Changes in Self-Rated Health After Sepsis in Older Adults

A Retrospective Cohort Study

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BACKGROUND: As more individuals survive sepsis, there is an urgent need to understand its effects on patient-reported outcomes.

RESEARCH QUESTION: What is the effect of sepsis on self-rated health, and what role, if any, does functional disability play in mediating this effect?

STUDY DESIGN AND METHODS: We conducted a survey- and administrative claims-based retrospective cohort study using the US Health and Retirement Study, a nationally representative cohort-based survey of older adults in the United States, from 2000 through 2016. We matched Medicare beneficiaries hospitalized with sepsis in 2000 to 2008 to nonhospitalized individuals. Self-rated health and functional disability were tracked biannually for 8 years. Differences in self-rated health between the cohorts were measured using mixed models with and without controlling for changes in functional disability.

RESULTS: Seven hundred fifty-eight individuals with sepsis were matched 1:1 to 758 nonhospitalized individuals, all aged 65 years and older. Among survivors, sepsis was associated with worse self-rated health in years 2 and 4 (adjusted absolute difference in self-rated health on a 5-point scale in year 2: -0.24 [95% CI, -0.38 to -0.10] and year 4: -0.17 [95% CI, -0.33 to -0.02]) but not in years 6 or 8. After accounting for changes in functional status, the association between sepsis and self-rated health was still present but reduced in year 2 (adjusted absolute difference in self-rated health, -0.18 [95% CI, -0.31 to -0.05]) and was not present in years 4, 6, or 8.

INTERPRETATION: Self-rated health worsened initially after sepsis but returned to the level of that of nonhospitalized control subjects by year 6. Mitigating sepsis-related functional disability may play a key role in improving self-rated health after sepsis.

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FOR EDITORIAL COMMENT, SEE PAGE 1808

ABBREVIATIONS: HRQOL = health-related quality of life; HRS = Health and Retirement Study

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Sepsis contributes to high in-hospital¹⁻³ and late mortality⁴ and also leaves survivors with lasting detrimental effects, such as functional disability (ie, requiring additional assistance with activities of daily living and instrumental activities of daily living), cognitive impairment, and depression.^{5,6} Others have examined the impact of sepsis on the broad yet related concept of health-related quality of life (HRQOL), which has been defined as “people’s level of ability, daily functioning, and ability to experience a fulfilling life.”⁷ This research on the relationship between sepsis and HRQOL has yielded mixed results, with some studies demonstrating meaningful declines after sepsis and others finding no change.⁸⁻¹⁰

This prior research on HRQOL or key components of HRQOL, such as functional disability, has focused more on what sepsis survivors are able to do than on how survivors feel about their health. Although function is indeed important, some have argued that assessing individuals’ own perceptions are equally important,¹¹ particularly because individuals may adapt to limitations over time.^{12,13} Such adjustments have been noted in other chronic, disabling conditions, such as spinal cord injury,^{14,15} although whether sepsis survivors experience a similar phenomenon is unclear. Studying sepsis survivors’ assessments of their own health, in conjunction with objective measures of functional disability, would help to better elucidate this relationship between self-perceptions and ongoing limitations.

In this study, we sought to examine the effect of sepsis on self-rated health, a well-established global measure of overall health, and specifically, individuals’ perceptions of their health status.¹⁶⁻¹⁸ Self-rated health is a single-item patient-reported outcome, highly correlated with more extensive measures of HRQOL,¹⁹⁻²¹ and an independent predictor of mortality.²² We also assessed functional disability over time to determine the mediating roles of activity limitations on individuals’ perceptions of their own health. To address methodological limitations of prior research on HRQOL after sepsis (eg, lack of pre-illness patient data, the absence of comparator groups, or small sample sizes²³), we used data from the US Health and Retirement Study (HRS), a longitudinal panel survey that provides detailed, individual-level data.²⁴ This dataset permits longitudinal analysis of sepsis survivors from before the onset of sepsis through 8 years of follow-up and allows for comparison of changes in self-rated health after sepsis with that of nonhospitalized individuals. We also employed a variety of statistical techniques to address the methodological challenges associated with assessing functional outcomes in the context of high mortality rates and the natural decline in functioning among the elderly.²⁵⁻²⁷ We hypothesized that self-rated health declines immediately among sepsis survivors but improves over time and that functional disability mediates the decline in self-rated health.

