

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-405>

Reviewer A

Thank you for asking me to review this audit of outcomes associated with sepsis and septic shock in patients with reasonable pre-sepsis function. The authors have used a national database to investigate functional decline.

Overall, the paper is generally well written but does have areas of improvement

1. It is unclear to me where the ECOG scores come from; are these self-reported ECOG? Were they formally assessed? Who assessed them? Is there consistency amongst the scoring? When was the scoring made. Does the ECOG continue to improve if you give it enough time?

Reply: As we described in the Methods and Discussion, ECOG performance status (ECOG PS) were formally assessed by the trained coordinators (registered nurses) of each hospital and then confirmed again by the study investigators (physicians). The ECOG scores were not self-reported. However, because the evaluation of ECOG PS was not the primary object of the Korean sepsis registry, data are insufficient for us to investigate the consistency or improvement of scoring PS. We admit this as a major limitation of our study. Nonetheless, because a two-step process was used, we may say that the data on ECOG scores are reliable. We described this in the Discussion section (the 6th paragraph) and also added in the limitation section (the 7th paragraph) as follows.

“Second, as aforementioned, ECOG was originally developed and validated for oncological patients, and we were not able to formally evaluate the inter-rater consistency or reliability of the ECOG scores.”

Regarding the time of data collection, ECOG scores were collected at two time points (i.e., at sepsis recognition [sepsis diagnosis] and at hospital discharge). For the first ECOG scores, although collected at sepsis recognition, we assessed patients' PS before sepsis (i.e., pre-sepsis PS), and for the second ECOG scores, we aimed to assess PS at hospital discharge after sepsis treatments. We hope that you understand this.

Additionally, the Reviewer B pointed out the drawback of the using ECOG score in non-oncological patients. Hence, we described this in the Discussion (the 7th paragraph)

2. The outcomes are of ICU survivors. I can't find any mention of ICU or hospital mortality until the limitation section.

Reply: The Reviewer B also suggested that the data of non-survivors may skew the results. So, we excluded the data of non-survivors from our analysis. Thank you for your comment.

Minor:

3. I assume the result section/study population/ page 8 line 145 median lactate was all patients in the cohort and at admission to ICU. This should be clarified.

Reply: We are sorry for the confusion. We revised the sentence for clarity as follows.

“The median lactate level of all 1,735 patients was 2.3 (1.4–3.8) mmol/L and the proportion of patients with septic shock was 19.0%.”

Reviewer B

Thank you for this important piece of work. It is part of the overall effort to characterize Post-intensive care syndrome (PICS) and to look at the outcomes of patients post-ICU discharge.

There are several queries that need addressing

1. ECOG is usually chosen to denote functional status of oncology patients. Reference 15, although ICU-related, are still made up of oncology patients mainly. I do note that there is a paper in ICM 2017 that showed a difference utilizing ECOG as the measure of functional status. However, most papers would utilise other measures such as Functional Independence Measure (AJRCCM 2016;194:831), WHODAS II (ICM 2017;43:992), Barthel Index (Crit Care med 2018;46:562). It would be important to explain why this measure was chosen rather than the above more well-validated measures of functional status among non-oncological patients. It would be a different issue if your intent is to validate ECOG as an outcome measure in comparison to the above.

Reply: We totally agree with you. As you pointed out, there are already well-validated measure for functional status for non-oncological patients such as the Functional Independence Measure (FIM), the World Health Organization’s Disability Assessment Schedule 2.0 (WHODAS II), and Barthel Index. However, in this nationwide sepsis registry, functional status was assessed using ECOG. Hence, there was no choice but to use ECOG in our study; this can be a limitation of our study. However, as we described in the Discussion (the 6th paragraph), ECOG is simple to use and easily understood by healthcare professionals, which may enhance the reliability of our data. We hope that you understand this.

In the Discussion (the 6th paragraph), we revised the paragraph and described what you pointed out as follows.

