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QUALITY OF LIFE UPON DISCHARGE FROM THE INTENSIVE CARE UNIT: A SYSTEMATIC REVIEW

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TABLE OF CONTENTS

SUMMARY.....	2
CONFLICT OF INTEREST.....	3
SOURCES OF FUNDING.....	3
ETHICS COMMITTEE CLEARANCE.....	3
ABBREVIATIONS LIST.....	4
TERMS.....	5
INTRODUCTION.....	6
AIM AND OBJECTIVES... ..	7
LITERATURE REVIEW.....	8
RESEARCH METHODOLOGY.....	13
RESULTS AND THEIR DISCUSSION.....	16
CONCLUSIONS.....	27
PRACTICAL RECOMMENDATIONS.....	27
LITERATURE LIST.....	28
ANNEXES.....	33

SUMMARY

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Quality of life upon discharge from the intensive care unit: a systematic review.

AIM: Assessment of the latest evidence investigating HRQOL of adults upon their discharge from the ICU by identifying, appraising and synthesizing the information gathered from researches taking care of this topic.

OBJECTIVES:

1. To evaluate the changes of HRQOL after ICU stay.
2. To give an overview of determinants of HRQOL.

METHODS: The search was conducted through popular electronic databases: PubMed and The Cochrane Library. After the design and application of eligibility criteria, several articles were excluded in a stepwise fashion: by title, by abstract and by full- text. Finally 28 articles were included for evaluation. Included researches were analyzed.

RESULTS: HRQOL was found to be lower in patients discharged from ICU when compared with the general population in 17 studies. Gradual improvements were found in at least 3 studies. These tend to occur from the 6 month after discharge and from there onwards, however one article identified a relapse of lower scores from the second to the fifth year after discharge. Despite these fluctuations, the HRQOL scores never reached those of the reference populations during the follow-up periods in any of the evaluated studies. Baseline levels of HRQOL tend to be lower in patients included in the ICU than those of the general population in at least 4 studies. Upon discharge from hospitalization these HRQOL scores tend to be lower than those measured at baseline. Several risk factors were found to be associated with lower scores in HRQOL between ICU populations: age, severity of illness, pre-morbid condition, number of comorbidities, presence of shock, diagnostic category, ICU length of stay, length of mechanical ventilation, duration of bed rest, depression, insomnia, delirium, delusional memories, optimism towards disease, awareness of surroundings, frightening experiences, optimism, social integration and financial status.

CONCLUSIONS:

HRQOL is lower in patients discharged from the ICU than that one of reference populations.

It also tends to be lower than that one of the patients prior to ICU admission; however is not significantly lower than that one of simply hospitalized patients. HRQOL measurements are subjected to significant time fluctuations. Several determinants of HRQOL have been identified.

CONFLICT OF INTEREST

There was not any conflict of interest.

SOURCES OF FUNDING

None.

ETHICS COMMITTEE CLEARANCE

It was not required.

ABBREVIATIONS LIST

ALI, Acute Lung Injury; APACHE, Acute Physiology And Chronic Health Evaluation; ARDS, Acute Respiratory Distress Syndrome; DM, Delusional Memories; EQ- 5D, EuroQol five dimensions questionnaire; HAD, Hospital Anxiety and Depression Scale; HRQOL, Health Related Quality Of Life; ICU, Intensive Care Unit; ICUAW, Intensive Care Unit Acquired Weakness; MCS, Mental Component Summary; PCS, Physical Component Summary; PICS, Post Intensive Care Syndrome; PTSD, Post- Traumatic Stress Disorder; QOL, Quality Of Life; SF-36, Medical Outcomes Trust Short Form -36

TERMS

Intensive Care Unit Acquired Weakness [ICUAW]: Refers to the clinically apparent muscle weakness in the critically ill patient which cannot be attributable to any etiology apart from ICU admission and the treatment carried out there. The term was proposed by Stevens et al. [4] in 2009, and since then it has been generally accepted and widely used in the scientific literature.

Health Related Quality Of Life [HRQOL]: The definition of this term is profoundly problematic. The term was coined in 1982 in a study carried out by Kaplan and Bush [1]. Since its first appearance a large number of studies focused their attention in the importance of defining this concept and differentiating it from those of “health status” and “quality of life”, because they were generally used interchangeably. To this day, the problem of defining this term persists, and there is no general agreement for its use in the scientific literature. However, several attempts have been made. Perhaps the definition provided by Ebrahim [2] is the one we find more appropriate in our study, according to which HRQOL is defined as “those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment”. By using this definition we focus on the factors that are related to medical practice, while other aspects also affecting the individual, such as the social or economic factor, stay out to form part of the wider concept of “quality of life”. But most importantly, it is not the purpose of our study to find a solution for this problem, so we will use an operational definition of HRQOL which focuses on the quantitative aspect of it, according to which HRQOL is defined as the scores obtained upon completion of the validated questionnaires SF-36 and EQ- 5D.

Post- Intensive Care Syndrome: The term was coined by Needham et al. [3] during a conference of the Society of Critical Medicine in 2012. It refers to the physical, cognitive and mental impairments commonly occurring to patients after discharge from the ICU. The associated mental impairment that could arise in a family member or caregiver next to the critically ill patient was referred to as PICS- F (family).

PRE-QOL: Refers to the Quality Of Life [QOL] previous to patient admission into the Intensive Care Unit [ICU]. This measure is also referred to as baseline quality of life in several studies.

INTRODUCTION

Advances in diagnostic and therapeutic procedures are leading to higher survival rates among critically ill patients. Short- term outcome measures (ICU mortality rate, in-hospital mortality, 28-day mortality as primary outcome measures) although useful and precise, are progressively becoming more limited in terms of measuring the outcomes from the ICU. On the other hand, long- term outcome measures, and specially HRQOL, are becoming more and more important for evaluation of morbidity associated with ICU admission. This has led to an increasing amount of researchers in the past two decades focusing their attention in how the patients are living upon discharge from the ICUs. In this manner, HRQOL has become a novel outcome parameter. The information regarding HRQOL obtained from the researches is large and rather segregated. This fact served us as the rationale to carry out a systematic review on the existing literature. Data extracted from the different studies will help us to identify some general tendencies observed and to reach some general conclusions. By analyzing data from the latest researches on the topic of HRQOL after the ICU, our ultimate purpose would be that one of putting some light into the issue, which ideally will serve as a guide orientation for further research to be designed. How ICU affects HRQOL of our patients, the factors influencing it, and possible new management strategies will be discussed in this research.

