Impact of sepsis on Eastern Cooperative Oncology Group performance status among fully ambulatory patients: a prospective nationwide multicenter cohort

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Background: Investigations of the impact of sepsis on the Eastern Cooperative Oncology Group performance status (ECOG PS) of fully ambulatory patients are scarce.

Methods: This is a retrospective analysis of prospectively collected nationwide data on septic patients recruited from 19 hospitals of the Korean Sepsis Alliance between August 2019 and December 2020. Adult septic patients with good ECOG PS (i.e., 0 or 1) before sepsis were enrolled in this study. The change in ECOG PS and the prevalence of disability (ECOG PS ≥2) at hospital discharge were recorded.

Results: Of the 4,145 septic patients, 1,735 (41.9%) patients who had ECOG PS of 0 or 1 before sepsis and eventually survived to discharge were selected. After treatment for sepsis, the ECOG PS deteriorated in 514 (29.6%) patients; 376 (21.7%) patients had poor ECOG PS (i.e., ≥2) at hospital discharge. The proportion of patients with poor ECOG PS at hospital discharge increased with increases in the initial sequential organ failure assessment (SOFA) score and lactate level. Furthermore, poor ECOG PS at hospital discharge was found in young patients (aged <65 years, 17.4%), those with no history of cancer (18.2%) or with low comorbidities [Charlson comorbidity index (CCI) ≤2; 13.6%], and those without septic shock (19.9%). In multivariable analysis, age, solid cancer, immunocompromised condition, SOFA score, mechanical ventilation, and use of inappropriate empirical antibiotics (odds ratio: 1.786; 95% confidence interval: 1.151–2.771) were significant risk factors for poor ECOG PS.

Conclusions: One in five septic patients who were fully ambulatory before sepsis were not functionally independent at hospital discharge. Incomplete functional recovery was also seen in a substantial proportion of younger patients, those with low comorbidities, and those without septic shock. However, the adequacy of empirical antibiotics may improve the functional status in such patients.

Keywords: Sepsis; functional status; Eastern Cooperative Oncology Group (ECOG); outcomes

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Introduction

Sepsis is a clinical syndrome caused by a dysregulated host inflammatory response to infections and is associated with organ dysfunction (1). It is considered a medical emergency due to high associated mortality and complication rates despite appropriate treatment (2-5).

Although the survival rates have increased with early diagnosis and treatment, sepsis survivors often do not recover their prior functional status (6). A prospective study of septic patients found incomplete recovery of health-related quality of life at 6 months after intensive care unit (ICU) discharge (7). In a retrospective study, 63% of patients with severe sepsis or septic shock had a good functional status before sepsis; however, only 36% of sepsis survivors had a good functional status at 1 year after hospital discharge (8). Importantly, sepsis can occur in healthy populations who are fully ambulatory and engaged in social activities. The consequent cognitive and physical dysfunction and increased dependency may cause serious economic problems for patients and their families (9).

However, there has been limited clinical research on the impact of sepsis on functional status in healthy populations.

Eastern Cooperative Oncology Group performance status (ECOG PS), an indicator of frailty, indicates a patient's ability to perform activities of daily living (10). Although the scale was validated for oncological patients (10-12), it has also been useful for patients with various conditions, including critically ill conditions where ECOG PS was associated with treatment outcomes (13-15). Therefore, using data from a nationwide, prospective sepsis registry by the Korean Sepsis Alliance (KSA), we evaluated the change in ECOG PS and the factors associated with its deterioration during the treatment of sepsis in patients who were fully ambulatory prior to sepsis. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-405/rc).

Highlight box

Key findings
- One in five septic patients who were fully ambulatory before sepsis were not functionally independent at hospital discharge.
- The adequacy of empirical antibiotics may improve the functional status in such patients.

What is known and what is new?
- Sepsis survivors often showed incomplete recovery of their functional status and health-related quality of life after hospital discharge in previous studies.
- In the present study, one in five septic patients who were fully ambulatory before sepsis did not recover their functional independence at hospital discharge. Incomplete functional recovery was also seen in a substantial proportion of younger patients (<65 years), those with low comorbidities, and those without septic shock.

What is the implication, and what should change now?
- Multidisciplinary efforts, including increased compliance with adequate empirical antibiotics, may improve the functional outcomes in sepsis patients, especially in those who are fully ambulatory.

Methods

Study population

We used sepsis data from an ongoing nationwide, multicenter cohort operated by the KSA. In total, 19 tertiary or university-affiliated hospitals (20 ICUs) in South Korea that run educational programs on sepsis bundles participated in this study. Regular audits were conducted by the KSA research committee members to verify the data quality (16). This is a retrospective analysis of data that were prospectively collected over a 17-month period between August 2019 and December 2020. We screened consecutive adult patients (aged ≥19 years) who were diagnosed with sepsis in emergency departments (EDs) or general wards. The third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were used to diagnose sepsis (17).