Methods

Study Population and Study Cohorts

We studied participants in the HRS, a biannual, longitudinal, nationally representative survey of older Americans with a response rate of approximately 90%.^{24,28} We identified Medicare beneficiaries aged 65 years or older who had linked Medicare fee-for-service claims and participated in at least one HRS survey from 2000 to 2008.

We identified two cohorts for this study: patients with sepsis and nonhospitalized individuals. Patients with sepsis were identified by the Angus method (e-Table 1).¹ Individuals were included if their first hospitalization after a baseline HRS survey was for sepsis. The nonhospitalized cohort included individuals who were not hospitalized from the time of their baseline HRS survey to the time of matching to the sepsis individuals. For the purposes of this study, “baseline survey” refers to the survey immediately preceding matching (ie, for the sepsis cohort, the survey

immediately preceding sepsis hospitalization). Each cohort was followed up for 8 years, or four follow-up surveys. This approach has been used previously.^{4,6,29,30}

To match patients with sepsis to nonhospitalized individuals, we first used a multivariable logistic regression to estimate each individual’s risk of hospital admission for sepsis in the 2 years after their baseline HRS survey.⁴ Individuals were then matched based on their risk of admission for sepsis, days from baseline survey to matching, and baseline demographics using nearest neighbor matching without replacement. Additional details can be found in the online data supplement (e-Appendix 1).

Measures, Outcomes, and Statistical Analyses

Self-rated health is an easily administered measure that correlates with more comprehensive assessments of health-related quality of life,¹⁹⁻²¹ has been used in many other research settings,^{31,32} and is highly correlated with measures of HRQOL, with Spearman rank correlations of 0.5 to 0.8.¹⁹⁻²¹ Self-rated health was measured on a five-point Likert scale (1-5) in response to the question, “Would you say your health is excellent, very good, good, fair, or poor?”, with higher scores indicating better self-rated health, and was treated as a continuous variable.³³⁻³⁵ Functional disability was measured as the number of activities of daily living and instrumental activities of daily living for which the respondent required assistance (0-11), with higher numbers indicating greater

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functional disability.⁵ For both outcomes, proxies provided responses in which participants were unable to answer questions themselves. Additional details can be found in the online data supplement (e-Appendix 1, e-Table 2).

Primary Outcome Analyses: Our primary outcome was the difference in self-rated health between the sepsis and nonhospitalized cohorts. In all analyses, changes in self-rated health were assessed every 2 years until 8 years after the baseline survey, and time was treated as a discrete variable. Additional details on the modeling approaches are available in the online data supplement (e-Appendix 1).

Examining long-term outcomes, such as self-rated health or functional disability, is challenging in sepsis, because of its high mortality.²⁶ If analyses only include survivors, results may be biased because patients who died might have had worse self-rated health or more functional disability than survivors. For this reason, we used two complementary statistical approaches. Our primary statistical approach included all surviving participants at each follow-up survey, using multilevel linear models. Missing surveys and those who had died were excluded from this analysis. As a secondary statistical approach, we repeated the analysis using a six-point Likert scale composite outcome, which consisted of either the self-rated health score in survivors or zero for those who had died or had missing survey data.²⁶

Each of these approaches has limitations. In the analysis in which those who died were excluded, sample sizes in later years would be expected to diminish markedly compared with earlier surveys, resulting in larger standard errors. It also would be impossible to differentiate whether changes in the average self-rated health over time was due to changes among those still alive or due to death of those with lower-than-average self-rated health. Using a composite outcome that incorporates death addressed these problems. However, the composite outcome approach would be expected to result in many individuals with a self-rated health score of 0 (ie, death). Higher mortality in the sepsis cohort could then be the primary driver of differences in self-rated health between the sepsis and nonhospitalized cohorts.

Consequently, we performed a post hoc analysis in which we included only those who survived at least 6 years post-baseline. By doing so, we created a subgroup in which all changes in the difference in self-rated

health between the two groups would be attributable to individual changes in self-rated health among living participants, rather than death.

Finally, we tested the hypothesis that improvements in average self-rated health scores over time were attributable to those with lower self-rated health having higher mortality rates by conducting a second post hoc analysis in which we assessed the mortality in years 2 through 6 of survivors with low self-rated health (1 or 2 out of 5) vs those with higher self-rated health (3, 4, or 5 out of 5) at the first follow-up survey in year 2.

