

Early Predictors of Ventilator-Free Days and Sustained Ventilatory Dependence in Patients With Sepsis: A Retrospective Cohort Study Using 24-Hour Admission Data

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Background: Sustained ventilatory dependence is associated with increased morbidity, mortality, and healthcare resource utilization in critically ill patients with sepsis. However, the early identification of patients at risk remains challenging, particularly when using variables available at intensive care unit (ICU) admission. This study aimed to identify potential early markers of ventilatory trajectory, assessed primarily using ventilator-free days through day 28 (VFD-28) and secondarily using sustained ventilatory dependence, based only on data obtained within the first 24 hours of ICU admission.

Methods: In this single-center retrospective cohort study, 137 adult patients with sepsis requiring invasive mechanical ventilation were included. The primary outcome was VFD-28, a mortality-inclusive continuous outcome, whereas sustained ventilatory dependence (≥ 7 days from intubation) was a secondary outcome. Demographic, clinical, and laboratory data obtained within the first 24 hours of ICU admission were univariably screened (25 candidates), and a clinically selected multivariate covariate set (age, admission Glasgow Coma Scale (GCS) score, Clinical Frailty Scale score, lactate, albumin, and prior stroke history) was modeled using Tobit regression for VFD-28 and logistic regression for the secondary binary outcome. Admission GCS score was retained as the sole severity measure after a component-overlap analysis indicated that in separate models evaluating each severity score, Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II did not remain independently associated with the outcome, whereas GCS did. Because GCS is itself a shared neurological component of both composite scores, this pattern likely reflects statistical overlap among correlated variables rather than evidence that GCS is a clinically superior severity measure. Cause-specific Cox regression was used to model liberation from ventilation and death while ventilated as competing risks.

Results: Higher admission GCS was independently associated with higher VFD-28 values (Tobit coefficient: 4.58, 95% confidence interval (CI): 1.95–7.20; $p < 0.001$). Sustained ventilatory dependence (a secondary, exploratory binary outcome that cannot by itself distinguish early death from early successful weaning, ≥ 7 days) occurred in 54.0% of patients. Higher admission GCS was independently associated with lower odds of this outcome (adjusted odds ratio (OR): 0.81, 95% CI: 0.72–0.92; $p = 0.001$). This association was also observed in an exploratory sensitivity analysis restricted to the smaller subgroup of patients surviving to day 7 (adjusted OR: 0.59, 95% CI: 0.43–0.80). Neither SOFA nor APACHE II scores remained independently associated with the outcome once component overlap with GCS was accounted for. Cause-specific competing-risks analysis showed that admission GCS was associated with the hazard of liberation from mechanical ventilation (hazard ratio (HR): 1.31, 95% CI: 1.15–1.48; $p < 0.001$) but not with the hazard of death while ventilated ($p = 0.851$), indicating a weaning-specific rather than mortality-related effect. Patients with sustained ventilatory dependence had significantly higher rates of tracheostomy, percutaneous endoscopic gastrostomy (PEG) placement, and prolonged ICU stay.

Conclusions: Admission GCS scores, evaluated in separate models from APACHE II and SOFA, were consistently associated with both ventilator-free days and the secondary binary outcome of sustained ventilatory dependence in patients with sepsis, and they may serve as a potential early marker of ventilatory trajectory in this population. Competing-risks analysis suggested that this association reflects an effect on the speed of weaning rather than on mortality. Given the modest sample size, internal-only validation, and the exploratory nature of several sensitivity analyses, these findings should be regarded as hypothesis-generating rather than confirmatory. A mortality-inclusive ventilator-free-days outcome alongside a single, non-overlapping severity measure may help address known methodological limitations of composite severity scores in this setting, but external validation is needed before these findings could inform individualized ventilatory management or resource allocation.

Keywords: sepsis; mechanical ventilation; ventilator dependence; GCS; ICU; weaning; critical care; ventilator-free days; competing risks

Introduction

Sepsis remains a major global health challenge and a leading cause of morbidity and mortality among critically ill patients [1,2]. Despite advances in early recognition and implementation of guideline-based bundle care, a substantial proportion of patients with sepsis or septic shock require invasive mechanical ventilation (IMV). In intensive care unit (ICU) cohorts, IMV is required in the majority of patients with septic shock. A large multicenter European cohort reported IMV use in 83.9% of septic shock patients admitted to the ICU [3], while administrative database analyses that included less severe, non-ICU hospitalized sepsis patients reported substantially lower overall IMV rates (approx. 21%) [4], reflecting the wide heterogeneity of sepsis severity across care settings and the particularly high burden of respiratory failure among ICU-admitted septic shock patients. Among mechanically ventilated patients, a considerable proportion develop prolonged dependence on ventilatory support [5]. The use of IMV in this population is consistently associated with higher mortality, prolonged ICU length of stay, and substantial healthcare resource utilization [6,7].

Sustained ventilatory dependence further complicates the clinical course of patients. Patients requiring extended ventilatory support face increased risks of ventilator-associated pneumonia, ventilator-induced diaphragmatic dysfunction, ICU-acquired weakness, and long-term functional impairment [8,9]. In sepsis, systemic inflammation, metabolic derangements, and organ crosstalk may further delay weaning and prolong ventilator dependence [10,11].

Prolonged mechanical ventilation (PMV) has traditionally been defined as ≥ 21 consecutive days of mechanical ventilation, particularly in the context of chronic critical illness, as proposed by the National Association for Medical Direction of Respiratory Care (NAMDR) [12,13]. However, there is no universally accepted definition, and substantial heterogeneity exists across studies regarding duration thresholds [5,14]. Moreover, contemporary weaning frameworks, including the International Consensus Conference on Weaning and the Weaning according to a New Definition (WIND) classification, support the clinical relevance of shorter time-based categorizations [15].

Given the need for early and actionable risk stratification in the acute phase of sepsis, shorter durations of mechanical ventilation have also been used to facilitate early prediction of sustained ventilatory support [16]. In this context, the concept of sustained ventilatory dependence can be used to describe patients who remain dependent on ventilatory support during the initial phase of critical illness. This approach is consistent with prior studies that have employed shorter duration thresholds to facilitate early prediction and clinical decision-making [17,18].

In this study, we operationally defined sustained ventilatory dependence as IMV lasting ≥ 7 days from the time of intubation, with the aim of identifying high-risk patients at an early stage of ICU admission rather than redefining classical PMV. To maintain this distinction consistently, all sensitivity analyses in this study, including the alternative ≥ 21 -day threshold reported below, are interpreted strictly within the early risk stratification framework of sustained ventilatory dependence and should not be read as a study of classical PMV populations or outcomes.

Previous studies have identified predictors of sustained ventilatory dependence in heterogeneous ICU populations, including higher illness severity (e.g., Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation [APACHE] II scores), comorbidities, and the extent of organ dysfunction [16,19]. Sepsis-specific predictive models have also been proposed [18]. However, these studies are limited by substantial heterogeneity in studied populations, definitions of PMV, and model construction approaches. Importantly, many rely on variables obtained after the first 24–48 hours of ICU admission or even later during the course of the ICU stay of patients, which limits their utility for early clinical decision-making [20,21].

The early identification of patients at high risk for prolonged ventilatory dependence using only data available within the first 24 hours of ICU admission could facilitate timely risk stratification, individualized weaning strategies, and more efficient allocation of critical care resources [17]. Nevertheless, robust data focusing on early baseline predictors in homogeneous sepsis cohorts remain limited [16,18], particularly from low- and middle-income countries and single-center settings that reflect local microbiology, antimicrobial resistance patterns, and variations in clinical practice [1].

