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Long-term consequences in survivors of critical illness. Analysis of incidence and risk factors

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Abstract

Aim. This study investigates the incidence of long-term consequences in survivors of critical illness 6 months after ICU care. A retrospective analysis of the risk factors was also completed.

Methods. A mixed-method design was used. A qualitative design was used in the questionnaire study (phase 1), and a quantitative design was used for the retrospective study (phase 2).

Results. 116 patients were interviewed. Forty-eight patients (41.4%) reported at least one long-term consequence 6 months after ICU discharge. The most frequent consequences were anxiety (n = 33, 28.4%), depression (n = 32, 27.6%) and chronic pain (n = 24, 20.7%). The interview showed the concurrent caseness of PTSD, anxiety and depression in 14 (12.1%) patients. Observed risk factors were age > 60 years (OR = 2.65, IC = 1.23-5.69; p = 0.0119), trauma diagnosis (OR = 5.3, IC = 1.60-17.76; p = 0.0033), length of mechanical ventilation > 7 days (OR = 2.18, IC = 1-4.74; p = 0.0471) length of ICU stay > 10 days (OR = 2.47, IC = 1.16-5.26; p = 0.0185) and clinical conditions at the ICU admission. The quality of life score was lower if the respondent had long-term consequences.

Discussion. A high incidence of long-term consequences is found in survivors of critical illness. In future, studies that investigate interventions to prevent these issues after ICU care are need.

Key words
- intensive care
- outcome assessment
- risk factors
- survivors

INTRODUCTION

Critical illness is recognized as being associated with a number of detrimental long-term sequelae that can impact the health of people for many years after discharge from an intensive care unit (ICU) [1].

These long-term sequelae are now recognized as cognitive impairment, psychological disability and ICU-acquired neuromuscular weakness [2-4].

Cognitive impairment has been reported to occur on average in 25-75% of ICU survivors, in the form of disturbed memory, amnesia and Alzheimer's disease [2, 3, 5]. The major risk factors associated with it are hypoxia (ARDS, cardiac arrest), respiratory failure, severe sepsis, trauma, requiring prolonged mechanical ventilation, use of renal replacement therapy, acute respiratory distress syndrome (ARDS), delirium during ICU stay and prior cognitive impairment (older age, pre-existing cognitive deficits) [6, 7].

Psychological disability has been reported to occur on average in 1-62% of ICU survivors, in the form of depression, anxiety, and post-traumatic stress disorder (PTSD) [3, 6, 8]. The major risk factors are same as for cognitive impairment and also include the use of sedation and analgesia in ICU, female gender, lower education level, and pre-existing disability [8-10].

ICU-acquired neuromuscular weakness is the most common form of physical impairment occurring more than 25% of ICU survivors (poor mobility, recurrent

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falls, or quadri or tetra paresis) [4, 11]. The major risk factors include prolonged mechanical ventilation (> 7 days), sepsis, multisystem organ failure, as well as prolonged duration of the lenght of ICU stay [12, 13].

Quality of life, chronic pain, psychological and psychiatric factors, physical fitness, functional capacity, are the long-term outcomes more commonly investigated in intensive care research [14-16].

The problem and the need for follow-up studies is increasingly relevant. A number of risk factors for individual long-term consequences in critical care survivors have been investigated. However, there is a lack of studies that analysing different symptoms after ICU care to date in critical care research. Furthermore, the studies available today do not pay attention to the risk factors that can be analysed before and during intensive care. In other words, if there are ICU-related risk or general risk factors. The present study was carried out maintaining the hypothesis that long-term consequences in survivors of critical illness is influenced not only by the ICU care but also by the clinical and general conditions at the time of ICU admission.

Aim

This study investigates the incidence of long-term consequences in survivors of critical illness 6 months after ICU care. A retrospective analysis of the risk factors was also completed.

Study design

For this study, a qualitative design was used in the questionnaire study (phase 1), and a quantitative design was used for the retrospective study (phase 2).

A questionnaire study is a research consisting of a series of questions (or other types of prompts) for the purpose of gathering information from respondents. Although questionnaires are often designed for statistical analysis of the responses, this is not always the case. Surveys and questionnaires are the most common technique for collecting quantitative or qualitative data.

