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The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical intensive care units

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Abstract

Objective: This study sought to examine mortality, health-related quality of life (HRQOL), and physical function among sepsis survivors who developed chronic critical illness (CCI).

Design: Single-institution, prospective, longitudinal, observational cohort study assessing 12-month outcomes.

Setting: Two surgical/trauma ICUs at an academic tertiary medical and level 1 trauma center.

Patients: Adult critically ill patients that survived 14 days or longer after sepsis onset.

Interventions: None.

Measurements and Main Results: Baseline patient characteristics and function, sepsis severity, and clinical outcomes of the index hospitalization were collected. Follow-up physical function (Short Physical Performance Battery, SPPB; Zubrod; hand grip strength) and HRQOL (EQ-5D-3L, SF-36) were measured at 3, 6, and 12 months. Hospital-free days and mortality were determined at 12 months. We compared differences in long-term outcomes between subjects who developed CCI (≥14 ICU days with persistent organ dysfunction) versus those with rapid recovery. The cohort consisted of 173 sepsis patients; 63 (36%) developed CCI and 110 (64%) exhibited rapid recovery. Baseline physical function and HRQOL did not differ between groups. Those who developed CCI had significantly fewer hospital-free days (196 ± 148 versus 321 ± 65, $p < 0.0001$) and reduced survival at 12-months compared to rapid recovery subjects (54% versus 92%, $p < 0.0001$). At 3- and 6-month follow-up, CCI patients had significantly lower physical function (3-month: SPPB, Zubrod, and hand grip; 6-month: SPPB, Zubrod) and HRQOL (3- and 6-month:

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EQ-5D-3L) compared to patients who rapidly recovered. By 12-month follow-up, CCI patients had significantly lower physical function and HRQOL on all measures.

Conclusions: Surgical patients who develop CCI after sepsis exhibit high health-care resource utilization and ultimately suffer dismal long-term clinical, functional and HRQOL outcomes. Further understanding of the mechanisms driving the development and persistence of CCI will be necessary to improve long-term outcomes after sepsis.

Keywords

chronic critical illness; critical care; sepsis; health related quality of life; long-term outcomes

Introduction

Although inpatient mortality after sepsis has dramatically decreased over the past several decades, long-term mortality, health-related quality of life (HRQOL), and functional outcomes amongst these sepsis survivors remain unclear. Survivors of sepsis have been shown to exhibit long-term physical and cognitive defects, increased number of infections, and readmissions due to sepsis recidivism [1–3].

Chronic critical illness (CCI) is an emerging phenotype of sepsis survivors that can be clinically identified by prolonged intensive care unit (ICU) stays with persistent yet sustainable organ dysfunction. As inpatient sepsis mortality declines, an increasing percentage of patients survive to develop CCI and an underlying pathophysiology of persistent inflammation, immunosuppression and catabolism [3, 6, 7]. The care burden of these patients has primarily shifted to long-term acute care (LTAC) and skilled nursing facilities (SNF), where ongoing costs, disability, suffering, and mortality are disturbingly high [4–6]. This study was designed to examine the impact of the development of CCI on long-term outcomes of critically ill surgical patients with sepsis. We hypothesized that patients who develop CCI would have significantly worse clinical, functional, and HRQOL outcomes than those who rapidly recover after sepsis.

Materials and Methods

Study Design

This is an analysis of an ongoing prospective, longitudinal, observational cohort study of critically ill surgical patients diagnosed with sepsis. We recruited critically ill septic patients from two surgical/trauma intensive care units (SICU) at an academic medical center (UF Health, Gainesville, FL) [8]. Patient characteristics, sepsis severity, and clinical outcomes of the index hospitalization were evaluated. Differences in long-term outcomes of sepsis survivors were compared between patients that developed CCI (≥14 ICU days with persistent organ dysfunction) as compared to those who exhibited rapid recovery (RAP; <14 ICU days with organ recovery). We defined “persistent organ dysfunction” as the presence of abnormal organ function in one or more systems as measured by Sequential Organ Failure Assessment (SOFA) score on day 14 (cardiovascular SOFA ≥ 1, or score in any other organ system ≥ 2). Patients with an ICU LOS less than 14 days also were classified as CCI if they exhibited persistent organ dysfunction at the time of discharge with disposition to one of the

following locations: hospice, another acute care hospital, or a long-term acute care facility (LTAC). Institutional Review Board approval was obtained prior to study initiation.

