

Psychiatric complications (depression, anxiety disorders, post-traumatic stress disorder) of ARDS: a systematic review

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Research Article

Keywords: acute respiratory distress syndrome, depression, anxiety disorders, post-traumatic stress disorder, prevalence, risk factor

Posted Date: June 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-514080/v1>

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Abstract

Background: ARSDS requires extensive resuscitation and has major physical sequelae. We evaluated the psychiatric sequelae by conducting a systematic review to determine prevalence of symptoms of depression, anxiety disorders and post-traumatic stress disorder (PTSD) following ARDS, as well as their risk factors.

Methods: We conducted a search on Pubmed by including all studies meeting our primary endpoint (prevalence of symptoms of depression, anxiety disorders and PTSD following ARDS) and secondary endpoint (associated risk factors).

Results: Included studies found prevalence ranging from 16 to 46% for symptoms of depression, 23 to 62% for symptoms of anxiety disorders and 16 to 47% for symptoms of PTSD. The data were too heterogeneous to conduct a meta-analysis.

Among the risk factors associated with a risk factor of depression, anxiety disorders or PTSD after ARDS were; factors related to patient (as an history of mental illness) risk factors related to ICU management (as use opioids and benzodiazepine). Effect of severity of ARDS is not known.

Conclusion: This systematic review shows that depression, anxiety disorders and PTSD following ARDS are frequent, long-lasting, disabling and have severe psychiatric consequences. Associated risk factors can be identified and among us use of opioids.

Introduction

It is known that there can be psychiatric consequences following a stay in ICU [1] and it seems likely that ARDS, which requires long and invasive management in ICU, can also be the cause of significant psychiatric comorbidities, of equal or greater frequency, especially as many of the physical sequelae of ARDS can be disabling in the long term. The link between depression and chronic pathologies has also been demonstrated.[2] Although many studies have evaluated the prevalence of co-morbidities following ARDS, there is to date no recent systematic review of the psychiatric complications (depression, anxiety disorders, post-traumatic stress disorder (PTSD)) of ARDS. However, a better understanding of the psychiatric sequelae of these patients would be valuable for psychiatrists, whether in current practice or in a context where we are regularly affected by new infectious diseases that generate ARDS, such as SARS ten years ago or COVID-19, more recently. [3]

The objective of this systematic review of all the studies in populations of ARDS survivors in the Medline database corresponding to the inclusion factors, is to have data on the prevalence and risk factors for symptoms of depression, anxiety disorders and PTSD following the management of ARDS in resuscitation.

Methods

Eligibility criteria

We searched for studies assessing the prevalence of the symptomatology of depression and/or anxiety disorders and/or PTSD following ARDS management. They could be longitudinal studies, prospective cohort studies, retrospective case-control studies. Randomized controlled trials that looked for the influence of a therapeutic parameter or component on depression and/or anxiety disorders and/or PTSD were also included if they looked for the prevalence of depression and/or anxiety disorders and/or PTSD in their population.

The following exclusion criteria were applied: case studies, commentaries on articles or editorials, studies looking for the validity of a scale, symptomatology of depression and/or anxiety disorders, and/or PTSD not assessed by specific scales and validated or diagnosed by a psychiatrist, and studies of less than thirty patients, in order to exclude studies of insufficient statistical power. However, the presence of a control group was not essential for a study to be included in the review.

Outcome

The analysis of the primary endpoint involved compiling the prevalence of depression (and/or) anxiety disorders (and/or) PTSD in the included studies. In addition to the main analysis, a subgroup analysis was performed for studies involving patient populations that required ECMO-VV management.

The secondary endpoint analysis consisted of collecting risk factors significantly associated in multivariate analysis with the risk of depression (and/or) anxiety disorders (and/or) PTSD. To be included in our analysis, the association or its absence had to be expressed as a numerical value (*β , relative risk or odds ratio*) accompanied by a confidence interval.

Search strategy

A literature search was conducted using the following electronic databases: Scopus, PubMed, Embase, CINAHL, Web of Science, and the Cochrane Library. The search was done according to the following formula (acute respiratory distress syndrome OR acute lung injury) AND (depression OR anxiety OR post-traumatic stress disorder). The search was conducted without any article format, data, nor language restrictions, and included studies published until April 15, 2020. Other references were also identified through reading previous systematic reviews and in reading the bibliographies of the included studies

Study selection and bias risk assessment

The titles for the articles retrieved from the search were manually reviewed by two authors. Only abstracts of original investigations were included and we removed letters to the editor, reviews, abstracts only, and non-article formats. All abstracts were read by two people, and if the studies met the inclusion and exclusion criteria after this reading, they were included in the final analysis and read in their entirety in order to extract from them the primary and secondary judgment criteria. The references of all included articles and those from selected reviews were checked for relevancy. The following data were also

extracted: year of publication, country in which the study was conducted, period of conduct of the study, inclusion and exclusion criteria, details on interventions, and characteristics of the studies.

If there was disagreement between the two readers of the abstracts, a third person decided whether or not to include the study in the journal. The quality of the included studies was assessed using the validated STROBE grid and the results of the qualitative analysis were synthesized in tabular form and subjected to meta-analysis for the main judgement criterion.

Results

Selected studies

The search initially returned 382 studies, 30 studies met the inclusion and exclusion criteria and were therefore read in full. Of these, 23 were selected for the final qualitative analysis [4-26]. The process of study selection is shown using a flow chart. (Fig.1)

The studies included in the review therefore looked for either the prevalence of symptoms of depression, the prevalence of symptoms of anxiety disorders, the prevalence of symptoms of PTSD, or the prevalence of symptoms of several of these conditions in the aftermath of ARDS. The main features of the 23 studies included in the review are summarized in Table 1.