Secondary Outcome Analyses: We were also interested in the potential mediating effect of functional disability as a secondary outcome. Changes in functional disability were assessed using similar methods to those described for self-rated health. We then performed the analytical approach previously described, using all survivors with survey data at each time period to compare differences in self-rated health between the sepsis and nonhospitalized cohorts after controlling for contemporaneous changes in functional disability.

Mortality analyses used Kaplan-Meier survival curves and Cox proportional hazard models. We examined balance of covariates between the sepsis and nonhospitalized cohorts, using standardized differences. Complete case analysis was used,²⁵ because missingness for any variable was always less than 4%. Additional sensitivity analyses comparing those admitted to the ICU with sepsis to those who were not can be found in the online data supplement (e-Appendix 1). We conducted data management using SAS 9.4 (SAS Institute Inc) and data analysis using Stata/MP 15.1 (StataCorp). We used two-sided hypothesis testing and set significance at $P < .05$.

Funding and Institutional Review Board

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The study was deemed exempt from review by the University of Michigan Institutional Review Board (HUM00166509).

Results

Of 13,330 HRS participants with linked Medicare fee-for-service claims who had at least one completed survey from 2000 to 2008, we identified 758 individuals for inclusion in the sepsis cohort who were matched to 758 individuals who were not hospitalized from the baseline HRS survey to the time of matching (e-Fig 1). The sepsis and nonhospitalized cohorts were generally well matched, except that more individuals from the sepsis cohort were enrolled in Medicaid, and fewer were married (Table 1).

Individuals in both the sepsis and nonhospitalized cohorts experienced high mortality. Eight years after the baseline survey, 618 (81.5%) individuals in the sepsis cohort and 496 (65.4%) in the nonhospitalized cohort had died. After adjusting for age, sex, comorbidities,

baseline self-rated health and functional status, and risk of sepsis, sepsis was associated with a higher risk of death at year 8 (adjusted hazard ratio, 1.9; 95% CI, 1.6 to 2.1; $P < .001$). The difference in mortality rates between the two cohorts was greatest in the first 2 years after the baseline survey (e-Fig 2).

Self-Rated Health

The adjusted self-rated health scores of the sepsis and nonhospitalized cohorts are shown in Figure 1 and e-Table 3.

Survivors Only: Compared with nonhospitalized individuals, sepsis was associated with lower self-rated health in year 2 (adjusted absolute difference, -0.24 ; 95% CI, -0.38 to -0.10 ; $P = .001$) and year 4 (adjusted absolute difference, -0.17 ; 95% CI, -0.33 to -0.02 ;

TABLE 1] Baseline Characteristics of Individuals in the Matched Sepsis and Nonhospitalized Cohorts With Standardized Differences Between Groups

Characteristic	Nonhospitalized (n = 758)	Sepsis (n = 758)	Standardized Difference
Age in years, mean (SD)	79.5 (9.0)	79.3 (8.3)	0.02
Female, No. (%)	439 (57.9)	420 (55.4)	0.05
White, No. (%)	629 (83.0)	609 (80.3)	0.07
Hispanic, No. (%)	56 (7.4)	55 (7.3)	0.01
Married, No. (%)	347 (45.8)	305 (40.2)	0.11 ^a
Educational attainment in years, mean (SD)	11.1 (3.7)	11.2 (3.6)	−0.02
Enrollment in SSI, No. (%)	61 (8.0)	70 (9.2)	0.04
Enrolled in Medicaid, No. (%)	145 (19.1)	185 (24.4)	0.13 ^a
Reside in nursing facility, No. (%)	114 (15.0)	103 (13.6)	0.04
Hospitalized in 2 years before baseline survey, No. (%)	401 (52.9)	413 (54.5)	0.03
Sepsis in the 2 years before baseline survey, No. (%)	23 (3.0)	25 (3.3)	0.02
Charlson comorbidity index, median (IQR)	6 (4-9)	6 (5-9)	0.04
Baseline functional disability score, median (IQR)	1.5 (0-5)	1 (0-5)	0.03
Baseline self-rated health, median (IQR)	2 (1-3)	2 (1-3)	<0.01

IQR = interquartile range; SSI = supplemental security income (government subsidy for individuals meeting income or disability eligibility requirements).

^aDenotes standardized difference with an absolute value greater than 0.10.

$P = .03$), but these differences were attenuated toward zero in years 6 and 8 (Table 2, Fig 1).