A retrospective study uses existing data that have been recorded for reasons other than research. A retrospective case series is the description of a group of cases with a new or unusual disease or treatment. Therefore, a retrospective study design should never be used when a prospective design is feasible. However, a retrospective study looks backwards and examines exposure to suspected risk or protection factors in relation to an outcome that is established at the start of the study.

Patients received a letter introducing the study at ICU discharge. The letter explained that they might receive a phone call from the study team and provided contact details for the study office. Written consent was obtained by the nursing staff at the time of discharge, or at the follow-up visit.

MATERIALS AND METHODS

Setting

The study was single centered, based in an Italian adult 8-bed ICU in a 950-bed secondary hospital in Northern Italy (Azienda Socio Sanitaria Territoriale di Lecco). This hospital is the largest and most important in terms of numbers and economic size of the territory. Each year Lecco hospital carries out about 35 000 admissions, almost 15 000 surgical procedures, about 3 000 000 outpatient appointments and around 80 000 emergency room visits. The hospital admits more than 350 patients to the general ICU per year.

Common conditions that are treated within the ICU include acute respiratory distress syndrome (ARDS), post-operative surgical, trauma, multiple organ failure and sepsis. The unit made up of dedicated full-time intensivists (registered nurses and medical doctors) trained in adult multidisciplinary medicine; 24 registered nurses and 12 medical anaesthesiologists working full-time in the department, (4 registered nurses on each shift, 2 medical doctors morning-afternoon and 1 on night shift).

Participant selection

All patients aged at least 18, admitted to Lecco Hospital ICU from 1 January 2018 to 30 November 2018, were eligible to be included in the study. The interview was carried out between June 2018 and May 2019 (6 months after ICU discharged). Patients were included in the study only if they were able to communicate at the time of the interview.

Phase 1: Questionnaire study

The first aim was addressed by the use of standardized questionnaires or interviews to collect data. A short one-on-one interview was designed for the purpose of investigating presence of anxiety, insomnia, depression, chronic pain, Post-Traumatic Stress Disorders, fatigue and quality of life. The interview was administered by an ICU registered nurse who was involved in the study. Face-to-face administration of the questionnaires was chosen to increase the response rate. The interview was conducted in a dedicated room within the intensive care unit department of the Lecco Hospital.

We used the previously validated Hamilton Anxiety Rating Scale (HAM-A) for the assessment of anxiety [17]; the Insomnia severity index (ISI) for the assessment of insomnia [18]; the Patient Health Questionnaire (PHQ-9) for the assessment of depression [19]; the Brief Pain Inventory (BPI) for the assessment of chronic pain [20]; the Post-Traumatic Stress Disorder Check List -Civilian (PCL-C) for the assessment of PTSD [21]; the Revised-Piper Fatigue Scale (PFS-R) for the assessment of fatigue [22] and Euroqol 5D instrument (EQ-5D) for the assessment of perceived quality of life [23].

These instruments can be both self-administered and administered in person, as we did in our study.

Phase 2: Retrospective study

After the interview, patients' clinical data were obtained from their electronic medical records (*Margherita3 2010 form*) stored at the ICU. The electronic medical records were used to obtain the data required to complete the retrospective study, including all risk factors and outcomes investigated.

The independent variables examined were defined in the research protocol and consisted of the risk factors

for long-term consequences highlighted previously in the literature. These included patient age, APACHE II and SOFA score, admission diagnosis, gender, ICU LOS, use of renal placement therapy, severe sepsis and ARDS.

Interpretation of instrument scores

All instruments used during the interview have specific cut-offs that indicate, based on the scores, the absence or presence (mild, moderate or severe/intense) of the assessed symptom.

Hamilton Anxiety Rating Scale: total score range of 0-56, < 17 indicates mild entity, 18-24 mild to moderate and 25-30 moderate to severe.

Insomnia severity index: total score range of 0-28, absence of insomnia (0 -7), insomnia below the threshold (8-14), moderate insomnia (15-21) and severe insomnia (22-28).

Patient health questionnaire: total score range of 0-27, absent (0-4), sub-threshold depression (5-9), mild major depression (10-14), moderate major depression (15-19) and severe major depression (20-27).