To evaluate the level of functioning of patients in terms of their ability to perform their activities of daily life, data on ECOG PS (score: 0 to 5) were collected at the time of sepsis diagnosis (i.e., PS before sepsis diagnosis) and at hospital discharge (i.e., PS after sepsis treatment) by trained study coordinators; data were confirmed by the study investigators of each hospital (10). We defined ECOG of 0

or 1 as good PS and ECOG ≥2 as poor PS (18,19). Patients with good ECOG PS (i.e., 0 and 1) before sepsis diagnosis were ultimately included in the study. Patients with do-not-resuscitate (DNR) orders, missing values, or disability before sepsis diagnosis (ECOG PS ≥2), and those who died in hospitals were excluded.

Data collection

The study coordinators at each participating center prospectively collected data and entered the information into a web-based database system (http://sepsis.crf.kr/). We collected the following data: demographic data, including age, sex, body mass index (BMI); underlying comorbidities, including Charlson comorbidity index (CCI); disease severity [sequential organ failure assessment (SOFA) score]; physiological and laboratory measurements; infection source and type (i.e., community- or hospital-acquired infections); presence of multidrug-resistant (MDR) pathogens in cases of culture-positive patients; sepsis treatment, including completion of the 3 h sepsis bundle, appropriateness of empirical antibiotic therapy, transfusions, use of steroids and vasopressors, mechanical ventilation (MV), and continuous renal replacement therapy (CRRT); and lengths of stay in the ICU and hospital

Community-acquired sepsis was defined as infection acquired in a community setting, whereas hospital-acquired sepsis was defined as infection that developed 48 h after hospitalization. The "time zero" for community-acquired sepsis was defined as the time of triage in the ED, whereas that for hospital-acquired sepsis was when the rapid response team diagnosed sepsis in the general ward (20,21). The appropriateness of empirical antibiotics was determined according to the drug susceptibility test results or according to the relevant guidelines (22,23). MDR pathogens were defined as those resistant to agents from at least three antimicrobial categories (24).

Data analysis and statistical methods

Primary outcomes were changes in ECOG PS between time zero (i.e., before sepsis) and hospital discharge, and the proportion of patients with poor ECOG PS (≥2) at hospital discharge. The secondary outcomes were as follows: risk factors for poor ECOG PS at hospital discharge, which were investigated using multivariable analysis; the prevalence of poor ECOG PS according to age (<65 vs. ≥65 years), history of cancer, underlying comorbidity

(i.e., CCI of ≤2 vs. >2), and septic shock; and the different prevalence of poor ECOG PS by the coronavirus disease 2019 (COVID-19) pandemic (pre- vs. intra-COVID-19 pandemic).

Descriptive analyses were used to summarize the characteristics of patients. Continuous data are expressed as means ± standard deviations or median [interquartile ranges (IQRs), 25th–75th percentiles], whereas categorical data are presented as frequency (percentage). The χ^2 test or Fisher's exact test was used to analyze categorical variables, whereas the Student's t-test and Mann-Whitney U test were used for continuous variables. 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). All tests were two-sided, and P<0.05 was considered to indicate statistical significance. The statistical analyses were performed using R software (version 4.3.0; R Foundation for Statistical Computing; Vienna, Austria).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review boards of all participating hospitals, including the Hallym University Institutional Review Board (approval No. 2018-09-004). Because this was an observational study with no interventions, the decision to obtain written informed consent from patients or their legal surrogates was at the discretion of the ethics committees of the participating hospitals.

Results

Study population

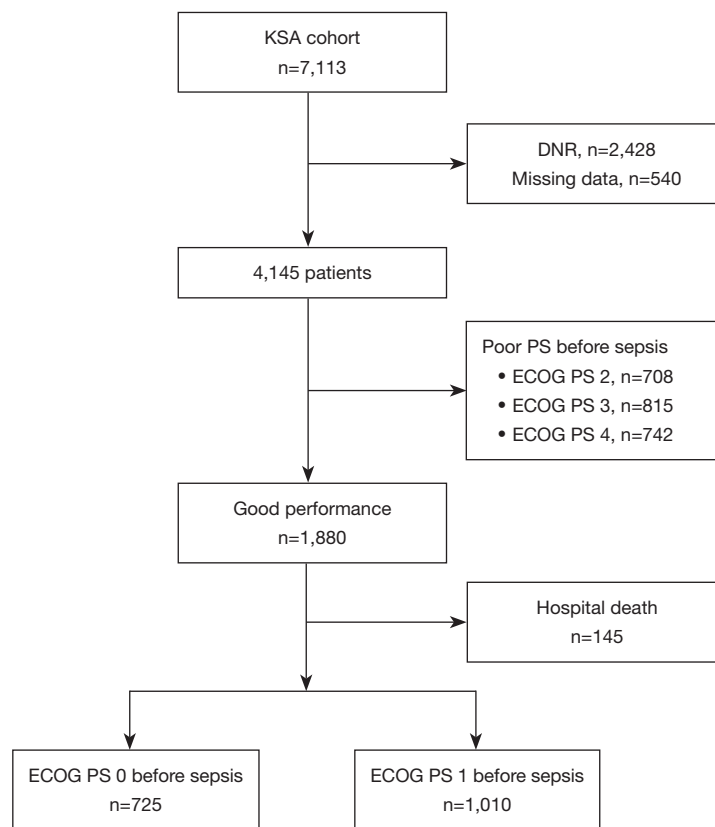Of the 7,113 septic patients in the KSA cohort, 2,968 were excluded due to DNR order (n=2,428) or missing

