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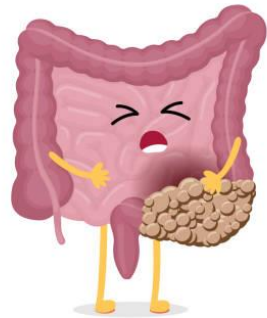
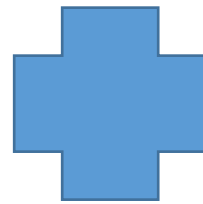
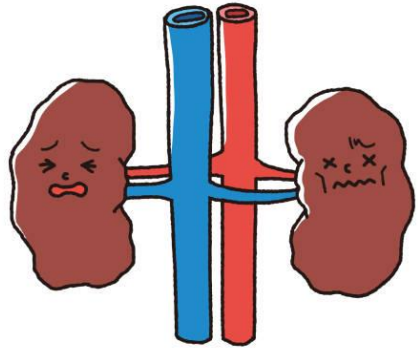
# Update of ICU rehabilitation

서울성모병원 호흡기내과  
이종민



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# The Disease





2013

- PAD GUIDELINE
- PAIN, AGITATION/SEDATION, DELIRIUM

2018

- PAD"IS"
- + IMMOBILITY, SLEEP DISRUPTION





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1. Post Intensive Care Syndrome (PICS)
2. Early mobilization & Rehab in ICU
3. COVID-19



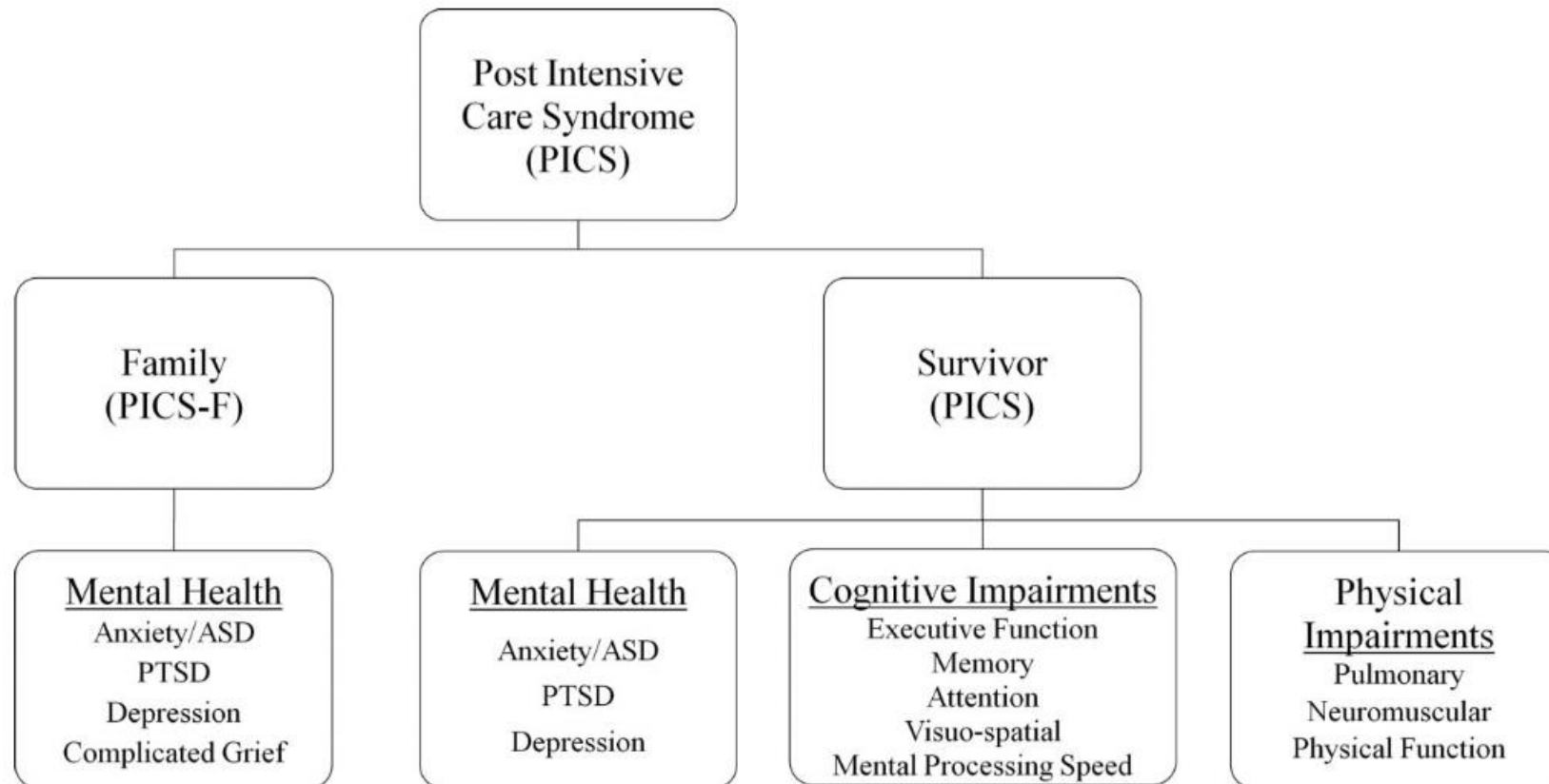
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# Post Intensive Care Syndrome (PICS)





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## **New Physical, Mental, and Cognitive Problems 1 Year after ICU Admission**

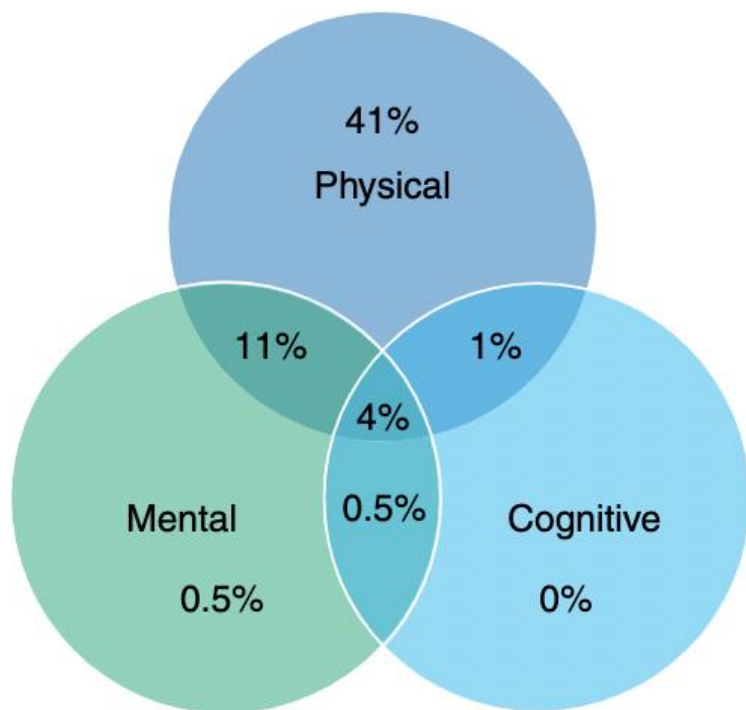
### **A Prospective Multicenter Study**

Wyske W. Geense<sup>1</sup>, Marieke Zegers<sup>1</sup>, Marco A. A. Peters<sup>2</sup>, Esther Ewalds<sup>3</sup>, Koen S. Simons<sup>4</sup>, Hester Vermeulen<sup>5,6</sup>, Johannes G. van der Hoeven<sup>1</sup>, and Mark van den Boogaard<sup>1</sup>

- **Prospective cohort, 4 hospitals (Netherlands), 2016 – 2019, N = 2,345**
- **Medical (28%) Urgent Surgical (12%) Elective Surgical (60%)**
- **Exposure: > 12 hr ICU admission**
- **Outcome: Physical, Frailty, Fatigue, Anxiety, Depression, PTSD, Cognition**

