Australian Critical Care xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc

Review Paper

Post-sepsis cognitive impairment and associated risk factors: A systematic review

Allan J.C. Calsavara [a,b,*]
Vandack Nobre [b]
Tatiana Barichello [c,d]
Antonio L. Teixeira [b,d]

[a] School of Medicine, Universidade Federal de Ouro Preto, Ouro Preto, MG, Brazil
[b] Postgraduate Program in Health Sciences: Infectology and Tropical Medicine, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
[c] Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil
[d] Translational Psychiatry Program, Department of Psychiatry and Behavioral Sciences, Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

ARTICLE INFORMATION

Article history:
Received 13 July 2016
Received in revised form 10 May 2017
Accepted 4 June 2017

Keywords:
Cognition
Neuropsychological tests
Sepsis
Sepsis-associated encephalopathy

ABSTRACT

Introduction: Post-sepsis cognitive impairment is one of the major sequelae observed in survivors of sepsis. This cognitive impairment can be global or may affect specific domains. A better understanding of these deficits and associated risk factors could influence the care of patients with sepsis.
Objective: To perform a systematic review to investigate the presence of cognitive impairment and its associated risk factors among patients who survived sepsis.
Methods: The search was conducted in MEDLINE (1966 to March 2017) and EMBASE (1988 to March 2017). We included studies with individuals who were 18 years or older with post-sepsis cognitive impairment.
Results: We analysed 577 articles. Sixteen studies met the inclusion criteria. More than 74,000,000 patients were evaluated in the selected studies. Significant variation was observed in the definition of sepsis and cognitive impairment. Twelve studies used ACCP/SCCM criteria for sepsis, while cognitive impairment was defined per test used. Post-sepsis cognitive impairment was observed in 12.5 to 21% of survivors of sepsis. Attention, cognitive flexibility, processing speed, associative learning, visual perception, work memory, verbal memory, and semantic memory were the specific domains affected. Depressive symptoms, central nervous system infection, length of hospitalisation due to infection, and temporal proximity to the last period of infection were associated with cognitive impairment.
Conclusion: The studies are heterogeneous, and there is urgent need for a common language, including definitions and neuropsychological tests, for the investigation of post-sepsis cognitive impairment. Despite this, there is mounting evidence for the clinical relevance of post-sepsis cognitive impairment.
Systematic review registration: PROSPERO CRD42017054583 (www.crd.york.ac.uk/PROSPERO).

1. Introduction

Sepsis is a systemic inflammatory response of the host to a pathogenic microorganism. Sepsis is a major health problem, with data demonstrating an increase in incidence rate[1–4] and mortality in certain groups.[5] A recent global study showed that one third of patients with sepsis die before leaving the hospital.[6] Furthermore, according to the Global Sepsis Alliance, at least 20% of survivors of sepsis have some form of sequelae,[7] such as physical or cognitive impairment, mood disorders, and poor quality of life.[8]

Cognitive dysfunction in patients who survive sepsis can be characterized by new deficits (or exacerbations of preexisting mild deficits) in global cognition or executive function.[9] Septic associated encephalopathy (SAE) may be defined as a cognitive dysfunction associated with sepsis, without the presence of infection, in the central nervous system (CNS) or structural brain injury after excluding metabolic causes. SAE may be acute, subacute, or chronic. SAE manifested only during the course of the disease with improvement after its control can be classified as acute.[10] Symptoms that

* Corresponding author. Permanent address: Escola de Medicina, Universidade Federal de Ouro Preto, Campus Morro do Cruzeiro, Ouro Preto, MG CEP 35400-000, Brazil. Fax: +55 3135591001.
E-mail address: allancalsavara@medicina.ufop.br (A.J.C. Calsavara).

http://dx.doi.org/10.1016/j.aucc.2017.06.001
1036-7314/

last weeks to months can be considered subacute, while symptoms that persist over a year are categorized as chronic. Subacute and chronic deficits elicit substantial interest as affected individuals may require rehabilitation or home care.

Recently, there has been a progressive increase of studies evaluating cognitive changes associated with sepsis. Due to the potential negative impact of such amendments, there is great interest from the scientific community, health managers, and patients' families on the subject. Conducting a systematic review on the topic could summarize the studies carried out so far, provide the reader with the best available evidence, and indicate the gaps that still exist. We conducted a systematic review to determine cognitive impairment and its associated risk factors among patients who survived sepsis.

2. Methods

2.1. Types of participants

Individuals who were 18 years or older with post-sepsis cognitive impairment were included in this study. Post-sepsis refers to any time after the diagnosis of sepsis. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[11] Patients with human immunodeficiency virus (HIV) infection were excluded as immunosuppression and use of antiretroviral drugs could have influenced the course of sepsis and cognition of these individuals.[12,13] Individuals under 18 were also excluded due to neurodevelopmental features that must be taken into consideration when studying children and adolescents.

2.2. Study selection criteria

Publications selected for review were case-control, cohort, and clinical trials studies written in English, Spanish, or Portuguese. To be included, studies needed to have assessed the association between cognitive dysfunction and sepsis and/or at least one potential risk factor for the occurrence of SAE. There was no restriction regarding date of publication and time of follow-up of each study.

Studies that reported subjective measures of cognitive outcome, such as the opinions of the staff regarding the cognitive state of patients were excluded. Single case reports, unpublished studies, scientific meeting abstracts, review studies, comments and letters to the editor were excluded.

2.3. Outcome measures

The primary outcome measure for this review was the cognitive performance of post-sepsis individuals as measured by cognitive tests, scales, or batteries such as, but not limited to, the Wechsler Adult Intelligence Scale, Boston Naming Test, Wechsler Memory Scale, Trail Making Test (TMT), Informant Questionnaire on Cognitive Decline in the Elderly, and Mini-Mental State Examination.

2.4. Search strategy

The search was conducted in the databases MEDLINE (1966–present) and EMBASE (1988–present) (see Appendix A, Supplementary data). The search was first conducted on May 10th, 2015, and was updated on October 17th, 2015, and on March 20th, 2017. The information that could not be extracted by reading the articles was requested by e-mail from the corresponding author.

2.5. Study selection

Two investigators independently reviewed the search results to identify relevant studies. Disagreements were resolved by consensus, and if necessary a third investigator was consulted. First, studies were excluded based on the title; titles that were not related to the subject sepsis or cognition were excluded. In the next stage, studies were evaluated by reading the abstracts; studies that did not examine cognition in the context of sepsis were excluded. After reading the abstracts, selected studies were thoroughly read; at this last stage, studies that met all the eligibility criteria described above were included in the review. The Newcastle-Ottawa form assigns a maximum of four points for selection, two points for comparability and three points for exposure or outcome. In the current study, we considered a study awarded seven or more points as a high-quality study.[14]

2.6. Data extraction process and literature quality assessment

We developed a data extraction table based on the Cochrane template.[15] One investigator (A.J.C.C) extracted the data and a second (A.L.T.) verified the extracted data. In addition, two investigators (A.J.C.C. and A.L.T.) independently cross-checked the risk of bias using the Newcastle-Ottawa Scale for observational studies. Any disagreement between investigators was resolved by consensus, and if necessary a third investigator (V.N.) was consulted.