“In clinical practice, it is crucial to accurately assess the PS of critically ill patients to inform clinical decisions. ECOG is simple and easily understood by nurses and physicians, which can enhance the consistency in recordings and lead to less variation among investigators (38, 39). However, ECOG was developed for oncological patients, and there are other well-validated scales for functional status for non-oncological patients, such as Functional Independence Measure (40), the World Health Organization's Disability Assessment Schedule 2.0 (WHODAS II) (41), and Barthel Index (42). Unfortunately, we could not use these scales, representing a limitation of our study. However, several studies reported the usefulness of ECOG PS for predicting outcomes in critically ill patients (14, 15). And, in our study, the data on ECOG were collected by trained study coordinators of each hospital and confirmed again

by the investigators, which may strengthen the reliability of our data.”

2. The study population should exclude patients who have died as they would definitely not be able to provide information on functional status. So there is already introduction of immortal time bias at the moment

Reply: As you recommended, we excluded patients who died and as a result, the total number of patients was changed from 1,880 to 1,735. Accordingly, the results were also changed in the main text and tables.

3. How did you define antibiotic adequacy? Just to be clear, it is based on whether the empirical antibiotic choice was appropriate, rather than when the antibiotics were switched to the more appropriate one after the culture results and drug sensitivities were out. If so, is there a difference those with MDR organisms?

Reply: In our study, we defined the appropriateness of empirical antibiotics according to the drug susceptibility test results or according to the relevant guidelines as described in the Methods section. Our focus was the use of empirical antibiotics, which were initially administered for sepsis treatment. Antibiotics switched from initial ones (after the results of drug sensitivity tests) were not considered in our study.

And, the appropriateness of empirical antibiotics was significantly different between patients with and without MDR organisms (78.7% vs. 96.7%, $p < 0.001$, data not shown in the main results). However, in multivariable logistic regression, there was no significant association between MDR organisms and poor ECOG PS

4. Lines 165-166 could be re-phrased better, such "More appropriate antibiotics were administered among those with good ECOG PS at hospital discharge". I did not understand the line till I read lines 200-202

Reply: We are sorry for the confusion. We re-phrased the sentence as follows.

“More appropriate antibiotics were administered among those with good ECOG PS at hospital discharge (94.6% vs. 89.6%, $P < 0.001$)”

5. What's the purpose of lines 168-174 and figure 3? Is this to highlight that PICS and functional decline even among those with few risk factors? Because this was not described in your discussion

Reply: We appreciated your comment. In fact, we meant to show that even those who were relatively healthy (i.e., a low disease severity, no history of cancer, or low comorbidity score) remained disabled after sepsis treatment, which we think can support our main result. This was described in the 3rd paragraph in the Discussion. We hope that you understand this. Thank you again.

6. "Post-sepsis syndrome" is synonymous with "post-intensive care syndrome (PICS)". May be good to change this given that this is current nomenclature that is being closely studied
Reply: With your permission, we want to use both expressions in the sentence as below.

““Post-sepsis syndrome,” or “post-intensive care syndrome (PICS),” is characterized by neurocognitive impairment, functional disability, psychological deficits, and worsening medical condition (6, 25).”

7. In lines 203-218, the authors are attempting to describe the factors that influence the development of PICS. In your study, illness severity, age, inappropriate antibiotics and BMI (High or low?) affected the development. Did this correlate with prior findings? It was only briefly touched upon in one sentence (Lines 211-213). This would need more elaboration on the reasons why your findings are similar or different, rather than a narrative of the different risk factors

Reply: First, as you pointed out, we removed the patients who died at hospital discharge from the main analyses. Consequently, the results for univariable and multivariable analyses changed a little. In the final model, contrary to the original one, BMI was not included, but a history of chronic heart disease was newly included. Exclusion of the non-survivors seemed to have affected this result (i.e., non-significance of BMI, and a protective effect of a history of chronic heart disease).

