Original Paper

Admission Acute Brain Dysfunction and In-ICU Mortality in a Single-Center Pre-Vaccination Romanian COVID-19 Cohort: A Retrospective Observational Analysis

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ABSTRACT: Background: Critically ill COVID-19 patients frequently develop organ dysfunction and acute brain dysfunction with features overlapping sepsis-associated encephalopathy (SAE). Real-world cohorts from Eastern European intensive care during the pre-vaccination period are scarce. Methods: We retrospectively analysed 389 consecutive adults with RT-PCR-confirmed SARS-CoV-2 admitted to a single regional Romanian tertiary ICU during 2020-2021, entirely preceding population-level vaccination. Organ dysfunction was defined as admission SOFA≥2, and acute brain dysfunction was op-erationalised from admission Glasgow Coma Scale and neurological SOFA (the acute brain dysfunction [ABD] proxy). Associations with in-ICU mortality were examined descriptively, with pre-specified sensitivity analyses restricted to non-ventilated pa-tients to address sedation confounding. Results: In-ICU mortality was 65.8%. The ABD proxy was present in 49.6% of the cohort; mortality was 96.9% in ABD-proxy-positive patients versus 45.9% in those with preserved consciousness, an absolute difference of 51.0 percentage points, which was of similar magnitude (49.4 points) in non-ventilated patients, arguing against sedation as the sole explanation. Higher inflammatory markers accompanied the ABD proxy, and the association between admission acute brain dys-function and mortality was consistent across analyses. Conclusions: Admission acute brain dysfunction was strongly associated with in-ICU mortality, and this association persisted in non-ventilated patients. The findings are descriptive associations within an extreme, single-center pre-vaccination cohort under surge conditions; they are not causal, and should not be generalised to vaccinated or contemporary critical care.

KEYWORDS: *COVID-19, critical care, multiple organ dysfunction syndrome, sepsis-associated encephalopathy, acute brain dysfunction, intensive care epidemiology.*

Introduction

Sepsis remains one of the leading causes of death in modern healthcare systems, accounting for an estimated 11 million deaths globally each year and consuming a disproportionate share of intensive care resources [1].

Despite three decades of incremental advances in early recognition, source control, antimicrobial stewardship, and goal-directed resuscitation, sepsis-related mortality in critically ill patients persists in the range of 25-40% across high-income settings [2], and substantially higher figures have been reported from referral cohorts of late-stage disease and from low- and middle-income systems [3].

The clinical syndrome that links the initial dysregulated host response to fatal outcome is multiple organ dysfunction syndrome (MODS), the cumulative, often non-linear failure of two or more organ systems that, once established, is notoriously refractory to current standard-of-care interventions [4].

The COVID-19 pandemic disrupted both the epidemiology and the delivery of intensive care. Critically ill SARS-CoV-2 patients frequently met SOFA-based criteria for organ dysfunction through viral pneumonia-driven respiratory failure and the dysregulated host response, with secondary bacterial superinfection in a substantial proportion [5].

Whether severe COVID-19 should be considered viral sepsis under the Sepsis-3 framework or a distinct entity remains debated [6].

We note that the Sepsis-3 framework operationalises organ dysfunction through the SOFA score; the quick SOFA (qSOFA) screening tool is a separate instrument, and the Surviving Sepsis Campaign has recommended against its use as a single screening tool for sepsis. All sepsis- and organ-dysfunction-

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related derivations in this study are based on the full SOFA score and its components, not on qSOFA. Reported ICU mortality of severe COVID-19 ranged widely (25-80%) across centres, time periods, and pandemic waves, with consistently higher figures in resource-constrained or saturated systems and during early pre-vaccination waves before standardized therapeutic protocols (dexamethasone, immunomodulation) were widely implemented [7].

In Eastern European intensive care units, including those in Romania, the combined effect of high baseline cardiometabolic comorbidity, regional disparities in pre-hospital care, and unprecedented surge demand produced ICU cohorts of exceptional severity, the epidemiology of which has been only partially characterized in the international literature [8].

Among the organ systems affected by critical illness, the brain is both highly vulnerable and clinically underdiagnosed. Sepsis-associated encephalopathy (SAE), an acute, diffuse cerebral dysfunction occurring in the setting of systemic infection without direct central nervous system involvement, has been reported in 10-70% of septic patients depending on the diagnostic threshold applied, and is consistently associated with a two- to three-fold increase in short-term mortality, prolonged ICU stay, and persistent neurocognitive deficits in survivors [9].

In the COVID-19 setting, neurological manifestations of critical illness were particularly common, raising the question of whether SARS-CoV-2 critical care produces a clinical phenotype of acute brain dysfunction with mechanistic and prognostic features overlapping with classical SAE [10].

Acute brain dysfunction has been described as more frequent and prolonged in COVID-19 ICU patients than in other forms of acute respiratory failure [11], and admission serum markers of inflammation and neuronal injury (e.g., S100B, neuron-specific enolase) have been linked to illness severity and short-term mortality in this population [12].

Yet SAE remains operationally elusive in routine practice: it has no validated bedside diagnostic criterion, its biomarker landscape is still maturing, and it is rarely a primary endpoint in interventional trials [13,14].

Mechanistic research has, in parallel, implicated microglial activation, blood-brain barrier dysfunction, and dysregulation of cerebral neurotransmission in the cellular response to systemic inflammation [15].

These insights have generated a growing pipeline of candidate molecular targets, but their translation to the bedside is constrained by the limited availability of well-characterized real-world cohorts in which the clinical phenotype of acute brain dysfunction can be tied to systemic inflammatory and physiological signatures. The present study contributes such a clinical and epidemiological characterization; it does not include neurological biomarkers, neuroimaging, or any measurement of the molecular pathways referenced above, and therefore cannot provide mechanistic evidence regarding them.

The pre-vaccination period is of particular interest because it captures the natural history of severe COVID-19 critical illness before standardized immunomodulatory protocols and population-level immunity altered ICU case-mix and outcome; in this setting, acute brain dysfunction at admission and its relationship to the exceptionally high ICU mortality of the period have been little characterized, particularly in Eastern European cohorts. In a single sentence, the aim of this study was to determine, in a pre-vaccination Romanian COVID-19 ICU cohort, how strongly acute brain dysfunction present at ICU admission is associated with in-ICU death. We undertook this study to address this gap in the specific context of pre-vaccination COVID-19 critical illness in a regional Romanian tertiary ICU, with a primary focus on acute brain dysfunction at admission and in-ICU mortality.

Specifically, we aimed to: (1) characterize the prevalence and case-mix of organ dysfunction, septic shock, and MODS in a consecutive cohort of adults admitted with RT-PCR-confirmed COVID-19; (2) quantify in-ICU mortality and the contribution of individual organ-system failures, comorbidity, and acute physiological derangement to outcome; (3) develop and apply a clinically operational proxy for acute brain dysfunction at ICU admission, assess its association with mortality and markers of systemic inflammation, and test whether these associations are confounded by sedation in ventilated patients; (4) explore whether unsupervised, exploratory cluster derivation reveals internally stable subgroups within the population with organ dysfunction; and (5) examine, by regression-coefficient decomposition, how much of the inflammation-mortality association is statistically accounted for by adjustment for acute brain dysfunction at admission.

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Materials and Methods

Study design and setting

We performed a retrospective observational study of consecutive adult admissions to the multidisciplinary intensive care unit of a regional Romanian tertiary university hospital between 2020 and 2021, a period spanning the alpha and delta SARS-CoV-2 variant waves and entirely preceding the rollout of population-level COVID-19 vaccination in the Romanian critical-care population.

The unit was designated as a COVID-19 ICU and operated under sustained surge conditions throughout the study period.

All included patients had microbiologically confirmed SARS-CoV-2 infection by RT-PCR on admission.

The unit functions as a referral endpoint for a wide geographical catchment area in southwestern Romania, with limited intermediate-level ICU capacity in the region during the study period.

Patient admissions included in the analysis spanned March 2020 to April 2021.

While the first COVID-19 vaccine doses became available in Romania from 27 December 2020, population-level vaccination coverage in the regional catchment remained below 30% throughout 2021, and no patient in the analytic cohort had documented complete vaccination at the time of ICU admission.

During the preparation of this manuscript, the authors used Claude (Anthropic, Claude Opus 4.7) for the purposes of language editing and structural review of methodological text.

The authors have reviewed and edited the output and take full responsibility for the content of this publica-tion.

Inclusion and exclusion criteria

All adult patients (age≥18 years) admitted to the COVID-designated ICU during the study period with RT-PCR-confirmed SARS-CoV-2 infection and a length of stay of at least 24 hours were eligible.

Patients younger than 18 years, those admitted for short-term post-procedural monitoring (LOS<24 hours) without organ dysfunction, and those with incomplete admission physiological data precluding calculation of SOFA and APACHE II scores were excluded.

The final analytic cohort comprised 389 consecutive patients.

Data collection and variables

Demographic, clinical, biochemical, physiological, and outcome variables were extracted from the institutional electronic health record and pseudonymised at source.

The full variable set comprised: demographics (age, sex, urban/rural residence); anthropometric data (body mass index); pre-existing comorbidities (hypertension, type 1 or 2 diabetes mellitus, chronic kidney disease, chronic heart failure, atrial fibrillation, chronic obstructive pulmonary disease, ischaemic heart disease, obesity, active malignancy, prior stroke); the Charlson Comorbidity Index (age-adjusted); admission physiological variables (Glasgow Coma Scale assessed prior to any sedation administration where feasible, arterial pH, PaO_2/FiO_2 ratio, 24-hour urine output); admission laboratory parameters (serum creatinine, lactate, leukocyte and platelet counts, C-reactive protein, procalcitonin, total bilirubin, serum albumin, D-dimers); admission and post-admission creatinine measurements; severity scores (APACHE II at admission; SOFA total and component scores at admission and on Day 3); organ-support variables (invasive mechanical ventilation, non-invasive ventilation or CPAP/HFNC, vasopressor administration with maximal noradrenaline dose, renal replacement therapy, systemic corticosteroids, systemic antibiotics); ICU length of stay; and final ICU outcome (alive at discharge versus in-ICU death).

