Health related-quality of life among patients who have survived an episode of sepsis in the United States: a systematic literature review

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Rationale

- Sepsis is a critical illness, experienced by at least 1.7 million adults in the United States (US) in 2023, of which almost 270,000 died.[1]
- Survivors of sepsis may experience long-term effects that profoundly affect their physical, cognitive, and psychological wellbeing,[2,3] and consequently, their health-related quality of life (HRQoL).[4]
- However, there is no current published review on the impact of sepsis on HRQoL among sepsis survivors in the United States (US).

Objective

To identify and summarize evidence on the impact of sepsis on HRQoL among sepsis survivors in the US.

Methods

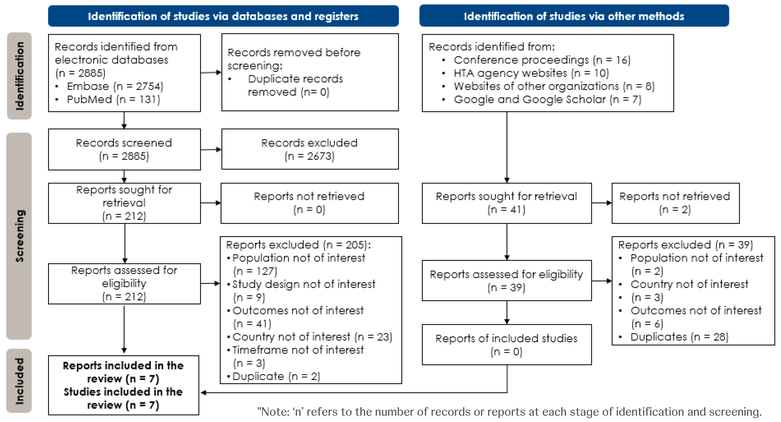
- A systematic literature review (SLR) was conducted to identify studies reporting on HRQoL in patients who survived an episode of sepsis in the United States, published between January 2010 and September 2023.
  - Data sources: bibliographic databases Embase and Medline using Embase.com (Elsevier) and Medline In-Process using PubMed; conference proceedings (2020–2023), websites of organizations, Google, and Google Scholar. Search terms included indexed and free text terms including 'bacteremia', 'septicemia', 'sepsis', and 'urosepsis'. This was part of a broader SLR on extraintestinal pathogenic *Escherichia coli* (ExPEC) disease with multiple outcomes.
  - Population: adults ≥18 years diagnosed with sepsis (irrespective of the cause of sepsis or the underlying conditions leading to sepsis). Geographic location: US
  - Outcomes: HRQoL, cognitive assessments, physical functioning assessments, evaluations of depression and anxiety

Results

Literature identification

- Of 2885 citations, 7 studies (7 publications) met the predefined eligibility criteria for population and outcomes (**Figure 1**). No additional studies were identified from other sources.

Figure 1. Flow chart of the literature search (PRISMA diagram)



"Note: 'n' refers to the number of records or reports at each stage of identification and screening.

Table 1. Characteristics of included studies

Author, year	Study type	Population	Sample size	HRQoL indicators	Cognitive impairment	Physical assessment	Depression / anxiety
Iwashyna, 2010[8]	Prospective	Patients ≥50 years who survived sepsis	• No limitations: 269 • Mild/moderate limitations: 195 • Severe limitations: 159	–	✓	✓	–
Kiely, 2012[10]	Retrospective	Patients undergoing ileal pouch–anal anastomosis (IPAA) who developed pelvic sepsis	• Overall: 2821 • With pelvic sepsis: 144 • Without pelvic sepsis: 2677	✓	–	–	–
Davydow, 2013[11]	Prospective	Severe sepsis survivors	• Overall: 471	–	–	–	✓
Dinglas, 2016[5]	Prospective	Sepsis associated with Acute Respiratory Distress Syndrome (ARDS) patients	• Randomized to rosuvastatin: 293 • Randomized to placebo: 275	✓	–	✓	✓
Ehlenbach, 2018[9]	Retrospective	Medicare patients discharged following severe sepsis hospitalization	• Discharges to a Skilled nursing facilities (SNF): 66,540 • Discharges to a non-SNF: 109,215	–	✓	✓	–
Gardner, 2019[6]	Prospective	Critically ill surgical patients admitted with/developed sepsis	• Patients who developed chronic critical illness: 63 • Patients with rapid recovery: 110	✓	–	✓	–
Williams Roberson, 2023[7]	Prospective	Adult patients with sepsis-induced respiratory and/or cardiovascular dysfunction	• Intervention group: 105 • Control group: 108	✓	✓	✓	✓
Total				4	3	5	3

