We assessed the association of EM with PI with and without controlling for risk factors. The retrospective chart review provided a sufficient sample size within a short period of time and with no financial burden. To our knowledge, this study is the first to look at PI as a main outcome and explore in-depth the EM association with PI occurrence that used logistic analysis to assess the association.

This study has several limitations. With the retrospective design we depended on the quality of the chart documentation. Some PI events were excluded because the site, severity, and date of occurrence were not reported. Nurses have different experience levels in dealing with PI events and PI documentation, which might lead to bias, for example they may under report PI. There was poor documentation for the duration of the EM session, which led us to drop this from the analysis; 95% of the sample did not have the duration documented. The second limitation was missing data for laboratory blood work, which led us to exclude it from the analysis. The missing data were because not all patients needed to have those laboratory tests. The final limitation was that data were collected only from one hospital, which limits this study's generalizability to other health care settings.

Table 1: Summary of Study Variables

Variables	Definition
History of Early Mobilization (EM)	Patients received EM within 72 hours or within 7 days of ICU admission.
Hours to EM	Total of hours patients waited before receiving EM intervention.
Level of EM	The EM intervention has four levels which include dangling, sitting, standing, and walking
EM Sessions	The total number of sessions patients received before the PI event for the case group or during the first 15 days of their ICU stay for the control group.
Braden Scale	Total score on Braden scale and score of sub-scales on sensory perception, activity, friction/shear, and moisture at ICU admission. A lower score on the scale or a sub-scale represents a higher risk for developing PI.
Blood Pressure (BP)	Total number of Systolic BP counts lower than 90 mm Hg and Diastolic BP < 60 mm Hg prior to the appearance of the PI for cases and during two weeks for the controls.
Body Temperature	Total number of body temperature counts higher than 38^{o}C or lower than 36^{o}C prior to the appearance of the PI for cases and during two weeks for controls.
Severity of Illness	Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission. This is a tool for assessing the severity of the patient's condition on a score of 0 to 71. Higher scores reflect more severe conditions.
Body Mass Index	Patients BMI at ICU admission.
Cardiac Arrest	History of cardiac arrest during operation, prior to ICU admission, or during 15 days of ICU admission.
Cardiopulmonary Assistive Device	History of using cardiopulmonary assistive device prior to PI event for cases or during 15 days for controls.
Hemodialysis	History of patients receiving hemodialysis before PI event for cases, or during the first 15 days of ICU stay for controls.
Laboratory Blood Work	Albumin, creatinine, hemoglobin, lactate, and pre-albumin level at ICU admission and at 48 hours prior to a PI event for cases or at the last reading in the first week for controls.

Table 2: **Comparison of PI Events Before EM, During EM, and During HE**

Groups	**MS-ICU**	**CT-ICU**	**Total**
Before EM, 2012	86 (30%)	67 (24%)	153 (27%)
During EM, 2014	109 (37%)	97 (35%)	206 (36%)
During HE, 2016	95 (33%)	113 (41%)	208 (37%)
Total	290	277	567

This analysis includes PI events that occurred after 24 hours of ICU admission to discharge during 2012, 2014 and 2016.
Number of PI events & percentage (%). Significant value is < .05.
Chi-Square Test [$X^2(2) = 4.320, P = 0.115$].

CT-ICU: *Cardiothoracic ICU;* **EM:** *Early Mobilization Intervention;* **HE:** *During Hospital Expansion;* **ICU:** *Intensive Care Unit;* **MS-ICU:** *Medical Surgical ICU;* **PI:** *Pressure Injury*

Table 3: **Descriptive Statistics for Matched Variables and Comparison of Patients with Acquired Pressure Injuries and Patients without Pressure Injurie**

Variables	**All Patients (n = 753)**	**Control (n = 572)**	**Case (n = 181)**	**P**
Age [a]	58 (15)	58 (15)	58 (15)	.88
Gender [b]				
Female	279 (37%)	213 (37%)	66 (36.5%)	.85
Male	474 (63%)	359 (63%)	115 (63.5%)	
Unit of Admission [b]				
MS-ICU	341 (45%)	260 (45.5%)	81 (45%)	.87
CT-ICU	412 (55%)	312 (54.5%)	100 (55%)	
Comorbidities				
Diabetes Mellitus [b]				
No	537 (71%)	416 (73%)	121 (67%)	.13
Yes	216 (29%)	156 (27%)	60 (33%)	
Cardiac History [b]				
No	284 (38%)	212 (37%)	72 (40%)	.51
Yes	469 (62%)	360 (63%)	109 (60%)	
Cardiopulmonary Disease [b]				
No	493 (65.5%)	377 (70%)	116 (64%)	.65
Yes	260 (34.5%)	195 (34%)	65 (36%)	
Vasopressors Use [b]				
No	240 (32%)	185 (32%)	55 (30%)	62
Yes	513 (68%)	387 (68%)	126 (70%)	
Surgical History [b]				
No	539 (72%)	401 (70%)	138 (76%)	.11
Yes	214 (28%)	171 (30%)	43 (24%)	

a. *Mean (Standard Deviation)*
b. *Frequency (Percentage)*

T-test and Chi-Square test. Significant value is < .05

MS-ICU: *Medical Surgical Intensive Care Unit;* **CT-ICU:** *Cardiothoracic Intensive Care Unit*

