

Natural History of Cognitive Impairment in Critical Illness Survivors: A Systematic Review

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Online Data Supplement

Supplemental Digital Content 1 – Search Strategy

Search History saved as "2017.07. Cognitive function_ neuropsychological testing_ICU_M"

Topic: cognitive function/dysfunction/impairment in ICU/ critically ill/ admitted with sepsis/acute respiratory distress syndrome/ventilated patients measured by using cognitive testing, neuropsychological testing, neurobehavioral testing, etc.

For: Dr Kimia Honarmand

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 (critical\$ adj2 ill\$.mp. or Critical Care/ or intensive care units/ or Critical Illness/ or exp Sepsis/ or Respiratory Distress Syndrome, Adult/ or APACHE.mp. or ((critical\$ or intensive or postintensive or post-intensive) adj care).mp. or (pyaemia\$ or pyemia\$ or pyohemia\$ or sepsis\$ or septicemia\$ or septicaemia\$.tw. or (((septic\$ or toxic\$ or endotoxic\$) adj2 shock\$) or (blood\$ adj2 poison\$)).tw. (367051)
 - 2 (intensive care unit\$ or ICU or (post-ICU or (post\$ adj3 ICU))).mp. (131853)
 - 3 **or/1-2 (373888)**
 - 4 exp Respiration, Artificial/ or exp Ventilators, Mechanical/ or (ventilat\$ adj2 (artificial\$ or mechanical\$)).tw. or (respirat\$ adj2 (artificial\$ or assisted\$ or mechanical\$)).tw. or (respirat\$ adj2 failure\$).tw. (119665)
 - 5 ((positive adj3 pressure adj5 (ventilat\$ or respir\$)) or (PPV and (pressure or ventilat*))).tw. or (ventilat\$ adj3 patient\$.ti. or (ventilat\$ and patient\$.ab. /freq=3 (30607)
 - 6 Respiratory Distress Syndrome, Adult/ or (respirator\$ adj2 distress\$ adj2 syndrom\$.tw. or ARDS.tw. or ((acute\$ or adult\$) adj3 (respirator\$ adj3 distress\$)).mp. or (lung\$ adj2 shock\$.tw. (33528)
 - 7 (((post traumatic\$ or posttraumatic\$) adj3 (respirator\$ or lung\$)) and failure\$.tw. (65)
 - 8 ((post traumatic\$ or posttraumatic\$) adj3 pulmonar\$ adj3 insufficienc\$.tw. (69)
 - 9 exp Respiratory Insufficiency/ or (respirat\$ adj3 (failure\$ or insufficien\$ or paralysis\$ or deficienc\$ or disturbanc\$ or depression)).tw. or (acute\$ and ((respirat\$ adj2 insufficienc\$) or (respirat\$ adj2 failure\$))).tw. (88925)
 - 10 Acute Lung Injury/ or (acute\$ and (lung\$ adj2 injur\$)).tw. or ((lung\$ or pulmonary\$) adj3 (failure\$ or insufficien\$)).tw. (24068)
 - 11 **or/4-10 (214792)**

12 3 or 11 (531847)

13 exp Cognition Disorders/ or exp Cognition/ or exp Cognitive Therapy/ (227117)

14 neurobehavioral manifestations/ or exp communication disorders/ or exp memory disorders/ or intellectual disability/ or exp perceptual disorders/ or exp sensation disorders/ (327857)

15 (cognition\$ or cognitive\$ or (aphasia\$ or neuropsycholog\$ or neuro-psycholog\$ or neurocognit\$ or neuro-cognit\$ or neurobehav\$ or neuro-behav\$)).mp. (438458)

16 or/13-15 (773692)

17 12 and 16 (7434)

18 ((visuospatial\$ or (visuo\$ adj2 spatial\$) or (verbal\$ adj2 fluen\$) or (process\$ adj2 speed\$) or psychomotor\$ or psycho-motor\$ or memory\$ or personality\$ or perceptual\$ or attention\$ or concentration\$ or auditory\$ or visual\$ or sensory\$ or sensation\$ or spatial\$ or IQ or intelligence\$ or intellectual\$) adj5 (impairment\$ or impaired or deficit\$ or deficien\$ or abnormal\$ or dysfunction\$ or function\$ or skill\$ or problem\$ of complain\$)).mp. (237720)