AIM

The aim of this systematic review is the assessment of the latest evidence investigating HRQOL of adults upon their discharge from the ICU by identifying, appraising and synthesizing the information gathered from researches taking care of this topic.

OBJECTIVES

1. To evaluate the changes of HRQOL after ICU stay.
2. To give an overview of determinants of HRQOL.

LITERATURE REVIEW

QUALITY OF LIFE CONCEPT

The concept of “quality of life” [QOL] has been used interchangeably with other terms, such as “health status” and “health related quality of life” [HRQOL] in the scientific literature of the past three decades [22]. Several theoretical studies have focused their attention towards clarifying this concept [22- 26]. However, to this day, no universal consensus has been made in order to identify a single unified concept [22]. Rapley [25] assures that all the definitions of QOL found in scientific literature are not only copious but also impossible to reconcile them. As it was observed in the literature review, there is ongoing research on the topic of QOL despite the conceptual issue is still present. Some authors, such as Hunt [26] raise the importance about the need for a background philosophical foundation. While in reality the majority of researchers keep on evaluating QOL without trying to define it, chiefly by using a quantitative approach, according to which QOL is the score obtained upon completion of a QOL questionnaire.

QUALITY OF LIFE MEASUREMENT

There are several modes of evaluation of QOL: dimension specific, population specific, generic, individualized and according to utility. These modes are clearly defined by Garratt et al. [27], according to whom: “Dimension specific measures focus on particular aspects of health such as psychological wellbeing and usually produce a single score—for example, Beck depression inventory. Disease or population specific measures include aspects of health that are relevant to particular health problems and may measure several health domains—for example, asthma quality of life questionnaire. Generic measures can be used across different patient populations; they usually measure several health domains—for example, SF-36. Individualized measures allow respondents to include and weight the importance of aspects of their own life; they usually sum to produce a single score—for example, patient generated index. Utility measures have been developed for economic evaluation, incorporate preferences for health states, and produce a single index—for example, EuroQol EQ-5D”.

The most commonly used instruments for measuring HRQOL after ICU are: the SF- 36, the EQ- 5D, the Nottingham Health Profile and the Sickness Impact Profile [32], however the SF- 36 and the EQ- 5D have been recommended as the most appropriate for this purpose [28].

According to Garratt et al. [27], the SF- 36 questionnaire was the most widely used, accounting for the 10% of the reports screened in their study. The SF- 36 was validated by the Brussels Roundtable Surviving Intensive Care in 2002 [28], together with the EQ- 5D, and since then they have been increasingly used.

The SF-36 (see Annex. 2) is a generic questionnaire and it can be administered to measure HRQOL holistically. It includes a multi-item scale which evaluates 8 different domains: vitality (4 items), physical functioning (10 items), bodily pain (two items), general health perceptions (5 items), physical role functioning (4 items), emotional role functioning (3 items), social role functioning (2 items), and mental health (5 items). Item scores for each dimension are summated and transformed using a scoring algorithm into a scale ranging from 0% (poor health) to 100% (good health) [29]. The Short Form 36 questionnaire was not designed to extract a single index, however it allows us to calculate two indexes of summary: the Physical Component Summary [PCS] and the Mental Component Summary [MCS], by standardization of the 8 domains [5]. According to the Brussels Roundtable Surviving Intensive Care in 2002 [28], SF- 36 is an ideal questionnaire to evaluate HRQOL upon discharge from ICU because it is standard, well- validated, straight forward, adequate to administer by telephone and applicable in different countries and languages. In addition, Chrispin et al. [30], confirmed the acceptability, reliability, and validity of SF- 36, describing it as a robust tool for its use in the assessment of HRQOL following critical illness. The possible suggested “ceiling effect”, according to which, scorings of 100 would be lower than those perceived by the patients, has been solved by the development of a second version, SF- 36 version 2, although this survey is not been used normally [29].

The EuroQOL Questionnaire- 5 Dimensions [EQ- 5D] (see Annex. 3) was developed in 1990 by the EUROQOL GROUP [31]. The EQ- 5D is a generic questionnaire consisting in three parts. The first part is named “self-classifier”, it consists of five dimensions: mobility, self-care, usual activity, pain/ discomfort and anxiety/ depression. The responder can estimate each of these dimensions by marking one of the three possible statements: having no problems, having some (moderate) problems, or having extreme problems. The second part is the EuroQol Visual Analogue Scale [VAS]. As its name implies the EQ- VAS scale is a visual metric where participants can score their self- perceived HRQOL status from 0 to 100, this is from the worst imaginable state to the best imaginable state respectively. The third part is the EuroQol index, which unifies the previous two parts into a single score describing the overall HRQOL. EQ index scores range from 0.109 to 1, the latter representing optimal health [33].

IMPORTANCE OF MEASURING HRQOL

Gerth et al. [34] founded the necessity of their systematic review highlighting the importance of measuring HRQOL in patients discharged from the ICU. ICU hospitalization does not only impose a high treatment burden in the patient, which is highly affected by it, but also it imposes a high economic burden for the health care provider and the community in general [34]. In addition, the growing information gathered from new researches provides a substantial amount of data. This data can serve the purpose of providing information about prognosis, which is beneficial to both patients and physicians. In relation to this Azoulay et al. [36] stated that “seriously ill patients base their preferences about life-sustaining therapies according to how burdensome the ICU will be and how much handicap is to be dreaded from the ICU experience”.

Moreover, advances in the fields of diagnostics and therapeutics led to survival rates that may reach up to 80% of the patients admitted to the ICUs, according to data obtained by INARC [35]. Therefore multiple studies highlight the importance of long- term parameters such as HRQOL, as the majority of patients survive after the ICU, for evaluation of ICU efficiency.

HRQOL AFTER THE ICU

In general, the majority of the reviewed literature encounters that the HRQOL of patients discharged from the ICU are lower than that one of the reference population [37- 41]. This statement is true for different disease conditions: severe sepsis [38]; Acute Respiratory Distress Syndrome [39]; prolonged mechanical ventilation [40]; trauma [41].

FACTORS DETERMINING HRQOL

Since it was discovered that the HRQOL decreases after ICU stay, it became interesting to evaluate which factors are associated with these changes, which ones of them are related to treatment within the ICU and, which ones of them are subjected for modification with novel treatment strategies.