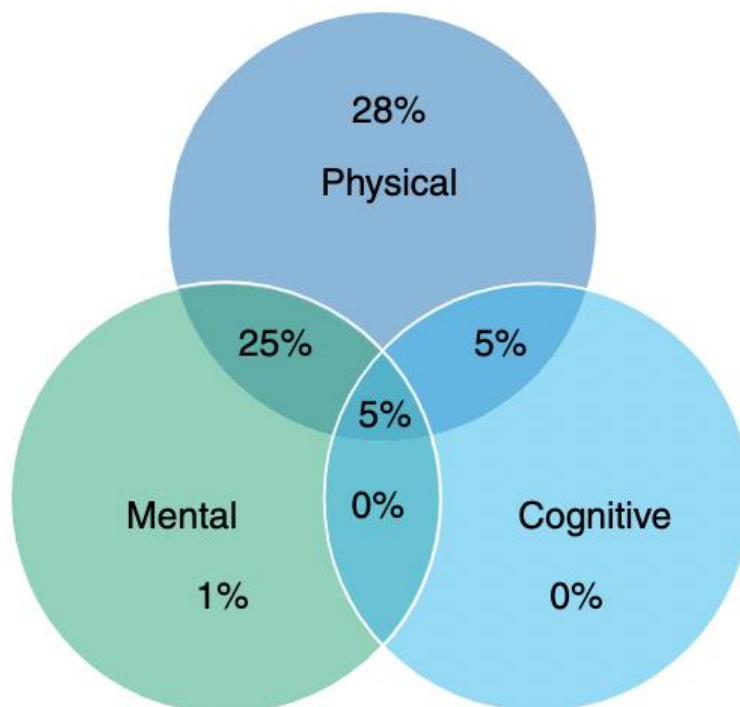


### Medical



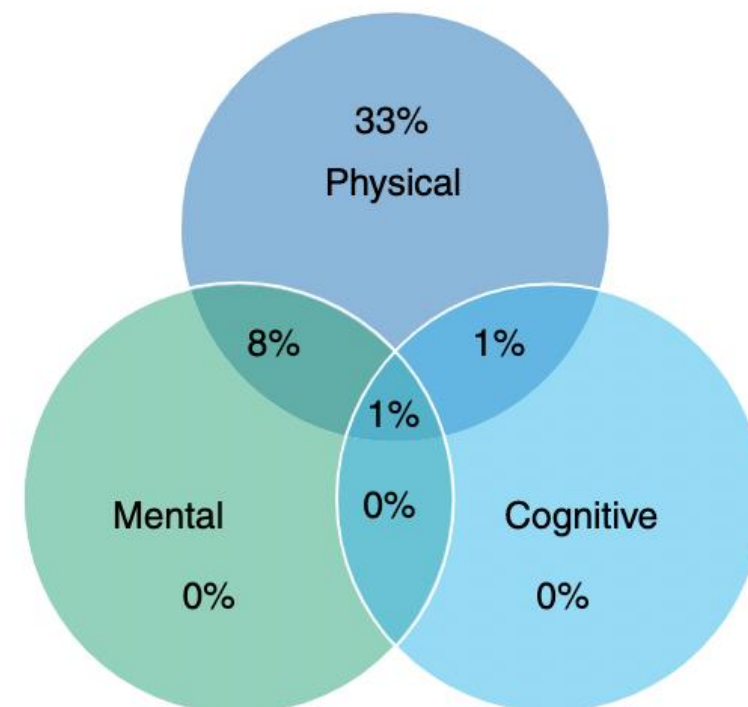
**Medical: 58%**

### Urgent surgical



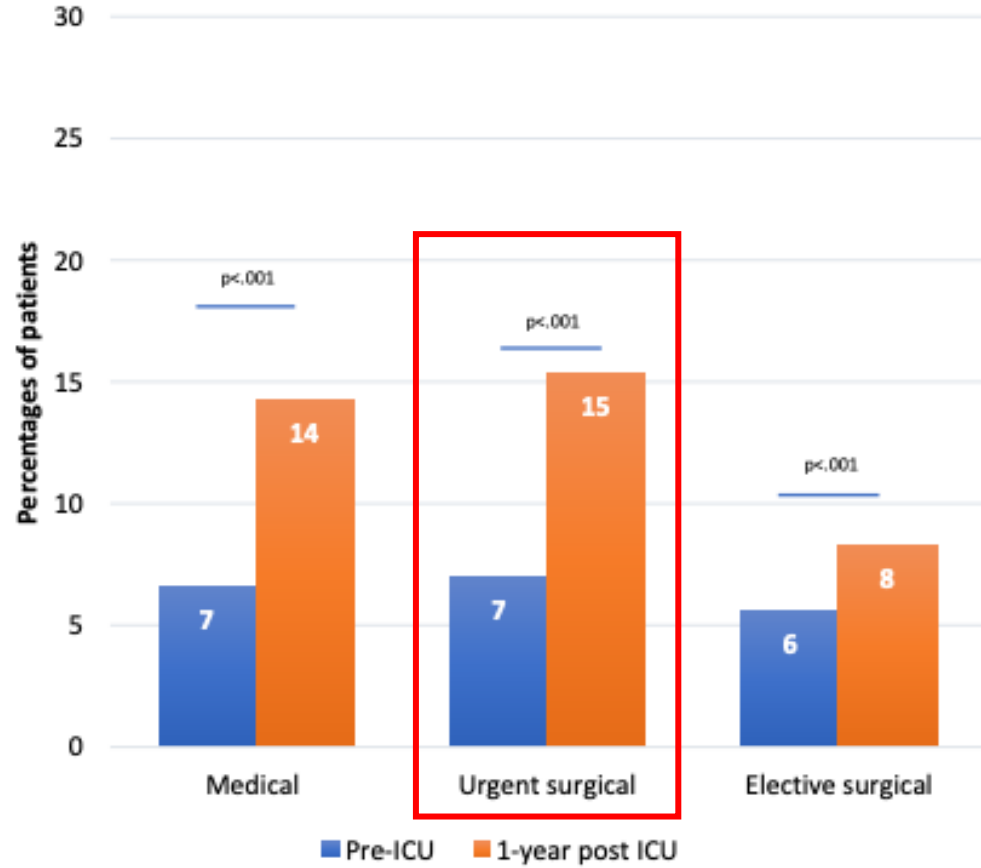
**Urgent Surgical: 64%**

### Elective surgical

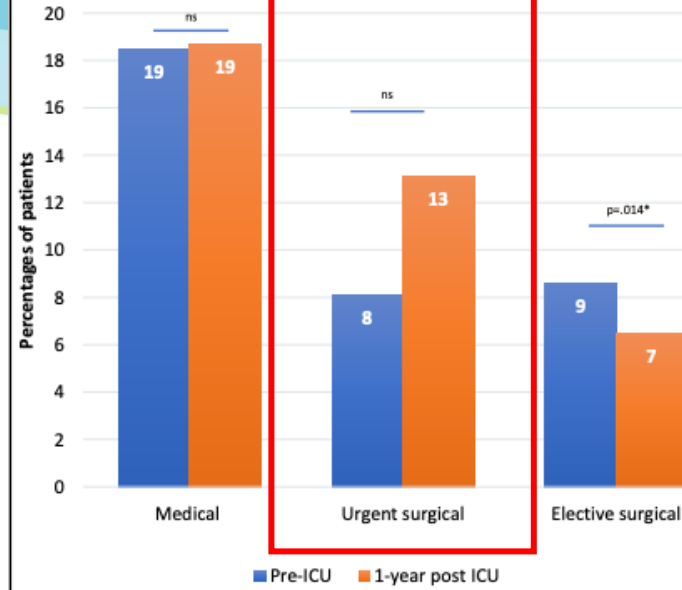


**Elective surgical: 43%**

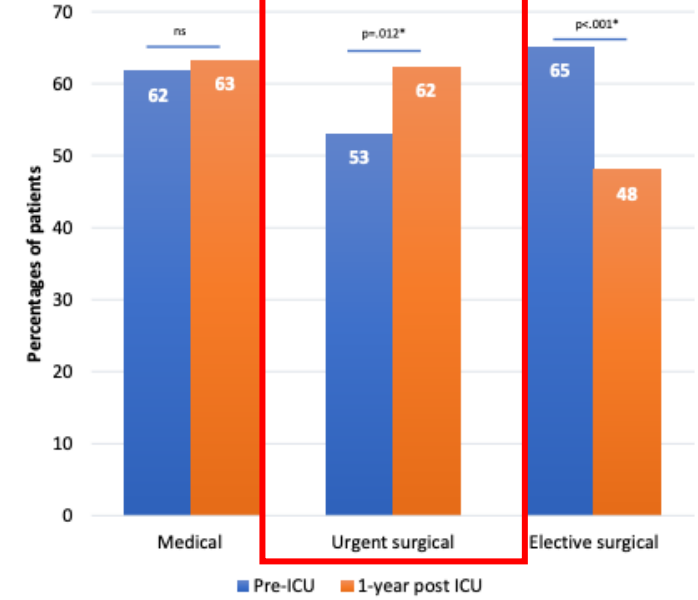
## Cognitive impairment



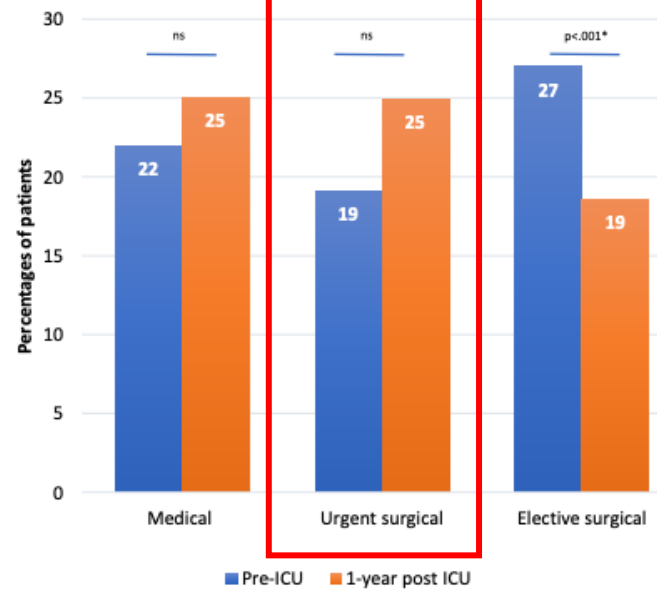
## Frailty



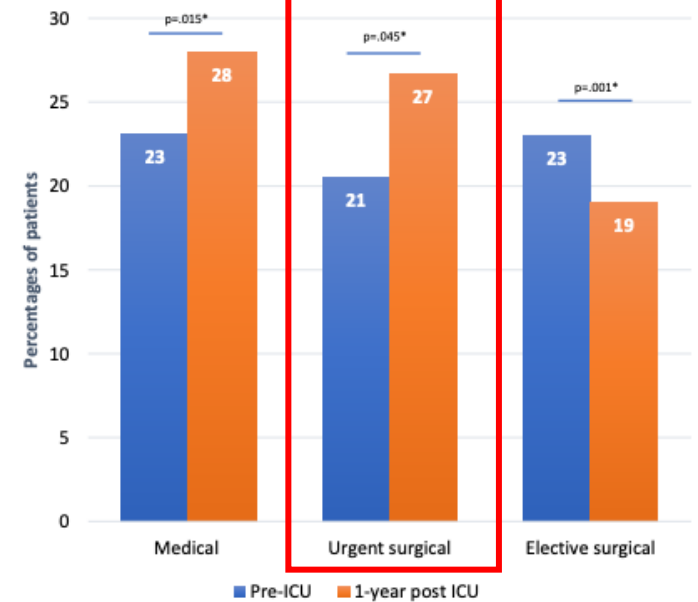
## Fatigue



## Anxiety



## Depression



Review Paper



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## Risk factors for post-intensive care syndrome: A systematic review and meta-analysis

Minju Lee, PhD <sup>a</sup>

Jiyeon Kang, PhD <sup>b,\*</sup>

Yeon Jin Jeong, PhD <sup>c</sup>

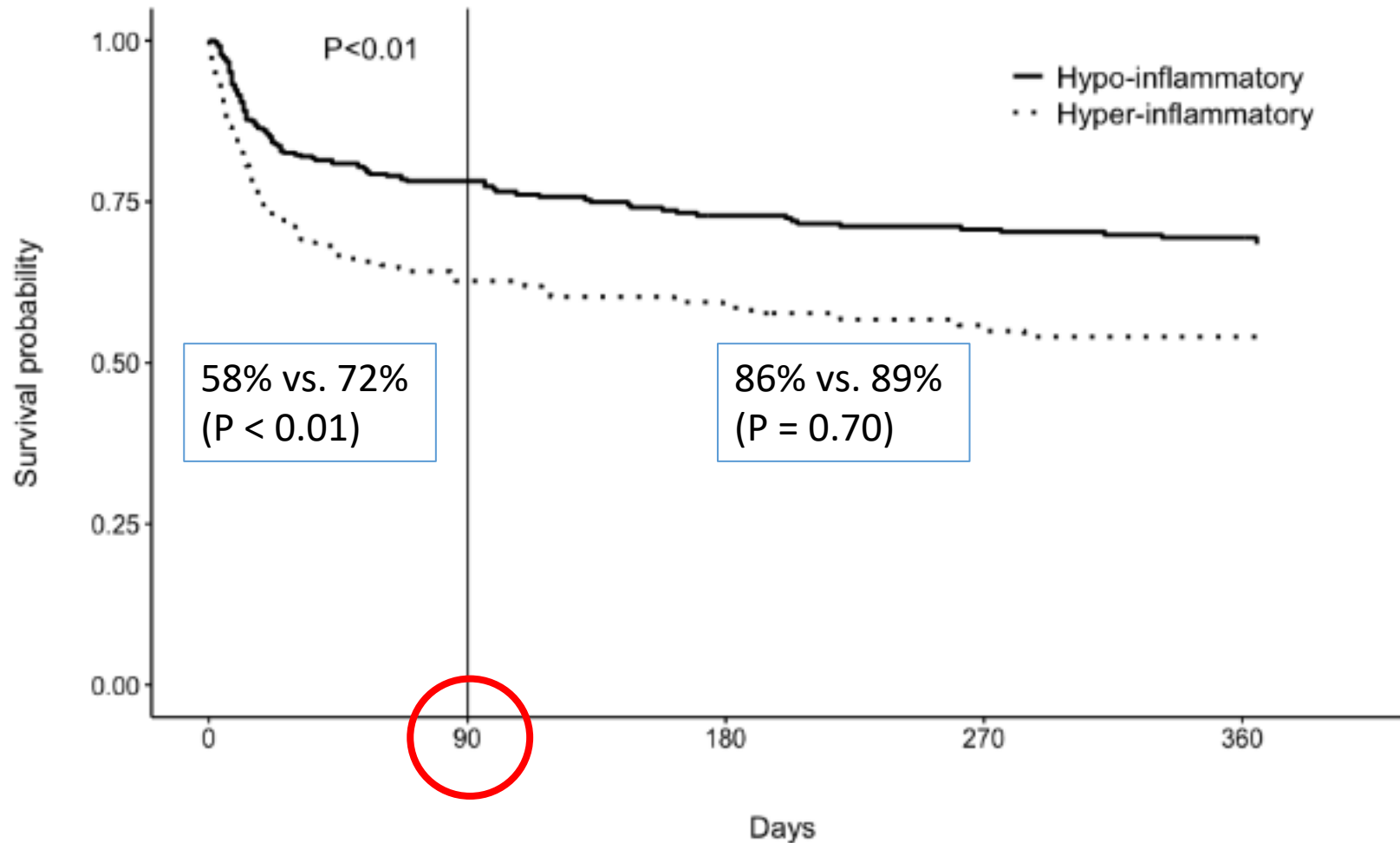
- English articles from 2008 – 2018 (2/3 from last 5 years)
- Results: 119,049 articles screened; 89 eligible studies
  - Quality: 80% “good” (Newcastle-Ottawa scale)
  - Sample size: 61% N = 100 – 300; 30% single ICU
- Risk factor of PICS (**most not modifiable**)
  - Physical: older age, severity of illness
  - Mental health: Female, prior mental health problem, **negative ICU experience**
  - Cognitive: **Delirium**

Original research

# Six-month and 12-month patient outcomes based on inflammatory subphenotypes in sepsis-associated ARDS: secondary analysis of SAILS-ALTOS trial

Mohamed D Hashem <sup>1</sup>, Ramona O Hopkins,<sup>2,3</sup> Elizabeth Colantuoni,<sup>4,5</sup> Victor D Dinglas,<sup>5,6</sup> Pratik Sinha,<sup>7</sup> Lisa Aronson Friedman,<sup>5,6</sup> Peter E Morris,<sup>8</sup> James C Jackson,<sup>9,10</sup> Catherine L Hough,<sup>11</sup> Carolyn S Calfee,<sup>12</sup> Dale M Needham <sup>5,6</sup>