Brief pain inventory: This instrument has different items. For this study we considered the item 3) please rate your pain by ticking the box beside the number that best describes your pain at its worst in the last 24 hours; 4) please rate your pain by ticking the box beside the number that best describes your pain at its least in the last 24 hours; 5) please rate your pain by ticking the box beside the number that best describes your pain on the average, and 6) please rate your pain by ticking the box beside the number that tells how much pain you have right now. Each item has a total score range of 0-10, no pain (0-3), mild or moderate pain (4-6) and intense pain (7-10).

Post-Traumatic Stress Disorder Check List – Civilian: total severity score 0-80. For this instrument we considered a PCL-C score ≥ 45 defined PTSD caseness.

Revised-Piper Fatigue Scale: for the final score, the scores of all the items of each subscale specific are added and divided by the number of items (n = 22), absent (0), mild (1-3), moderate (4-6), severe (7-10).

Euroqol 5D: three different levels of problem severity within each of five health domains. The levels are none, moderate and severe/extreme (coded 1 through 3, respectively), whilst the domains are mobility, capacity for self-care, conduct of usual activities, pain/discomfort and anxiety/depression, ordered as such. The conscious health states are therefore limited to 243 severity/domain vectors, ranging from 11111 (no problems in any domain) to 33333 (severe problems in all five domains). Having located the current health state, the respondent then evaluates his or her health using a visual analogue scale (VAS). This is a vertical, calibrated, line, bounded at 0 ("worst imaginable health state") and at 100 ("best imaginable health state").

Data analysis

The data were analysed using the Statistical Package for SS version 21.0 (SPSS Inc., Chicago, IL, USA).

Patients' demographic and clinical characteristics were analysed by using descriptive statistics and presented as numbers and percentages for the categoric variables and means (M) and standard deviations (±) for the continuous variables.

Comparisons between groups were performed with the chi-square test for the categorical data and with Student's t-test for the continuous data.

Variables were included in the analysis only if they were statistically significant at $p < 0.05$.

For the multivariate analysis, logistic regression with backward stepwise elimination by using the likelihood test statistic was used to assess potential predictors of development of long-term consequences in survivors of critical illness. For the univariate analysis, a Mann-Whitney *U* test was performed for comparisons between the continuous variables.

Odds, ratios and the 95% confidence intervals were calculated for each risk factor regarding ICU admission.

Relative risk and the 95% confidence intervals were calculated for each variable analysed during the follow-up interview.

As a number of studies have suggested that the risk of developing disability after ICU discharge, ranges from 1 to 62 percent (%) [3, 6, 8] we needed at least 100 patients in total. 6 months post ICU discharge, the sample provided sufficient patients to achieve this number, allowing for mortality and loss to follow-up.

Statistical significance for the identification of independent risk factors was set at $p < 0.05$.

Ethical statement

The project was promoted by the Azienda Socio Sanitaria Territoriale di Lecco and the study protocol was approved by the Human Research Ethics Committee of Brianza.

All participants provided their informed written consent to participate at the time of interview.

Consent was obtained by the nursing staff.

RESULTS

Three hundred eight patients were admitted to Lecco Hospital ICU between 1 January 2018 and 30 November 2018. Six months post ICU discharge, the participation rate in the study was 116 (37.66%) *(Table 1)*. Of these patients, 74 (63.8%) were males, with a mean age of 67.2 ± 13.49 years, and 42 (36.2%) were females, with a mean age of 62 ± 11.6 years. Most patients were surgical patients (n = 69, 59.5%).

Long-term consequences

Forty-eight patients (41.4%) reported at least one long-term consequences.

Twenty patients (17.2%) had 3 consequences, fifteen (12.9%) 2 consequences, and thirteen (11.2%) 4 consequences.

The most frequently were anxiety (n = 33, 28.4%) depression (n = 32, 27.6%) and chronic pain (n = 24, 20.7%) *(Table 2)*.

The interview showed the concurrent caseness of PTSD, anxiety and depression in 14 (12.1%) patients.

Patients with PTSD had an increased anxiety and depression risk (RR = 6.16, IC = 2.72-13.97; $p < 0.001$).