In this line, old age was identified as a predictor of lower scores in physical domains [42], female gender was found to be a predictor of poorer mental health [28], prolonged length of stay in the ICU (>7 days) was identified as a predictor of poorer vitality and physical activity after cardiac surgeries [43], severity of illness was a predictor of lower physical functioning and general health perceptions [37], pre-existing disease condition was found as a strong predictor of general HRQOL [44], length of mechanical ventilation, number of organ failures, ICU diagnostic group, number of comorbidities were also identified as predictors of HRQOL scores [45].

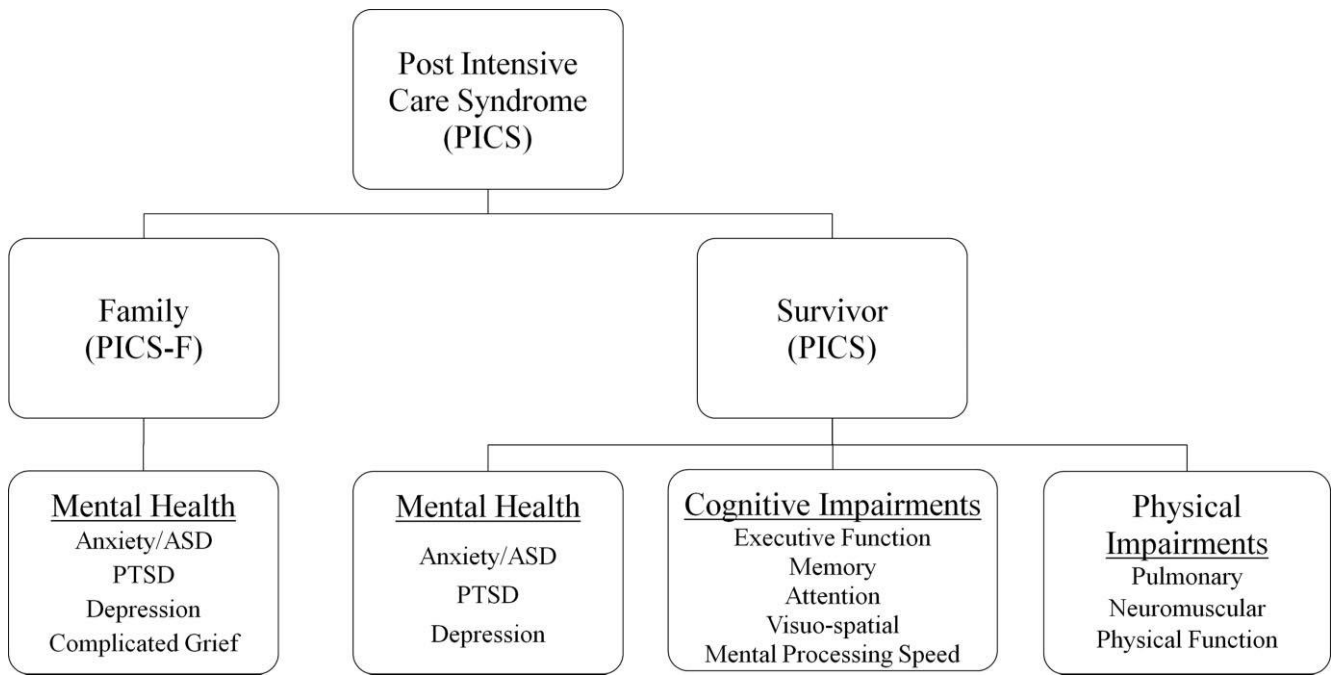


Fig. 1Diagram showing the conceptual framework of PICS [Needham et al. (3)]

SEQUELS POST- ICU

According to Jones [51] “Gross muscle mass loss and weakness can take some months to recover after the patients’ Intensive Care Unit (ICU) discharge; in addition critical illness polyneuropathies can further complicate physical recovery. Psychological problems such as anxiety, depression and post-traumatic stress disorder (PTSD) are common and have a negative impact on the patients’ ability to engage in rehabilitation after ICU discharge. Finally cognitive deficit affecting memory can be a significant problem.” To this conglomerate of health impairments occurring in ICU survivors, Needham et al. [3], suggested the term: Post- Intensive Care Syndrome. According to the diagram (Fig. 1), PICS involves three domains that are usually affected in survivors: physical, cognitive and mental, the latter being present in family members, relatives or caregivers. McPeake [53] suggest the inclusion of the social domain. The most common physical complication of critical illness is muscle wasting and weakness [51]. To this important complication, Stevens et al. [4] in 2009 suggested the name ICUAW. ICUAW is divided into critical illness myopathy [CIM] and critical illness polyneuropathy [CIP]. Although difficult to differentiate them clinically, this subdivision is important

as CIM was found to be associated with better prognosis [51]. “Cognitive impairments occur in patients of all ages and across ICU etiologies as over half of all survivors develop cognitive impairments and in some subgroups such as ARDS it may be higher” [52]. The cognitive impairment associated to the ICU Impairments in memory, attention, executive function, mental processing speed, visuo-spatial ability [3]. The mental health impairments are found in both, the patients and the associated familiar (usually spouse). [3, 51]. Among these psychological impairments the most common ones are anxiety, depression and post- traumatic stress disorder [PTSD]. The psychological sequels have been shown in one study as independent causative factors of social and economic adverse events [54].

RESEARCH METHODOLOGY

PRIMARY SEARCH

The search was carried out through two online databases: the National Library of Medicine (PubMed) and the Cochrane Library.

We constructed our search by making two basic entities: one gathering the terms referring to quality of life, cross-matched with another one gathering terms referring to the intensive care unit.

The definitive search was as follows: (“quality of life” OR “QOL” OR “health related quality of life” OR “HRQOL”) AND (“intensive care unit” OR “ICU” OR “critical care”).

Furthermore, we limited the results by adding filters. Only studies carried out in the past ten years (2007- 2017), in humans, and those that were written in English or Spanish language were included to this point. After searching in both electronic databases we came out with 1721 papers.

Our last search was performed in April 2017.

ASSESEMENT OF ELEGIBILITY

After this search we went through three levels of selection (figure 1): title, abstract and full text, applying to the list of articles our eligibility criteria presented below.