Figure 1 Flow chart of study population. KSA, Korean Sepsis Alliance; DNR, do-not-resuscitate; ECOG PS, Eastern Cooperative Oncology Group performance status.

values (n=540), and 4,145 were initially included. Of them, 1,880 (45.4%) patients were previously fully ambulatory (i.e., ECOG PS 0 or 1), and after the exclusion of patients who eventually died in the hospital (n=145), 1,735 were finally included in the analysis (*Figure 1*). The mean age was 66.1±13.5 years, and 60.3% were males (*Table 1*). 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%. The most common site of sepsis origin was the abdomen (38.4%), followed by the lungs (30.8%) and urinary tract (16.6%). The median SOFA score was 5.0 (3.0–7.0), and the median CCI was 5.0 (3.0–6.0). Bacteremia was found in 19.6% (340/1,735) of patients, and hospital-acquired infections accounted for 31.2% of infections. The baseline laboratory parameters are presented in Table S1.

Changes in ECOG performance status

Of the 1,735 patients with good ECOG PS (0 or 1) before

sepsis diagnosis, the PS deteriorated at hospital discharge in 514 (29.6%) patients, and 21.7% of each ECOG PS group (0 or 1) had poor ECOG PS (≥2) at hospital discharge (*Figure 2* and Table S2).

Comparison of patients with good and poor ECOG PS at hospital discharge

As shown in *Tables 1,2*, there were significant differences in the baseline characteristics and treatments between the two ECOG PS groups. Patients with good ECOG PS at hospital discharge (n=1,359) were younger, had lower CCI scores compared to those with poor ECOG PS (n=376). The former group also showed a lower disease severity at sepsis diagnosis, reflected by a lower SOFA score and lactate level, and less frequently received treatments with transfusions, MV, or CRRT compared to the latter group. However, more appropriate empirical antibiotics were administered among those with good ECOG PS at hospital

Table 1 Baseline characteristics between patients with good and poor ECOG PS at hospital discharge

Variables	Total (n=1,735)	Good ECOG PS[†] (n=1,359)	Poor ECOG PS[‡] (n=376)	P value
Age, years	66.1±13.5	65.5±13.7	68.4±12.2	<0.001
Sex, male	1,046 (60.3)	817 (60.1)	229 (60.9)	0.829
BMI, kg/m^2	22.9±4.0	23.0±4.0	22.8±4.1	0.425
Charlson comorbidity index	5.0 (3.0–6.0)	5.0 (3.0–6.0)	5.0 (4.0–7.0)	<0.001
ECOG 0/ECOG 1 before sepsis	725/1,010	568/791	157/219	0.989
Underlying comorbidities				
Diabetes	642 (37.0)	494 (36.4)	148 (39.4)	0.313
Chronic heart disease	450 (25.9)	393 (28.9)	57 (15.2)	<0.001
Chronic lung disease	276 (15.9)	223 (16.4)	53 (14.1)	0.315
Chronic liver disease	211 (12.2)	161 (11.8)	50 (13.3)	0.501
Chronic kidney disease	252 (14.5)	196 (14.4)	56 (14.9)	0.883
Cerebrovascular accident	196 (11.3)	148 (10.9)	48 (12.8)	0.355
Solid cancer	590 (34.0)	431 (31.7)	159 (42.3)	<0.001
Hematologic disease	101 (5.8)	74 (5.4)	27 (7.2)	0.251
Immunocompromised	93 (5.4)	61 (4.5)	32 (8.5)	0.003
Origin of sepsis				
Abdomen	667 (38.4)	528 (38.9)	139 (37.0)	0.545
Catheter-associated infection	11 (0.6)	7 (0.5)	4 (1.1)	0.267
Neurology	142 (8.2)	106 (7.8)	36 (9.6)	0.315
Pulmonary	534 (30.8)	410 (30.2)	124 (33.0)	0.326
Skin and soft tissue	85 (4.9)	64 (4.7)	21 (5.6)	0.575
Urinary	288 (16.6)	238 (17.5)	50 (13.3)	0.062
Sepsis without clear origins	8 (0.5)	6 (0.4)	2 (0.5)	0.686
Initial SOFA score	5.0 (3.0–7.0)	5.0 (3.0–7.0)	6.0 (4.0–8.0)	<0.001
Initial lactate, mmol/L	2.3 (1.4–3.8)	2.2 (1.4–3.6)	2.6 (1.6–4.6)	<0.001
HAI	542 (31.2)	423 (31.1)	119 (31.6)	0.896
Septic shock	329 (19.0)	233 (17.1)	96 (25.5)	<0.001
Pathogen identified	1,023 (59.0)	792 (58.3)	231 (61.4)	0.297
Bacteria/virus/fungus/others	932/35/39/17	722/29/27/14	210/6/12/3	0.455
Bacteremia[§]	340 (36.5)	272 (37.7)	68 (32.4)	0.161
MDR pathogens[§]	300 (32.2)	220 (30.5)	80 (38.1)	0.037