Table 1
Demographic and clinical characteristics of patients included in the study

Characteristics	(n = 116)
Age, mean (±) y	57.12 (12.9)
Gender, n (%)	
Male	74 (63.8)
Female	42 (36.2)
Weight, mean (±), kg	74.12 (13.6)
BMI, mean (±)	25.8 (3.59)
APACHE II, mean (±)	13.2 (5.6)
SOFA at ICU admission, mean (±)	5.8 (3.9)
Diagnosis, n (%)	
Medical	31 (26.7)
Surgical	69 (59.5)
Trauma	16 (13.8)
Advanced cardiovascular support, n (%)	14 (12.1)
Advanced respiratory support, n (%)	82 (70.7)
Neurological support, n (%)	2 (1.7)
Renal support, n (%)	8 (6.9)
Septicaemia and septic shock, n (%)	6 (5.2)
Acute pancreatitis, n (%)	5 (4.3)
Diabetic ketoacidosis, n (%)	2 (1.7)
Acute myocardial infarction, n (%)	4 (3.5)

BMI (body mass index); ASA (American society of anesthesiologists) physical status classification system before surgery; APACHE II (acute physiology and chronic health evaluation II) it is applied within 24 hours of admission of a patient to an ICU; SOFA (sepsis-related organ failure assessment score) scoring system is useful in predicting the clinical outcomes of critically ill patients, it is applied within 24 hours of admission.

Patients with anxiety had an increased depression risk (RR = 0.66, IC = 0.47-0.95; p = 0.0475).

Patients with chronic pain had an increased fatigue risk (RR = 3.50, IC = 1.34-9.11; p = 0.0089).

No other significant association was observed between the variables analyzed during the interview.

Quality of life

Sixty-two different EQ-5D vectors were represented in this recruitment sample, although 11111 (no health problems in any of the five domains) was the most frequently cited, by 58.6 per cent (n = 68) of subjects. For the individuals recording the 11111 health state, the mean EQ VAS score was 86.0 (±11.9).

More severe health problems in any dimension gave rise to a lower EQ VAS value for self-reported health. For any given EQ-5D health state classification, the EQ VAS score was lower if the respondent had pain, fatigue, insomnia, was likely to be anxious and/or depressed as assessed by the HAM-A and PHQ-9 or if they showed severe symptoms of PTSD.

For the 48 individuals with long-term consequences the mean EQ VAS score was 58.0 (± 16.7).

Risk factors in the intensive care unit

Table 3 highlights the results of the subgroup analysis, investigating the risk factors for the long-term consequences analysed in our study.

Significant risk factors with odds, ratios and the 95% confidence intervals are presented.

The significant risk factors for the 48 patients observed were age ≥ 60 years (OR = 2.65, IC = 1.23-5.69; p = 0.0119), trauma diagnosis (OR = 5.3, IC = 1.60-17.76; p = 0.0033), length of mechanical ventilation ≥ 7 days (OR = 2.18, IC = 1-4.74; p = 0.0471) length of ICU stay ≥ 10 days (OR = 2.47, IC = 1.16-5.26; p = 0.0185).

In addition, the severity of the patient at the time of admission to the Intensive Care Unit is to be reported among the risk factors. Indeed, the data APACHE II score ≥ 15 (OR = 2.64, IC = 1.06-6.53; p = 0.0328) and SOFA score ≥ 10 (OR = 2.7, IC = 1.06-6.89; p = 0.0340) at the ICU admission are also significant.

DISCUSSION

We present a result of self-reported anxiety, depression, insomnia, chronic pain, PTSD, fatigue and quality of life of ICU survivors to date. A high burden of post-ICU psychopathological issues was reported in about 4 respondents in 10. A high degree of symptom and long-term consequences concurrency between these six conditions was observed.

Long-term consequences are increasingly recognized as a problem in survivors of critical illness.

This study reported that 40% about of patients were experiencing chronic symptoms at least 6 months after ICU discharge. These consequences have a negative impact on the quality of life perceived by the patients themselves.

Our findings are comparable with incidence of persistent psychopathological issues in longer-term follow-up studies of survivors of ARDS where both the overall incidence of anxiety, depression and PTSD of psychopathological issues are similar [24]. However, we observed a reduction in chronic pain (20.7%) compared to 40% in a previous study [16].