Prevalence of Depressive Symptoms

We included 17 studies in the systematic review looking for the prevalence of symptoms of depression following ARDS in their population (n=3713). Data are summarized in Table 2. In qualitative analysis, a prevalence range of 16 to 46% was found across all studies and 25% to 39% in ECMO patients (Table 2).

Unfortunately, the great heterogeneity of the data (highly different durations of observation to assess prevalence) did not allow to carry out the meta-analysis originally planned in the design of our review.

Prevalence of Anxiety Disorder Symptoms

We included 13 studies in the systematic review and looked for the prevalence of symptoms of anxiety disorders following ARDS in their population (n=3497). The data are summarized in Table 3. In qualitative analysis, a range of prevalence from 23 to 62% was found across all studies and 34% to 40% in ECMO patients (Table 3).

Prevalence of symptoms of post-traumatic stress disorder

We included 12 studies in the systematic review looking for the prevalence of PTSD symptoms following ARDS in their population (n=3817). The data are summarized in Table 3. In qualitative analysis, a prevalence ranging from 16 to 47% was found across all studies. The prevalence was 16% to 47% in ECMO patients (Table 3).

Co-occurrences of symptoms of depression, anxiety disorders and PTSD

Only 3 studies in our review examined the co-occurrences of the 3 mental illnesses studied and reported the following results: co-occurrence of symptoms of 2 mental illnesses from 20 to 60%.[16, 19, 20]; co-occurrence of symptoms of 3 mental illnesses from 20 to 40%.[16, 19] A co-occurrence of symptoms of depression and anxiety disorders in 18% of patients, a co-occurrence of symptoms of anxiety disorders and PTSD in 22% of patients, and a co-occurrence of symptoms of depression and PTSD in 3% of patients were reported.[20]

Risk factors significantly associated in multivariate analysis with the risk of depression, anxiety disorders or PTSD

The risk factors associated with symptoms of depression, anxiety disorders and PTSD are presented respectively in Tables 5, 6 and 7. All associations found in multivariate analysis are expressed with the confidence interval found in the studies of the systematic review.

Risk factors can be divided in 3 categories.

- Patient-dependent risk factors: past history of mental illness, female gender, young age, low socio educational level unemployment or disability, high BMI and presence of co-morbidities or a history of addictions.

- Risk factors associated with severity of the disease.

-Risk factors associated with used drugs or ICU stay: In particular, high opioid consumption was found associated with symptoms of depression, anxiety disorders and PTSD.

Discussion

For the symptoms of the 3 psychiatric conditions in the aftermath of ARDS the systematic review found prevalence ranging between 16-46% for depression, 23-62% for anxiety disorders and 16-47% for PTSD, with comparable results in various collection periods. Furthermore, some risk factors associated with the development of these psychiatric conditions following ARDS, related to ICU management (use of opioids and benzodiazepines), can be highlighted.

Most studies assess the presence or absence of psychiatric symptoms using psychometric scales, but not a clinical diagnosis by a psychiatrist. Therefore our study referred to the symptoms of a given pathology and not to the pathology itself. Indeed, studies with diagnosis made by psychiatrists are difficult to conduct. We included only studies using validated scales in the diagnosis of depression, anxiety disorders and PTSD. The used scales were all validated by the literature as being sensitive and specific for the diagnoses, whether it is the HADS [27, 28] Arnau, 2001 #28}, the BDI[29], the Zung Self-Rating Depression Scale [30], the BAI [31, 32], the IES-R[33], the IES [34], the PTSS-10 [35]. This suggests that the results synthesized in our review are well predictive of the diagnoses of depression, anxiety

disorders and PTSD. Unfortunately, the insufficient and too heterogeneous data of our study did not allow a meta-analysis which could have allowed us to obtain a figure more representative of reality. Globally, the prevalence of depression worldwide is estimated at 6% and it is estimated that 15%-18% of the world population will be affected by depression at least once in their lifetime [36]; the population of ARDS survivors therefore appears to be at greater risk than the general population developing depressive disorder [36]. Similarly, the estimated global prevalence of anxiety disorders ranges worldwide ranges from 3.8% to 25% [37]) and the prevalence of PTSD has been estimated at 3.9%. [38] Our results are therefore higher than those for the general population, but are comparable to those found in studies of populations that have been managed in intensive care units. [1, 39]

For risk factors associated by multivariate analysis with the development of depression, anxiety disorders and PTSD following ARDS, the data in the current state of research (especially those from studies with a correct methodology and expressed with a confidence interval), are still scarce (in studies of psychiatric disorders following either ARDS or, more generally, resuscitation management) and do not allow any real conclusions to be drawn. However, some slight trends should be highlighted:

People with a history of mental illness are at greater risk of developing after ARDS depression, anxiety disorders or PTSD. Certain factors associated with the patient such as female gender, young age (for anxiety disorders), low socio educational level (for depression), unemployment or disability, high BMI (for both depression and anxiety disorders), co-morbidities (for anxiety disorders) or a history of addictions also appear to induce greater risk of developing mental illness. Indeed, it is now accepted that a history of depression, anxiety disorder or post-traumatic stress disorder makes the patient more at risk of developing a mental disorder again, as it is known that mental pathologies are often associated with each other. Moreover young age, female gender, socio-economic difficulties, chronic pathologies and addictive pathologies are also risk factors for depression, anxiety disorders and PTSD. [40]

Risk factors associated with intensive care management seem to be generally weakly associated with psychiatric symptoms following ARDS. Only heavy opioid use was associated with the risk of symptoms of the 3 psychiatric pathologies studied, and heavy benzodiazepine use was found for 2 pathologies as a risk factor associated with depression in multivariate analysis.