Participants

The cohort consisted of critically ill surgical patients that were either admitted with, or subsequently developed sepsis. Full details of the parent study cohort design, criteria, and study protocols have been published previously [8]. Key eligibility criteria included the following: (1) presence in the SICU, (2) age of ≥18 years, (3) entrance into the electronic medical record (EMR)-based sepsis protocol, and (4) ability to obtain subject/proxy informed consent within 96 hours of enrollment. Study exclusion criteria consisted of the following: (1) sepsis protocol initiation greater than 24 hours from initial sepsis diagnosis (i.e. patients treated for extended periods at outside facilities), (2) significant traumatic brain injury (CT scan evidence of neurologic injury and Glasgow Coma Scale <8), (3) refractory shock (i.e., death within 12 hours), (4) uncontrollable source of sepsis (e.g., irreversible disease state such as unresectable dead bowel), (5) patient/proxy not committed to aggressive management and/or pre-existing 'do not resuscitate' status, (6) severe congestive heart failure (NY Heart Association Class IV), (7) Child-Pugh Class B or C liver disease, (8) known HIV infection with CD4 count <200 cells/mm^3, (9) organ transplant recipient on immunosuppressive agents, (10) chemotherapy or radiotherapy within 30 days prior to sepsis, (11) pregnancy, (12) prisoners, and (12) institutionalized or other vulnerable patient populations. For this analysis, patients who experienced 'early death" (death <14 days from protocol onset) were excluded, as by definition they are ineligible for classification as CCI/rapid recovery at day 14.

Baseline measures collected during initial enrollment hospitalization included patient and infection characteristics, sepsis severity, EMR-based clinical and laboratory data, complications and inpatient disposition [8]. Following discharge, patients were contacted by telephone on a monthly basis to acquire information related to subsequent hospitalizations, changes in health history, mortality, and disposition (e.g. home, inpatient rehabilitation, LTAC, SNF, nursing home, or other hospital). At 3, 6, and 12 months after sepsis onset, we completed assessments of physical function and health-related quality of life (HRQOL). Patients were scheduled for follow-up visits, which were conducted at the University of Florida's Institute on Aging, the patient's home, or via telephone, with a tiered priority structure, respectively. This follow-up methodology stems from retention strategies previously used among ICU survivors [9–10]. Hospital-free days, readmissions and mortality were determined at 12 months.

Definition of Outcomes

Mortality and cause of death were assessed by monthly phone calls post-discharge. For patients lost to follow-up, the social security death index database was cross-referenced. We calculated hospital-free days as the number of days alive and not admitted to an inpatient hospital facility over the 12-month follow-up period. To account for differences in length of index hospital stay between CCI and RAP patients, hospital-free days were calculated beginning at day 14.

HRQOL was assessed by the EuroQol-5D-3L (EQ-5D-3L) and Medical Outcome Study Short Form-36 (SF-36), both instruments with established validity in critical care survivors and as a surrogate-completed proxy measure [11–14]. The EQ-5D-3L is a descriptive system of HRQOL consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Patients were asked to retrospectively report their baseline (i.e., pre-admission, within the past 4 weeks) level of functioning, as well as their current state. When the patient was unavailable, the measure was completed by available proxy.

We assessed physical function using the Short Physical Performance Battery (SPPB), grip strength, and Zubrod scale. The SPPB is based on a timed short-distance (4 meter) walk, repeated chair stands, and balance test [15–17]. Grip strength was measured on the participant's dominant hand using an adjustable, hydraulic dynamometer (Jamar Hydraulic Hand Dynamometer, Model No. BK-7498, Fred Sammons, Inc. Burr Ridge, IL). The best of two trials was scored. The Zubrod Scale is a 5-point scale that measures the performance status of a patient's ambulatory nature: 0) Asymptomatic (fully active), 1) Symptomatic but completely ambulatory (restricted in physically strenuous activity), 2) Symptomatic, <50% in bed during the day (ambulatory and capable of all self-care but unable to perform any work activities), 3) Symptomatic, >50% in bed, but not bedbound (capable of only limited self-care), 4) Bedbound (completely disabled, incapable of any self-care), and 5) Death. Pre-sepsis baseline Zubrod scores were independently adjudicated by three investigators (AG, SB, SA) based on the EQ-5D-3L mobility, self-care, and usual activities items. The majority score was used for analysis. In the same fashion, Zubrod estimates were completed for participants with missing follow-up data based on qualitative notes taken during monthly phone calls.

