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# Abdominal sepsis patients have a high incidence of chronic critical illness with dismal long-term outcomes

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ABSTRACT

*Background:* As hospital sepsis mortality has decreased, more surgical ICU survivors are progressing into chronic critical illness (CCI). This study documents the incidence of CCI and long-term outcomes of patients with abdominal sepsis. We hypothesized that patients developing CCI would have biomarker evidence of immune and metabolic derangement, with a high incidence of poor 1-year outcomes.
*Methods:* Review of abdominal sepsis patients entered in a prospective longitudinal study of surgical ICU sepsis.
*Results:* Of the 144 study patients, only 6% died early, 37% developed CCI (defined as ICU days $\geq$14 with organ dysfunction) and 57% were classified rapid recovery (RAP). Compared to RAP, CCI patients a) were older (66 vs 58), males who were sicker at baseline (Charlson Comorbidity Index 4 vs 2), b) had persistently elevated biomarkers of dysregulated immunity/metabolism (IL-6, IL-8, sPDL-1, GLP1), c) experienced more secondary infections (4.9 vs 2.3) and organ failure (Denver MOF frequency 40 vs 1%), d) were much more likely to have poor dispositions (85 vs 22%) with severe persistent disabilities by Zubrod Score and e) had a notably higher 1-year mortality of 42% (all $p < 0.05$).
*Conclusion:* Over 1/3rd surgical ICU patients treated for abdominal sepsis progress into CCI and experience dismal long-term outcomes.



## Introduction

Despite extensive research, sepsis remains a lethal, debilitating, and expensive condition.[1] Fortunately, hospital mortality has decreased substantially over the past decade as a result of rapid implementation of evidenced based interventions.[2–4] Unfortunately, this success has created a growing epidemic of "sepsis survivors" who are now progressing into a lingering state of chronic critical illness (CCI).[5,6] Emerging literature is documenting the dismal long-term outcomes of CCI after sepsis, but most of these reports focus on medical intensive care unit (ICU) patients being treated for pneumonia or urinary tract infections.[7] Abdominal infections are the most common cause of sepsis in the surgical ICU (SICU) and their care largely falls within the domain of surgeons.[8] While short-term outcomes have been well described, long-term outcomes remain poorly defined. Abdominal infections are also unique because they are associated with invasive intervention (either for source control, or being caused by a complication from surgery), which can further contribute to poor long-term outcomes.[9] The purpose of this study was to analyze data from an ongoing prospective longitudinal cohort study of SICU sepsis to specifically evaluate the current epidemiology of patients treated for abdominal sepsis to determine their rate of progression into CCI, and to compare their outcomes to those who with rapid recovery (RAP). By characterizing abdominal sepsis patients who develop CCI, we hoped to gain insight into who is most likely to develop a complicated clinical course, providing both prognostic information for patients, and guidance towards future interventional research in this common surgical population. We hypothesized that patients developing CCI would have biomarker evidence of immune and metabolic derangement, with a high incidence of poor 1-year outcomes.

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## Material and methods

### Study design

This is a subset analysis of patients treated for abdominal sepsis from an ongoing prospective cohort study of SICU patients treated for sepsis at a quaternary academic level one trauma center (University of Florida [UF] Health, Gainesville, FL). A detailed description of the study design and standard operating procedures (SOPs) utilized has been published.[10] In brief, this study is approved by the UF institutional review board and registered with *clinicaltrials.gov* (NCT02276417). Critically ill surgical patients with sepsis were enrolled from January 2015 to May 2018 and followed for 1 year. Routine sepsis screening and electronic medical record (EMR) evidence based protocols were utilized to ensure timely and consistent SICU care.[10,11] Data were prospectively collected into a sepsis database, with all subjects undergoing clinical adjudication by physician investigators at weekly meetings to ensure accurate diagnosis of sepsis severity, and source of sepsis. Informed consent was obtained from the patient or legal next of kin within 96 h of study enrollment. Inclusion criteria include: 1) age $\geq$18 years; 2) clinical diagnosis of sepsis, severe sepsis, or septic shock as defined by the 2001 International Sepsis Definition Conference[12]; 3) abdominal source of sepsis; 4) SICU admission; 5) initiation of EMR based sepsis SOPs. Exclusion criteria eliminated patients whose baseline immunosuppression, end-stage comorbidities or severe injuries would be a primary determinant of their long-term outcomes and thus confound outcome assessment.[10]

