

Risk Factors for Post-Intensive Care Syndrome in Family Members (PICS-F) of Adult Patients: A Systematic Review.

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Research

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Abstract

Background: Relatives of critically ill patients who either die or survive the intensive care unit (ICU) may develop substantial mental health problems that are collectively defined as Post-Intensive Care Syndrome in Family (PICS-F). It is important to document in a systematic manner all of the possible risk factors associated with the development of the latter.

Methods: By using a systematized search strategy we included studies that focused on PICS-F in relatives of adult ICU patients and reported the risk factors associated with its development. The search was conducted within PubMed, Embase, SCOPUS, clinicaltrials.gov and Cochrane Library on the 2nd of May, 2021. PRISMA guidelines were implemented for appropriate reporting.

Results: We included 52 papers covering 8293 relatives. The prevalence of PICS-F varied between 2.5-69%. We identified over 70 different risk factors of PICS-F, among which we distinguished patient-related (n=28), relative-related (n=33) and medical staff-related (n=9) risk factors. Among 17 studies with the highest quality we identified the 7 following factors associated with the development of PICS-F: younger age of a patient, death of a patient, depression in relatives during the ICU stay, history of mental disorders in relatives, being a spouse and low satisfaction with communication & care in the ICU.

Conclusions: PICS-F is a highly prevalent phenomenon that may be exacerbated by a number of risk factors. Special attention should be paid to proper identification of susceptible relatives in order to prevent PICS.

Introduction

Due to the extensive development in the medical area, short-term outcomes of intensive and critical care patients' have been drastically improving over the last decades. The psychological repercussions in the intensive care unit (ICU) survivors had already been noticed and reported thoroughly in the past century [1, 2]. However, the burden of critical illness of the beloved ones is also tremendous for their families. The ICU is possibly the most unfamiliar and intimidating part of the hospital since it requires the most advanced monitoring and involves major medical procedures that may not be understood by unacquainted relatives. The admission to such a ward is usually sudden and unexpected, which causes immense stress and pain for the families. Uncertainty and poor prognoses keep the family members constantly in a precarious position. The relatives usually play the role of caregivers and surrogate decision makers for their spouses, parents, children or siblings. Because of all these reasons, family members of critically ill patients are at high risk of anxiety, depression, post-traumatic stress disorder (PTSD) and other psychiatric disorders [3]. In order to describe this phenomenon, the term PICS-F (Post-Intensive Care Syndrome in Family) was developed [3]. It's occurrence may be devastating for the relatives and should not be belittled. The perseverance of the patient's relatives well-being should be a matter of utmost priority, as the number of ICU admissions is rising together with population aging [4]. It is crucial to determine which factors may increase the risk of PICS-F incidence in order to provide the best

care for both patients and their families. Therefore, we decided to collect and analyze all the available data regarding this issue in a systematic manner, according to the PRISMA checklist [5]. A PICO criteria is presented on Table 1.

Methods

Protocol and registration

We did not register the protocol of this systematic review.

Eligibility criteria

We included studies that only focused on relatives of adult patients who were hospitalized in the ICU in the past (who were either discharged or died during hospitalization). We primarily focused on the prevalence and risk factors associated with the occurrence of post-intensive care syndrome (defined as either anxiety, depression, PTSD, complicated grief, burden/overload or activity restriction). We included studies in which full, peer-reviewed reports were published before the day of search (2nd May 2021). Additionally, the papers had to be published in English, regardless of the year of publication. Qualitative studies, case reports, case series, systematic reviews, meta-analyses and papers that assessed mental health of relatives only during ICU hospitalization were excluded.

Information sources

The search was conducted within PubMed, Embase, clinicaltrials.gov, SCOPUS and Cochrane Library on the 2nd of May, 2021.

Search

Search string (titles and abstracts): (((((((family) OR (families])) OR (next of kin)) OR (relative*)) OR (spouse*)) OR (loved one*)) OR (caregiver*)) AND (((((((post-traumatic stress disorder) OR (PTSD)) OR (posttraumatic stress disorder)) OR (depression)) OR (anxiety)) OR (post-intensive care syndrome)) OR (burden)) OR (complicated grief))) AND (((intensive care) OR (ICU])) OR (critical care)) OR (critically ill))

Study selection & # 10. Data collections process

After importing all the papers from the initial search using search string, three independent investigators (ZP, NR, KMe) assessed studies by analyzing titles and abstracts (via Mendeley®). The study was processed further if all adjudicators agreed to include the paper for review. If only two reviewers agreed to proceed with the manuscript, the second assessment of the paper was performed by the fourth investigator (ŁJK).

Data items

Authors, year of publication, type of a study, relatives' and patients' characteristics (number of individuals, sex ratio, median or mean age, relationship between patients and relatives, organ failure severity of patients, enrollment criteria), time-point at which mental health assessment of families was performed, mental health assessment tools, any risk factors for the occurrence of PICS-F and prevalence of PICS-F. We analyzed how many times a risk factor appeared in the included papers and how many times a risk factor achieved statistical significance. Multivariable analyses took priority over univariable analyses. In order to improve the readability of our article, we decided to move the Table with results of the individual studies to the Additional file (Table 1,2,3,4 and 5 in Additional file 1) and, instead, designed a table that would more comprehensively grasp the characteristics of all papers. We calculated the range values, the median values and their interquartile ranges for certain variables that were reported by the studies (Table 2).