Statistical Analysis

Since the analyses focused on 12-month outcomes, participants who a) withdrew consent while inpatient, b) withdrew consent post-discharge, or c) were lost to follow-up were excluded from the final analysis (see Figure 1 CONSORT diagram). Data are presented as frequency and percentage, mean and standard deviation, or median and 25th/75th percentiles. Fisher's exact test and the Kruskal–Wallis test were used for comparison of categorical and continuous variables, respectively. Inverse probability weighting based on concurrent adjudicated Zubrod scores was used to account for missing follow-up data, as well as absence due to death, for EQ-5D-3L and SPPB. The log-rank test was used to compare Kaplan-Meier product limit estimates of survival between groups. Additionally, we utilized Cox proportional hazard modeling to assess chronic critical illness as an independent predictor of 12-month mortality, controlling for all confounding covariates significant via univariate analysis not a component of the definition (i.e. SOFA score, ICU LOS). All significance tests were two-sided, with p-value ≤ 0.05 considered statistically significant. Statistical analyses were performed with SAS.

Results

Figure 1 shows overall subject enrollment, withdrawal, mortality, and 12-month follow-up compliance. A total of 205 patients were enrolled and consented into the study, of which 6

(3%) were early deaths (expired prior to day 14), 21 (10 %) withdrew from the study and 5 (2 %) were lost to follow-up. Thus, there were 173 early sepsis survivors eligible for follow-up analyses. Of these, the majority of participants were evaluated at 3 months (n = 114; 75%), 6 months (n = 126; 88%), and 12 months (n = 124; 90%). Figure 1 displays participant flow through this study and delineates reasons for missed follow-up visits.

Sepsis survivors who developed CCI had a significantly higher mean age, higher comorbidity burden, and were more often received as transfer patients from an outlying institution when compared to subjects who rapidly recovered (Table 1). Additionally, CCI patients had higher incidence of vasopressor dependence (i.e., shock) and greater physiologic derangement within 24 hours of sepsis protocol onset (Table 1). CCI patients also had significantly greater incidence and severity of multiple organ failure (MOF), a higher incidence of secondary infections, and higher inpatient resource utilization as assessed by hospital and ICU length of stay (Table 2). Additionally, post-discharge resource utilization was higher amongst CCI patients as shown by a higher incidence of hospital readmission (Table 2) and significantly fewer 12-month hospital-free days compared to the RAP group (195 ± 148 days versus 321 ± 65 days, $p < 0.0001$).

Figure 2 displays the results of 12-month survival analysis. The CCI cohort had a significantly lower 12-month survival (55%) compared to subjects who rapidly recovered (93%; Log-rank test, $P < 0.0001$). Of note, death among CCI patients appears to plateau around the 3-month mark. Primary causes of post-discharge death for all subjects were recurrent sepsis (n = 6; 20%), end-stage cancer (n = 6; 20%), and non-infectious multiple organ failure (n = 5; 16%). Approximately 72% of CCI and 30% of rapid recovery post-discharge deaths involved limitation or withdrawal of active care measures.

Supplemental Digital Content (SDC) 1 provides mean (± SD) scores across all assessed measures of HRQOL and physical function. At baseline, there was no significant difference in HRQOL between groups (based on SF-36, Zubrod, and EQ-5D-3L mean scores). However, at 3 and 6 months, subjects who developed CCI had significantly lower levels of HRQOL (based on EQ-5D-3L) and physical function (based on SPPB, hand grip, and Zubrod at 3 months, and SPPB and Zubrod at 6 months) compared to participants who rapidly recovered. By 12 months, the CCI group had significantly lower levels of HRQOL and physical function on *all* measures compared to the rapid recovery group.

CCI participants had significantly greater adverse functional outcomes as measured by Zubrod score at 3, 6, and 12 months (SDC 1 and Figure 3). Subjects who rapidly recovered were still limited in physically strenuous activity at each follow-up. However, they were ambulatory more than 50% of waking hours and able to complete most activities of daily living (i.e. self-care, housework). In contrast, CCI patients were limited in completing activities of daily living and confined to a bed or chair most of the day. Univariate analysis identified age (Hazard ratio 1.05, 95% CI 1.02–1.08), APACHE II score (1.06, 95% CI 1.02–1.09), septic shock (vasopressor requirement despite appropriate volume resuscitation; 2.00, 95% CI 1.02–3.90), CCI (7.51, 95% CI 3.55–15.9), and Charlson Comorbidity Index (1.30, 95% CI 1.20–3.90) as significant predictors of 12-month mortality. Multivariate analysis confirmed CCI (7.87, 95% CI 3.62–17.07) and Charlson Comorbidity Index (1.37,

95% CI 1.23–1.51) as independent predictors of 12-month mortality after controlling for age, APACHE II score at 24 hours after sepsis, and septic shock in the initial model selection process.