Values are presented as mean ± SD, median (interquartile range), or number (%). [†], ECOG of 0 or 1 at hospital discharge. [‡], ECOG of 2 or more at hospital discharge. [§], among patients with bacterial infections. ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; SOFA, sequential organ failure assessment; HAI, hospital-acquired infection; MDR, multidrug-resistant; SD, standard deviation.

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discharge (94.6% *vs.* 89.6%, P<0.001).

Prevalence of poor ECOG PS by subgroups

A substantial proportion of patients younger than 65 years [17.4% (126/724)], those with low comorbidities [i.e., CCI ≤2; 13.6% (41/301)], those without a history of cancer
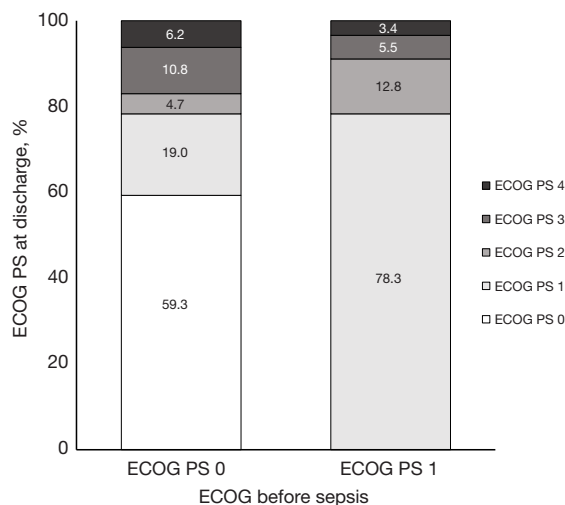
[18.2% (193/1,058)], and those without septic shock [19.9% (280/1,406)] had poor ECOG PS at hospital discharge (*Figure 3*). The frequency of poor ECOG PS increased with increasing baseline SOFA score quartiles and lactate levels (P<0.001 and P=0.011, respectively; *Figure 4*).

Multivariable analysis of risk factors for disability at hospital discharge

Initially, 16 variables with P<0.10 in the univariable analysis (Table S3) were incorporated into the logistic regression analysis. Ultimately, eight variables remained in the final model, and among them, age, chronic heart disease, solid cancer, immunocompromised condition, SOFA score, use of inappropriate empirical antibiotics, and MV were significantly associated with poor ECOG PS at hospital discharge (*Table 3*). Especially, the use of inappropriate empirical antibiotics [odds ratio (OR): 1.786; 95% confidence interval (CI): 1.151–2.771] was the only modifiable factor.

Prevalence of poor ECOG PS according to the COVID-19 pandemic period

The prevalence rates of poor ECOG PS at hospital discharge

Figure 2 Changes in the ECOG PS. ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Initial treatments and outcomes between patients with good and poor ECOG PS at hospital discharge

Variables	Total (n=1,735)	Good ECOG PS[†] (n=1,359)	Poor ECOG PS[‡] (n=376)	P value
Treatments				
Steroid therapy	296 (17.1)	221 (16.3)	75 (19.9)	0.109
Vasopressors	439 (25.3)	317 (23.3)	122 (32.4)	<0.001
Antibiotic adequacy	1,623 (93.5)	1,286 (94.6)	337 (89.6)	<0.001
Mechanical ventilation	279 (16.1)	162 (11.9)	117 (31.1)	<0.001
Transfusion	300 (17.3)	204 (15.0)	96 (25.5)	<0.001
CRRT	112 (6.5)	69 (5.1)	43 (11.4)	<0.001
3-h bundle compliance	922 (53.1)	721 (53.1)	201 (53.5)	0.936
ICU admission	744 (42.9)	546 (40.2)	198 (52.7)	<0.001
Hospital outcomes				
Length of hospital stay, days	13.0 (7.0–22.0)	12.0 (7.0–19.0)	18.0 (7.5–36.0)	<0.001
Length of ICU stay, days[§]	4.0 (2.0–8.0)	4.0 (2.0–6.0)	7.0 (3.0–14.3)	<0.001