Quality assessment

Newcastle-Ottawa scale (NOS) was implemented to assess the quality of cohort studies [6]. A modification of NOS was introduced to assess the quality of cross-sectional studies [7]. The total NOS score of each study was converted to Agency for Healthcare Research and Quality standards [8]. Thus, the studies were rated as either good, fair or poor. All authors participated in the quality assessment of the included studies. Any disagreements were resolved by a discussion.

Results

Study selection

By using the search string within various medical databases (look at *Information sources*) we identified 4608 articles in total. After removing duplicates ($n = 1079$) we screened the remaining papers by evaluating titles and abstracts ($n = 3529$). By using the PICO criteria and the inclusion and the exclusion criteria, we distinguished 340 papers for the full-text read assessment. After excluding the articles for numerous reasons, the final 52 papers were included in the systematic review. We identified 40 prospective cohort studies [6–18, 20–24, 26, 28, 29, 31–33, 35, 38–45, 47, 48, 50, 52–54, 57], 6 randomized controlled trials (RCT) [25, 27, 30, 34, 37, 51], 5 cross-sectional studies [19, 36, 46, 55, 56] and 1 non-randomized trial [49] from which we extracted all the relevant data. Study selection process is presented on a flowchart (Fig. 1).

Quality assessment

The quality assessment was implemented in 45 studies (the 7 remaining studies were either RCTs or non-randomized interventional trials from which we only extracted available risk factors). Overall, 12 studies were rated as “good” [16–18, 20, 23, 31, 48, 49, 53, 56–58], 9 studies as “fair” [11–13, 22, 24, 34, 38, 45, 46] and 24 studies as “poor” [9, 10, 14, 15, 19, 21, 25–27, 29, 32, 35, 38, 39, 41–44, 47, 50, 51, 55, 59, 60] (Additional file 1: Table 6). Firstly, the majority of papers lacked in terms of selection criterion: “demonstration that outcome of interest was not present at start of study”, as they did not exclude

relatives with mental health disorders, such as depression, anxiety or PTSD. Only 9 studies excluded participants due to the above mentioned issue [16, 17, 20, 22, 39, 41, 42, 48, 57]. Secondly, a number of studies included only relatives of survivors [14, 15, 22, 24, 32, 34–37, 41, 44, 51, 57, 60] or only relatives of deceased patients [12, 28, 33, 39, 47, 55, 59] which limited the representativeness of exposed cohorts. Thirdly, 21 out of 45 assessed studies did not implement multivariable analyses and did not control for the most important confounding factors such as gender, age or marital status. Lastly, the outcomes were often self-reported by the participants (n = 18) [10, 11, 15, 19, 21, 22, 25–27, 29, 32, 39, 42–44, 47, 50, 51, 55, 59, 60].

Study characteristics

The majority of studies were conducted in either North America (n = 22) or Europe (n = 20). Nearly half of the studies (n = 25) explored more than one PICS-F area. The total number of patients and relatives included across the studies was 7448 and 8102 respectively. The summary of included studies is presented on Table 2.

Post-intensive care syndrome in families

Overall, the prevalence of PICS-F varied from 2.5 to 69% (Table 2). The area of PICS-F that seemed to be the most prevalent was the complicated grief (the median = 46%; IQR = 27-49.9%) [26, 28, 44, 47, 55] and caregiver burden/strain (the median = 45%; IQR = 29-62.7%) [21, 37, 45, 56, 57, 60]. The median frequencies of anxiety, depression and PTSD were similar: 28%, 24% and 31% respectively (Table 2).

The studies varied in terms of PICS-F assessment: PTSD was the most frequently studied outcome (n = 31) [9, 14, 15, 17, 19–26, 28, 29, 34, 39–54], followed by depression (n = 27) [9, 12–17, 19–39], anxiety (n = 18) [9–26], caregiver burden/strain (n = 6) [21, 37, 45, 56, 57, 60], complicated grief (n = 5) [26, 28, 44, 47, 55], lifestyle disruption (n = 2) [35, 36], psychological distress (n = 1) [58] and composite outcome of PICS-F (n = 1) [59]. The studies also varied in terms of time-point at which they assessed the outcomes. 3-month period was the most frequent time-point of PICS-F assessment (n = 30) [10, 12, 13, 16–18, 20, 23, 24, 27, 29, 40–42, 44, 50, 53, 60], followed by 6-month period (n = 26) [10, 12, 20, 23, 24, 26–29, 33, 35, 36, 40–42, 44, 47, 50, 53, 57], 1-month period (n = 14) [12, 16, 17, 19, 26, 28, 43, 48] and 2-month period (n = 11) [19, 25, 32, 34–38, 47].