Subsequently the majority of the articles were excluded. Upon the most common reasons of exclusion the studies were: centered in pediatric populations, centered in neonatology populations, centered in health care worker population (for example nurses), inaccessible, duplicates, not performed in the ICU, focused on preadmission HRQOL measurements, studied quality of end of life within the ICU, aimed at philosophical, ethical or economic issues alone, not used the appropriate questionnaires.

INCLUSION CRITERIA

Articles meeting these criteria were eligible for our systematic review: English or Spanish language; published between 2007 and 2017; were conducted on humans; focused on quality of life after the intensive care unit; had either quantitative or qualitative data; included populations aged older than 16 years old.

EXCLUSION CRITERIA

Articles meeting these criteria were ruled out from our systematic review: Focused on population aged younger than 16 years old; used non- validated questionnaires for assessment of HRQOL i.e. different from the SF- 36 and EQ- 5D; studied uncommon and specific disease conditions; studied populations undergoing a specific treatment procedure.

INCLUDED ARTICLES

Finally, a total of 28 studies were included according to the eligibility criteria and as they were thought to be the most relevant ones from the initial pool of offered results.

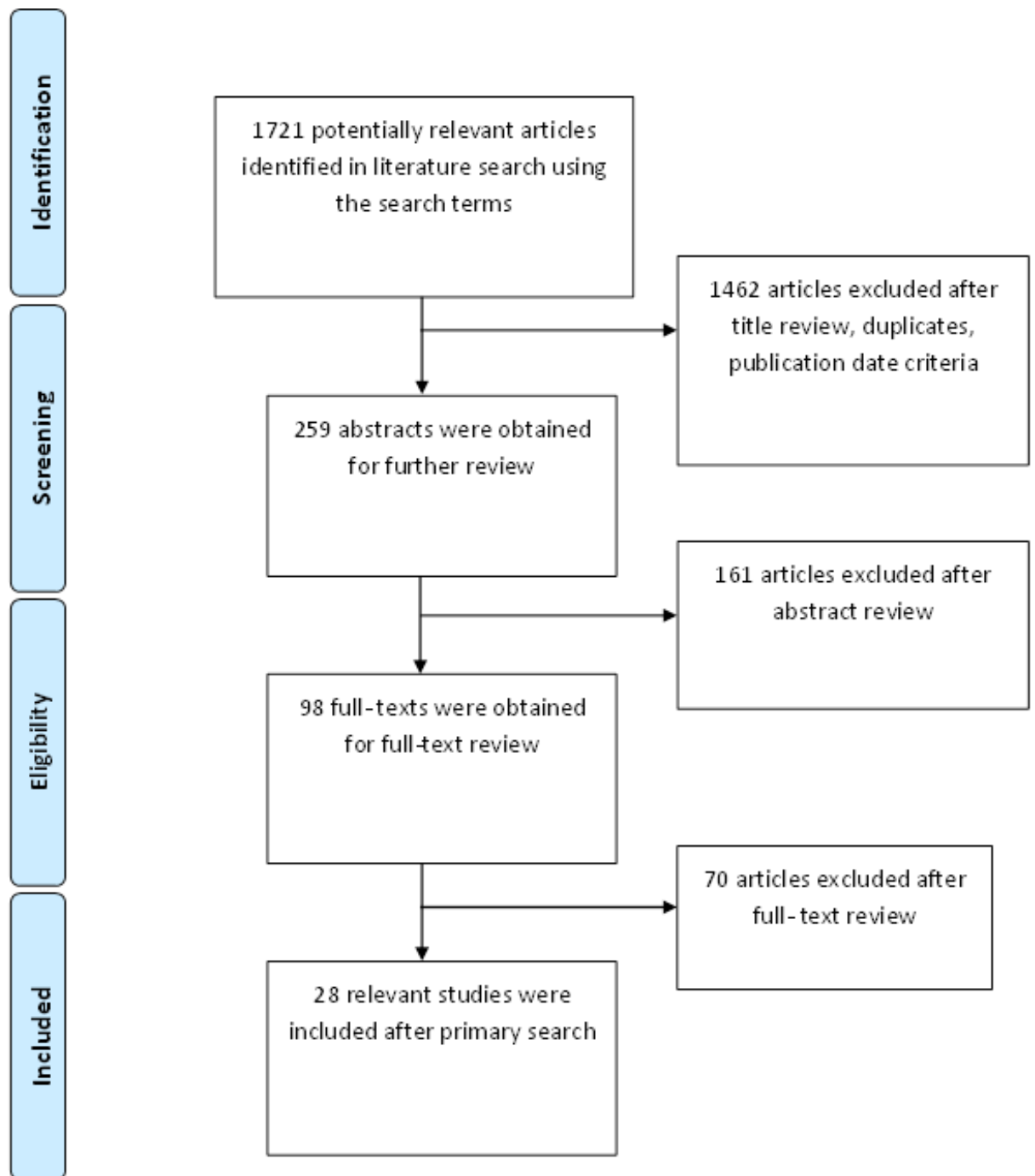


Fig. 1. Article selection process

RESULTS AND THEIR DISCUSSION

The general characteristics of the included articles are presented in Table. 1. However not all the evaluated articles are included in the table, only those which study design consisted in the evaluation of a subset of patients. Included systematic reviews and overviews cannot be analyzed by the criteria conforming the table. Nonetheless results obtained from the latter are also included in this text.

According to Angus et al. [28] “The best approach to understand causality in clinical medicine is to conduct a prospective randomized trial”. Thus, the study design of the majority of researches was prospective cohort.

The countries where the studies were carried out are developed countries, principally in Europe, followed by the United States and one research from Argentina. The ICU of these countries is associated with a high economic burden, and their results cannot be compared to those of developing countries. In addition, long- term parameters such as HRQOL are eclipsed by the primary importance of survival, therefore studies regarding our topic were generally lacking.

Most of the reports, except that one of Castelló et al. [5], were available in English language and were published after 2010. This is particularly important in studies related to ICU performance, since the activity in these units is being questioned by the increasingly amount of research focusing in long-term outcomes and finding morbidity associated solely to ICU treatment. Accordingly, new management strategies are being proposed and put into action, which may be already having an impact in measurements of quality of life.