2.7. Data items

The following information was taken from each selected study: (1) country where the study was conducted, (2) type of study, (3) follow-up period, (4) sample size, (5) characteristics of the study population (mean age, sex, eligibility criteria, classifications used, and data collection location), (6) primary and secondary outcome, (7) cognitive outcome evaluated, and (8) main results of the study. Other data such as (1) the definition of sepsis used, (2) definition of cognitive impairment used, (3) cognitive impairment associated with sepsis found, and (4) risk factors associated with post-sepsis cognitive impairment were also extracted.

In general, studies that have not incorporated multivariate techniques to identify risk factors have little value. For the purposes of this synthesis, only variables for which at least one study reported either a risk ratio (RR) or odds ratio (OR) (regardless of statistical significance reported) or a statistically significant association (regardless of the OR/RR reported) were considered.

3. Results

3.1. Description of studies

The search results are presented in Fig. 1. Five hundred seventy-seven potentially relevant articles were identified. After exclusion of 57 duplicate studies, by judging the title and abstract, 490 articles were excluded, as they did not meet the inclusion criteria. Thirty articles were retained for in-depth inspection. Sixteen articles were retained for this systematic review. There was 100% agreement between reviewers in the selection of articles that met the inclusion criteria of the study.

3.2. Characteristics of included studies

The sixteen selected studies comprised six prospective cohort with control group,[8,16–20] six prospective cohort without control group,[21–26] three retrospective cohort without control group,[27–29] and one case-control study.[30] No clinical trials met the inclusion criteria.

The sixteen studies included 74,313,495 patients in total, with the majority of patients from Iwashyna et al.,[27] while the remaining studies contributed with 193,907 patients. The average age of the subjects included in the studies showed wide variation in range from 19[29] to 81 years.[22] In most studies the mean age of patients was over 60 years[8,18,21–28] (Table 1).

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

Table 1
Characteristics of studies included.

Reference (country)	Type of study	Follow-up period	Sample size	Study population	Measurements
Götz et al.[20] (Germany)	Prospective cohort study with control group	Severe sepsis or septic shock: until 10–15 months after ICU discharge Cirrhosis: not followed up Healthy: until 12 months after hospital discharge	Severe sepsis or septic Shock: 36 Cirrhosis: 24 Healthy: 23	Patients survived severe sepsis or septic shock, patients with cirrhosis and healthy individuals discharged from a University Hospital. Mean age: severe sepsis or septic shock: 58.9 ± 2, cirrhosis: 55.4 ± 6, healthy: 58 ± 2. The authors did not indicate the mean educational level.	Visual evoked responses using a set of familiar vs. unfamiliar pictures measured with magnetoencephalography.
Pierrakos et al.[26] (Belgium)	Prospective cohort study	1 year	28 patients with sepsis, 14 with cognitive decline (CD) and 14 without CD	Consecutive patients with sepsis discharged from the ICU between January 2013 and January 2014. Mean age: CD: 69 ± 15, No-CD: 65 ± 16. Did not provide data on educational level.	Pulsatility index and cerebral blood flow index measure by transcranial Doppler in patients with CD and without-CD.
Götz et al.[19] (Germany)	Prospective cohort study with control group	Severe sepsis or septic shock: until 10–15 months after ICU discharge Healthy: until 12 months after hospital discharge	Severe sepsis or septic Shock: 36 Healthy: 30	Patients that had survived severe sepsis or septic shock, and healthy individuals discharged from a University Hospital. Mean age: severe sepsis or septic shock: 58.9 ± 2, healthy: 50.9 ± 3. The authors did not indicate the mean educational level.	Peak resting activity (frequency and power) measured by magnetoencephalography.
Azabou et al.[25] (France)	Prospective cohort study	Until day 28 of hospitalisation or until ICU discharge	110 patients with sepsis included (45 septic shock, 37 severe sepsis and 28 sepsis)	Patients admitted to the ICU for sepsis between November 2011 and April 2014. Mean age was 63.8 years. The authors did not indicate the mean educational level.	ICU mortality and relationship between EEG abnormalities and occurrence of delirium.
Benros et al.[29] (Denmark)	Retrospective cohort	From birth to age 19	161,696 individuals	Cognitive ability data from Danish Conscription Registry of men over 18, born in Denmark between 1976 and 1994. Mean age of patients was 19.4 years. Mean educational level was not provided.	Cognitive performance using the Danish Conscription Registry database.
Pierrakos et al.[24] (Belgium)	Prospective cohort study	4 months	38 patients	Patients diagnosed with sepsis within 24-h from onset. Mean age of patients with pulsatility index (PI) <1.29 was 62 years and PI >1.3 was 72 years. Data on educational level was not provided.	Pulsatility Index measured with transcranial Doppler in patients with and without SAE.
Lahariya et al.[18] (India)	Prospective cohort study with control group	Until occurrence of delirium or ICU discharge	309 patients (81 with delirium and 228 without delirium)	Patients admitted to the cardiology ICU between May and June 2010 who had delirium during hospitalisation. Mean age in the group with delirium was 61.69 and 77.01 in the group without delirium. Mean educational level in the group with delirium was 7.87 years and in the group without delirium 9.7 years.	Incidence and prevalence of delirium in the population studied, risk factors, and mortality associated with delirium.
Merli et al.[16] (Italy)	Prospective cohort study with control group	Three months after discharge for cirrhotic patients and controls with cognitive changes during the infectious condition	231 (150 patients with cirrhosis and 81 patients without liver disease)	Patients with cirrhosis hospitalized between October 2008 and June 2009 (mean age 63.4 years) and patients without cirrhosis, between January 2010 and December 2010 (mean age 58 years). Each group was divided into 3 subgroups: without sepsis or infection, with infection without systemic inflammatory response syndrome, and with sepsis. The mean educational level was not indicated by the authors.	Measurement of psychometric parameters.
Semmler et al.[17] (Germany)	Prospective cohort study in two centers with control group	From 6 to 24 months after ICU discharge	44 patients (25 with sepsis/severe sepsis and 19 without sepsis)	Patients admitted to the ICU between January 2004 and August 2006 with sepsis or severe sepsis. Mean age of patients with sepsis: 55.64 years and non-septic: 52.15 years. Data on educational level were not provided.	Cognitive performance, magnetic resonance imaging of the brain, EEG, psychiatric health, and quality of life evaluated between 6–24 months after discharge from the ICU.

