

Long-term health related quality of life in patients with sepsis after intensive care stay: A systematic review

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Abstract

Sepsis is a major health care issue and sepsis survivors are often confronted with long-term complications after admission to the intensive care unit (ICU) which may negatively influence their health related quality of life (HRQOL). This study aimed to systematically evaluate the outcome in terms of HRQOL in patients with sepsis after ICU discharge.

A literature search was conducted in the bibliographic databases PubMed, EMBASE, and CINAHL, including reference lists of published guidelines, reviews and associated articles.

Sixteen studies were included, thirteen (81.3%) reported that sepsis survivors suffer from impaired HRQOL in physical and mental domains which persist from months to years after a sepsis episode.

More focus on improving long-term outcomes for patients surviving sepsis and the ICU is needed.

Keywords

Sepsis, Health Related Quality of Life (HRQOL), Intensive Care, Mortality.

Key points

- Survivors of sepsis have significantly impaired quality of life in physical and mental domains.
- These impairments may last months to years after treatment has ceased.
- More focus on improving long-term outcomes for patients surviving sepsis and the ICU is needed.

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Introduction

Sepsis is a serious threat to public health, with a high incidence, which continues to rise. Contributory factors include an aging population, an increased use of chemo- and immunotherapy and antibiotic resistance.¹ Patients with severe sepsis have high morbidity and mortality rates, predominantly caused by acute organ dysfunction. The need for vital organ support often necessitates admission to the intensive care unit (ICU) and prolonged use of these (costly) healthcare facilities.² The incidence of severe sepsis in the ICU, either acquired at admission or during ICU stay, has also increased and currently 11% to 15% of all ICU patients have a diagnosis of severe sepsis or septic shock.³⁻⁵

Patients who survive following ICU admission may suffer from impairments in physical (e.g. critical illness neuropathy, chronic pain) and mental (e.g. cognitive impairment, depression) health and these impairments may have extensive effects on the health-related quality of life (HRQOL).⁶⁻⁹ Recent work has underlined this by stating¹⁰ that elderly patients admitted to a medical ICU have a low survival rate (49%) up to 12 months after discharge. Moreover, these elderly survivors had a twofold increase in the prevalence of geriatric syndromes (mainly polypharmacy, urinary incontinence and depression), even at long-term follow-up.

These impairments could negatively influence the HRQOL.

In the past, critical care research has mainly focused on outcomes such as (short-term) mortality, however considering the profound impact sepsis and ICU admission might have, recently more attention is being paid to HRQOL as an equally important outcome. A review regarding HRQOL after stay at ICU in patients with critical illnesses was performed in 2010 by Oeyen et al.¹¹ This study focused on multiple critical illnesses, of which sepsis related studies were a relatively small group. Only three of the 53 studies included, solely focused on patients with sepsis. The authors found that HRQOL differed with each diagnostic category and that patients with severe sepsis, amongst other diagnoses (such as severe acute respiratory distress syndrome) had the most severe reduction in HRQOL. Only one review¹² primarily focusing on long-term mortality and HRQOL in all patients with sepsis has been published in 2010. This work demonstrated that patients with sepsis were found to have ongoing mortality, even years after an episode of sepsis and survivors suffered from impaired HRQOL. Thus, both ICU survivors and survivors of sepsis, may suffer for months or years from long lasting impairments that arise during or after their lengthy stay in the intensive care and hospital.

Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review

Many advances have been made improving the survival of patients with sepsis in the last few decades.^{13,14} International guidelines have been successfully developed and implemented and have shown to reduce hospital mortality rates and optimize care for sepsis patients. In addition, with the advent of modern intensive care, with improved facilities, surveillance, diagnostic and therapeutic options, more patients will survive their stay in ICU.² However, it is still unclear what impact these advancements have in improving long-term HRQOL for patients admitted to the ICU who survive sepsis. Therefore, the aim of this systematic review is to provide an insight in the health-related quality of life of sepsis survivors after ICU stay.

Material and Methods

Study identification / search strategy

To identify all relevant publications, we performed a systematic search in the bibliographic databases PubMed, EMBASE, and CINAHL from inception to July 2016. Search terms included free text terms as well as controlled terms from MeSH in PubMed and The Cochrane Library, EMtree in EMBASE and Thesaurus in CINAHL. In PsychINFO only free text terms were used. Search terms expressing 'sepsis' were used in combination with search terms comprising 'quality of life'. Filters were applied where possible to limit the results to adults, and to exclude certain publication types such as newspaper articles and case reports. Subsequently, the references of identified articles were manually searched for relevant publications.