19 12 and 18 (2240)

20 17 or 19 (9087)

21 language tests/ or exp neuropsychological tests/ or exp "Severity of Illness Index"/ or di.fs. (2535444)

22 (measure\$ or tool\$ or scale\$ or assess\$ or test\$ or score\$ or scoring\$ or checklist\$).mp. (8035573)

23 or/21-22 (9469835)

24 20 and 23 (6136)

25 exp Survivors/ or surviv\$.mp. or (post\$ adj2 discharg\$).mp. or (post-ICU or (post\$ adj3 ICU)).mp. or incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos\$.tw. or predict\$.tw. or course\$.tw. or exp Prognosis/ or (followup or follow-up).tw. [Prognosis filter MEDLINE] (4684547)

26 24 and 25 (3135)

27 limit 26 to english language (2861)

28 (pediatr\$ or paediatr\$ or child\$ or adolescent\$ or infan\$ or newborn\$ or boy\$1 or neonat\$ or prenatal\$ or (mice or rat or rats or cat\$1 or cattle\$1 or dog\$1 or goat\$1 or horse\$1 or rabbit\$1 or sheep\$1 or swine\$1 or pig\$1 or canine\$1 or feline\$1 or porcine\$ or calf)).ti. (2892857)

29 27 not 28 (1903)

30 limit 29 to "all adult (19 plus years)" (1182)

31 limit 29 to "all child (0 to 18 years)" (427)
32 29 not (31 not (30 and 31)) (1688)
33 meta analysis.mp.pt. or MEDLINE.tw. or systematic review.tw. (231512)
34 32 and 33 (53)
35 limit 29 to "review articles" (305)
36 32 not 35 (1419) [Review articles excluded but SRs retained]
37 34 or 36 (1464)
38 case report.ti. (201170)

39 37 not 38 (1444)

40 ("23328935" or ("20179286" or "21173281" or "17521481" or "18384589" or "21443796" or
"21575208" or "15542793" or "12682497" or "17215737" or "11313077" or "22092200" or "20473145" or
"20032274" or "19144052" or "16525845" or "16115244" or "14702249" or "22492988" or
"21998261")).an. [validation set Medline] (24)

41 40 not 37 (0) [All records from a validation set are in the search results]

42 17 and 39 (1203) [could reduce the number if line #18 not included - All records from a validation set would be in the search results]

Supplemental Digital Content 2. Characteristics of included studies.

First Author, Year	Country	Study Design	Setting	Patient Population	Sample Size	Cognitive Measure(s)	Definition of Cognitive Impairment	Time Points Assessed	NOS Risk of Bias
Adhikari, 2009 (1)	Canada	Prospective cohort	ICU	ARDS	61	MAC-S	MAC-S score <1.5 SD below norms	6-48 mos post-ICU discharge (median 22)	Fair
Adhikari, 2011 (2)	Canada	Prospective cohort	ICU	ARDS	47	MAC-S	MAC-S score <1.5 SD below norms	61-64 mos post-ICU discharge (median 62)	Fair
Ambrosino, 2002 (3)	Italy	Prospective Case-control	Respiratory intermediate ICU	COPD with respiratory failure	63 vs. 34 controls 6 mos f/u: 36 vs. 20 controls	MMSE	MMSE score <24.	At ICU discharge + 3 mos + 6 mos	Good
Baumbach, 2016 (4)	Germany	Prospective cohort	Mixed ICU	Minimum LOS of 24 days	3 mos: 127 patients + 52 families 6 mos: 103 patients + 36 families	FACT-Cog Questionnaire	PAM cluster analysis divided patients into impaired and non-impaired.	3 mos post 6 mos post	Good
Brummel, 2014 (5)	USA	RCT	MICU + SICU	Respiratory failure, or septic, cardiogenic, or haemorrhagic shock who lived close to centre; critically ill < 72 hours at recruitment	Randomized: 22 usual care, 22 physical treatment, 43 cognitive + physical treatment. F/u at 3 mos: 12 usual care, 14 physical treatment, 18 cognitive + physical treatment.	DKEFS Tower Test "Cognitive outcomes", MMSE	No cutoff defined	ICU discharge 3 mos post	RCT
Christie, 2006 (6)	USA	Cross-sectional	ARDS survivors contacted by phone	ARDS survivors from Internet support website	79	Telephone based cognitive tool being developed/ validated by authors	2 item scores \geq 1 SD below population norm or a single test score 1.5 SD below population norm.	Average 5 years post discharge	Poor
Chung, 2017 (7)	Korea	Cross-sectional	MICU + CCU + SICU	Patients referred for psychiatric assessment at discharge from ICU.	30	Mini-Cog	Recall of < 9 items or abnormal clock.	ICU discharge	Poor