Detailed sedation regimens, individual therapeutic exposures (dexamethasone, tocilizumab, baricitinib, remdesivir, anticoagulation), and adjudicated secondary bacterial infection were not consistently available in the structured electronic record across the study period and could not be analysed as covariates; these limitations are addressed analytically through the sensitivity analyses described below and discursively in the limitations section of the manuscript.

Operational definitions

Because the conceptual application of the Sepsis-3 framework to COVID-19 critical illness remains debated, we use the term "organ dysfunction" rather than "sepsis" to describe our primary phenotype throughout, while noting the operational equivalence to a SOFA-based Sepsis-3 derivation in patients with confirmed primary infection.

Specifically, organ dysfunction was defined as an admission SOFA score ≥2 in the context of confirmed SARS-CoV-2 infection [16-18].

Septic shock was defined as the concurrent requirement of vasopressor therapy and an arterial lactate >2mmol/L on admission. MODS was defined as dysfunction (SOFA component ≥2) in two or more organ systems among the six standard SOFA domains.

Acute kidney injury (AKI) was defined according to a KDIGO-equivalent criterion as a maximum 7-day creatinine ≥1.5 × baseline value or an absolute rise ≥ 0.3mg/dL above baseline; AKI status was treated as missing in patients without an available baseline creatinine measurement.

A clinically operational proxy for acute brain dysfunction at ICU admission, termed the ABD proxy in subsequent analyses, was defined as the concurrence of (i) admission SOFA ≥2 and (ii) Glasgow Coma Scale <15 and/or a neurological SOFA component ≥1 documented at the time of ICU admission, before initiation of continuous sedation where this distinction could be made from the electronic record.

A more conservative threshold for severe acute brain dysfunction was defined as the presence of admission SOFA ≥2 with admission GCS ≤12.

We did not exclude patients with prior stroke from the descriptive estimates of ABD-proxy prevalence, but did exclude them from the multivariable model designed to identify acute determinants of SAE, in order to reduce contamination by primary cerebrovascular pathology.

We emphasize that this is a clinical proxy rather than a diagnostic instrument: in patients on invasive mechanical ventilation, distinguishing intrinsic encephalopathy from sedation-mediated depression of consciousness is impossible without systematic sedation interruption protocols and structured neurological assessment, neither of which was available in this retrospective dataset.

To make clear how the ABD proxy should be understood in this study, three points are worth stating explicitly.

First, the proxy is intended as a reproducible, operational marker of depressed consciousness at admission, derived entirely from routinely recorded variables (GCS and the neurological SOFA component); its reliability is that of a standardized, low-subjectivity measure that can be applied uniformly across all patients, not that of a validated diagnostic test.

Second, it differs from delirium, which is a fluctuating disturbance of attention and awareness requiring serial structured screening (e.g., CAM-ICU, ICDSC) that was not available here; the ABD proxy captures a single admission snapshot of reduced consciousness and is therefore insensitive to hypoactive or fluctuating delirium.

Third, it differs from sepsis-associated encephalopathy (SAE), which is a mechanistic diagnosis of diffuse cerebral dysfunction attributable to systemic infection after exclusion of other causes; our proxy does not exclude such alternative causes and should therefore be read as a clinical correlate that may overlap with, but is not equivalent to, either delirium or SAE.

Statistical analysis

All analyses were performed in Python 3.12 using the pandas, NumPy, SciPy, statsmodels, and scikit-learn libraries.

Continuous variables are presented as median and interquartile range (IQR) and were compared between groups using the Mann-Whitney U test.

Categorical variables are presented as frequencies and percentages and were compared using the χ^2 test, with Fisher's exact test substituted when expected cell counts were below five.

Wilson's score interval was used for 95% confidence intervals around proportions.

Two-sided *p*-values <0.05 were considered statistically significant; given the exploratory nature of several analyses, no formal correction for multiple comparisons was applied, but exact *p*-values are reported throughout.

Discrimination of mortality

Discrimination of in-ICU mortality by individual scores and biomarkers was assessed by the area under the receiver operating characteristic curve (AUC).

Confidence intervals (95%) for AUCs were obtained from 2,000 stratified bootstrap resamples.

Pairwise comparisons of AUCs were performed using a bootstrap-based equivalent of the DeLong test, with two-sided *p*-values derived from the empirical bootstrap distribution of paired AUC differences.

The change in SOFA score from admission to Day 3 (Δ SOFA) is reported among predictors but is calculable only in patients surviving to Day 3 and is therefore subject to immortal time bias (patients who died before Day 3 could not contribute a Day-3 measurement, so the surviving subset is systematically healthier); the proportion of patients with LOS <3 days is reported alongside this analysis for full transparency.

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Multivariable modelling

Two parallel multivariable logistic regression models were constructed to address concerns about circularity, the risk of using the SOFA score both to define the patient groups and to predict their outcome, which can artificially inflate apparent performance, between SOFA-based group definitions and outcome prediction.

The primary model included age, Charlson Index, admission lactate, admission CRP, admission albumin, and admission GCS, explicitly excluding the SOFA total score, since the latter was used in the operational definition of organ dysfunction itself.

A secondary model additionally included SOFA total to allow comparison with conventional severity-score-driven prediction. Vasopressor use was excluded from both multivariable models for a statistical reason: in this cohort, vasopressor administration was almost perfectly determined by the cardiovascular SOFA component (which is itself defined by blood pressure and vasopressor requirement), so including both would introduce severe collinearity and unstable coefficient estimates.

Excluding vasopressors from the model does not mean that hypotension is unimportant; on the contrary, hypotension and its treatment are captured through the cardiovascular SOFA component and through admission lactate, both of which are retained.

Model performance was assessed by both apparent AUC (with 2,000-resample bootstrap CI) and 5-fold stratified cross-validated AUC (chosen over 10-fold to provide more stable per-fold estimates given the high outcome rate), the McFadden pseudo-R^2, and the Hosmer-Lemeshow goodness-of-fit χ^2 with 8 degrees of freedom.

With 231 deaths across 351 complete cases and six predictors, the events-per-variable ratio (the number of deaths per predictor included in the model, a standard indicator of whether a regression model is adequately powered and not over-fitted) was 38.5, well above the conventional threshold of 10-15.

Adjusted odds ratios with 95% confidence intervals are reported.

We did not fit a Cox proportional-hazards model because length of ICU stay in this cohort is defined retrospectively by the timing of either death or live discharge, precluding a clean separation of time-to-event from outcome status; logistic regression with in-ICU death as a binary outcome was therefore preferred.

Unsupervised cluster derivation

Unsupervised clinical phenotyping was performed on the cohort with admission organ dysfunction (n=302) using k-means clustering on standardized admission features (age, lactate, CRP, albumin, GCS, PaO_2/FiO_2, creatinine, bilirubin, total SOFA). Missing values were imputed using variable-wise medians prior to standardization.

We evaluated solutions for k=2 to 5 using silhouette analysis. Although the silhouette score was numerically maximal at k=2 (silhouette=0.235), this two-cluster solution separated only the extremes of severity and provided no granularity for characterising intermediate clusters.

We therefore report the four-cluster solution (silhouette=0.183) as our primary analysis, on the explicit grounds of clinical interpretability rather than statistical optimality.

Cluster stability was evaluated by two complementary procedures: (i) consistency across 50 random initializations of the k-means algorithm at fixed n_init, and (ii) bootstrap stability assessed across 100 resamples of the input data, with concordance between resampled cluster assignments and the original clustering quantified by the Adjusted Rand Index (ARI).

As an additional sensitivity analysis, cluster stability with respect to the missing-data strategy was assessed by repeating the clustering under multiple imputation (iterative/MICE) and k-nearest-neighbor imputation, quantifying concordance with the median-imputation solution by the Adjusted Rand Index.

Cluster-specific outcomes were compared by χ^2 test (with pairwise comparisons against the lowest-mortality cluster) and by Kaplan-Meier survival analysis with multivariate log-rank testing.

We adopt the α/β/γ/δ labelling convention for descriptive convenience only and do not claim these clusters correspond directly to those derived in larger published datasets [19].

Adjustment of inflammation-mortality association for acute brain dysfunction

To explore whether acute brain dysfunction at admission accounts for part of the association between systemic inflammation and mortality, we fitted two nested logistic regression models in the cohort with admission organ dysfunction: a base model regressing in-ICU death on

admission CRP, age, and Charlson Index; and an extended model additionally including the ABD proxy.

We report the coefficient for CRP from each model, the absolute and relative attenuation of the CRP coefficient between the two models, and 95% bootstrap confidence intervals for the absolute attenuation from 2,000 resamples.

We report this as the attenuation of the CRP coefficient after adding the ABD proxy to the model, and interpret it descriptively, as how much of the CRP-mortality association is statistically accounted for by the ABD proxy, rather than as a formal mediation analysis, which the outcome prevalence (65.8%) and admission-only timing of the data would not support.

Correlation structure

The Spearman rank correlation matrix among 20 clinical, biochemical, physiological, and outcome variables was computed to characterise the global covariance structure of the cohort.

Pairwise sample sizes reflect available data after listwise deletion.

Sensitivity analyses for sedation confounding

Because admission GCS in mechanically ventilated patients may be confounded by sedation, we performed two pre-specified sensitivity analyses to test the robustness of the ABD-proxy association with mortality and inflammation.

First, we re-estimated all ABD-proxy outcome associations restricted to the subcohort not receiving invasive mechanical ventilation at admission (n=235; non-VMI subcohort with admission organ dysfunction n=161), in whom sedation contribution to GCS is minimal. Second, we re-estimated the inflammation-mortality coefficient attenuation analysis in this same non-VMI subcohort.