The main limitation that was identified in the majority of studies was the lacking of a pre- ICU HRQOL measurement, or baseline measurement. For the indication of “no baseline measurement” as a limitation, we followed the instructions suggested by Dowdy et al. in relation to study quality criteria [37]. According to Dowdy and colleagues, a study regarding HRQOL after ICU, should include the following four elements: 1, have no major exclusion criteria; 2, description of responder vs. non-responder groups; 3, measuring HRQOL at baseline and at follow- up; 4, contrast the results from those of the general population. The first two requirements were met by all the included reports. The third requirement was lacking in [15, 13, 8, 11, 7, 16]. The only study not comparing the results with those of the general population was [13]. Therefore, we can say that the study quality of the majority of included reports was 3 out of 4, the main limitation being no measurement of baseline HRQOL.

The reason for the above discussed is that measurement of baseline HRQOL is rather a complicated and problematic task. Chiefly because we cannot conjecture which persons from the general

community will be admitted to the ICU, except for those undergoing major elective surgeries. Different strategies have been tried in our reviewed reports: Castelló et al. [5], used the questionnaires SF- 36 and EQ- 5D lightly modified in order to highlight that the measurement was about HRQOL previous to the admission by adding the sentence “4 weeks previous to your admission”. The patient filled up the questionnaires in the first 48 hours from admission or at the time of discharge. Fan et al. [14], Myhren et al. [12] and Oeyen et al. [18] followed a similar strategy; this is, asking the patients to recall their HRQOL retrospectively. Cuthbertson et al. [6], on the other hand, as well as Nesseler et al. [17] and Stergiannis et al. [20], asked the relatives to complete the questionnaires evaluating the health of the critically ill patient previous to hospitalization. Oeyen et al. [18] used this strategy of measuring baseline HRQOL when it was not possible for the patient to answer the questionnaires.

Withal, probably neither of these strategies might be accurate, as suggested by Scales et al. [55], because retrospective preadmission HRQOL estimation by the patient may result in overestimation, while when the relative is asked the HRQOL of the patient tends to be underestimated.

One additional study from our pool [9], followed a unique and pioneer strategy in order to overcome these bias. In fact, Feemster et al. [9] is the first research to study HRQOL prospectively. They did so by tracing a very large cohort of patients (11243) along a period of three years, evaluating HRQOL administering the SF- 36 questionnaire at the beginning of this period. From the initial cohort of patients, 6% of them (668) experienced at least one ICU hospitalization. This type of design is an example of a proper baseline HRQOL measurement, however not always possible to execute by other researchers.

But, why is measurement of baseline HRQOL so relevant?

We found a significant number of articles assuring that baseline HRQOL is lower in patients admitted to the ICU compared to the reference population. In this line, Soliman et al. [11] suggest that patients might be deteriorating (in general health and HRQoL) in the period leading up to their critical illness. Feemster et al. [9] stress the importance of pre- ICU measurements: “A major challenge to studying post- ICU morbidity is the need to identify patients’ pre-ICU health status”. The conclusion that can be extracted from both is that, in order to identify what is the role of ICU admission and treatment, we should have pre- ICU HRQOL accurate measurements, since these ones have been largely found to be decreased in comparison with age and sex matched populations, meaning that the influence of ICU could be lower than we think. Regarding the latter, we encountered some interesting findings from the studies included in this research. Particularly Feemster et al. [9] did not find major differences between ICU and non-ICU hospitalization groups, suggesting that decrements in HRQOL are associated to

acute illnesses rather than critical illness and care. Berkus et al. [15], compared measurements of HRQOL of COPD patients hospitalized in the ICU with that one of COPD patients hospitalized in the pulmonology department. They concluded that, while at 6 months ICU- COPD patients showed lower HRQOL scores, this difference was not significant at 12 months (table 3).

Table 1. Main information regarding included researches

Study	Study Design	Language	Study Location	Year	Limitations	Additional evaluations
Berkius et al. [15]	Prospective longitudinal cohort	English	Sweden	2013	No baseline measurement, small sample.	Compared with a COPD reference population that was not admitted to ICU.
Castelló et al. [5]	Prospective observational	Spanish	Spain	2007	Not identified	Evaluates determinants. Compares SF-36 with EQ-5D
Cuthbertson et al. [6]	Prospective longitudinal cohort	English	UK	2010	Not identified	Long follow-up period
Das Neves et al. [13]	Prospective cohort	English	Argentina	2015	No baseline measurement; No comparison of results with reference population.	Young patients, 76% previously healthy, mechanically ventilated.
Fan et al. [14]	Prospective longitudinal cohort	English	US	2014	Not identified	Evaluates determinants. Measures muscle weakness objectively.
Feemster et al. [9]	Prospective longitudinal cohort	English	US	2014	Very specific group: Veterans, old, white, not severely ill.	Compares ICU hospitalization vs. Non-ICU hospitalization populations.
McKinley et al. [8]	Prospective observational	English	Australia	2016	No baseline measurement	Evaluates sleep disturbances
Myhren et al. [12]	Prospective cohort	English	Norway	2010	Not identified	Evaluates optimism using Life Orientation Test.
Nessler et al. [17]	Prospective observational	English	France	2012	Single center study with a small sample.	Not identified
Oeyen et al. [18]	Prospective observational cohort	English	Belgium	2015	Single center study with a small sample.	Compared HRQOL between AKI-RRT and non-AKI-RRT critically ill patients
Parsons et al. [19]	Cross-sectional	English	US	2014	Small cohort.	Uses a validated insomnia-specific sleep metric
Ringdal et al. [21]	Prospective observational	English	Sweden	2010	Not identified	Measured the relationship of DM with HRQOL. Long follow up period.
Soliman et al. [11]	Prospective cohort	English	The Netherlands	2014	No baseline measurement	Big sample size
Steenbergen et al. [7]	Retrospective cohort	English	The Netherlands	2015	No baseline measurement	Long term ICU stay (>72 h)
Stergiannis et al. [20]	Prospective observational	English	Greece	2014	Small cohort.	Measured the relationship between financial status and HRQOL
Villa et al. [16]	Prospective observational	English	Spain	2016	No baseline measurement	Evaluate functional status using Barthell Index.