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

Table 1 (*Continued*)

Reference (country)	Type of study	Follow-up period	Sample size	Study population	Measurements
Iwashyna et al.[27] (USA)	Retrospective cohort study without control group	From 1996 to 2008	34,782,442 and 39,337,348 Medicare beneficiaries in 1996 and 2008, respectively	Beneficiaries of health insurance older than 65 years that generated service payment tax between 1996 and 2008. The average age in the studied population in 1996 was 73 years, with 59% women and in 2008 the average age was 73 years, with 57% women. Data on educational level were not provided.	Three years' survival rate after admission for severe sepsis, evaluation of functional status by combined score for activities of daily living (ADL) and instrumental activities of daily living (IADL), and degree of cognitive impairment.
Guerra et al.[28] (USA)	Retrospective cohort study without control group	3 years (2006– 2008)	25,368 individuals	Cohort of 5% of all Medicare beneficiaries older than 65 years, who were admitted to the ICU and survived to hospital discharge, with no prior cognitive impairment or history of cardiac surgery. Mean age 76.6 years. Data on educational level were not provided.	Dementia presence.
Davydow et al.[21] (USA)	Prospective cohort study	Until 2006 or death, whichever occurred first	447 individuals	Participants in the Health and Retirement Study (HRS) with at least one evaluation between 1998 and 2004 without cognitive impairment, and who were registered for severe sepsis hospitalization in the Medicare database between 1998 and 2005, and had at least one evaluation for depression after sepsis. Mean age: 76.1 years. 38.5% of patients to complete high school, 34.8% with incomplete higher education and 26.7% with college education.	Classification into mild or moderate to severe cognitive impairment.
Arinzon et al.[23] (Israel)	Prospective cohort study	To full or partial recovery from delirium, unchanged delirium, or death	92 patients	Patients aged 65 or more admitted to a geriatric medical center between January 2000 and December 2002 for a week or longer, who had delirium. Average age of 79.86 years Data on educational level were not provided.	Risk factors associated with delirium, delirium duration, and mortality rate.
Iwashyna et al.[8] (USA)	Prospective cohort study with control group	Until 2006 or death, whichever occurred first	5033 patients (516 surviving respondents with sepsis and 4517 surviving respondents without sepsis)	Data from patients aged over 50 years from the Medicare database with baseline cognitive assessment between 1998–2004 and subsequent hospitalization due to severe sepsis; or patients without sepsis between 1998–2003 that survived to conduct one follow-up visit. Patients surviving sepsis: mean age 76.9 years. 19% of patients with severe cognitive impairment, 20% with mild to moderate and 30% without cognitive impairment had completed higher education.	Measurement of functional status (combined score of ADLs and IADL) and degree of cognitive impairment.
Lazosky et al.[30] (Canada)	Case-control study	1–4 years	23 (8 with sepsis and 15 with acute myocardial infarction – AMI), On retired subgroup evaluated: 5 septic and 8 AMI	Patients with sepsis or acute myocardial infarction (AMI) (matched by age) from one to four years prior to selection and who answered the administered questionnaire. Average age: 49.6 years in the septic group and 58.5 years in the AMI group. The mean educational level in the septic group was 12.6 years and 13 years in the AMI group.	Health status of survivors of sepsis and number of new neuropsychological issues (problem solving, language, speech, math skills, nonverbal skills, concentration and awareness, memory, motor and coordination, sensory, physical and behavioural).
Regazzoni et al.[22] (Argentina)	Prospective cohort study	1 year	116 patients	Patients from both genders over 69 years admitted between September 2002 and August 2003. Mean age: 80.81 years. Data on educational level were not provided.	In-hospital and 1-year mortality.

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

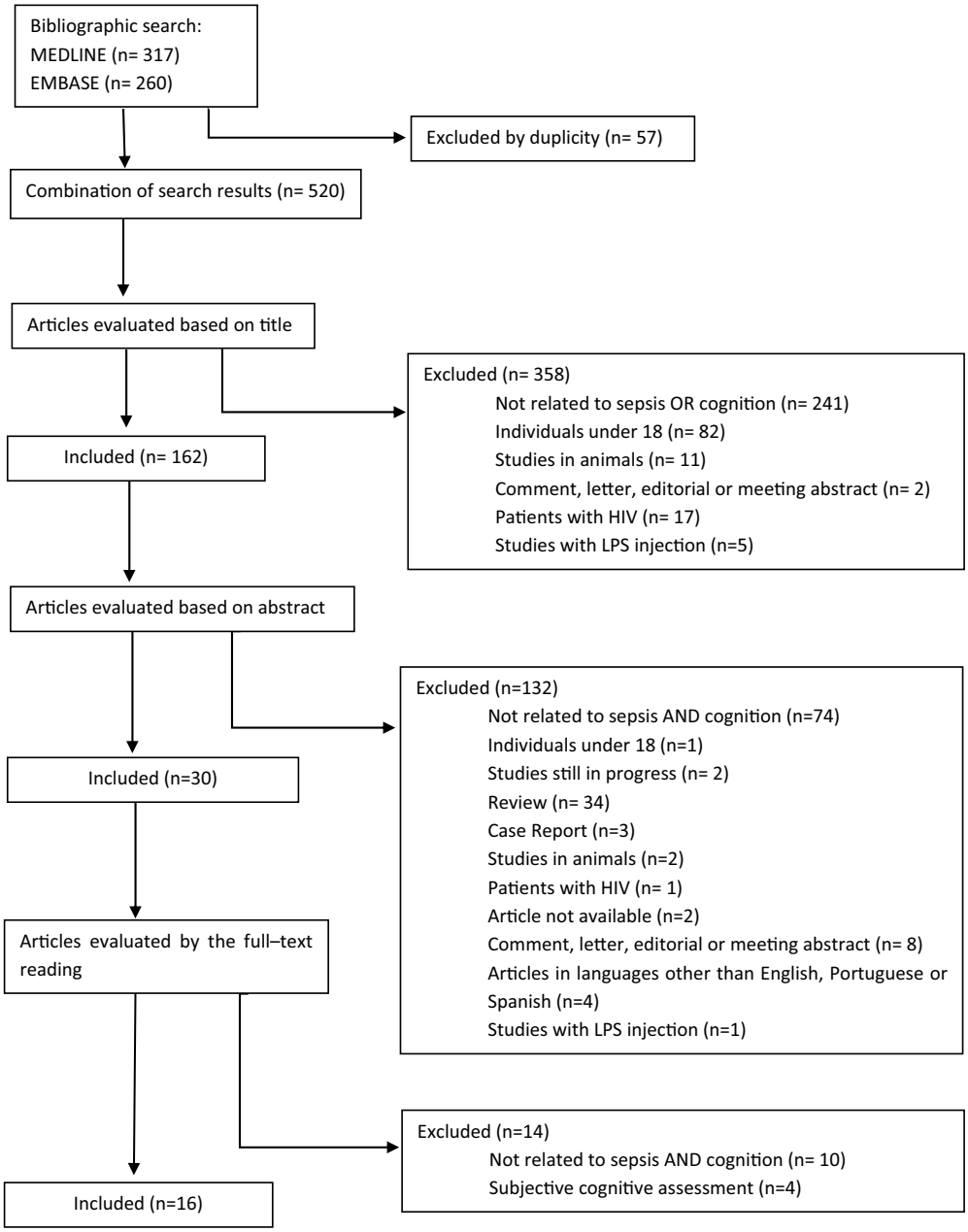

Fig. 1. Searching results.