### Staging, outcomes and definitions

Sepsis staging was based on PIRO classification[13]: *Predisposition* is characterized by baseline demographics, comorbidities and reason for admission. *Insult* variables included sepsis source, primary sepsis versus procedure related, initial sepsis severity and source control interventions. *Response* variables included serial biomarkers of proinflammation, immunosuppression, and metabolic derangement. *Organ dysfunction* variables included multiple organ failure (MOF) by Denver score,[14] incidence and severity acute kidney injury (AKI) by Kidney Disease Improving Global Outcomes (KDIGO) classification,[15] and Sequential Organ Failure Assessment (SOFA) scores.[16] *Hospital outcomes* variables included hospital length of stay (LOS), ICU LOS and ICU free days (number of ICU days subtracted from 30), need for mechanical ventilation and ventilator free days. *Clinical trajectory* was divided into three categories: "early death' (within 14 days of onset), "chronic critical illness" (CCI, defined as ICU LOS $\geq$14 days with persistent evidence of organ dysfunction by SOFA score), and "rapid recovery" (RAP, patients discharged from the ICU within 14 days with resolution of organ dysfunction).[17] The investigators prospectively adjudicated secondary infections as any probable or microbiologically confirmed bacterial, yeast, fungal, or viral infection requiring antimicrobial treatment and occurring at least 48 h after sepsis onset during index hospitalization. Secondary infections were presented as mean per patient and adjusted for the time at risk (i.e. secondary infections per 100 hospital person days). Discharge disposition was defined as either "good" (discharged to home or an inpatient rehabilitation facility), or "poor" (skilled nursing facility (SNF), long term acute care hospital (LTAC), another inpatient hospital, hospice, or inpatient mortality) based on known associations with long-term outcomes.[18] For patients with a poor discharge disposition, the last available in-hospital component scores were carried forward. For patients with a good disposition, respiratory and central nervous system (CNS) components were assumed to be 0 after discharge. The primary long-term outcomes of interest were 1-year mortality and performance status. Performance status (i.e. physical function and ability to perform activities) was assessed using the World Health Organization (WHO)/Zubrod scale. Briefly, this six point scale: 0) designates fully activity, 1) symptomatic but normal daily activities (light work); 2) symptomatic in bed $\leq$ 50% of day, capable of self-care; 3) symptomatic in bed $\geq$50% of day, limited self-care: 4) completely bedbound and 5) death.[19]

### Laboratory analysis

Blood samples were collected within 12-h, and on days 1, 4, 7, and 14 after sepsis onset and were analyzed for biomarkers of inflammation (Interleukin [IL]-6, IL-8), immunosuppression (soluble programed death ligand one [sPDL1]), and metabolic derangement (glucagon-like peptide 1 [GLP-1]).[17,20] Abdominal sepsis patients were compared to a cohort of age-, sex-, and ethnicity-matched healthy controls (n = 27) for IL-6, IL-8, and sPDL1. Biomarker analysis was performed utilizing the Luminex MAGPIX (Luminex corp., Austin, Texas, U.S.A.), MILLIPLEX Multiplex (Merck KGaA, Darmstadt, Germany), and R&D Systems' ELISA Kits (Bio-Techne, Minneapolis, Minnesota, U.S.A.).

*Statistical analysis:* Data are presented as frequency and percentage, mean with standard deviation, or median with interquartile range. We used Fisher's exact test for comparison of categorical variables and the Mann–Whitney *U* test, Student's T-test, or Kruskal-Wallis tests for comparison of continuous variables as indicated. All significance tests were two-sided, with p-value $\leq$ 0.05 considered statistically significant. We performed multivariate logistic regression using stepwise selection to determine independent risk factors of CCI at 72 h after sepsis diagnosis, considering univariate significance and clinical relevancy. Adjusted odds ratios (OR) with 95% confidence intervals (CI) and area under the receiver operating curve (AUC) were used. We performed similar selection for 1-year dismal performance status (Zubrod score of 4 or 5) for patients that survived to 14 days. Sensitivity analysis was used to determine optimal dichotomous cutoffs where appropriate. Inverse probability weighting was used to account for missing data.[21] Statistical analysis was performed with SAS (v9.4, Cary, NC).

## Results

### Overall cohort characteristics

Over the 40-month study period, 328 patients were enrolled into the ongoing SICU sepsis study database of which 144 (44%) patients had abdominal sepsis and were included in this analysis. Overall, roughly half of these patients were males with a median age of 63 years of which 44% were elderly ($\geq$65 years). They had a moderate comorbidity burden by Charlson Comorbidity Index (Median 3, IQR 1–5) and significant physiologic derangement by APACHE II (median 17, IQR 12–23). There was also a high incidence of septic shock, with 29% of patients developing a vasopressor requirement following resuscitation. Nearly half (44%) of the patients were inter-facility transfers. Of note, while the majority (67%) of patients were admitted with a primary diagnosis of acute abdominal sepsis, 20% were admitted for elective surgery, with the rest being admitted for either chronic health condition (9%) or trauma (4%). Overall, 37% met Centers for Disease Control and Prevention (CDC) criteria of surgical site infection (SSI) as secondary to another procedure.[22] The most common causes of abdominal sepsis included bowel ischemia (ischemic colitis/mesenteric ischemia, 16%), followed by various procedure related complications including anastomotic leak or staple line leak (11%), iatrogenic bowel perforation (11%) and post-operative abscess (10%). Almost all patients (90%) required a source control procedure, with 10%

treated with antimicrobials alone. The most common source control procedures were laparotomy or other open interventions (60%), followed by percutaneous drainage (20%), laparoscopic intervention (5%), and endoscopic intervention (5%).

