



OPEN The impact of withholding and withdrawal life-sustaining treatment issues on patients with sepsis: a prospective, nationwide, multicenter cohort study

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Approximately half of the patients with sepsis require intensive care unit (ICU) management and their mortality rate remains high. The concept of withholding and withdrawal life-sustaining treatment (WWLST) issue was introduced to limit the suffering of critically ill patients. However, little is known about the characteristics and outcomes of WWLST in patients with sepsis. We conducted a nationwide cohort study of adult patients with sepsis prospectively collected from the Korean Sepsis Alliance Database of 20 tertiary referral or university-affiliated hospitals in South Korea between September 2019 and December 2021. Patients were classified according to WWLST issues and characteristics, and their prognoses were compared. Among the 11,981 patients with sepsis included in the study, 4430 (37.0%) had WWLST issues. The WWLST group was older, frailer, and had higher Sequential Organ Failure Assessment (SOFA) scores than the no-WWLST group. The WWLST group had more underlying diseases, including solid tumors (45.2% vs. 30.6%, $p < 0.001$) and hematologic malignancies (8.0% vs. 5.2%, $p < 0.001$), than the no-WWLST group. Regarding patient outcomes and interventions in the ICU, the WWLST group used vasopressors (35.4% vs. 32.8%, $p = 0.003$) more frequently; invasive mechanical ventilation (62.9% vs. 41.9%, $p < 0.001$) and continuous renal replacement therapy (40.8% vs. 17.6%, $p < 0.001$) were applied more frequently in the WWLST group than in the no-WWLST group. Logistic regression analysis revealed the factors associated with WWLST group to be old age, low body mass index, higher Charlson comorbidity index, clinical frailty scale, SOFA score, underlying diseases such as solid tumors and hematologic malignancies, invasive mechanical ventilation, and continuous renal replacement therapy. We predicted that the WWLST group would have a fewer ICU admissions and less invasive treatment. However, the admission rate was equivalent, and the percentage of invasive treatment, length of ICU stays, and mortality rate were higher and longer in the WWLST group. In patients with sepsis who have factors related to WWLST, appropriate communication with the patient and their family about WWLST can improve the quality of life and quality of death.

Keywords Withholding treatment, Intensive care unit, Do-not-resuscitate, End-of-life care, Well-dying

Abbreviations

BMI	Body mass index
CCI	Charlson comorbidity index
CCRT	Continuous renal replacement therapy
CFS	Clinical frailty scale
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein

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DNR	Do-not-resuscitate
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
LST	Life-sustaining treatment
WWLST	Withholding and withdrawal life-sustaining treatment
SOFA	Sequential organ failure assessment
WBC	White blood cell
CPR	Cardiopulmonary resuscitation
APACHE	Acute physiology and chronic health evaluation
POLST	Physician orders for life-sustaining treatment

Background

Sepsis is one of the most prevalent illnesses in hospitalized patients and one of the main causes of death worldwide, including in South Korea^{1,2}. More than half of patients with sepsis require intensive care unit (ICU) management³. These patients often receive critical interventions, such as insertion of a central line for vasopressor administration, invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT), and tracheostomy. Despite these efforts, the mortality rate of hospitalized patients with sepsis remains high at 35.3%⁴. This situation is complicated in older patients, as advanced age is consistently associated with increased ICU mortality^{5–7}. The number of older patients with sepsis continues to increase, and this demographic reality reflects global aging trends⁸. This has brought increased attention to the quality of end-of-life care, highlighting the need for improved understanding and decision-making regarding life-sustaining treatments (LST) among patients and their families. As a result, there is growing interest in exploring options for end-of-life care, with an emphasis on the preferences and values of those receiving care⁹.

The concept of dignified death, often referred to as “well-dying,” is gaining significant traction in South Korea, where the proportion of older patients is increasing significantly as the country becomes an aging society¹⁰. Based on these demographic changes and interest in well-dying, South Korea established a national management system for withholding and withdrawal life-sustaining treatment (WWLST, Central Hospice Center: September 2017, National Agency for Management of LST: February 2018) with the enactment of the “Act on Hospice and Palliative Care and Decisions on LST for Patients at the End of Life” (thereafter referred to as “LST Decision Act”)¹¹. Several papers on end-of-life care have been published after the enactment of the End-of-Life Decision Act and the establishment of related organizations. Yoon et al. explained that the number of participants who do not want to receive LST care is twice as high as that of participants who want to receive LST care¹². Park et al. reported that, according to a study based on National Health Insurance billing data, in the 20 months between February 2018 and October 2019, 71,327 patients (42,796 patients in 1 year) wrote statements on the decision to suspend LST in Korea¹¹. Interest in WWLST appears to be higher in patients with malignancies. Won et al. observed that 26.4% of patients with cancer complied with the WWLST process; however, the existence or non-existence of documentation regarding the patient’s WWLST did not influence the decision to withhold or withdraw treatment¹³.

The incidence of sepsis is on the rise, leading to an increasing number of hospital and ICU admissions^{14–16}. This trend, combined with a growing focus on end-of-life care, particularly with regard to WWLST issues, underscores the need for a deeper understanding of the characteristics and clinical outcomes of these patients. To address this gap, our study examines the characteristics and prognosis of sepsis patients in relation to WWLST, marking the first analysis of WWLST considerations in sepsis patients in both the ward and ICU settings. Furthermore, this study is unique in that it focuses on WWLST issues within a comprehensive, nationwide, multicenter cohort of sepsis patients, which distinguishes it from previous sepsis research.