The severity of initial impairment presents contradictory results, because it was found once as a risk factor for anxiety disorders and PTSD, and also found once as a protective factor against depression and PTSD. Finally, hypoglycemia was found once to be a risk factor for depression (with a strong level of evidence because of the association established by a randomized trial) and once as a risk factor for PTSD, and high corticosteroid consumption was found once to be a protective factor against anxiety disorders and once against PTSD. Returning to work seems to protect against depression, and cognitive disorders seem to favor anxiety disorders (associations established by one of the studies in the review).

Our study is the first systematic review[41] on the prevalence of psychiatric symptoms (depression, anxiety disorders, PTSD) including studies conducted since the reduction of mortality rate of ARDS (which fell from 50% in the 1990s to 33% in the 2000s).[42] And survivors are more likely to develop

somatic and psychiatric complications during the convalescence phase, which is one of the challenges of ARDS management.[43-45] However, very few studies involving ECMO-VV patients were available to perform analysis in management of ARDS, but the prevalence found is similar to that found in other populations managed for ARDS.

Limitations

This systematic review has some limitations. Firstly, the heterogeneity of the studies included, due to their methodological differences (a few retrospective studies with a lower level of evidence were included with mostly prospective studies), but also due to the heterogeneous measurement instruments, made impossible a meta-analysis. Secondly, diagnostic scales tend to overestimate the prevalence of the pathologies as they detect pathologies with high sensitivity and low specificity.[23, 46] Moreover, the semi-structured psychiatric interview remains the reference to diagnose mental illness combining the exhaustive aspect of a scale and the clinical finesse of a face-to-face interview with an experienced practitioner.[47] In our review, only 2 studies of PTSD used the SCID-II, one as first-line and one as diagnostic confirmation after a scale. [5, 12] Thirdly, the inclusion criteria for studies are also sometimes heterogeneous, some excluding patients with a history of mental illness and others not, considering mental illness only as a risk factor. In addition, many studies have reported difficulties to determine some of the patients' characteristics prior to their ARDS, particularly with regard to psychiatric history. Fourthly, we have tried to synthesize at best the associations found in different studies, which used different ways to define certain variables. In particular, different thresholds were used for numerical variables such as age, biological values or the consumption of certain drugs. It would have been too complex to take this into account, so we have described each association generically without numerical values. Finally, since we only included studies published until April 15, 2020, we did not include very recent publications.[48]

Conclusion

Beyond the long-term physical consequences of ARDS, our review shows that there are also frequent, long-lasting, disabling and severe psychiatric consequences. While much research is still needed, it seems important for physicians, and particularly psychiatrists, to better understand and detect the symptoms of depression, anxiety disorders and PTSD, and thus to continue the work carried out in intensive care, to improve the health and quality of life of patients and their families.

Declarations

-Ethical Approval and Consent to participate: Not applicable

-Consent for publication: Not applicable

-Availability of supporting data: Not applicable

-Competing interests: All authors listed on the title page have no competing interest to declare

-Funding: Solely on departmental fund

-Authors' contributions:

NK: this author contributed to the study concept, performed the data collection and drafted the manuscript.

MN: this author contributed to the study concept and design; performed the data analysis, and drafted the manuscript.

PA: this author performed the data analysis, and substantially revised the manuscript.

NF: this author contributed to the study concept and performed the data collection.

PGG: this author contributed to the study concept, the analysis of data, and substantially revised the manuscript.

JCCG: this author contributed to the study concept and substantially revised the manuscript.

BB: this author contributed to the study concept and design, performed the data analysis and drafted the manuscript.

All authors read and approved the final manuscript

Acknowledgements: none

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Tables

Table 1 Presentation of studies included in the systematic review after reading the full articles

Study designation	Type	Setting	Inclusion period	Data collection
Prospective interventional studies				
Deja et al. 2006 [4]	randomized controlled	1 hospital	1991 - 2000	Median time: 57 months
Prospective observational cohort studies				
Schelling et al., 1998 [5]	Prospective cohort	1 ICU from 1 hospital	1985 - 1995	Median time: 4 years
Orme et al., 2003 [6]	Prospective cohort	1 ICU from 1 hospital	1994 - 1999	1 year
Hopkins et al., 2004 [7]	Prospective cohort	1 ICU from 1 hospital	1994 - 1999	1 year
Hopkins et al., 2005 [8]	Prospective cohort	1 ICU from 1 hospital	1994 - 1999	2 years
Dowdy et al., 2008, [9]	Prospective cohort	13 ICU in 4 hospitals	2004 - 2007	3 months
Dowdy et al., 2009 [10]	Prospective cohort,	13 ICU in 4 hospitals	2004 -2007	6 months
Adhikari et al., 2009, [11]	Prospective cohort	ICU from 4 hospitals	1998 - 2001	1 year
Hauer et al., 2009 [12]	Prospective cohort	Data base population.	Unspecified	Variable
Hopkins et al., 2010 [13]	Prospective cohort	a previous ARDS study	1994 - 1999	1 and 2 years
Adhikari et al., 2011 [14]	Prospective cohort	ICU from 4 hospitals	1998 - 2001	5 years
Bienvenu et al. ,2012, [15]	Prospective cohort	13 ICU in 4 hospitals	2004 - 2007	3 and 6 months, 1 and 2 years
Mikkelsen et al., 2012, [16]	Prospective cohort	ICUs from 28 hospitals	2000 - 2005	1 year
Stevenson et al., 2013, [17]	Prospective cohort	13 ICU in 4 hospitals	2004 - 2007	3 months
Bienvenu et al., 2013 [18]	Prospective cohort	13 ICU in 4 hospitals	2004 - 2007	3 and 6 months, 1 and 2 years
Bienvenu et et al., 2015, [19]	Prospective cohort	ICU in 4 hospitals	2004 - 2007	2 years
Huang et al. 2016, [20]	Prospective cohort	41 ARDS Network hospitals	No defined	Collection at 6 months and 1 year