Eligibility Criteria

An extensive number of studies (n=3085) was extracted during this search. Thereafter, all titles were reviewed for an initial screening to identify the studies that could potentially contain longitudinal data involving long-term outcomes of patients with sepsis, subsequently an abstract selection was performed. Studies were selected for review if they met the following inclusion criteria:

1. the study was a retrospective, a prospective observational, or a case-controlled study;
2. the study population consisted of patients (age 18 years and above) admitted to the ICU with sepsis;
3. the study reported HRQOL as a (primary) outcome;
4. HRQOL assessment tools were used.

Exclusion criteria were:

1. no full text available (in English);
2. certain publication types such as editorials, letters, legal cases, interviews, posters etc.

Study selection and Data Collection

Three reviewers (NA, RN, JH) independently screened all potentially relevant titles and abstracts for eligibility. If necessary, the full text article was checked for the eligibility criteria. Differences in opinions were resolved by consensus. All retrieved abstracts were available in English. Data was extracted independently from the selected articles, a standardized data-worksheet including the following variables was used for data extraction: type of study, patient characteristics, methodology, study outcomes, conclusion, limitations, and study quality.

Quality assessment data

Study quality was assessed by using four criteria adapted from the U.S. Preventive Services Task Force:^{15,16}

1. no systematic exclusion of >10% of the adult ICU population;
2. description of patients lost to follow-up and comparison with those remaining in the study;
3. HRQOL assessment before ICU admission (baseline); and
4. adjustment for confounders such as age and gender, or comparison with a matched population. The reviewers assessed each of the criteria independently. Quality criteria were not used in decisions regarding inclusion or exclusion of eligible studies.

Results

Study Characteristics

Of the total 3085 citations were identified, 16 articles were included (Figure 1. Flow chart). A total of 5333 septic patients and hospitalized controls were enrolled in the 16 included studies. A total number of included patients in the control group cannot be provided as some studies did not mention the sample size of the control group,¹⁷⁻²² which consisted of controls of the general population or an age and/or gender-matched population. Table 1 gives a complete overview of the characteristics in the reviewed studies.

Setting

The 16 included studies took place in hospitals across different countries, from which eleven in Europe (65%),¹⁷⁻²⁷ two in North America,^{28, 29} one in South America,³⁰ one in Asia.³¹ One study took place in both Europe and North America.³² The publication dates of these studies ranged from 1995 until 2015. Five studies included patients from a medical/surgical intensive care unit (M/SICU),^{17, 21, 26, 27, 30} four included patients from a surgical intensive care unit (SICU)^{23-25, 31} and seven studies included patients from a general ICU.^{18-20, 22, 28, 29, 32} Nine studies^{17, 19, 21, 23-26, 29, 30} were single centre, five multi-centre^{18, 20, 27, 31, 32} and of

Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review

two studies^{22, 28} the number of participating centres remained unclear.

Sepsis type

All studies used the international criteria (from the International Sepsis Definitions Conference) to define sepsis.³³ Two studies^{28, 29} included patients in categories of sepsis, severe sepsis and septic shock. Six studies^{18, 23-27} had a population of patients with either severe sepsis or septic shock, while six studies^{17, 20, 22, 30-32} only focused on patients with severe sepsis and two on patients with septic shock only.^{19, 21} Three studies had a population which consisted of patients with sepsis of a specific organ system, namely abdominal^{23, 24} and community acquired sepsis.²⁷

Quality of life assessment methods

The majority of the studies used standardized instruments to measure the HRQOL. An overview of the different methods used to assess HRQOL can be found in the supplementary article. The EuroQol five dimensions questionnaire (EQ-5D) and the Short-Form³⁶ (SF-36) were most frequently used, whereas some studies used alternative methods of assessment to calculate HRQOL. The EQ-5D was used in seven studies (43.8%)^{18, 20, 25-27, 30, 32} and the SF-36 in six studies (37.5%),^{17, 19-21, 28, 31} see Table 3 Assessment of HRQOL.

Assessment of HRQOL

HRQOL was assessed by patients themselves, proxies or a combination in respectively 43.8%,^{19, 20, 22, 24, 26-28} 6.2%,²³ 50%,^{17, 18, 21, 25, 29-32} of the studies. During follow-up, HRQOL of patients was evaluated in two studies^{26, 31} through personal interviews, in five studies through mail,^{18, 22, 23, 27, 29} in four studies,^{20, 25, 28, 30} by telephone and in five studies^{17, 19, 21, 24, 32} a combination was used.

Response rate and follow-up

A minority of the studies^{17, 21, 26, 27} used a follow-up period of six months, while the remaining twelve studies^{18-20, 22-24, 28-32} used a follow-up period which ranged from one to eight years (see Table 3).

Response rates varied from 26 percent to 100 percent: nine studies (56.4%)^{8, 18, 22, 24-27, 31, 32} had a response rate between 26% and 54%, three studies (18.8%)^{23, 26, 28} had a response rate between 58% and 78% and three studies (18.8%)^{17, 19, 21} between 81 and 100%. One study,³² did not disclose the response rate.