Methods

Study design and population

We conducted a nationwide cohort study of adult patients with sepsis, prospectively collected from the Korean Sepsis Alliance database of 20 tertiary referrals or university-affiliated hospitals in South Korea. Community-onset sepsis (COS) and hospital-onset sepsis (HOS) patients were included in this study. For COS patients, the inclusion criteria were: (1) adults aged ≥ 19 years who underwent blood culture testing in the emergency department, and (2) patients meeting at least two of the three quick SOFA criteria upon emergency department admission; if mental status evaluation was not feasible, patients meeting at least one of the two remaining criteria (respiratory rate or systolic blood pressure) were included. For HOS patients, the inclusion criteria were adults aged ≥ 19 years who were identified by the Rapid Response Team at each hospital (Fig. 1). Patients who did not have sepsis were excluded from the study. A total of 11,981 patients were enrolled between September 2019 and December 2021.

This study was approved by the Institutional Review Board (IRB) of Chungnam National University Hospital (IRB No: 2019-11-048). The requirement for informed consent was waived because this was a standard-of-care observational study with minimal risk and no intervention.

Definitions

We enrolled patients according to the criteria outlined in the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3). This included patients with sepsis characterized by life-threatening organ dysfunction due to a dysregulated host response to infection and patients with septic shock characterized

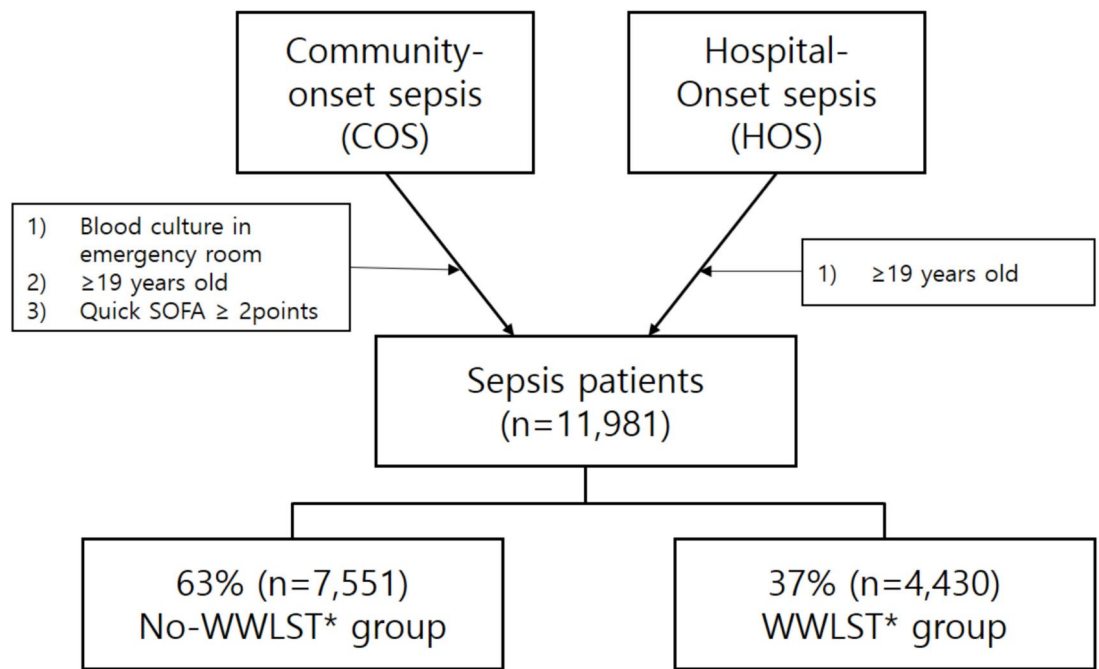


Fig. 1. Study flow diagram of patients with sepsis. *WWLST withholding and withdrawal life sustaining treatment.

by underlying circulatory and cellular/metabolic abnormalities significant enough to increase mortality substantially.

This study defined patients with WWLST as those who completed a Do Not Resuscitate (DNR) order or a withhold/withdraw LST document. The study adopted the LST Decision Act definition, which characterizes LST as "medical treatment that merely prolongs the end-of-life process without a curative effect". This includes, but is not limited to, cardiopulmonary resuscitation (CPR), mechanical ventilation, vasopressors, hemodialysis, ECMO, blood transfusion, and chemotherapy. While DNR specifically refers to withholding CPR in the event of cardiac or respiratory arrest, WWLST encompasses broader treatment limitations beyond CPR. Thus, all DNR orders fall under WWLST, but not all WWLST cases are limited to DNR. In South Korea, LST decisions are based on the prior wishes of the patient. Documentation can be done through advanced directives (for adults aged ≥ 19 years) or a life-sustaining treatment plan (for terminally ill patients with decision-making capacity). If a patient lacks capacity, LST decisions require either family testimony confirming prior wishes or unanimous agreement among all family members. For this study, individuals with WWLST documentation (including DNR orders) were classified as the WWLST group, while those without such documentation were classified as the no-WWLST group. A detailed decision-making process is shown in Supplementary Fig. 1.