Table 2
Distribution of anxiety, insomnia, depression, chronic pain, PTSD and fatigue, 6 months after ICU discharge

Variable, n (%)	No caseness	Mild symptoms	Moderate symptoms	Severe symptoms
Anxiety[a]	83 (71.6)	22 (18.9)	6 (5.2)	5 (4.3)
Insomnia[b]	96 (82.8)	9 (7.8)	4 (3.4)	7 (6.1)
Depression[c]	84 (72.4)	12 (10.3)	14 (12.1)	6 (5.2)
Chronic pain[d]	92 (79.3)	-	16 (13.8)	8 (6.9)
PTSD[e]	101 (87.1)	-	---	15 (12.9)
Fatigue[f]	98 (84.5)	11 (9.5)	5 (4.3)	2 (1.7)

[a]Hamilton Anxiety Rating Scale (HAM-A); [b]Insomnia severity index (ISI), [c]Patient health questionnaire (PHQ-9), [d]Chronic pain (BPI), and [e]Post-Traumatic Stress Disorder Check List-Civilian (PCL-C), [f]Fatigue (PFS-R).

Table 3
Risk factors of patients which at least one of long-term consequences

Risk factors	Patients with long-term consequences n = 48	Patients without long-term consequences n = 68	OR (95% CI)	p-value
Age (years) > 60, n (%)	26 (54.2)	21 (30.9)	2.65 (1.23-5.69)	0.0119
APACHE II > 15, n (%)	15 (31.3)	10 (14.7)	2.64 (1.06-6.53)	0.0328
SOFA > 10, n (%)	14 (29.2)	9 (13.3)	2.7 (1.06-6.89)	0.0340
Gender, n (%)				
Female	19 (39.6)	23 (33.8%)	1.28 (0.60-2.76)	0.5250
Reason for admission, n (%)				
Surgical	25 (52.1)	44 (64.7%)	0.59 (0.28-1.26)	0.1726
Non-surgical	11 (22.9)	20 (29.4%)	0.71 (0.30-1.67)	0.4362
Trauma	12 (25)	4 (5.9%)	5.3 (1.60-17.76)	0.0033
MV (days) > 7, n (%)	22 (45.8)	19 (27.9)	2.18 (1-4.74)	0.0471
ICU LOS > 10, n (%)	29 (60.4)	26 (38.2)	2.47 (1.16-5.26)	0.0185
Use of renal replacement therapy, n (%)	5 (10.4%)	3 (4.4%)	2.52 (0.57-11.1)	0.2087
Severe sepsis, n (%)	5 (10.4)	2 (2.9)	3.84 (0.7-20.68)	0.0959
ARDS	6 (12.5)	11 (16.2)	0.74 (0.25-2.16)	0.5813
Total of patients; n (%)	48 (41.4%)	68 (58.6%)		

MV = mechanical ventilation;
LOS = length of stay;
OR = odds ratio;
For comparisons, an indipendent sample *Chi-square test* were used.

In line with the literature, age, trauma, length of mechanical ventilation and length of ICU stay were the major risk factors highlighted. In addition to what is described in the literature, age and clinical conditions at the time of admission influence the outcome 6 months after ICU discharge. Under a clinical and public health perspective, these observations potentially inform and support targeted interventions aimed at reducing the occurrence of adverse outcome after ICU discharge. The identified risk factors can be targeted in order to improve the health trajectories of subjects surviving critical illnesses. Given the greatest risks that emerged among elderly patients and with comorbidity, it is necessary to set specific therapeutic pathways for these patients at the time of discharge. Early identification of patients at greater risk means reducing the impact that these long-term consequences have on people's health and on their psycho-social sphere.

Therefore, clinicians' priorities and standards of therapy for the prevention of long-term consequences should take into account the potential effects on patient health, with the goal of improving long-term outcomes through early and effective treatment.

The set of these long-term consequences, after ICU treatment, is often recognized as post-intensive care syndrome (PICS) [25, 26]. Healthcare professionals involved in the follow-up activity and assessment of all survivors of ICU should be aware of the co-occurrence of psychopathological conditions as part of PICS [25].