While considering formal education data, only four studies indicated the average level of education of patients.[8,18,21,30] Two studies indicated the average schooling of their patients as 7.9[18] and 12.6 years.[30] The others referred to the patients' education level by categorizing them into having graduated or not from Secondary education and having graduated or not from Higher education[8,21] (Table 1).

The quality of the studies was assessed with the Newcastle-Ottawa Score and the results are presented in Tables 2 and 3. Four studies were classified as high quality.[8,17,21,29] The mean value for the sixteen studies assessed was 5.3 indicating a low overall quality.

3.3. Definition of sepsis, severe sepsis, and septic shock

There was variation in the definition of sepsis, severe sepsis, and septic shock among the selected studies. The majority of studies used as reference the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM).[8,16,17,19–22,24,25,27,28,30] Others used the International Statistical Classification of Diseases (ICD-8 and/or ICD-10).[29,31]

No reference was made to the definition of sepsis by Lahariya et al.[18], Arinzon et al.[23] and Pierrakos et al.[26]

3.4. Definition of cognitive impairment patients

The definition of cognitive impairment patients showed great variation among the selected studies (Table 4). Iwashyna et al.[8,27] and Davydow et al.[21] used the "Telephone Interview for Cognitive Status (TICS)" test to categorize patients into mild to moderate or severe cognitive impairment, the cutoff points used were based on previous studies.[32] Other studies used the Informant Questionnaire on Cognitive Scale Decline in the Elderly (IQCODE) with predefined cutoffs to classify patients into moderate to severe cognitive impairment[27] or suspected dementia.[18]

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

Table 2
Newcastle-Ottawa quality assessment scale for cohort studies included in this review.

First author	Year	Selection[a]				Comparability[b]	Outcome[a]			Overall quality score[c]
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study		Assessment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up	
Götz[20]	2017	⋆	0	⋆	0	⋆⋆	⋆	⋆	0	6
Götz[19]	2016	⋆	0	⋆	0	⋆⋆	⋆	⋆	0	6
Pierrakos[26]	2016	⋆	⋆	⋆	0	⋆	⋆	0	0	5
Azabou[25]	2015	⋆	0	⋆	0	0	⋆	⋆	0	4
Benros[29]	2015	⋆	⋆	⋆	0	⋆	⋆	⋆	⋆	7
Pierrakos[24]	2014	⋆	0	⋆	0	⋆	⋆	0	0	4
Lahariya[18]	2014	⋆	⋆	0	0	0	⋆	0	⋆	4
Merli[16]	2013	⋆	⋆	⋆	0	0	⋆	⋆	0	5
Semmler[17]	2013	⋆	⋆	⋆	0	⋆⋆	⋆	⋆	⋆	8
Iwashyna[27]	2012	⋆	0	⋆	0	0	⋆	0	0	3
Guerra[28]	2012	⋆	0	⋆	⋆	0	⋆	⋆	⋆	6
Davydow[21]	2012	⋆	0	⋆	⋆	⋆⋆	⋆	⋆	0	7
Arinzon[23]	2011	⋆	0	0	0	0	⋆	0	0	2
Iwashyna[8]	2010	⋆	⋆	⋆	0	⋆⋆	⋆	⋆	0	7
Regazzoni[22]	2008	⋆	0	⋆	⋆	⋆	⋆	⋆	0	6
									Mean	5.3

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories.
[b] A maximum of two stars can be given for Comparability.
[c] Maximum of 9 points.

Table 3
Newcastle-Ottawa quality assessment scale for case control studies included in this review.

First author	Year	Selection[a]				Comparability[b]	Exposure[a]			Overall quality score[c]
		Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Lazosky[30]	2010	⋆	0	0	⋆	⋆	⋆	⋆	0	5

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories.
[b] A maximum of two stars can be given for Comparability.
[c] Maximum of 9 points.

A diagnosis of cognitive impairment was made by Merli et al.[16] with the Trail Making Test A, B or a Digit-Symbol Test Z-score[33] greater than two standard deviations from the mean of a healthy Italian population, adjusted for age and education.[34]

Semmler et al.[17] calculated a composite Z-score for cognition using the NeuroCogFX, Trail-making Tests A and B and Multiple Choice Word Test-B. The score considered the results of applied cognitive tests after sepsis (NeuroCogFX and Trail-making Tests A and B), and Multiple Choice Word Test-B German vocabulary test, which aim is to quantify the patients' premorbid cognitive status. A Z-score between −1.5 and −2.0 was considered denoting mild cognitive impairment.

Other strategies to define cognitive impairment were the use of the "Confusion Assessment Method in the Intensive Care Unit" (CAM-ICU),[18,23–26] an MMSE score less than 24,[26] Glasgow Coma Score <8 despite resolution of sepsis after exclusion of any underlining pathology that could explain this state,[26] abnormal Clock Drawing Test,[26] or searching predetermined International Classification of Diseases (ICD-9-CM) codes[35] in databases.[28]

Although most studies did not state this, all tools described in this section to assess cognitive impairment had been previously validated.[36–45] The neurocognitive outcomes reported by each author were assessed and are presented in Table 5.

Some studies did not explain their categorization methods or cutoff points used to define cognitive impairment.[19,20,22,29,30]

3.5. Post-sepsis global cognitive impairment

Analysing the selected studies in this review, we found that Iwashyna et al.[27] showed moderate to severe cognitive impairment after 3 years in 16.7% (95% CI: 12.3, 21.0%) of patients who survived sepsis. The same author had found an odds ratio (OR) of 3.34 for moderate to severe cognitive impairment after sepsis in a study published two years earlier.[8] In a study by Davydow et al.,[21] cognitive impairment ranged from 14 to 20%, with 60% of individuals being classified as moderately to severely impaired. It was also shown by Benros et al.[29] that hospital contact due to any infectious condition worsened global cognitive performance, assessed by a Danish Intelligence Test by 76% (95% confidence interval, 61–92%), sepsis was associated with a mean score of 1.60-units lower cognitive ability.

3.6. Post-sepsis specific cognitive domains impairment

Some studies have reported cognitive changes in specific domains. Visual search, perceptual/motor speed, speed of processing, working memory, and general intelligence are among the most frequently cited constructs thought to contribute to Trail Making Test performance.[41] Merli et al.[16] showed that median Z-scores for Trail Making Test-A were significantly lower in patients with sepsis when compared to patients without infection. Associative learning,

Table 4
Definitions, changes, and risk factors associated with post-sepsis cognitive impairment.