These analyses are reported alongside the primary results.

Missing data handling

Missing data were handled by listwise deletion in all primary models, with the exception of the unsupervised clustering, where median imputation was used to preserve sample size.

The proportion of missingness for each variable used in primary analyses was below 25%, with most variables completely available.

Reporting

The study was conducted and is reported in accordance with the STROBE statement for observational studies.

The full analysis pipeline (Python scripts, derived datasets, and figure-generation code) is available from the corresponding author upon reasonable request.

Results

Results are organized in six subsections, following the order of the study objectives.

We first describe the cohort and the burden of organ dysfunction, then the prevalence and prognostic implications of acute brain dysfunction at admission, the prognostic performance of severity scores in the context of high outcome saturation, unsupervised cluster derivation, and finally the regression-coefficient decomposition of the inflammation-mortality association by adjustment for the ABD proxy.

Cohort characteristics

During 2020-2021, 389 consecutive adult patients with RT-PCR-confirmed SARS-CoV-2 infection were admitted to the regional tertiary ICU and met inclusion criteria.

The cohort had a median age of 68 years (IQR 59-77), with 41.4% (n=161) female patients and a predominantly urban catchment (69.4%; n=270).

Pre-existing comorbidity burden was substantial: hypertension was documented in 65.6% of patients, type 2 diabetes in 30.6%, chronic heart failure in 20.3%, chronic kidney disease in 17.0%, and prior stroke in 10.0%.

The median Charlson Comorbidity Index was 3 (IQR 1-4).

Body mass index distribution was consistent with a high prevalence of metabolic burden (median 26.8 kg/m²; obesity in 22.6%).

On admission, illness severity was high, with a median APACHE II score of 23 (IQR 15-29) and a median total SOFA score of 6 (IQR 2-10).

Glasgow Coma Scale was 15 in 46.3% of patients on admission, while 37.4% presented with moderate to severe depression of consciousness (GCS ≤12).

Detailed baseline characteristics, stratified by in-ICU outcome, are presented in Table 1.

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Table 1. Baseline characteristics of the regional Romanian ICU cohort (N=389), stratified by in-ICU outcome.

Variable	Survivors (n=133)	Non-survivors (n=256)	p-value
Demographics & Comorbidity			
Age, years (median, IQR)	63 (53-71)	71 (63-78)	< 0.0001
Female sex, n (%)	60 (45.1)	101 (39.5)	0.334
Urban residence, n (%)	71 (53.4)	199 (77.7)	< 0.0001
BMI, kg/m² (median, IQR)	26.1 (23.3-30.1)	27.2 (24.3-30.8)	0.036
Charlson Index (median, IQR)	2 (1-3)	3 (2-4)	< 0.0001
Hypertension, n (%)	81 (60.9)	174 (68.0)	0.201
Diabetes, n (%)	24 (18.0)	95 (37.1)	< 0.001
Chronic kidney disease, n (%)	10 (7.5)	56 (21.9)	< 0.001
Chronic heart failure, n (%)	9 (6.8)	70 (27.3)	< 0.0001
Atrial fibrillation, n (%)	9 (6.8)	66 (25.8)	< 0.0001
COPD, n (%)	9 (6.8)	22 (8.6)	0.664
Active malignancy, n (%)	5 (3.8)	24 (9.4)	0.072
Prior stroke, n (%)	3 (2.3)	36 (14.1)	< 0.001
Severity Scores at Admission			
APACHE II (median, IQR)	13 (9-16)	27 (23-32)	< 0.0001
SOFA total (median, IQR)	2 (1-3)	8 (6-11)	< 0.0001
SOFA neurological (median, IQR)	0 (0-0)	2 (1-2)	< 0.0001
Δ SOFA (D3 − admission)	-1 (-2--1)	1 (0-2)	< 0.0001
GCS, admission (median, IQR)	15 (15-15)	12 (11-14)	< 0.0001
Biomarkers at Admission			
Lactate, mmol/L (median, IQR)	1.9 (1.4-2.3)	3.1 (2.5-5.3)	< 0.0001
CRP, mg/L (median, IQR)	44 (26-65)	152 (108-197)	< 0.0001
Procalcitonin, ng/mL (median, IQR)	0.4 (0.2-0.6)	1.9 (0.6-3.9)	< 0.0001
D-dimer, ng/mL (median, IQR)	901 (627-1197)	2860 (1981-4164)	< 0.0001
Leukocytes, ×10³/μL (median, IQR)	8.3 (6.2-10.9)	13.2 (10.0-16.7)	< 0.0001
Platelets, ×10³/μL (median, IQR)	212 (192-232)	171 (120-196)	< 0.0001
Albumin, g/dL (median, IQR)	3.7 (3.6-3.8)	3.0 (2.8-3.3)	< 0.0001
Bilirubin, mg/dL (median, IQR)	0.8 (0.5-1.0)	1.0 (0.7-1.3)	< 0.0001
Creatinine, mg/dL (median, IQR)	0.9 (0.7-1.1)	2.0 (1.4-2.6)	< 0.0001
PaO_2/FiO_2, mmHg (median, IQR)	321 (281-350)	180 (127-264)	< 0.0001
pH (median, IQR)	7.4 (7.4-7.4)	7.4 (7.3-7.4)	< 0.0001
Clinical Phenotypes			
Sepsis-3, n (%)	65 (48.9)	237 (92.6)	< 0.0001
Septic shock, n (%)	4 (3.0)	130 (50.8)	< 0.0001
MODS (≥ 2 systems), n (%)	6 (4.5)	214 (83.6)	< 0.0001
ABD proxy, n (%)	6 (4.5)	187 (73.0)	< 0.0001
Severe ABD (GCS ≤ 12), n (%)	3 (2.3)	121 (47.3)	< 0.0001
Organ Support			
Invasive ventilation, n (%)	15 (11.3)	139 (54.3)	< 0.0001
Non-invasive ventilation/CPAP, n (%)	84 (63.2)	117 (45.7)	0.002
Vasopressors, n (%)	9 (6.8)	138 (53.9)	< 0.0001
Renal replacement therapy, n (%)	0 (0.0)	43 (16.8)	< 0.0001
Corticosteroids, n (%)	119 (89.5)	233 (91.0)	0.757
Antibiotics, n (%)	124 (93.2)	239 (93.4)	1.000
LOS, days (median, IQR)	10 (6-16)	8 (4-14)	0.011

Continuous variables presented as median (IQR) and compared with Mann-Whitney U test; categorical variables presented as n (%) and compared with χ^2 test.

The neurological SOFA component and admission GCS both reflect the same bedside assessment of consciousness (the neurological SOFA component is derived directly from the GCS); both are reported for transparency, the GCS as the raw scale value and the neurological SOFA component as its ordinal score used within the total SOFA, and they should not be interpreted as independent measurements.

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; ABD, Acute Brain Dysfunction; CRP, C-reactive protein; MODS, Multiple Organ Dysfunction Syndrome; SAE, Sepsis-Associated Encephalopathy; LOS, length of stay.

Organ dysfunction burden and mortality

An admission SOFA score ≥2, the operational threshold for organ dysfunction in this cohort with confirmed primary infection, was met by 302 patients (77.6%), of whom 134 (34.4% of the total cohort) fulfilled criteria for septic shock. MODS, defined as ≥2 organ systems with a SOFA component ≥2, was present in 220 patients (56.6%) on admission.

The most frequently dysfunctional systems were respiratory (69.4%, consistent with COVID-19 pneumonia as the primary admitting pathology), renal (40.4%), cardiovascular (37.8%), and neurological (35.2%).

The distribution of organ involvement and corresponding case-fatality is shown in Figure 1A,B,D. AKI, defined by a KDIGO-equivalent threshold, occurred in 62.7% (183/292) of patients with available baseline values.

Overall in-ICU mortality was 65.8% (256/389; 95% CI 61.0-70.3%).

This figure substantially exceeds the typical 25-35% reported in pre-pandemic ICU sepsis cohorts [20] but is concordant with mortality rates reported for COVID-19 critical illness during pre-vaccination European pandemic surges, and should be interpreted strictly within this temporal and clinical context.

Mortality scaled steeply with the number of dysfunctional organ systems: 7.6% (6/79) with no SOFA component ≥2, 40.0% (36/90) with one system, 92.2% (71/77) with two systems, and 100% with three or more concurrent failures (n=143; specifically 65, 39, 26, and 13 patients with three, four, five, and six failing systems respectively, all with 100% mortality) (Figure 1B).

When stratified by phenotype, mortality was 78.5% (237/302) in patients with admission organ dysfunction, 97.3% (214/220) in MODS, and 97.0% (130/134) in septic shock (Figure 1F).

Median ICU length of stay was 8 days (IQR 4-15).

In total, 60 patients (15.4%) had LOS <3 days, of whom 76.7% died; this group is necessarily excluded from any analysis involving Day 3 measurements.