Risk factors for PICS-F

We distinguished several subgroups of risk factors. In total, 70 potential risk factors for PICS-F were identified, among which the most common were relative-related risk factors (n = 33), followed by patient-related (n = 28) and medical-staff-related (n = 9) factors. The highest number of risk factors associated with development of anxiety, depression, PTSD and complicated grief were variables involving the relatives, while the presence of caregiver burden was rather connected with worse condition and lower level of patient's activity after ICU stay. The complicated grief was considerably determined by factors regarding the patient's death. The most prevalent (identified by at least 3 studies) risk factors for particular outcomes were the following: for anxiety: medical history of mental disorders among the

relatives; for PTSD and depression: death and worse condition of a patient, female sex of the relative, being a spouse, as well as mental disorders of the relative in medical history or during patient's ICU stay. The risk factors related to each outcome and their occurrence are listed in Table 3.

In regards to studies of best quality (risk factors acquired from 11 cohort studies, 5 RCTs and 1 cross-sectional study), a total of 7 most important factors were established and are presented on Fig. 2 (a given risk factor must have co-occurred in at least 3 "good" papers in order to be included in the Figure) [16–18, 20, 23, 28, 30, 31, 33, 40, 47, 48, 46, 53, 56–58].

Discussion

In this systematic review, we focused on identifying risk factors associated with the development of PICS-F. The majority of participants consisted of women below 65 years who were spouses of the ICU patients. We described over 70 potential risk factors, among which, younger age of a patient, death of a patient, depression in relatives during the ICU stay, history of mental disorders in relatives, being a spouse and low satisfaction with communication & care in the ICU seem to be most well-documented. Secondly, the prevalence of PICS-F is high and seems to depend on its subtype (e.g. complicated grief/caregiver burden possibly occurring more frequently than anxiety, depression or PTSD). Importantly, the majority of included studies presented poor quality and substantial heterogeneity, therefore, we failed to conduct meta-analysis.

The majority of studies were conducted in Western countries (n = 45). Noteworthy, there was a considerable difference in terms of healthcare, income, culture, and structure of societies between these countries and other parts of the world. This divergence could influence the way the risk factors shape the development of PICS-F. For instance, as developed countries may exhibit higher ICU-survival rates, the importance of certain outcomes, e.g. caregiver burden may be markedly different for countries with higher mortality rates, where, in contrast, complicated grief may be expressed more strongly.

The heterogeneity among the studies was noticeable in terms of selection of the participants, representativeness of patient populations, mental health screening-tools and assessment of the outcomes (outcome defined as either continuous change in psychiatric scores or as a presence of clinically significant PICS-F). It is important to note that the majority of the outcomes were reported by the participants and not diagnosed by specialists in psychiatry and psychology. This introduces a significant limitation in terms of either prevalence of PICS-F or the association between certain risk factors and PICS-F. Moreover, a number of studies did not implement multivariable analyses to assess the significance of risk factors. Lastly, we observed a considerable proportion of studies with loss-to-follow-up exceeding 20% which also introduces bias to our analysis (Table 2).

In order to assess the power of certain risk factors, we analyzed what frequency a given risk factor was statistically significantly associated with PICS-F in regards to all studies that examined that factor (Table 3 and Additional file 1: Tables 7 & 8). For instance, "mental disorders during an ICU stay" (Table 3, depression) was reported to be significant in 4 out of 6 studies that explored this risk factor. In contrast,

“lower level of education” was reported only in 1 out of 10 studies (Table 3, anxiety). The above mentioned proportions could shape the way we interpret every risk factor. Importantly, death of a patient was not always identified as a significant risk factor for PICS-F (5/16). This finding could suggest that a fraction of patients who survive the ICU may require excessive care and their quality of life may be significantly reduced. This would result in relatives experiencing higher burden, higher stress and lifestyle disturbances that promote the occurrence of PICS-F in a similar fashion as would the death of a patient. To summarize, although we defined over 70 risk factors, it is possible that a number of them are rather controversial and should be confirmed in further studies, particularly because many of those factors were explored just once across the literature.

Conclusions

There are a plethora of possible risk factors associated with the development of PICS-F that also seem to depend on its subtype. Among others, younger age of a patient, death of a patient, depression in relatives during the ICU stay, history of mental disorders in relatives, being a spouse and low satisfaction with communication & care in the ICU are associated with the development of PICS-F. Therefore, special attention should be paid to relatives who represent the above mentioned factors. The definitive conclusions are considerably limited by the quality and heterogeneity of the included studies.