Reference	Definition of cognitive impairment	Cognitive impairment associated with sepsis found	Risk factors associated with cognitive impairment
Götz et al.[20]	The cutoff points for the DemTect and Clock Drawing Test (CDT) were not specified.	Not assessed	Impaired response to periodic visual stimulation was associated with DemTect and CDT sum scores in patients with sepsis. Non-affecting factors: APACHE II, CRP, length of stay in the ICU, and months after ICU discharge.
Pierrakos et al.[26]	Persistent coma (Glasgow Coma Score <8), despite resolution of sepsis and after exclusion of any underlying pathology that could explain this state, positive CAM-ICU on discharge, MMSE <24, abnormal Clock Drawing Test.	Not assessed	Univariate analysis: delirium and pulsatility index on first day were associated with cognitive decline (CD). Multivariate analysis: only delirium was associated with CD.
Götz et al.[19]	The cutoff points for DemTect and CDT were not specified.	Not assessed	Within sepsis group peak resting frequency increase with time after ICU discharge and with DemTect and CDT sum score and decrease with age. Non-affecting factors APACHE II, CRP, and length of stay in the ICU.
Azabou et al.[25]	Delirium was defined by the CAM-ICU and coma was defined in non-sedated patients by GCS ≤8 and in sedated patients by RASS ≤4.	Not assessed	Delirium in septic patients was associated with SAPS-II score, septic shock, and delta frequency dominant, Synek grade ≥3 and Young grade ≥1 in early EEG.
Benros et al.[29]	No cut off point was given for the test applied.	Infection was associated with poor overall cognitive performance assessed by the Børge Priens test. (OR: −1.76, 95% CI: −1.92, −1.61).	Central nervous system infection was associated with greater decline in cognitive ability. Other associated factors: number of visits to hospital due to infection, temporal proximity to the last infection, length of stay, and family history of infection. Non-affecting factors: age, history of psychiatric disorders or substance abuse, history of cancer, and normal weight at birth.
Pierrakos et al.[24]	CAM-ICU for delirium.	Not assessed	No association was found between age or APACHE II with positive CAM-ICU.
Lahariya et al.[18]	CAM-ICU for delirium. IQCODE score greater than 3.31–3.38 as an indication of suspected dementia.	Sepsis was associated with the development of delirium as diagnosed with the CAM-ICU.	Patients with cognitive impairment measured by the IQCODE showed increased risk of developing delirium. Other risk factors associated with the development of delirium: hypokalemia, SOFA scores, using >3 drugs, cardiogenic shock, history of coronary artery bypass grafting, ejection fraction <30, use of opioids, age >65 years, diabetes, a history of seizures, congestive heart failure, percutaneous transluminal coronary angioplasty, atrial fibrillation, current depression, use of benzodiazepines, warfarin, ranitidine, steroids, or NSAIDs, polypharmacy, increased creatinine, anemia, hypoglycemia, APACHE II, and the Comorbidity Index of Charlson.
Merli et al.[16]	Z-score >2 SD of healthy Italian population, adjusted for age and education.	Patients with cirrhosis and sepsis showed changes in the Trail-Making Tests A and B and Digit-Symbol Test. Patients without cirrhosis with sepsis had poorer performance on the Track Tests and Digit Symbol than the group without infection (39% of septic individuals had subclinical cognitive impairment damage, remaining unchanged).	In the cirrhotic subgroup, the MELD score, albumin, and creatinine were not found to be independent risk factors for cognitive impairment. Sepsis was the only risk factor found. Risk factors were not evaluated in the control group.
Semmler et al.[17]	Z-score compared to the historical norm. Composite score for cognition through the simple average of the NeuroCogFX and Trail Making Test A and B Z-scores, minus the estimated premorbid verbal ability by the Multiple Choices Word Test Z-score.	Patients with sepsis post-ICU hospitalization had poor performance on the Digit Span test, 2-Back Test, alertness, GoNoGo, verbal memory, and phonetic verbal fluency. Patients without sepsis post-ICU had low performance in the Digit Span test, 2-Back test, interference, and phonetic verbal fluency.	Cognitive deficits were not influenced by the length of stay in the ICU, time after ICU discharge, number of days on mechanical ventilation, APACHE II, and SOFA scores.
Iwashyna et al.[27]	The cutoff point for m-TICS was not specified. The cutoff point for IQCODE was 4.59–5.00, denoting moderate to severe cognitive impairment, according to the authors.	Hospitalisation for severe sepsis was associated with a 3.34-fold increased risk of developing moderate to severe cognitive impairment.	Not assessed

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

Table 4 (*Continued*)

Reference	Definition of cognitive impairment	Cognitive impairment associated with sepsis found	Risk factors associated with cognitive impairment
Guerra et al.[28]	ICD-9-CM codes: 290.0–290.4, 294.0, 294.1, 294.8, 331.0, 331.1, 331.2, 331.7, and 797.X recorded from fee-for-service claims in the subsequent three years of follow-up.	Neuropsychological tests were not applied.	Risk factors associated with post-ICU dementia: a critical illness with infection, especially if severe sepsis, acute neurologic dysfunction during ICU stay, and use of renal replacement therapy (increased risk only 6 months after discharge), patients with hospitalisation due to clinical causes and patients with previous hospitalization. Not associated: mechanical ventilation, organ dysfunction, length of stay in the ICU and total hospital stay.
Davydow et al.[21]	Categorisation of cognitive function as mild, and moderate to severe using the m-TICS.	17% of patients with severe sepsis showed global cognitive impairment assessed by the TICS; most had moderate to severe deficits.	Pre-sepsis depressive symptoms were a risk factor for post-sepsis cognitive impairment.
Arinzon et al.[23]	CAM-ICU for diagnosis of delirium and Delirium Rating Scale (a score higher than 10–12 points indicated patients with delirium).	The increase in the duration of delirium was associated with the occurrence of sepsis.	Sepsis was associated with the duration of delirium and increased mortality in patients with delirium.
Iwashyna et al.[8]	The cutoff points for the m-TICS and IQCODE were not specified.	An OR of 3.34, 95% CI: 1.53–7.25 was found for moderate to severe cognitive impairment after-sepsis. No moderate to severe cognitive impairment was found after hospitalisation for reasons other than sepsis.	Not assessed
Lazosky et al.[30]	Number of new problems identified in the 'Adult Neuropsychological History form'.	There were no cognitive changes in the evaluated samples.	None
Regazzoni et al.[22]	There was no categorisation or cutoff point definition for the MMSE.	Global cognitive status evaluated with the MMSE did not predict in-hospital mortality after sepsis. In a univariate analysis, the MMSE predicted mortality after 1 year; however, in a COX model this effect was not maintained.	Not assessed (cognition as covariate)

Table 5
Reported neurocognitive outcomes by author.