Therefore, this study aimed to identify independent early clinical and laboratory predictors of ventilator-free days through day 28 (VFD-28), a mortality-inclusive continuous outcome, in adult patients with sepsis requiring IMV, using data collected within the first 24 hours of ICU admission. Because prior severity scores combining several correlated physiological components (e.g., APACHE II, SOFA) may not be simultaneously interpretable when modeled together with their individual components (e.g., admission Glasgow Coma Scale [GCS] scores), a further aim was to identify a single, non-overlapping severity measure suitable for early risk stratification. Secondary objectives included evaluating the same predictors for the more conventional binary threshold of sustained ventilatory dependence (≥ 7 days), including its discriminatory performance by receiver operating characteristic (ROC) analysis and a sensitivity analysis restricted to patients surviving to day 7, describing associations between early sustained ventilatory dependence and clinically relevant secondary

outcomes (in-hospital all-cause mortality, tracheostomy requirement, need for renal replacement therapy, and ICU length of stay), and examining the robustness of findings through sensitivity analyses using alternative duration thresholds (≥ 10 , ≥ 14 , and ≥ 21 days).

Methods

Study Design

This was a single-center retrospective cohort study aimed at identifying early clinical and laboratory predictors of sustained ventilatory dependence in mechanically ventilated patients with sepsis. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

Setting and Participants

The study was performed in the medical-surgical ICU of Gazi Yaşargil Training and Research Hospital, University of Health Sciences, a tertiary referral center in Diyarbakır, Türkiye. All adult patients (≥ 18 years of age) admitted to the ICU between January 2025 and December 2025 with a diagnosis of sepsis according to the Sepsis-3 definition [2] were screened for eligibility.

Sepsis was defined as suspected or confirmed infection with an acute increase in the SOFA score of ≥ 2 from baseline.

Inclusion and Exclusion Criteria

Patients were included if they were adult (≥ 18 years) inpatients admitted to the medical-surgical ICU with a diagnosis of sepsis meeting Sepsis-3 criteria [2] (suspected or confirmed infection plus an acute increase in SOFA score of ≥ 2 points. Microbiological confirmation, such as culture positivity, was not a mandatory inclusion requirement, consistent with the Sepsis-3 framework's allowance for clinically suspected infection) and required IMV for more than 24 hours during their ICU stay, with a complete set of baseline demographic, clinical severity (SOFA, APACHE II, GCS, Clinical Frailty Score [CFS], Charlson Comorbidity Index [CCI]), and laboratory variables recorded within the first 24 hours of ICU admission. Exclusion criteria included age younger than 18 years ($n = 18$), ICU length of stay shorter than 24 hours ($n = 12$), mechanical ventilation duration shorter than 24 hours ($n = 9$), incomplete baseline clinical data ($n = 15$), missing laboratory data ($n = 10$), and ICU readmission during the study period ($n = 6$). Accordingly, a total of 70 patients were excluded (**Supplementary Fig. 1**).

Of the 207 consecutive patients with sepsis initially identified based on electronic health records, 137 patients who received IMV met the eligibility criteria and constituted the final sample of the study.

Outcome Definitions

The primary outcome was VFD-28, a mortality-inclusive continuous outcome defined and justified in the Statistical Analysis section. The secondary binary outcome was sustained ventilatory dependence, operationally defined as IMV lasting ≥ 7 days from the day of intubation. This threshold was selected a priori to facilitate the early identification of patients at risk for sustained dependence on ventilatory support during the acute phase of sepsis, and is retained to preserve comparability with prior studies in the relevant literature using this definition.

Although PMV has traditionally been defined as ≥ 21 consecutive days according to the NAMDRRC consensus [12], no universally accepted definition exists, and shorter duration thresholds have increasingly been used in contemporary critical care studies to support early clinically actionable prediction models and ICU resource planning. Accordingly, in this study, the 7-day threshold was used as an early risk stratification endpoint rather than an attempt to redefine classical PMV.

To assess the robustness of the findings across different ventilation durations, sensitivity analyses were performed using alternative thresholds for sustained ventilatory dependence (≥ 10 days, ≥ 14 days, and ≥ 21 days).

Secondary outcomes were as follows:

- In-hospital all-cause mortality, defined as death from any cause during the index hospitalization, ascertained via electronic health records (patients discharged from the ICU alive were followed for in-hospital mortality even if death occurred after ICU discharge and beyond 28 days from ICU admission),
- Need for tracheostomy during ICU stay,
- Need for percutaneous endoscopic gastrostomy (PEG) placement during ICU stay,
- Requirement for renal replacement therapy (RRT) during ICU stay,
- ICU length of stay (in days).

Data Collection

Data were retrospectively collected from the electronic health record system of the hospital by two independent researchers. Any discrepancies were resolved by consensus with a third researcher. Because exclusion criteria 4 and 5 removed patients with incomplete data on key baseline variables at the screening stage (**Supplementary Fig. 1**), the final analytical cohort ($n = 137$) had no missing data for any of the demographic, severity-related, or laboratory variables used in the primary and sensitivity analyses. Therefore, no imputation was required, and all analyses were performed on a complete-case basis.

All baseline variables were recorded within the first 24 hours of ICU admission. Because a minority of patients may have been intubated before or after ICU admission, the 24-hour predictor window does not guarantee perfect temporal alignment with intubation for every patient, and these

variables are, therefore, best regarded as early rather than strictly pre-intubation predictors.

Collected data included:

- Demographic and clinical characteristics: age, sex, comorbidities (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, prior stroke, Alzheimer's disease/dementia, pulmonary arterial hypertension, chronic kidney disease, hematologic malignancy, and solid malignancy), CCI values, and CFS values.

- Severity of illness: SOFA score, APACHE II score, and GCS score at admission.

Severity and frailty scores were calculated using their original published methodologies. The SOFA score (range: 0–24) quantifies dysfunction across six organ systems (respiratory, coagulation, hepatic, cardiovascular, neurological, and renal) [22]. The APACHE II score (range: 0–71) combines acute physiological variables, age, and chronic health status obtained within the first 24 hours of ICU admission [23]. The CFS score (range: 1–9) is a clinician-assessed ordinal scale of pre-admission functional frailty [24]. CCI is a weighted composite of pre-existing comorbid conditions used to estimate 10-year survival [25]. All scores, including baseline SOFA scores, were calculated by the treating ICU team at the bedside using data from the first 24 hours of ICU admission. These bedside-calculated values were subsequently extracted from the electronic health records of patients and verified by trained researchers. Hence, they were not independently recalculated from raw physiological data by the research team. No patient in the final analytical cohort had a missing baseline SOFA value, since incomplete baseline clinical data constituted a pre-specified exclusion criterion. Admission GCS was specifically assessed and recorded at the time of ICU admission, prior to the administration of sedative or analgesic agents in the ICU, to minimize measurement bias associated with pharmacologically altered consciousness.

- Laboratory parameters: blood gas analysis (pH, $p\text{CO}_2$, HCO_3^-), serum lactate, C-reactive protein (CRP), albumin, creatinine, complete blood count (including platelet count), and serum electrolytes (including phosphorus, magnesium, and chloride).

Data on complete blood count parameters (white cell, neutrophil, lymphocyte, and platelet counts, hemoglobin, and hematocrit), serum electrolytes (sodium, potassium, chloride, calcium, magnesium, and phosphorus), glucose, urea, and transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were collected for the general clinical characterization of the cohort but were not considered a priori candidate predictors of sustained ventilatory dependence and are therefore not reported in Table 1 or entered into the predictive models. Mechanical ventilation duration was calculated as the total number of calendar days on IMV from the calendar day of intubation until the calendar day of successful extubation or death (whichever

came first). Re-intubations within 48 hours were considered as the continuation of the same episode.

Available admission blood gas parameters included pH, partial pressure of carbon dioxide ($p\text{CO}_2$), bicarbonate (HCO_3^-), and partial pressure of oxygen ($p\text{O}_2$). $p\text{O}_2$ was screened univariably (**Supplementary Table 1**) but was not associated with the outcome ($p = 0.948$) and is not reported descriptively in Table 1, consistent with the other laboratory parameters not carried forward as candidates. Oxygenation indices such as the $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios could not be reliably calculated because FiO_2 and arterial oxygen saturation data were inconsistently available in the retrospective records. Additionally, because many blood gas parameter measurements were obtained from venous rather than arterial samples and because the sampling source could not be retrospectively ascertained or standardized for individual patients, $p\text{CO}_2$ and HCO_3^- values represent a mixed arterial/venous measurement set, and no arterial-venous conversion was applied. These two parameters are, therefore, reported descriptively (Table 1) but were not entered into the multivariate predictive model.