Table 4: Pressure Injury Information Analysis

Characteristics	**N and or %**
Total number of patients with PI	181
Number of PIs during first 15 days	213
Pressure Injury Stage	
Stage 1	77 (36%)
Stage 2	115 (54%)
Stage 3	18 (8%)
Stage 4	3 (1%)
Deep tissue injury	0 (0)
Pressure Injury Location	
Occipital area	11 (5%)
Back	9 (4 %)
Coccyx/Sacrum	79 (38 %)
Buttock	37 (17 %)
Thigh	15 (7 %)
Heel	15 (7 %)
Other	47 (21%)
Time until Pressure Injury Detection	**N and % of Patients with PI**
During first three days of ICU admission	35 (19%)
During first week of ICU admission	124 (69 %)
During second week of ICU admission	57 (31%)

Pressure injuries occurring in first 24 hours were not counted as an ICU acquired pressure injury.
Number, frequency and percentage is represented in this table.
ICU: Intensive Care Unit; **PI:** Pressure injury

Table 5: Descriptive Statistics of Study Variables and Comparison of Patients in Case and Control Groups

Variables	Control (n = 572)	Case (n = 181)	P
Braden Scale Variables [a]			
*Total Score**	12 (3)	10 (2)	< .001
*Sensory**	2 (1)	2 (1)	< .001
*Activity**	1 (.37)	1 (.20)	< .001
*Moisture**	3 (1)	2 (1)	< .001
*Friction**	2 (1)	1 (.31)	< .001
Vital Signs [a]			
Count of SBP ≤ 90 mm Hg	20 (24)	23 (30)	.31
Count of DBP ≤ 60 mm Hg	67 (54)	71 (58)	.37
Count of Temperature ≥ 38°C	2 (6)	3 (8)	.47
Count of Temperature ≤ 36°C	2 (4)	2 (6)	.63
Other ICU variables [a]			
APACHEII	16 (6)	17 (6)	.001
BMI	29 (8)	28 (8)	.08
Cardiac Arrest [b]			
No	513 (90%)	166 (91%)	.43
Yes	59 (10%)	15 (8%)	
Cardiopulmonary Assistive Device [b]			
No	513 (90%)	163 (90%)	.89
Yes	59 (10%)	18 (10%)	
Hemodialysis [b]			
No	495 (87%)	142 (79%)	.009
Yes	77 (14%)	39 (23%)	
Hemoglobin [a]	10 (2)	9 (2)	.016
Mechanical Ventilation [b]			
No	143 (25%)	22 (12%)	< .001
Yes	429 (75%).	159 (88%)	

a. *Mean (Standard Deviation)*
b. *Number (Percentage)*
** Lower score indicates higher risk*

This table presents T-test and Chi-square. Significant value is < .05.

APACHEII: *Acute Physiology and Chronic Health Evaluation II;* **BMI:** *Body mass index;* **DBP:** *Diastolic Blood Pressure;* **SBP:** *Systolic Blood Pressure.*

Table 6: **Comparison of Case and Control in Relation to Receiving EM**

EM Variables	**Control (n = 572)**	**Case (n = 181)**	**P**
EM received within 72 hours [a]			
No	189 (33%)	108 (60%)	< .001
Yes	383 (67%)	73 (40%)	
EM received within 7 days [a]			
No	74 (13%)	71 (39%)	< .001
Yes	498 (87%)	110 (61%)	
Levels of EM [b]			
Dangling	2 (4)	1 (2)	< .001
Sitting	13 (13)	6 (9)	< .001
Standing	1 (2)	1 (1)	< .001
Walking	4 (6)	1 (2)	< .001
Total hours before receiving EM [b]	39 (45)	33 (46)	.17
Total count of EM sessions [b]	21 (18)	9 (12)	< .001

a. Number (Percentage)
b. Mean (Standard Deviation)
This table present T-test, Chi-Square. Significant value is < .05 .