Table 2. Information about characteristics of study assessment

Study	Patient group	Instrument of assessment	Time of assessment	Follow-up interview method	Participation rate	Population #	Median age	Reference population
Berkius et al. [15]	COPD	EQ-5D, SF-36	6, 12, 24 months	Mail	45%	31 out of 58	58	Two: Swedish population norms + COPD hospitalized (not in ICU)
Castelló et al. [5]	General ICU, categorized according diagnosis.	SF-36, EQ 5-D	Baseline, 12 months.	Telephone, consultation	41,35%	189	60	Published spanish population norms
Cuthbertson et al. [6]	General ICU	SF-36, EQ 5-D	Baseline, 3, 6, 12 months, 2.5 years, 5 years	Telephone	65%	195 out of 300	63	Published british population norms
Das Neves et al. [13]	Mechanically ventilated	EQ-5D	1, 3, 6, 12 months	Face to face, telephone	59%	57 out of 208	33	Not identified
Fan et al. [14]	Acute Lung Injury	SF- 36	3, 6, 12, 24 months	Face to face, telephone	65%	146 out of 224	52	Published population norms
Fernster et al. [9]	General ICU, non-ICU hospitalized, not hospitalized.	SF-36	Baseline, 3, 6, 12, 18, 24, 30 months	Mail	62%	668	65	Control arm of not hospitalized patients
McKinley et al. [8]	General ICU	SF-36	6 months	Telephone	65%	193 out of 344	59	Published australian population norms
Myhren et al. [12]	General ICU	SF-36	Baseline, 4 weeks, 3 months, 12 months	Mail	47%	194 out of 413	49	Published norwegian population norms
Nesseker et al. [17]	Septic shock	SF-36	Baseline, 6 months	Mail Telephone	46%	96 out of 180	69	Published french population norms
Oeyen et al. [18]	AKI- RRT ³	SF-36, EQ 5-D	Baseline, 3, 12 months, 4 years	Mail Telephone	59%	28 out of 47	57	Reference population norms
Parsons et al. [19]	Insomnia	SF-12, ISI ⁴	Baseline, 12 months	Telephone	27,50%	33 out of 120	48	Reference population norms
Ringdal et al. [21]	Trauma, Delusional Memories [DM]	SF- 36, HAD ⁵	Baseline, 6-15 months, 4,5- 5 years	Mail	71%	153 out of 215	45	Reference population norms
Soliman et al. [11]	General ICU	EQ- 6D- 3L	12 months	Mail	68%	3034 out of 4465	64	Published dutch population norms
Steenbergen et al. [7]	Long term treated ICU (>72 h)	RAND-36 ²	5 years	Telephone	63%	195 out of 306	61	Published amsterdam's population norms
Stergiannis et al. [20]	Multiple trauma	EQ- 5D	Baseline, 6, 12, 18, 24 months	Mail Telephone	61%	81 out of 120	38	Reference population norms
Villa et al. [16]	Elderly >75 y.o.	SF- 36, Barthell index	3, 6, 12 months	Telephone	54%	54 out of 110	81	Age matched spanish population norms

In table 2 we can see the characteristics of the study assessment. Our preference was to find those studies that did not focus on a specific condition, but rather evaluated the ICU population as a whole or in default, those that focused on the main disease- conditions seen in the ICU i.e. ALI, COPD exacerbation, sepsis, mechanically ventilated patients, elderly and traumatic patients.

The measurement questionnaires were always SF- 36 or EQ- 5D, as recommended by the Brussels roundtable: Surviving Intensive Care [28]. Castelló et al [5] compared both questionnaires by making relations of the different dimensions being measured; they concluded that, despite some differences in structure and content (especially in the mental component), both are valid and measure similar aspects of HRQOL in critically ill patients.

We also chose researches that traced patients for longer follow- up periods. To perform this type of research is time- consuming and expensive. All of the studies followed the patients for more than 12 months, except for that one carried out by McKinley et al. [8]. This is important because, as we can see in our table of results (table 3), there are significant differences in HRQOL scores depending on the time the questionnaires are filled. Studies following- up patients for longer periods of time could elucidate how these time fluctuations in HRQOL after discharge from the ICU are occurring.

The mean participation rate was 56, 2 %. This part is important because patients with poorest HRQOL could be lost in the follow-up, becoming a source of bias. However, Cuthbertson et al. [6] theorize that patients being satisfied with their recovery may lose the interest in answering the questionnaires. All of the articles measured the difference between respondents and non- respondents. The majority of them found no statistically significant differences between the two groups [6, 8, 11, 13, 15, 16, 17, 18, and 20]. Statistically significant differences were found by Feemster et al. [9] according to whom non-respondents were younger, suffered less comorbidity and had increased rates of depression. Younger patients were also identified as non- respondents by Myhren et al. [12] and Fan et al. [14]. The study about traumatic patients carried out by Ringdal et al. [21] found that victims of intentional accidents were more commonly found as non- respondents.

According to HRQOL measurements, the vast majority of the reviewed studies found that HRQOL was lower in patients discharged from the ICU compared to population norms [15, 5, 14, 9, 8, 12, 17, 18, 21, 11, 7, 20, and 16].

Time of assessment and fluctuations: By looking at the results obtained from McKinley et al. [8] HRQOL is decreased upon patient discharge from the ICU. However many follow- up studies have shown that repeating the questionnaires sometime later, for example, at two years, a subtle increase in HRQOL scores can be noticed. According to McKinley et al. [8], levels of HRQOL show

improvements in several studies even between 6 and 12 months after discharge. But usually, these levels don't reach those of the reference population [18, 21].

Other study from Cuthbertson et al. [6] use longer follow-up periods – up to 5 years- and show different results: “between 2.5 and 5 years after discharge from the ICU patients experience a significant decrement in the physical component of the QOL according to SF 36 and EQ 5D questionnaires”.

Fildissis et al [17] found that the HRQOL in 242 patients with an ICU stay improved at 18 months after discharge, particularly their daily activities. Stress and anxiety improved at a slower pace. They also found that age is associated with HRQOL. However, in contrast with the results of this study, they indicate that HRQOL is influenced by gender, with men showing greater improvement than women.[20]

Thus, the time at which the QOL is assessed is crucial in determining the results.

The influence of the ICU in these decrements in HRQOL is uncertain. According to the results, it seems to be true that after the ICU the HRQOL level, is not only lower than that one of the general population norms, but also lower than the baseline measurements [9, 12, 20], however the latter may be confusing [9]. From the results obtained from Feemster et al. [9] and Berkus et al. [15], ICU influence on HRQOL might be not significantly different from that one of general hospitalizations. These findings may subtract some weight put on the critical care.