Discussion

In this study we have shown differences in long-term outcomes, including long-term survival, physical function, and HRQOL, among adult early sepsis survivors who developed CCI as compared to those who rapidly recovered. Despite surviving to hospital discharge, those patients who developed CCI had significantly higher 12-month mortality as compared to patients who rapidly recovered. In addition, despite similar baseline levels of physical functioning between groups, CCI patients had significant deficits in self-reported HRQOL and objective measures of physical function. Furthermore, these deficits persisted at 3, 6 and 12-month follow-up, suggesting the presence of long-term severe disability. This study and its findings are novel in that we have successfully completed an intensive, prospective 1-year follow-up program with extremely low loss to follow up, and that the development of CCI during the index hospitalization places inpatient sepsis survivors at high risk for severe and persistent deficits across multiple functional and HRQOL domains. This is important in that the identification of CCI during index hospitalization may serve to identify an enhanced population of patients for targeted pre- and post-discharge interventions in order to prevent these dismal long-term outcomes.

The presence of long-term functional deficits after prolonged critical illness are widely described, most prominently in the Acute Respiratory Distress Syndrome population, and commonly pooled together and described as a rather vague constellation of health problems and functional deficits (e.g., ‘Post-Intensive Care Syndrome’).[18–19] Previous, large-scale studies indicated that sepsis survivors have poor long-term health outcomes. However, these studies are limited by: a) assessment of only one type of sepsis severity, and b) use of a single measure to assess physical function. For example, a prospective cohort study in Scotland found that over half of patients surviving sepsis died within 3.5 (58%) and 5 years (61%) [20]. Furthermore, self-reported physical function scores as assessed by SF-36 were significantly lower among sepsis survivors compared to population controls at both follow-up time points. A similar study by Iwashyna et al. [21], found that approximately 41% died by 90 days post-discharge, while 82% expired within five years. In addition, sepsis survivors with no pre-hospitalization physical limitations reported a significantly higher number of new physical limitations following hospitalization compared to those who were hospitalized for non-sepsis reasons. Additionally, Poulsen et al. [22] discovered that survivors of septic shock, had markedly decreased physical function at one-year follow-up compared to age- and sex-adjusted general population controls (based on SF-36 and Functional Comorbidity Index scores).

However, those studies did not discriminate among sepsis survivors with different in-hospital clinical trajectories. In this report, we have shown that only 7% of sepsis patients who could be successfully initially resuscitated died during their index hospitalization. This relatively low inpatient mortality is primarily due to ongoing improvements in sepsis screening, resuscitation protocols and critical care supportive measures. Whereas mortality

was low, a surprisingly large number of patients (35%) subsequently developed CCI. We show here that the dismal long-term outcomes seen in sepsis patients can be attributed in large part to the cohort of sepsis survivors that now survive to develop CCI. Our findings clearly demonstrate that the development of CCI is an excellent predictor of poor long-term outcomes, including dismal functional outcomes and 12-month mortality.

We have previously described a syndrome of persistent inflammation, immunosuppression and catabolism (PICS) that develops among CCI patients after pro-inflammatory insults including severe trauma and sepsis [23–24]. This includes demonstration of this post-sepsis immuophenotype (e.g., persistent elevations of IL-6, IL-8, IL-10, sPDL1) among subsets of patients within the cohort utilized for this current outcomes analysis. The development of this underlying pathophysiology of low-grade inflammatory and metabolic dysfunction is associated with adverse clinical outcomes, recurrent infections and inpatient discharge dispositions (i.e. long-term acute care hospitals, skilled nursing facilities) which are associated with poor post-discharge outcomes [3, 6, 24]. We hypothesize that the failure to resolve the PICS pathophysiology after CCI leads to a chronic state of low-grade inflammation and muscle mass wasting that limit physical rehabilitation and result in a chronically debilitated physical state. Despite surviving their initial sepsis episode, these CCI patients enter a vicious cycle of recurrent hospitalizations, and an inability to subsequently rehabilitate ultimately leads to an indolent death. Identifying a clinical phenotype of CCI at day 14 may help guide long-term prognostication for patients and families. More importantly, identifying those patients at high risk for developing CCI is a critical first step to the successful design and implementation of future interventional clinical trials designed to improved long-term outcomes after sepsis.

We acknowledge several limitations in this study. Enrollment was limited to primarily trauma and surgical sepsis at a single university hospital. Therefore, extrapolation of findings to other critical care areas (i.e. medical ICUs) requires further study. Furthermore, despite very low overall rate of loss to follow-up (90% at 12 months), compliance with in-person assessments at 3 and 6 months remained a challenge, as many of these patients felt too sick and/or overwhelmed to participate. Therefore, some selection bias may be present in the summary statistics of objective measures at these time points. However, if anything, this bias most likely underestimates functional and HRQOL measures in the CCI group.