Composite Outcome: In the composite outcome analysis in which individuals who died were assigned a self-rated health of zero, the sepsis and nonhospitalized cohort both experienced declines in self-rated health compared with baseline in all follow-up years (e-Table 4). Sepsis was associated with worse composite self-rated health in every year of follow-up relative to that of the nonhospitalized cohort (e-Table 5).

Six-Year Survivors: In a post hoc analysis to test whether late improvement in self-rated health was due to recovery of self-rated health, 161 individuals with sepsis (21.2%) survived to 6 years compared with 256 nonhospitalized individuals (33.8%) who survived to 6 years. Among these survivors, at baseline, there was no significant difference in self-rated health scores between the groups (adjusted absolute difference, -0.12 ; 95% CI, -0.32 to 0.08 ; $P = .24$). At year 2, there was lower self-rated health in the sepsis cohort compared with the nonhospitalized cohort (adjusted absolute difference, -0.27 ; 95% CI, -0.48 to -0.06 ;

Figure 1 – Adjusted mean self-rated health scores for the sepsis and nonhospitalized cohorts for the baseline year and 4 biannual follow-up surveys. Scores were adjusted for age, sex, Charlson comorbidity index, and time from baseline survey to matching. Scores were not adjusted for changes in functional disability over time. This analysis included only survivors, and the number of survivors with complete data in each year is given below the figure. Asterisks denote $P < .05$ for difference between the sepsis and nonhospitalized cohorts' scores. Error bars denote 95% CIs.

TABLE 2] Differences in Adjusted Self-Rated Health Scores Between the Sepsis and Nonhospitalized Cohorts From Baseline Through 8 Years of Follow-up, With and Without Adjustment for Changes in Functional Disability

Survey Year	Difference in Adjusted Self-Rated Health, Not Controlling for Changes in Functional Disability		Difference in Adjusted Self-Rated Health, Controlling for Changes in Functional Disability	
	Difference (95% CI)	P	Difference (95% CI)	P
Baseline	−0.02 (−0.13 to 0.08)	.67	−0.02 (−0.12 to 0.08)	.69
2	−0.27 (−0.40 to −0.13)	<.001	−0.18 (−0.31 to −0.05)	.007
4	−0.17 (−0.33 to −0.02)	.03	−0.11 (−0.26 to 0.04)	.16
6	−0.10 (−0.28 to 0.08)	.26	−0.04 (−0.21 to 0.13)	.65
8	−0.07 (−0.27 to 0.13)	.50	−0.02 (−0.22 to 0.17)	.82

Self-rated health scores were adjusted for age, sex, and Charlson comorbidity index collected at baseline as well as time from baseline survey to matching. Baseline year denotes pre-matching survey date. Positive numbers indicate higher self-rated health in the sepsis cohort relative to the nonhospitalized cohort.

$P = .01$). At years 4 and 6, these differences converged toward zero (Table 3).

Mortality Among Survivors With High vs Low Self-Rated Health: In a second post hoc analysis to test whether late improvement in self-rated health was due to the death of individuals with lower self-rated health scores, sepsis survivors with low self-rated health scores at the first follow-up point (ie, year 2) had higher mortality compared with other survivors in years 2 through 6 (adjusted hazard ratio, 2.2; 95% CI, 1.6 to 3.2; $P < .001$).

Functional Disability

Both the sepsis and nonhospitalized cohorts experienced increasing functional disability relative to baseline in all years of follow-up (e-Table 6, Fig 2). Compared with

the nonhospitalized cohort, functional status was worse in the sepsis cohort in all years after the baseline survey (e-Table 7, Fig 2). After accounting for changes in functional status among survivors, the association between sepsis and self-rated health was still present but reduced in year 2 (adjusted absolute difference in self-rated health, −0.18; 95% CI, −0.31 to −0.05; $P = .007$) but was attenuated toward zero in years 4, 6, and 8 (Table 2).

Sensitivity Analyses

Results of sensitivity analyses comparing ICU and non-ICU sepsis subgroups (e-Table 8) can be found in the online data supplement (e-Tables 9, 10).

Interpretation

In this retrospective cohort study comparing self-rated health in sepsis survivors with that of matched nonhospitalized control subjects from a pre-sepsis baseline through 8 years of follow-up, sepsis survivors experienced worse self-rated health at years 2 and 4 after sepsis. However, these differences attenuated over time. Sepsis survivors also experienced lasting functional disability relative to control subjects. Accounting for these changes in functional disability attenuated the relationship between sepsis and self-rated health.