- **Effect of inflammation in mid-long term prognosis**
- **SAILS trial**
  - Rosuvastatin vs Placebo on ARDS (NEJM 2014)
- **Hyper- vs. Hypo-inflammation**



Number at risk

	0	90	180	270	360
Hypo-inflammatory	367	287	176	164	79
Hyper-inflammatory	201	126	68	61	28

Days



Patient-related outcome 6 mon after	Total (N = 232)	Hypo-inflammatory (N = 165)	Hyper-inflammatory (N = 67)	P value
Health-related QoL (SF-36 score)	36 (23 – 48)	36 (23 – 49)	34 (21 – 47)	0.12
Physical functioning (FPI-SF)	1.9 (1.3 – 2.5)	2.0 (1.4 – 2.6)	1.7 (1.2 – 2.4)	0.14
6 min walk distance (%)	66 (48 – 80)	66 (48 – 80)	66 (49 – 79)	0.76
Hand Grip (%)	78 (63 – 105)	84 (65 – 107)	77 (62 – 90)	0.28
Language	32 (23 – 39)	33 (24 – 39)	29 (23 – 38)	0.48

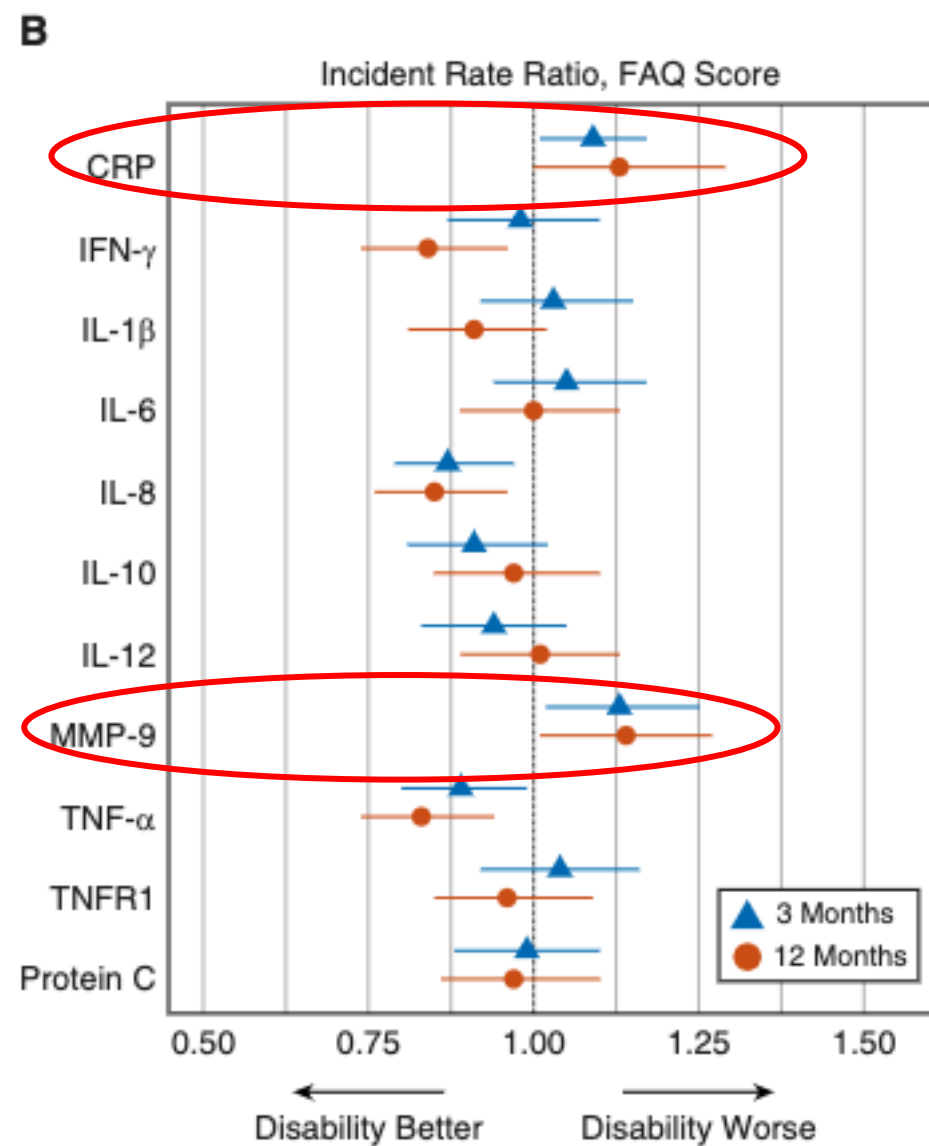
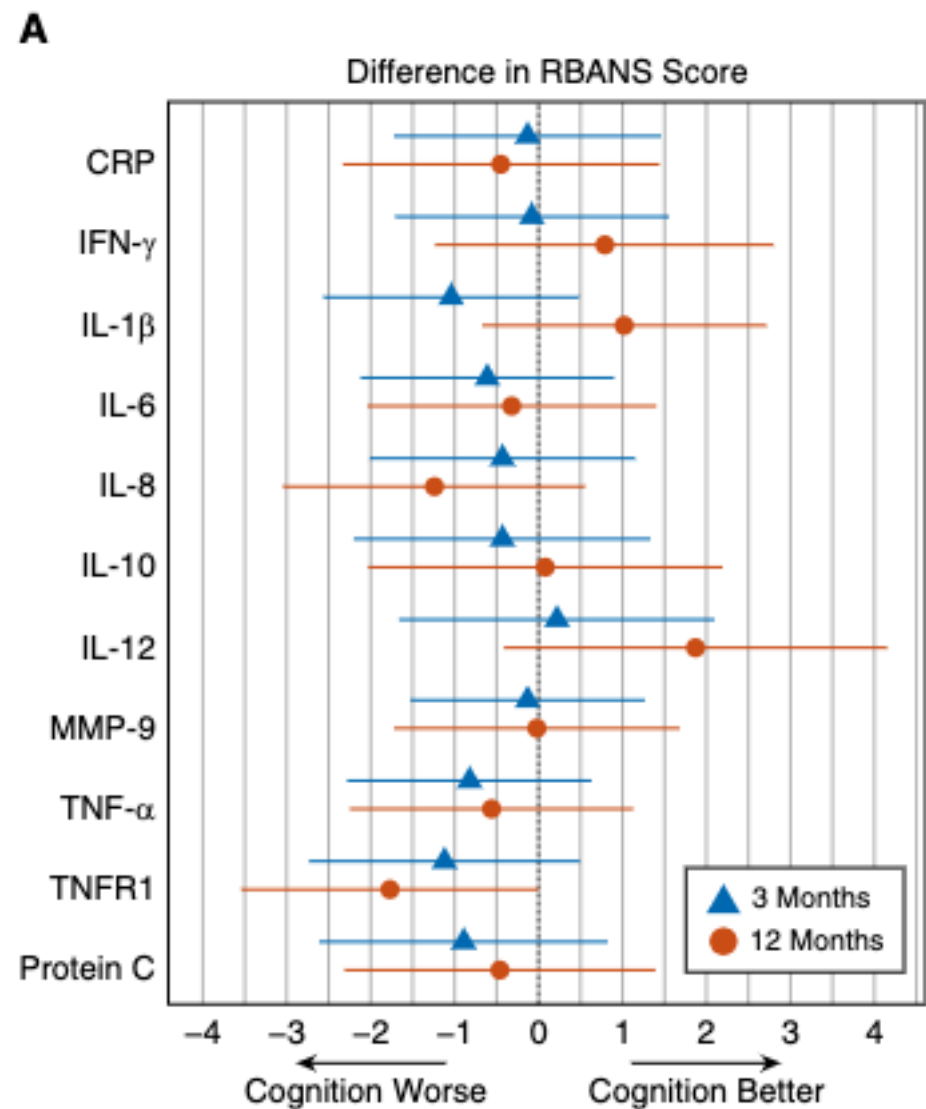
## ORIGINAL ARTICLE



# Inflammation and Coagulation during Critical Illness and Long-Term Cognitive Impairment and Disability

Nathan E. Brummel<sup>1,2,3</sup>, Christopher G. Hughes<sup>3,4</sup>, Jennifer L. Thompson<sup>3</sup>, James C. Jackson<sup>3,5,6,7</sup>, Pratik Pandharipande<sup>3,4</sup>, J. Brennan McNeil<sup>3,5</sup>, Rameela Raman<sup>3,8</sup>, Onur M. Orun<sup>3,8</sup>, Lorraine B. Ware<sup>3,5</sup>, Gordon R. Bernard<sup>3,5</sup>, E. Wesley Ely<sup>3,5,7,9,10</sup>, and Timothy D. Girard<sup>3,11</sup>

- Association of Inflammation & Coagulation Biomarkers & Cognitive impairment
- Day 1, 3, 5
  - CRP, IFN-r, IL-1, IL-6, IL-8, IL-19, IL-12, MMP-9, TNF-a, TNF-receptor 1, Protein C
- 3 & 12 mon cognition, activity, daily living





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# Fatigue Symptoms During the First Year Following ARDS



*Karin J. Neufeld, MD, MPH; Jeannie-Marie S. Leoutsakos, PhD, MHS; Haijuan Yan, PhD; Shihong Lin, MS; Jeffrey S. Zabinski, MD; Victor D. Dinglas, MPH; Megan M. Hosey, PhD; Ann M. Parker, MD; Ramona O. Hopkins, PhD; and Dale M. Needham, MD, PhD*



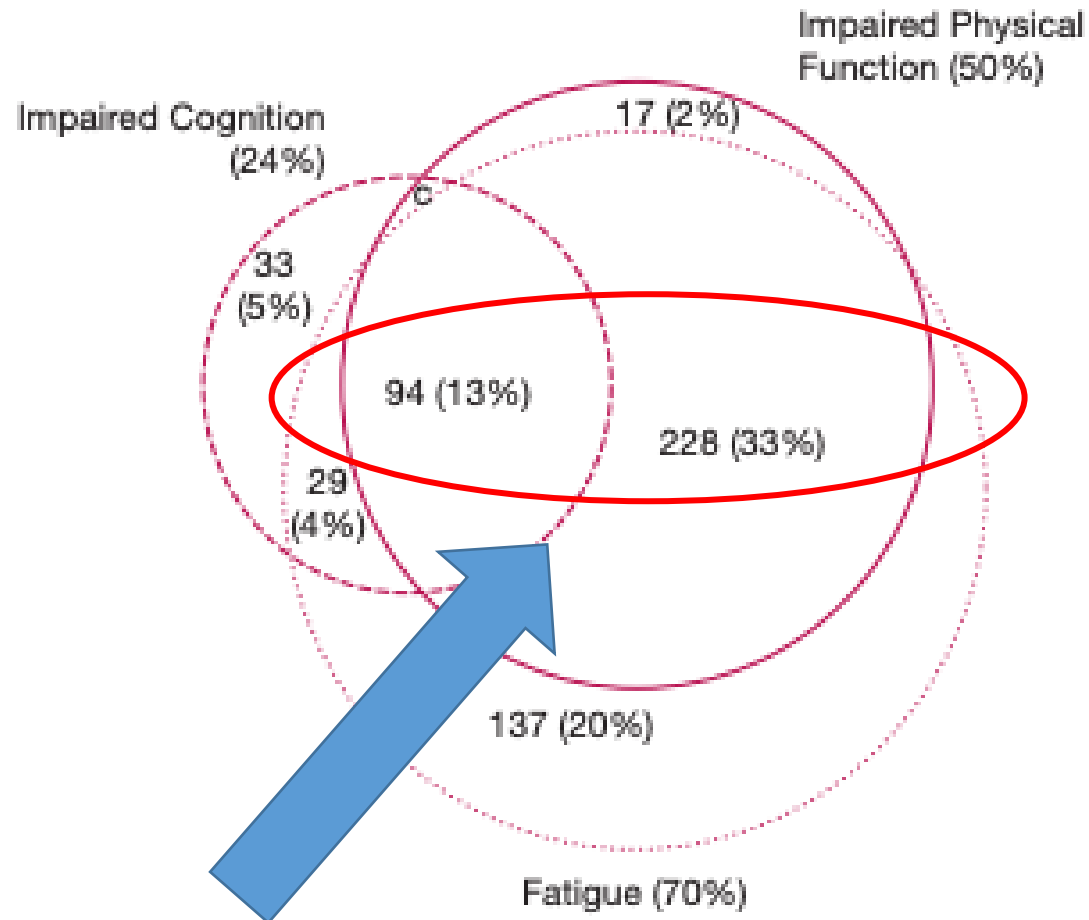
- **Prospective study at 38 US hospitals (2008 – 2014)**
- **ARDS patients (n = 732)**
- **6 & 12 mon outcomes**
  - Fatigue (FACIT-F)
  - Physical (SF-36, FPI-SF)
  - Cognitive (MMSE)
  - PTSD (IES-R)
  - Anxiety & depress (HADS)