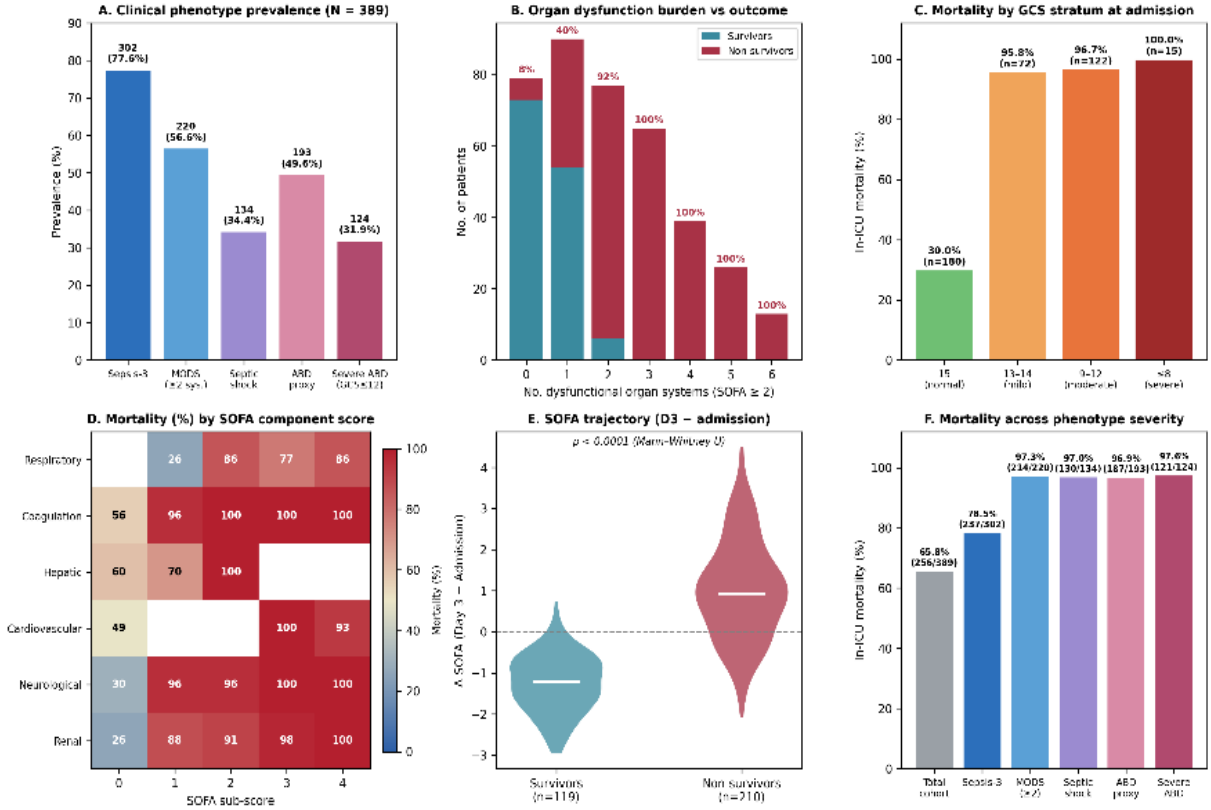

Figure 1. Cohort overview, organ dysfunction patterns, and mortality. (A) Prevalence of clinical phenotypes among the 389 ICU patients. (B) Stacked bar chart of organ dysfunction burden (number of SOFA components ≥ 2) by outcome. (C) In-ICU mortality stratified by Glasgow Coma Scale at admission. (D) Heatmap of in-ICU mortality (%) by SOFA component score (rows: organ systems; columns: sub-score 0-4). (E) Δ SOFA between Day 3 and admission in survivors versus non-survivors (Mann-Whitney U test). Note: this analysis is subject to immortal time bias because patients dying before Day 3 are excluded. (F) Mortality cascade across phenotype severity, with absolute counts shown over each bar.

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Acute brain dysfunction at ICU admission

Acute brain dysfunction at ICU admission, operationalized as GCS<15 or neurological SOFA component ≥1 in a patient with admission organ dysfunction, defined an ABD proxy that was present in 193 patients (49.6% of the entire cohort and 63.9% of those with admission organ dysfunction).

A more conservative threshold (GCS≤12 with admission organ dysfunction) identified 124 patients (31.9%).

Mortality in the ABD-proxy subgroup was 96.9% (95% CI 93.4-98.6%; 187/193), compared with 45.9% (95% CI 36.8-55.2%; 50/109) among patients with admission organ dysfunction but preserved consciousness, an absolute risk difference of 51.0 percentage points (χ^2 test, *p*<0.0001).

Mortality stratified by GCS category at admission revealed a steep gradient: 30.0% in patients with GCS 15, 95.8% with GCS 13-14, 96.7% with GCS 9-12, and 100.0% with GCS ≤8 (Figure 1C; χ^2 test, *p*<0.0001).

Patients meeting the ABD-proxy definition were on average older than those with preserved consciousness (median age 72 vs 65 years; difference 7 years; p<0.001) and exhibited markedly elevated systemic inflammation and tissue hypoperfusion.

Median CRP was 155 mg/L (IQR 114-201) versus 64 mg/L (IQR 39-130; *p*<0.0001); procalcitonin 1.87ng/mL (IQR 0.58-7.76) versus 0.59ng/mL (IQR 0.35-1.51; *p*<0.0001); arterial lactate 3.28mmol/L (IQR 2.66-5.67) versus 2.10mmol/L (IQR 1.78-2.70; *p*<0.0001);

D-dimers 3046ng/mL (IQR 2046-5239) versus 1241ng/mL (IQR 702-2390; *p*<0.0001); and serum albumin was lower at 3.0g/dL (IQR 2.76-3.24) versus 3.62g/dL (IQR 3.41-3.75; *p*<0.0001).

The substantial elevation of procalcitonin in the ABD-proxy-positive subgroup, in particular, raises the possibility of secondary bacterial superinfection as an unmeasured contributor to the observed inflammatory signature.

In a multivariable logistic regression restricted to patients without prior stroke (n=201; events-per-variable=17.6), independent predictors of acute brain dysfunction at admission were lower serum albumin (adjusted OR 0.10 per g/dL; 95% CI 0.03-0.32; *p*<0.001), higher SOFA total score (adjusted OR 1.37 per point; 95% CI 1.16-1.61; *p*<0.001), older age (adjusted OR 1.05 per year; 95% CI 1.00-1.10; *p*=0.034), and higher CRP (adjusted OR 1.009 per mg/L; 95% CI 1.001-1.017; *p*=0.025).

Because GCS in mechanically ventilated patients may be confounded by sedation, we re-examined the ABD-proxy-mortality association in the subcohort not receiving invasive mechanical ventilation at admission (n=235 overall; non-VMI subcohort with admission organ dysfunction n=161).

Among these unventilated patients with organ dysfunction, the ABD proxy was present in 46.0% (74/161), and was associated with a mortality of 91.9% (95% CI 83.4-96.2%; 68/74) versus 42.5% (95% CI 32.7-53.0%; 37/87) in those with preserved consciousness, an absolute difference of 49.4 percentage points (χ^2 test, *p*<0.0001).

The similar magnitude of the ABD-proxy mortality difference in the non-VMI subgroup (49.4 percentage points) and the full subgroup with organ dysfunction (51.0 percentage points) indicates that the association between admission acute brain dysfunction and mortality persisted in patients in whom sedation contributes minimally to GCS.

We emphasize, however, that this analysis does not adequately control sedation confounding in ventilated patients, and that hypoxaemia, delirium, metabolic encephalopathy, and prior neurological disease may also contribute to reduced consciousness and cannot be excluded as confounders in this retrospective dataset.

Prognostic performance of severity scores and biomarkers

All routinely available severity scores and acute-phase biomarkers discriminated in-ICU mortality with high accuracy in this severely ill cohort (Figure 2 A,B).

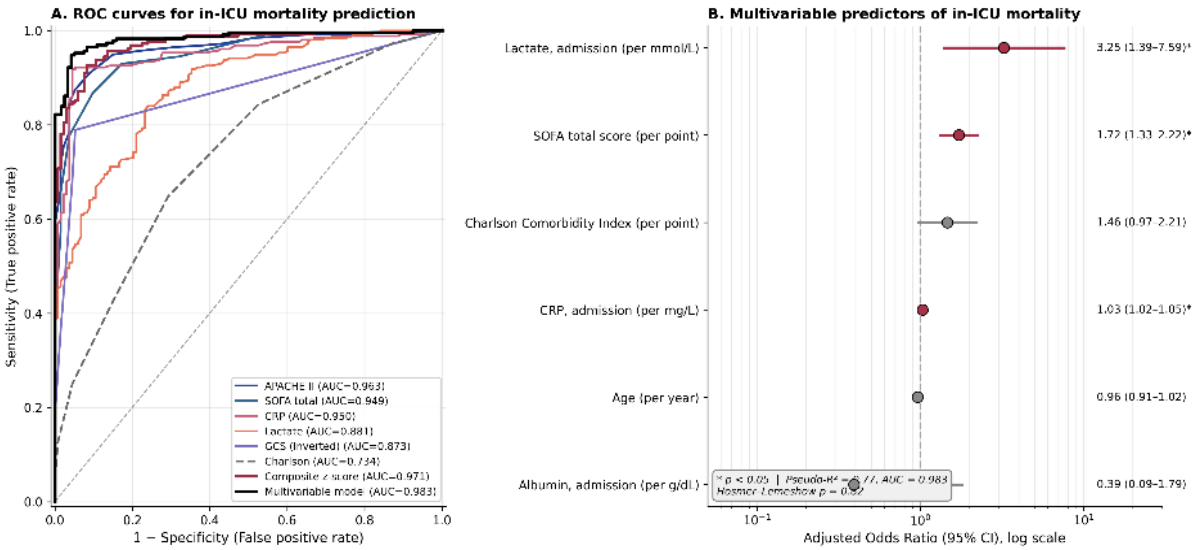

Figure 2. Discrimination and multivariable predictors of in-ICU mortality. (A) ROC curves with bootstrap-derived AUC values. The full multivariable model achieved an apparent AUC of 0.983; the SOFA-free primary model achieved AUC 0.974 (cross-validated 0.971). (B) Forest plot of adjusted odds ratios from the parsimonious multivariable model. Red markers denote variables significant at p<0.05.

Bootstrapped AUC values (95% CI from 2,000 resamples) were 0.963 (0.944-0.979) for APACHE II, 0.950 (0.927-0.970) for CRP, 0.949 (0.928-0.968) for SOFA total, 0.881 (0.847-0.913) for arterial lactate, 0.873 (0.842-0.902) for inverted GCS, and 0.734 (0.683-0.783) for the Charlson Comorbidity Index.