Reference	EEG	MEG	CAM-ICU	GCS	MMSE	m-TICS	IQCODE	TMT	Digit-Symbol Test	Multiple Choice Word Test-B	Neuro-CogFx[a]	Auditory Verbal Learning Test	Rey Complex Figure Test	Børge Prien's Prøve[b]	Delirium Rating Scale	ICD	Adult Neuropsy-chological History form	DemTect[c]	Clock Drawing Test
Götz et al.[20]		√																√	√
Pierrakos et al.[26]	√		√		√	√													√
Götz et al.[19]		√																√	√
Azabou et al.[25]	√		√		√														
Benros et al.[29]														√					
Pierrakos et al.[24]			√																
Lahariya et al.[18]			√				√												
Merli et al.[16]					√			√	√										
Semmler et al.[17]	√									√	√	√	√						
Iwashyna et al.[27]						√	√												
Guerra et al.[28]																√			
Davydow et al.[21]						√													
Arinzon et al.[23]			√		√										√				
Iwashyna et al.[8]						√	√												
Lazosky et al.[30]																	√		
Regazzoni et al.[22]			√		√											√			

[a] NeuroCogFx (Digit Span, 2-back-test, alertness, go-no-go, interference, verbal memory, figural memory, phonetic verbal fluency).
[b] A Danish intelligence test.
[c] A screening instrument for dementia and mild cognitive impairments.

processing speed, visual perception, and working memory assessed by the Digit Symbol Test was also lower in patients with sepsis.[16]

Semmler et al.[17] found long term mild cognitive impairments in attention, verbal fluency, executive function, and verbal memory in survivors of sepsis when compared to their previously estimated intelligence level.

A long-term visual processing impairment in patients with sepsis post-infection was observed by Götz et al. with magnetoencephalographic measurements.[20]

3.7. Associations between sepsis and cognition

Most studies assessed the association between cognitive impairment and sepsis (Table 4).[8,16,17,21,27,29,30] Some studies showed that sepsis is a risk factor for worsening cognitive performance after ICU discharge[28] or demonstrated an association between sepsis and delirium, a clinical syndrome that encompasses several cognitive changes.[18,23–25]

The presence of pre-sepsis depressive symptoms was considered a risk factor for post-sepsis cognitive impairment.[21] Infection in the CNS, number of hospital visits due to infection, length of hospitalization due to infection, family history of infection, and temporal proximity to the latest episode of infection were identified as risk factors for cognitive impairment observed after infectious conditions.[29] Critical illness in the presence of infection, especially severe sepsis, was identified as one of the risk factors for the subsequent diagnosis of dementia within three years of hospital discharge.[28]

Sepsis was a risk factor for the development[18] and longer duration[23] of delirium. Moreover, Arinzon et al.[23] showed that a diagnosis of sepsis increased the mortality rate in patients with delirium.

Several risk factors were evaluated in the included studies, but many did not affect the outcome evaluated (Table 4). For instance, it was found that cognitive deficits related to sepsis were not influenced by the length of stay in the ICU, ICU discharge time, number of days on mechanical ventilation, APACHE II, and SOFA scores.[17] The patient's age, family history of psychiatric illness, and substance abuse similarly did not affect cognitive performance after infection.[29]

3.8. Workup on sepsis associated encephalopathy

The diagnosis of sepsis-associated cognitive dysfunction was additionally evaluated by the selected studies.[17,24,25]

An association between SAE and electroencephalography (EEG) parameters was observed; as the occurrence of cognitive impairment in the days after EEG recording was associated with previous EEG findings, such as delta frequency dominant EEG, absence of EEG reactivity, Synek grade $\geq$3 (an EEG classification with prognostic value for comatose patient that range from 0 to 5), and Young grade $\geq$1 (an ECG classification for septic encephalopathy that ranges from 0 to 4).[25]

The diagnosis of SAE with the pulsatility index, an indicator of cerebrovascular resistance, measured by transcranial Doppler was evaluated. A pulsatility index greater than 1.3 at 24-h post sepsis diagnosis correlated with SAE (OR: 5.66, 95% confidence interval: 1.1–29.11).[24] Although no correlation between cognitive dysfunction after sepsis and pulsatility index was found, when multivariate analysis was performed in another study by the same author.[26]

Magnetoencephalographic (MEG) techniques were used to study the long-term brain electrophysiology changes after sepsis. Combining MEG data with neuropsychological tests, suggested abnormal thalamocortical dynamics[19] and a disruption in neural networking, especially complex networking, in patients with long-term post-sepsis.[20]

Computerized volumetric techniques of magnetic resonance images showed significant differences in left and total hippocampal volumes between patients with sepsis and healthy controls. The hippocampal volume in patients without sepsis admitted in the ICU was between that of patients with sepsis and healthy controls. A correlation analysis between cognitive performance and hippocampal volume was not performed.[17]

4. Discussion

To the best of our knowledge, this is the first systematic review to identify and synthesize the best available evidence on post-sepsis cognitive impairment. The analysed studies showed that sepsis can worsen cognitive performance in the short, medium, and long terms. The available studies did not provide robust evidence to determine the risk factors that modulate the association between sepsis and cognitive impairment. Regarding the great heterogeneity in the definition of cognitive impairment and the use of several cognitive tests, the comparison among studies was impaired.

The use of batteries and tests evaluating global cognitive function was most frequently employed. This strategy is in line with the theory that sepsis causes wide brain function alterations. The cognitive test batteries Telephone Interview for Cognitive Status (m-TICS),[8,21,27] NeuroCogFx,[17] MMSE,[16,22,23,26] Clock Drawing Test,[26] Adult Neuropsychological History form,[30] BØrge-Priens test,[29] IQCODE,[8,18,27] and DemTect[19,20] were used for global cognitive assessment. Some tests as the Symbol-Digit test,[16] Trail Making Test A and B,[16,17] Rey Complex Figure Test[17] provided more specific information about cognitive domains. Only one study, by Semmler et al.,[17] showed changes in certain cognitive domains, such as attention, verbal fluency, executive function, and verbal memory. Semmler et al.[17] proposed that an asymmetric distribution of neurotransmitters in the human brain would lead to increased vulnerability of the left hemisphere to inflammatory insults.

In a cohort study performed with patients with critical illness by Pandharipande et al.[9] the cognitive sequelae ranged between 24 to 40% depending on the timing of cognitive evaluation. This study used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) that was not used in the studies included in this review. As shown, our analysis suggests that equally important to timing is the choice of testing means, for cognitive evaluation. To compare the incidence and prevalence of cognitive dysfunction between patients with sepsis and patients with other diseases it is necessary to achieve a consensus on the appropriated test to be used, beforehand.