## Results

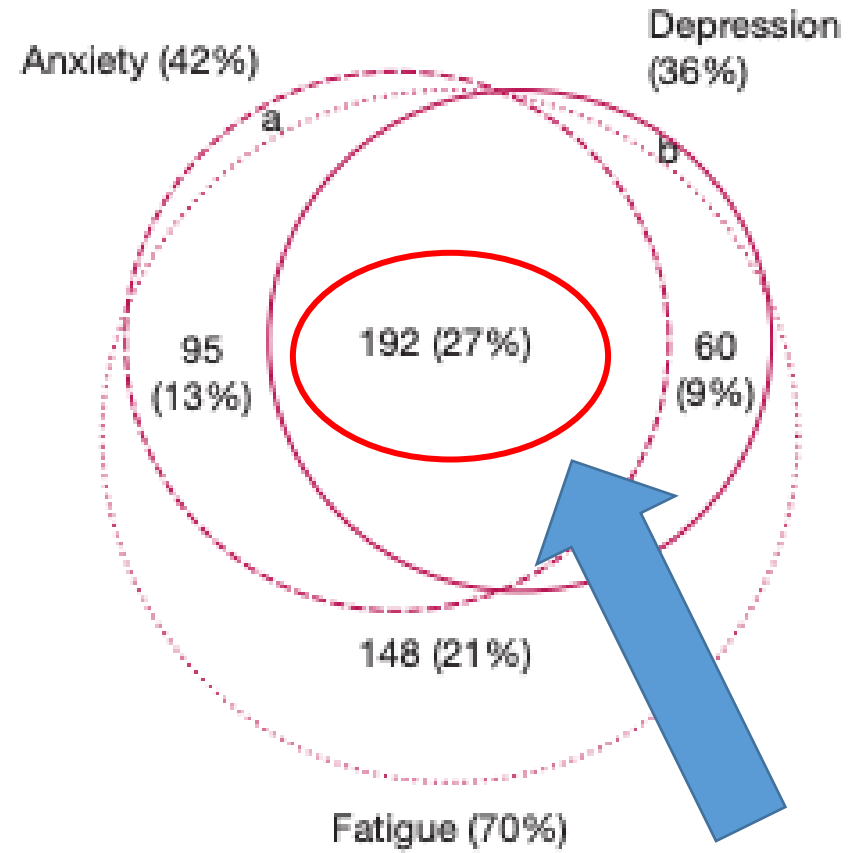
- **Fatigue**
  - 6 mon: **70%**
  - 12 mon: **66%** (28% worsen, 31% no change, 41% improved)
  
- **No association with**
  - **ICU / ARDS severity**
  
- **Increased fatigue associated with**
  - Baseline: Female & Unemployed status
  - 6 / 12 mon: **↓ Physical function & ↑ Psychologic symptoms**

n = 698 (% of total)



46%: Fatigue & Physical impairment

n = 705 (% of total)



27%: Fatigue & Psychologic symptom

# Bodily pain in survivors of acute respiratory distress syndrome: A 1-year longitudinal follow-up study



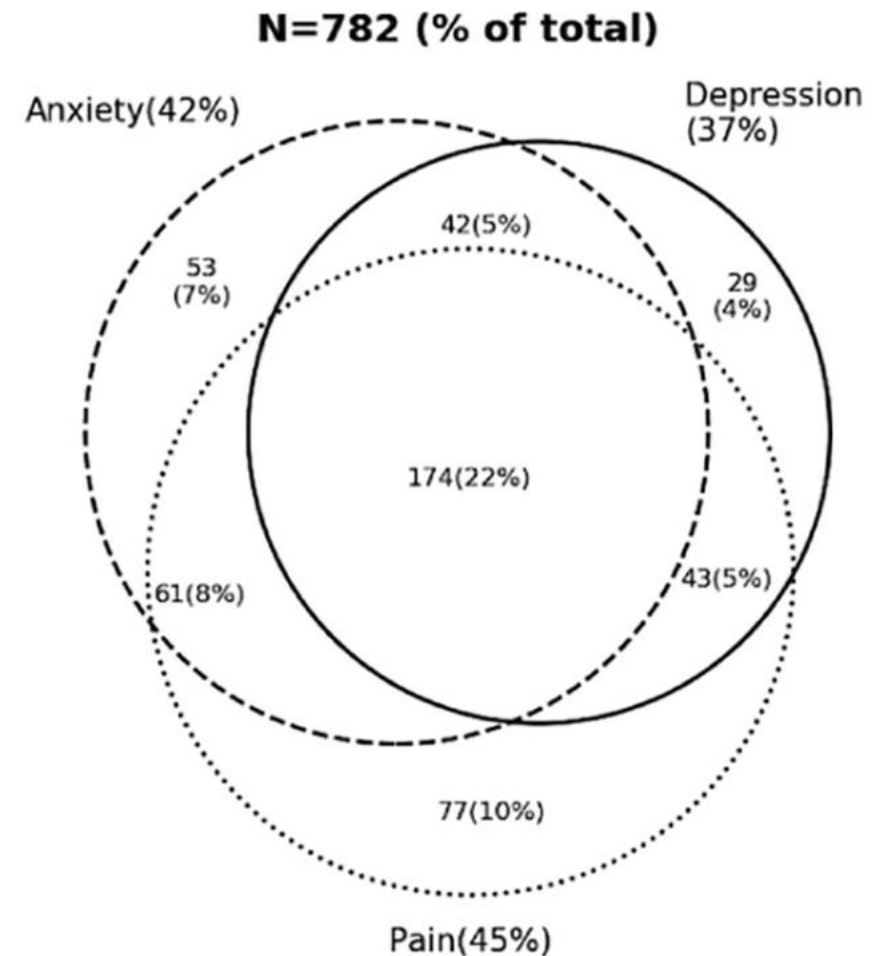
Julia M. Probert<sup>a</sup>, Shihong Lin<sup>g</sup>, Haijuan Yan<sup>b</sup>, Jeannie-Marie S. Leoutsakos<sup>b</sup>, Victor D. Dinglas<sup>c</sup>, Megan M. Hosey<sup>d</sup>, Ann M. Parker<sup>c</sup>, Ramona O. Hopkins<sup>e</sup>, Dale M. Needham<sup>c,d,1</sup>, Karin J. Neufeld<sup>f,1,\*</sup>

- **Prospective study at 38 US hospitals (2008 – 2014)**
- **ARDS patients (n = 826), Opioids use: 95%**
- **Outcome**
  - **Bodily pain**
  - Physical (SF-36, FPI-SF)
  - Cognitive (MMSE)
  - Anxiety & depress (HADS)



## Results

- Pain
  - 6 mon: **45%** / 12 mon: **42%**
- Of patients with Pain
  - **78%: anxiety or depressive Sx**
  - **78%: cognitive & physical impairment**
- Risk factors for pain
  - **Smoker**
  - **Unemployment**
  - **Opioids use in ICU**

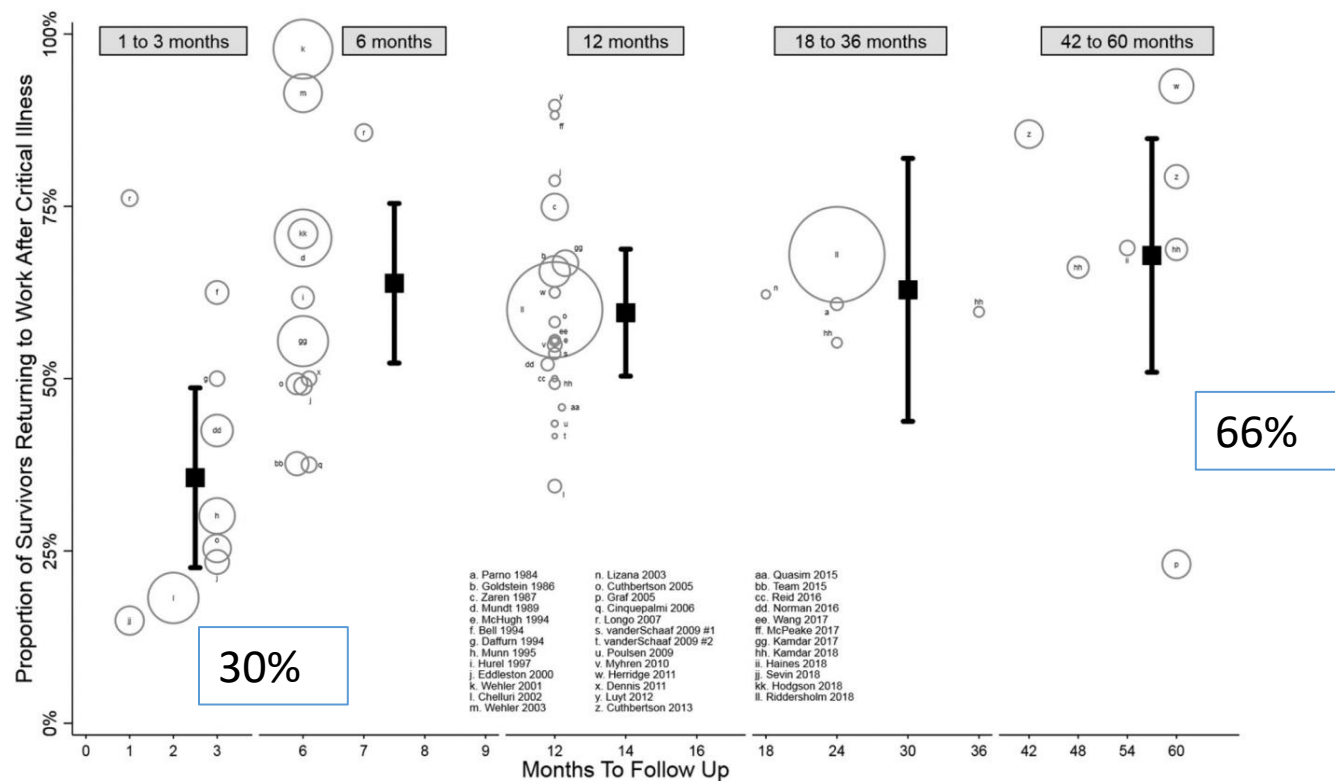




# Return to Work After Critical Illness: A Systematic Review and Meta-Analysis

Biren B. Kamdar, MD<sup>1</sup>, Rajat Suri, MD<sup>2</sup>, Mary R. Suchyta, DO<sup>3</sup>, Kyle F. Digrande, MD<sup>1,4</sup>, Kyla D. Sherwood, MD<sup>5</sup>, Elizabeth Colantuoni, PhD<sup>6,7</sup>, Victor D. Dinglas, MPH<sup>6,8</sup>, Dale M. Needham, MD PhD<sup>6,8,9</sup>, Ramona O. Hopkins, PhD<sup>10,11,12</sup>

- 52 studies in 10,015 previously-employed ICU survivors





## Additional outcomes

- No difference for ARDS severity
- **20 – 36%: lost job after returning to work**
- 17 – 66%: occupation change
- 5 – 84%: worsening employment status
- **- 70%: accrued lost earnings**

→ Vocational interventions needed for ICU survivors



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# Bed rest

<b>Problem</b>	<b>How fast</b>
<b>Maximal oxygen uptake and muscle strength</b>	1 – 1.5% per day
<b>Blood volume</b>	5% in 24 hrs, 10% in 6 days
<b>Bone Density</b>	Decreased mineralization within days
<b>Respiratory Tract</b>	Increased risk of pneumonia within a day
<b>Continenence &amp; constipation</b>	17 – 50% become incontinent after 24 hrs Constipation within days
<b>Blood Glucose</b>	Within 3 days