The change in SOFA score from admission to Day 3 (Δ SOFA) discriminated mortality with an AUC of 0.908 (0.874-0.937); however, this analysis is restricted to the 329 patients (84.6%) who survived to at least Day 3 in the ICU, and is therefore subject to immortal time bias because the 60 patients (15.4%) with LOS <3 days, among whom mortality reached 76.7%, are necessarily excluded.

To avoid any confusion, we emphasize that this bias affects only the Day-3 Δ SOFA analysis, which requires survival to Day 3; it does not affect the overall in-ICU mortality figure (65.8%) or any admission-based analysis, all of which include the complete cohort of 389 patients. Δ SOFA values should accordingly be interpreted as predictive only in the subset of patients surviving the early high-mortality phase.

These uniformly high AUC values reflect the dramatic outcome stratification of this pre-vaccination COVID-19 ICU cohort, in which mortality approached 100% in patients with even moderate organ dysfunction.

They should be interpreted as evidence of outcome saturation, that is, mortality being so high across the cohort that almost any severity marker separates survivors from non-survivors, rather than of intrinsically superior or transportable score performance: AUC values are bounded above by the achievable separability of a binary outcome with ceiling-level event rates, and similar score performance has not been reported in less severely ill cohorts.

We therefore do not present these models as adding clinically useful predictive value: under near-ceiling mortality they convey little beyond what the baseline characteristics (Table 1) already show, and we retain them only to demonstrate transparently that the high apparent discrimination is an artefact of outcome saturation rather than evidence of a useful prediction tool.

To address concerns regarding circularity between SOFA-based group definitions and SOFA-based prediction, we constructed a primary multivariable logistic regression model deliberately excluding SOFA (age, Charlson Index, lactate, CRP, albumin, GCS; n=351 with complete data; 231 deaths; events-per-variable=38.5).

This SOFA-free model achieved an apparent AUC of 0.974 (95% CI 0.954-0.989) and a 5-fold stratified cross-validated AUC of 0.971±0.020 (range across folds 0.935-0.995).

Internal cross-validation guards against in-sample optimism but does not assess transportability; in a cohort with near-ceiling event rates these values are expected to be inflated by outcome separability and are unlikely to be reproduced in less severely ill or external populations.

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A secondary model additionally including SOFA achieved closely similar discrimination, indicating that the performance is not driven by inclusion of the SOFA score per se but by the underlying severity stratification of this cohort.

The Hosmer-Lemeshow test did not indicate significant miscalibration for either the primary SOFA-free model (χ^2=7.17, p=0.52; McFadden pseudo-R^2=0.72) or the secondary SOFA-inclusive model (χ^2=4.37, p=0.82; pseudo-R^2=0.77).

We note that the Hosmer-Lemeshow test alone is a limited assessment of calibration; calibration plots, calibration slope and intercept, and decision-curve analysis would provide a more complete evaluation and were not performed here, which we acknowledge as a limitation.

Adjusted odds ratios for in-ICU mortality from the primary SOFA-free model were 3.76 per mmol/L of lactate (95% CI 1.69-8.38; p=0.001), 1.56 per Charlson point (95% CI 1.06-2.28; p=0.024), 1.04 per mg/L of CRP (95% CI 1.02-1.05; p<0.001), and 0.23 per g/dL of albumin (95% CI 0.06-0.97; p=0.045), with non-significant contributions from age (OR 0.97 per year; 95% CI 0.92-1.01; *p*=0.156) and admission GCS (OR 0.74 per point; 95% CI 0.54-1.01; *p*=0.056).

Unsupervised clinical clusters (exploratory)

To explore whether distinct clinical patterns could be identified within the cohort with admission organ dysfunction, we applied k-means clustering on standardized admission features in the 302 patients meeting this threshold.

We present this clustering as an exploratory analysis only. Silhouette analysis was numerically maximal at k=2 (silhouette=0.235); we additionally examined the four-cluster solution (silhouette=0.183), which we report for descriptive purposes because it separates intermediate groups that the two-cluster solution collapses.

We emphasize that k=4 was not the silhouette-optimal solution, and that selecting it on grounds of interpretability rather than statistical optimality is a recognized limitation of this exploratory analysis.

We therefore frame these results as data-derived clusters, not as validated clusters. The four clusters accounted for 56.3% of the total variance on the first two principal components (Figure 3A,B).

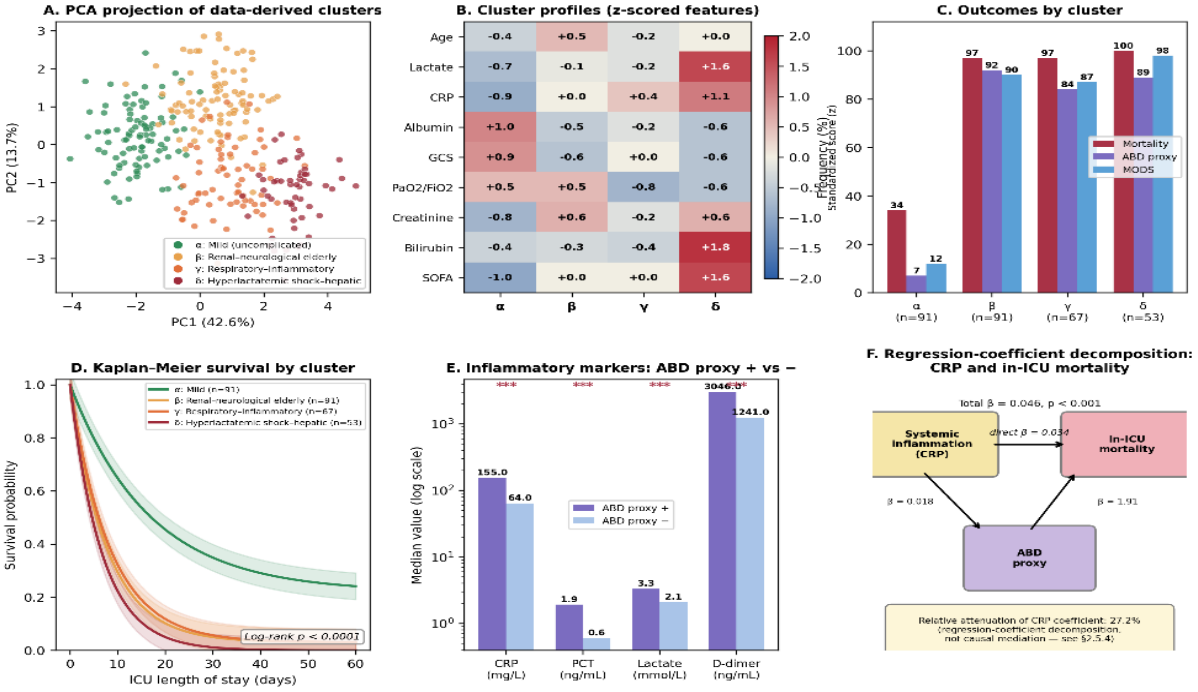

Figure 3. Unsupervised clinical clusters, ABD-proxy biomarker contrasts, and regression-coefficient decomposition.(A) PCA projection with k-means cluster assignments (α/β/γ/δ; bootstrap ARI=0.71). (B) Heatmap of cluster centroids (z-scored). (C) Mortality, ABD proxy prevalence, and MODS prevalence per cluster. (D) Kaplan-Meier survival curves stratified by cluster (multivariate log-rank p<0.0001). (E) Median admission values of CRP, procalcitonin, lactate, and D-dimers in patients with versus without ABD proxy. (F) Decomposition diagram of the CRP-mortality association before and after adjustment for the ABD proxy (27.2% relative attenuation; framed as regression decomposition rather than causal mediation.

Internal stability of the four-cluster solution was confirmed by two complementary procedures: identical assignments across 50 random initialisations of the k-means algorithm, and a bootstrap Adjusted Rand Index of 0.71 (95% CI 0.53-0.94 from 100 resamples), indicating substantial concordance of cluster assignments across resampled inputs.

To assess whether the four-cluster solution depended on the median-imputation strategy, we repeated the clustering using multiple imputation (iterative/MICE, 20 imputed datasets) and compared the resulting assignments with the original solution. Concordance was high (Adjusted Rand Index 0.91±0.03; range 0.86-0.97), with closely similar silhouette values, and pairwise concordance across imputed datasets was likewise high (ARI 0.91±0.04); a k-nearest-neighbour imputation check yielded ARI values of 0.90-0.99.

Cluster assignments were therefore robust to the choice of imputation method and were not an artefact of median imputation.

We use the descriptive labels α, β, γ, and δ for convenience and do not claim correspondence with phenotypes derived from larger non-COVID cohorts[19]; in particular, no cluster in our pre-vaccination COVID-19 cohort exhibited the low absolute mortality (<15%) seen in the α cluster of pre-pandemic derivations.

An inherent limitation of the clustering procedure is that admission GCS and SOFA, which are central to the operational definition of the ABD proxy and to the mortality associations, also enter the clustering feature set; cluster α (with preserved consciousness) is therefore enriched for ABD-proxy-negative patients by construction.

The clustering consequently does not provide independent validation of the ABD-proxy findings, but partly recapitulates the same variables used to define them.

The differentiation reported here should accordingly be interpreted as descriptive of the joint distribution of admission features in data-derived clusters, not as confirmatory evidence.

Mortality differed dramatically between the α cluster and the three more severe clusters (Figure 3C,D; pairwise χ^2 tests vs α all *p*<10^{-14}): 34.1% (95% CI 25.2-44.3%; 31/91) in α, 96.7% (95% CI 90.8-98.9%; 88/91) in β, 97.0% (95% CI 89.8-99.2%; 65/67) in γ, and 100.0% (95% CI 93.2-100.0%; 53/53) in δ.