Spencer-Segal et al. 2017, [21]	Prospective cohort	6 ICU from 3 hospitals	2004 - 2009	6 months
Bienvenu et al., 2018 [22]	Prospective cohort	13 ICU in 4 hospitals	2004 - 2007	3 and 6 months, 1, 2 and 5 years
Retrospective studies				
Kapfhammer et al., 2004 [23]	Retrospective cohort	data collection from 1 hospital	1985 - 1995	Median time: 8 years
Mikkelsen et al., 2009 [24]	Retrospective	1 ARDS survivor support site	No defined	Variable collection
Schmidt et al. 2013 [25]	Retrospective	Patients treated with ECMO-VV in 3 ICU	2008 - 2012	6 months
Sanfilippo et al. 2019, [26]	Retrospective	patients treated with ECMO-VV from ICU	2009 - 2016	Collection in 2017 for all patients

Table 2 Prevalence of Depressive Symptoms by Study

Study	Scale used	Population characteristics	Number of patients analyzed at the end*	Time of examination					Not defined
				3 months	6 months	1 year	2 years	5 years	
Dowdy, 2008 [9]	HAD-D ≥ 8	Mean age 48 years, F/M ratio (46%/54%)	104	28%					
Dowdy, 2009 [10]	HAD-D ≥ 8	Mean age 49 years, F/M ratio (44%/56%)	160		26%				
Bienvenu, 2012[15]	HAD-D ≥ 8	Mean age 49 years, F/M ratio (44%/56%)	174 (3 months) 174 (6 months), 156(1year) 146 (2 years)	26%	25%	24%	32%		
Schmidt, 2013 [25]	HAD-D ≥ 8	Mean age 37 years, F/M ratio (54%/46%)	67		25%				
Bienvenu, 2015 [19]	HAD-D ≥ 8	Mean age 49 years, F/M ratio (44%/56%)	174 (3 months) 173 (6 months) 156 (1year) 146 (2 years)	26%			33%		46% [†]
Huang, 2016 [20]	HAD-D > 8	Mean age 49 years, F/M ratio (52%/48%)	613 (6 months) 576 (12 months)		36%	36%			
Spencer-Segal, 2017 [21]	HAD-D > 8	Placebo: Mean age 49, F/M ratio (36.9%/63.1%); GM-CSF: Mean age 50 F/M ratio (48%/52%)	132		32% ^{\$}				
Bienvenu, 2018 [22]	HAD-D ≥ 8	Mean age 49 years, F/M ratio (44%/56%)	At 3 and 6 months, 1 and 2 years see [19] 123 (5 years)						32% [¶]
San Filippo, 2019 [26]	HAD-D > 7	Mean age 41.3, F/M ratio (27%/73%)	33						39%
Adhikari, 2009 [11]	BDI-II ≥ 20	Mean age 42 years, F/M ratio (46%/54%)	61						41%
Adhikari, 2011 [14]	BDI-II ≥ 20	Median age 48 years, F/M ratio (48%/52%)	43					18,60%	
Orme, 2003 [6]	BDI > 16	Mean age 46 years, F/M ratio (55%/45%)	66			16%			
Hopkins, 2004 [7]	BDI > 16	Mean age 46 years, F/M ratio (55%/45%)	66			16%			
Hopkins, 2005 [8]	BDI > 16	Mean age 46 years, F/M ratio (55%/45%)	62				23%		
Hopkins, 2010 [13]	BDI > 16	Mean age 46 years old, F/M ratio (55%/45%)	66 (1 year) 62 (2 years)			16%	23%		

HAD-D: Hospital Anxiety and Depression Scale; GM-CSF: granulocyte macrophage-colony stimulating factor; BDI: Beck Depression Inventory, F/M ration (female/male ratio); *: number of patients actually assessed for depressive symptoms according to the study protocol, not including the deceased and those lost to follow-up. [†]: of the total population, to at least one

collection; ¶: prolonged depressive symptomatology over 5 years; §: valid prevalence for the entire study population