Data collection

Patients' age, sex, body mass index (BMI), underlying diseases, laboratory findings, and other data were collected. Charlson comorbidity index (CCI), clinical frailty scale (CFS), and Sequential Organ Failure Assessment (SOFA) scores were also collected when patients were admitted to the hospital. The SOFA score was determined based on the worst values recorded during the first 24 h after admission. We collected data on the presence and types of procedures (high-flow nasal cannulation, invasive mechanical ventilation, ECMO, CRRT, and tracheostomy) the patients underwent. We also collected in-hospital duration of stay, period of ICU admission, and mortality data to evaluate patient prognosis. Patients were classified according to the presence or absence of WWLST issues.

Statistical analysis

The data were analyzed according to the variable type. Continuous variables were expressed as mean $\pm$ standard deviation and median plus interquartile range. Student's t-test or Mann–Whitney U test was used to validate statistical significance. Categorical variables were expressed as numbers (percentages), and Pearson's chi-squared or Fisher's exact test was used. Univariate and multivariate logistic regression analyses were performed to evaluate factors associated with WWLST issues and in-hospital mortality. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to represent variables independently associated with WWLST issues and in-hospital mortality. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS software (version 22.0; IBM Corporation, Armonk, NY, USA).

Characteristics	All patients	No-WWLST group	WWLST group	P-value
Patients (n)	11,981	7,551	4,430	
Age, year	71.3 ± 13.7	70.1 ± 13.9	73.3 ± 13.0	< 0.001
Male	6,904 (57.6)	4,324 (57.3)	2,580 (58.2)	0.297
Body mass index, kg/m ²	21.9 ± 4.2	22.2 ± 4.2	21.3 ± 4.2	< 0.001
Charlson comorbidity index	5.7 ± 2.6	5.3 ± 2.5	6.3 ± 2.5	< 0.001
Clinical frailty scale	5.3 ± 2.1	4.9 ± 2.1	5.9 ± 2.0	< 0.001
SOFA score	6.3 ± 3.1	5.8 ± 2.9	7.2 ± 3.2	< 0.001
Underlying disease				
Diabetes mellitus	4170 (34.8)	2757 (36.5)	1413 (31.9)	< 0.001
Solid tumor	4310 (36.0)	2308 (30.6)	2002 (45.2)	< 0.001
Chronic kidney disease	1441 (12.0)	989 (13.1)	452 (10.2)	< 0.001
Liver disease	1105 (9.2)	686 (9.1)	419 (9.5)	0.495
Heart failure	743 (6.2)	415 (5.5)	328 (7.4)	< 0.001
Chronic obstructive lung disease	776 (6.5)	488 (6.5)	288 (6.5)	0.934
Cerebrovascular disease	2311 (19.3)	1463 (19.4)	848 (19.1)	0.755
Dementia	1793 (15.0)	1016 (13.5)	777 (17.5)	< 0.001
Connective tissue disease	323 (2.7)	225 (3.0)	98 (2.2)	0.012
Hematologic malignancy	745 (6.2)	390 (5.2)	355 (8.0)	< 0.001
Laboratory findings				
White blood cell, × 10 ³ /uL	12.87 ± 11.14	12.61 ± 10.45	13.32 ± 12.21	< 0.001
Hemoglobin, g/dL	10.7 ± 2.5	10.9 ± 2.5	10.3 ± 2.5	< 0.001
Platelet, × 10 ³ /uL	182.5 ± 119.2	185.6 ± 114.6	176.8 ± 126.6	< 0.001
Total bilirubin, mg/dL	1.9 ± 3.5	1.6 ± 2.8	2.3 ± 4.4	< 0.001
Albumin, g/dL	2.9 ± 1.1	3.1 ± 1.2	2.7 ± 0.7	< 0.001
Creatinine, mg/dL	1.86 ± 1.82	1.82 ± 1.89	1.93 ± 1.69	0.001
CRP, ng/mL	13.24 ± 10.17	12.63 ± 10.14	14.27 ± 10.15	< 0.001
Lactate, mmol/L	3.80 ± 3.35	3.28 ± 2.90	4.66 ± 3.83	< 0.001

Table 1. Baseline characteristics of enrolled patients. Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. WWLST Withholding and withdrawal life sustaining treatment, SOFA sequential organ failure assessment score, CRP C-reactive protein.

Results

Clinical characteristics of patients and cause of sepsis

A total of 11,981 patients diagnosed with sepsis were enrolled in this study. Of these patients, 7,551 (63.0%) were classified into the no-WWLST group, while 4,430 (37.0%) were included in the WWLST group (Fig. 1). Table 1 presents the patients' baseline characteristics. Patients in WWLST group were older (73.3 ± 13.0 vs. 70.1 ± 13.9 years, $p < 0.001$) and had lower BMI (21.3 ± 4.2 vs. 22.2 ± 4.2, $p < 0.001$). The CCI (6.3 ± 2.5 vs. 5.3 ± 2.5, $p < 0.001$), CFS (5.9 ± 2.0 vs. 4.9 ± 2.1, $p < 0.001$), and SOFA score (7.2 ± 3.2 vs. 5.8 ± 2.9, $p < 0.001$) were higher in the WWLST group than in the no-WWLST group.

Regarding underlying diseases, solid tumors (45.2% vs. 30.6%, $p < 0.001$), hematologic malignancies (8.0% vs. 5.2%, $p < 0.001$), heart failure (7.4% vs. 5.5%, $p < 0.001$), and dementia (17.5% vs. 13.5%, $p < 0.001$) were more frequent in the WWLST group than in the no-WWLST group. Diabetes mellitus (36.5% vs. 31.9%, $p < 0.001$), chronic kidney disease (13.1% vs. 10.2%, $p < 0.001$), and connective tissue disease (3.0% vs. 2.2%, $p = 0.012$) were more common in the no-WWLST group. There were no differences between the two groups based on sex and underlying conditions, such as chronic obstructive pulmonary disease (COPD), liver disease, and cerebrovascular disease.