Abbreviations

PICS-F

Post-intensive care syndrome in family

PTSD

Post-traumatic stress disorder

NOS

Newcastle-Ottawa Scale

RCT

Randomized controlled trial

n

number of studies

ICU

intensive care unit

MV

mechanical ventilation

Σ

the sum

R

the range between the lowest and the highest value

M

the median
IQR
interquartile range
APACHE II
Acute Physiology and Chronic Health Evaluation II
SOFA
Sequential Organ Failure Assessment score
SAPS II
Simplified Acute Physiology Score II
HADS-A
Hospital Anxiety and Depression scale-subscale for anxiety
GAD-7
Generalized Anxiety Disorder-7
HADS-D
Hospital Anxiety and Depression scale-subscale for depression
CES-D
Center for Epidemiologic Studies Depression Scale
BDI-13
Beck Depression Inventory-13
PHQ
Patient Health Questionnaire depression scale
IES
Impact of Events Scale
IES-R
Impact of Events Scale-Revised
PCL-C
PTSD Checklist for DSM-IV (civilian)
PCL-S
PTSD Checklist for DSM-IV (specific)
PCL-5
PTSD Checklist for DSM-V
PTSS
PTSD Symptom Scale
PC-PTSD
Primary Care PTSD Screen for DSM-V
TSQ
Trauma Screening Questionnaire

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

ŁJK and ZP: conception of the work; ZP, NR, KMa and KMe: design of the work; ZP, NR and KMe: the acquisition of data; ZP, NR, KMa, KMe and ŁJK: draft of the work. All authors have approved the submitted version and have agreed to be accountable for their contributions and the integrity of the work.

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Tables

Table 1. The PICO criteria.

PICO	Description
Participants	Relatives of adults who were hospitalized in the ICU
Interventions (Exposure)	Risk factors for the occurrence of PICS-F
Comparisons	Not having risk factors for PICS-F
Outcomes	Anxiety, depression, PTSD, complicated grief, burden/overload and activity restriction in families of patients in the post-ICU period

Table 2. Summary of the included studies.

Studies (n=52) [6-57]		
Continent (n=52)	North America	n=22 [10,11,14,18,19,22,26,27,29-38,40,41,43,59]
	Europe	n=20 [9,13,15,20,21,23,24,28,39,44-47,49,52,53-55,57,58,]
	South America	n=4 [16,17,48,56]
	Australia	n=3 [42,50,60]
	Asia	n=2 [12,25]
	Africa	n=1 [51]
	Study design (n=52)	Cohort
	Randomized controlled trial	n=6 [28,30,33,37,40,54]
	Cross-sectional	n=5 [22,39,49,58,59]
	Non-randomized trial	n=1 [52]
Number of PICS-F areas by the studies (n=52)	1 outcome	n=27 [10,11,18,27,30-32,34,38,40-42,45,47-60]
	> 1 outcomes	n=25 [9,12-17,19-26,28,29,33,35-37,39,43,44,46]
Patient population (n=45)	$\Sigma=7448$; R 17-1212; M=118; IQR 73-192 (no. of patients) [9,10,12-24,27,28,30-32,34-38,40-50,52-54,56-60]	
Age (n=40)	< 65 years	n=29 [9,10,14,15,17-19,27,28,30,32,34-40,45,47-50,52-54,56,58,60]
	\geq 65 years	n=11 [12,13,16,20,23,24,31,44,57,59]
Female sex (n=37)	R 19-63%; M=38%; IQR 33.5-44% [9,10,12-20,22,23,27,28,30-32,33,34-38,39,40,44,45,47-50,52,53,56-60]	
Inclusion criteria (n=53)	ICU survival	n=14 [14,15,22,24,32,34-37,41,44,51,57,60]
	ICU death	n=7 [12,28,33,39,46,55,59]
	ICU stay/ MV > 24/48/72/more hrs	n=31 [9,16,17,19,21,22,25,26,28-30,31,34-38,40,42,44,45,47-54,56,58,60]
	Others	n=10 [10,11,13,18,20,23,27,31,20,49]
ICU length of stay (n=26)	< 7 days	n=6 [9,17,18,48,49,60]
	\geq 7 days	n=21 [12,14,16,20,21,23,31-38,42,44,45,47,50,52,54,58]

Organ failure assessment (n=26)	SOFA (n=7)	R 1.5-14.73 pts; M=8.1 pts; IQR 2.4-14 pts [12,15-17,20,23,30,48]
	APACHE II (n=16)	R 15.2-56 pts; M=23.5 pts; IQR 19.9-31.3 pts [12,14,18,21,22,32,35,36,42,44,47,49,50,53,54,60]
	SAPS II (n=10)	R 29.6-64 pts; M=42.3 pts; IQR 39.7-61.2 pts [15,17,19,42,49,50,52,55,56,58]
Overall mortality (n=36)	R 0-100%; M=21.5%; IQR 0-68.7% [12,14,15,16,18-20,22-24,28,30-37,39,41,42,44-47,49,51-57,59,60]	
Population of relatives (n=52)	Σ =8293; R 28-1212; M=104; IQR 67-189 (no. of relatives) [9-60]	
Age (n=46)	< 65 years	n=45 [9-21,23,25-30,32-45,47-49,51,53-56,58-60]
	>= 65 years	n=1 [31]
Female sex (n=47)	R 25-84%; M=71%; IQR 64-74% [9-23,25-45,47-49,51,53-56,59,60]	
Kinship	Spouses (n=45)	R 13-100%; M=48%; IQR 36.5-66% [9-16,18-45,47-50,52-56,58,60]
	Children (n=38)	R 3-54%; M=26%; IQR 17.5-35.5% [9,10,12-15,18-23,25-31,33-45,47-50,52-56,58,60]
	Parents (n=31)	R 2-27%; M=13%; IQR 9-18% [9,10,12-15,18,19,21-23,26,27,29-32,34-36,38-45,49.50,53-35,58,60]
Higher education (n=29)	R 14-91%; M=42%; IQR 34-73.5% [9-14,16,18,20,22,23,25-27,29,31,33,34,37,38,40,41,43,44,48,49,51,54,56,58]	
Primary caregivers	100%	n=19 [10,11,21,22,27,29,30,34-38,41,44,48,50,56,57,60]
	Unspecified/Other	n=26 [9,12-20,23-26,28,31-33,39,40,42,43,45-47,49,51-55,58,59]
Surrogate decision makers	100%	n=11 [12,13,19,23,40,42,43,46,49,53,59]
Anxiety studies (n=18)	R 3.3-69%; M=28%; IQR 15-39% [9,10,12-21,23-26]	
Diagnostic tool (n=18)	HADS-A	n=17 [9-13,15-26]
	GAD-7	n=1 [14]
Prevalence (n=16)	1 month (n=5)	R 10.7-34.2%; M=21%; IQR 15.1-28.07% [12,16,17,19,26]
	3 months (n=9)	R 7.4-48%; M=32%; IQR 10.8-39.7% [10,12,13,16-18,20,23,24]
	6 months (n=3)	R 3.3-32%; M=15% [10,12,26]