Values are presented as number (%) or median (interquartile range). [†], ECOG of 0 or 1 at hospital discharge. [‡], ECOG of 2 or more at hospital discharge. [§], among 744 patients who were admitted to the ICU. ECOG PS, Eastern Cooperative Oncology Group performance status; CRRT, continuous renal replacement therapy; ICU, intensive care unit.
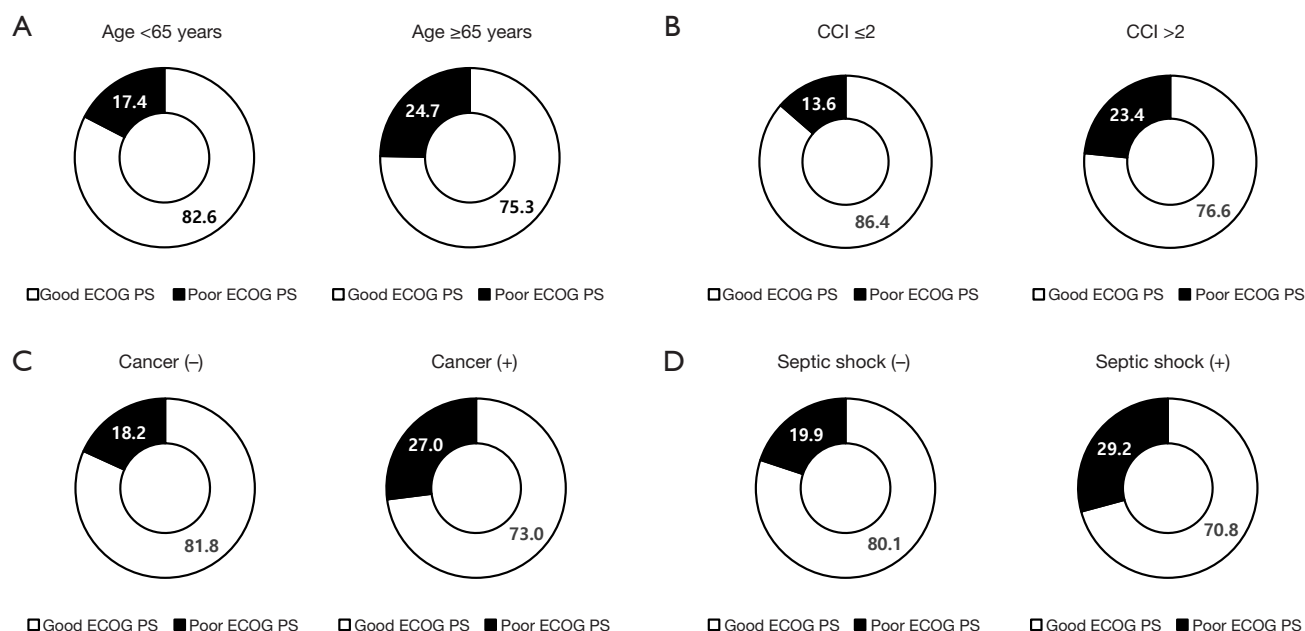
Figure 3 Prevalence of poor ECOG PS (ECOG of 2 or more) at hospital discharge by subgroups. (A) age (<65 *vs.* ≥65 years; P<0.001), (B) CCI (CCI ≤2 *vs.* CCI >2; P<0.001), (C) a history of cancer (yes *vs.* no; P<0.001), and (D) septic shock (yes *vs.* no; P<0.001). ECOG PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson comorbidity index.
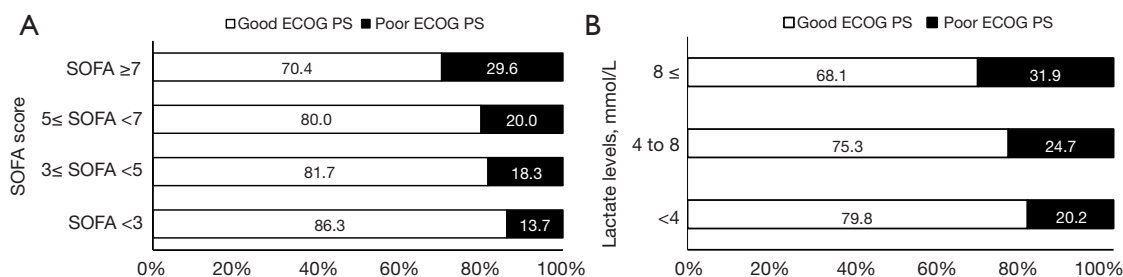