Laboratory findings revealed that hemoglobin (10.3 ± 2.5 vs. 10.9 ± 2.5, $p < 0.001$), platelet (176.8 ± 126.6 vs. 185.6 ± 114.6, $p < 0.001$), and albumin (2.7 ± 0.7 vs. 3.1 ± 1.2, $p < 0.001$) levels were lower in the WWLST group. In contrast, the white blood cell (WBC) (13.32 ± 12.21 vs. 12.61 ± 10.45, $p < 0.001$), total bilirubin (2.3 ± 4.4 vs. 1.6 ± 2.8, $p < 0.001$), creatinine (1.93 ± 1.69 vs. 1.82 ± 1.89, $p = 0.001$), c-reactive protein (CRP) (14.27 ± 10.15 vs. 12.63 ± 10.14, $p < 0.001$), and lactate (4.66 ± 3.83 vs. 3.28 ± 2.90, $p < 0.001$) levels were higher in the WWLST group.

Table 2 shows the suspected sites of sepsis infection. In all patient groups, most infections were pulmonary (43.8%). In the WWLST group (51.9%) and no-WWLST group (39.1%) groups, pulmonary sepsis was the main cause of sepsis. Sepsis due to abdominal, urinary, and skin/soft tissue infections was more common in the no-WWLST group than in the WWLST group. Sepsis caused by catheter-related and neurologic have no differences between both groups.

Characteristics	All patients	No-WWLST group	WWLST group	P-value
Pulmonary	5,248 (43.8)	2951/7551 (39.1)	2297/4430 (51.9)	<0.001
Abdominal	3377 (28.2)	2249/7551 (29.8)	1128/4430 (25.5)	<0.001
Urinary	2400 (20.0)	1715/7551 (22.7)	685/4430 (15.5)	<0.001
Skin/soft tissue	387 (3.2)	295/7551 (3.9)	92/4430 (2.1)	<0.001
Catheter-related	101 (0.8)	67/7551 (0.9)	34/4430 (0.8)	0.489
Systemic infection without clear primary site of infection	1192 (9.9)	670/7551 (8.9)	522/4430 (11.8)	<0.001
Neurologic	81 (0.7)	57/7551 (0.8)	24/4430 (0.5)	0.169

Table 2. Suspected infection site of sepsis. WWLST withholding and withdrawal life sustaining treatment;

Characteristics	All patients (n = 11,981)	No-WWLST group (n = 7551)	WWLST group (n = 4430)	P-value
In hospital outcome				
Admission to the ICU	900 (7.5)	547/7551 (7.2)	353/4430 (8.0)	0.146
In-hospital mortality	3420 (28.5)	554/7551 (7.3)	2866/4430 (64.7)	<0.001
Hospital stay, days	13.0 (7.0–25.0)	14.0 (8.0–26.0)	11.0 (4.0–24.0)	<0.001
Vasopressors	4044 (33.8)	2474/7551 (32.8)	1570/4430 (35.4)	0.003
Norepinephrine	4017 (33.5)	2450/7551 (32.4)	1567/4430 (35.4)	0.001
Epinephrine	724 (6.0)	269/7551 (3.6)	455/4430 (10.3)	<0.001
Vasopressin	1601 (13.4)	690/7551 (9.1)	911/4430 (20.6)	<0.001
Dopamine	302 (2.5)	172/7551 (2.3)	130/4430 (2.9)	0.027
Inotropic	421 (3.5)	188/7551 (2.5)	233/4430 (5.3)	<0.001
Dobutamine	366 (3.1)	159/7551 (2.1)	207/4430 (4.7)	<0.001
Transfusion	2372 (19.8)	1360/7551 (18.0)	1012/4430 (22.8)	<0.001

Table 3. Intervention and outcome in whole patients (n = 11,981). WWLST withholding and withdrawal life sustaining treatment, ICU intensive care unit.

Treatment and prognosis of patients

Table 3 shows outcomes and interventions in the overall patient population. Hospital mortality was significantly higher in the WWLST group ($p < 0.001$). The WWLST group also received more vasopressors (35.4% vs. 32.8%, $p = 0.003$), inotropes (5.3% vs. 2.5%, $p < 0.001$), and transfusions (22.8% vs. 18.0%, $p < 0.001$). ICU admission rates were 7.2% in the no-WWLST group and 8.0% in the WWLST group, with no significant difference ($p = 0.146$). Supplementary Table 1 shows outcomes and interventions in ICU patients. The WWLST group had higher ICU mortality (54.4% vs. 6.2%, $p < 0.001$) and a longer ICU stay (5.0 [2.0–12.0] vs. 4.0 [2.0–9.0], $p = 0.006$) than the no-WWLST group. The WWLST group received more invasive mechanical ventilation (62.9% vs. 41.9%, $p < 0.001$) and CRRT (40.8% vs. 17.6%, $p < 0.001$) after ICU admission.