Daly, 2009 (8)	USA	Prospective cohort	Four ICUs	Chronic critical illness (ventilated > 72h) recruited into separate RCT.	257	Katzman Short Orientation-Memory Concentration Test (0-28)	Katzman score > 6.	ICU discharge	Good
de Azevedo, 2017 (9)	Brazil	Prospective cohort	MICU + SICU	Unselected ICU patients without previous cognitive impairment	724 at discharge. 413 at follow-up.	Forward/ backward digit span, Rey Auditory Verbal Learning Test (RAVLT), Clock-drawing test, verbal fluency, MMSE	Mild or moderate CI = two test scores 1.5 SD below mean or one test 2 SD below mean. Severe CI = 3+ tests 1.5 SD below mean or 2+ tests 2 SD below mean.	Min 3 mos (average 11 mos, range 3-18)	Good
Dennis, 2011 (10)	Australia	Prospective cohort	MSICU	>48 h length of stay	71	FIM Cognition category	“worse than before”	6 mos post	Good
de Rooji, 2008 (11)	Netherlands	Retrospective cohort	MSICU	80+ years of age who were alive at time of recruitment	204, with 35 excluded due to no relative to assess CI. 164 relatives.	IQCODE-SF	IQCODE-SF > 3.1	1-5.9 yrs (median 3.7)	Good
Detsky, 2017 (12)	USA	Prospective cohort	MICU + SICU	Life-sustaining therapy (ventilated >48h or vasopressors >24 h), with >3 day ICU stay	166 full follow-up. 169 partial follow-up.	Phone interview with patient. Or surrogate.	Patient/surrogate report of change in ability to remember most things, think clearly and solve day-to-day problems.	6 mos post	Poor
Duggan, 2017 (13)	USA	Prospective cohort	MICU + SICU	Respiratory failure, cardiogenic shock or septic shock. Sample from BRAIN-ICU study.	136	IQCODE/ Clin Dementia Rating used to exclude pre-existing CI pts BRIEF-A patient and family, Trails B	BRIEF-A ≥ 65 (range 0-100, pop mean 50, SD 10). Trails B adjusted t-score ≤ 35 (0-100, 50, SD 10).	3 mos post	Good
Duning, 2010 (14)	Germany	Case control	SICU	18 to 80 year old patients with >72h length of stay who had 1 or more hypoglycemic episodes	37 hypoglycemic episode patients + 37 matching controls.	MMSE, Boston Naming Test, Nuernberg Gero Inv, Digit Symbol Sub, Color word interference, Wechsler Memory Scale (WMS) Digit Span forward/ backward, Trails A, Trails B, Regensburg Word Fluency test, Rey Osterrieth	No defined cutoff	1+ years	Good