The β, γ, and δ clusters converged on near-universal mortality and were not statistically distinguishable from one another in outcome terms (β vs γ: *p*=1.00; β vs δ: *p*=0.27; γ vs δ: *p*=0.51, all by χ^2 with continuity correction).

The log-rank test across all four clusters confirmed the strong overall difference in survival trajectory (*p*<0.0001).

Time to ICU death among non-survivors was similar across clusters (median 7-8 days; α 7 [IQR 4-18], β 7 [IQR 2-12], γ 8 [IQR 4-18], δ 8 [IQR 5-15] days), arguing that the δ cluster represents a biologically distinct high-severity pattern rather than a pre-mortem state at admission.

The α cluster was characterised by younger age, preserved consciousness, high serum albumin, and low SOFA, with only 6.6% meeting ABD-proxy criteria.

The δ cluster combined extreme hyperlactataemia (z=+1.6), elevated bilirubin (z=+1.8), and high CRP (z=+1.1) with universal MODS (98.1%) (Figure 3E).

The β cluster identified an elderly subgroup with marked renal dysfunction and depressed consciousness, while γ comprised patients with predominant respiratory failure (PaO_2/FiO_2 z=−0.8) and intermediate inflammatory burden. ABD-proxy prevalence ranged from 6.6% in α to 92.3% in β, paralleling the mortality gradient.

Adjustment of inflammation-mortality association for acute brain dysfunction

Given the strong univariate associations between inflammatory biomarkers, the ABD proxy, and outcome, we examined how much of the CRP-mortality association is accounted for by adjustment for acute brain dysfunction at admission (Figure 3F).

In logistic regression adjusted for age and Charlson Index, the CRP log-odds coefficient for in-ICU mortality (per mg/L) was 0.0478 (p<0.001) before adjustment for the ABD proxy, and 0.0348 (p<0.001) after adjustment, an absolute attenuation of 0.0130 (95% bootstrap CI 0.0073-0.0219 from 2,000 resamples), corresponding to a 27.2% relative attenuation of the CRP regression coefficient.

The auxiliary logistic regression of the ABD proxy on CRP yielded a coefficient of 0.018 per mg/L (p<0.001), and the conditional log-odds coefficient for the ABD proxy in the CRP-and-ABD-adjusted mortality model was 1.91 (p<0.001).

In the pre-specified sedation-confounding sensitivity analysis restricted to patients with

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admission organ dysfunction not receiving invasive mechanical ventilation (n=161), the analogous CRP log-odds coefficient was 0.0391 before ABD-proxy adjustment and 0.0339 after adjustment, corresponding to a 16.3% relative attenuation.

The qualitative finding was preserved, although the attenuation was smaller than in the full subgroup with organ dysfunction (27.2%), suggesting that residual sedation confounding may inflate the primary estimate by roughly 1.5-fold without accounting for it entirely.

We frame these results as regression-coefficient attenuation rather than causal mediation.

The Spearman correlation matrix (Figure 4) further confirmed the centrality of inflammatory and neurological axes: CRP and SOFA total were the strongest correlates of mortality (ρ=0.74 each), while admission GCS showed a strong negative correlation with mortality (ρ=−0.65).

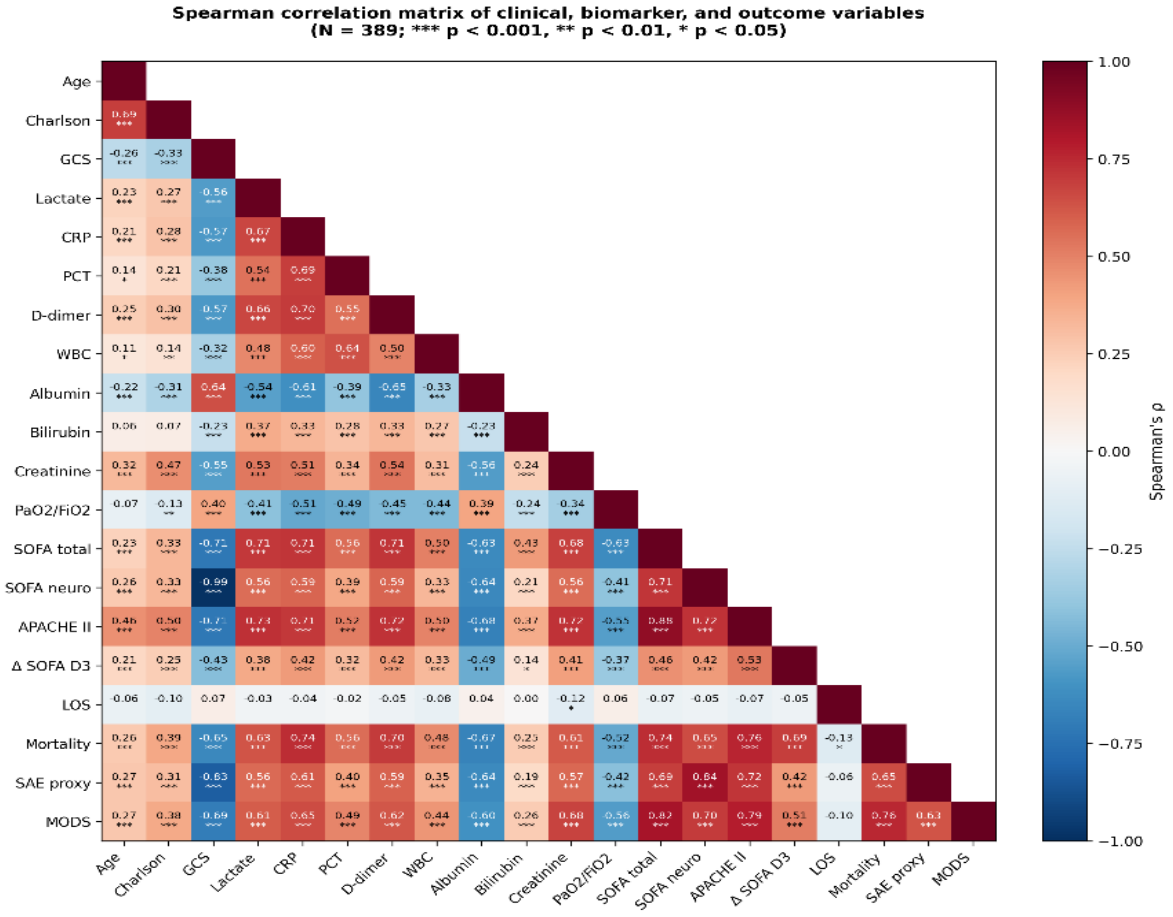

Figure 4. Spearman correlation matrix of clinical and outcome variables.
Lower-triangle Spearman rank correlation matrix among 20 clinical, biochemical, physiological, and outcome variables in the full cohort (N=389). Significance: *** p<0.001, ** p<0.01, * p<0.05.

Discussion

Principal findings

Before discussing our findings, we emphasise that this cohort represents an extreme, single-center, late-presenting ICU population managed under sustained pre-vaccination surge conditions; the exceptionally high death rate reported here does not apply to larger, better-resourced, or more recent ICU populations, and our results should not be read as generalisable estimates of COVID-19 or ICU mortality.

Within these boundaries, in a regional Romanian ICU cohort of 389 consecutive adults with RT-PCR-confirmed SARS-CoV-2 infection admitted during the pre-vaccination 2020-2021 period, we documented an exceptionally high burden of organ dysfunction (admission SOFA≥2 in 77.6%) and multiple organ dysfunction syndrome (56.6%), with overall in-ICU mortality of 65.8%.

Mortality scaled steeply with the cumulative number of failing organ systems and reached 100% in patients with three or more concurrent failures; in this severely ill cohort even a limited comorbidity burden (e.g., two or more comorbidities) was associated with high mortality, consistent with the advanced case-mix at admission.

A clinically operational proxy for acute brain dysfunction at admission was identifiable in nearly two-thirds of patients with admission organ dysfunction and was associated with a mortality of 96.9%, an absolute difference of 51.0 percentage points compared with those with preserved consciousness.

Critically, this association was preserved with closely similar magnitude (49.4 percentage points) in the subcohort not receiving invasive mechanical ventilation at admission, in whom sedation-induced depression of consciousness is unlikely to substantially confound GCS measurement.

Standard severity scores discriminated mortality with high accuracy under conditions of outcome saturation, and a multivariable model deliberately excluding SOFA achieved 5-fold cross-validated AUC of 0.971, demonstrating that the predictive signal is not an artefact of circularity between SOFA-based group definitions and SOFA-based outcome prediction.

Unsupervised clustering revealed four internally stable, data-derived clusters (bootstrap Adjusted Rand Index 0.71) that differed in their inflammatory and physiological profiles, most notably an inflammatory-shock δ cluster and a neuro-renal β cluster.

Adjustment for the ABD proxy attenuated the CRP-mortality regression coefficient by 27% in the full cohort and by 18% in the sedation-controlled sensitivity analysis, providing the first epidemiological signal in this Romanian COVID-19 ICU population that acute brain dysfunction is closely linked to the inflammation-mortality axis, while explicitly stopping short of a causal mediation claim that the available data do not support.

Interpretation within the pre-vaccination COVID-19 critical care context

The case-mix and outcome profile of our cohort must be interpreted strictly within the pre-vaccination COVID-19 surge context in which it was assembled.

International prospective ICU studies conducted before the pandemic, such as ICON, EPIC III, and the ANZICS data, reported ICU sepsis mortality in the range of 25-35%, with septic shock mortality between 35% and 50% [21,22].

The 78.5% in-ICU mortality observed among patients with admission organ dysfunction in our cohort and the 97% mortality among those with septic shock are markedly higher than these pre-pandemic benchmarks, but are concordant with mortality figures reported from European COVID-19 ICUs during pre-vaccination pandemic surges, which ranged from 35-60% in better-resourced settings to 60-80% in resource-constrained or saturated systems [23].