*Breakdown by clinical trajectory*

Table 1 lists predisposition and insult characteristics including patient demographics, septic source, and source control characteristics by the clinical trajectories of early death, RAP and CCI. Early deaths were notably low [n = 9 (6%)] Not surprisingly, these early death patients were older (median age 74), had high comorbidity burden by Charlson (median index 4), with high APACHE II (median 21), and incidence of septic shock (78%) Of the remaining 135 patients who survived 14 days, 82 (57%) were classified as RAP and 53 (37%) were classified as CCI. Compared to RAP, CCI were more likely to be male, older, with higher comorbidity burden by Charlson Index, higher initial predicted mortality by

**Table 1**
Patient Demographics, Septic Source, and Source Control Characteristics.
RAP, Rapid recovery; CCI, Chronic critical illness; BMI, Body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SSI, Surgical site infection; IR, Interventional Radiology. *, univariate analysis comparing CCI and RAP.

| | Early Death n = 9 (6%) | RAP n = 82 (57%) | CCI n = 53 (37%) | P-value* |
|---|---|---|---|---|
| Male, n (%) | 4 (44) | 33 (40) | 32 (60) | 0.03 |
| Age in years, median (25th, 75th) | 74 (66, 78) | 58 (47, 69) | 66 (59, 74) | 0.001 |
| Age ≥65 years, n (%) | 7 (77.78) | 27 (32.9) | 30 (56.6) | 0.008 |
| Race, n (%) | | | | 0.75 |
| Caucasian (White) | 8 (89) | 75 (92) | 48 (91) | |
| African American | 1 (11) | 6 (7) | 4 (8) | |
| American Indian | 0 (0) | 1 (1) | 0 (0) | |
| Other | 0 (0) | 0 (0) | 1 (2) | |
| Hispanic, n (%) | 0 (0) | 4 (5) | 0 (0) | 0.15 |
| BMI, median (25th, 75th) | 28.6 (22.6, 40.1) | 28.2 (24.8, 33.4) | 28.3 (23.9, 34.2) | 1 |
| Charlson Comorbidity Index, median (25th, 75th) | 4 (3, 5) | 2 (1, 4) | 4 (3, 6) | <0.001 |
| Reason for Hospital Admission, n (%) | | | | 0.26 |
| Active Infection | 6 (67) | 56 (68) | 35 (66) | |
| Elective Surgery | 1 (11) | 15 (18) | 13 (25) | |
| Trauma | 0 (0) | 5 (6) | 0 (0) | |
| Chronic Health Condition | 2 (22) | 6 (7) | 5 (9) | |
| APACHE II, median (25th, 75th) | 21 (20, 29) | 14 (9, 18) | 22 (17, 27) | <0.001 |
| Emergency Surgery Within 24hrs, n (%) | 4 (44) | 41 (50) | 23 (43) | 0.48 |
| Active Cancer, n (%) | 3 (33) | 14 (17) | 14 (26) | 0.2 |
| Primary Sepsis Diagnosis, n (%) | | | | 0.59 |
| Intra-abdominal | 6 (67) | 50 (61) | 35 (66) | |
| Ischemic Colitis/Mesenteric Ischemia | 4 (44) | 10 (12) | 9 (17) | |
| Pancreaticobiliary Infection | 1 (11.1) | 4 (5) | 6 (11) | |
| Diverticulitis | 0 (0) | 7 (9) | 2 (4) | |
| Abdominal Abscess Unrelated to Surgery | 0 (0) | 5 (6) | 4 (8) | |
| Bowel Obstruction with Perforation | 0 (0) | 5 (6) | 3 (6) | |
| Cholecystitis | 0 (0) | 6 (7) | 1 (2) | |
| Incarcerated Hernia with Strangulation | 0 (0) | 3 (4) | 4 (8) | |
| Appendicitis | 0 (0) | 6 (7) | 0 (0) | |
| Gastroduodenal Perforation | 1 (11) | 2 (2) | 3 (6) | |
| Pseudomembranous/Infectious Colitis | 0 (0) | 2 (2) | 1 (2) | |
| Esophageal Perforation | 0 (0) | 0 (0) | 2 (4) | |
| SSI/Procedure Related | 3 (33) | 32 (39) | 18 (34) | |
| Anastomotic/Staple Line Leak | 0 (0) | 10 (12) | 6 (11) | |
| Iatrogenic Bowel Perforation | 2 (22) | 8 (10) | 6 (11) | |
| Postoperative Abscess | 1 (11) | 9 (11) | 5 (10) | |
| Infected Biloma | 0 (0) | 5 (6) | 1 (2) | |
| Sepsis severity, n (%) | | | | <0.001 |
| Sepsis | 1 (11) | 32 (39) | 6 (11) | |
| Severe Sepsis | 1 (11) | 42 (51) | 20 (38) | |
| Septic Shock | 7 (78) | 8 (10) | 27 (51) | |
| Inter-facility Transfer, n (%) | 6 (67) | 30 (37) | 28 (53) | 0.08 |
| Hospital-Acquired Sepsis, n (%) | 2 (22) | 28 (34) | 22 (42) | 0.47 |
| Sepsis Source Control Procedure, n (%) | 7 (7) | 73 (89) | 48 (91) | 1 |
| Type of Sepsis Source Control, n (%) | | | | 0.74 |
| Surgical Source Control | 6 (67) | 51 (62) | 35 (66) | 0.72 |
| Laparotomy/Open Incision | 6 (67) | 46 (56) | 33 (62) | |
| Laparoscopic intervention | 0 (0) | 5 (6) | 2 (4) | |
| Minimally Invasive Source Control | 1 (11) | 22 (27) | 13 (24) | 0.84 |
| Percutaneous drainage | 1 (11) | 19 (23) | 9 (17) | |
| Endoscopic intervention | 0 (0) | 3 (4) | 4 (8) | |
| Antibiotics Only | 2 (22) | 9 (11) | 5 (10) | 1 |
| Culture positive, n (%) | 2 (22) | 41 (50) | 23 (43.4) | 0.48 |
| Surgeries post sepsis, median (25th, 75th) | 1 (1, 3) | 1 (0, 2) | 2 (1, 4) | <0.001 |
| IR/endoscopic procedures post sepsis, median (25th, 75th) | 0 (0, 0) | 0 (0, 1) | 0 (0, 1) | 0.58 |
| Total interventions post sepsis, median (25th, 75th) | 2 (1, 3) | 1 (1, 2) | 3 (2, 5) | <0.001 |
| Open abdomen, n (%) | 6 (67) | 19 (23) | 33 (62) | <0.001 |