						Complex Figure (ROCF), Auditory Verbal Learning Test			
Ely, 2004 (15)	USA	Prospective cohort	MICU + coronary ICU	Mechanically ventilated	128	MMSE	MMSE < 24.	At ICU discharge	Good
Girard, 2010 (16)	USA	Prospective cohort (nested within ABC RCT)	MICU	Ventilated 12h to 2 weeks. Previously living independent.	128 eligible. 77 at 3 mos. 52 at 12 mos.	Digit span, Trails A, Digit Symbol coding, RAVLT, ROCF, Verbal Fluency, MMSE	Mild-mod CI = two tests > 1.5 SD below mean or one tests > 2 SD below mean. Severe CI = 3+ tests > 1.5 SD below mean or 2+ tests > 2 SD below mean.	3 mos post 12 mos post	Good
Granja, 2005 (17)	Portugal	Prospective cohort	10 ICUs	Unselected ICU survivors	464	Author developed questionnaire about recollect of experiences lived by ICU survivors Two questions from questionnaire re: (1) difficulties in concentration, and (2) difficulties in remembering recent events	“yes”	6 mos post	Poor
Gunther, 2012 (18)	USA	Prospective cohort	MICU + SICU + cardiac ICU	Respiratory failure or shock. Could undergo MRI.	43	RBANS, Trails A+B	CI = Extremely low + borderline	3 mos post 12 mos post	Good
Hopkins, 1999 (19)	USA	Prospective follow-up	ICU	ARDS	55	WAIS–Revised, WMS–Revised, RAVLT, ROCF (copy, immediate and 30-min delayed recall), Trails A and B, Verbal Fluency (letters F, A, S)	Impaired on at least one cognitive test.	At hospital discharge 1 year post	Poor
Hopkins, 2005 (20)	USA	Prospective follow-up	ICU	ARDS	66 patients at 1-year follow-up. 62 patients at 2-year follow-up.	WAIS–Revised, WMS–Revised, RAVLT, ROCF (copy, immediate and 30-min delayed recall), Trails A and B, Verbal Fluency (letters F, A, S)	Two or more cognitive test scores >1.5 SD or 1 test score >2 SD below the normative population mean.	At hospital discharge 1 year 2 year	Poor
Hughes, 2017 (21)	USA	Prospective cohort	ICU	MIND-ICU and BRAIN-ICU study patients	494 patients at 3-month follow-up 413 patients at 12-	RBANS Trials B	<78 on RBANS (>1.5 SD below adjusted population mean)	3 mos 12 mos	Good

					month follow-up		Trials B >1 SD below adjusted population mean		
Jackson, 2003 (22)	USA	Prospective follow-up	MICU + coronary ICU	Mechanically ventilated	41	MMSE, Digital Symbol Coding, Thurstone Word Fluency, Letter Number Sequencing, Verbal Paired Associates, Digit Symbol Paired Recall, Faces, ROCF	Either two neuropsychological test scores at least 2 SD below the norm-referenced mean or three scores at least 1.5 SD below the norm-referenced mean.	6 mos [MMSE at hospital discharge 6 mos post]	Fair
Jackson, 2010 (23)	USA	RCT substudy (ABC trial)	ICU	Ventilated >12h	89 intervention, 91 controls.	MMSE, Digit Span, Digit Symbol Coding, RAVLT, ROCF, Trails A and B, Verbal Fluency	If (1) scored 1.5 SDs or more below the mean on two or more of the nine cognitive tests, or (2) scored 2 or more SDs below the mean on one or more of the nine cognitive tests.	3 mos post 12 mos post	RCT
Jackson, 2012 (24)	USA	Pilot RCT	MICU + SICU	Subset of patients from RETURN RCT. Previously living independently.	12 intervention, 8 controls.	Screened with TOWER test for cognition at discharge 3 mos: TOWER, MMSE, Dysexecutive Questionnaire	No cutoff defined	At hospital discharge 3 mos post	RCT
Jones, 2006 (25)	UK	Prospective cohort	ICU	ICU stay > 6 days), ventilated > 48h	30 within ICU. 30 one week post-discharge. 16 two months post-discharge.	CANTAB “Stocking of Cambridge”, CANTAB pattern recognition recall	≤25th percentile compared with age- and sex-matched controls.	Within ICU, 1 week post ICU d/c 2 mos post ICU d/c	Fair
Kapfhammer, 2004 (26)	Germany	Prospective longitudinal	ICU	ARDS	46	Syndrom Kurz test	Syndrom Kurz scores > 5 are “clinically significant”.	3-13 years f/u	Good
Ketterer, 2016 (27)	USA	Prospective longitudinal	ICU	Unselected ICU patients	107	Mini-Cog	Impairment on any of the tasks (results only for those who were alert & oriented).	Within ICU	Good
Larson, 2007 (28)	USA	Prospective cohort	ICU	Sample from RCT of high vs. low tidal volume in ARDS.	70	WAIS-R	2 or more test scores > 1.5 SD or 1 test score > 2SD below norms for age, gender, education corrected t scores.	At hospital discharge 1 yr post 2 yrs post	Good