Figure 4 Prevalence of poor ECOG PS (ECOG of 2 or more) at hospital discharge by initial disease severity. (A) SOFA score quartiles (i.e., SOFA <3 *vs.* 3≤ SOFA <5 *vs.* 5≤ SOFA <7 *vs.* SOFA ≥7), and (B) lactate levels (<4 *vs.* 4 to 8 *vs.* >8 mmol/L). ECOG PS, Eastern Cooperative Oncology Group performance status; SOFA, sequential organ failure assessment.

were significantly different between the pre- and intra-COVID-19 pandemic periods [102 (18.2%) *vs.* 274 (23.3%), P=0.017; Figure S1]. When included in the multivariable model, the intra-COVID-19 pandemic period was associated with increased risk of poor ECOG PS at hospital discharge (OR: 1.411; 95% CI: 1.078–1.860) (Table S4).

Discussion

In this prospective sepsis cohort, we found that one in five

septic patients with good functional status (ECOG PS of 0 or 1) before sepsis did not recover their previous functional status at hospital discharge. Second, incomplete functional recovery was also found in a substantial proportion of young patients (aged <65 years), patients with low comorbidities, and patients without septic shock. Third, age, solid cancer, immunocompromised condition, SOFA score, use of inappropriate empirical antibiotics, and MV were significant predictors for poor ECOG PS at hospital discharge. In particular, the identification of the use of inappropriate

Table 3 Multivariable analysis for risk factors for poor ECOG PS among survivors (n=1,735)[†,‡]

Variables	P value	OR	95% CI
Age, years	<0.001	1.031	1.020–1.042
Chronic heart disease	<0.001	0.403	0.289–0.560
Solid cancer	0.001	1.514	1.177–1.948
Immunocompromised	0.002	2.130	1.315–3.449
SOFA score	0.001	1.080	1.032–1.130
Lactate	0.074	1.042	0.996–1.091
Inappropriate antibiotics	0.010	1.786	1.151–2.771
MV	<0.001	3.030	2.258–4.064

[†], Sixteen variables with a P value <0.1 in univariable analyses were initially 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 antibiotics, MV, transfusion, CRRT, and ICU admission. [‡], Hosmer-Lemeshow test: chi-square =6.943, df =8, P value =0.543. ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio; CI, confidence interval; SOFA, sequential organ failure assessment; MV, mechanical ventilation. CCI, Charlson Comorbidity Index; MDR, multi-drug resistant; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

empirical antibiotics as a risk factor for poor ECOG was remarkable, which may be modifiable by performance improvement programs in clinical practice.

Sepsis is a life-threatening organ dysfunction by a dysregulated host response to infections and frequently causes long-term consequences (17). "Post-sepsis syndrome", or "post-intensive care syndrome (PICS)", is characterized by neurocognitive impairment, functional disability, psychological deficits, and worsening medical condition (6,25). Although the mechanism is multifactorial, systemic inflammatory processes, leading to altered muscle integrity and function, may play a role in the development of physical impairment (26,27). In previous studies, old age, low BMI, disease severity, and prolonged MV were associated with functional impairment after critical illnesses (27,28). The increasing severity of sepsis or organ failure was also linked to worsening functional status (29). 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 populations 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).

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). However, in the present study, we found that a significant proportion of young patients (aged <65 years), those with low comorbidities or no history of cancer, and those without septic shock had poor ECOG PS at hospital discharge, implying that they may not be able to return to their previous level of activity immediately. This can be linked to socioeconomic burden of sepsis. 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.

Another important finding is that the use of inappropriate empirical antibiotics was significantly associated with poor ECOG PS at hospital discharge. 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 the 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.

Interestingly, in another multivariable model in our study (Table S4), the COVID-19 pandemic period was associated with increased risk of poor ECOG PS at hospital discharge. which was consistent with previous studies reporting an increased burden of severe COVID-19 in terms of functional outcomes (36,37). However, in the model, inappropriate empirical antibiotics, as well as other factors (i.e., age, immunocompromised, SOFA score, and MV), were still significant risk factors for poor ECOG PS.

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 (11,38). 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 (39), the World Health Organization's Disability Assessment Schedule 2.0 (WHODAS II) (40), and Barthel Index (41). 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.