Factors associated with WWLST issue

Table 4 shows the results of the univariate and multivariate statistical analyses of the factors related to WWLST issue. Following the multivariate analysis of variables that were significant in the univariate analysis, factors associated with WWLST issue included older age (OR 1.009; 95% CI 1.005–1.013; $p < 0.001$), high CCI (OR 1.103; 95% CI 1.075–1.132; $p < 0.001$), high CFS (OR 1.225; 95% CI 1.198–1.253; $p < 0.001$), high SOFA score (OR 1.149; 95% CI 1.132–1.167; $p < 0.001$), presence of solid tumors (OR 1.967; 95% CI 1.738–2.226; $p < 0.001$), presence of hematologic malignancy (OR 2.392; 95% CI 1.982–2.888; $p < 0.001$), and interventions such as invasive mechanical ventilation (OR 1.511; 95% CI 1.320–1.729; $p < 0.001$) and CRRT (OR 2.540; 95% CI 2.185–2.953; $p < 0.001$). Lower BMI (OR 0.958; 95% CI 0.948–0.969; $p < 0.001$), absence of diabetes (OR 0.707; 95% CI 0.642–0.779; $p < 0.001$), absence of chronic kidney disease (OR 0.469; 95% CI 0.402–0.546; $p < 0.001$), and non-use of vasopressor (OR, 0.679; 95% CI, 0.601–0.767; $p < 0.001$) were also significantly associated with WWLST issue.

Factors associated with in-hospital mortality

Table 5 shows the results of the univariate and multivariate statistical analyses of the factors related to in-hospital mortality. After adjustment of the confounders, predictors of in-hospital mortality were revealed to be old age (OR 1.009; 95% CI 1.005–1.012; $p < 0.001$), high CFS (OR 1.059; 95% CI 1.038–1.079; $p < 0.001$), high SOFA score (OR 1.040; 95% CI 1.026–1.054; $p < 0.001$), solid tumors (OR 1.122; 95% CI 1.035–1.215; $p = 0.005$), high CRP (OR 1.007; 95% CI 1.003–1.011; $p < 0.001$), high lactate (OR 1.074; 95% CI 1.063–1.084; $p < 0.001$) and interventions such as invasive mechanical ventilation (OR 1.239; 95% CI 1.108–1.385; $p < 0.001$), CRRT (OR 1.303; 95% CI 1.176–1.442; $p < 0.001$), and WWLST issue (OR 8.306; 95% CI 7.475–9.229; $p < 0.001$). In addition, low albumin levels (OR 0.893; 95% CI 0.839–0.950; $p < 0.001$) and lower vasopressor use (OR 0.831; 95% CI 0.743–0.929; $p = 0.001$) were related to in-hospital mortality.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, year	1.018	1.015–1.021	<0.001	1.009	1.005–1.013	<0.001
Male	0.961	0.891–1.036	0.297			
Body mass index, kg/m ²	0.952	0.943–0.962	<0.001	0.958	0.948–0.969	<0.001
Charlson comorbidity index	1.172	1.154–1.190	<0.001	1.103	1.075–1.132	<0.001
Clinical frailty scale	1.256	1.233–1.280	<0.001	1.225	1.198–1.253	<0.001
SOFA score	1.160	1.145–1.174	<0.001	1.149	1.132–1.167	<0.001
Underlying disease						
Diabetes mellitus	0.814	0.753–0.881	<0.001	0.707	0.642–0.779	<0.001
Solid tumor	1.873	1.735–2.023	<0.001	1.967	1.738–2.226	<0.001
Chronic kidney disease	0.754	0.670–0.848	<0.001	0.469	0.402–0.546	<0.001
Liver disease	1.045	0.920–1.188	0.495			
Heart failure	1.375	1.184–1.597	<0.001	1.183	0.992–1.409	0.061
Chronic obstructive lung disease	1.006	0.866–1.170	0.934			
Cerebrovascular disease	0.985	0.897–1.082	0.755			
Dementia	1.368	1.236–1.515	<0.001	1.021	0.893–1.167	0.761
Connective tissue disease	0.737	0.579–0.937	0.013	0.805	0.607–1.068	0.132
Hematologic malignancy	1.600	1.378–1.856	<0.001	2.392	1.982–2.888	<0.001
Interventions of the patients						
Vasopressors	1.127	1.042–1.218	0.003	0.679	0.601–0.767	<0.001
Invasive mechanical ventilation	1.537	1.406–1.680	<0.001	1.511	1.320–1.729	<0.001
Continuous renal replacement therapy	2.209	1.973–2.474	<0.001	2.540	2.185–2.953	<0.001

Table 4. Univariate and multivariate Logistic regression analysis addressing the factors for withholding and withdrawal life-sustaining treatment issue. *SOFA* sequential organ failure assessment, *OR* odds ratio, *CI* confidence Interval.

Identification of factors associated with ICU mortality

Supplementary Table 2 shows the results of univariate and multivariate statistical analyses of the factors related to ICU mortality. According to the multivariate analysis, factors of ICU mortality included high CFS (OR 1.082; 95% CI 1.016–1.153; $p=0.014$), low platelet levels (OR 0.998; 95% CI 0.996–0.999; $p<0.001$), high lactate (OR 1.049; 95% CI 1.017–1.082; $p=0.003$), vasopressor use (OR 3.151; 95% CI 1.377–7.208; $p=0.007$), CRRT (OR 1.680; 95% CI 1.257–2.244; $p<0.001$), and WWLST issue (OR 1.669; 95% CI 1.249–2.232; $p=0.001$).