Variables such as tracheostomy, PEG placement, and RRT administration were recorded but excluded from the primary predictive models, as they typically represent consequences rather than baseline risk factors for prolonged ventilatory dependence.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range (IQR), as appropriate. The normality of distribution was assessed using the Shapiro–Wilk test. Categorical variables are expressed as frequencies and percentages.

For descriptive comparisons, patients were divided into two groups according to the secondary binary outcome (sustained ventilatory dependence: ≥ 7 days vs. < 7 days). Between-group differences were compared using the independent-samples t -test or Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables.

Univariate logistic regression analysis was performed for all available candidate variables, including demographic, comorbidity-related, severity-related, and laboratory variables, to screen for potential predictors of sustained ventilatory dependence. Full univariate results for all 25 candidate variables are reported in **Supplementary Table 1**. Admission GCS ($p = 0.003$) met the pre-specified $p < 0.10$ screening threshold, and prior stroke history approached it ($p = 0.085$). CCI values did not ($p = 0.883$) meet this threshold. $p\text{CO}_2$ also met the $p < 0.10$ threshold ($p = 0.003$, **Supplementary Table 1**) and was excluded in advance from the multivariate model because of the unresolved arterial/venous sampling heterogeneity that precluded the reliable interpretation of its regression coefficient. HCO_3^- did not meet the univariate screening thresh-

Table 1. Baseline characteristics according to sustained ventilatory dependence (≥ 7 days) status.

Variable	Sustained ventilatory dependence (≥ 7 days) (n = 74)	<7 days (n = 63)	Test statistic	p-value
Demographic and Clinical Variables				
Age, years	64.0 (60.2–69.0)	66.0 (59.0–77.0)	Z = -0.57	0.568
Male sex, n (%)	40 (54.1)	31 (49.2)	$\chi^2 = 0.32$	0.571
GCS	9.5 (6.3–12.0)	12.0 (10.0–13.0)	Z = -3.14	0.002
CFS	7.0 (6.0–7.0)	7.0 (5.0–8.0)	Z = -1.08	0.269
CCI	6.0 (5.0–7.0)	6.0 (5.0–7.0)	Z = -0.21	0.830
SOFA	8.0 (6.0–8.0)	8.0 (7.0–8.0)	Z = 0.13	0.892
APACHE II	22.0 (19.0–24.0)	24.0 (19.0–27.5)	Z = -1.14	0.254
Comorbidities, n (%)				
Diabetes mellitus	25 (33.8)	18 (28.6)	$\chi^2 = 0.43$	0.512
Hypertension	41 (55.4)	32 (50.8)	$\chi^2 = 0.29$	0.590
Coronary artery disease	22 (29.7)	20 (31.7)	$\chi^2 = 0.07$	0.799
Congestive heart failure	22 (29.7)	14 (22.2)	$\chi^2 = 0.99$	0.320
Atrial fibrillation	13 (17.6)	11 (17.5)	$\chi^2 = 0.00$	0.987
COPD	17 (23.0)	12 (19.0)	$\chi^2 = 0.31$	0.575
Prior stroke	21 (28.4)	10 (15.9)	$\chi^2 = 3.04$	0.081
Chronic kidney disease	24 (32.4)	22 (34.9)	$\chi^2 = 0.09$	0.759
Solid malignancy	11 (14.9)	7 (11.1)	$\chi^2 = 0.42$	0.517
Hematologic malignancy	3 (4.1)	2 (3.2)	Fisher's exact test	1.000
Admission Laboratory Variables				
pH	7.36 (7.23–7.42)	7.33 (7.26–7.38)	Z = 0.58	0.561
pCO ₂ , mmHg†	42.0 (34.0–56.0)	37.0 (31.9–45.0)	Z = 2.67	0.008
HCO ₃ ⁻ , mmol/L†	23.8 (19.3–26.7)	20.8 (17.2–23.0)	Z = 2.86	0.004
Lactate, mmol/L	2.2 (1.6–3.1)	2.5 (1.9–4.7)	Z = -1.80	0.072
Creatinine, mg/dL	1.4 (0.7–2.0)	1.2 (0.9–2.3)	Z = -0.68	0.495
Albumin, g/L	25.0 (21.0–30.5)	26.0 (22.0–30.5)	Z = -0.48	0.631
CRP, mg/L	120.7 (55.3–207.5)	99.7 (48.6–171.6)	Z = 0.93	0.353

Data are presented as median (IQR) or n (%). Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using Pearson's chi-squared test. Fisher's exact test was used when any expected cell count was <5. Significant *p*-values (*p* < 0.05) are shown in bold. †Blood gas samples were of mixed arterial/venous origin and could not be retrospectively distinguished or converted. pCO₂ and HCO₃⁻ values should, therefore, be interpreted with caution and were not entered into the multivariate model.

old (*p* = 0.785, **Supplementary Table 1**). Although Table 1 shows a statistically significant unadjusted between-group difference in HCO₃⁻ values (Mann–Whitney U test, *p* = 0.004), this reflects a distributional shift rather than a linear association with the outcome and does not contradict the non-significant univariate logistic regression analysis result used for candidate screening. Therefore, HCO₃⁻ was not a candidate for the multivariate model on statistical grounds, independently of the arterial/venous sampling limitation noted above, which nonetheless still applies to its interpretation in Table 1.

Because admission GCS, SOFA, and APACHE II scores share overlapping physiological components (APACHE II incorporates a GCS-derived neurological term, and the neurological sub-score of SOFA is also GCS-based), entering all three simultaneously risks unstable, mutually adjusted coefficients that cannot be interpreted as independent effects, even when variance inflation factors remain below conventional thresholds. To address this issue

directly, we fitted three separate single-score multivariate models, each combining one severity score in turn with age, CFS, lactate, and albumin values. Admission GCS was the only severity-related score that remained an independent, statistically significant predictor when modeled without the other two (*p* = 0.001). APACHE II lost statistical significance when modeled without GCS (*p* = 0.283), and SOFA was not significant in any specification (*p* = 0.344). On this basis, admission GCS was selected as the sole severity measure carried forward into the multivariate model, and neither SOFA nor APACHE II was retained in the main analysis.

The final clinically selected multivariable covariate set, therefore, comprised the age, admission GCS, CFS, lactate, albumin, and prior stroke history parameters. Prior stroke history was included despite narrowly missing the univariate screening threshold (*p* = 0.085) because it is a plausible clinical determinant of ventilator weaning capacity and because omitting it despite the stated *p* < 0.10 rule

was identified as an internal inconsistency in a previous round of review. Its inclusion did not materially change the effect estimates for the other covariates. This clinically selected covariate set was used directly in the multivariate model. An automated backward-stepwise or other data-driven selection procedure was not used, as such procedures are prone to unstable variable selection at this sample size. Results are reported as adjusted odds ratios (ORs) for logistic models, or as Tobit regression coefficients for the primary model described below, with 95% confidence intervals (CIs).

To avoid conflating early death with successful early liberation from mechanical ventilation, a limitation of the binary ≥ 7 -day threshold identified in a previous round of review, the primary outcome for the multivariate analysis was redefined as VFD-28, a continuous, mortality-inclusive outcome. Patients who died during the index hospitalization, or who remained mechanically ventilated at day 28, were assigned VFD-28 = 0. All other patients were assigned 28 minus their total days of IMV. Because the exact calendar date of death was not available for patients who died in a general ward after ICU discharge, all in-hospital deaths were assigned VFD-28 = 0 irrespective of the exact timing of death relative to day 28. This is a deviation from the strict VFD-28 convention, in which non-survivors within the 28-day window are censored at zero [26]. Here, all in-hospital deaths were assigned a VFD-28 value of zero irrespective of timing, which may misclassify a small number of patients who died well after day 28 and is discussed further as a limitation below. Because VFD-28 was left-censored at zero for a large proportion of the cohort (107/137, 78.1%), it was modeled using Tobit (censored-normal) regression [27] with the clinically selected covariate set described above. This Tobit model constitutes the primary analysis of this study.