Table 3 Prevalence of anxiety disorder symptoms by studies

Study	Uses scale	Population characteristics	Number of patients analyzed at the end*	Time of examination				Not defined
				3 months	6 months	1 year	2 years	
Stevenson, 2013 [17]	HAD-A>8	Median age 49. F/M ratio (41%/59%)	152	38%				
Bienvenu, 2015, [19]	HAD-A>8	Average age 49 years, F/M ratio (44%/56%)	174 (3 months) 173 (6 months) 156 (1year) 146 (2 years)	38%		44%	56% [†]	
Bienvenu, 2018 [22]	HAD-A>8	Average age 49 years, F/M ratio (44%/56%)	At 3 and 6 months, 1 and 2 years [19] 123 (5 years)				52% [‡]	
Orme, 2003 [6]	BAI >16	Average age 46 years, F/M ratio (55%/45%)	66			24%		
Hopkins, 2004 [7]	BAI >16	Average age 46 years, F/M ratio (55%/45%)	66			24%		
Hopkins, 2005 [8]	BAI >16	Average age 46 years, F/M ratio (55%/45%)	62				23%	
Hopkins, 2010 [13]	BAI >16	Average age 46 years, F/M ratio (55%/45%)	66 (1 year) 62 (2 years)			24%	23%	
Mikkelsen, 2009 [24]	BAI (threshold not specified)	Average age 43.3, F/M ratio (84%/16%)	79				48%	
Mikkelsen, 2012 [16]	BAI (threshold not specified)	Average age 49 years, F/M ratio (57%/43%)	102			62%		
Sanfilippo, 2019 [26]	HAD-A > 7	Average age 41.3, F/M ratio (27%/73%)	33				40%	
Schmidt, 2013 [25]	HAD-A>8	Average age 37 years, F/M ratio (54%/46%)	67		34%			
Huang, 2016 [20]	HAD-A > 8	Average age 49 years, F/M ratio (52%/48%)	613 (6 months) 576 (12 months)		42%	42%		
Schmidt, 2013 [25]	HAD-A>8	Average age 37 years, F/M ratio (54%/46%)	67		34%			
Spencer-Segal, 2017 [21]	HAD-A>8	Placebo: Mean age 49, F/M ratio (37%/63%); GM-CSF: Mean age 50, F/M ratio (48%/52%)	132		32%		^{\$}	

HAD-A: Hospital Anxiety and Depression Scale (part of the scale about anxiety disorders); BAI: Beck Anxiety Inventory; GM-CSF: granulocyte macrophage-colony stimulating factor;

BDI: Beck Depression Inventory, F/M ration (female/male ratio); *: number of patients actually assessed for symptoms of anxiety disorders according to the study protocol, not including the deceased and those lost to follow-up; †: out of the general population, at least one caseload; ¶: percentage of patients with symptoms of prolonged anxiety disorders over the five years; §: prevalence valid for the entire study population;

Table 4 Prevalence of PTSD symptoms by studies

Study	Scales	Population characteristics	Number of patients analyzed at the end*	Time of examination				
				3 months	6 months	1 year	2 years	Not defined
Bienvenu, 2013 [18]	IES-R \geq 1.6	Mean age 49 years, F/M ratio (44%/56%)	174 (3 months) 173 (6 months) 156 (1year) 146 (2 years)	24%	20%	23%	24%	
Bienvenu, 2015, [19]	IES-R \geq 1.6	Mean age 49 years, F/M ratio (44%/56%)	3 months (174) 6 months (173) 12 months (156) 24 months (146)		22%		24%	33% [†]
Huang, 2016 [20]	IES-R>1.6	Mean age 49 years, F/M ratio (52%/48%)	613 (6months) 576 (1 year)		24%	23%		
Bienvenu, 2018 [22]	IES-R \geq 1.6	Mean age 49 years, F/M ratio (44%/56%)	At 3 and 6 months, 1 and 2 years [19] 123 (5 years)					23% [‡]
Sanfilippo, 2019 [26]	IES-R (cut-off 21 and 33)	Mean age 41 years, F/M ratio (27%/73%)	33					47% and 21% (cut-off 21 and 33)
Schmidt, 2013 [25]	IES \geq 30	Mean age 37 years, F/M ratio (54%/46%)	67		16%			
Schelling, 1998 [5]	PTSS-10 >35	Non-ECMO: Mean age 36 years F/M ratio (51%/49%) ECMO: Mean age 34 years F/M ratio (35%/65%)	80 Non-ECMO : 66 ECMO :14					28% [§]
Deja, 2006 [4]	PTSS-10 >35	Mean age 33 years, F/M ratio (40%/60%)	65					29%
Hauer, 2009 [12]	PTSS-10 and confirmation with SCID-II	Mean age 40 years F/M ratio (52%/48%)	33					29%
Mikkelsen, 2012 [16]	PTSS-10>35	Mean age 49 years, F/M ratio (57%/43%)	102			39%		
Spencer-Segal,	PTSS-10 >35) and IES >19	Placebo: Mean age 49 years	132		20% (PTSS-			

2017 [21]		F/M ratio (37%/63%) GM-CSF: Mean age 50 years F/M ratio (48%/52%)		10) 25% (IES) ^{\$}
Kapfhammer, 2004 [23]	Interviews via SCID by 2 psychiatrists	Mean age 36.5 years F/M ratio (48%/52.%)	46	44%

Clinical Interview for the DSM-IV; F/M ratio (Female/Male ratio); *i.e., number of patients actually assessed for symptoms of PTSD according to the study protocol, not including the deceased and those lost to follow-up; † out of the general population, at least one collection; ¶: percentage of patients with symptoms of prolonged PTSD over five years; \$ prevalence valid for the entire study population