These findings highlight two key points. First, sepsis was associated with a decline in self-rated health initially, but over time, the differences between self-rated health scores of sepsis survivors and nonhospitalized control subjects disappeared. Second, improvements in self-rated health occur despite ongoing functional disability, relative to nonhospitalized control subjects.

Initial Decline but Subsequent Improvements in Self-Rated Health: Prior studies focused on HRQOL in the first 1 or 2 years after critical illness have

TABLE 3] Differences in Adjusted Self-Rated Health Scores Between the Sepsis and Nonhospitalized Cohorts From Baseline Through 8 Years of Follow-up for Those Surviving to at Least Year 6 Post-Baseline

Survey Year	Difference in Adjusted Self-Rated Health for Those Who Survived to Year 6 or Later	
	Difference (95% CI)	P
Baseline	−0.12 (−0.32 to 0.08)	.24
2	−0.27 (−0.48 to −0.06)	.01
4	−0.21 (−0.41 to 0.002)	.05
6	−0.18 (−0.39 to 0.03)	.10
8	−0.11 (−0.34 to 0.11)	.33

Includes 161 individuals from the sepsis cohort and 265 individuals from the nonhospitalized cohort. Scores were adjusted for age, sex, and Charlson comorbidity index collected at baseline as well as time from baseline survey to matching. Baseline year denotes prematching survey date. Positive numbers indicate higher self-rated health in the sepsis cohort relative to the nonhospitalized cohort.

Figure 2 – Adjusted mean functional disability scores for the sepsis and nonhospitalized cohorts for the baseline year and four biannual follow-up surveys. Scores were adjusted for age, sex, Charlson comorbidity index, and time from baseline survey to matching. This analysis included only survivors, and the number of survivors in each year with complete data is given below the figure. Asterisks indicate $P < .05$ for difference between the sepsis and nonhospitalized cohorts' scores. Error bars denote 95% CIs.

demonstrated lower HRQOL.^{8,10} Studies with follow-up periods of 5 years or longer have demonstrated no meaningful change in HRQOL among survivors after critical illness.^{36–38} Taken together, these findings are consistent with our results demonstrating a decline in self-rated health for sepsis survivors relative to matched control subjects in the first 2 to 4 years after sepsis, only to have these differences in self-rated health wane in later years of follow-up.

This late convergence in self-rated health between individuals with and without sepsis may have two possible explanations. One possibility is that individuals who survive sepsis have an initial decline in self-rated health (relative to matched control subjects) that improves over time. To examine this possibility, we conducted a post hoc analysis of individuals who survived to at least 6 years after matching, finding a similar pattern to our main results. This suggests that “recovery” of self-rated health among sepsis survivors is at least part of the explanation.

A second possibility is that individuals with lower self-rated health died in the later follow-up years, resulting in a higher average self-rated health for the remaining participants—even if those survivors had no change in self-rated health themselves. This so-called “truncation due to death” is a problem in any study of long-term outcomes in the context of high mortality.²⁶ With 1-year and 8-year mortality of 47.5% and 81.5%, respectively, in the sepsis cohort—consistent with the findings of others^{4,8}—the latter explanation was a distinct possibility. We and others have found that individuals with lower self-rated health scores had higher mortality.²² Taken together, these results

demonstrate that recovery in self-rated health occurred over time for those who survived sepsis. At the same time, however, those with lower self-rated health scores immediately after sepsis had a higher risk of mortality. Thus, self-rated health scores immediately after sepsis may be a marker to identify patients at high risk of death.

In the face of high mortality, an alternative way to assess the impact of sepsis on self-rated health in the context of high mortality is to use a composite outcome, as others have recommended.²⁶ Using this approach, in which those who died were assigned the lowest possible self-rated health score, we demonstrated that sepsis was associated with worse self-rated health in all years after matching. The limitation of this approach, however, is that it prohibits separated examination of the effect of sepsis on survival and self-rated health among survivors. As shown, the interplay between sepsis, mortality, and self-rated health is more complicated than can be accurately summarized in a single metric.