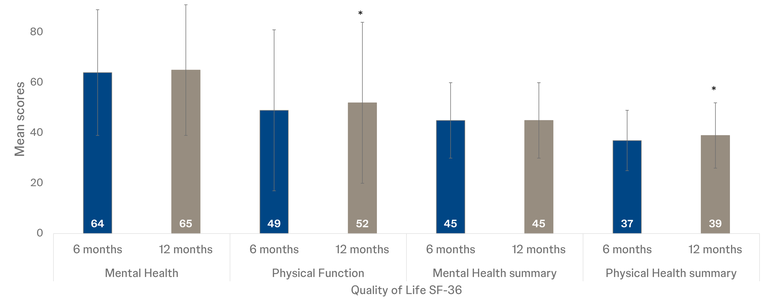
Study characteristics

- Five of the included studies reported on physical assessments,[5–9] 4 reported on various HRQoL indicators,[5–7,10], 3 on cognitive indicators,[7–9] and 3 on depression and anxiety[5,7,11] in patients who had a sepsis episode and/or were recovering from sepsis (**Table 1**).
- Most studies were conducted in a hospital setting (4 studies),[5–7,9] followed by a community setting (2 studies),[8,11] and one study was conducted in a medical center.[10]
- Two studies exclusively focused on patients who had severe sepsis,[9,11] while others investigated a broader population of patients with sepsis (**Figure 1**).[5–8,10] The mean age of participants was reported in 6 studies,[5,6,8–11] ranging between 38.1[10] and 82.1[9] years, while the proportion of male patients varied between 29%[5] and 64%[8] across all 7 studies.
- Six studies reported data on racial demographics, in which the proportion of Caucasian patients ranged between 54.3%[7] and 90%[6], and African Americans ranged between 7.9%[6] and 35.2%.[7]

Health related quality of life measures

- Four studies reported results for the following HRQoL measures, EuroQol 5-Dimensional questionnaire (EQ-5D; score range -0.11–1), 36-item Short Form survey (SF-36; range 0-100), Cleveland Global Quality of Life (CGQL; 0–1) and Functional Performance Inventory-Short Form (FPI; 0–3), across a total of 3775 patients.[5–7,10]
- Among patients who underwent surgery, overall CGQL scores of patients who developed sepsis were significantly worse than those who did not (0.74 vs. 0.79; $p < 0.001$).[10]
- Patients who survived ≥14 days in intensive care units (ICU) who developed chronic critical illness had a decline in the SF-36 physical functioning ($p< 0.05$) (34 [6 months] vs 26 [12 months]) and mental health scores (42 [6 months] vs 26 [12 months]), while those who rapidly recovered had improved SF-36 scores compared to chronic critical illness group (physical functioning: 47 [6 months] vs 42 [12 months]; mental health: 43 [6 months] vs 49 [12 months]).[6]
- At 6 months follow up, patients with sepsis-induced acute respiratory and/or cardiac dysfunction who survived to discharge or day 30 had a median (IQR) EQ-5D-3L score of 70 (50–85).[7]
- A linear regression analysis (main effect treatment, adjusted for sex and age) showed that, at 6 months follow-up post-sepsis, patients who had sepsis-associated Acute Respiratory Distress Syndrome (ARDS) had lower SF-36 physical and mental health domain and summary scores compared with age- and sex-matched population norms. These patients did not demonstrate statistically significant improvements between 6- and 12-month follow-up (except for physical health domains and summary scores; **Figure 2**).[5]