Subgroup analysis in SOFA score

We stratified patients into high SOFA (≥ 6) and low SOFA (<6) groups based on the median SOFA score (6) of the entire sepsis cohort ($n=11,981$) to further investigate the impact of WWLST within different severity levels. Supplementary Table 3 shows that WWLST status showed a statistically significant correlation with mortality in both groups ($p<0.001$, both). Also, in the high SOFA and low SOFA groups, patients who underwent WWLST had higher mortality rates.

Supplementary Tables 4 and 5 show the results of separate analyses for ICU-admitted and ward-admitted patients. In both ICU and ward subgroups, WWLST status showed a statistically significant correlation with mortality in both groups ($p<0.001$, both). Also, in the high SOFA and low SOFA groups, patients who underwent WWLST had higher mortality rates.

Supplementary Table 6 shows ICU admission days and hospital admission days among deceased patients, comparing those with and without WWLST. Interestingly, in both the high SOFA and low SOFA groups, there was no significant difference in ICU or hospital length of stay among deceased patients, regardless of WWLST status.

Supplementary Tables 7 and 8 show Cox multivariate analysis of factors associated with WWLST in both the low SOFA and high SOFA groups. In the high SOFA group, WWLST decisions were significantly associated with old age, lower BMI, higher CCI and CFS, absence of diabetes, CKD, connective tissue disease, presence of solid tumors, heart failure, and hematologic malignancies. In the low SOFA group, in contrast to the high SOFA group, old age, heart failure, and the presence of connective tissue disease did not significantly influence WWLST decisions. We found that mechanical ventilation and CRRT use were strongly associated with WWLST decisions in both high and low SOFA groups.

Discussion

This nationwide multicenter prospective cohort study focused on adult patients diagnosed with sepsis. In this study, we compared and analyzed the characteristics, interventions, and outcomes of patients with sepsis based on the presence or absence of WWLST issues. The WWLST group was significantly older and frailer, with higher CCI, CFS, and SOFA scores. The WWLST group also presented with a higher prevalence of underlying diseases,

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, year	1.014	1.011–1.016	<0.001	1.009	1.005–1.012	<0.001
Male	0.927	0.861–0.997	0.041	1.079	0.998–1.167	0.055
Body mass index, kg/m ²	0.989	0.980–0.998	0.013	1.001	0.992–1.011	0.771
Charlson comorbidity index	1.102	1.088–1.116	<0.001	1.001	0.982–1.022	0.887
Clinical frailty scale	1.135	1.115–1.155	<0.001	1.059	1.038–1.079	<0.001
SOFA score	1.122	1.111–1.134	<0.001	1.040	1.026–1.054	<0.001
Underlying disease						
Diabetes Mellitus	0.938	0.870–1.011	0.094	0.947	0.874–1.025	0.178
Solid tumor	1.425	1.326–1.532	<0.001	1.122	1.035–1.215	0.005
Chronic kidney disease	1.060	0.958–1.174	0.259			
Heart failure	1.236	1.079–1.415	0.002	0.995	0.860–1.151	0.944
Dementia	1.107	0.997–1.230	0.058	0.915	0.808–1.036	0.161
Connective tissue disease	0.915	0.739–1.133	0.413			
Hematologic malignancy	1.064	0.943–1.201	0.312			
Laboratory findings						
White blood cell, $\times 10^3/\mu\text{L}$	1.003	1.000–1.006	0.034	0.999	0.995–1.003	0.553
Platelet, $\times 10^3/\mu\text{L}$	0.999	0.999–0.999	<0.001	1.000	0.999–1.000	0.091
Total bilirubin, mg/dL	1.028	1.021–1.036	<0.001	0.992	0.984–1.001	0.091
Albumin, g/dL	0.608	0.575–0.644	<0.001	0.893	0.839–0.950	<0.001
Creatinine, mg/dL	1.052	1.039–1.066	<0.001	1.011	0.988–1.034	0.343
CRP, ng/mL	1.012	1.008–1.015	<0.001	1.007	1.003–1.011	<0.001
Lactate, mmol/L	1.109	1.100–1.118	<0.001	1.074	1.063–1.084	<0.001
Interventions of the patients						
Vasopressors	1.294	1.204–1.391	<0.001	0.831	0.743–0.929	0.001
Invasive mechanical ventilation	1.565	1.453–1.684	<0.001	1.239	1.108–1.385	<0.001
Continuous renal replacement therapy	2.106	1.944–2.282	<0.001	1.303	1.176–1.442	<0.001
WWLST issue	10.327	9.375–11.375	<0.001	8.306	7.475–9.229	<0.001

Table 5. Univariate and multivariate Cox regression analysis addressing the factors for In-hospital mortality. SOFA sequential organ failure assessment, CRP c-reactive protein, WWLST withholding and withdrawal life sustaining treatment, OR odds ratio, CI confidence interval.

particularly solid tumors and hematologic malignancies, and exhibited differences in laboratory findings. We expected the WWLST group to have fewer ICU admissions and interventions; however, they had approximately the same rate of ICU admissions, more interventions, longer ICU stays, and higher mortality rates.