Self-Rated Health Improvements Despite Ongoing Functional Disability:

One explanation for the improvement in self-rated health, relative to that of nonhospitalized control subjects, despite ongoing functional disability could be that survivors of sepsis “adapt” to their new condition, with self-rated health improving even as functional disability persists.³⁹ Alternatively, sepsis survivors may change the ways that they think about their own health (a phenomenon known as “response shifting”) through recalibration of their own “self-rated health scales,” reprioritization of the components of “self-rated health,” or

reconceptualization of what “self-rated health” means to them.¹² These theories would make sepsis similar to other, chronically disabling conditions such as spinal cord injuries.^{14,15,40} Consistent with this hypothesis, others have found that, among the elderly, factors such as resilience affect HRQOL more than objective measures of physical health and functioning.⁴¹ These results suggest that health-care practitioners caring for survivors of sepsis and their families should address resilience, coping mechanisms, and expectations as a means of improving overall satisfaction and perceptions of health after sepsis.^{11,12} At the same time, we found that controlling for changes in functional disability weakened the relationship between sepsis and self-rated health. Therefore, efforts to preserve or regain functional abilities after sepsis—an area of increasing importance^{23,42,43}—also may improve sepsis survivors’ self-rated health.

Strengths and Limitations: Our study has several other strengths. First, by using the HRS, we were able to generate a sepsis cohort with a matched nonhospitalized comparator group and measure pre-illness demographics, comorbidities, self-rated health, and functional disability. Second, we were able to track individuals for 8 years post-baseline survey, longer than many previous studies of sepsis survivors. Third, by using several approaches to analyze the change in self-rated health among sepsis survivors compared with that of nonhospitalized control subjects, we were able to mitigate some of the methodological challenges of

assessing functional outcomes in a high-mortality population.

At the same time, the study should be considered in the context of several limitations. First, it was a retrospective observational study, and unmeasured confounders could not be excluded. Second, administrative data were used to identify sepsis patients, which may be imperfect but was necessary to identify a sufficient sample size that could be matched to nonhospitalized control subjects and for whom pre-sepsis functional and quality of life data were available. Third, self-rated health and functional disability were measured every 2 years; thus, we were not able to assess for shorter-term effects of sepsis in the immediate posthospital period. Finally, other, unmeasured mediators also may play a role in self-rated health after sepsis.

Conclusions

Sepsis was associated with initial reductions in self-rated health for survivors compared with that of nonhospitalized control subjects, although these differences disappeared over time. Functional disability may be a key mediator of this effect, and efforts to reduce functional disability after sepsis should be an important focus for research. Most importantly, even amid grim objective measures such as high mortality and lasting functional disability, sepsis survivors’ perceptions of their health status recover over time.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