As a secondary analysis, the original binary outcome (sustained ventilatory dependence, ≥ 7 days) was also modeled using multivariate logistic regression with the same clinically selected covariate set to preserve comparability with the ≥ 7 -day threshold used in existing literature. To further address the conflation of early death and early liberation within the < 7 -day group, we additionally repeated this logistic model within a cohort restricted to patients who survived to the 7th day of mechanical ventilation (i.e., excluding the 43 patients who died while ventilated before day 7; $n = 94$ remaining).

As neither the Tobit nor the logistic multivariate models fully separate the competing processes of death and liberation, a complementary competing-risks framework was additionally applied. Cause-specific Cox proportional hazards models were fitted for (i) liberation from mechanical ventilation (with death treated as a competing/censoring event) and (ii) death while still ventilated (with liberation treated as a competing/censoring event), using mechanical ventilation duration as the time scale and the same

clinically selected covariate set (age, admission GCS, CFS, lactate, albumin, and prior stroke history). Of the 137 patients, 94 died while ventilated (events for the death-hazard model, censored for the liberation-hazard model), and 43 were successfully liberated alive (events for the liberation-hazard model, censored for the death-hazard model). All patients had a fully observed ventilation outcome, so, no additional censoring (e.g., loss to follow-up) occurred. Mechanical ventilation duration (in days) was used as the shared time scale for both events, and this interval time was completely and reliably recorded for all 137 patients. The cause-specific hazards approach was chosen over a Fine–Gray subdistribution hazard model primarily because our research question concerned etiological, covariate-specific associations with the hazard of each process (liberation and death) considered separately, which cause-specific Cox regression estimates directly, rather than the absolute cumulative incidence of one event in the presence of the other, which is the quantity targeted by the Fine–Gray model. Cause-specific Cox regression is the recommended approach for this type of etiological question [28,29]. A secondary, practical consideration is that the Fine–Gray approach requires artificially extending the at-risk period of patients who experienced the competing event up to a common administrative endpoint, and for patients discharged from the ICU before their eventual in-hospital death, we could not reliably reconstruct this extended follow-up window from the available data, which would have complicated a Fine–Gray implementation.

The discriminatory performance of the secondary logistic model was evaluated using the area under the receiver operating characteristic curve (AUC-ROC). Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, together with graphical calibration analysis comparing predicted and observed event probabilities. Since the apparent AUC-ROC is subject to optimism from evaluating the model on the same data used to fit it, an internal validation procedure was additionally performed. In this process, 2000 bootstrap resamples were drawn with replacement, the model was refit in each resample, and the difference between the apparent AUC of the resample and its AUC when applied to the original cohort was averaged to estimate optimism. This optimism was subtracted from the apparent AUC to obtain an optimism-corrected AUC (Harrell’s method). The same bootstrap resampling procedure was used to obtain 95% CIs for the AUCs of admission GCS alone and APACHE II alone.

Pre-specified sensitivity analyses were conducted by repeating the secondary logistic model using alternative duration thresholds for sustained ventilatory dependence (≥ 10 , ≥ 14 , and ≥ 21 days). Subgroup analyses were planned beforehand according to age (≥ 65 years) and baseline SOFA scores (≥ 8).

All statistical tests were two-tailed, and a p -value of < 0.05 was considered statistically significant. Analyses

Table 2. Secondary outcomes according to sustained ventilatory dependence (≥ 7 days) status.

Outcome	Sustained ventilatory dependence (≥ 7 days) (n = 74)	<7 days (n = 63)	Test statistic	p-value
In-hospital mortality, n (%)	51 (68.9)	43 (68.3)	$\chi^2 = 0.01$	0.933
Renal replacement therapy, n (%)	25 (33.8)	14 (22.2)	$\chi^2 = 2.23$	0.135
Tracheostomy, n (%)	31 (41.9)	2 (3.2)	$\chi^2 = 27.90$	<0.001
PEG placement, n (%)	15 (20.3)	3 (4.8)	$\chi^2 = 7.17$	0.007
ICU length of stay, days	29.5 (13.25–74.0)	5.0 (2.5–9.0)	Z = 8.31	<0.001

Data are presented as median (IQR) or n (%). Significant p-values are shown in bold.

were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 137 adult patients with sepsis who required IMV for more than 24 hours were included. The median duration of IMV was 7 days (IQR: 2–25). Sustained ventilatory dependence (≥ 7 days) occurred in 74 patients (54.0%), while 63 patients (46.0%) required ventilation for <7 days.

Because the <7-day group could include both patients who were successfully liberated early and patients who died before reaching the 7-day threshold, we further characterized this group. Among the 63 patients who were ventilated for <7 days, 43 (68.3%) died before liberation, and 20 (31.7%) were successfully weaned within <7 days. Consequently, “<7 days” is not equivalent to successful early weaning, and the binary outcome does not by itself distinguish early death from early liberation. This limitation motivated the complementary cause-specific competing-risks analysis reported below, which separately models liberation from mechanical ventilation and death while ventilated.

Baseline Characteristics

Baseline characteristics according to sustained ventilatory dependence status are presented in Table 1. Age and sex distributions were similar between the groups. Patients who developed sustained ventilatory dependence had significantly lower admission GCS scores (median: 9.5 [IQR 6.3–12.0] vs. 12.0 [IQR 10.0–13.0], $p = 0.002$; Table 1).

There were no significant differences in CFS scores, SOFA scores, APACHE II scores, admission lactate values, or albumin levels between the groups (all $p > 0.05$; Table 1). Median ICU length of stay was substantially longer in patients with early sustained ventilatory dependence (29.5 days [IQR 13.25–74.0] vs. 5.0 days [IQR 2.5–9.0], $p < 0.001$; Table 2).

Predictors of Sustained Ventilatory Dependence

A clinically selected multivariate Tobit (censored-normal) regression model was fitted for VFD-28, using the covariates specified in the Statistical Analysis section (age, admission GCS, CFS, lactate, albumin, and prior stroke).

Higher admission GCS was independently associated with more ventilator-free days (Tobit coefficient: 4.58, 95%

CI: 1.95–7.20; $p < 0.001$). Because Tobit coefficients reflect the effect on the latent variable underlying VFD-28 rather than a strict linear effect on the observed outcome, this is best interpreted qualitatively. Higher admission GCS was associated with more ventilator-free days through day 28.

Age (coefficient: -0.37 , 95% CI: -0.87 – 0.14 ; $p = 0.155$), CFS (coefficient: -2.23 , 95% CI: -5.91 – 1.44 ; $p = 0.234$), lactate (coefficient: 0.16 , 95% CI: -2.58 – 2.91 ; $p = 0.906$), albumin (coefficient: 0.50 , 95% CI: -0.37 – 1.38 ; $p = 0.260$), and prior stroke (coefficient: -10.84 , 95% CI: -27.10 – 5.42 ; $p = 0.191$) were not independently associated with VFD-28. Full model results are presented in Table 3.

Secondary Analysis: Binary Outcome (≥ 7 Days)

As a secondary analysis, the same clinically selected covariate set was used in a multivariate logistic regression model for the original binary outcome (sustained ventilatory dependence, ≥ 7 days) to preserve comparability with prior studies in the relevant literature (Table 3). Higher admission GCS remained independently associated with lower odds of sustained ventilatory dependence (adjusted OR: 0.81, 95% CI: 0.72–0.92; $p = 0.001$), where, each 1-point increase in admission GCS was associated with a 19% decrease in the odds of sustained ventilatory dependence.

A history of prior stroke showed a non-significant trend toward higher odds of sustained ventilatory dependence (adjusted OR: 2.23, 95% CI: 0.90–5.51; $p = 0.083$). The inclusion of this parameter did not materially change the GCS effect estimate relative to models excluding it. Age, CFS, lactate, and albumin outcomes were not independently associated with the sustained ventilatory dependence outcome (all $p \geq 0.14$). No significant multicollinearity problem was detected among the included variables (all variance inflation factors: <2).