Patients in the WWLST group were generally older, had a lower BMI, had worse indicators of the patient's overall health, such as CCI and CFS, and had a higher SOFA score, which indicates severity. The WWLST group also had a significantly higher frequency of medical conditions, especially solid tumors. Laboratory test results indicated that markers indicative of severe sepsis, such as CRP and lactate levels¹⁷, were higher in the WWLST group. Both groups showed elevated WBC counts compared to the normal levels. However, WBC counts were higher in the WWLST group than in the no-WWLST group, suggesting a more severe condition in the WWLST group¹⁸. Bilirubin and creatinine levels were also higher in the WWLST group, indicating a higher prevalence of organ failure^{19,20}. These findings are similar to those observed in previous studies on WWLST. Previous research has demonstrated the characteristics of WWLST group. Chang et al. study on septic medical ICU patients found that the group with a DNR directive was older, had higher CCI scores and Acute Physiologic and Chronic Health Evaluation II scores, and had a higher incidence of malignancy compared to the group without DNR directives²¹. Similarly, Serrano and Eanelli reported that the patients opting for WWLST were older²². In a study by Devanand et al. comprising patients admitted to an ICU after out-of-hospital cardiac arrest, patients > 65 years old with a higher CCI index and APACHE II scores were more likely to withdraw from LST²³. The present study found no significant difference in the prevalence of LST issues between the groups with conditions such as COPD, liver disease, and cerebrovascular disease. This observation correlates with the findings of Lee et al. who found that WWLST issue registration was particularly low among patients with progressed COPD or liver cirrhosis²⁴. Conditions such as progressed COPD and liver cirrhosis are legally recognized as end-of-life conditions; however, engagement in end-of-life care is likely to be lower in the patient populations. This suggests the need to expand discussions and counseling on end-of-life issues in these diverse populations.

Before conducting this study, we hypothesized that patients with WWLST issues would be less likely to be admitted to the ICU and receive invasive treatment based on previous research findings. Robert et al. reported that the “limited additional interventions” or “comfort measures only” physician orders for life-sustaining treatment (POLST) group was less likely to receive ICU admission and intervention compared to the “full

treatment” hoping group²⁵. David et al. reported that the POLST group spent fewer days in the hospital and ICU²⁶. Daniel et al. showed that early DNR patients within 48 h of ICU admission underwent significantly fewer non-beneficial procedures²⁷. However, our study showed no statistically significant difference in the ICU admission rates between patients with and without WWLST issues. The ICU admission rate for individuals with and without WWLST issues was 8.0% and 7.0%, respectively, indicating a similar admission rate between the two groups. Furthermore, after ICU admission, WWLST group underwent more invasive treatments, such as ventilator use and CRRT. These findings are similar to those of previous studies on LST in South Korea. Won et al. demonstrated similar ICU admission rates and ventilator use among patients with cancer with and without LST issues¹³. A single-center study by Lee et al. showed a higher incidence of invasive treatments in patients with WWLST issues or those with a formal DNR order²⁸. We also observed that WWLST group had longer ICU admission durations and higher in-hospital mortality rates. This indicates that invasive treatments are more common and are associated with poorer outcomes in patients with WWLST issues.

Although interest in WWLST is growing in Korea, many patients still receive invasive treatments at the end of life. There are several factors contributing to this trend. First, many individuals perceive the terminal stage as the appropriate time for WWLST documentation, resulting in decisions being made in the last moments^{7,15}. Second, Korea’s strong family-centered culture influences end-of-life care, with many viewing aggressive treatment as an expression of love and filial piety²⁹. In addition, societal reluctance to discuss death often leads to unnecessary invasive treatments when comfort care may be more appropriate¹⁶. Kim et al. found that ICU admission and intensive care were more common when WWLST decisions involved family discussion, suggesting that family decisions often deviate from the patient’s own wishes³⁰. Similarly, Kim et al. highlighted that many families in Korea equate continuing LST with fulfilling filial duty, sometimes withholding prognostic information from the patient to avoid distress³¹. Even when an advanced directive for LST is in place, implementation can be challenging. Families may be unaware of or question the authenticity of the directive, leading to disputes and emotional distress that pressure healthcare providers to continue LST against the documented wishes of the patient. Furthermore, the growing number of elderly people living alone in Korea is a concern, as they often have limited awareness of WWLST and end-of-life planning^{15,17,18}. Ensuring that patients understand WWLST, while improving family awareness and respecting patient autonomy, is critical to reducing unnecessary invasive treatments at the end of life.

Analysis revealed that the factors determining WWLST issues increased by 1.009 times in older patients and were associated with lower BMI, worse CCI, CFS, and SOFA scores, and underlying conditions such as solid tumors and hematologic malignancies. In invasive procedures, the use of vasopressors was associated with a decrease in WWLST issues compared with non-use (Table 4, OR 0.679, p value < 0.001). Conversely, procedures involving intubation and CRRT were associated with increased WWLST issue (OR 1.511, 2.540 respectively, p value both < 0.001). Similarly, in the high SOFA group, the WWLST group showed increased use of ventilators and CRRT (Supplementary Table 7, OR 1.505 and 2.498, respectively, p -value both < 0.001). This trend was also observed in the low SOFA group, where ventilator and CRRT use were significantly higher in the WWLST group (Supplementary Table 8, OR 1.807 and 4.428, respectively, p -value both < 0.001). These findings are consistent with those reported in other studies. Park et al. reported that a high CCI and a history of hospitalization influence patients’ self-determination concerning WWLST decisions¹¹. Skjaker et al. reported that older age, high CCI, and higher Simplified Acute Physiology Score II, which represents the illness severity rating for ICU patients, were independently associated with LST restrictions³². In Wu et al. study, age ≥ 85 years, low albumin, and high CCI were independently related to DNR documents³³. Hakim et al. reported that DNR documents were written more rapidly for patients > 75 years old, regardless of their prognosis³⁴. Before this study, we anticipated that dementia would play a significant role in determining decisions regarding WWLST, owing to the increasing prevalence of dementia³⁵ and the economic burden on families³⁶. However, in our study, although dementia was more prevalent in the WWLST group, it was not a significant factor in WWLST decision-making or mortality outcomes. Similar trends were observed in studies from Japan³⁷ and the United States^{38–40}, emphasizing the importance of comprehensive discussions between caregivers and healthcare providers regarding WWLST issues, given the challenges in decision-making and preferences of patients with dementia.