Convertino, Med Sci Sports Exerc. 1997 Feb;29(2):191-6

Fortney et al., J Clin Pharmacol. 1994 May;34(5):434-9

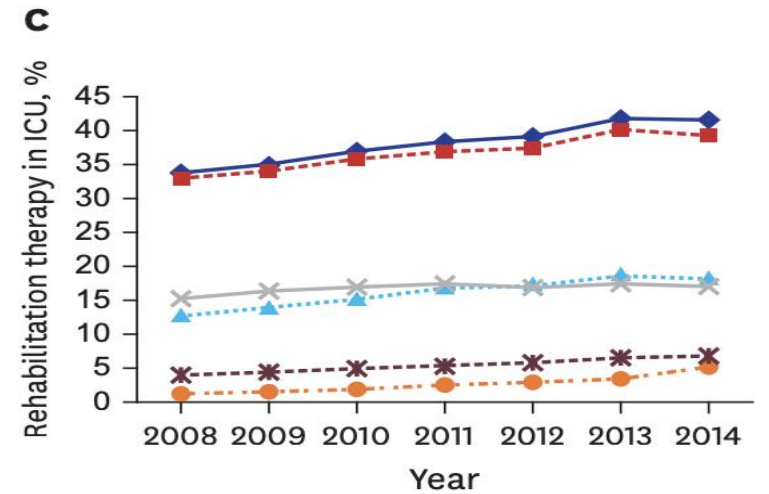
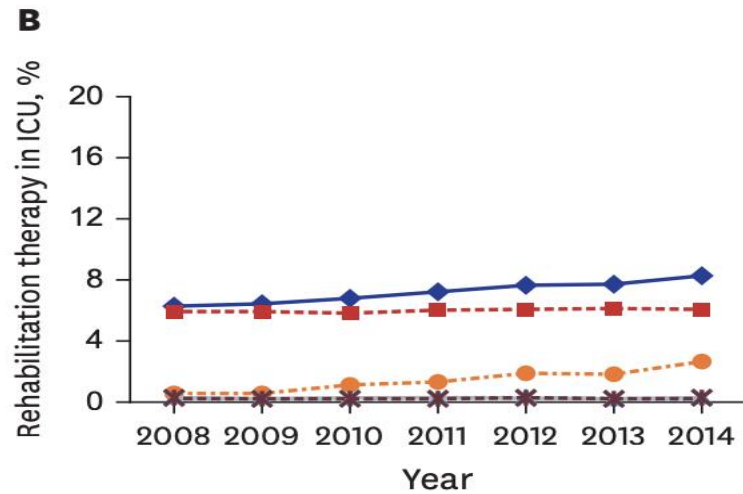
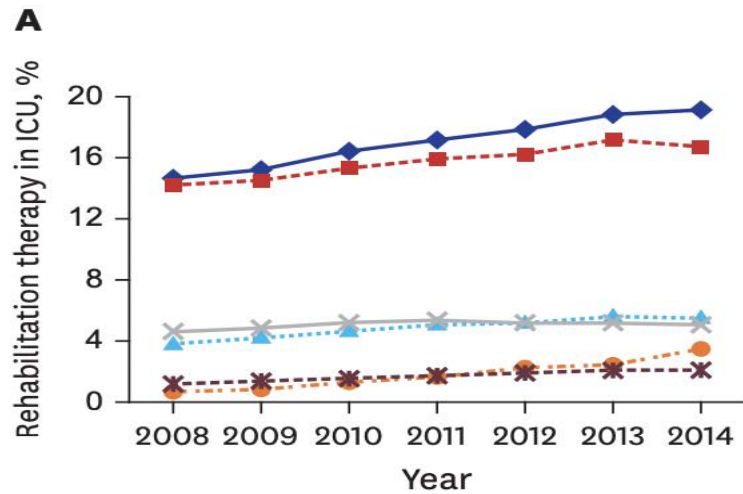
Guedes et al., Rev. bras. Geriatr. Gerontol. 21 (04)

# Relationship between Use of Rehabilitation Resources and ICU Readmission and ER Visits in ICU Survivors: the Korean ICU National Data Study 2008–2015



Yun Hee Park # 1, Ryoung Eun Ko # 2, Danbee Kang 3 4, Jinkyong Park 2, Kyeongman Jeon 2 5, Jeong Hoon Yang 2 6, Chi Min Park 2 7, Joongbum Cho 2, Young Sook Park 1, Hyejung Park 3 4, Juhee Cho 3 4, Eliseo Guallar 3 4 8, Gee Young Suh 2 5, Chi Ryang Chung 2 9

- 2008 – 2015, Korean ICU, n = 1,465,776, HIRA data
- 17.1% patients received rehab





## Results

- Type of rehabilitation
  - Physical therapy (91.9%)
  - Neuromuscular electrical stimulation (29.6)
  - Occupational (28.6), Respiratory (11.6), Swallowing (10.3)

Outcomes	No rehabilitation	Rehabilitation	Univariable Cox regression		Multivariable Cox	
	No (%)	No (%)	HR (95% CI)	P value	HR (95% CI)	P value
ICU readmission	67,166 (5.7)	13,250 (5.4)	0.95 (0.97 – 1.04)	0.281	<b>0.70 (0.65 – 0.75)</b>	<b>&lt; 0.001</b>
ER Revisit	115,144 (9.7)	23,622 (9.6)	0.99 (0.91 - 1.07)	0.768	<b>0.83 (0.77 – 0.88)</b>	<b>&lt; 0.001</b>





# Barriers to mobilizing patients with life-support devices

- Patient safety concerns (cath. dislocation, bleeding ...)
- Limited resources (time, staff, equipment)
- Unit culture
- Lack of nursing knowledge ...

# Rehabilitation of adult patients on extracorporeal membrane oxygenation: A scoping review



Kate Hayes, PT, MPT <sup>a, b, \*</sup>, Carol L. Hodgson, PT, PhD <sup>a, c</sup>, Melissa J. Webb, PT, BPT <sup>a</sup>, Lorena Romero, Research Librarian, MBIT <sup>d</sup>, Anne E. Holland, PT, PhD <sup>a, e</sup>

- **185 studies – small retrospective studies**

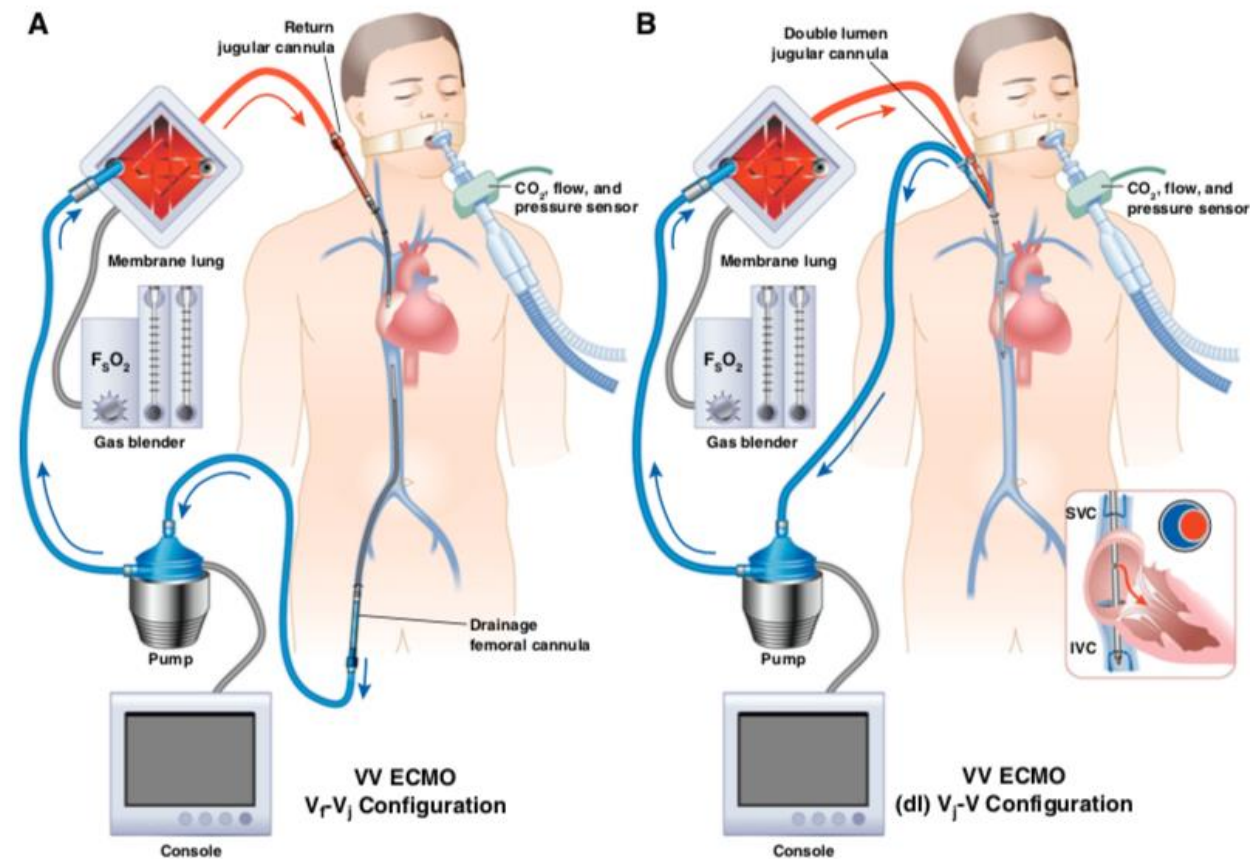
Type of rehab (136 studies)	Studies (%)
Bed-based	60 (44%)
Sitting on the bed edge	44 (32%)
Standing	55 (40%)
<b>Ambulation</b>	<b>95 (70%)</b>

Safety issues (60)	Studies (%)
<b>Zero adverse events</b>	<b>30 (50%)</b>
Adverse not linked to rehab	15 (25%)
Adverse associated with rehab	15 (25%)

Equipment for rehab (49)	Studies (%)
<b>In-bed cycle ergometer</b>	<b>15 (31%)</b>
<b>Upright cycle</b>	<b>13 (27%)</b>
Tilt table	12 (24%)
Gait aid / walking frame	9 (18%)
Treadmill	8 (16%)
Rehabilitation chairs	8 (16%)
EMS including FES	5 (10%)
Hand weights	5 (10%)

Facilitator of rehab	Studies (%)
Upper body cannulation	336 (38)
Weaning of sedation	332 (34)
Multidisciplinary team	231 (33)
Vent weaning / extubation	123 (24)
Tracheostomy	115 (16)
Screening tool for rehab	913 (14)
Method to secure cannula (sutures ...)	59 (10)
Appropriate equipment for rehab	44 (4)

Barrier to rehab	Studies (%)
Femoral cannulation	115 (37)
Sedation level	912 (29)
Medical instability/bleeding	810 (24)
Resources (Staffing, time, equipment)	410 (24)
Psychological issues	33 (7)



## **E Early Mobilization during Extracorporeal Membrane Oxygenation for Cardiopulmonary Failure in Adults**

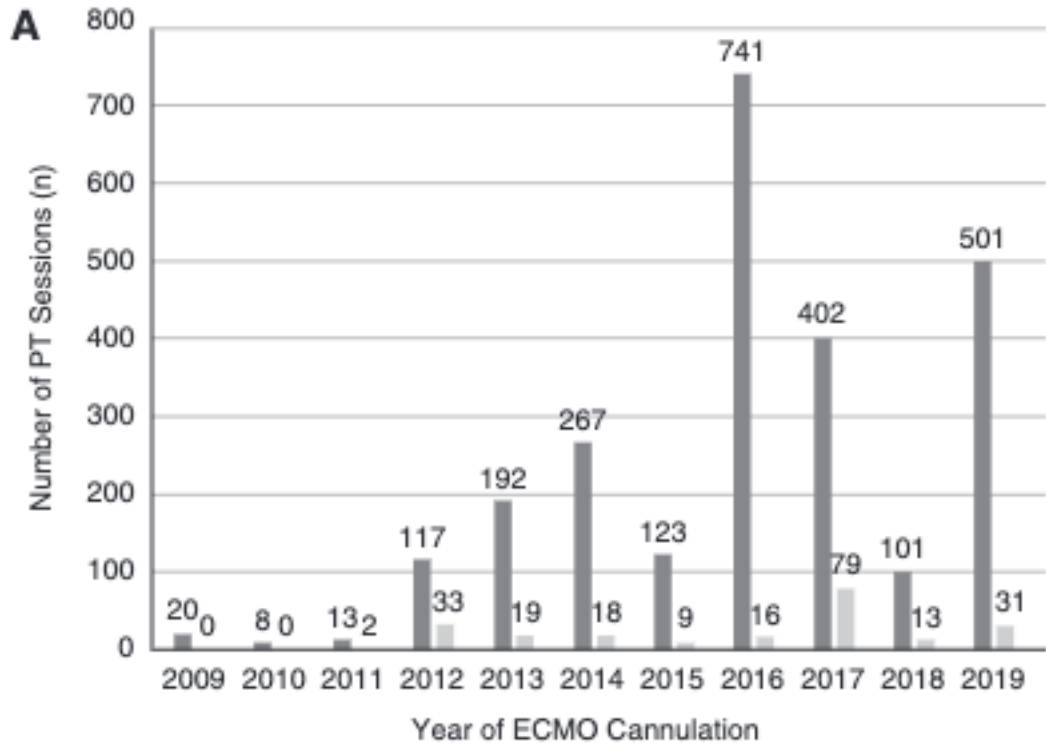
### **Factors Associated with Intensity of Treatment**

- **Single center retrospective, 10 yrs, n = 511**
- **Factors associated with out-of-bed rehabilitation**
- **Factors**
  - Reason for performing ECMO (Bridge to LT vs. Bridge to recovery)
  - Location of cannulation (Upper body vs. Femoral cannulation)
  - ICU severity
  - With or without ventilator ...