APACHE II, and higher incidence of septic shock. There were no differences in invasiveness of initial source control procedure (surgery vs percutaneous/endoscopic), or incidence of SSI (procedure related/post-operative sepsis) as septic source. However, CCI patients had higher utilization of temporary abdominal closure (i.e. "open abdomen"), as well as higher total source control surgeries and procedures post-sepsis.

*Clinical outcomes by trajectory*

The 9 early death patients had a median ICU LOS of 6 days and their causes of death included MOF in 5, respiratory failure in 2, and progression of vascular disease in 2, with 8 involving withdraw of care. Table 2 shows clinical outcomes of the remaining RAP versus CCI patients. Not surprisingly, CCI patients required significantly higher ICU resource utilization, with twice the need for mechanical ventilation with less ventilator free days, over a five-fold increase in ICU LOS, and over double the hospital LOS. CCI patients had more AKI, more severe AKI, higher maximum SOFA score and higher incidence of MOF. Fig. 1A depicts daily SOFA scores. Compared to RAP, CCI start much higher and failed to resolve their organ dysfunction over the first 14 days. CCI patients also had a higher number of secondary infections, even after correcting for hospital duration. Along with a higher 30-day mortality (19% vs 1%), CCI patient required more resource utilization past discharge, as 85% of CCI patients had a "poor" discharge disposition. Of the 53 patients who developed CCI, 87% were discharged to either an LTAC, SNF, another inpatient facility, or hospice. In contrast 78% of RAP patients were either discharged home, or to an inpatient rehabilitation facility.

*Biomarker response by clinical trajectory*

Fig. 2 depicts immune and metabolic biomarkers of the RAP versus CCI patients over 14 days. The biomarkers of markers of inflammation (IL-6, IL-8) and immunosuppression (sPDL1) for RAP and CCI are higher than healthy controls at all time points (all $p < 0.001$). Compared to RAP, the CCI patients showed a more robust early response and persistent elevation over time, with significantly higher levels of each biomarker at all time points (all $p < 0.05$). While no GLP-1 levels were collected on healthy controls, published reference ranges are shaded.[23] Following similar levels of elevation at 12-h, RAP patients trended to normal reference values while CCI patients remained significantly elevated (all $p < 0.001$), showing persistent metabolic derangement.