Our study had several limitations. First, our results may be influenced by the inherent selection bias in this observational study. However, the data were prospectively collected from all consecutive patients diagnosed with sepsis at 19 hospitals in South Korea. 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. Third, data on long-term outcomes, such as 6-month and 1-year mortalities and quality of life, were not evaluated. In particular, the cognitive and psychological functions were not investigated. These data would have provided additional information regarding sepsis burden. 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 (42,43). 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. Finally, although early rehabilitation programs in the ICU can improve the PS outcomes, this was not investigated. However, despite these limitations, a distinct feature of our study is that we focused on relatively healthy patients who lived independently before sepsis. We also identified a modifiable factor that affects the PS outcomes in these patients. Therefore, our results may aid the estimation of the sepsis burden and contribute to improving sepsis outcomes.

Conclusions

One in five septic patients who were fully ambulatory before sepsis were not functionally independent at hospital discharge. In particular, incomplete functional recovery was also found in a substantial proportion of younger patients, those with low comorbidities, and those without septic shock. However, the inadequacy of empirical antibiotics was a risk factor for poor ECOG PS; its prevention may improve the functional outcomes. Further studies are warranted to elucidate the sepsis burden more accurately and to identify additional modifiable factors of functional outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review boards of all participating hospitals, including the Hallym University Institutional Review Board (approval No. 2018-09-004). Because this was an observational study with no interventions, the decision to obtain written informed consent from patients or their legal surrogates was at the discretion of the ethics committees of the participating hospitals.

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Table S1 Baseline laboratory findings between patients with good and poor ECOG PS at hospital discharge

Variables	Total (n=1,735)	Good ECOG PS[a] (n=1,359)	Poor ECOG PS[b] (n=376)	P value
WBC, ×10³/μL	10.7 (6.1–16.2)	10.7 (6.3–16.1)	10.6 (5.6–17.0)	0.245
Hb, g/dL	11.17±2.53	11.29±2.53	10.74±2.48	<0.001
Hematocrit, %	33.52±7.46	33.82±7.42	32.40±7.54	0.001
Platelet, ×10³/μL	158.0 (95.0–238.5)	159.0 (97.0–236.0)	157.0 (86.5–244.5)	0.936
[Na⁺], mEq/L	135.19±6.05	135.39±5.81	134.48±6.82	0.018
[K⁻], mEq/L	4.13±0.79	4.12±0.77	4.19±0.86	0.108
[Cl⁻], mEq/L	100.86±7.16	101.14±6.99	99.89±7.65	0.004
BUN, mg/dL	24.8 (17.0–38.4)	24.0 (16.3–38.0)	27.0 (18.7–41.0)	<0.001
Cr, mg/dL	1.27 (0.86–2.04)	1.26 (0.85–1.97)	1.33 (0.95–2.37)	0.033
Bilirubin, mg/dL	0.90 (0.58–1.70)	0.90 (0.57–1.70)	0.90 (0.60–1.65)	0.972
AST, U/L	38.0 (22.0–77.0)	39.0 (22.0–78.0)	35.0 (22.0–69.0)	0.748
ALT, U/L	25.0 (15.0–54.0)	26.0 (15.0–56.0)	24.0 (14.0–49.0)	0.547
Albumin, g/dL	3.08±0.65	3.13±0.65	2.89±0.65	<0.001
CRP, mg/dL	11.13 (4.35–19.98)	10.62 (4.03–19.51)	12.83 (5.56–20.98)	0.031
Glucose, mg/dL	142.0 (111.0–195.0)	141.0 (110.0–192.0)	149.5 (116.0–218.0)	0.026
pH	7.41±0.11	7.41±0.10	7.39±0.12	0.002
$PaCO_2$, mmHg	31.86±10.11	31.91±9.39	31.69±12.39	0.751
PaO_2, mmHg	87.65±40.41	87.34±39.05	88.77±45.02	0.574
[HCO₃⁻], mEq/L	20.34±5.37	20.62±5.22	19.32±5.79	<0.001

Values are presented as mean ± SD or median (interquartile range). [a], ECOG of 0 or 1 at hospital discharge. [b], ECOG of 2 or more at hospital discharge.

Table S2 Changes in the ECOG PS between time zero (baseline) and hospital discharge

Baseline ECOG PS	ECOG PS at hospital discharge				
	0	1	2	3	4
Total (n=1,735)	430 (24.8%)	929 (53.5%)	163 (9.4%)	134 (7.7%)	79 (4.6%)
0 (n=725)	430 (59.3%)	138 (19.0%)	34 (4.7%)	78 (10.8%)	45 (6.2%)
1 (n=1,010)	–	791 (78.3%)	129 (12.8%)	56 (5.5%)	34 (3.4%)

Table S3 Univariable analysis for risk factors for poor ECOG PS among survivors (n=1,735)