Conclusions

While advances in critical care have significantly decreased inpatient mortality after sepsis, those who survive and subsequently develop CCI demonstrate poor long-term outcomes including high post-discharge health care resource utilization, significant and persistent physical function deficits, poor health-related quality of life, and higher long-term mortality as compared to those that rapidly recover. It will therefore be important to identify patients that develop a trajectory of CCI in order to implement screening, monitoring and intervention strategies to improve long-term outcomes among initial survivors of sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Guirgis FW, Brakenridge S, Sutchu S, et al.: The long-term burden of severe sepsis and septic shock: Sepsis recidivism and organ dysfunction. J Trauma Acute Care Surg 2016; 81(3):525–32. [PubMed: 27398984]
2. Yende S, Austin S, Rhodes A, et al.: Long-term quality of life among survivors of severe sepsis: Analyses of two international trials. Crit Care Med 2016; 44(8):1461–7. [PubMed: 26992066]
3. Stortz JA, Murphy TJ, Raymond SL, et al.: Evidence for persistent immune suppression in patients who develop chronic critical illness after sepsis. Shock 2017; 49(3):249–258.
4. Elliott D, Davidson JE, Harvey MA, et al.: Exploring the scope of post-intensive care syndrome therapy and care: Engagement of non-critical care providers and survivors in a second stakeholders meeting. Crit Care Med 2014; 42(12):2518–2526. [PubMed: 25083984]
5. Kress JP, Hall JB: ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014; 371(3):287–288.
6. Stortz JA, Mira JC, Raymond SL, et al.: Benchmarking clinical outcomes and the immunocatabolic phenotype of chronic critical illness after sepsis in surgical intensive care unit patients. J Trauma Acute Care Surg 2017; 84(2):342–349.
7. Mathias B, Delmas AL, Ozrazgat-Baslanti T, et al.: Human myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/septic shock. Ann Surg 2017; 265(4):827–834. [PubMed: 27163951]
8. Loftus TJ, Mira JC, Ozrazgat-Baslanti T, et al.: Sepsis and critical illness research center investigators: Protocols and standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients. BMJ Open 2017; 7(7):e015136.
9. Robinson KA, Dennison CR, Wayman DM, et al.: Systematic review identifies number of strategies important for retaining study participants. J Clin Epidemiol 2007; 60(8):757–65. [PubMed: 17606170]
10. Tansey CM, Matté AL, Needham DM, et al.: Review of retention strategies in longitudinal studies and application to follow-up of ICU survivors. Intensive Care Med 2007; 33(12):2051–7. [PubMed: 17701161]
11. EuroQol G: EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990; 16(3):199–208. [PubMed: 10109801]
12. McPhail S, Beller E, Haines T: Two perspectives of proxy reporting of health-related quality of life using the Euroqol-5D, an investigation of agreement. Med Care 2008; 46(11):1140–1148. [PubMed: 18953224]

13. Pickard AS, Knight SJ: Proxy evaluation of health-related quality of life: a conceptual framework for understanding multiple proxy perspectives. Med Care 2005; 43(5):493–499. [PubMed: 15838415]
14. Dinglas VD, Gifford JM, Husain N, et al.: Quality of life before intensive care using EQ-5D: Patient versus proxy responses. Crit Care Med 2013; 41(1):9–14. [PubMed: 23232287]
15. Guralnik JM, Simonsick EM, Ferrucci L, et al.: A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994; 49(2):M85–94. [PubMed: 8126356]
16. Pavasini R, Guralnik J, Brown JC, et al.: Short physical performance battery and all-cause mortality: Systematic review and meta-analysis. BMC Med 2016; 14(1):215. [PubMed: 28003033]
17. Guralnik JM, Ferrucci L, Simonsick EM, et al.: Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995; 332(9):556–561. [PubMed: 7838189]
18. Needham DM, Davidson J, Cohen H, et al.: Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders conference. Crit Care Med 2012; 40:502–509. [PubMed: 21946660]
19. Elliott D, Davidson JE, Harvey MA, et al.: Exploring the scope of post-intensive care syndrome therapy and care: engagement of non-critical care providers and survivors in a second stakeholders meeting. Crit Care Med 2014; 42(12):2518–26. [PubMed: 25083984]
20. Cuthbertson BH, Elders A, Hall S, et al.: Mortality and quality of life in the five years after severe sepsis. Crit Care 2013; 17(2):R70. [PubMed: 23587132]
21. 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. [PubMed: 20978258]
22. Poulsen JB, Moller K, Kehlet H, Perner A: Long-term physical outcome in patients with septic shock. Acta Anaesthesiol Scand 2009; 53(6):724–730. [PubMed: 19388891]
23. Mira JC, Cuschieri J, Ozrazgat-Baslanti T, et al.: The epidemiology of chronic critical illness after severe traumatic injury at two level-one trauma centers. Crit Care Med 2017; 45(12):1989–96. [PubMed: 28837430]
24. Mira JC, Gentile LF, Mathias BJ, et al.: Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med 2017; 45(2): 253–62. [PubMed: 27632674]
25. Brakenridge SC, Efron PA, Stortz JA, et al.: The impact of age on the innate immune response and outcomes after severe sepsis/septic shock in trauma and surgical intensive care unit patients. J Trauma Acute Care Surg 2018; doi: 10.1097/TA.0000000000001921.