*Long-term outcomes*

Fig. 1B depicts 1-year survival probabilities by clinical trajectory. While CCI patients had higher 30-day mortality (19 vs 1%, $p < 0.001$), the difference was more pronounced at one year (42 vs 7%, $p < 0.001$, Fig. 1B). Fig. 1C depicts performance status (by WHO/Zubrod score) at baseline, 3, 6 and 12 months for RAP versus CCI patients. While there was no difference in RAP versus CCI patients

**Table 2**
**Clinical Outcomes of Interest of RAP and CCI Patients**.
RAP, Rapid recovery; CCI, Chronic critical illness; ICU, Intensive care unit; AKI, Acute kidney Injury; SOFA, Sequential Organ Failure Assessment; MOF, Multiple organ failure.

| | RAP n = 82 (57%) | CCI n = 53 (37%) | P-value |
|---|---|---|---|
| Hospital length of stay, median (25th, 75th) | 11 (7, 19) | 28 (22, 41) | <0.001 |
| ICU length of stay, median (25th, 75th) | 4 (2, 9) | 21 (16, 29) | <0.001 |
| ICU free days (30 days), median (25th, 75th) | 25 (22, 27) | 6 (0, 12) | <0.001 |
| Need for mechanical ventilation, n (%) | 44 (54) | 51 (96) | <0.001 |
| Ventilator free days (30 days), median (25th, 75th) | 29 (27, 30) | 21 (13, 25) | <0.001 |
| AKI, n (%) | 36 (44) | 34 (64) | 0.023 |
| Max AKI Stage, n (%) | | | 0.001 |
| 0 | 45 (55) | 17 (32) | |
| 1 | 12 (15) | 11 (21) | |
| 2 | 20 (24) | 9 (17) | |
| 3 | 4 (5) | 14 (26) | |
| Baseline ESRD | 1 (1) | 2 (4) | |
| Maximum SOFA Score, median (25th, 75th) | 5.5 (4, 8) | 10 (8, 14) | <0.001 |
| Organ system dysfunction by SOFA, n (%) | | | |
| Pulmonary | 24 (29) | 41 (77) | <0.001 |
| CNS | 27 (33) | 43 (81) | <0.001 |
| Cardiovascular | 13 (16) | 34 (64) | <0.001 |
| Renal | 45 (55) | 43 (81) | 0.002 |
| Coagulation | 1 (1) | 13 (25) | <0.001 |
| Hepatic | 1 (1) | 6 (11) | 0.015 |
| Denver MOF frequency, n (%) | 1 (1) | 21 (40) | <0.001 |
| Secondary Infections/patient, mean (SD) | 0.35 (0.71) | 1.49 (1.09) | <0.001 |
| Secondary infections/100 patient days, mean (SD) | 2.3 (6.5) | 4.86 (4.07) | <0.001 |
| 30 day mortality, n (%) | 1 (1) | 10 (19) | <0.001 |
| Discharge disposition, n (%) | | | <0.001 |
| "Good" Disposition | 64 (78) | 8 (15) | <0.001 |
| Home | 22 (35) | 0 (0) | |
| Homecare | 38 (59) | 6 (75) | |
| Rehab | 4 (6) | 2 (25) | |
| "Poor" Disposition | 18 (22) | 45 (85) | <0.001 |
| Long Term Care Hospital | 2 (11) | 25 (56) | |
| Skilled Nursing | 16 (89) | 7 (16) | |
| Another Hospital | 0 (0) | 2 (4) | |
| Hospice | 0 (0) | 5 (11) | |
| Death | 0 (0) | 6 (13) | |
| Number of readmissions, mean (SD) | 1.72 (2.16) | 1.06 (1.56) | 0.043 |
| 1 year Mortality, n (%) | 6 (7) | 22 (42) | <0.001 |