Variables	ORs	95% CI	P value
Age	1.020	1.010–1.030	<0.001
Sex, *vs.* male	0.968	0.766–1.220	0.783
BMI, kg/m^2	0.988	0.960–1.020	0.420
Underlying comorbidities			
Charlson comorbidity index	1.080	1.040–1.130	<0.001
Diabetes	1.140	0.899–1.440	0.285
Chronic heart disease	0.439	0.324–0.596	<0.001
Chronic lung disease	0.836	0.605–1.160	0.278
Chronic liver disease	1.140	0.812–1.600	0.446
Chronic kidney disease	1.040	0.753–1.430	0.818
Cerebrovascular accident	1.200	0.846–1.700	0.310
Solid cancer	1.580	1.250–1.990	<0.001
Hematologic disease	1.340	0.851–2.120	0.205
Immunocompromised	1.980	1.270–3.090	0.003
Pulmonary *vs.* non-pulmonary	1.140	0.892–1.450	0.296
Initial SOFA score	1.100	1.060–1.150	<0.001
MDR pathogens	1.400	1.050–1.860	0.021
Lactate, mmol/L	1.090	1.050–1.130	<0.001
Bacteremia	0.882	0.657–1.180	0.404
HAI	1.020	0.801–1.310	0.846
Septic shock	1.660	1.260–2.170	<0.001
ECOG 1 *vs.* 0 before sepsis	1.000	0.795–1.260	0.989
Treatment-related factors			
Receiving steroid therapy	1.280	0.959–1.720	0.093
Receiving vasopressors	1.580	1.230–2.030	<0.001
Inappropriate empirical antibiotics	2.040	1.360–3.060	0.001
Receiving MV	3.340	2.540–4.390	<0.001
Receiving transfusion	1.940	1.470–2.560	<0.001
Receiving CRRT	2.410	1.620–3.600	<0.001
3-h bundle compliance	1.020	0.808–1.280	0.890
ICU admission	1.660	1.320–2.080	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; CRRT, continuous renal replacement therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HAI, hospital-acquired infection; ICU, intensive care unit; MDR, multidrug-resistant; MV, mechanical ventilation; SOFA, sequential organ failure assessment.
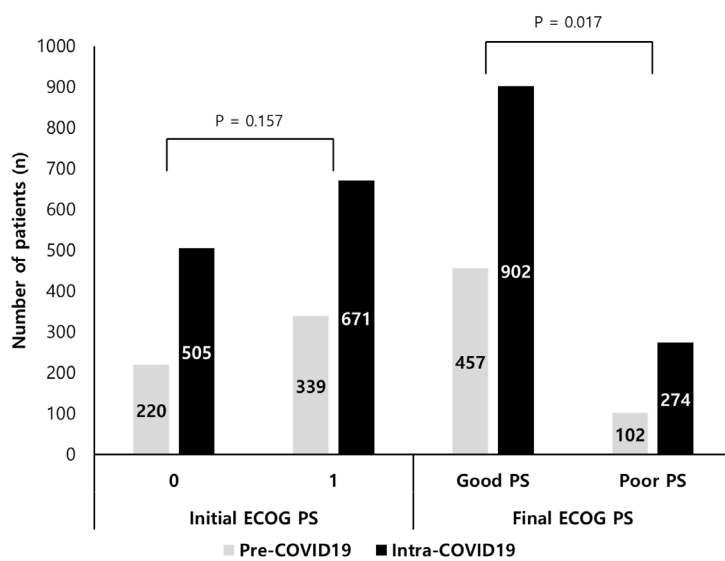
Figure S1 Frequencies of ECOG PS according to COVID-19 periods. Pre-COVID-19 indicates the time period between August 2019 and January 2020, and intra-COVID-19 indicates between February and December 2020.

Table S4 Multivariable analysis for risk factors for poor ECOG PS including COVID-19 variable (n=1,735)[a,b]

Variables	P value	OR	95% CI
Age, years	<0.001	1.025	1.013–1.036
CCI	0.002	1.086	1.030–1.145
Chronic heart disease	<0.001	0.349	0.249–0.484
Immunocompromised	0.011	1.875	1.142–3.031
SOFA score	0.029	1.055	1.005–1.107
Lactate	0.079	1.042	0.995–1.091
Vasopressor	0.137	1.250	0.929–1.673
Inappropriate antibiotics	0.006	1.857	1.190–2.861
MV	<0.001	3.092	2.300–4.153
COVID-19 pandemic	0.013	1.411	1.078–1.860

[a], Seventeen variables with a P value <0.1 in univariable analyses were initially included in the model: age, CCI, chronic heart disease, solid cancer, immunocompromised, SOFA score, multi-drug resistant (MDR) pathogens, lactate, septic shock, steroid therapy, use of vasopressors, inappropriate antibiotics, MV, transfusions, continuous renal replacement therapy (CRRT), intensive care unit (ICU) admission, and COVID-19 pandemic period. [b], Hosmer-Lemeshow test: chi-square =9.7242, df =8, P=0.2849.