Second, as we used a backward stepwise selection method, some variables with $P < 0.1$ in univariable analysis, such as CCI, ICU admission, and the use of vasopressors, were not selected in the final model. We hope that you understand this.

We revised the sentences in the Discussion (in the middle of the 2nd paragraph) as follows.

“Similarly, in the present study, we found that old age, comorbidities (solid cancer and immunocompromised), and severity of illness (initial SOFA and MV) were associated with poor ECOG PS at hospital discharge, which reflects the adverse effects of malnutrition, severe underlying illness, or systemic inflammation on patients’ functional outcomes. However, contrary to previous studies, we could not find any associations of low BMI with poor ECOG PS, and unexpectedly, a history of chronic heart disease showed a protective effect. These can be explained by different population and low statistical power of our study. However, the exclusion of the non-survivors might have affected the results; BMI was lower, and a history of chronic heart disease was more frequent in the non-survivors than in the survivors (data not shown).”

8. Similarly, in lines 219-233, I believe the authors are trying to highlight that poor functional status post-discharge leads to higher economic burden, but lines 219-226 did not add much to the discussion and if not necessary, should be omitted. Education level has been touted to be a prognostic factor for functional status post-ICU discharge (Crit Care Med 2018;46:1393), but that is in the setting of gradual recovery. It is an important consideration as those with higher education levels are purportedly able to have better support system and recovery programs, which would impact the economic burden of these patients

Reply: We agree with you. As you recommended, we removed the sentences in line 291 ~ 226, and emphasized the importance of educational levels, with a citation of the reference (Crit Care Med 2018;46:1393), in the last part of the 3rd paragraph.

The revised sentences are as below.

“Experts say that lower productivity and indirect medical costs after hospital discharge, rather than initial hospitalization costs, account for the majority of the total costs (32). Particularly, education levels, which are associated with a better support system and recovery program, have been found to be associated with functional status post-ICU discharge (33). Therefore, these should be considered important when assessing socioeconomic burden of sepsis.”

9. Lines 234-243 was attempting to talk about the possibility of the only variable that appears to be modifiable - antibiotic appropriateness. Perhaps, postulations of why this is so should be elaborated upon (ie they spend less days in hospital, recover faster, mobilise faster?!)

Reply: Thank you for your comments. As you recommended, we added additional explanation on the association of inappropriate empirical antibiotics with poor ECOG PS in the 4th paragraph in the Discussion.

“Previously, the appropriateness of empirical antibiotics was known to be important for improving patient outcomes in sepsis (34). However, our results suggest that it may also improve the ECOG PS, not just decrease in-hospital mortality. This is likely to be associated with faster recovery or shorter hospital stay (35), but its exact mechanism remains to be established in future studies. Notably, the rate of appropriate empirical antibiotics was high in our cohort (93.5%), making it hard to expect a further improvement in clinical practice, However, on the other hand, the prevention of the inadequacy of empirical antibiotics may have a greater effect on a system with lower antibiotic compliance rate.”

10. I don't agree with the second limitation. It's precisely because your mortality is low which is why there is so much data on functional outcome. In fact, this demonstrates that the methodology needs adjusting. Those who have died have no functional outcome measures of note, which would skew the results

Reply: We agree with you that the data on patients who have died could skew the results. So, we excluded them from the results.

Reviewer C

The authors report on the impact of sepsis on the performance status (PS), measured by the Eastern Cooperative Oncology Group (ECOG) scale among patients with good pre-sepsis PS. The manuscript is well-written and the topic is timely and of importance for both clinical practice and future research.

Major comments

1. What is the evidence to date on the performance status of sepsis survivors at the time of hospital discharge and what is known on factors driving PS at that stage?