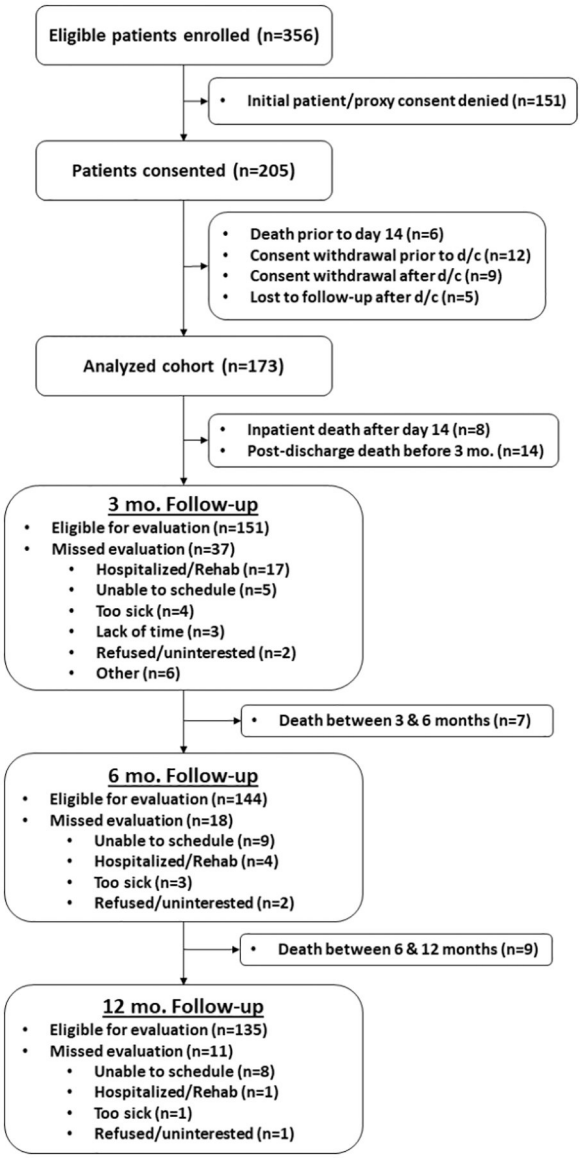

Figure 1.
CONSORT diagram and retention rates of 12-month follow-up.