Factors influencing HRQOL

-Age: Fildissis et al. [47] found age is associated with HRQOL: “older patients actually seem to have higher mental scores than their younger counterparts and although this may seem surprising it may be in keeping with normal data”. Cuthbertson et al. [6], also found that elderly patients have higher mental scores, and Villa et al. found that HRQOL of elderly patients was affected only in some domains, mainly those forming part of the physical component. Further, it may be that older patients have lower expectations for quality of life after critical illness and therefore do not score the metrics as low as younger patients [6].

- Severity of illness: McKinley et al. [8] found that APACHE 2 independently related to the PCS. In addition Cuthbertson et al. [6] found that APACHE II scores above 18 points were independent predictors of poorer HRQOL levels.

- ICU length of stay: Was found to be independently related to the PCS by Mckinley et al. [8]; In this line, Cuthbertson et al. [6] found that prolonged stays in the ICU (>2 days) were independently associated with lower HRQOL levels. Villa et al. [16] found that factors independently associated with poor functional recovery were low baseline BI and ICU stay longer than 4 days.

- Pre- existing disease: Ringdal et al. [21] found preexisting disease to strongly influence on a poorer health-related quality of life. Cuthbertson et al. [6] found that premorbid state, including the physical and the mental component, influenced negatively in HRQOL after the ICU.

-Diagnostic category: Oeyen and colleagues [50] concluded that long-term HRQOL depends largely on the patient's diagnostic category. Patients who experienced severe adult respiratory distress syndrome, severe sepsis, or severe trauma as well as those who require prolonged mechanical ventilation tended to have a larger decrement in ratings of in QoL that persisted for a longer duration. Soliman et al. [11] found that after cardiac surgery HRQOL scores were: 0.93 in average, showing improve in HRQOL after ICU stay at 12 months after discharge. These scores were even higher than those of the age and sex matched Dutch population norms (0.86). Patients suffering from chronic renal failure (0.65) or those with sepsis were associated with greater long term decrements in HRQOL. Traumatic patients are a special group, usually with better health before trauma than most other critical care patients. Myhren et al. [12] found that they show greater decrements than other patients from other diagnostic groups, probably due to greater baseline levels. According to Mckinley, measurements of HRQOL after ICU in traumatic patients were significantly worse than baseline measurements, and continued to be worse in a 2-yr follow-up study [8]. ARDS patients tend to have greater decreases in the physical component; therefore they tend to improve gradually after 6 months from ICU discharge [14]. Finally Mckinley et al. [8] found a difference between scheduled and non-scheduled. surgical patients: non-scheduled showed significantly higher HRQOL deteriorations.

- Optimism: Measured by Mckinley et al. [8] by means of the Life orientation Test. They found that optimism was a substantial factor for recovery and an independent predictor of both physical and mental aspects of quality of life and return to work. Being employed was also found as a determinant of HRQOL.

- Length of mechanical ventilation: was identified by Das Neves et al. [13] to be a factor negatively influencing HRQOL.
- Economic income, financial status: Lower financial status was found by Villa et al. [16] to be a predictor of slower recovery and lower HRQOL levels after ICU stay.
- Social integration: Was identified by Orwelius et al. [44] to be a determinant of HRQOL scores.
- Awareness of surroundings and frightening experiences [8].
- Depression after ICU: Clinically diagnosed depression was found to be independently related to the MCS by Mckinley et al. [8] contributing to significant decrements in HRQOL measurements.
- Sleep quality after ICU: Post- ICU insomnia was identified in 25 % of patients in the research carried out by Parsons et al [19]. It was found to be strongly associated with mood disorders appearing upon discharge from ICU. Domains such as vitality, bodily pain, and physical function were also affected apart from the MCS [19, 51].
- Stress after ICU: Independently related to the MCS [8].
- Comorbidities: Increase in number of comorbidities in medical patients were found to be a determinant in HRQOL scores [11].
- Duration of bed rest and/or immobility: “Immobility and enforced bed rest are modifiable risk factors during critical illness that can result in substantial disuse atrophy and accelerated muscle breakdown contributing to the development of ICUAW” [14]. This fact contributes for the greater decrements in PCS showed by the ARDS patients.
- Presence of shock: [13]
- Delirium: In general ICU patients the average rate of developing Delirium was 32.3%. Delirium has been associated with an increased risk of long-term cognitive impairment [51]
- In- ICU development of AKI and requirement of renal replacement therapy: AKI develops in 20-30% of the critically ill population. Its development leads to a condition that is more severe than the original one. And its associated with higher mortality rates. However, upon survivors from the hospital, no

significant changes between HRQOLs are seen between patients who develop this syndrome within the ICU and those who don't [18].

- Delusional memories: Patients usually have memories from the injury and from the ICU stay that may influence HRQOL and psychological well-being after the injury [21]. “ The recall of delusional memories from ICU, such as hallucinations or paranoid delusions, deep sedation, physical restraint and a previous history of psychological problems has been shown to increase the risk of developing PTSD after discharge” [51].