Reply: Unfortunately, data on the performance status of sepsis survivors at the time of hospital discharge are limited. As you know, most studies have described the performance status over the long-term period (e.g., 6 month or 1 year after discharge); old age, BMI, underlying comorbidities, and disease severity were known to be risk factors for functional decline. However, we found several articles reporting functional outcomes at the time of hospital discharge. A large-scale retrospective study performed in the US hospitals demonstrated that functional deterioration occurred in 29.3% of nonsurgical patients (from ICU admission to hospital discharge), and the magnitude of functional deterioration increased over time, with hematologic, sepsis, neurologic and pulmonary diseases having the highest odds of severe deterioration (Ingraham et al. *Crit Care Med.* 2020;48:1556-1564). Another single-center retrospective study, where Barthel Index was used, showed that among sepsis survivors, 42.5% had hospital-acquired functional decline (HAFD). In this study, lower pre-hospital functional status and longer time to initial ambulation were associated with HAFD (Takahashi et al. *Int J Rehabil Res.* 2021;44:307-313). Besides, a single-center prospective study on ICU patients also showed that educational level and longer ICU stay were risk factors for new-onset functional disability at 2 months after hospital discharge (Schandl et al. *Crit Care.* 2014;18:455).

Hence, we added the following sentences in the Discussion (the 3rd paragraph).

“Unlike previous studies that reported functional outcomes over the long-term period (e.g., 6 months or 1 year after discharge), our study focused on the functional status at hospital discharge. Although this can be one of the limitations of our study and attributable to a problem of using registry data, several studies also reported functional outcomes at the time of hospital discharge. In a retrospective study in the United States, 29.3% of non-surgical patients had functional decline between ICU admission and hospital discharge (30). Another single-center study reported 42.5% of sepsis survivors who had hospital-acquired functional decline. In this study, lower pre-hospital functional status and longer time to initial ambulation were associated with the functional decline (31).”

Thank you.

2. The study took place in part during the first year of the COVID-19 pandemic. COVID-19 related strain on health care resources could have affected care processes and thus outcomes of sepsis patients with and without COVID and can confound the interpretation of the reported findings on the magnitude of change in ECOG PS among hospital survivors. How many of the of the patients had COVID-19? What was the change in ECOG PS prior to vs during the pandemic period? How does adding the study period (e.g., pre-pandemic vs intra-pandemic surge periods) affect effect size of various modeled predictors of change in ECOG PS?

Reply: None of patients with COVID-19 were included in the sepsis registry during the study period.

And, as you recommended, we analyzed data according to the COVID-19 pandemic status and newly described them in the end of the Result. The change of ECOG PS according to the COVID-19 pandemic status is shown in Supplementary Figure S1, and the multivariable analysis, with the COVID-19 period (i.e., pre-pandemic vs. intra-pandemic) included, is shown

Supplementary Table S4.

3. The authors identified a subgroup of patients with “no comorbidities” as those with Charlson Comorbidity Index (CCI) 0. However, many of the comorbidities included in CCI are assigned 0 points due their being no longer associated with mortality (e.g., MI, peptic ulcer disease, diabetes without complications, and more [Quan H, et al. *Am J Epidemiol* 2011;173:676-682]). Moreover, absence of the 17 comorbidities included in CCI does not preclude presence of many other, clinically relevant comorbid conditions. The designation of those with CCI 0 should be revised in the manuscript, including abstract and the meaning of CCI 0 clarified in the Methods.

Reply: Thank you for your comments and we totally agree with you.

We discarded the phrase “patients with no comorbidities” and instead, used “patients with low comorbidities (CCI \leq 2)” in the Abstract, the main text, and Figure 3.

Previously, in several studies as well as the original study, CCI scores were divided into the four subgroups: 0 vs. 1-2 vs. 3-4 vs. \geq 5. (Charlson et al. *J Chronic Dis.* 1987;40:373-83; Jouffroy et al. *Am J Emerg Med.* 2022;60:128-133; Hsu et al. *Biomed Res Int.* 2020 Feb 25;2020:9076739). Hence, in the revised manuscript, we decided to use the threshold of \leq 2, indicating low severity of comorbidities. Accordingly, we also revised the Figure 3.