Table 5 Factor associated with depression in ARDS patients

Potential Risk Factors	Risk factors for ARDS	Protective factors	No significative association
Age			15 OR=1.13 (0.93-1.36) (B); 18 1.03 (0.95. 1.12); (B) 22 OR 0.6 (0.3-1.2)(B); 21 β =-0.058 (-0.14. 0.028) (B)
Women	20 RR=1.26 (1.01. 1.58); (B)		15 OR=0.70 (0.39-1.24)(B); 22 OR 1.7 (0.9-3.2) (B); 21 β =-0.15 (-2.6. 2.3) (B)
High BMI	10 1.9 (1.0. 3.4) (B) ; 9 RR=3.3 (1.2. 4.2) (B)		15 OR=1.05 (0.56-1.96)(B); 20 RR=1.07 (0.96. 1.20)(B)
Unemployment or disability	20 RR1.35 (1.09. 1.69) (B)		15 OR= 1.78 (0.86-3.69)(B); 22 OR=1.6 (0.9-3.4)(B)
Low socio-educational level	15 OR=3.14 (1.49-6.58); (B) 9 RR=2.1 (0.7. 4.3) (B)		
Loss of autonomy			10 RR= 1.4 (0.7. 2.4) (B)
Comorbidities			15 OR=1.10 (0.98-1.23)(B)
History of stroke			20 RR=1.39 (0.74. 2.58)(B)
History of hemodialysis			20 RR=1.54 (0.86. 2.75)(B)
History of diabetes			20 RR=1.06 (0.86. 1.30)(B)
Psychiatric disorders	10 RR=2.0 (1.1. 3.6) (B); 22 OR=2.4 (1.1-5.2) (B); 9 RR=3.9 (1.5. 6.5) (B)		
Smoking			22 OR=1.6 (0.8-3.5)(B)
Alcohol abuse			22 OR=0.7 (0.3-1.5)(B)
Drug abuse	20 RR=1.39 (1.09. 1.77) (B)		22 OR=1.7 (0.9-3.5)(B)
Surgical ICU (vs. medical)	10 RR = 2.2 (1.1. 4.2) (B)		15 OR=1.53 (0.72-3.23) (B); 20 RR=0.99 IC 95% (0.82. 1.20)(B)
APACHE score		20 RR=0.90 (0.82. 0.99) (B)	22 OR=0.6 (0.3-1.1) (B); 21 β =0.044 (-0.051. 0.14) (B)
SOFA score	10 RR=2.1 (1.2. 3.5) (B)		15 OR=1.28 (0.70-2.36) (B); 22 OR=0.9 (0.5-1.7)(B); 20 RR=0.90 (0.78. 1.05)(B)
Sepsis			22 OR = 1.4 (0.7-2.5) (B); 20 RR=0.88 (0.71. 1.08)(B)
PaO2/FiO2 ratio			20 RR=1.01 (0.98. 1.04) (B)
Muscular blocker			20 RR=1.00 (0.87. 1.17) (B)
Vasopressor agents			20 RR=0.94 (0.78. 1.14)(B)
Opiods (high doses)	20 RR=1.11 (1.03. 1.20)(B)		22 OR=1.1 (0.6-2.0)(B)
Benzodiazepines (high doses)	10 RR=2.1 (1.2. 3.5)(B) ; 9 RR=2.4 (1.1. 3.8) (B)		15 OR=1.29 (0.64-2.58) (B); 22 OR=1.3 (0.7-2.6)(B)
Corticoids (high doses)			22 OR=1.9 (0.7-4.8)(B); 21 β = -0.089 (-0.23. 0.055)(B); 20 RR=1.02 (0.96. 1.08) (B)
Administration of GM-CSF	21 β = 2.8 (0.37. 5.2) (A)		

hypoglycemia (Frequent or severe)	9 RR=2.6 (1.2. 4.2) (B)	15 OR=1.42 (0.74-2.70) (B); 20 RR=1.00 (0.91. 1.10) (B)
Prolonged sedation		15 OR=1.02 (0.91-1.14) (B)
Renal replacement therapy		20 RR=0.69 (0.45. 1.04)(B)
Duration of mechanical ventilation		20 RR=1.02 (0.95. 1.08) (B)
ICU length of stay		15 OR=0.99 (0.98-1.01)(B); 22 OR=1.2 (0.6-2.2) (B); 20 RR=1.01 (0.95. 1.07)(B)
Delirium		15 (OR=1.00 (0.92-1.10) (B); 22 OR 0.7 (0.4- 1.3)(B)
Cognitive disorders		24 (OR=2.33 (0.83-6.55) (B)
SF-36 (mental component)	22 OR=4.2 (1.9-9.0)(B)	-
SF-36 (physical component)	22 OR=2.8 (1.3-6.1)(B)	-
Loss of autonomy (IADL)		15 (OR=1.29 (0.67-2.47)(B)
Return to employment		11 OR 0.21; [0.07 . 0.62] (B)

ARDS Acute respiratory distress syndrome; BMI: body mass index; APACHE (Acute Physiology and Chronic Health Evaluation III); PaO₂: partial arterial pressure of oxygen; FiO₂: Fraction of inspired oxygen; GM-CSF: Granulocyte-macrophage colony-stimulating factor; SOFA; sequential organ failure assessment; IADL: Instrumental Activities of Daily Living; ICU: Intensive care unit

Results are given as odd ratio (OR) relative risk (RR) or correlation coefficients (β) and 95% confidence interval (A) Randomized control trial (B) cohort study (C) case-control study