Most of the evaluated studies were conducted with patients over the age of 60 years.[8,18,21–28] Despite sepsis increased incidence and mortality in the elderly compared to younger patients,[46] it is important to evaluate the impact of sepsis on young individuals who are still part of the workforce. Whereas cognitive reserve has been identified as a protective factor for cognitive impairment in several studies,[47–49] the possibility of young patients exhibiting less post sepsis deficits could be explained at least in part by their higher cognitive reserve.

Differences were observed in the criteria used to classify patients with sepsis. In some cases, they were classified by combinations of disease codes, and in others through the direct analysis of clinical history and laboratory data. Disagreements regarding diagnosis of sepsis depended on the purpose of the study. Studies that focus on sepsis diagnosis in individuals, usually have therapeutic and/or prognostic implications; therefore, these need to be more pragmatic and their diagnostic criteria should be easily applicable. In contrast, an epidemiological definition, often used in clinical trials, would need to be rigorous and robust.[5] In 2015, the Sepsis-3 guideline, a new clinical criteria for sepsis and septic shock was

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

developed, and, for the first time, the recommended primary ICD-9 and ICD-10 codes and a framework for implementation for coding and research in an attempt to facilitate research and increase accuracy of coding.[11]

The criteria used to classify individuals as presenting with cognitive impairment also differed among studies, even when using the same cognitive tests. The choice of cut-offs depends on the authors' choice between higher specificity and higher sensitivity. When the goal is to identify individuals with cognitive impairment, tests with greater sensitivity are preferred, but when the objective is to determine the exact nature of the patient's deficit, specific tests are preferable. A method to compare the performance of tests that measure different cognitive abilities is through standardized scores, such as the Z-score. Only two studies reported cognitive data through standardized scores,[16,17] their scarce use may be due to lack of good quality standardized data or even lack of sufficient data in the studied population, especially among ethnic minorities.[50]

We did not locate studies with a design that robustly assessed the risk factors associated with the development of post-sepsis cognitive impairment. Factors such as pre-sepsis depressive symptoms, infection in the CNS, length of stay, and temporal proximity to the latest episode of infection seem to be involved in cognitive impairment associated with sepsis. Studies with patients post-ICU hospitalization have suggested the influence of some factors on cognition, such as sedatives and analgesics,[51] antipsychotics,[52] antibiotics,[53] glycemic control,[54] corticosteroids,[55] and cognitive reserve.[56] The influence of these factors must be better investigated in future studies.

In a study published by Larson et al.,[56] cognitive reserve associated with the magnitude of cognitive impairment in patients with acute respiratory distress syndrome. In this systematic review, the issue was not explored. In the study of Semmler et al.,[17] although the author estimated cognitive reserve with neuropsychological testing, a correlational analysis between cognitive reserve and post-sepsis cognitive performance was not performed. Lahariya et al.[18] used the IQCODE score to evaluate the pre-morbidity cognitive reserve in a sample, finding that patients with low cognitive reserve (i.e. IQCODE > 3.3) had an odds ratio of 10.81 for delirium.

Our study had a number of limitations. The search conducted did not involve a comprehensive list of search terms. The heterogeneity of the tests and cutoff points used in the studies analyzed did not provide the necessary data for performing a meta-analysis. There was no consensus among the authors regarding the best tests to evaluate post-sepsis cognitive changes. The limited number of available studies, the marked differences among the populations studied, and the diversity of outcomes complicated the generalisability of the study findings. The quality of the studies varied widely.

Our review revealed several gaps in the accumulated knowledge on post-sepsis cognitive impairment. We observed that there is need for studies to assess the most appropriate neuropsychological tests and to compare global cognitive assessment tests to domain specific tests (e.g. attention and memory). Furthermore, the assessment of post-sepsis cognitive impairment in subgroups of young and elderly patients could provide clues about the role of cognitive reserve on post-sepsis cognitive impairment. Studies with cognitive impairment biomarkers (e.g. neurotrophic, neurodegenerative, inflammatory, and oxidative stress biomarkers) and neuroimaging have also been perceived as missing or sparse.

In conclusion, this systematic review demonstrates that there is increasing evidence for the existence of post-sepsis cognitive impairment. Due to lack of consistent findings, the same cannot be stated about its associated risk factors.

Funding

This research did not receive any specific grant from funding agencies of the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.aucc.2017.06.001.

References

1. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014;**311**:1308–16.
2. Shen HN, Lu CL, Yang HH. Epidemiologic trend of severe sepsis in Taiwan from 1997 through 2006. *Chest* 2010;**138**:298–304.
3. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med* 2011;**40**:754–61.
4. Taniguchi LU, Bierrenbach AL, Toscano CM, Schettino GP, Azevedo LC. Sepsis-related deaths in Brazil: an analysis of the national mortality registry from 2002 to 2010. *Crit Care* 2014;**18**:608.
5. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis* 2015;**15**:581–614.
6. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014;**2**:380–6.
7. *Global Sepsis Alliance: fact sheet sepsis*; 2015. http://www.world-sepsis-day.org/CONTENTPIC/2015_WSD_FactSheet_long_English.pdf. [Accessed 18 January 2017].
8. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;**304**:1787–94.
9. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;**369**:1306–16.
10. Gamache Jr FW, Ducker TB. Alterations in neurological function in head-injured patients experiencing major episodes of sepsis. *Neurosurgery* 1982;**10**:468–72.
11. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;**315**:801–10.
12. Silva JM, dos Santos SDS. Sepsis in AIDS patients: clinical, etiological and inflammatory characteristics. *J Int AIDS Soc* 2013;**16**:17344.
13. Watkins CC, Treisman GJ. Cognitive impairment in patients with AIDS—prevalence and severity. *HIV AIDS (Auckl)* 2015;**7**:35–47.
14. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol* 2011;**106**:1911–22.
15. *Cochrane Consumers and Communication: data extraction template for included studies*; 2013. http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/det_2015_revised_final_june_20_2016_nov_29_revised.doc. [Accessed 18 January 2017].
16. Merli M, Lucidi C, Pentassuglio I, Giannelli V, Giusto M, Di Gregorio V, et al. Increased risk of cognitive impairment in cirrhotic patients with bacterial infections. *J Hepatol* 2013;**59**:243–50.
17. Semmler A, Widmann CN, Okulla T, Urbach H, Kaiser M, Widman G, et al. Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors. *J Neurol Neurosurg Psychiatry* 2013;**84**:62–70.
18. Lahariya S, Grover S, Bagga S, Sharma A. Delirium in patients admitted to a cardiac intensive care unit with cardiac emergencies in a developing country: incidence, prevalence, risk factor and outcome. *Gen Hosp Psychiatry* 2014;**36**:156–64.
19. Götz T, Baumbach P, Huonker R, Kranczioch C, Witte OW, Debener S, et al. Slowed peak resting frequency and MEG overactivation in survivors of severe sepsis and septic shock. *Clin Neurophysiol* 2016;**127**:1247–53.
20. Götz T, Baumbach P, Reuken P, Huonker R, Kranczioch C, Debener S, et al. The loss of neural synchrony in the post septic brain. *Clin Neurophysiol* 2017;**127**:2200–7.
21. Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Presepsis depressive symptoms are associated with incident cognitive impairment in survivors of severe sepsis: a prospective cohort study of older Americans. *J Am Geriatr Soc* 2012;**60**:2290–6.
22. Regazzoni CJ, Zamora RJ, Petrucci E, Pisarevsky AA, Saad AK, De Mollein D, et al. Hospital and 1-year outcomes of septic syndromes in older people: a cohort study. *J Gerontol Ser A Biol Sci Med Sci* 2008;**63**:210–2.
23. Arinzon Z, Peisakh A, Schrire S, Berner YN. Delirium in long-term care setting: indicator to severe morbidity. *Arch Gerontol Geriatr* 2011;**52**:270–5.
24. Pierrakos C, Attou R, Decorte L, Kolyviras A, Malinverni S, Gottignies P, et al. Transcranial Doppler to assess sepsis-associated encephalopathy in critically ill patients. *BMC Anesthesiol* 2014;**14**:1–6.
25. Azabou E, Magalhaes E, Braconnier A, Yahiaoui L, Moneger G, Heming N, et al. Early standard electroencephalogram abnormalities predict mortality in septic intensive care unit patients. *PLoS One* 2015;**10**:e0139969.