Quality of life outcomes

Majority (81.3%) of the included studies reported survivors of sepsis suffer from an impaired quality of life.^{17-22, 24, 25, 28-32} An overview of the findings concerning HRQOL per study can be found in

table 3. Four studies comparing HRQOL with other critically ill ICU survivors without sepsis, found that sepsis survivors have a similar HRQOL.^{25-27, 31} Twelve studies^{17-22, 26-31} which compared HRQOL of sepsis survivors with that of a general or age- and/or gender matched population, found significant reductions in HRQOL, in physical as in social domains of life. Both McLauchlan²³ and Haraldsen²⁴ et al., who specifically investigated HRQOL after abdominal sepsis, found that functional status of survivors restored and QOL was reasonable at time of follow-up. Overall, although some recovery was reported,^{23, 24} the decline in HRQOL could persist many months until years after an episode of sepsis.^{17, 20, 21}

Mortality

Eleven of the sixteen studies^{17-21, 23-28} provided hospital mortality data. Hospital mortality rates varied from 10% to 63%. Eight studies^{17, 18, 20, 21, 24, 26-28} had an in-hospital mortality rate varying from 10 to 50%, while two studies^{23, 25} had an in-hospital mortality rate of over 50%. Eight studies^{17, 18, 20, 21, 23, 25-27} provided ICU mortality rate of the sepsis group, which ranged between 11.9% to 48%.

Accumulated mortality after discharge was measured at one or more time points after discharge. In three studies^{17, 21, 26} mortality was measured up to 6 months after discharge. In these groups, mortality rate was between 30 and 45%. Seven studies^{18, 20, 24, 25, 29-31} looked at long-term mortality up to 5 years after discharge and their mortality rates ranged between 9.5% and 67%. Heyland et al.²⁸ found a mortality after discharge of 40% and Poulsen et al.¹⁹ a mortality of 53%, but both studies did not disclose the time point at which mortality was measured. The remainder of the studies^{22, 23, 32} did not provide information on mortality after discharge of the sepsis group.

Study quality criteria

One study¹⁸ (6.3%) met all of the four predefined study quality criteria as adapted from the U.S. Preventive Services Task Force.^{15, 16} Seven studies^{17, 19, 21, 22, 25, 28, 30} (43.8%) fulfilled three of the four quality criteria. Two studies^{26, 31} had major exclusion criteria, excluding more than 10% of the patients, whilst four studies^{17, 27, 29, 32} did not adequately describe their exclusion criteria. See table 4. Study quality criteria.

Discussion

In this systematic review we aimed to provide an overview of the HRQOL of sepsis survivors after an ICU stay. The majority of the 16 eligible studies demonstrated that patients who undergo an episode of sepsis experience a decreased quality of life in both mental and physical domains. This deficit in HRQOL becomes more evident when compared

Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review

to an age and/or gender-matched or the general population. Although recovery was reported in two studies,^{23, 24} this was often incomplete and does not reach the same level as preadmission status. In addition, this review shows HRQOL when compared to the general population can remain impaired many years after hospital discharge.^{21, 31} The wide ranges in follow-up periods and the different type of septic patients included in the studies caused heterogeneity in HRQOL.

Survivors of sepsis have higher mortality rates than other critically ill patients without sepsis.^{18, 25, 30} Those who survive and are discharged, remain at risk for death in the following years.^{36, 37} Even though it is generally assumed that the treatment of septic patients has improved over the years,^{2, 3} all of our included studies, including the recent ones, show that these advances in interventions have not resulted in improvement of HRQOL of septic patients after ICU discharge. The impairments in HRQOL, such as a cognitive decline and physical limitations can persist long after a sepsis episode and significant influences daily life after hospitalization. A sepsis episode may be a stressful traumatic experience, and apart from having severe negative effects on the HRQOL it might also influence the HRQOL of their caregivers.^{22, 32} The HRQOL of caregivers can also worsen in areas of mental health, physical health and may even have financial impacts due to a shift in responsibilities within the family.

The included studies in this review show that an episode of sepsis has significant impact on survivors which continues long after medical treatment has ceased. Therefore the following aspects and interventions which could potentially limit this decrease in HRQOL might be beneficial.