Table 6 Factor associated with anxiety disorder in ARDS patients

Potential Patient-related Risk Factors	Risk factors for ARDS	Protective factors	No significative association
Young age	<u>21</u> $\beta=-0.13(-0.21, -0.053)$ (B); <u>20</u> RR 1.16 (1.07, 1.26) (B)		<u>17</u> OR=1.01 (0.99, 1.04) (B); <u>22</u> OR=1.1 (0.6, 2.0) (B)
Women	<u>20</u> RR=1.43 (1.18, 1.74) (B)		<u>17</u> OR=1.13 (0.57, 2.22), (B); <u>21</u> $\beta=0.38$ (-1.8, 2.6) (B)
High BMI	<u>17</u> OR=1.06 (1.00, 1.13) (B); <u>20</u> RR=1.14 (1.03, 1.26) (B)		
Socio-educational level			<u>17</u> OR=0.59 (0.28, 1.21) (B)
Profession	<u>20</u> RR=1.26 (1.05, 1.52) <i>unemployed</i> (B)		<u>17</u> OR=0.71 (0.36, 1.42) (B); <u>22</u> OR=1.3 (0.7, 2.4) (B)
Comorbidities	<u>17</u> OR=1.28 (1.00, 1.64) (B)		
History of cardiovascular disease			<u>17</u> OR=0.26 (0.06, 1.10) (B); <u>20</u> RR=1.04 (0.49, 2.18) (B)
History of hemodialysis			<u>20</u> RR=1.05 (0.63, 1.77) (B)
History of diabetes			<u>20</u> RR=0.99 (0.82, 1.20) (B)
Chronic lung disease	<u>17</u> OR=3.41 (1.22, 9.57) (B)		
Smoking			<u>22</u> OR=1.5 (0.8, 3.1) (B)
Alcohol dependency	<u>20</u> RR=1.45 (1.18, 1.79) (B)		<u>22</u> OR=1.5 (0.8, 3.0) (B)
Drug abuse			<u>17</u> OR=1.87 (0.71, 4.92) (B); <u>22</u> OR 1.6 (0.7, 3.5) (B)
Psychiatric disorders	<u>17</u> OR=3.59 (1.25, 10.30) (B); <u>22</u> OR 2.5 (1.1, 5.4) (B)		
Surgical ICU (vs. medical)			<u>17</u> OR=1.75 (0.67, 4.59) (B); <u>20</u> RR=1.02 (0.87, 1.21) (B)
APACHE score (2 or 3)	<u>21</u> $\beta=0.104$ (0.018, 0.19) (B)		<u>17</u> OR= 1.01 (0.97, 1.05) (B); <u>22</u> OR=0.7 (0.3, 1.2) (B); <u>20</u> RR=0.95 (0.88, 1.02) (B)
SOFA score			<u>17</u> OR=1.01 (0.91, 1.12) (B); <u>22</u> OR=0.7 (0.4, 1.4) (B); <u>20</u> RR=0.88 (0.73, 1.07) (B)
Sepsis			<u>17</u> OR=1.05 (0.97, 1.14) (B); <u>22</u> OR= 1.2 (0.7, 2.2) (B); <u>20</u> RR=0.99 (0.82, 1.20) (B)
PaO ₂ / FiO ₂ ratio			<u>20</u> RR= 0.99 (0.97, 1.01)(B)
Prolonged muscular blockade			<u>20</u> RR=1.12 (0.99, 1.27) (B)
Opioids (high doses)	<u>20</u> RR=1.08 (1.01, 1.15) (B)		<u>17</u> OR=0.98 (0.50, 1.92) (B); <u>22</u> OR=0.8 (0.4, 1.4) (B)
Benzodiazepines (high doses)			<u>17</u> OR=1.01 (0.97, 1.05) (B); <u>22</u> OR 0.8 (0.4-1.5) (B)
Corticoids (high doses)		<u>21</u> $\beta=-0.16$ (-0.29, -0.025) (B)	<u>17</u> OR=0.99 (0.95, 1.03) (B); <u>22</u> OR=2.0 (0.8, 5.1) (B); <u>20</u> RR=1.02 (0.97, 1.07) (B)
Administration of GM-CSF			<u>21</u> $\beta=-1.97$ (-0.23, 4.2) (A)

Hypoglycemia (Frequent or severe)	<u>17</u> OR=1.00 (0.98, 1.02) (B); <u>20</u> RR=0.96 (0.87, 1.05) (B)
Renal replacement therapy	<u>20</u> RR=0.77 (0.53, 1.12) (B)
Duration of mechanical ventilation	<u>20</u> RR=0.99 (0.93, 1.05) (B)
ICU length of stay	<u>17</u> OR=1.05 (0.97, 1.14) (B); <u>22</u> OR=0.9 (0.5,1.6) (B); <u>20</u> RR=0.98 (0.93, 1.03) (B)
Occurrence of delirium	<u>22</u> OR=1.0 (0.6, 1.9) (B)
Cognitive disorders	<u>24</u> OR=3.95 (1.49, 10.44) (B)
SF-36 (mental component)	<u>22</u> OR 3.5 (1.6, 7.5) (B)
SF-36 (physical component)	<u>22</u> OR 1.9 (0.9, 4.1) (B)

ARDS : acute respiratory distress syndrom ; BMI : body mass index ; SF-HS : Short-Form Health Survey ; APACHE : Acute Physiology and Chronic Health Evaluation PaO₂: partial arterial pressure of oxygen; FiO₂: Fraction of inspired oxygen; GM-CSF: Granulocyte-macrophage colony-stimulating factor; SOFA: sequential organ failure assessment; ICU: intensive care unit