	Other (n=6)	R 18-69%; M=39.5%; IQR 30.6-48% [9,14,15,19,21]
Loss-to-follow-up (n=23)	>20%	n=8 [9,10,12,16,19,24-26]
Depression studies (n=27)		R 5.3-56%; M=24%; IQR 19-34% [9,12-17,19-21,23,24,26-29,31-38]
Diagnostic tool (n=27)	HADS-D	n=15 [9,12,13,15-17,19-24,26-28]
	PHQ	n=4 [14,29,30,33]
	CES-D	n=7 [31,32,34-38]
	BDI-13	n=1 [39]
Prevalence (n=23)	1 month (n=6)	R 5.8-49.3%; M=20.3%; IQR 8-42% [12,16,17,19,26,28]
	2 months (n=7)	R 5.25-56%; M=33.93%; IQR 31.1-43.3% [19,32,34-38]
	3 months (n=9)	R 5.3-39%; M=20%; IQR 15.9-29% [12,13,16,17,20,23,24,27,29]
	6 months (n=7)	R 6-30.8%; M=19.2%; IQR 14.9-30% [12,26-28,33,35,36]
	12 months (n=2)	R 22.8-29.2% [35,36]
	Other (n=4)	R 21-55%; M=28.2%; IQR 21.7-44.5% [9,14,21,31]
Loss-to-follow-up (n=26)	>20%	n=11 [9,12,16,19,24,26,27,30,32,34,37]
PTSD studies (n=31)		R 2.5-67.6%; M=31%; IQR 17-45% [9,14,15,19-21,23-26,28,29,34,40-54]
Diagnostic tool (n=31)	IES/IES-R	n=21 [9,15,17,20,23-29,39,40,42,43,46,48-54]
	PCL-C/S/5	n=6 [14,19,34,41,47,51]
	Other (n)	n=4 [19,22,44,45]
Prevalence (n=28)	1 month (n=3)	R 2.5-7.9%; M=7.7% [19,43,48]
	2 months (n=3)	R 11.1-35%; M=22.9% [19,25,47]
	3 months (n=10)	R 15-51%; M=29.9%; IQR 18-39% [20,23,24,29,40-42,44,50,53]
	6 months (n=8)	R 14-57.1%; M=39.3%; IQR 19.5-46.9% [26,28,34,41,43,46,51,54]
	Other (n=7)	R 15.7-67.6%; M=45%; IQR 31-59.1% [9,14,15,21,45,49,52]
Loss-to-follow-up (n=29)	>20%	n=8 [9,19,25,26,41,43,46,48]
Complicated grief studies		R 21.7-52.1%; M=46%; IQR 27-49.9% [26,28,44,47,55]

(n=5)		
Diagnostic tool (n=5)	ICG/ICG-R	n=5 [26,28,44,47,55]
Prevalence (n=5)	6 months (n=4)	R 21.7–52.1%; M=39.2%; IQR 27-49% [26,28,44,47]
	9 months (n=1)	47.7% [55]
Loss-to-follow-up (n=5)	>20%	n=3 [44,47,26]
Caregiver burden/strain studies (n=6)		R 21-72.4%; M=45%; IQR 29-62.7% [21,37,45,56,57,60]
Diagnostic tool (n=6)	ZBI	n=2 [56,57]
	CSI	n=2 [21,45]
	Other	n=2 [37,60]
Prevalence (n=4)	Various time points	R 21-72.4%; M=45%; IQR 29-62.7% [21,45,46,57]
Loss-to-follow-up (n=5)	>20%	n=3 [37,45,58]
Other PICS-F areas (n=4)	Look at chapter: <i>Post-intensive care syndrome in families</i>	