One of these interventions could be the development of specific clinical pathways aimed at optimizing care of patients with sepsis and their caregivers during and after ICU admission. In the past, patients with other critical, time-dependent illnesses such as acute coronary syndrome, multiple trauma and stroke³⁴ have also profited from such clinical pathways. These pathways should have a multidisciplinary approach, aimed at bringing different health care providers together and focus on the treatment of the acutely ill septic patient, as well as prevention and reduction of possible long-term complications. Previous studies investigating the use of certain intervention programmes in the ICU for mechanically ventilated patients,³⁵⁻³⁷ showed that implementation led to a shorter duration of delirium and more importantly an improvement in functional and physical outcomes. In addition, Jones et al. showed that the use of intervention programmes

lead to a reduction of the risk of depression after ICU discharge.³⁷

Post hospital rehabilitation programmes can also be beneficial for sepsis survivors in improving cognitive performance and functional outcomes.³⁸ Although these studies did not specifically compare groups of septic patients, these results might be translatable to septic patients in the ICU. Specific rehabilitation programs targeting physical and cognitive rehabilitation should start early, preferably from the time of admission and continue till acceptable recovery. Creating clinical pathways to optimize sepsis care might not only limit the decrease of HRQOL³⁵⁻³⁸ but might also decrease the length of stay in the ICU and hospital. Despite the cost associated with these intervention programs, implementation may lead to long-term financial benefits.³⁹ Moreover, it might decrease readmission and mortality after discharge.⁴⁰

This decrease in readmission rate might also benefit the Acute Medical Unit (AMU), which often functions as a gateway between the ED and ICU. To the best of our knowledge no studies have been conducted on the association between sepsis related readmissions and strain on the AMU. Future work on this subject is therefore warranted.

Furthermore, it is important to identify risk factors associated with low HRQOL in order to raise the standard of care and improve HRQOL for these patients. One of these risk factors is age, as sepsis usually occurs in the elderly population. A thorough assessment of elderly patients prior to discharge should take place to evaluate their need for intermediate care and further recovery.⁴¹ Inclusion of family members and other informal caregivers must not be forgotten in the treatment and rehabilitation.

Our study has many strengths. First, the studies included for this review contain patients from different continents. This large diversity in the population group means that the findings are probably not limited to one country or one continent. Secondly, the studies in our review included patients with varying severity of sepsis and patients of both the medical and surgical unit of intensive cares. Thirdly, the included studies span from a period of 1996 until 2016 with both short and long follow-up time. Moreover, almost all studies used validated HRQOL instruments such as the SF-36 and EQ-5D to assess the quality of life, the use of specific non validated instruments was limited.

However, while interpreting the results of the included studies some limitations should be taken into account. We could not perform a meta-analysis due to the heterogeneity in the methodology and the study populations. The different types of methods in assessing HRQOL may also influence the results.

Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review

Some studies in our review assessed the HRQOL questionnaires via telephone, which might give a distorted view of the reality, since literature has shown that patients are more likely to rate their health more favourable in phone interviews and face to face assessments, compared to self-administered questionnaires.^{42, 43} A possible explanation for this might be the perceived anonymity that patients who fill in self-administered questionnaires experience.⁴³ Another important consideration, is that patients with the worst HRQOL are often those who do not participate in follow-up assessments.¹² This might cause an underestimation of the actual effect of sepsis in decreasing the HRQOL in sepsis survivors.

Another potential flaw in assessing the HRQOL is 'the response shift', which is the phenomenon in which patients think that their health improves over time, while in reality they have the same or an even worse health status. The patient either gets used to or adapts to their decreased health status.^{44, 45} This would mean that in the included studies, the HRQOL could have been even worse than patients described, thus underestimating the found impact of sepsis on the HRQOL. Most studies in our review used a questionnaire that was assessed retrospectively to determine the baseline quality of life. This could be less accurate, since patients might not be able to recall this information correctly. Only five studies assessed baseline HRQOL before hospitalization.^{17, 18, 21, 26} Although proxies can be used for assessing (baseline) HRQOL, the use of proxies may cause bias in assessing HRQOL accurately, as they may underestimate it.⁴⁶

Another important aspect is that patients who suffer from sepsis differ from the general

population, not only in age and gender but also in their comorbidities and diagnostic category.⁴⁷ Some studies compared HRQOL of sepsis survivors with that of a general population, however the baseline health status of patients who survive the ICU and an episode of sepsis may not be the same.⁴⁶ Except for age- and/or gender none of the studies specifically adjusted for other potential confounders.

It is important for both health care providers and patients to understand the impact a sepsis episode can have on the HRQOL of survivors and their caregivers. Sepsis and related ICU admission should not be considered a temporary physical burden, but as a serious illness which has a significant impact on the HRQOL. Apart from focusing on improving short-term outcomes, more attention is needed to prevent and reduce long-term complications, which might negatively influence the HRQOL.

Conclusion

This review aimed to give an comprehensive overview of the literature available on HRQOL of sepsis survivors after ICU admission. Survivors of sepsis show (significantly) impaired quality of life in both physical and mental domains. These impairments may last several years after hospital discharge. Upcoming trials should look beyond improving short term mortality but also on improving HRQOL and thereby reintegrating patients back into society.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Long-term health related quality of life in patients with sepsis after intensive care stay: a systematic review

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