Results are given as odd ratio (OR) relative risk (RR) or correlation coefficients (β) and 95% confidence interval; (A) Randomized control trial (B) cohort study (C) case-control study

Table 7 Factor associated with post-traumatic stress disorder in ARDS patients

Potential risk factors	Risk factors for ARDS	Protective factors	No significant association
Age			<u>18</u> OR=0.83 (0.36, 1.90) (> 55yo) (B); <u>22</u> OR=1.9 (0.9, 3.8) (B)
Women	<u>21</u> β =11.6 (3.4, 19.7) (B); <u>20</u> RR=1.80 (1.31, 2.48) (B)		<u>18</u> OR=1.14 (0.68, 1.92) (B); <u>22</u> OR=1.7 (0.8, 3.3) (B)
BMI			<u>18</u> RR=1.67 (0.93, 3.01) (B); <u>20</u> RR=1.07 (0.93, 1.24) (B)
Socio-educational level			<u>18</u> OR=0.92 (0.82, 1.04) (B)
Profession	<u>20</u> RR=1.40 (1.03, 1.90) (B)		
Comorbidities			<u>18</u> RR=1.11 (0.6, 2.06) (B)
History of cardiovascular disease			<u>20</u> RR=1.61 (0.76, 3.43) (B)
History of hemodialysis			<u>20</u> RR=1.39 (0.72, 2.67) (B)
History of diabetes			<u>20</u> RR=0.85 (0.63, 1.14) (B)
Smoking			<u>18</u> RR=1.98 (0.88, 4.43) (B); <u>22</u> OR=2.1 (0.7, 6.0) (B)
Drug abuse			<u>18</u> RR=1.12 (1.06, 2.09) (B); <u>22</u> OR=1.6 (0.7, 3.5) (B)
Alcohol dependency	<u>20</u> OR=1.79 (1.31, 2.46) (B)		<u>18</u> RR=1.03 (0.56, 1.88) (B); <u>22</u> OR=1.2 (0.6, 2.7) (B)
Psychiatric disorder	<u>18</u> RR=1.96 (1.06, 3.64) (B); <u>22</u> OR=2.9 (1.3, 6.5) (B); <u>20</u> OR=1.39 (1.06, 1.83) (B)		
Surgical ICU (vs. Medical)			<u>20</u> RR=1.00 (0.77, 1.28) (B)
APACHE score	<u>21</u> β =0.48 (0.16, 0.8) (B)	<u>20</u> RR=0.88 (0.79, 0.98) (B)	<u>18</u> OR=0.99 (0.96, 1.03) (B); <u>22</u> OR=0.6 (0.3, 1.3) (B)
SOFA score			<u>22</u> OR=1.7 (0.8, 3.4) (B); <u>20</u> RR=0.99 (0.81, 1.21) (B)
Sepsis	<u>18</u> OR=1.08 (1.00, 1.16) (B)		<u>22</u> OR=1.1 (0.6, 2.2) (B); <u>20</u> RR=0.91 (0.68, 1.21) (B)
PaO ₂ /FiO ₂ ratio	<u>20</u> RR=1.01 (0.98, 1.04) (B)		
Muscular blocker	<u>20</u> RR=1.23 (1.02, 1.49) (B)		
vasopressor agents			<u>20</u> RR=1.12 (0.87, 1.44) (B)
Opioids (high doses)	<u>18</u> OR=2.13 (1.02, 4.42) (B)		<u>20</u> RR=1.09 (0.98, 1.22) (B)
Benzodiazepines (high doses)			<u>18</u> OR=1.63 (0.85, 3.13) (B); <u>22</u> OR=0.8 (0.4, 1.5) (B)
Corticoids (high doses)		<u>18</u> OR=0.91 (0.84, 0.99) (B)	<u>22</u> OR=2.8 (0.8, 9.9) (B); <u>21</u> β =-0.47 (-0.95, 0) (B); <u>20</u> RR=1.04 (0.96, 1.12) (B)
Administration			<u>21</u> β =6.9 (0.5, 13.4) (A)

of GM-CSF		
Hypoglycemia (Frequent or severe)	20 RR=0.96 (0.87, 1.06) (B)	
Prolonged sedation		18 OR=1.02 (0.90, 1.16) (B)
Renal replacement therapy		20 RR=0.95 (0.64, 1.43) (B)
Duration of mechanical ventilation		20 RR=1.02 (0.94, 1.11) (B)
ICU length of stay	18 OR=1.39 (1.06, 1.83) (B)	22 OR=1.4 (0.7, 2.8) (B); 20 RR=0.93 (0.83, 1.04) (B)
Delirium		18 OR=0.79 (0.29, 2.15) (B); 22 OR=1.2 (0.6, 2.5) (B)
SF-36 (mental component)	22 OR=3.7 (1.5, 9.0) (B)	

Table 7 Factor associated with post-traumatic stress disorder in ARDS patients

ARDS : acute respiratory distress syndrom ; BMI : body mass index ; APACHE : Acute Physiology and Chronic Health Evaluation PaO₂: partial arterial pressure of oxygen; FiO₂: Fraction of inspired oxygen; GM-CSF: Granulocyte-macrophage colony-stimulating factor; SOFA: sequential organ failure assessment; ICU: Intensive care unit Results are given as odd ratio (OR) relative risk (RR) or correlation coefficients (β) and 95% confidence interval; (A) Randomized control trial (B) cohort study (C) case-control study

Figures



Figure 1

Flowchart showing the systematic review process