PICS has cognitive, psychiatric and physical components [26] and describes the consequences that remain in the surviving the critical illness and it is due to the associated neuropsychological, physical and functional disability [26]. However, its exact prevalence remains unknown.

It is important to study the chronicity and consequences of patients discharged from the ICU due to negative factors of public health [27]. Often in the post-ICU population, the observed association between depression and mortality can in part explained by the severity of chronic illness both pre-discharge and post-discharge. However, we did not adjust these factors in this study. The best knowledge, an association between long-term consequences and an increased rate of mortality after discharge from ICU has not been demonstrated previously.

Collecting data on pre-morbid psychological and medical co-morbidities would also be essential in terms of understanding the risk factors for developing set of these long-term consequences, as current illness severity scoring, organ support information and severity scoring is clearly insufficient when it comes to understanding which individuals are at greatest risk [28].

ICU survivors are known to experience impairment in cognition or psychological health and physical function [28]. However, there is a lack of studies that have examined the association among two or more of these variables. We suggest that using methodologies and standardized instruments in ICU survivor populations has the potential to contribute to the development of treatments, preventative strategies and screening guidelines, for this clinically condition.

Study limitation

The main limitations of the study are that the risk factors data were collected retrospectively and that the loss to interview exceeded 15%, which may have introduced an attrition bias. In addition, this study is a single-center study with a limited number of patients included.

The manuscript refers to an interesting issue concerning public health, but it covers a limited number of patients all from the same hospital, and is therefore not representative of a broader situation.

This study had limited access to pre-morbid condi-

tions, specifically pre-existing psychopathological conditions. Indeed, patients with pre-existing psychological and psychiatric conditions are at higher risk of both developing new symptoms and worsening existing problems following treatment in the ICU. At the same time, patients were not asked if they suffered from insomnia and chronic pain before their ICU admission.

Any data concerning the type /destination of discharge (e.g. other department, house, rehabilitation service) was not collected.

Furthermore, having simultaneously found several symptoms in the same subjects, it was not possible to carry out a stratification of the risk factors for each individual clinical condition emerged at the follow-up.

CONCLUSION

A high incidence of long-term consequences is found in survivors of critical illness. The major risk factors are increasing age, clinical and general conditions at the time of admission (APACHE II ≥ 15 or SOFA ≥ 10), prolonged ICU stay and mechanical ventilation.

These results concur with the findings of a number of previous studies but also highlight areas for further research.

In future, potentially beneficial research would include studies that investigate various clinical therapeutic interventions to prevent these long-term consequences experienced by patients after ICU care.

In conclusion we suggest informing patients at the time of hospital discharge of: the palliative care network, the role of specialist pain physician, the role of the psychologist and the counselling psychology. In addition, it is important to clarify the positive effect of early patient care in reducing the long-term consequences and related disabilities.

An awareness of the risk factors for the onset of long-term consequences allows the healthcare professionals caring for the patient to potentially address contributing factors, such as sheltered discharge and the patient's early acceptance by a multidisciplinary team of physician, nurses and psychologists.

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Conflict of interest statement

None.

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REFERENCES

1. Cuthbertson BH, Roughton S, Jenkinson D, MacLennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. Crit Care. 2010;14(1):R6.
2. Davydow DS, Zatzick D, Hough CL, Katon WJ. In-hospital acute stress symptoms are associated with impairment in cognition 1 year after intensive care unit admission. Ann Am Thorac Soc. 2013;10(5):450-7.
3. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;3-369(14):1306-16.
4. Fan E, Dowdy DW, Colantuoni E, Tellez PA, Sevransky JE, Shanholtz C, Himmelfarb CR, Desai SV, Ciesla N, Herridge MS, Pronovost PJ, Needham DM. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med. 2014;42(4):849-59.
5. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, Wozniak AW, Colantuoni E, Ely EW, Rice TW, Hopkins RO; NIH NHLBI ARDS Network. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am J Respir Crit Care Med. 2013;188(5):567-76.
6. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(4):340-7.
7. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787-94.
8. Rawal G, Yadav S, Kumar R. Post-Traumatic Stress Disorder: A Review from Clinical Perspective. Int J Indian Psychol. 2016;5(2):90-2.
9. Wunsch H, Christiansen CF, Johansen MB, Olsen M, Ali N, Angus DC, Sørensen HT. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. JAMA. 2014;311(11):1133-42.
10. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, Pun BT, Vasilevskis EE, Morandi A, Shintani AK, Hopkins RO, Bernard GR, Dittus RS, Ely EW; Bringing to light the Risk Factors And Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study investigators. Depression, post-traumatic stress disorder, and functional disability in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir. 2014;2(5):369-79.
11. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, Casaer MP, Meersseman P, Debaveye Y, Van Cromphaut S, Wouters PJ, Gosselink R, Van den Berghe G. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness: A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410-20.
12. Schweickert WD, Hall J. ICU-acquired weakness. Chest. 2007;131(5):1541-9.
13. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, Mendez-Tellez PA, Shanholtz C, Ely EW, Colantuoni E, Hopkins RO; National Insti-