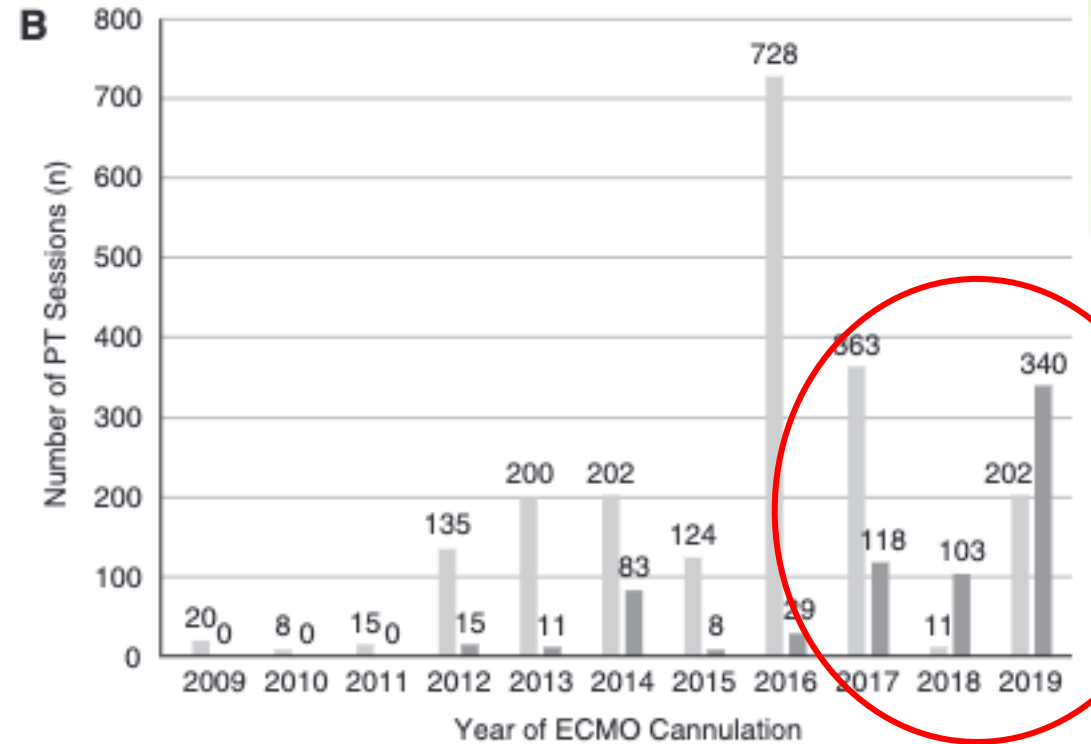


# Predictors of out-of-bed physical therapy

Adjusted model	All physical therapy sessions		
	OR	95% CI	P value
Incremental age	1.0	0.97 – 1.02	0.99
APACHE II score	1.05	0.97 – 1.14	0.23
SOFA score	1.08	0.92 – 1.27	0.36
Charlson comorbidity index	1.53	1.07 – 2.19	0.02
Bridge to lung transplantation	17.2	4.12 – 72.1	< 0.001
Incremental days on ECMO	0.99	0.97 – 1.0	0.06
Venovenous configuration	2.83	1.29 – 6.22	0.01
Femoral cannula present	0.19	0.04 – 0.92	0.04
On ventilator during PT	0.11	0.05 – 0.25	< 0.001



■ : Bridge to lung T  
■ : Bridge to recovery



■ : Presence of femoral cannula  
■ : absence of femoral cannula



# Early mobilization in neurocritical care patients



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*Monisha A. Kumar<sup>a,b,c</sup>, Francisco G. Romero<sup>a</sup>, and Kiruba Dharaneeswaran<sup>a</sup>*

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- Hemodynamic instability
- Acute hemiplegia
- Altered consciousness, visual field deficit
- Cerebral ischemia – may be exacerbated when upright or active



# Specific consideration in neurocritical patients

Diagnosis	Time to mobilization	Consideration	Proposed solution
Ischemic stroke	> 24h	Cerebral perfusion	Close BP monitoring Avoid mobilization with vasopressors
Subarachnoid hemorrhage	24 – 48h after Ruptured aneurysm secured	EVD dislocation ICP elevation	Ensure EVD secure Single transient spike → can mobilize
Intracranial hemorrhage	> 24 h Hemorrhagic stable	ICP elevation	Close BP monitoring Avoid mobilization with vasopressors
Spinal cord injury	24 h post spine stabilization	Orthostatic hypotension	Close BP monitoring Avoid mobilization with vasopressors
Traumatic brain injury	24 h after hemorrhage stable	ICP elevation	Monitor ICP closely Single transient spike → can mobilize



# Criteria for mobilization in neurocritical patients

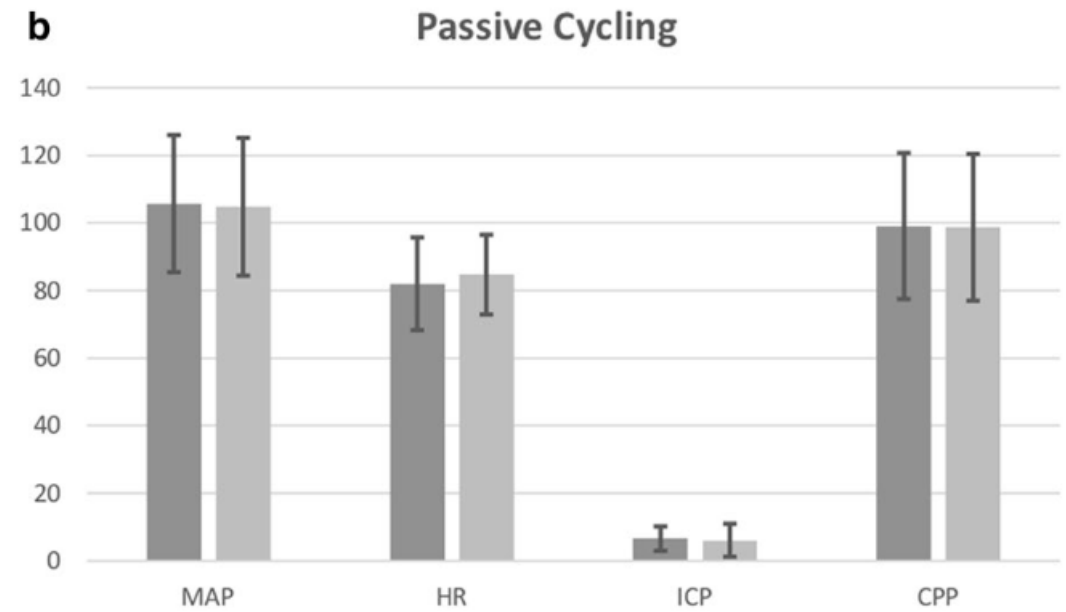
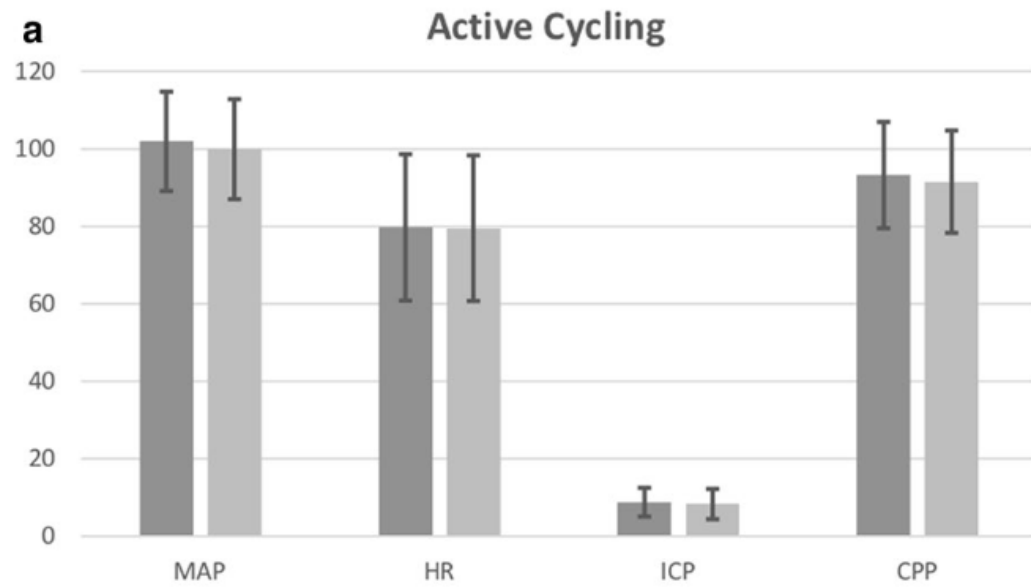
Organ system	Inclusion criteria	Abort criteria
Neurological	GCS > 3 Spinal stability	Reduced consciousness Lightheadedness Agitation Fall Device dislodgement
Cardiovascular	HR 60 – 130 bpm SBP 90 – 180 mmHg MAP 60 – 100 mmHg	Brady / Tachycardia Hypo/Hypertension Arrhythmia development New chest pain
Respiratory	RPM 5 – 40 O2 Sat > 88% FiO2 < 60% PEEP < 10	RPM < 5 or > 40 Desaturation Vent dys-synchrony Airway device dislodgement



# Physiological Responses to In-Bed Cycle Ergometry Treatment in Intensive Care Unit Patients with External Ventricular Drainage

Elizabeth K. Zink<sup>1,5\*</sup> , Sowmya Kumble<sup>2</sup>, Meghan Beier<sup>2</sup>, Pravin George<sup>3</sup>, Robert D. Stevens<sup>4,5</sup> and Mona N. Bahouth<sup>5</sup>