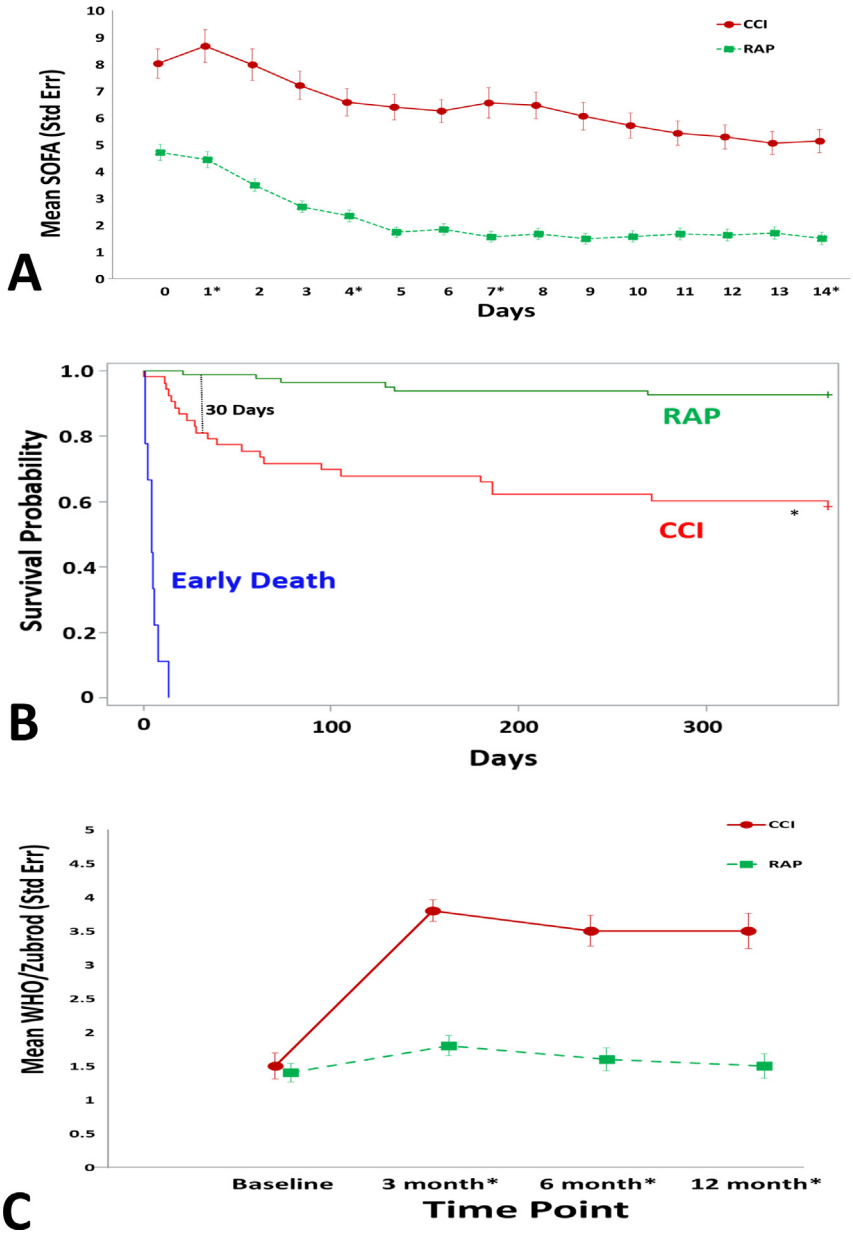


**Fig. 1. Organ Failure Trajectory, 1-year Mortality, and Long-term Performance Status. 1A**. Daily SOFA score trajectory comparing CCI and RAP patients. *Indicates CCI with significantly higher SOFA scores at all time points tested (days 1, 4, 7, 14). **1B.** Kaplan Meier Survival Curve comparing CCI, RAP, and Early Death. *Indicates lower survival ($p < 0.001$) in CCI group at 1-year. **1C.** Long-term performance status after sepsis. *Significantly worse performance status in CCI than RAP at time point. SOFA, Sequential Organ Failure Assessment; CCI, chronic critical illness; RAP, rapid recovery; WHO, World Health Organization.

at baseline (1.4 vs 1.5), CCI patients had significantly worse performance function at three (3.8 vs 1.8) months, persisting at six (3.5 vs 1.6), and 12 months (3.5 vs 1.5, all $p < 0.001$).

*Predictors of poor outcomes*

Table 3 contains the results of two multivariate prediction models for **A)** CCI or early death and **B)** 1 year Zubrod 4 or 5 (reflecting a dismal outcome) using data available at 72 h (following initial physiologic derangement). Charlson Comorbidity Index, early MOF at day 3, septic shock, and utilization of open abdomen were identified as independent predictors of CCI or early death. Excluding the early death patients in model B, the independent predictors of dismal 1-year performance status were early MOF and Charlson Comorbidity Index.

## Discussion

In this observational cohort study we have characterized the epidemiology of abdominal sepsis patients, and found that CCI is a common trajectory. Although only 6% of patients succumbed to death within 14 days, over one-third progressed to CCI. We found that abdominal sepsis patients who develop CCI are older, more comorbid, and sicker at presentation (with worse physiologic derangement and higher likelihood of septic shock) than patients that rapidly recover. We also characterized their immunologic and metabolic response, with CCI patients having higher sustained biomarkers of proinflammation (IL-6, IL8), immunosuppression (sPDL1), and metabolic derangement (GLP-1). Finally, we found that abdominal sepsis CCI patients undergo more surgical procedures, have higher incidence of organ dysfunction that fails to return