tutes of Health NHLBI ARDS Network. Risk Factors for Physical Impairment after Acute Lung Injury in a National, Multicenter Study. Am J Respir Crit Care Med. 2014;189(10):1214-24.
14. Jacodic HK, Jacodic K, Podbregar M. Long term outcome and quality of life of patients treated in a surgical intensive care: a comparison between sepsis and trauma. Crit Care. 2006;10(5):R134.
15. Dowdy DW, Eid MP, Sedrakyan A, Mendez-Tellez PA, Pronovost PJ, Herridge MS, Needham DM. Quality of life in adult survivors of critical illness: a systematic review. Intensive Care Med. 2005;31(5):611-20.
16. Battle CE, Lovett S, Hutchings H. Chronic pain in survivors of critical illness: a retrospective analysis of incidence and risk factors. Crit Care. 2013;29-17(3):R101.
17. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50-5.
18. Castronovo V, Galbiati A, Marelli S, Brombin C, Cugnata F, Giarolli L, Anelli MM, Rinaldi F, Ferini-Strambi L. Validation study of the Italian version of the Insomnia Severity Index (ISI). Neurol Sci. 2016;37(9):1517-24.
19. Gilbody S, Richards D, Barkham M. Diagnosing depression in primary care using self-completed instruments: a UK validation of the PHQ-9 and CORE-OM. Brit J Gen Pract. 2007;57(541):650-2.
20. Bonezzi C, Nava A, Barbieri M, Bettaglio R, De-martini L, Miotti D, Paulin L. Validazione della versione italiana del Brief Pain Inventory nei pazienti con dolore cronico. Minerva Anestesiologica. 2002;68(7-8):607-11.
21. Andrykowski MA, Cordova MJ, Studts JL, Miller TW. Posttraumatic stress disorder after treatment for breast cancer: prevalence of diagnosis and use of the PTSD Checklist – Civilian Version (PCL-C) as a screening instrument. J Consult Clin Psychol. 1998;66(3):586-90.
22. Annunziata MA, Muzzatti B, Mella S, Narciso D, Giacalone A, Fratino L, Tirelli U. The revised piper fatigue scale (PFS-R) for Italian cancer patients: a validation study. Tumori. 2010;96(2):276-81.
23. Whynes DK and the TOMBOLA Group. Correspondence between EQ-5D health state classifications and EQ VAS scores. Health and Quality of Life Outcomes. 2008;6:94.
24. Hatch R, Young D, Barber V, Griffiths J, Harrison DA, Watkinson P. Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. Crit Care. 2018;22(1):310.
25. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Schmidt DM, Scruth E, Spill GR, Storey CP, Render M, Votto J, Harvey MA. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit Care Med. 2012;40(2):502-9.
26. Rawal G, Yadav S, Kumar R. Post-intensive Care Syndrome: an Overview. J Transl Int Med. 2017;5(2):90-2.
27. Damico V, Murano L, Cazzaniga F, Dal Molin A. Pain prevalence, severity, assessment and management in hospitalized adult patients: a result of a multicenter cross sectional study. Ann Ist Super Sanità. 2018;54(3):194-200.
28. Damico V, Cazzaniga F, Murano L, Ciceri R, Nattino G, Dal Molin A. Impact of a clinical therapeutic intervention on pain assessment, management, and nursing practices in an intensive care unit: a before-and-after study. Pain Management Nursing. 2018;19(3):256-66.