References

- Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
- Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA*. 2017;318(13):1241-1249.
- Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. *Am J Respir Crit Care Med*. 2016;193(3):259-272.
- Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. *BMJ*. 2016;353:i2375.
- Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.
- Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Symptoms of depression in survivors of severe sepsis: a prospective cohort study of older Americans. *Am J Geriatr Psychiatry*. 2013;21(9):887-897.
- ISQOL. What is QOL? 2019. <https://www.isoqol.org/what-is-qol/>. Accessed April 14, 2020.
- Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276-1283.
- Karlsson S, Ruokonen E, Varpula T, Alakokko TI, Pettilä V. Long-term outcome and quality-adjusted life years after severe sepsis. *Crit Care Med*. 2009;37(4):1268-1274.
- Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. *Crit Care Med*. 2010;38(12):2386-2400.
- Turnbull AE, Hurley MS, Oppenheim IM, Hosey MM, Parker AM. Curb your enthusiasm: definitions, adaptation, and expectations for quality of life in ICU survivorship. *Ann Am Thorac Soc*. 2020;17(4):406-411.
- Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med*. 1999;48(11):1507-1515.
- Ubel PA, Loewenstein G, Schwarz N, Smith D. Misimagining the unimaginable: the disability paradox and health care decision making. *Health Psychol*. 2005;24(4s):S57-S62.
- Abrantes-Pais Fde N, Friedman JK, Lavallo WR, Ross ED. Psychological or physiological: why are tetraplegic patients content? *Neurology*. 2007;69(3):261-267.
- Dijkers MP. Correlates of life satisfaction among persons with spinal cord injury. *Arch Phys Med Rehabil*. 1999;80(8):867-876.
- Fayers PM, Sprangers MA. Understanding self-rated health. *Lancet*. 2002;359(9302):187-188.
- Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. *JAMA*. 1994;272(8):619-626.
- Ayalon L, Covinsky KE. Spouse-rated vs self-rated health as predictors of mortality. *Arch Intern Med*. 2009;169(22):2156-2161.
- Frick S, Uehlinger DE, Zurcher Zenklusen RM. Assessment of former ICU patients' quality of life: comparison of different quality-of-life measures. *Intensive Care Med*. 2002;28(10):1405-1410.
- Krantz E, Wide U, Trimpou P, Bryman I, Landin-Wilhelmsen K. Comparison between different instruments for measuring health-related quality of life in a population sample, the WHO MONICA Project, Gothenburg, Sweden: an observational, cross-sectional study. *BMJ Open*. 2019;9(4):e024454.
- Cunney KA, Perri M III. Single-item vs multiple-item measures of health-related quality of life. *Psychol Rep*. 1991;69(1):127-130.
- Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav*. 1997;38(1):21-37.
- Prescott HC, Iwashyna TJ, Blackwood B, et al. Understanding and enhancing sepsis survivorship: priorities for research and practice. *Am J Respir Crit Care Med*. 2019;200(8):972-981.
- Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the Health and Retirement Study (HRS). *Int J Epidemiol*. 2014;43(2):576-585.
- Iwashyna TJ, Netzer G, Langa KM, Cigolle C. Spurious inferences about long-term outcomes: the case of severe sepsis and geriatric conditions. *Am J Respir Crit Care Med*. 2012;185(8):835-841.
- Colantuoni E, Scharfstein DO, Wang C, et al. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. *BMJ*. 2018;360:j5748.
- Zhang JL, Rubin DB. Estimation of causal effects via principal stratification when some outcomes are truncated by "death." *J Educ Behav Stat*. 2003;28(4):353-368.
- HRS Staff. *Sample Sizes and Response Rates*. Ann Arbor, MI: Survey Research Center, Institute for Social Research, University of Michigan; 2017.
- Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Depressive symptoms in spouses of older patients with severe sepsis. *Crit Care Med*. 2012;40:2335-2341.
- Prescott HC, Langa KM, Liu V, Escobar GJ, Iwashyna TJ. Increased 1-year healthcare use in survivors of severe sepsis. *Am J Respir Crit Care Med*. 2014;190:62-69.
- Moons P, Van Deyk K, De Geest S, Gewillig M, Budts W. Is the severity of congenital heart disease associated with the quality of life and perceived health of adult patients? *Heart*. 2005;91(9):1193-1198.
- Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul study. *JAMA*. 2003;290(2):215-221.
- Norman G. Likert scales, levels of measurement and the "laws" of statistics. *Adv Health Sci Educ*. 2010;15(5):625-632.
- David Richard J, James CC. Ordinal measures in multiple indicator models: a simulation study of categorization error. *Am Sociol Rev*. 1983;48(3):398-407.
- HRS Codebook: 2000 Core (Final Release). *U.S. Health and Retirement Study Codebooks* 2019. http://hrsonline.isr.umich.edu/modules/meta/2000/core/codebook/h00_00.html?_ga=2.255836232.1120212750.1575954161-1593824071.1575845026. Accessed December 10, 2019.
- Stricker KH, Sailer S, Uehlinger DE, Rothen HU, Zuercher Zenklusen RM, Frick S. Quality of life 9 years after an intensive care unit stay: a long-term outcome study. *J Crit Care*. 2011;26(4):379-387.

37. Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Spronk PE. ICU survivors show no decline in health-related quality of life after 5 years. *Intensive Care Med.* 2015;41(3):495-504.
38. Flaatten H, Kvale R. Survival and quality of life 12 years after ICU: a comparison with the general Norwegian population. *Intensive Care Med.* 2001;27(6):1005-1011.
39. Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. *Soc Sci Med.* 1999;48(8):977-988.
40. van Leeuwen CM, Post MW, van der Woude LH, et al. Changes in life satisfaction in persons with spinal cord injury during and after inpatient rehabilitation: adaptation or measurement bias? *Qual Life Res.* 2012;21(9):1499-1508.
41. Etxeberria I, Urdaneta E, Galdona N. Factors associated with health-related quality of life (HRQoL): differential patterns depending on age. *Qual Life Res.* 2019;28(8):2221-2231.
42. Govindan S, Iwashyna TJ, Odden A, Flanders SA, Chopra V. Mobilization in severe sepsis: an integrative review. *J Hosp Med.* 2015;10(1):54-59.
43. Azoulay E, Vincent JL, Angus DC, et al. Recovery after critical illness: putting the puzzle together—a consensus of 29. *Crit Care.* 2017;21(1):296.