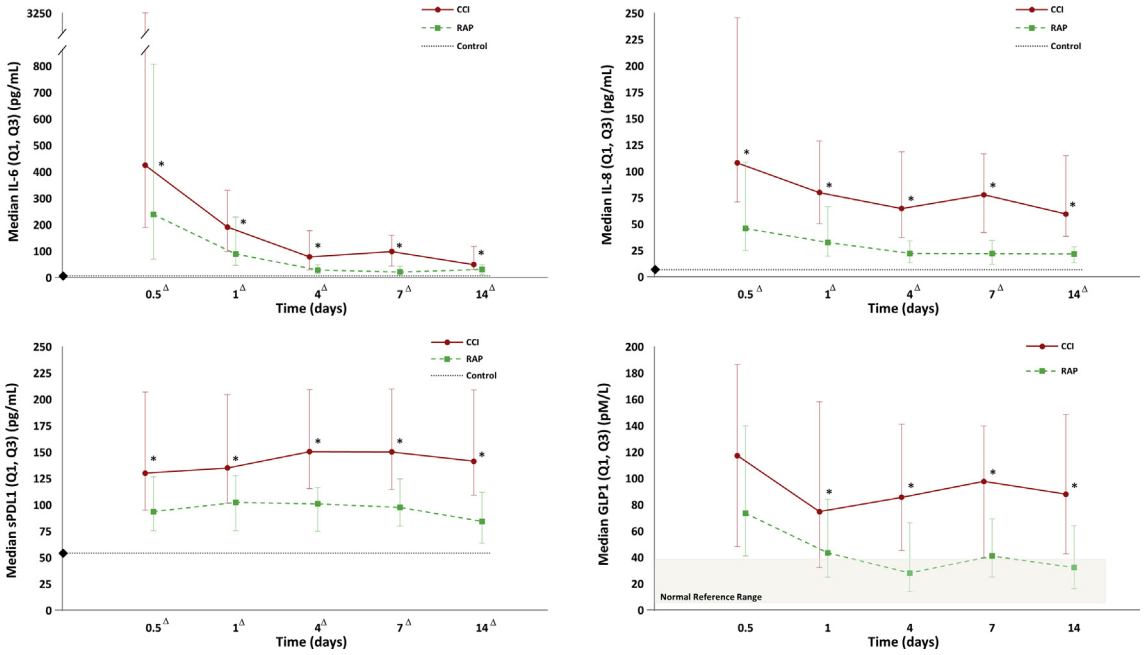


**Fig. 2. Biomarker Trajectories for inflammation, immunosuppression, and metabolic derangement.** Peripheral blood samples of multiple biomarkers (IL-6, IL-8, sPDL1, GLP-1) collected at 0.5, 1, 4, 7, and 14 days following sepsis diagnosis compared to matched healthy controls. * indicates CCI significantly higher ($p < 0.05$) than RAP at that time point. Δ indicates each cohort significantly higher ($p < 0.01$) than healthy controls at that time point. CCI, chronic critical illness; RAP, rapid recovery.

to baseline, and have persistently worse performance status through one-year compared to those that rapidly recover.

While 30-day mortality has historically been considered the primary outcome of interest in both surgery and sepsis populations, as compliance with evidenced based critical care improves, more patients are surviving beyond their initial septic insult.[4,5] However, this early survival improvement has concurrently been associated with an increasing number of patients progressing to a state of chronic critical illness.[5,24] Thus, it is reasonable to conclude that improved care has merely shifted the burden of disease from early death to a state of prolonged organ dysfunction and high intensity care. While abdominal sepsis CCI patients had significantly higher need for and duration of ventilator requirement, there was significant other organ dysfunction including AKI, and higher maximum scores of each SOFA component. Ultimately, abdominal sepsis CCI patients had high resource utilization through increased ICU and hospital LOS, and post-discharge resource utilization through high rates of discharge to SNFs or LTACs, which in the CCI patient has been associated with poor rehabilitation and decreased quality of life.[18,25] In our study, rates of one-year mortality were over double those of 30-day mortality in CCI patients, who also had marked decrease in performance status at one-year. As patient-centered care becomes increasingly important in all aspects of medicine, understanding which patients are most at risk for poor long-term outcomes will be of paramount importance for open and honest discussions with patients and families. This is particularly true in the abdominal sepsis patient, who may face difficult decisions on repeat surgical interventions. In our study, using data available at day 3 post sepsis the strongest predictors of CCI in abdominal sepsis were sepsis severity, comorbidity burden, organ failure, and utilization of temporary abdominal closure during surgery. Of patients who survived to 14 days, strong predictors of dismal long-term performance status were comorbidity burden and MOF. One area in which this may lead to intervention and improvement is through the earlier involvement of palliative care in these patients with risk factors for a complicated clinical course. Indications for palliative care consultation in surgical populations have been difficult to define.[26] However, medical CCI literature has suggested earlier involvement may lead to improvement in accomplishing patient centered goals of care, while at the same time more efficiently utilizing health care resources and cutting hospital costs.[27,28]