Model Performance

ROC analyses showed that the apparent AUC of the secondary logistic model was numerically higher than that of admission GCS or APACHE II alone (Fig. 1). The AUC values were 0.656 (95% CI: 0.565–0.748) for admission GCS alone, 0.557 (95% CI: 0.460–0.655) for APACHE II alone, and 0.701 (95% CI: 0.639–0.810) for the secondary single-score multivariate model. After bootstrap optimism correction (2000 resamples), the AUC for the secondary

Table 3. Univariate screening and pre-specified single-score multivariate models (primary: VFD-28; secondary: sustained ventilatory dependence ≥ 7 days).

Variable	Univariate OR (95% CI)	<i>p</i> -value	Multivariate OR (95% CI) ¹	<i>p</i> -value	Tobit coefficient (95% CI) ²	<i>p</i> -value
Age, years	0.99 (0.97–1.01)	0.462	0.99 (0.96–1.02)	0.481	–0.37 (–0.87–0.14)	0.155
Admission GCS	0.84 (0.75–0.94)	0.003	0.81 (0.72–0.92)	0.001	4.58 (1.95–7.20)	<0.001
CFS	0.99 (0.84–1.17)	0.915	1.05 (0.84–1.31)	0.692	–2.23 (–5.91–1.44)	0.234
Lactate, mmol/L	0.94 (0.83–1.07)	0.337	0.90 (0.78–1.04)	0.143	0.16 (–2.58–2.91)	0.906
Albumin, g/L	0.99 (0.95–1.04)	0.757	1.01 (0.95–1.06)	0.837	0.50 (–0.37–1.38)	0.260
Prior stroke	2.10 (0.90–4.88)	0.085	2.23 (0.90–5.51)	0.083	–10.84 (–27.10–5.42)	0.191

OR, odds ratio; CI, confidence interval. Continuous variables are expressed per unit increase. Univariate results are shown for the six clinically selected covariates only. Full univariate screening results for all 25 candidate variables, including comorbidities and laboratory parameters, are reported in **Supplementary Table 1**. SOFA and APACHE II scores were not entered in the multivariate models because of component overlap with GCS. GCS was retained as the sole severity measure. ¹Secondary multivariate logistic regression model for the binary ≥ 7 -day outcome. ²Primary multivariate Tobit (censored-normal) regression model for VFD-28. Coefficients represent effects on the latent continuous variable underlying the censored VFD-28 outcome and should not be interpreted directly as the number of observed ventilator-free days gained per unit increase in a covariate. This covariate set was clinically selected and not derived by stepwise selection. Significant *p*-values are shown in bold.

model was 0.646, which was no longer clearly higher than the apparent AUC for admission GCS alone (0.656), indicating that the additional covariates (age, CFS, lactate, albumin, and prior stroke) may have added little incremental discriminative value beyond admission GCS once overfitting was accounted for, and admission GCS itself was the main driver of the performance of the model. Calibration was acceptable according to the Hosmer–Lemeshow goodness-of-fit test results ($\chi^2 = 3.79$, $df = 8$, $p = 0.876$), with a Brier score of 0.219 (Fig. 2).

At the optimal predicted-probability threshold (0.514; Youden index: 0.322), sensitivity was 70.3%, specificity was 61.9%, positive predictive value was 68.4%, and negative predictive value was 63.9%.

Day-7-Survivor Sensitivity Analysis

To further isolate the association between admission GCS and ventilator weaning from the competing influence of early death, rather than relying solely on the mortality-inclusive VFD-28 outcome, the secondary logistic model was additionally repeated in a cohort restricted to the 94 patients who survived to the 7th day of mechanical ventilation, excluding the 43 patients who died while ventilated before day 7. In this restricted cohort, admission GCS remained associated with sustained ventilatory dependence (adjusted OR: 0.59, 95% CI: 0.43–0.80; $p = 0.001$), with an apparent AUC of 0.858 (95% CI: 0.793–0.953). The age, CFS, lactate, albumin, and prior stroke parameters were not independently associated with the outcome in this restricted cohort (all $p \geq 0.12$).

Severity-Score Selection Analysis

Because admission GCS, SOFA, and APACHE II scores share overlapping components, entering all three simultaneously in a single model risks unstable, mutually adjusted coefficients that cannot be interpreted as indepen-

dent effects, even though variance inflation factors were <2 for all variables when they were entered together. To resolve this and determine which single score to retain in the clinically selected model above, we fitted three separate multivariate models, each including only one severity score (GCS, SOFA, or APACHE II) together with the age, CFS, lactate, and albumin parameters. Admission GCS remained an independent, statistically significant predictor of sustained ventilatory dependence when modeled without SOFA or APACHE II (adjusted OR: 0.82, 95% CI: 0.72–0.92; $p = 0.001$; model AUC: 0.685). In contrast, APACHE II scores were no longer independently associated with sustained ventilatory dependence when modeled without GCS (adjusted OR: 0.97, 95% CI: 0.90–1.03; $p = 0.283$; model AUC: 0.578), and SOFA scores were not associated with the outcome in any specification (adjusted OR: 1.12, 95% CI: 0.89–1.40; $p = 0.344$; model AUC: 0.575). On this basis, admission GCS, rather than SOFA or APACHE II, was selected as the sole severity measure retained in the clinically selected multivariate model reported above.

Competing Risk Analysis

As neither the primary (VFD-28) nor the secondary (binary) multivariate models fully separated the competing processes of death and liberation, cause-specific Cox proportional hazards models were additionally fitted for liberation from mechanical ventilation and for death while ventilated, using the same clinically selected covariate set (Table 4). Higher admission GCS was associated with a higher cause-specific hazard of liberation from mechanical ventilation (HR: 1.31, 95% CI: 1.15–1.48; $p < 0.001$) but was not associated with the hazard of death while ventilated (HR: 0.99, 95% CI: 0.93–1.07; $p = 0.851$). This direction-specific pattern suggested that the association of admission GCS may be more closely related to the rate of liberation from mechanical ventilation than to mortality risk.