EM: *Early Mobilization*

Table 7: Early Mobilization and Comparison of Pressure Injury Stage and Site among Pressure Injury Patients

Pressure injury characteristics	Mobilized within 72 hours			Mobilized within 7 days		
	No (n = 108)	Yes (n = 73)	P	No (n = 71)	Yes (n = 110)	P
Stages						
Stage 1	43 (56%)	34 (44%)	.37	27 (35%)	50 (65%)	.32
Stage 2	75 (65%)	40 (35%)	.045	52 (45%)	63 (55%)	.029
Stage 3	11 (61%)	7 (39%)	.90	10 (56%)	8 (44%)	.14
Stage 4	1 (33%)	2 (67%)	.35	0 (0)	3 (100%)	.16
Sites						
Back	4 (44%)	5 (56%)	.340	3 (33%)	6 (67%)	.71
Coccyx/Sacrum	44 (56%)	35 (44%)	.338	31(39%)	48 (61%)	.99
Buttock	22 (60%)	15 (40%)	.977	14 (38%)	23 (62%)	.85
Thigh	11 (73%)	4 (28%)	.260	7 (47%)	8 (53%)	.54
Heel	10 (67%)	5 (33%)	.564	5 (33%)	10 (67%)	.63

This analysis includes only the pressure injury patients (n = 181), and there were 213 pressure injury events.
Number (Percentage). Chi-Square test. Significant value is < .05 .

Table 9: ***Significant Variables in Univariate and Multivariate Logistic Regression Analysis***

Study Variables	B	S.E.	Wald	df	Sig.	OR	95% C.I. of OR Lower	95% C.I. of OR Upper
Univariate Analysis								
Total Braden Score	-1.163	.125	86.275	1	<.001	.312	.244	.399
Braden Sensory	-.809	.106	57.915	1	<.001	.445	.361	.548
Braden Activity	-.460	.154	8.881	1	.003	.632	.467	.854
Braden Moisture	-.801	.092	76.601	1	<.001	.449	.375	.537
Braden Friction	-1.002	.136	54.564	1	<.001	.367	.281	.479
Hemoglobin	-.230	.096	5.751	1	.016	.794	.658	.959
APACHE II	.269	.085	9.949	1	.002	1.309	1.107	1.547
Dialysis Usage	.568	.218	6.777	1	.009	1.766	1.151	2.709
MV	.879	.247	12.659	1	<.001	2.409	1.484	3.910
EM within 7 days	-1.469	.197	55.745	1	<.001	.230	.157	.339
EM within 72 hours	-1.098	.176	39.064	1	<.001	.334	.236	.471
Dangling	-.504	.154	10.745	1	<.001	.604	.447	.817
Sitting	-.866	.132	42.842	1	<.001	.421	.324	.545
Standing	-.585	.169	11.980	1	<.001	.557	.400	.776
Ambulating	-1.613	.241	44.633	1	<.001	.199	.124	.320
EM Count Sessions	-1.050	.137	58.719	1	<.001	.350	.268	.458
Multivariate logistic Regression (Model.1) – EM Within 72 Hours								
Total Braden Score	-.907	.263	11.877	1	.001	.404	.241	.676
Braden-Moisture	-.293	.127	5.310	1	.021	.746	.581	.957
Braden-Friction	-.406	.172	5.542	1	.019	.666	.475	.934
Receiving EM within 72 hours	-.475	.228	4.329	1	.037	.622	.398	.973
Constant	-1.271	.338	14.119	1	<.001	.281		
N = 753, Nagelkerke R^2 = 0.258, Hosmer and Lemeshow $X^2(8)$ = 8.073, P = 0.426.								
Multivariate logistic Regression (Model.2) – EM Within 7 Days								
Total Braden Score	-.890	.268	11.057	1	.001	.411	.243	.694
Braden Moisture	-.267	.130	4.228	1	.040	.766	.594	.988
Braden Friction	-.405	.173	5.443	1	.020	.667	.475	.937
Body Mass Index	-.206	.105	3.866	1	.049	.814	.663	.999
Receiving EM within 7 days	-.990	.249	15.805	1	<.001	.372	.228	.605
Constant	-.798	.362	4.874	1	.027	.450		
N=753, Nagelkerke R^2 = 0.279, Hosmer and Lemeshow X^2 (8) = 10.950, P = 0.205								

APACHE II: Acute Physiology and Chronic Health Evaluation II; **B:** Logistic regression coefficient; **BMI:** Body mass index; **CI:** Confidence interval; **Df:** Degree of freedom; **EM:** early mobilization; **MV:** Mechanical ventilation; **S.E.:** Standard Error, **OR:** Odds Rati; **ICU:** Intensive Care Unit

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CHAPTER 5

Conclusions and Recommendations

Critically ill patients in ICU settings have a higher rate of PIs than other patients.[1,2] These patients are at increased risk due to more severe physiological instability and immobility. Immobility is one of the major risk factors of PI development. [3,4] Such patients may experience more skin pressure, friction, and shear than patients who are mobile. Mobilizing patients out of bed could be one way of preventing the development of PIs.