Legend: n: number of studies; ICU: intensive care unit; MV: mechanical ventilation; Σ : the sum; R: the range between the lowest and the highest value; M: the median; IQR: interquartile range; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment score; SAPS II: Simplified Acute Physiology Score II; HADS-A: Hospital Anxiety and Depression scale-subscale for anxiety; GAD-7: Generalized Anxiety Disorder-7; HADS-D: Hospital Anxiety and Depression scale-subscale for depression; CES-D: Center for Epidemiologic Studies Depression Scale; BDI-13: Beck Depression Inventory-13; PHQ: Patient Health Questionnaire depression scale; IES: Impact of Events Scale; IES-R: Impact of Events Scale-Revised; PCL-C: PTSD Checklist for DSM-IV (civilian); PCL-S: PTSD Checklist for DSM-IV (specific); PCL-5: PTSD Checklist for DSM-V; PTSS: PTSD Symptom Scale; PC-PTSD: Primary Care PTSD Screen for DSM-V; TSQ: Trauma Screening Questionnaire

Table 3. Summary of risk factors associated with the development of PICS-F.

Anxiety	
Patient-related	Mental disorders after ICU stay - anxiety (2/5) [10,15], worse condition during ICU stay (1/10) [25]
Relative-related	<p>Demographic factors:</p> <p>Female sex (2/12) [17,20], younger age (1/13) [26], worse economical situation - unemployment (1/4) [13], atheism (1/4) [16], lower level of education (1/10) [25]</p> <p>Psychiatric factors:</p> <p>Medical history of mental disorders (4/6) [10,14,18,19], mental disorders during patient's ICU stay (2/5) [10,11], mental disorders after patient's ICU stay - depression (1/1) [13], worse coping mechanism (1/1) [19], presence of additional stressors (1/1) [20]</p> <p>Caregiving-related factors:</p> <p>Caregiver strain (1/1) [21]</p> <p>Other factors:</p> <p>Lack of previous ICU experience (1/1) [16] Cortisol awakening response (1/1) [18]</p>
Medical staff-related	Lower satisfaction with communication and care (1/7) [23], physician-surrogate prognostic communication (1/1) [12]
Depression	
Patient-related	<p>Demographic factors:</p> <p>Younger age (2/14) [28, 30], older age (1/14) [36], female sex (1/11) [35]</p> <p>Psychiatric factors:</p> <p>Mental disorders after ICU stay - depression (2/5) [15, 27]</p> <p>Other clinical factors:</p> <p>Death (4/6) [9,13,20,30], worse condition during ICU stay (4/12) [13, 29, 34, 35], lower level of activity before or after ICU stay (3/10) [20, 31, 32], residence in institution after ICU stay (1/6) [34]</p>
Relative-related	<p>Demographic factors:</p> <p>Female sex (7/20) [17, 20, 28, 31, 33, 34, 39], being a spouse (5/18) [20, 23, 28, 30, 39], being a parent (1/18) [39], worse economical situation (1/5) [32], lower level of education (2/15) [27, 33], higher level of education (1/15) [16], younger age (1/19) [26], living alone (1/1) [28]</p>

Psychiatric factors:

Mental disorders during patient's ICU stay (4/6) [27, 30, 34, 37], medical history of mental disorders (4/6) [13, 14, 19, 33], Mental disorders after patient's ICU stay - anxiety (2/2) [12, 13]

Caregiving - related factors:

More hours spent daily helping a patient (1/2) [38], caregiver strain (1/1) [21], using a paid assistance to take care of a patient (1/1) [36]

Other factors:

Living with the patient (2/6) [16, 32] Fewer years of association with patient (1/1) [33]

Medical staff-related

Conducting a family meetings (1/1) [12], being a witness of a CPR by a medical team (1/1) [13]

PTSD

Patient-related

Demographic factors:

Younger age (2/18) [28, 48]

Psychiatric factors:

Mental disorders after ICU stay (2/6) [45, 54]

Other clinical factors:

Death (3/10) [9, 48, 53], worse condition during ICU stay (6/16) [29, 40, 43, 46, 47, 53], longer ICU stay (1/15) [47], no comorbidities before ICU stay (1/1) [14]

Relative-related

Demographic factors:

Female sex (10/23) [14, 20, 23, 33, 39, 46, 47, 49, 51, 53], being a spouse (3/17) [23, 28, 39], being a parent (1/17) [39], being a child (1/17) [53], worse economical situation (2/6) [42, 49], lower level of education (1/15) [47]

Psychiatric factors:

Medical history of mental disorders (4/5) [14, 19, 33, 49], mental disorders during patient's ICU stay (7/9) [24, 25, 40, 41, 47, 48, 50], worse coping mechanism (1/1) [19], presence of additional stressors (1/1) [20], no chance to say final goodbye (1/1) [46], presence at the time of patient's death (1/1) [46]

Caregiving - related factors:

Caregiver strain (1/1) [21], daily visits at patient's bed (1/1) [43]

Other risk factors:

Weaker bond with patient (1/1) [41], being a surrogate decision-maker (1/8) [53], Fewer years of association with patient (1/1) [33]