ROC Curves for Sustained Ventilatory Dependence

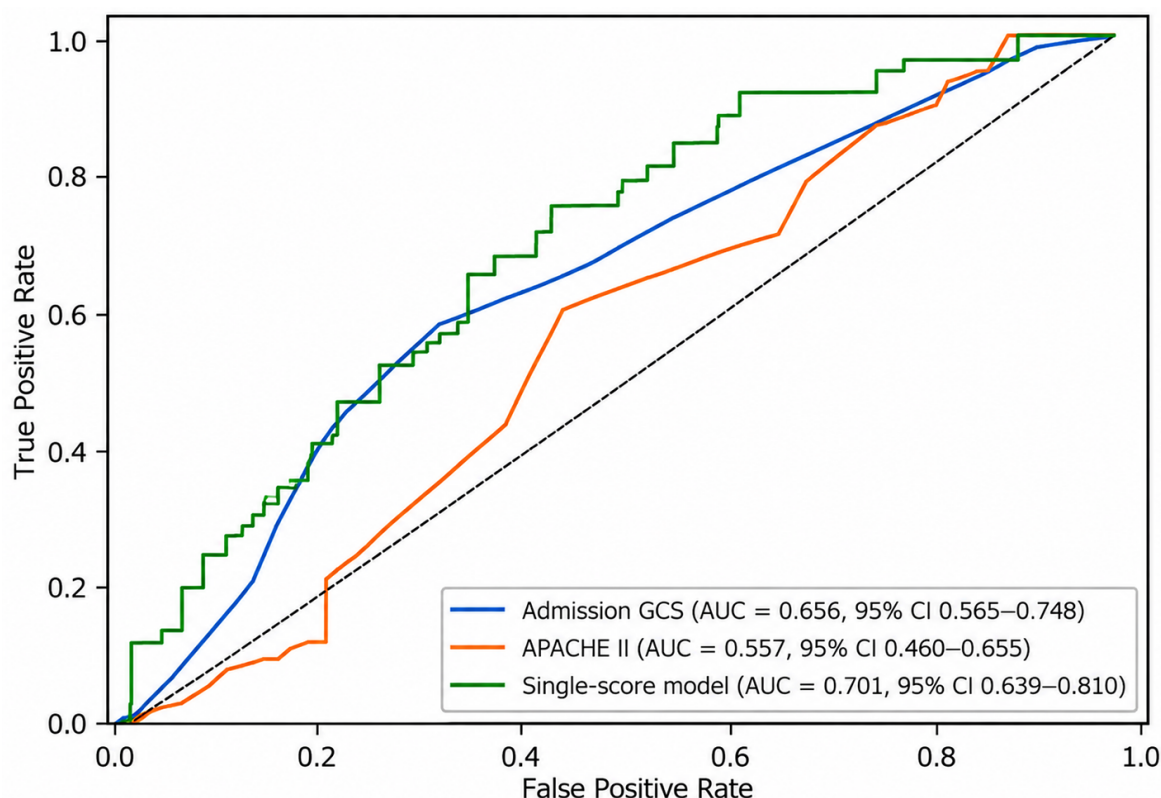


Fig. 1. Receiver operating characteristic (ROC) curves for the secondary binary outcome (sustained ventilatory dependence, ≥ 7 days), comparing admission GCS alone, APACHE II alone, and the secondary single-score multivariate model. The apparent discriminative performance of the secondary model was numerically higher than either individual predictor alone. Ninety-five percent confidence intervals (bootstrap, 2000 resamples) are shown for all three AUCs in the legend, as annotated in the legend.

Table 4. Cause-specific cox proportional hazards models for liberation from mechanical ventilation and death while ventilated.

Outcome	Variable	HR (95% CI)	p-value
Liberation from MV (death = competing event)	Age, years	0.98 (0.96–1.00)	0.061
	Admission GCS	1.31 (1.15–1.48)	<0.001
	CFS	0.80 (0.68–0.94)	0.007
	Lactate, mmol/L	1.05 (0.92–1.21)	0.464
	Albumin, g/L	1.01 (0.97–1.06)	0.637
	Prior stroke	0.20 (0.07–0.57)	0.003
Death while ventilated (liberation = competing event)	Age, years	1.025 (1.004–1.047)	0.020
	Admission GCS	0.99 (0.93–1.07)	0.851
	CFS	1.17 (1.01–1.36)	0.043
	Lactate, mmol/L	1.04 (0.97–1.12)	0.279
	Albumin, g/L	1.02 (0.99–1.06)	0.149
	Prior stroke	0.75 (0.45–1.25)	0.268

HR, hazard ratio; CI, confidence interval; MV, mechanical ventilation. Models adjusted for the clinically selected single-score covariate set (age, admission GCS, CFS, lactate, albumin, and prior stroke). SOFA and APACHE II scores were not included. For each outcome, the competing event was treated as censored (cause-specific hazards approach). Of 137 patients, 94 died while ventilated (events for the death model, censored for the liberation model), and 43 were liberated alive (events for the liberation model, censored for the death model). All patients had a fully observed outcome. Significant *p*-values ($p < 0.05$) are shown in bold.

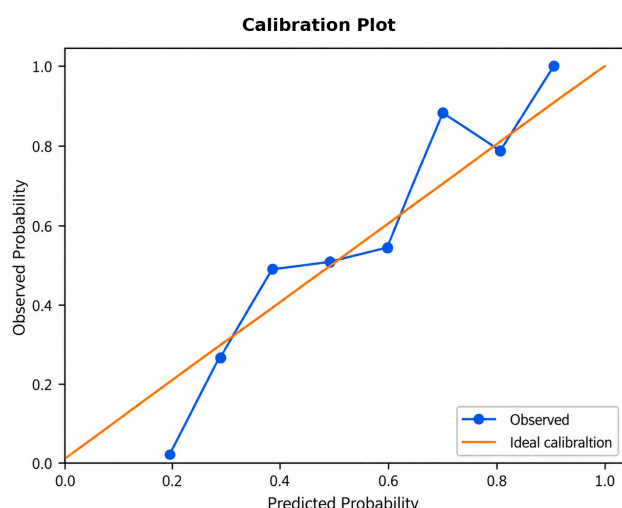


Fig. 2. Calibration plot comparing predicted and observed probabilities of sustained ventilatory dependence (≥ 7 days). The model demonstrated good agreement between predicted and observed outcomes.

Higher CFS scores were associated with both a lower hazard of liberation (HR: 0.80, 95% CI: 0.68–0.94; $p = 0.007$) and a higher hazard of death while ventilated (HR: 1.17, 95% CI: 1.01–1.36; $p = 0.043$), suggesting that frailty affects both weaning capacity and mortality risk. A history of prior stroke was associated with a significantly lower hazard of liberation (HR: 0.20, 95% CI: 0.07–0.57; $p = 0.003$) but not with the hazard of death (HR: 0.75, 95% CI: 0.45–1.25; $p = 0.268$), consistent with a specific effect on weaning capacity rather than survival. Older age was associated with a higher hazard of death while ventilated (HR: 1.025, 95% CI: 1.004–1.047; $p = 0.020$) but not with liberation (HR: 0.98, 95% CI: 0.96–1.00; $p = 0.061$).

Of the 137 patients, 94 died while ventilated (events for the death-hazard model, censored for the liberation-hazard model), and 43 were successfully liberated alive (events for the liberation-hazard model, censored for the death-hazard model). All patients had a fully observed ventilation outcome, so no additional censoring (e.g., loss to follow-up) occurred. Mechanical ventilation duration was used as the shared time scale for both events, and this interval was completely and reliably recorded for all 137 patients.

Sensitivity Analyses

Pre-specified sensitivity analyses were conducted by repeating the secondary logistic model, using the single-score covariate set, with alternative duration thresholds for sustained ventilatory dependence (≥ 10 , ≥ 14 , and ≥ 21 days). Across all threshold models, higher admission GCS remained consistently and independently associated with a lower likelihood of sustained ventilatory dependence (ad-

justed OR range: 0.81–0.87, all $p < 0.05$). Detailed results are presented in Table 5.

Subgroup Analyses

Pre-specified subgroup analyses stratified by age (≥ 65 vs. < 65 years) and baseline SOFA scores (≥ 8 vs. < 8) were performed to explore potential effect modifications (Table 6). The association between lower admission GCS and sustained ventilatory dependence was stronger in patients aged < 65 years (univariate OR: 0.74, 95% CI: 0.62–0.89; $p = 0.002$) than in patients aged ≥ 65 years (OR: 0.93, 95% CI: 0.80–1.08; $p = 0.313$). Conversely, the inverse association between APACHE II scores and sustained ventilatory dependence was more pronounced in older patients (≥ 65 years, OR: 0.88, 95% CI: 0.80–0.97; $p = 0.014$; SOFA ≥ 8 : OR: 0.92, 95% CI: 0.85–0.99; $p = 0.033$) than in younger patients or those with lower baseline SOFA scores (both $p > 0.10$). Given the reduced sample size within each subgroup, no formal interaction terms were tested, and these stratified comparisons should be regarded as, at most, exploratory descriptions of the data rather than evidence of genuine effect modification. The apparent differences between strata should not be interpreted as a confirmed comparative finding and require confirmation in larger, adequately powered cohorts. This table retains APACHE II alongside admission GCS for descriptive completeness and comparability with the univariate screening presented in **Supplementary Table 1**. Since these unadjusted, stratum-specific associations are not corrected for the component overlap between GCS and APACHE II, the APACHE II associations shown here should not be interpreted as evidence of an independent effect and are presented for descriptive purposes only.

Secondary Outcomes

Sustained ventilatory dependence was associated with greater resource utilization (Table 2). Tracheostomy was required significantly more frequently in patients with sustained ventilatory dependence (41.9% vs. 3.2%, $p < 0.001$; Table 2).

PEG placement was also more common in these patients (20.3% vs. 4.8%, $p = 0.007$; Table 2).