Maley, 2016 (29)	USA	Cross-sectional	2 MICUs	Length of stay > 2 days	43	Health Utilities Index-3 (HUI-3) cognitive questions	Survivor reporting being “somewhat forgetful” or worst or having more than “a little difficulty” in ability to think and solve day-to-day problems.	6-12 mos post hospital discharge (median 8 mos)	Poor
Mikkelsen, 2009 (30)	USA	Cross-sectional	ARDS survivor website respondents	ARDS	79	Telephone interview administered tests: NCSE: Orientation, WAIS III: Digit Span, WAIS III: Letter-Number Sequencing, WAIS-III: Logical Memory I, WAIS III: Similarities, NCSE: Judgement, Hayling Sentence Completion Test, COWAT	CI on each test = > 1 SD below norms. CI = score of > 1 SD below norms on 2 or more tests or > 1.5 SD below norms on 1 test.	Mean no. of mos since ARDS onset 27.6 (SD 35.2)	Poor
Mikkelsen, 2012 (31)	USA	Prospective cohort	ICU (ACOS and FACTT study patients)	ARDS. Sample from FACTT and EA-PAC studies	102 at 12 mos (75 for risk factor analysis)	Telephone neuropsych battery	Impairment on a domain = > 2SD below norms. CI = impairment in memory, verbal fluency, or executive function in those who completed tests in each of these domains.	2 mos post 12 mos post	Good
Needham, 2013 (32)	USA	Prospective longitudinal follow-up	ICUs	Acute lung injury. Sample from EDEN study	514 at 6 mos. 487 at 12 mos.	MMSE telephone version	Telephone MMSE score ≤24.	6 mos post 12 mos post	Good
Needham, 2016 (33)	USA	RCT	35 ICUs	Sepsis-associated ARDS	130 at 6 mos. 149 at 12 mos.	Hayling Sentence Completion Test, Controlled Oral Word Association (COWA), WMS-III Logical Memory I and Logical Memory II, WAIS-III Similarities, WAIS-III Digit Span	Having either one cognitive test within the battery with a score at least 2 SDs below population norms (i.e., bottom 2.5%) or at least two tests with a score equal to or greater than 1.5 SDs below norms (i.e., bottom 6.7% for both tests).	6 mos post 12 mos post	RCT
Pandharipande, 2013 (34)	USA	Prospective cohort	MICU + SICU	Respiratory failure, cardiogenic shock or septic shock	821 in-hospital. 467 at follow-up.	RBANS, Trails B	RBANS scores “similar to TBI”.	3 mos post 12 mos post	Good