ICU-
related

Therapeutic measures perceived as insufficient (1/11) [49], feeling that information from medical team was incomplete (1/11) [53], large ICU (>12 beds) (1/1) [24]

Complicated grief

Patient-
related

Demographic factors:

Younger age (1/2) [28]

Other clinical factors:

Refusal to treatment (1/1) [46], patient died when intubated (1/1) [46]

Relative-
related

Demographic factors:

Female sex (1/4) [46], being a spouse (1/2) [28], living alone (2/2) [28, 46]

Psychiatric factors:

Not understanding the concept of brain death (1/1) [55], no chance to say final goodbye (1/1) [46], presence at the time of patient's death (1/1) [46]

Medical
staff-
related

Unsatisfactory communication with the medical staff (1/3) [46], Intensivist board certification before 2009 (1/1) [46]

Caregiver burden/strain

Patient-
related

Lower level of activity after ICU stay (2/3) [21, 57], residence in institution after ICU stay (1/1) [37]

Relative-
related

Being a child (1/3) [37]

Medical
staff-
related

None

Others - insomnia (1), lifestyle disruption (2), psychological distress (3), composite outcome - depression, anxiety, panic and complicated grief (4)

Patient-related	Female sex ² (1/2) [35], tracheostomy ² (1/2) [35], functional dependency before or after ICU stay ² (2/2) [35, 36], higher education ² (1/1) [35], disease duration <5 years ⁴ (1/1) [59], residence in an institution after ICU stay ³ (1/1) [58]
Relative-related	Anxiety ¹ (1/1) [21], being a spouse ⁴ (1/1) [59], presence of additional stressor ⁴ (1/1) [59], environmental strain ³ (1/1) [58], unemployment/absence from work ³ (1/1) [58], less hope for the situation to get better ³ (1/1) [58]
Medical staff-related	Failure to find a comforting physician ⁴ (1/1) [59]

Explanation: Number in brackets: A risk factor significantly associated with PICS-F/ a total number of times a certain risk factor was studied across the studies (see Additional file 1: Table 7 & 8).