There was no significant difference in terms of in-hospital all-cause mortality rates between the groups (68.9% vs. 68.3%, $p = 0.933$; Table 2).

The need for RRT was numerically higher in the sustained ventilatory dependence group, but this difference did not reach statistical significance (33.8% vs. 22.2%, $p = 0.135$; Table 2).

Discussion

This single-center retrospective cohort study showed that admission GCS score were consistently associated with the primary outcome of VFD-28 and with the secondary and exploratory outcome of sustained ventilatory depen-

Table 5. Sensitivity analyses using alternative thresholds for sustained ventilatory dependence.

Threshold for sustained ventilatory dependence	Variable	Adjusted OR	95% CI	<i>p</i> -value
≥7 days	Admission GCS	0.81	0.72–0.92	0.001
≥10 days	Admission GCS	0.86	0.77–0.97	0.012
≥14 days	Admission GCS	0.87	0.78–0.98	0.024
≥21 days	Admission GCS	0.87	0.77–0.99	0.030

For each threshold, the adjusted OR for admission GCS is from the clinically selected single-score multivariate model (age, GCS, CFS, lactate, albumin, and prior stroke), applied to the binary outcome redefined at each alternative duration threshold. SOFA and APACHE II scores were not included, consistent with the primary and secondary models reported in Table 3. OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale.

Table 6. Pre-specified subgroup analyses (univariate associations).

Subgroup	n (events)	Variable	OR (95% CI)	<i>p</i> -value
Age ≥65 years	67 (33)	Admission GCS	0.93 (0.80–1.08)	0.313
		APACHE II score	0.88 (0.80–0.97)	0.014
Age <65 years	70 (41)	Admission GCS	0.74 (0.62–0.89)	0.002
		APACHE II score	1.06 (0.97–1.15)	0.209
SOFA ≥8	77 (40)	Admission GCS	0.89 (0.77–1.03)	0.119
		APACHE II score	0.92 (0.85–0.99)	0.033
SOFA <8	60 (34)	Admission GCS	0.75 (0.62–0.92)	0.005
		APACHE II score	1.08 (0.97–1.21)	0.164

OR, odds ratio (per 1-unit increase); CI, confidence interval. Univariate logistic regression within each subgroup; models not adjusted for other covariates due to limited subgroup sample size. Significant *p*-values (*p* < 0.05) are shown in bold.

dence (≥7 days). Because this binary threshold cannot by itself distinguish patients who died before liberation from those who survived without prolonged ventilation, it is not regarded as the primary clinical evidence in this study. A competing risks analysis was performed to aid in the interpretation of this distinction. These findings were obtained from 137 critically ill patients with sepsis requiring IMV. In separate models evaluating each severity score, SOFA and APACHE II did not remain independently associated with either the primary or the secondary outcomes, whereas admission GCS did. Thus, GCS was retained as the sole severity measure in the clinically selected multivariate models.

Importantly, our study focused on an early and clinically actionable phenotype of sustained ventilatory dependence rather than the classical definition of PMV. While PMV has traditionally been defined as ≥21 days of mechanical ventilation [12], our aim was to identify patients at risk during the early phase of critical illness, when clinical decisions regarding weaning strategies and resource allocation are most relevant [13,30].

Admission GCS showed the most consistent association across the analyses performed in this study, including the primary Tobit model, the secondary logistic model, the day-7-survivor-restricted sensitivity analysis, and the cause-specific competing-risks model. In the Tobit model, higher admission GCS was associated with a higher value

of the latent variable underlying VFD-28, while in the secondary logistic model, each 1-point increase in GCS was associated with a 19% reduction in the odds of sustained ventilatory dependence. This association was also observed in the exploratory analysis restricted to patients surviving to day 7 (adjusted OR: 0.59), although this restricted analysis was subject to conditioning-related selection bias and should be interpreted cautiously. This finding aligned with previous studies in the relevant literature demonstrating that neurological status at ICU admission is a strong determinant of weaning success and duration of mechanical ventilation [31,32,33]. Impaired consciousness may reflect both direct central nervous system involvement and the severity of systemic inflammation, metabolic encephalopathy, or increased sedative requirements, all of which can prolong ventilator dependence [34,35].

In an earlier analysis of this cohort, admission APACHE II scores also appeared as an independent, counterintuitive inverse predictor of sustained ventilatory dependence, which we interpreted as reflecting a competing risk of early mortality (survivor bias). However, when GCS, SOFA, and APACHE II scores, which share overlapping physiological components, including a GCS-derived neurological term in APACHE II and a GCS-based neurological sub-score in SOFA, were modeled separately rather than jointly, APACHE II no longer remained independently as-

sociated with the measured outcome (adjusted OR: 0.97, 95% CI: 0.90–1.03; $p = 0.283$), whereas GCS remained statistically significantly associated with the outcome across the evaluated model specifications. Cause-specific Cox regression using the single-score covariate set corroborated this pattern from a different angle. Here, admission GCS was associated with the cause-specific hazard of liberation from mechanical ventilation (HR: 1.31, 95% CI: 1.15–1.48; $p < 0.001$) but not with the hazard of death while ventilated (HR: 0.99, 95% CI: 0.93–1.07; $p = 0.851$), indicating a weaning-specific rather than mortality-related effect. We, therefore, no longer interpret the previously reported APACHE II association as an independent finding, and it more likely reflected a statistical artifact of jointly modeling structurally overlapping severity scores, compounded by the competing risk of early mortality among the sickest patients, a pattern also reported in other high-mortality critical care cohorts [36,37]. This revision illustrates the importance of explicitly testing for score component overlap before attributing independent predictive value to multiple correlated severity indices. The competing-risks analysis also revealed two further, direction-specific associations worth highlighting. CFS scores were associated with both a lower hazard of liberation from mechanical ventilation and a higher hazard of death while ventilated, suggesting that frailty, unlike admission GCS, affects both weaning capacity and survival, consistent with the recognized role of frailty as a marker of reduced physiological reserve across multiple organ systems rather than a single neurological pathway. A history of prior stroke, in contrast, was associated with a significantly lower hazard of liberation but not with the hazard of death, a pattern consistent with a specific effect on weaning capacity (e.g., through impaired airway protection, respiratory muscle weakness, or swallowing dysfunction) rather than on overall survival.

The secondary logistic model, constructed exclusively with variables available within the first 24 hours of ICU admission, achieved modest discriminative performance in the full cohort (AUC-ROC: 0.701, optimism-corrected: 0.646) but substantially better performance when restricted to patients who survived to day 7 (AUC: 0.858), once the competing influence of early death was removed. This pattern suggests that admission GCS may be more closely associated with ventilatory trajectory among patients surviving to day 7, and the more modest full-cohort AUC may partly reflect the noise introduced by conflating early death with prolonged ventilation in a single binary outcome, the concern that motivated our adoption of VFD-28 as the primary outcome. Nevertheless, this subgroup analysis was exploratory and susceptible to selection bias. The calibration of the secondary model was acceptable according to the Hosmer–Lemeshow test and Brier score. Sensitivity analyses using alternative duration thresholds (≥ 10 , ≥ 14 , and ≥ 21 days) showed directionally consistent associations between admission GCS and the binary outcome.

Sustained ventilatory dependence was strongly associated with increased healthcare resource utilization, including higher rates of tracheostomy and PEG placement, and significantly prolonged ICU length of stay (Table 2). These are reported as descriptive secondary outcomes rather than as evidence of predictive or causal association, since they are themselves direct consequences of prolonged ventilation rather than independent risk factors. These findings were consistent with prior studies demonstrating that prolonged ventilatory dependence is associated with increased resource use and long-term healthcare burden [38,39,40,41]. In-hospital mortality did not differ significantly between groups (68.9% vs. 68.3%), consistent with the cause-specific hazard analysis results above. Frailty (CFS scores) and age, rather than admission GCS, were the variables independently associated with the hazard of death while ventilated in our cohort.