Table 3. Results obtained from the included researches

Study	Results
Berkius et al. [15]	Lower HRQOL compared to population norms. Lower HRQOL in COPD patients hospitalized in the ICU at 6 months compared to COPD patients hospitalized in other departments. At 24 months, COPD (icu) and COPD (not-icu) showed no significant difference in HRQOL scores.
Castelló et al. [5]	Lower HRQOL at 12 months compared to baseline. Significant difference among different diagnostic category.
Cuthbertson et al. [6]	Physical scores decreased at 3 months compared to baseline, increased at 12 months to baseline levels, and decrease again at 2 and 5 years. Mental scores at 5 years were better than baseline, probably attributable to a "cheated death" phenomena.
Das Neves et al. [13]	Gradual improvement in HRQOL from 1 month after discharge until 12 months after discharge. Length of mechanical ventilation was identified as a determinant of lower HRQOL scores.
Fan et al. [14]	Lower HRQOL compared to population norms. The PCS was the most greatly determinant. Duration of bed rest was identified as a modifiable risk factor for low HRQOL values.
Feemster et al. [9]	Lower baseline HRQOL in patients requiring ICU admission. Lower HRQOLs in hospitalized (ICU and non-ICU) patients compared to those not hospitalized. No significant difference between ICU and non- ICU hospitalizations.
McKinley et al. [8]	Lower HRQOL compared to population norms. Determinants of HRQOL identified: APACHE II, length of stay, depression, stress, sleep quality. APACHE II and length of stay were independently related to PCS. Depression and stress with MCS.
Myhren et al. [12]	Lower HRQOL compared to population norms. Lower HRQOL at 12 months compared to baseline. Lower baseline HRQOL compared to population norms. Traumatic patients associated with the greater decreases in HRQOL, the physical and the mental component. Medical patients showed more stable decrements in HRQOL scores.
Nessler et al. [17]	Lower HRQOL compared to population norms. Higher scores at 6 months compared to baseline.
Oeyen et al. [18]	Lower HRQOL compared to population norms in both groups: AKI-RRT and non-AKI-RRT critical patients. HRQOL decreased to the third month, improve at 1 and 4 years, never reaching baseline levels. No significant difference in HRQOL was found between AKI-RRT patients and non AKI-RRT admitted into the ICU.
Parsons et al. [19]	25% of critically ill patients from the cohort discharged from the ICU were diagnosed with clinically relevant insomnia. Post-icu insomnia association with lower MCS and lower vitality, bodily pain and physical function subdomains.
Ringdal et al. [21]	Lower HRQOL scores compared to population norms. Improvement of HRQOL from the first measurement (1 year) to the second measurement (5 years), however remained lower than that one of the reference population. Found DM as a determinant of lower HRQOL scores. Prevalence of DM in trauma patients from the cohort was 23%. Pre-existing disease was found to be a strong determinant of lower HRQOL scores after ICU treatment.
Soliman et al. [11]	Lower HRQOL compared to population norms. Marked variations of HRQOL scores between subgroups. Cardiac surgery : 0.94, CRF, sepsis: 0,65. Identification of a determinant: comorbidities.
Steenbergen et al. [7]	Lower HRQOL compared to population norms.
Stergiannis et al. [20]	Lower HRQOL compared to population norms. Lower HRQOL scores compared to baseline measurements. Found financial status as a determinant of HRQOL. After two years, HRQOL improved gradually along the follow-up period but did not reach baseline levels.
Villa et al. [16]	Lower HRQOL compared to population norms. Lowest scores were in vitality, physical function, physical role functioning domains and mental health. Scores similar to the matched population were found in the rest of the domains.

CONCLUSIONS

From our systematic review several conclusions can be made:

- 1- HRQOL measured using the SF- 36 and the EQ- 5D questionnaires is lower in patients discharged from the ICU than that one of the age and sex matched population norms.
- 2- HRQOL measured after ICU tends to be lower than that one of the patients prior to ICU admission; however is not significantly lower than that one of simply hospitalized patients.
- 3- There HRQOL scores obtained from the validated questionnaires are subjected to time fluctuations after ICU, generally showing gradual improvements from the sixth month after discharge; however these scores never reach those of the age and sex matched population norms.
- 4- Identified determinants of HRQOL were: age, severity of illness, pre-morbid condition, number of comorbidities, presence of shock, diagnostic category, ICU length of stay, length of mechanical ventilation, duration of bed rest, depression, insomnia, delirium, delusional memories, optimism towards disease, awareness of surroundings, frightening experiences, optimism, social integration and financial status.

PRACTICAL RECOMMENDATIONS

It is important to identify the factors that are causing these decrements in quality of life upon discharge from the intensive care unit in order to be able to target them with novel management strategies. Several factors have been identified to contribute to decrements in QOL of patients after ICU stays. These factors can be organized into two groups: modifiable and non- modifiable. Non-modifiable factors are for example age, previous employment status, life orientation optimism, acute disease category, and severity of illness. Modifiable factors are for example, duration of ICU stay, bed rest and immobility, insomnia, stress, and depression. New management strategies should focus in the latter subgroup of factors affecting the quality of life. Probably, it would be positive to screen patients for risk factors that are determinant of HRQOL upon admission to the ICU, and specific management strategy could be directed towards the specific patient.

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ANNEXES

ANNEX 2: SF- 36 QUESTIONNAIRE

Standard Form – 36 (SF-36)			
Patient Name:		Date:	
<p>Standard Form 36 Survey: The SF-36 Form is one of many outcomes assessments designed by the Medical Outcomes Trust in Boston, MA. It is designed to approximate the improvement in health status from a medical intervention.</p> <p>INSTRUCTIONS: This survey asks for views about your health. This information will help keep track of how you feel and how well you are able to do your usual daily activities. Answer every question marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.</p>			
1. In general, would you say your health is: (Circle One)		1. Excellent 2. Very Good 3. Good 4. Fair 5. Poor	
2. Compared to one year ago, how would you rate your health in general at this time? (Circle One)		1. Much better now than one year ago 2. Somewhat better now than one year ago 3. About the same as one year ago 4. Somewhat worse than one year ago 5. Much worse now than one year ago	
3. The following items are about activities you might do during a typical day. Does your health now <u>limit you</u> in these activities? If so, how much? (Circle the appropriate number for each question)			
Activities	Yes, limited a lot	Yes, limited a little	No, not limited
a. Vigorous activities, such as running, lifting heavy	1	2	3

Objects, or participation in strenuous sports			
b. Moderate activities, such as moving a table, Vacuuming, bowling or golfing	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
i. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health? (Circle the appropriate number for each question)

a. Cut down on the amount of time you spent on work or other activities	Yes = 1	No = 2
b. Accomplished less than you would like	Yes = 1	No = 2
c. Were limited in the kind of work or other activities	Yes = 1	No = 2
d. Had difficulty performing the work or other activities (For example – requiring an extra effort)	Yes = 1	No = 2

5. During the past four weeks, have you had any of the following problems with your work or other regular daily activities as result of any emotional problems (such as feeling depressed or anxious)? (Circle the appropriate number for each question)

a. Cut down on the amount of time you spent on work or other activities	Yes = 1	No = 2
b. Accomplished less than you would like	Yes = 1	No = 2
c. Didn't do work or other activities as carefully as usual	Yes = 1	No = 2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (Circle one)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
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7. How much bodily pain have you had during the past 4 weeks? (Circle one)	1. None 2. Very mild 3. Mild 4. Moderate 5. Severe 6. Very severe
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8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Circle one)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks: (Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6

d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?(Circle one)	1. All of the time 2. Most of the time 3. Some of the time 4. A little of the time 5. None of the time
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11. How TRUE or FALSE is each of the following statements to you?(Circle one for each line).					
	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

ANNEX 3: EQ- 5D QUESTIONNAIRE

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐

I am moderately anxious or depressed

☐

I am extremely anxious or depressed

☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