Figure 2. 6-month and 12-month follow-up evaluation of patients with sepsis-associated ARDS, SF-36 physical function and mental health domains †



Note: †SF-36 Physical Function and Mental Health domains (range: 0 to 100; higher score is better); SF-36 Physical and Mental Health Summary normalized scores (mean = 50; standard deviation = 10; higher score is better). Calculations from linear or logistic regression models with random intercept for subject and an indicator for time (12- vs. 6-month follow-up). *P value < 0.05. Bars represent standard deviation. Abbreviations: ARDS: acute respiratory distress syndrome; SF-36: Medical outcomes Study Short-Form 36 version 2. Source: Dinglas *et al.* (2016)[5]

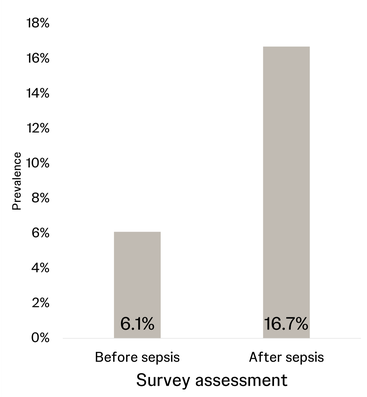
Depression and anxiety measures

- Three studies reported on depression, anxiety, and post-traumatic stress disorder (PTSD) indicators in 1252 patients.[5,7,11]
- Davydow *et al.* (2013) used the Center for Epidemiologic Studies Depression Scale (CES-D) scale to assess 471 severe sepsis survivors.[11]
  - A propensity score was adjusted to account for the likelihood of missing post-sepsis depression data.[11]
  - The adjusted relative risk of depression before (per additional year), during, and after sepsis were 1.03, 0.95, and 1.01. respectively. The study concluded that the prevalence of depression is high among severe sepsis survivors, but severe sepsis was not independently associated with an increased risk of subsequent substantial depressive symptoms.[11]
- Dinglas *et al.* (2016) assessed Hospital Anxiety and Depression Scale (HADS) scores of 568 patients following sepsis associated with ARDS:[5]
  - At 6- and 12-months post-sepsis, the mean HADS anxiety score was 7 (SD=5). The proportion of patients reporting a HADS-anxiety score >8 decreased from 46% at 6 months (out of 217 patients assessed) to 41% at 12 months (out of 203 patients assessed). At 6- and 12-month follow-up, patients treated with rosuvastatin had greater odds of substantial anxiety symptoms (HADS anxiety score ≥8) compared to the placebo group.[5]
  - Median HADS depression score was 6 (SD=5) at 6- and 12-months post sepsis; 37% percent of patients at both 6 and 12 months reported a score >8 on the HADS-depression scale.[5]
- Williams Roberson *et al.* (2023) reported that among patients who had sepsis-induced acute respiratory and/or cardiac dysfunction, rates of depression and PTSD were aligned with previous findings[12,13] and consistent with the typical outcomes observed in patients with post-intensive care syndrome.[7,14,15]

Cognitive measures

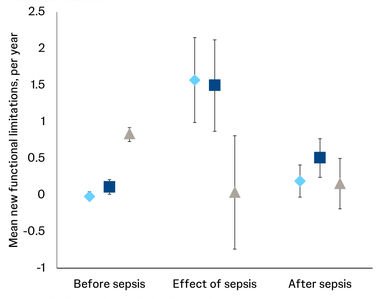
- Three studies reported cognitive function assessments for 155,807 patients who had an episode of sepsis.[7–9]
- Iwashyna *et al.* (2010) assessed cognitive function in biennial interviews using different scales for participants aged ≥65 years and those <65 years. Prevalence of moderate-to-severe cognition impairment before and after sepsis was 6.1% and 16.7%, respectively, among 623 patients who had survived a severe sepsis episode (**Figure 3**).[8]
- Ehlenbach *et al.* (2018) noted that among 66,539 patients discharged following severe sepsis, 34% reported severe or very severe cognitive impairment using the Minimum Data Set - Cognition scale (MDS-COGS) categories.[9]
- Williams Roberson *et al.* (2023) reported that survivors of severe sepsis who received ICU care had similar cognitive indicator scores (Telephone Interview for Cognitive Status (TICS), Wechsler Adult Intelligence Scale (WAIS-IV), Hayling Sentence completion, Controlled Oral Word Association Test (COWA-T) score, WMS-IV Logical Memory I and II) to those reported in other cohorts of ICU survivors.[7,16,17]