Pfoh, 2015 (35)	USA	Cross-sectional secondary analysis of two prospective cohort studies	ICU	ARDS Sample from ARDSNet long-term outcome study (ALTOS) and ABC study	242	ALTOS group: Telephone MMSE + neuropsych battery (Neurobehavioral Cognitive Status Examination orientation score, WAIS-III Digit Span, WAIS-III Logical Memory I and II, Verbal Fluency Test) ABC group: In-person MMSE + neuropsych battery (Digit Span and Digit Symbol from WAIS-III, RAVLT, ROCF-Copy and Delayed Recall, Trails A and B, Verbal Fluency Test)	CI = MMSE < 24 or < 27 (only the former reported). CI on neuropsych testing = 1+ test \geq 2 SDs below norms or 2+ tests \geq 1.5 SD below norms.	ALTOS group: 6 mos + 12 mos ABC group: at hospital discharge + 3 mos + 12 mos	Good
Rothenhausler, 2001 (36)	Germany	Prospective cohort with longitudinal follow-up	ICU	ARDS	46	SKT	CI= score >8. Sub-threshold cognitive disorder= score of 5 to 8. No cognitive deficits= score of 0 to 4.	Median 6 years post	Poor
Sacanella, 2011 (37)	Spain	Prospective cohort	ICU	> 65 years of age who survived a medical ICU admission > 12 months. Previously autonomous.	112	MMSE, IQCODE	MMSE < 24.	Discharge, 12 mos	Good
Sakuramoto, 2015 (38)	Japan	Prospective cohort	ICU	Medical and surgical ICU patients	79	MMSE	MMSE < 24	Discharge	Good
Semmler, 2013 (39)	Germany	Prospective cohort	ICU	ICU patients	44	NeuroCogFx Trials A Trials B	Impaired when compared the pre-morbid verbal ability	6-24 mos post-ICU discharge	Good
Sukantarat, 2005 (40)	UK	Prospective cohort	MSICU	Survived \geq 72 hrs	51	Hayling Sentence Completion Test, Modified Six Element Test, Raven's Standard Progressive Matrices	Impaired on at least one test (below 5th percentile).	3 mos 9 mos	Fair

Timmers, 2011 (41)	Netherlands	Prospective cohort	SICU	Surgical ICU patients	575	EQ-6D Cognitive Functioning question	Number reporting problem in cognitive dimension.	Minimum 6 years Mean 8.4 (SD 1.4), range 6-11 years	Poor
Torgersen, 2011 (42)	Norway	Prospective cohort	Primarily SICU	Length of stay ≥ 24 h and MMSE ≥ 24 .	55 included. 28 completed full battery.	CANTAB	Z-score below -2.0 standard deviations (SDs) on two or below -1.5 SDs on three out of 10 results reported from standardized neuropsychological testing.	Within 14d of ICU discharge (in hospital) 3 mos post 12 mos post	Good
van der Schaaf, 2008 (43)	Netherlands	Prospective cohort	Mixed ICU	Consecutively admitted patients with MV > 48h	69	MMSE	MMSE <24.	3-7 days after hospital discharge	Good
Viana, 2017 (44)	Brazil	Prospective cohort	2 ICUs	COPD with respiratory failure	20 completed final visit.	MMSE	No defined cutoff	First week post ICU discharge, 1 mo post 3 mos post	Poor
Woon, 2012 (45)	USA	Prospective cohort	Shock, Trauma + Resp ICU	Ventilated > 48h, age 18-85.	70 enrolled. 53 completed follow-up.	MMSE, Mini-Cog, WRAT-3, WASI, Stroop Color-Word Test-Golden Version, Finger Tapping Test, COWAT, WMS-III Logical Memory subtest, California Verbal Learning Test-II, ROCF, WAIS-Revised Digit Symbol subtest, Trails A and B, Hayling Sentence Completion Test	Scores on two or more cognitive tests >1.5 SD or one test score that was >2 SD below the normative population mean.	At hospital discharge 6 mos post	Poor
Zhao, 2017 (46)	China	RCT	PACU, Neuro ICU + MICU	Unselected ICU patients	167 intervention, 165 control	MoCA, Author developed questionnaire	MOCA <26, questionnaire score 0 to 1.	72 hrs post ICU discharge 3 mos post	RCT

Supplemental Digital Content 3. Risk of bias assessments for randomized controlled trials using the Cochrane Risk of Bias tool.

	Random Sequence Generation	Allocation Concealment	Blinding [participants & personnel]	Blinding [outcome assessors]	Attrition Bias [Incomplete Outcome Data]	Selective Outcome Reporting
Brummel, 2017 (5)	Low	Low	High	Low	High	Low
Jackson, 2010 (23)	Low	Low	Low	Low	High	Low
Jackson, 2012 (24)	Low	Low	Low	Low	Low	Low
Needham, 2016 (33)	Low	Low	Low	Low	Low	High
Zhao, 2017 (46)	Low	Low	Unknown	Unknown	Low	Low

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