Three structural factors situate our cohort at the upper end of this range.

First, the catchment of a Romanian regional tertiary ICU functions as a referral endpoint for a wide geographical area with limited intermediate-level ICU capacity, leading to selection of patients already in advanced stages of respiratory and multi-organ failure at admission.

The median admission SOFA of 6 and the fact that 56.6% of patients met MODS criteria on admission corroborate this interpretation.

Second, the comorbidity burden of the cohort was substantial, median Charlson Index 3, with hypertension in two thirds and diabetes in nearly one third of patients, reflecting both an ageing regional demographic and the elevated prevalence of cardiometabolic disease in Romania.

Third, the unit operated at sustained surge capacity throughout a pre-vaccination period during which standardised therapeutic protocols (dexamethasone, immunomodulation with IL-6 receptor antagonists or JAK inhibitors) were either not yet established or were inconsistently available; this is a known independent driver of elevated mortality across European ICU systems during early pandemic waves [24].

Detailed records of individual therapeutic exposures were not consistently available in the structured electronic record and could not be analysed as covariates.

Our findings should therefore not be generalised to vaccinated populations, to contemporary post-pandemic ICU sepsis, or to bacterial sepsis in lower-acuity settings, nor should they be read as a generalisable model of COVID-19 sepsis, SAE, or ICU mortality.

The cohort is best understood as a highly selected, late-presenting population managed under sustained surge conditions, in which

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mortality reached 97% in MODS and septic shock and 100% in patients with three or more failing organ systems; these figures reflect the extremity of this specific setting.

The value of the analysis lies instead in providing a localized historical benchmark for the natural history of COVID-19-associated MODS and acute brain dysfunction in an Eastern European regional tertiary ICU during a defined and historically circumscribed pre-vaccination period, rather than a broader translational or mechanistic model.

Mortality gradient and the centrality of organ-failure burden

One of the most striking features of our data is the near-deterministic relationship between the cumulative number of failing organ systems and mortality.

Mortality rose from 7.6% in patients with no organ dysfunction to 40.0% with one system, 92.2% with two, 100% with three, 100% with four, and 100% with five or more concurrent failures.

This dose-response pattern, while consistent with the original conceptualisation of MODS, is more pronounced in our pre-vaccination COVID-19 ICU cohort than in most pre-pandemic reports, and likely reflects the combined effect of viral-pneumonia-driven respiratory failure, the late stage at which patients reached this regional referral centre, the surge-era constraints on intermediate care, and the absence of standardized early immunomodulation.

From a research-design perspective, this distribution has direct consequences for interventional trials targeting late-stage critical illness: studies that recruit broadly across the severity spectrum will be diluted by the very-mild end (the α cluster in our data, with 34% mortality and minimal organ failure) and dominated outcome-wise by the very-severe end, where futility may be the dominant biological signal.

Stratified enrolment based on organ-failure burden, or on phenotypic features of the intermediate β/γ clusters, may offer a more tractable target for novel therapies, a point we expand upon below.

Acute brain dysfunction in COVID-19 critical illness: from bystander to effector

The most conceptually important observation in this cohort is the association between acute brain dysfunction at ICU admission and in-ICU death.

The ABD-proxy prevalence is consistent with the 10-70% range described in the pre-pandemic SAE literature and with reports of neurological manifestations in COVID-19 critical illness [25,26].

This association was not attributable to age or general illness severity alone: the ABD-proxy-positive subgroup was older by 7 years (median age 72 vs 65 years; $p < 0.001$) but exhibited marked elevations in every measured biomarker of systemic inflammation, endothelial activation, and tissue hypoperfusion (CRP 2.4-fold higher; procalcitonin 3.2-fold; D-dimers 2.5-fold; lactate 1.6-fold).

The interpretation of these associations requires attention to three concerns. The first is sedation confounding in ventilated patients. The association persisted with closely similar magnitude in the non-ventilated subgroup, indicating that it is not solely an artefact of sedation; this does not, however, establish that sedation confounding has been adequately controlled, since the non-ventilated subgroup remains subject to hypoxaemia, delirium, metabolic encephalopathy, and prior neurological disease, none of which could be adjudicated here.

It is also important to note that delirium is the principal bedside clinical sign of sepsis-associated encephalopathy [27], and that validated delirium-screening instruments such as the CAM-ICU and ICDSC were not part of routine documentation in this retrospective dataset; our admission-GCS-based proxy therefore captures depressed consciousness rather than formally screened delirium, and is correspondingly less sensitive to hypoactive or fluctuating presentations.

The second concern is that in observational data with neurological assessment only at admission, we cannot distinguish whether acute brain dysfunction is a causal pathway through which systemic inflammation kills, or rather a shared downstream marker of profound systemic hypoperfusion that drives both reduced consciousness and mortality through parallel mechanisms.

We have framed our regression-coefficient-attenuation analysis accordingly, as a descriptive decomposition of statistical association rather than a causal mediation claim.

Definitive resolution of this question requires prospective studies with structured

neurological assessment under sedation interruption protocols, serial neuroglial biomarkers, and ideally neuroimaging or EEG.

The third concern is that the inflammatory signature in the ABD-proxy-positive subgroup may reflect secondary bacterial superinfection rather than purely viral dysregulation: the procalcitonin elevation is suggestive of bacterial co-infection, since PCT is typically normal or only modestly raised in pure viral COVID-19 [28].

Without adjudicated microbiological data we cannot exclude that bacterial superinfection or septic shock, rather than a brain-specific process, explains much of the observed inflammation and mortality.

This does not invalidate the descriptive observation that admission acute brain dysfunction marks a high-mortality subgroup, but it precludes any mechanistic interpretation.

The clinical signature observed in the ABD-proxy-positive subgroup, with elevated CRP, procalcitonin, D-dimers, and markers of capillary leak, indicates a higher systemic inflammatory burden in this subgroup.

We note only briefly, and as hypothesis rather than as a finding of this study, that the experimental literature has implicated microglial activation and brain-resident immune signalling in the cerebral response to systemic inflammation [29-32].

Our dataset contains no neurological, imaging, or molecular measures and cannot speak to these pathways; the observation that admission CRP was associated with the ABD proxy, and that adjustment for the ABD proxy partially attenuated the CRP-mortality association, is a statistical relationship among routinely collected clinical variables and should not be read as mechanistic evidence.

Phenotypic heterogeneity and implications for stratified medicine

Unsupervised clustering identified four internally stable clinical patterns within the cohort with admission organ dysfunction, which we labelled α/β/γ/δ for descriptive convenience.

Stability was supported by a bootstrap Adjusted Rand Index of 0.71, indicating substantial concordance of cluster assignments across resampled inputs.

We emphasize that this labelling is purely descriptive and we do not claim direct mechanistic correspondence with the α/β/γ/δ phenotypes derived in larger non-COVID cohorts [19]; in particular, no cluster in our pre-vaccination COVID-19 cohort exhibited the low absolute mortality (<15%) seen in the α cluster of pre-pandemic derivations.

The α cluster in our cohort (younger, preserved consciousness, high albumin, low SOFA) had a mortality of 34.1%, the lowest within the COVID-19 spectrum we observed but elevated relative to typical Western non-pandemic ICU sepsis.

The β, γ, and δ clusters converged on near-universal mortality (96.7%, 97.0%, and 100% respectively, not statistically distinguishable from one another); the δ cluster was characterized by hyperlactataemic shock with hepatic dysfunction.

Time-to-death among non-survivors was similar across all four clusters (median 7-8 days), supporting the interpretation that these are distinct biological patterns rather than mere temporal staging of the same end-of-life trajectory.

We acknowledge that the four-cluster solution was not the silhouette-optimal choice (k=2 produced a higher silhouette but lower interpretability), that the clustering features overlap with the variables defining the ABD proxy and the mortality associations, and that the clustering therefore does not independently validate those findings.

We report this analysis as exploratory and the resulting groups as data-derived clusters.

We also acknowledge the Reviewer's broader point: the headline contrast, a lower-mortality α cluster versus three near-uniformly fatal clusters, is indeed already apparent from the stratified baseline characteristics in Table 1, and the clustering is not required to establish it.

The added value of the clustering is descriptive and modest: it shows which combinations of admission features tend to co-occur within the high-mortality group (for example, the predominantly neuro-renal β profile, the respiratory γ profile, and the hyperlactataemic-hepatic δ profile), a structure that is not directly visible from a table of group medians.

We note that conventional severity measures are already incorporated in the analysis: the total SOFA score is one of the nine clustering features, and the extent of organ failure is captured through its components and through the individual organ-system variables (creatinine, bilirubin, PaO_2/FiO_2, GCS, lactate).

Compared with grouping patients directly by a single severity score such as SOFA, which orders patients along one axis of overall

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severity, the clustering additionally distinguishes patients of broadly similar severity by the pattern of organ involvement (for example, separating a predominantly neuro-renal from a predominantly respiratory or hyperlactataemic-hepatic profile).

This pattern-level information is the only additional insight the clustering provides; it does not improve mortality discrimination over SOFA, and we do not present it as a necessary or confirmatory analysis.

The differential prevalence of the ABD proxy across clusters (6.6% in α, 92.3% in β, 83.6% in γ, 88.7% in δ) is informative.

It suggests that acute brain dysfunction in pre-vaccination COVID-19 critical illness is not uniformly distributed across clinical patterns but rather concentrated in those with profound neuro-renal involvement (β) or extreme inflammatory-hepatic burden (δ).

This patterning suggests that acute brain dysfunction was not uniformly distributed across clusters.