Our group has previously described the persistent inflammation, immunosuppression, and catabolism syndrome (PICS) in both blunt trauma and septic patients, which acts as a pathophysiologic explanation for the subset of patients that undergo complicated clinical trajectories.[6,29] Our study supports similar findings in abdominal sepsis patients who develop CCI. Abdominal sepsis CCI patients have profoundly elevated early markers of proinflammation (by levels of IL-6 and IL-8) that remain significantly elevated over time. One contributing factor to this could be the higher number of source control procedures required over time, acting as "multiple hits" contributing to low grade, dysfunctional inflammation. However other pathophysiologic explanations have been proposed, including persistent circulation and deposition of

**Table 3**
Multivariate Prediction Models for CCI and Dismal 1-year Performance Status.
*Covariates based on 72-h
data including age, KDIGO stage 3 acute kidney injury, inter-facility transfer (Model AUC =
0.880). †Analysis of 14-day survivors. Covariates include age, septic shock, primary vs SSI/procedure related sepsis, use of open abdomen (Model AUC = 0.867). CCI, Chronic critical illness; Early MOF, multiple organ failure (day 3); KDIGO, Kidney Disease Improving Global Outcomes.

| Risk Factors | OR | 95% CI | P-value |
|---|---|---|---|
| A)Predictors of CCI or Early Death* | | | |
| Charlson Comorbidity Index | 1.29 | (1.08, 1.53) | 0.004 |
| Early MOF by Denver score | 33 | (3.84, 283.7) | 0.001 |
| Septic shock | 5.01 | (1.77, 14.18) | 0.002 |
| Use of Open abdomen | 3.89 | (1.51, 9.89) | 0.005 |
| B)Predictors of 1-year Zubrod 4 or 5† | | | |
| Charlson Comorbidity Index | 1.81 | (1.39, 2.35) | <0.001 |
| Early MOF by Denver score | 8.29 | (2.30, 29.85) | 0.001 |

myeloid derived suppressor cells (MDSCs) and alarmins such as cell free DNA.[30–32] These abdominal sepsis CCI patients also showed evidence of persistent immunosuppression through both prolonged elevation of sPDL1 levels, as well as clinical manifestations by higher number of recurrent infections than those that rapidly recovered. While our study did not study the immunophenotype of sepsis survivors past discharge, Yende et al. recently showed certain subsets of sepsis survivors show proinflammation (by C-reactive protein) and immunosuppression (by sPDL1) out to six months which was associated with increased readmissions and death.[33] Given past failures at attempts to modulate early robust proinflammation in sepsis,[34] targeting prolonged immunosuppression through sPDL1 inhibitors may be benefit for long-term sepsis survival in the future. Finally, CCI patients showed prolonged elevation of GLP-1. This gut-derived incretin hormone plays an important role in insulin regulation, is activated by proinflammation, and has been associated with intestinal ischemia.[23] Elevated levels in sepsis have been associated with poor outcomes after controlling for other markers of inflammation and peak glucose levels, although mechanisms behind this remain unclear.[20,35] This is the first study specific to abdominal sepsis showing a persistent GLP-1 elevation in those with a poor clinical trajectory, and modulation of this hormone may have future benefit in precision medicine. However, given its complex associations in metabolic regulation and inflammatory derangement, more work is needed to elucidate GLP-1 as a potential therapeutic target.

There are limitations to our study that should be recognized. First, it is a post hoc review of an ongoing prospective analysis of patients in our SICU. Second, there is inherent selection bias in abdominal sepsis patients admitted to surgical services excluding those considered to have prohibitive surgical risk, and where aggressive care is deemed futile or inconsistent with patient goals of care. Thus, our cohort is likely not completely representative of the entire abdominal sepsis population.

In conclusion, inpatient mortality from abdominal sepsis continues to decrease with advancements in surgical and critical care. However, a high proportion of abdominal sepsis patients are progressing to CCI, which signals a dismal prognosis through one year. The immunophenotypic profile of these patients show evidence of prolonged inflammation, immunosuppression, and metabolic derangement which may provide immune modulation targets for long-term benefit in the future. More work is needed to develop multimodal therapy for improving poor long-term outcomes.

## Author contributions

MC, SB, JS, RH, DD, AM, LM, PE, SA and FM contributed to the conception and design of the project, as well as drafting of the manuscript, revision of its content, and approved the manuscript in its final form. GG contributed to the conception and design of the project as well as data analysis and approved the manuscript in its final form.

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## Declaration of competing interest

All authors declare no conflicts of interest.

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