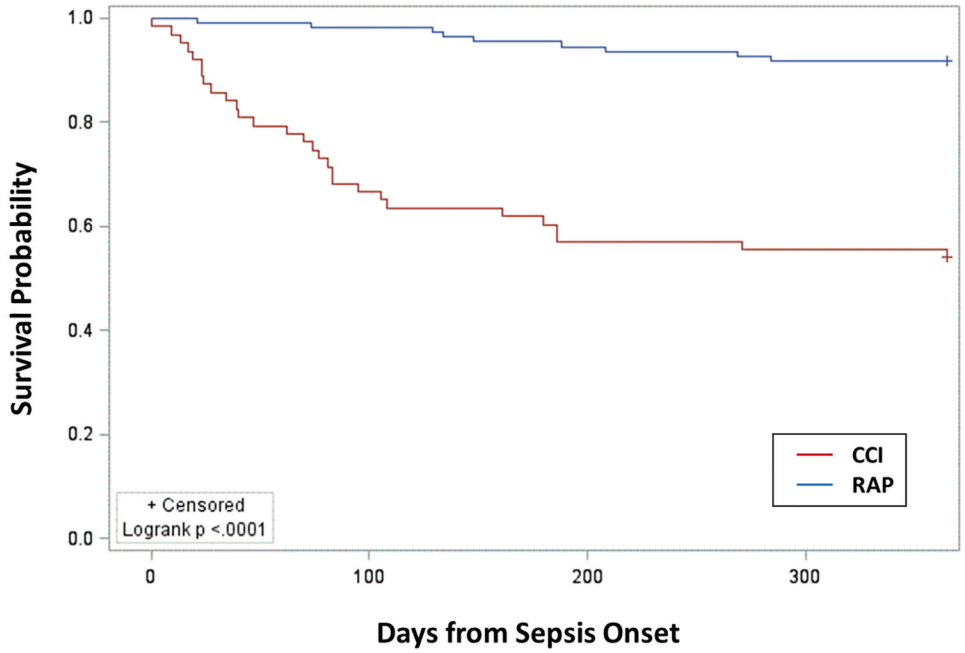

Figure 2.
12-month survival among chronic critical illness (CCI) versus rapid recovery (RAP) patients.

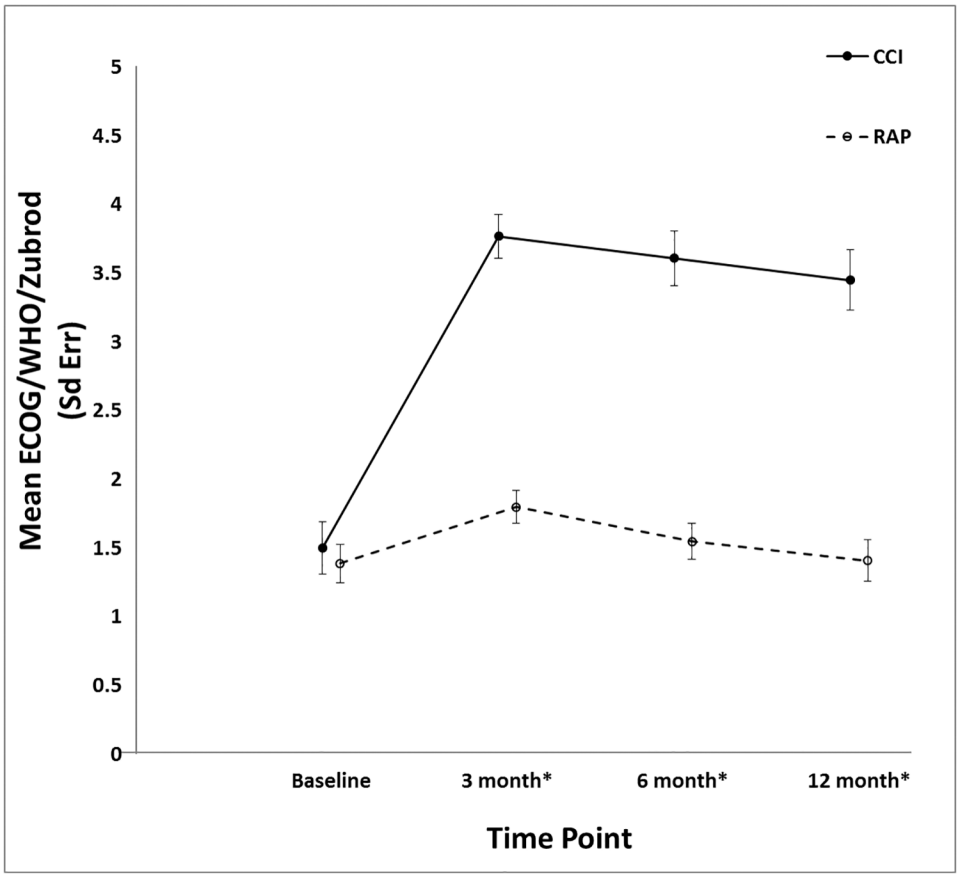

Figure 3. 12-month performance status differences in CCI versus RAP patients.

Zubrod Score; (0) Asymptomatic [Fully active, able to carry out all pre-disease activities without restriction], (1) Symptomatic but completely ambulatory [Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature], (2) Symptomatic, <50% in bed during the day [Ambulatory and capable of all self-care but unable to carry out any work activities], 3) Symptomatic, >50% in bed, but not bedbound [Capable of only limited self-care, confined to bed or chair 50% or more of waking hours], 4) Bedbound [Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair], 5) Death. CCI, chronic critical illness; RAP, rapid recovery; *, $p<0.05$.

Table 1.

Baseline clinical characteristics comparison of CCI versus RAP after sepsis.