Our study has several strengths. First, we focused on a relatively homogeneous cohort of mechanically ventilated patients with sepsis defined according to Sepsis-3 criteria, unlike many previous studies that included mixed ICU populations. Second, all predictor variables were strictly limited to the first 24 hours of ICU admission, enhancing the applicability of the model for early clinical decision-making. Third, the study was conducted in a middle-income country setting, providing valuable real-world data from a region where local microbiology, antimicrobial resistance patterns, and resource constraints differ from high-income settings. Finally, the use of multiple duration thresholds in sensitivity analyses allowed the assessment of the consistency of the observed associations across alternative definitions.

From a clinical perspective, these findings are exploratory and hypothesis-generating rather than immediately actionable. If externally validated, the early identification of patients with potentially prolonged ventilatory trajectories could eventually contribute to individualized ventilator management, optimization of sedation strategies, early rehabilitation planning, timely consideration of tracheostomy in selected patients, ICU resource allocation, and communication with the families of patients regarding anticipated clinical course and prognosis. At present, however, these remain potential future applications rather than validated clinical recommendations.

Some limitations of this study should also be acknowledged. First, the single-center retrospective design of the study limits the generalizability of the findings and introduces the possibility of residual confounding and selection bias. In particular, the inclusion criterion of IMV for more than 24 hours necessarily excluded patients who were extubated very early, which may have selected for a cohort with somewhat greater baseline severity than an unrestricted sepsis population and could have affected the generalizability of the reported associations to patients with very brief ventilation courses. Second, the relatively small sample size

may have reduced statistical power for subgroup analyses and increased the risk of model overfitting despite clinically guided variable selection. From a related perspective, the secondary binary outcome of sustained ventilatory dependence cannot by itself distinguish early death from early successful weaning and should not be regarded as the primary evidence for clinical prediction in this study. Notwithstanding, it is retained only for comparability with prior studies in the literature and interpreted alongside the primary VFD-28 analysis and the competing-risks analysis. Third, important respiratory severity markers, including the $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios, could not be evaluated because FiO_2 and arterial oxygen saturation data were not consistently available in the retrospective records, and many blood gas measurements were obtained from venous samples. Consequently, respiratory assessment was limited to available admission blood gas parameters, such as pH, PCO_2 , and HCO_3^- . As the latter two reflected a mixed arterial/venous sample source that could not be standardized, they were reported descriptively but excluded from the multivariate predictive model, and subgroup analyses by age and baseline SOFA scores should be regarded as exploratory, given the limited sample size within the strata.

Furthermore, cause-specific Cox regression was used to examine the competing processes of liberation from mechanical ventilation and death because our competing-risk research question concerned covariate-specific hazards for each process rather than the absolute cumulative incidence targeted by a Fine–Gray subdistribution hazard model. A Fine–Gray model was, therefore, not the primary analytical choice, though reconstructing the extended follow-up windows it requires for patients who experienced the competing event would, in any case, have been complicated by incomplete event-time data for patients discharged from the ICU before their eventual in-hospital death. Therefore, these competing-risk findings should be regarded as complementary and hypothesis-generating, pending confirmation in prospective cohorts with standardized event-time ascertainment.

Two further limitations relate specifically to the primary and sensitivity analyses introduced in this revision. First, the primary Tobit model for VFD-28 assigned a value of zero to any patient who died during the index hospitalization, regardless of the exact timing of death relative to day 28, because exact death dates were not available for patients who died after transfer from the ICU to a general ward. This was a deviation from the strict VFD-28 convention and meant that a small number of patients who died well after day 28 were treated identically to patients who died on day 1, which could attenuate or bias the estimated covariate effects. Moreover, the large proportion of structural zero values (107/137, 78.1%) meant that a conventional Tobit model may not have fully captured the complex mixture of mortality-related zeros and censored ventilation outcomes underlying VFD-28. Thus, the To-

bit estimates should be interpreted cautiously and considered hypothesis-generating. On a related point, only 30 of 137 patients (21.9%) contributed an uncensored (non-zero) VFD-28 value. This small effective sample for the continuous portion of the outcome, combined with the large proportion of structural zeros noted above, means that the corresponding coefficients, particularly for covariates other than admission GCS scores, should be interpreted cautiously and considered preliminary, pending replication in a larger cohort. Second, the sensitivity analysis restricted to the 94 patients who survived to the 7th day of ventilation was conditioned on survival to that time point. While this analysis was designed specifically to remove the confounding effects of early death from the weaning-related association of interest, conditioning on survival to a later time point could itself introduce a form of selection bias (a variant of immortal-time bias [42]) if the covariates of interest also influenced the probability of surviving to day 7. This restricted analysis should, therefore, be interpreted as a robustness check that isolated the weaning-specific signal under a stated conditioning assumption, rather than as an unconditional estimate of effect in the entire population.

Additionally, potentially relevant clinical variables, including the source of sepsis, adequacy of early resuscitation, detailed microbiological findings, ventilator mechanics, and anthropometric measurements, such as the body mass index, were not systematically recorded in the electronic medical records, and therefore, they could not be incorporated into the analyses. The moderate discriminative performance of the model further suggested that additional predictors, including dynamic variables beyond the first 24 hours or biomarkers such as procalcitonin or interleukin-6, may have improved predictive accuracy. Finally, although calibration was acceptable based on statistical testing, graphical calibration assessment should be interpreted cautiously given the limited sample size.

Two additional points regarding time-zero and score sourcing warrant explicit acknowledgment. First, baseline predictor variables were defined as those available within the first 24 hours of ICU admission, whereas the primary outcome clock began at the time of intubation. Because a minority of patients may have been intubated prior to ICU admission (e.g., in the emergency department), the 24-hour predictor window and the intubation-referenced outcome window were not perfectly aligned for every patient. Both were anchored to ICU admission for consistency of measurement, but this potential misalignment could not be fully resolved retrospectively and is noted as a limitation. Prospective studies should standardize the zero point to either ICU admission or intubation uniformly. Second, SOFA and APACHE II scores were calculated in real time by the treating ICU team using bedside FiO_2 values available at the point of care, whereas a discrete FiO_2 field was not consistently captured in the retrospective electronic data extraction process used for this analysis. This explains why

PaO₂/FiO₂-based indices could not be reconstructed post hoc even though the original SOFA and APACHE II respiratory sub-scores were complete.

Conclusions

In conclusion, this study demonstrates that lower admission GCS, evaluated in a model separate from global illness-severity scores such as APACHE II or SOFA, was the severity indicator most consistently associated with both ventilator-free days and sustained ventilatory dependence in this cohort, an association that appears related to an effect on the speed of liberation from mechanical ventilation rather than on mortality. When the physiological overlap among GCS, SOFA, and APACHE II scores was explicitly accounted for by modeling each score separately, only GCS remained associated with the outcome in this cohort. As GCS is a shared neurological component of both composite scores, this pattern cannot simply be interpreted as GCS being clinically superior to SOFA or APACHE II, and the previously observed APACHE II association may be more parsimoniously explained as a statistical artifact of score overlap and early-mortality competing risk than as an independent illness-severity effect. Nonetheless, this interpretation remains exploratory given the single-center design and modest sample size of this study. These findings suggest a potential role for a single, non-overlapping bedside severity measure and a mortality-inclusive outcome (ventilator-free days) in early risk stratification in this population, but they should be regarded as hypothesis-generating rather than confirmatory. External validation is needed before these observations could inform individualized weaning strategies, resource allocation, or clinical decision-making. Prospective multicenter studies incorporating larger cohorts, complete death-timing data, and competing-risk methodologies are warranted to validate and extend these findings.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization, AD and SK; methodology, AD; formal analysis, AD; investigation, AD and SK; data curation, AD; writing—original draft, AD; writing—review and editing, AD and SK; visualization, AD; supervision, SK. Both authors gave final approval of the version to be published. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Gazi Yaşargil Training and Research Hospital (approval number: 176; date of approval: 24 April 2026). Patient consent was waived by the Ethics Committee due to the retrospective nature of the study and the use of anonymized data collected during routine clinical care.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.24976/Discover.Med.202638213.252>.

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