This dissertation studied the association between PI development and mobilizing patients out of bed within the first seven days of ICU admission. Three chapters provided a comprehensive exploration of the association between EM and PI development. *Chapter 2* presented detailed background information about EM, as well as a meta-analysis of the effects of EM on critically ill patients. The meta-analysis showed that mobilizing critically ill patients reduces their ICU and hospital LOS. Moreover, the EM group experienced better QoL six months after discharge. There were no significant effects of EM on mechanical ventilator days, the number of ventilator free days, vasopressors, sedation, delirium, or patient physical function. Of note, PI was not an outcome in all the reviewed studies. The paper presented in Chapter 2 includes a recommendation that future studies provide more detailed information regarding the dose and duration of EM for use in other meta-analyses. Larger multicenter studies would also be beneficial to test the effects of EM on critically ill patients.

In addition to a review of the pathophysiology of PI development, *Chapter 3* provided a systematic review of the PI risk factors in critically ill patients in ICU settings. There is limited evidence concerning the association between EM interventions and PI development, so this chapter presented a conceptual framework exploring how EM could mitigate PI development. The framework introduced conceptual links between EM and PI development using Braden and

Bergstrom's conceptual scheme and demonstrates that immobility, shear, and friction are factors that can be mediated directly when ICU patients are mobilized out of bed.

Finally, *Chapter 4* reported a study that examined the relationship between EM and PI development in ICU patients. The study was comprised of a retrospective chart review of PI and EM events. Two sub-study designs, which did not and did control for other PI risk factors, were used to examine this association. The first phase used a cohort design that compared PI events before EM, during EM, and during hospital expansion. This phase found that there was no significant increase in PI events between these three periods. The second phase used a case control design that compared PI patients (cases) to non-PI patients (controls). When comparing the characteristics of the cases to the controls, we found that the cases had a significantly higher risk of PI development, higher APACHE II scores, a higher use of hemodialysis, a higher use of MV, and lower hemoglobin levels compared to the control group. The univariate logistic regression revealed that the following risk factors were significant predictors of PI development: total Braden score, Braden subscale scores (sensory,, activity, moisture, and friction), hemoglobin level, APACHE II score, hemodialysis, MV usage, EM received within 72 hours and EM received within seven days, dangling, sitting, standing, ambulating, and EM sessions count. The multivariate logistic regression included two models. Model one used EM within 72 hours and model two used EM within 7 days as the main risk factors in the second block of the logistic analysis. Model one showed four significant variables: total Braden score, Braden moisture, Braden friction, and receiving EM within 72 hours. Model two revealed five significant risk factors: Braden score, Braden moisture, Braden friction, BMI, and receiving EM within 7 days.

Recommendations

Patients are exposed to different levels of EM depending on their condition. Most patients mobilized in this study experienced sitting on a chair more often than other EM techniques. As seated patients are exposed to the chair's surface, health-care providers should

consider whether the chairs in use are designed to reduce pressure and prevent PI events. In our observational study, we did not evaluate this factor because we were not initially aware that most of the mobilized patients would experience more chair-sitting than other EM levels. Future studies should evaluate the type of chairs used for EM.

Most PIs appeared in the first week of ICU hospitalization, which is similar to the incidence reported in the literature.[5-10] Sixty percent of cases did not receive EM within 72 hours of ICU admission, because of their physiologic instability. Several factors led to PI development within the first week of ICU hospitalization, such as severity of illness and physiologic instability, MV usage, and immobility. Mobilizing patients out of bed within 72 hours might be impractical for those cases; therefore, providing in-bed activity such as cycling may be a way to reduce PI development. Studies are needed that examine the association between in-bed activity and PI events for critically ill patients who cannot be mobilized out of bed in the first week of hospitalization.

Future studies should continue to assess the relationship between PI development and EM intervention in depth. We used a retrospective observational study design to assess the association. In our study, we struggled with poor documentation for EM and PI events. Some PI events were not documented correctly: for example, information about the PI stages and locations was missing, and the same was apparent for the EM documentation. As a result, we could not assess the relationship between EM duration and PI development. A prospective observational study design could help avoid the documentation problem.

There is a gap in the knowledge about the relationship between PI and EM. The systematic review and studies presented as a part of this dissertation expand the body of science and our knowledge of this relationship and the additional benefit of EM.

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