4. Specify in the Methods section the covariates included in the models and note covariate entry approach together with the discussion on multivariable analysis.

Reply: We specified the covariates of our final model in the Method section and also described again covariate entry approach.

The revised sentences were as below (Data analysis and statistical methods in the Methods)

“Logistic regression analysis was performed using covariates with $P < 0.10$ in univariable analysis to identify factors associated with poor ECOG PS at the time of hospital discharge. Initially, a total of sixteen variables ($P < 0.10$) were included in the model; age, CCI, chronic heart disease, solid cancer, immunocompromised, SOFA score, MDR pathogens, lactate, septic shock, steroid therapy, use of vasopressors, inappropriate empirical antibiotics, MV, transfusions, CRRT, and ICU admission. A backward stepwise selection method based on the likelihood ratio was used, and eight variables finally remained in the multivariable model. For the model calibration, Hosmer-Lemeshow test was used (chi-square = 6.943, $P = 0.543$).”

If you are not satisfied with this, please let us know. We will revise again.

Thank you.

5. Abdominal infections were the most frequent sepsis source, with frequency much higher than in most reported sepsis cohorts. This may affect the generalizability of the reported findings.

Reply: We agree with you on that point. We added it in the limitation section as follows.

“Fourth, the study was conducted in a single country, thus limiting the generalizability of our findings. Particularly, abdominal infections were the most frequent source of sepsis, which was different from those in other sepsis studies. This may be associated with the exclusion of the patients who have died (that is, the proportion of pneumonia was 40.0% [58/145 patients] of the non-survivors). Hence, caution should be taken when interpreting our data.”

6. The finding of an association of initially inadequate antibiotics with deterioration of PS among sepsis survivors is novel and intriguing, though it has been a target for sepsis care in general, given its well-documented association with mortality. However, in the practice setting described in the present study, with nearly 94% of sepsis patients received appropriate, how practical are performance improvement efforts likely to be systemwide?

Reply: We totally agree with you on that point. It would be difficult to demand a higher rate of antibiotic appropriateness in institutions (or systems) where the rate is already of > 90%. Hence, we added (revised) it in the 4th paragraph in the Discussion as follows.

“Notably, the rate of appropriate empirical antibiotics was high in our cohort (93.5%), making it hard to expect a further improvement in clinical practice, However, on the other hand, the prevention of the inadequacy of empirical antibiotics may have a greater effect on a system with lower antibiotic compliance rate.”

Minor comments

7. Specify the diagnostic method used to examine model calibration in the Methods prior to first use.

Reply: As you recommended, we added the method for model calibration in the Methods section. Thank you.

Line 203: By the Sepsis-3 framework sepsis is defined as “life threatening organ dysfunction...”. Revise the statement that sepsis is “frequently accompanied” by organ dysfunction.

Reply: We revised the statement as below (the 2nd paragraph in the Discussion).

“Sepsis is a life-threatening organ dysfunction by a dysregulated host response to infections and frequently causes long-term consequences (17).”

8. Lines 242-243: the last sentence does not belong topically in that paragraph.

Reply: We removed the sentences in the paragraph.

9. Table 1: specify the timing of lactate (first value, other?).

Reply: We specified the timing of lactate in Table 1 (i.e., initial lactate)

10. Supplementary Table 1: a) Na and K values are identical b) Na, K, and Cl mEq/L values are improbable as reported

Reply: We are sorry for these errors.

We corrected the values in the Supplementary Table S1.

11. Figure 5 is redundant, duplicating the detailed data in Table 3; the point estimate symbols for age, SOFA score, and lactate in Figure 5 appear to denote odds ratios 1.

Reply: As you recommended, we removed Figure 5 in the results.

Thank you.