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001

26. Pierrakos C, Attou R, Decorte L, Velissaris D, Cudia A, Gottignies P, et al. Cerebral perfusion alterations and cognitive decline in critically ill sepsis survivors. *Acta Clin Belg* 2016;**3286**:1–6.
27. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in Older Americans. *J Am Geriatr Soc* 2012;**60**:1070–7.
28. Guerra C, Linde-Zwirble WT, Wunsch H. Risk factors for dementia after critical illness in elderly medicare beneficiaries. *Crit Care* 2012;**16**:R233.
29. Benros ME, Sorensen HJ, Nielsen PR, Nordentoft M, Mortensen PB, Petersen L. The association between infections and general cognitive ability in young men—a nationwide study. *PLoS One* 2015;**10**:e0124005.
30. Lazosky A, Young GB, Zirul S, Phillips R. Quality of life after septic illness. *J Crit Care* 2010;**25**:406–12.
31. WHO. *International statistical classification of diseases and related health problems (International Classification of Diseases) (ICD) 10th Revision—Version:2010*. WHO (World Health Organisation); 2010.
32. Langa KM, Chernew ME, Kabeto MU, Herzog AR, Ofstedal MB, Willis RJ, et al. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med* 2001;**16**:770–8.
33. Iverson GL. Z scores. In: Kreutzer JS, DeLuca J, Caplan B, editors. *Encyclopedia of clinical neuropsychology*. New York, NY: Springer New York; 2011. p. 2739–40.
34. Amodio P, Campagna F, Olianas S, Iannizzi P, Mapelli D, Penzo M, et al. Detection of minimal hepatic encephalopathy: normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. *J Hepatol* 2016;**49**:346–53.
35. Centers for Disease Control and Prevention, National Center for Health Statistics. ICD – ICD-9-CM – International Classification of Diseases, Ninth Revision, Clinical Modification. *Classif Dis Funct Disabil* 2013;**2008**:1–2.
36. Fliessbach K, Hoppe C, Schlegel U, Elger CE, Helmstaedter C. NeuroCogFX—Eine computergestützte neuropsychologische testbatterie für verlaufsuntersuchungen bei neurologischen erkrankungen. *Fortschritte Neurol Psychiatr* 2006;**74**:643–50.
37. Gusmao-Flores D, Salluh JIF, Chalhub RÁ, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit Care* 2012;**16**:R115.
38. Herzog AR, Wallace RB. Measures of cognitive functioning in the AHEAD Study. *J Gerontol B Psychol Sci Soc Sci* 1997;**52**:37–48 (Spec No).
39. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int Psychogeriatr* 2004;**16**:275–93.
40. Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand* 1995;**91**:335–45.
41. Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, Rodriguez-Sanchez JM, Rios-Lago M, Tirapu J, et al. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc* 2009;**15**:438–50.
42. Schroeder RW, Twumasi-Ankrah P, Baade LE, Marshall PS. Reliable Digit Span: a systematic review and cross-validation study. *Assessment* 2012;**19**:21–30.
43. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* 1992;**40**:922–35.
44. Welsh KA, Breitner JCS, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1993;**6**:103–10.
45. Scheurich A, Müller MJ, Siessmeier T, Bartenstein P, Schmidt LG, Fellgiebel A. Validating the DemTect with 18-fluoro-2-deoxy-glucose positron emission tomography as a sensitive neuropsychological screening test for early alzheimer disease in patients of a memory clinic. *Dement Geriatr Cogn Disord* 2005;**20**:271–7.
46. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: an overview. *World J Crit Care Med* 2012;**1**:23–30.
47. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994;**271**:1004–10.
48. Clouston SA, Glymour M, Terrera GM. Educational inequalities in aging-related declines in fluid cognition and the onset of cognitive pathology. *Alzheimers Dement (Amst)* 2015;**1**:303–10.
49. Hindle JV, Hurt CS, Burn DJ, Brown RG, Samuel M, Wilson KC, et al. The effects of cognitive reserve and lifestyle on cognition and dementia in Parkinson's disease—a longitudinal cohort study. *Int J Geriatr Psychiatry* 2016;**31**:13–23.
50. Rivera Mindt M, Byrd D, Saez P, Manly J. Increasing culturally competent neuropsychological services for ethnic minority populations: a call to action. *Clin Neuropsychol* 2010;**24**:429–53.
51. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care* 2010;**14**:R38.
52. Desamericq G, Schurhoff F, Meary A, Szoke A, Macquin-Mavier I, Bachoud-Levi AC, et al. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. *Eur J Clin Pharmacol* 2014;**70**:127–34.
53. Khalifa AE. Antiinfective agents affecting cognition: a review. *J Chemother* 2007;**19**:620–31.
54. Duning T, van den Heuvel I, Dickmann A, Volkert T, Wempe C, Reinholz J, et al. Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction. *Diabetes Care* 2010;**33**:639–44.
55. Hauer D, Kaufmann I, Strewe C, Briegel I, Campolongo P, Schelling G. The role of glucocorticoids, catecholamines and endocannabinoids in the development of traumatic memories and posttraumatic stress symptoms in survivors of critical illness. *Neurobiol Learn Mem* 2014;**112**:68–74.
56. Larson MJ, Weaver LK, Hopkins RO. Cognitive sequelae in acute respiratory distress syndrome patients with and without recall of the intensive care unit. *J Int Neuropsychol Soc* 2007;**13**:595–605.

Please cite this article in press as: Calsavara AJC, et al. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care* (2017), http://dx.doi.org/10.1016/j.aucc.2017.06.001