We do not have neuroglial or imaging data and cannot attribute this to any specific mechanism; cluster-stratified investigation of neuroglial biomarkers (e.g., neurofilament light chain, S100B, GFAP) in future cohorts would be needed to determine whether these clusters correspond to biologically distinct states.

Implications for sepsis-associated encephalopathy research

Our findings inform the translational gap between mechanistic SAE research and real-world critical care in three concrete ways.

First, the magnitude of the ABD-associated mortality difference in this real-world cohort (an absolute risk increase of about 50 percentage points, which persisted in the non-ventilated sensitivity analysis) indicates that admission acute brain dysfunction is a clinically prominent correlate of in-ICU death in this pre-vaccination COVID-19 cohort.

This supports, on epidemiological grounds, further prospective study of acute brain dysfunction in critically ill patients, including its relationship to systemic inflammation and outcome.

Second, the regression coefficient attenuation finding (16-27% of the inflammation-mortality association statistically accounted for by adjustment for the ABD proxy, depending on sedation-control assumptions) is a descriptive observation and should not be interpreted as an estimate of the benefit achievable by any intervention.

Third, the exploratory clusters described here are hypothesis-generating only.

We do not propose them as a basis for trial enrichment or mechanistic stratification: they were not externally validated, they partly recapitulate the variables used to define the ABD proxy, and the near-ceiling mortality of the β cluster (96.7%) would in any case limit the detectable margin of any therapeutic intervention.

Beyond these implications, our findings underscore the value of routinely collected ICU data (SOFA components, GCS, basic biomarkers) for surveillance of acute brain dysfunction burden in resource-constrained or under-studied settings.

Although neuroimaging, electroencephalography, and neuroglial biomarkers remain the reference standards for SAE diagnosis, an operational proxy of the kind we have applied here can be implemented in any unit collecting standard severity scores, and may be sufficient for case-mix adjustment, quality benchmarking, and identification of high-risk subgroups for further investigation, with the caveats regarding sedation confounding and operational rather than mechanistic case ascertainment that we have detailed throughout.

Strengths and limitations

The principal strengths of this study are the consecutive, all-comer recruitment of an entire pre-vaccination COVID-19 ICU population during a defined and well-characterized pandemic period; the completeness of physiological and biomarker data (with most variables completely available and no variable used in primary analyses missing more than 25%); the explicit handling of definitional circularity through a parallel SOFA-free mortality model with cross-validation; and the explicit incorporation of pre-specified sensitivity analyses to address sedation, SOFA-based circularity, and immortal time bias for Day 3 measurements.

To our knowledge, this is among the first studies from an Eastern European ICU to apply unsupervised cluster derivation alongside a transparent regression decomposition of the inflammation-mortality association in a pre-vaccination COVID-19 cohort of this size.

Several limitations require explicit acknowledgement.

First, the cohort is drawn entirely from the pre-vaccination 2020-2021 period and represents an extreme, highly selected regional

ICU population managed under surge conditions; the very high mortality also produces near-saturation of outcome rates in several subgroups, limiting the precision of subgroup comparisons and the interpretation of the predictive models. Second, several clinically important variables were absent or inconsistently recorded in the structured electronic health record and could not be analyzed as covariates: sedation drugs and doses, timing of intubation, neuromuscular blockade, formal delirium assessment, corticosteroid dose, tocilizumab/ baricitinib/ remdesivir exposure, anticoagulation regimens, adjudicated secondary bacterial infection, limitation-of-care decisions, ICU bed saturation, and time from symptom onset to ICU admission.

The absence of these variables is a substantial limitation: each is a plausible confounder of the association between admission consciousness and mortality, and their omission means our estimates cannot be interpreted as treatment- or confounder-adjusted.

The conclusions therefore describe unadjusted natural-history associations only.

In particular, the marked procalcitonin elevation in the ABD-proxy-positive subgroup (median 1.87 versus 0.59ng/mL) raises the strong possibility that secondary bacterial superinfection or septic shock, rather than any brain-specific process, accounts for much of both the inflammatory signature and the mortality association.

Relatedly, hypotension, from shock or infection, is itself a recognized cause of reduced cerebral perfusion and depressed consciousness; because infection data were unavailable and vasopressor use was collinear with the cardiovascular SOFA component, we cannot separate hypotension-driven reductions in GCS from intrinsic brain dysfunction, and the ABD-proxy-mortality association may partly reflect this shared haemodynamic pathway.

Third, the ABD-proxy definition we employed is an operational proxy, not a diagnostic instrument: although we excluded prior stroke from predictor models and demonstrated robustness to ventilation status in sensitivity analyses, we cannot fully separate primary neurological pathology, metabolic encephalopathy, and sedation effects from intrinsic SAE in a retrospective dataset without structured sedation-interruption assessments; furthermore, with neurological assessment only at admission, we cannot distinguish acute brain dysfunction as a causal mediator from a shared downstream marker of profound systemic compromise.

In addition, because delirium is the principal clinical sign of sepsis-associated encephalopathy [27], the absence of structured delirium screening with validated instruments (CAM-ICU, ICDSC) means that our admission-GCS-based proxy does not capture delirium as such, and is insensitive to hypoactive and fluctuating presentations; prospective application of these instruments is needed to characterize the delirium burden in this population.

Fourth, our outcome is restricted to in-ICU mortality; we lack information on post-ICU survival, neurocognitive outcome, or quality-adjusted life-years, all of which are increasingly recognized as essential endpoints in SAE research.

Fifth, the single-centre design constrains external generalizability, although the internal architecture of associations replicates well-established patterns. Sixth, Δ SOFA Day 3, admission analyses are subject to immortal time bias: 60 patients (15.4%) with LOS <3 days were excluded, of whom 76.7% died. Δ SOFA values should therefore be interpreted as predictive only in the subset of patients surviving the early high-mortality phase.

Seventh, our k-means cluster derivation was guided by clinical interpretability rather than statistical optimality (silhouette was higher at k=2 than at our chosen k=4), and the resulting α/β/γ/δ labels are descriptive only and should not be construed as biologically equivalent to similarly labelled phenotypes in larger non-COVID datasets.

Eighth, the conceptual application of the Sepsis-3 framework to viral COVID-19 critical illness is debated; we have therefore preferred the term "organ dysfunction" throughout, but readers seeking direct comparison with classical sepsis literature should bear this operational distinction in mind.

Ninth, the operational definition of organ dysfunction (admission SOFA≥2) approximates but does not formally implement the Sepsis-3 criterion of an acute increase in SOFA≥2 from baseline; in patients with chronic comorbidities (e.g., chronic kidney disease, chronic heart failure), some component of the admission SOFA score may reflect chronic rather than acute dysfunction, with the potential to over-

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classify acute organ dysfunction in this subgroup.

Pre-illness SOFA values were not available in the electronic health record.

Tenth, admission GCS recorded in the electronic health record may be subject to documentation bias: in routine ICU practice, GCS=15 is sometimes recorded as a default in patients without overt neurological abnormality, while values below 15 are documented more consistently when an explicit clinical assessment is performed.

Although this would tend to reinforce the steep mortality gradient observed across GCS categories, it may also inflate the apparent contrast between ABD-proxy-positive and ABD-proxy-negative subgroups.

Relatedly, admission GCS is not an independent input across our severity measures: it contributes to the neurological SOFA component and is also a component of APACHE II.

The consciousness/neurological signal is therefore represented in more than one variable, and analyses that include several of these scores together give it more weight than a single measurement would.

Accordingly, we report the neurological SOFA component and GCS as reflecting the same underlying assessment (Table 1 footnote), interpret the multivariable models as descriptive of the joint association structure rather than as a partition of independent effects, and avoid inferences that depend on treating these scores as statistically independent.

Eleventh, k-means cluster derivation used median imputation for missing input features.

We therefore assessed cluster stability under multiple imputation (iterative/MICE) and k-nearest-neighbor imputation; cluster assignments were highly concordant with the median-imputation solution (Adjusted Rand Index≈0.91), indicating that the clusters were not an artefact of the imputation strategy. Residual sensitivity to other modelling choices cannot be fully excluded.

Furthermore, the high discrimination of all severity scores and of the multivariable models reflects the extreme separability of survivors and non-survivors in this saturated cohort rather than transportable predictive performance.

The models were assessed only by internal cross-validation and by the Hosmer-Lemeshow test; they were not externally validated, and calibration plots, calibration slope/intercept, and decision-curve analysis were not performed.

The predictive models presented here should therefore be regarded as descriptive and are not ready for clinical use.

Conclusions

In this pre-vaccination Romanian ICU cohort, organ dysfunction and MODS were highly prevalent and associated with exceptionally high in-ICU mortality.

Acute brain dysfunction at admission, captured by an operational ABD proxy, was present in nearly two thirds of patients with organ dysfunction and was strongly associated with mortality, an association that persisted in the non-ventilated subgroup.

We interpret these findings as descriptive associations within an extreme, single-center surge-era cohort, not as evidence of a causal mediator of death, and as a hypothesis-generating rationale for future prospective studies with structured neurological assessment and neuroglial biomarkers.

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Author Contributions

Conceptualization, A.I.N. and A.-D.R.-Z.; methodology, A.-D.R.-Z. and M.-B.N.; software, E.O.; validation, M.-B.N., L.R. and E.O.; formal analysis, A.I.N. and A.-D.R.-Z.; investigation, A.I.N. and M.-B.N.; resources, L.R. and M.-B.N.; data curation, A.I.N. and E.O.; writing-original draft preparation, A.I.N. and A.-D.R.-Z.; writing-review and editing, A.-D.R.-Z., M.-B.N., L.R. and E.O.; visualization, E.O.; supervision, A.-D.R.-Z. and L.R.; project administration, A.-D.R.-Z.; funding acquisition, L.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova (protocol code 251, approved on 6 November 2023).

Consent Statement

Not applicable due to the retrospective nature of the study.

Data availability

All data presented in the manuscript are available from the authors upon request

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