Figure 3. Prevalence of moderate-to-severe impairment in cognition before and after sepsis



Source: Iwashyna *et al.* (2010)[8]

Figure 4. Functional limitations following sepsis, by functional class at baseline



Note: Functional limitations "before" and "after sepsis" periods refers to new functional limitations. Functional limitations during the "effect of sepsis" period refers to limitations acquired at hospitalization for severe sepsis. Patients with **severe** limitations before sepsis did not show further increased limitations. Patients **without** pre-sepsis limitations or with **mild/moderate** pre-sepsis limitations showed statistically significant increases in new limitations at effect of sepsis and after sepsis. Bars represent 95% confidence interval. Source: Iwashyna *et al.* (2010)[8]

Physical functioning measures

- Five studies evaluated functional status across a total of 136,593 patients, using various instruments: Katz Activities of Daily Living Score (Katz ADLS), Functional Activities Questionnaire (FAQ), Physical test (total), Zubrod Scale, Minimum Data Set - Activity of daily living Scale (MDS-ADL), 6 Minute Walk Distance, 4 Meter Gait Speed, Manual Muscle Test Score, Hand Grip Strength, maximal inspiratory pressure, and Instrumental activities of daily living (IADLs).[5–9]
- Iwashyna *et al.* (2010) reported changes in ADLs or Instrumental ADLs from baseline functioning (no limitations, mild to moderate limitations, or severe limitations). Patients with no functional limitations or mild-to-moderate limitations before a severe sepsis episode experienced 0.19 and 0.51 new functional limitations respectively following sepsis (**Figure 4**). Patients with severe limitations before sepsis, did not tend to have new limitations as an affect of sepsis and after sepsis, as were already severely burdened.[8]
- Ehlenbach *et al.* (2018) reported that 72.5% (48,212) of patients discharged following severe sepsis hospitalization had an ADL Hierarchal Scale score (0 – 6) indicating maximal dependence (4) or total dependence (6).[9]
- Poor physical functioning and performance [6,7], as well as high cumulative mortality[5], were reported in three studies[5–7] of post-sepsis patients assessed at 6 and/or 12 months.

Discussion

- In the US, published data are available for impacts of sepsis on HRQoL for sepsis survivors in general and for patients who had an episode of sepsis associated with selected possible high risks: cardiovascular, respiratory, or specific surgical interventions. However, additional data are needed for these high-risk groups and for multiple other sub-populations who may also have a high risk for sepsis.
- HRQoL instruments used were not specific to assessment of patients who survived an episode of sepsis.
- Surviving one episode of sepsis can result in profound and potentially long-term negative impacts on a patient's HRQoL. However, differences in quality of life, cognitive function, physical health, and mental wellbeing can vary among sepsis survivors depending on the heterogeneity of the populations studied.
- The findings of this review are consistent with the results of the existing literature that indicate long-term quality of life decrements among sepsis survivors.[18]

Conclusion

These findings highlight that patients who survive sepsis may experience profound and often long-term negative impacts for HRQoL including ability to perform activities of daily living, cognitive abilities and physical wellbeing. Additionally, given the heterogeneity of populations of sepsis survivors, there is some variability in impact of sepsis on quality of life, and other measures. There remain important evidence gaps in understanding the relationship between sepsis occurring in specific comorbidity risk groups and its impact for these risk groups on patients' long-term quality of life. In the US, available HRQoL data are very limited for patients with sepsis, and the absence of disease-specific HRQoL measures for sepsis may prevent a comprehensive understanding of the HRQoL impact.

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