- Active or passive in-bed cycle ergometry in patients with EVD
- N = 27





 : Pre-cycling session  
 : Post-cycling session



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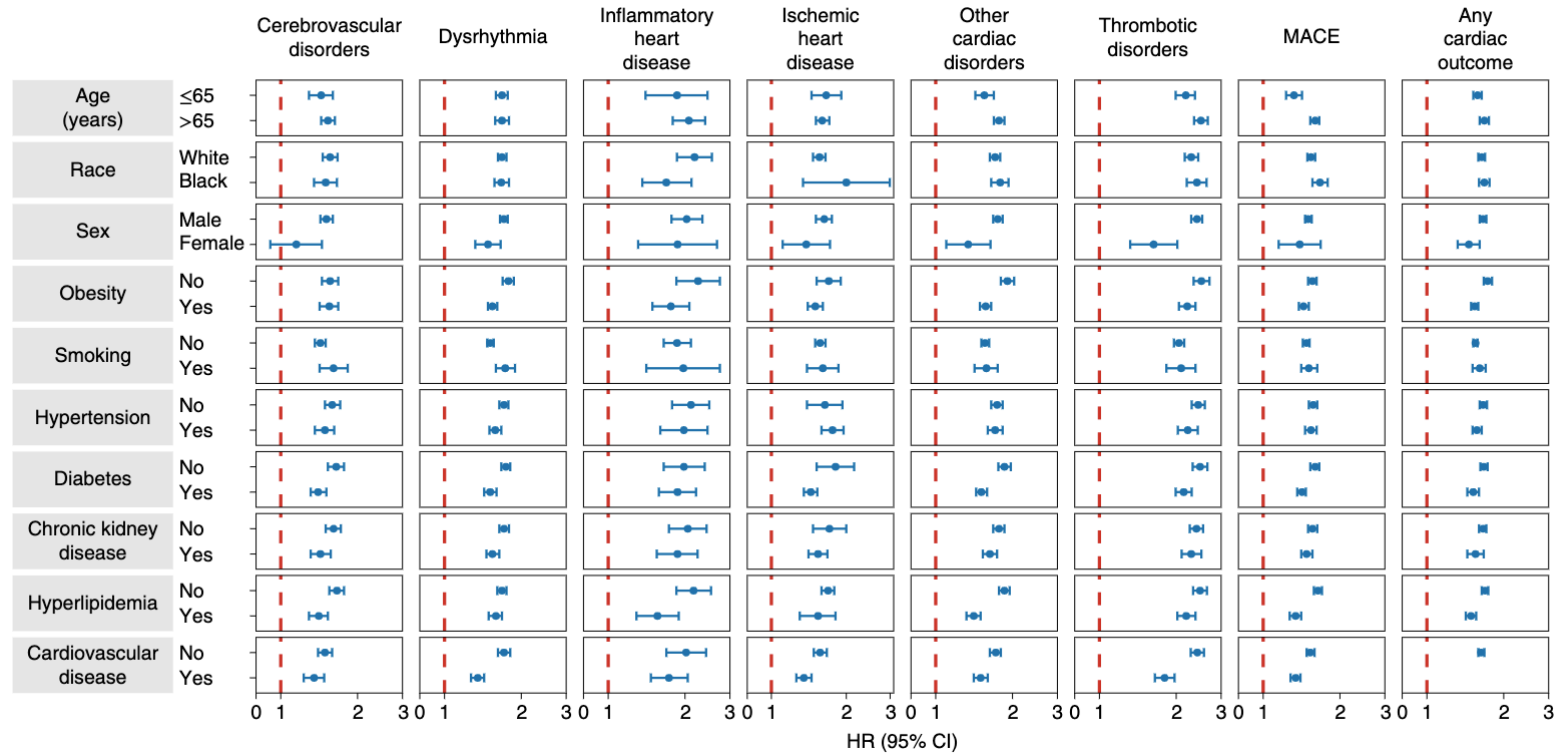
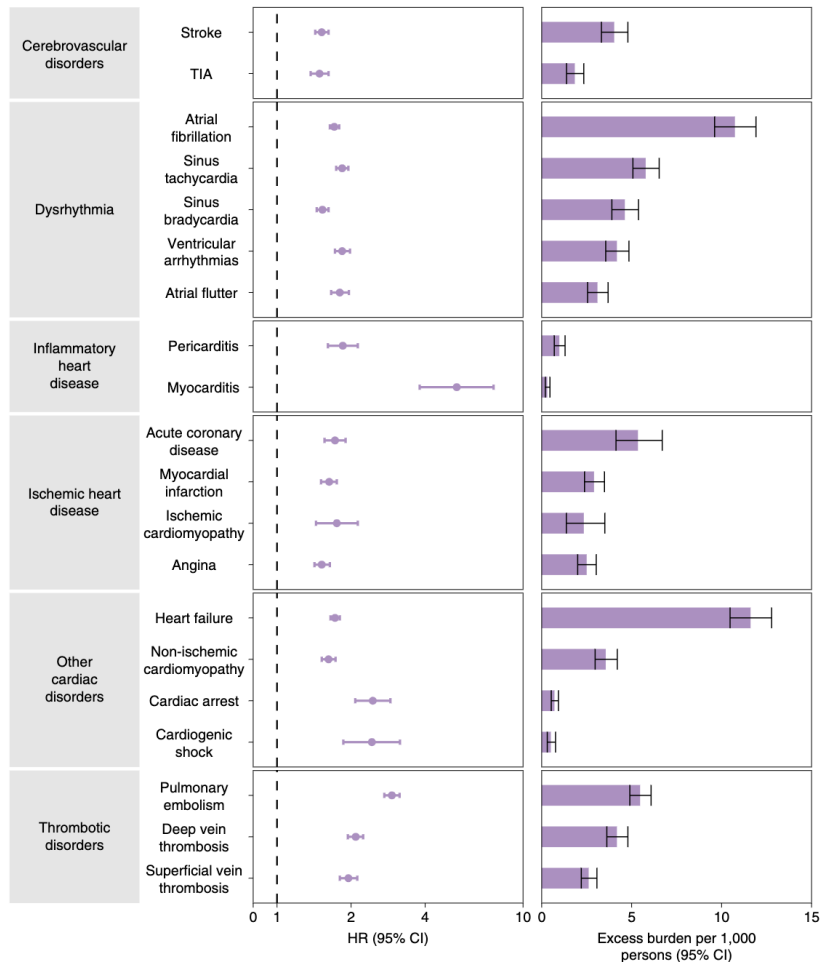
1. Post Intensive Care Syndrome (PICS)
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OPEN

# Long-term cardiovascular outcomes of COVID-19



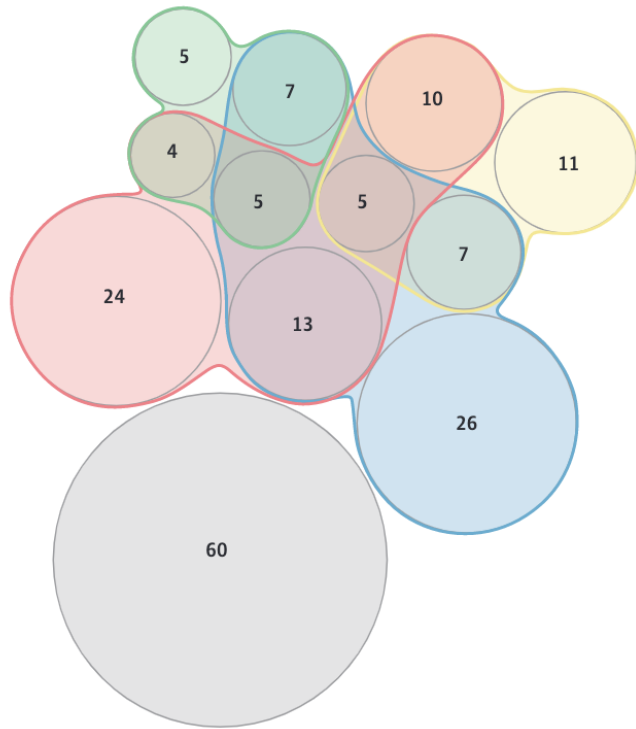
Yan Xie <sup>1,2,3</sup>, Evan Xu <sup>1,4</sup>, Benjamin Bowe <sup>1,2</sup> and Ziyad Al-Aly <sup>1,2,5,6,7</sup> ✉





# Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19

The Writing Committee for the COMEBAC Study Group



■ Cognitive impairment (n=61)    ■ Psychiatric symptoms (n=63)  
■ Dysfunctional breathing (n=21)    ■ No symptoms reported (n=60)  
■ Fibrotic lesions (n=33)

Symptoms	All patients	Nonintubated	Intubated
<b>Dyspnea</b>	78 (16.3)	53 (13.1)	<b>25 (34.2)</b>
<b>Cough</b>	21/420 (5)	16/358 (4.5)	<b>5/62 (8.1)</b>
<b>Chest discomfort</b>	34/418 (8.1)	25/356 (7)	<b>9/62 (14.5)</b>
Fatigue	134/431 (31.1)	110/368 (29.9)	24/63 (38.1)
<b>Anorexia</b>	34/436 (7.8)	25/370 (6.7)	<b>9/66 (13.6)</b>
Memory difficulties	73/416 (17.5)	63/354 (17.8)	10/62 (16.2)
Mental slowness	42/415 (10.1)	38/353 (10.8)	4/62 (6.4)
Concentration problems	41/412 (10.0)	35/351 (10.0)	6/61 (9.8)

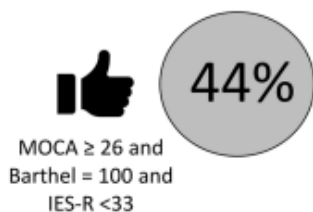


# Post-intensive care syndrome after a critical COVID-19: cohort study from a Belgian follow-up clinic

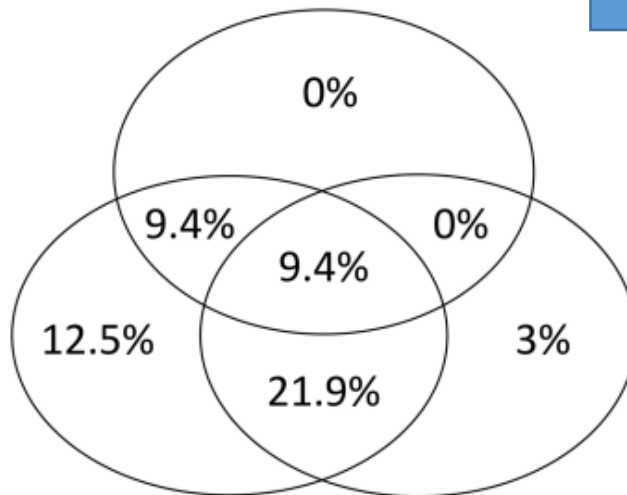


Anne-Françoise Rousseau<sup>1\*</sup>, Pauline Minguet<sup>1</sup>, Camille Colson<sup>1</sup>, Isabelle Kellens<sup>1</sup>, Sourour Chaabane<sup>1</sup>, Pierre Delanaye<sup>2,4</sup>, Etienne Cavalier<sup>3</sup>, J. Geoffrey Chase<sup>5</sup>, Bernard Lambermont<sup>1</sup> and Benoit Misset<sup>1</sup>

- Single center prospective, Belgium, n = 32
- Proportions of patients experiencing PICS
- Effect of rehab in COVID-19 ICU patients



PICS: 56%  
(Cognitive: 53%)





Variables	Rehab (n = 17)	No rehab (n = 15)	P value
MV duration, days	24 (18 – 32)	16 (11 – 26)	0.004
ICU LOS, days	39 (23 – 43)	16 (11 – 26)	0.011
MoCA (cognitive)	26 (23 – 28)	27 (22 – 28)	NS
IES-R (mental)	6 (4 – 24)	9 (3 – 34)	NS
EQ-5D score	7 (6 – 9.5)	6 (5.7 – 7.2)	NS
Barthel Index	100 (75 – 100)	100 (100 – 100)	0.03
Handgrip strength	21 (14 – 27)	32 (28 – 42)	0.005



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JAMA | **Original Investigation** | **CARING FOR THE CRITICALLY ILL PATIENT**

## Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19

Hidde Heesakkers, MD; Johannes G. van der Hoeven, MD, PhD; Stijn Corsten, MD; Inge Janssen, MD; Esther Ewalds, MD; Koen S. Simons, MD, PhD; Brigitte Westerhof, MD; Thijs C. D. Rettig, MD, PhD; Crétien Jacobs, MD; Susanne van Santen, MD, PhD; Arjen J. C. Slooter, MD, PhD; Margaretha C. E. van der Woude, MD, PhD; Mark van den Boogaard, RN, PhD; Marieke Zegers, PhD

- Multicenter prospective, Dutch, n = 246 / 452,
- Proportions of patients experiencing PICS

Domain	1 Domain	2 Domains	All 3 Domains
Physical	107 / 245 (43.5)	35 / 246 (14.2) + Mental	26/246 (10.5)
Mental	1 / 244 (0.4)		
Cognitive		15 / 246 (5.9) + Physical	