Characteristic	CCI (n=63)	RAP (n=110)	p-value
Male, n (%)	38 (60)	52 (47)	0.11
Age in years, mean ± SD	63 ± 14	56 ± 15	0.002
Age ≥ 65, n (%)	31 (49)	32 (29)	0.009
Race, n (%)			0.95
Caucasian (White)	57 (90)	95 (86)	
African American	5 (7.9)	11 (10)	
Other	1 (1.6)	3 (2.7)	
Charlson Comorbidity Index, median (25^{th}, 75^{th})	5 (3, 8)	3 (2, 5)	0.003
APACHE II, median (25^{th}, 75^{th})	21 (16, 26)	14 (10, 21)	<0.0001
Inter-facility hospital transfer, n (%)	36 (57)	38 (34)	0.004
Hospital Admission Diagnosis, n (%)			0.11
Planned surgical procedure	8 (12)	23 (21)	
Intra-abdominal sepsis	7 (11)	21 (19)	
NSTI	8 (12)	17 (15)	
Surgical site infection	9 (14)	11 (10)	
Trauma	9 (14)	5 (4.6)	
Other- non-infectious	7 (11)	7 (6.4)	
Vascular disease- aorta/mesenteric	6 (9.5)	7 (6.4)	
UTI	0 (0)	8 (7.3)	
Other acute infection	5 (7.9)	4 (3.6)	
Pneumonia	1 (1.6)	3 (2.7)	
Necrotizing pancreatitis	2 (3.2)	2 (1.8)	
Vascular disease- extremity	1 (1.6)	2 (1.8)	
Sepsis severity, n (%)			<0.0001
Sepsis	12 (19)	51 (46)	
Severe sepsis	29 (46)	42 (38)	
Septic shock	22 (35)	17 (15)	
Primary sepsis diagnosis, n (%)			0.14
Intra-abdominal sepsis	24 (38)	42 (38)	
Pneumonia	15 (23)	19 (17)	
NSTI	7 (11)	20 (18)	
Surgical site infection	9 (14)	16 (14)	
UTI	3 (4.8)	10 (9.1)	
Empyema	3 (4.8)	0 (0)	
Bacteremia	1 (1.6)	0 (0)	
CLABSI	1 (1.6)	2 (1.8)	

Characteristic	CCI (n=63)	RAP (n=110)	p-value
Other	0 (0)	1 (0.9)	

Table 2.

Clinical outcomes comparison between CCI versus RAP after initial sepsis survival.

Outcome	CCI (n=63)	RAP (n=110)	p-value
In-hospital mortality, n (%)	8 (13)	0 (0)	<0.0001
ICU LOS, median (25^{th}, 75^{th})	21 (15, 39)	5 (3, 9)	<0.0001
Hospital LOS, median (25^{th}, 75^{th})	31 (21, 47)	11 (7, 20)	<0.0001
Maximum SOFA score, median (25^{th}, 75^{th})	11 (8, 13)	6 (3, 8)	<0.0001
MOF incidence, n (%)	50 (80)	34 (31)	<0.0001
Organ system dysfunction, n (%)			
Pulmonary	53 (84)	46 (42)	<0.0001
CNS	44 (70)	36 (33)	<0.0001
Cardiovascular	39 (62)	28 (25)	<0.0001
Renal	34 (54)	26 (23)	0.0001
Coagulation	12 (19)	3 (3)	0.0004
Hepatic	5 (8)	0 (0)	0.0058
# of secondary infections (index admission), mean (SD)	1.06 (1.06)	0.15 (0.41)	<0.0001
≥1 secondary infection (12-month), n (%)	39 (62)	47 (43)	0.018
Discharge disposition, n (%)			<0.0001
”Good” disposition	7 (11)	87 (79)	<0.0001
Home	0 (0)	34 (31)	
Home with healthcare services	5 (8)	49 (44)	
Rehabilitation facility	2 (3)	4 (4)	
”Poor” disposition	56 (89)	23 (21)	<0.0001
Long-term acute care facility	28 (44)	1 (1)	
Skilling nursing facility	7 (11)	22 (20)	
Another hospital	8 (12)	0 (0)	
Hospice	5 (8)	0 (0)	
Death	8 (12)	0 (0)	
Hospital readmissions (12-month)			
≥1 readmission, n (%)	28 (44)	72 (66)	0.010
# of readmissions, adjusted†, mean (SD)	1.46 (2.19)	2.19 (3.65)	0.21

CCI, chronic critical illness; RAP, rapid recovery; ICU LOS, intensive care unit length of stay; MOF, multiple organ failure; CNS, Central nervous system; SD, standard deviation;

†Adjusted to 12-month number of readmissions/days at-risk (alive);