In analyzing the cofactors associated with in-hospital and ICU mortality, our study identified several key risk factors: a high CFS score, elevated lactate levels, use of CRRT, and WWLST issues. These were major contributors to in-hospital and ICU mortality rates. Bruno et al. showed that a high CFS score, high SOFA score, and older age increased the ICU mortality rate⁴¹. Wernly et al. demonstrated the significant impact of CFS on 30-day mortality in older critically ill patients in the ICU⁴². Mendonca et al. and Elseviers et al. reported acute renal failure requiring renal replacement as a risk factor for overall mortality in ICU patients^{43,44}. Other studies revealed that lactate is a valuable predictive marker for ICU mortality^{45–47}. Table 1 shows that the WWLST group had higher CCI, CFS, and SOFA scores, making their higher mortality rate somewhat expected. However, even when stratifying patients based on SOFA score, which is commonly used to assess sepsis prognosis, mortality remained significantly higher in the WWLST group in both the high and low SOFA groups (Supplementary Table 3, both $p < 0.001$). Furthermore, when analyzing only ICU-admitted patients, the WWLST group had significantly higher mortality in both the high and low SOFA groups (Supplementary Table 4, both $p < 0.001$), and this trend was similarly observed in ward-admitted patients (Supplementary Table 5, both $p < 0.001$). Additionally, an analysis of hospital admission days and ICU admission days among deceased patients, stratified by WWLST status, revealed no significant difference between the two groups (Supplementary Table 6). Moreover, in Cox multivariate analysis examining factors associated with WWLST, stratified by high and low SOFA groups, mechanical ventilation and CRRT use were significantly more frequent in the WWLST group (Supplementary Tables 7 and 8). These findings suggest that WWLST decisions were made when patients had already reached a critical stage with minimal survival probability, reinforcing its role as an end-of-life decision rather than an early treatment limitation. The timing of WWLST decisions at the end-of-life stage not only hinders well-dying

but also contributes to an increase in invasive treatments, which may impose a greater economic burden on Korean society. As the population ages, these economic costs are expected to rise further^{2,48}. Therefore, this study highlights the need to ensure that WWLST decisions are not delayed until the end of life but rather made at an appropriate time through discussions between patients and their families to respect the patient's wishes and promote a more ethical and sustainable approach to end-of-life care in Korea.

This study had several strengths. First, using data from a large, nationwide, multicenter cohort in South Korea, this study examines the characteristics and outcomes of patients with sepsis in relation to WWLST decisions. Second, some domestic studies have shown that WWLST issues exhibit different results depending on whether the region is rural or urban^{11,13,24,49}. This study attempted to minimize regional bias using national multicenter data from 16 hospitals of different sizes and locations. Third, the study is unique because it comprehensively analyzed WWLST problems in patients with sepsis in hospitals and was not limited to ICUs.

Our study has some limitations. First, we did not distinguish between withholding and withdrawing LST. As a result, our data includes patients who underwent invasive treatments prior to WWLST documentation. However, this limitation is mitigated by our results, which showed no significant differences in ICU or ward length of stay between deceased patients with and without WWLST. This suggests that WWLST decisions were predominantly made at the end of life, when survival was unlikely, highlighting the need for earlier discussions to align care with patients' values and goals. Second, we did not capture the exact timing of WWLST decisions (e.g., before admission or ICU care). This reflects the retrospective nature of our study and the challenges of obtaining such data in a multicenter cohort. However, our analysis showed that WWLST patients had significantly higher mortality rates regardless of SOFA score, with no significant differences in hospital or ICU length of stay. In addition, mechanical ventilation and CRRT use were strongly associated with WWLST in both high and low SOFA groups, suggesting that WWLST decisions were made when the probability of survival was already extremely low. Future studies should include time-stamped WWLST decisions to assess their impact on patient outcomes. Finally, we did not differentiate between self-determined and family-determined WWLST decisions, which may have influenced clinical outcomes. Nevertheless, our study provides valuable insights into the overall impact of WWLST documentation on end-of-life care. Future research should explore the influence of different decision-making pathways to develop more tailored, patient-centered approaches to WWLST implementation.

Conclusions

We initially expected that the WWLST group would have lower rates of ICU admission and fewer invasive procedures. However, our results showed that ICU admissions and invasive procedures were not significantly reduced and in some cases were more frequent in the WWLST group. This suggests that WWLST decisions were often made late in the clinical course rather than proactively. To align medical care with patient preferences, early discussions about WWLST should be prioritized to ensure that decisions are made before the end of life. Proactive LST planning can help improve both quality of life and quality of death for patients with sepsis.

Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Author contributions

SYK, DHK and SIL contributed to conception and design; All authors contributed to data analysis and interpretation; SYK, DHK and SIL contributed to drafting the manuscript for intellectual content; SYK, DHK, HKJ, and SIL contributed to revision of the manuscript. All the authors have read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Chungnam National University Hospital (approval number: 2019-11-048) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. At enrollment, written informed consent was obtained from each patient or an authorized surrogate.

Additional information

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