- New physical problems

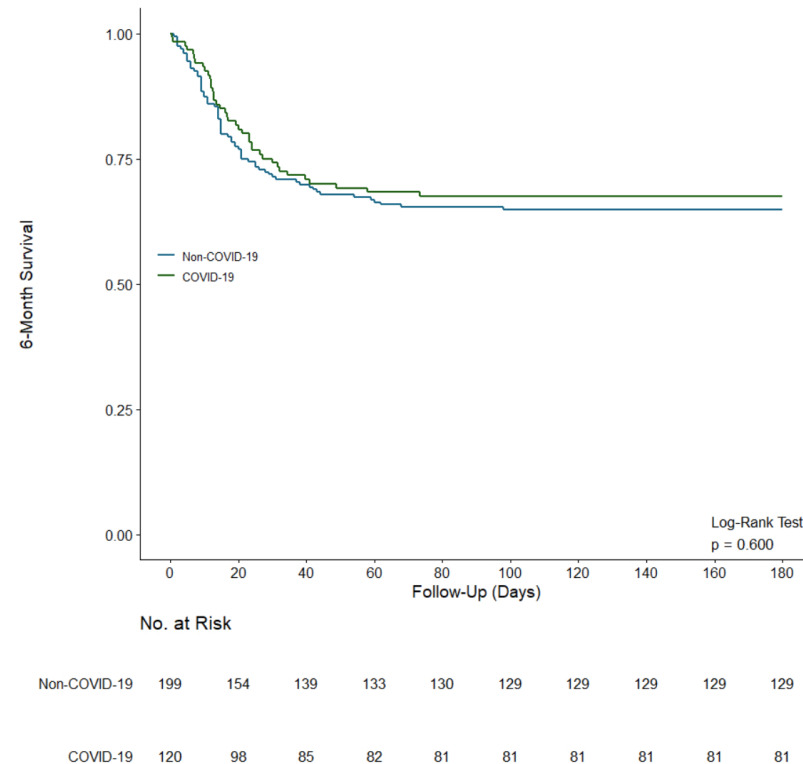
New physical problems	Percentage
Weakened condition	38.9
Joint stiffness	26.3
Joint pain	25.5
Muscle weakness	24.8
Myalgia	21.3
Dyspnea	20.8
Numb sensation in limbs	20.6
Lung disease	18.5
Neuropathic pain	17.4
Voice problems	11.9
Dizziness	11.5



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# Comparison of 6-Month Outcomes of COVID-19 vs Non-COVID-19 Survivors of Critical Illness

- COVID-19 (n = 120, SPRINT-SARI) vs. non-COVID-19 (n = 199, PREDICT)
- Mechanically ventilated patients for acute respiratory failure





Functional outcomes	COVID-19	Non-COVID-19	P value
EQ-5D-5L	0.8 (0.7 – 0.9)	0.7 (0.5 – 0.9)	0.140
EuroQol-visual analogue scale	70 (60 – 85)	70 (50 – 80)	0.511
New disability	19/54 (35.2)	29/80 (36.2)	0.653
IADL	8 (7 – 8)	8 (6 – 8)	0.275
HADS anxiety	2 (0 - 6)	4 (1 – 9)	0.302
HADS depression	2 (1– 5)	3 (1 – 7)	0.917
PTSD	9/44 (20.5)	7/49 (14.3)	0.802
Cognitive dysfunction	14/34 (41.2)	13/44 (29.5)	0.430



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- **Rehabs in COVID-19 ICU**





# Early rehabilitation with dedicated use of belt-type electrical muscle stimulation for severe COVID-19 patients



Kensuke Nakamura , Hidehiko Nakano, Hiromu Naraba, Masaki Mochizuki and Hideki Hashimoto





# Rehabilitation Levels in Patients with COVID-19 Admitted to Intensive Care Requiring Invasive Ventilation

## An Observational Study

David McWilliams<sup>1</sup>, Jonathan Weblin<sup>1</sup>, James Hodson<sup>2</sup>, Tonny Veenith<sup>3</sup>, Tony Whitehouse<sup>3</sup>, and Catherine Snelson<sup>3</sup>; on behalf of the Queen Elizabeth Hospital Birmingham COVID-19 Research Team

- Single center, prospective, n = 110/177
- COVID-19 Patients who required MV
- First mobilize: sitting on the edge of the bed

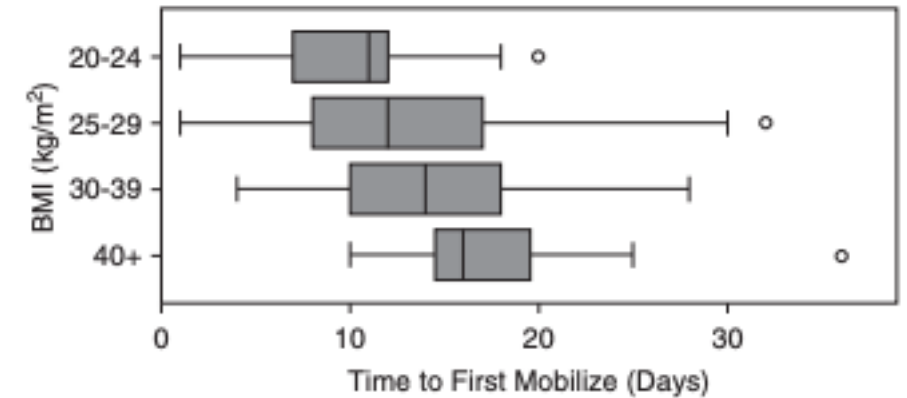
ICU therapy	
Mechanical ventilation	110 (100%)
Duration of vent, day	19 ± 10
Tracheostomy	85 (77)
Prone position	74 (67)
Neuromuscular blockade	99 (90)

ICU outcomes	
ICU acquired weakness	110 (100%)
Delirium	76 (69%)
Mobilized in ICU	110 (100%)
Time to first mobilize, day	14 ± 7
ICU LOS, day	22 ± 11



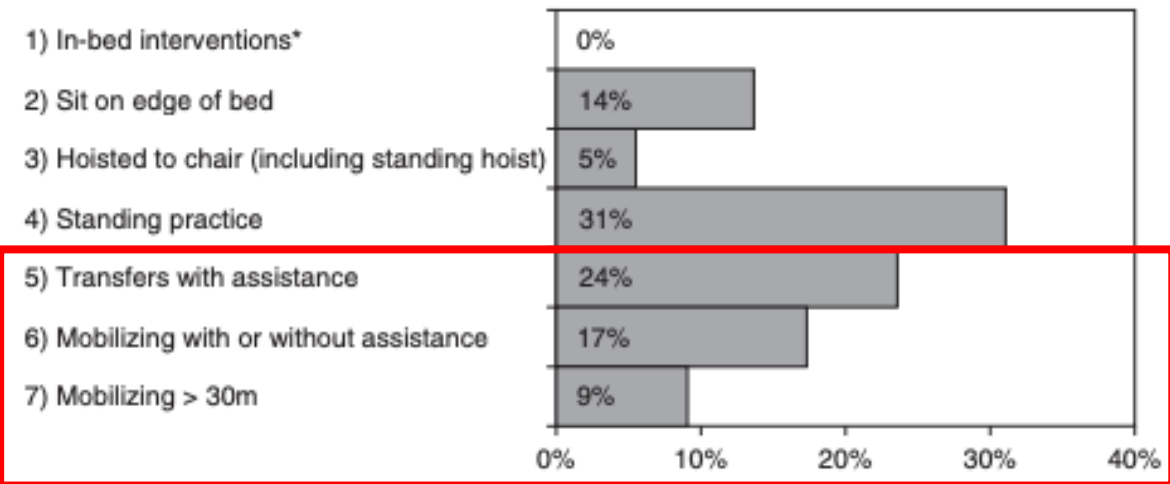
- Factors associated with initiate rehab

Factor	Days to first mobilize	P value
BMI, kg/m <sup>2</sup>		< 0.001
20 - 24	10 ± 5	
25 - 29	13 ± 7	
30 - 39	14 ± 6	
40 +	18 ± 6	
Age		0.094
APACHE II		0.108
Clinical frailty score		0.317



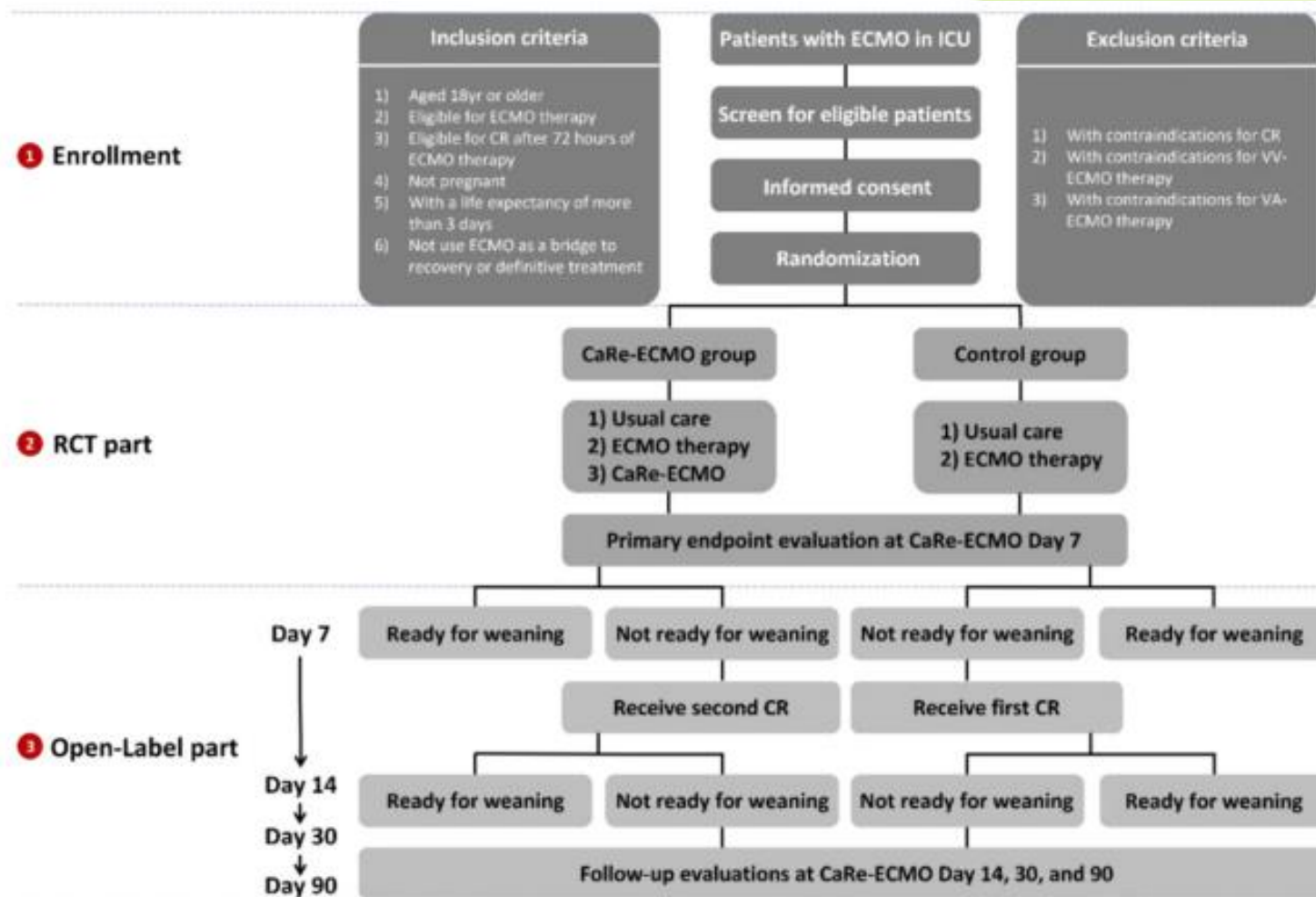


- Factors associated with physical outcome



	MMS 5+ at ICU discharge	P value
<b>Clinical frailty score</b>		<b>0.033</b>
1	14 (61)	
2	18 (56)	
3	17 (49)	
<b>Cardiovascular dz</b>	6 (30)	
No	53 (53)	<b>0.019</b>
Yes	2 (20)	
APACHE II		0.420
BMI		0.262

# Can Cardiopulmonary Rehabilitation Facilitate Weaning of Extracorporeal Membrane Oxygenation (CaRe-ECMO)? Study Protocol for a Prospective Multidisciplinary Randomized Controlled Trial





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**Thank you for your attention!**