Figures

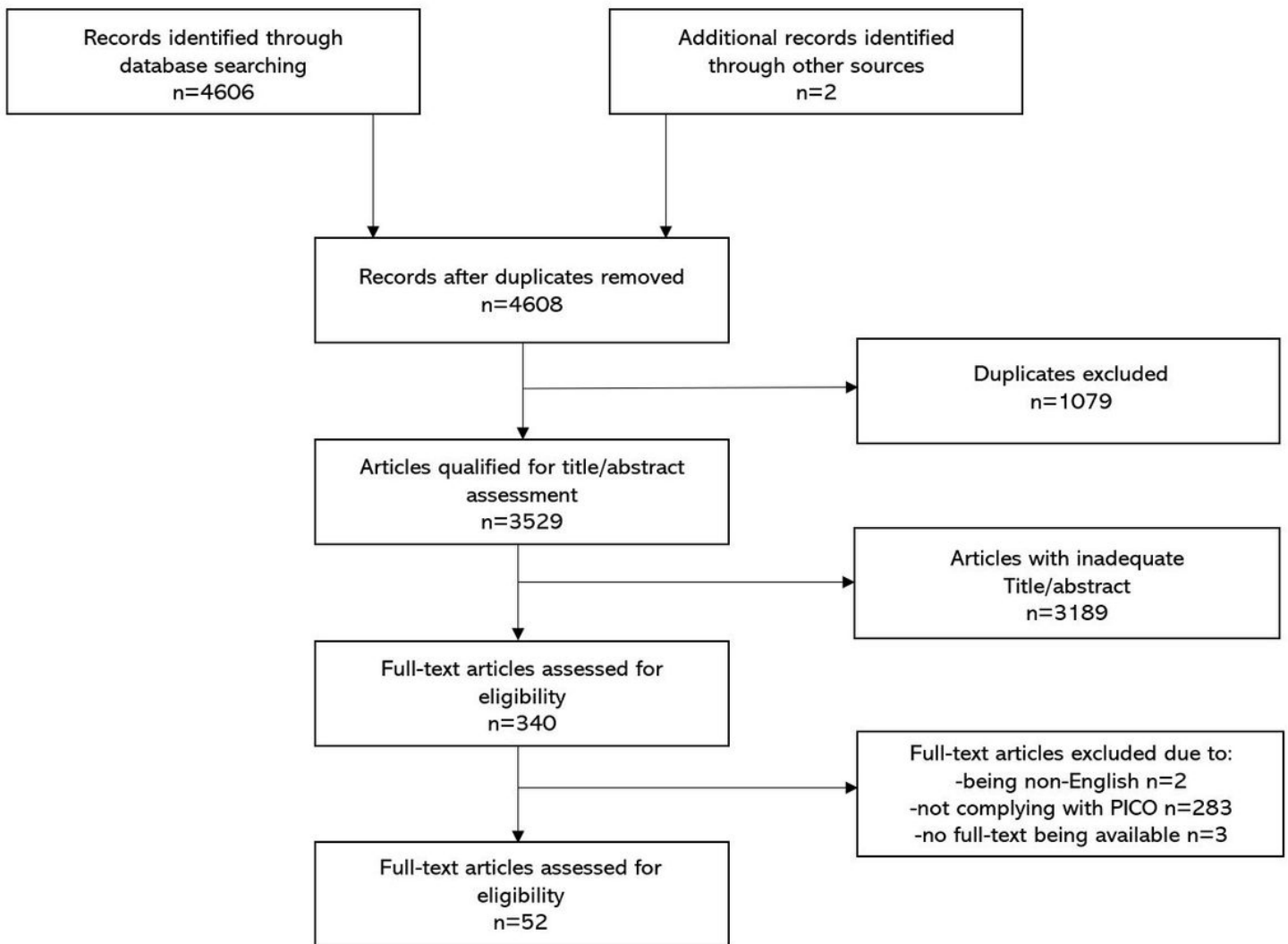


Figure 1

Study selection process.

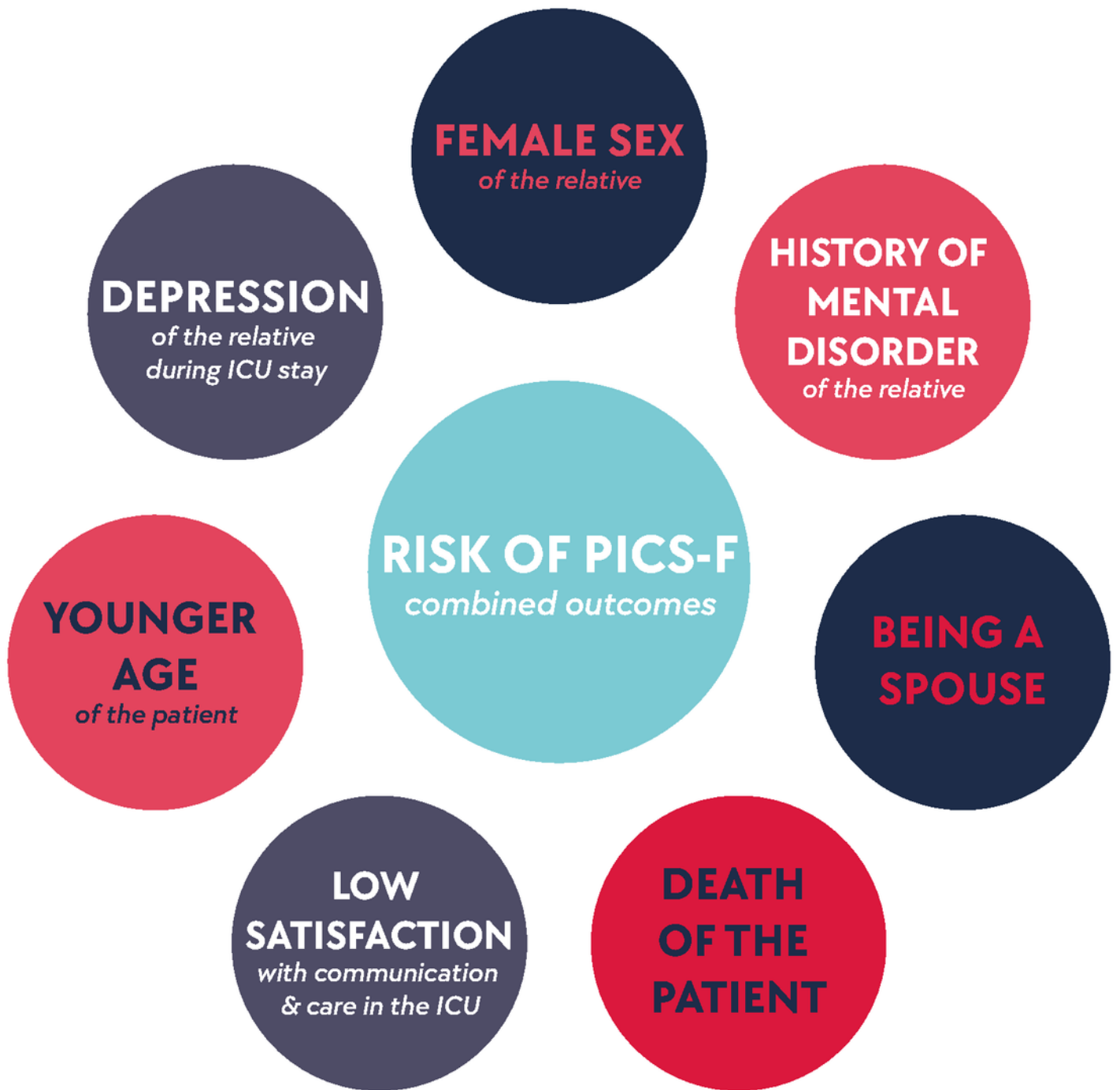


Figure 2

Seven, most common risk factors of PICS-F, derived from the studies of best quality.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1PICSF2.docx](#)
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