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Fatigue after critical illness: prevalence, trajectories, and longitudinal associations in a multicenter ICU survivor follow-up program

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ABSTRACT

Background

Fatigue is a common and disabling sequela among survivors of critical illness, yet its long-term trajectory and clinical correlates during recovery remain poorly understood, particularly its dynamic evolution over time and its relationship with physical and psychological domains of recovery.

Methods

We conducted a prospective multicenter observational study embedded in a structured ICU follow-up program across six Italian hospitals. Outcomes were assessed during standardized in-person visits at 3, 6, 12, and 24 months after ICU discharge.

Fatigue was assessed using the Fatigue Severity Scale (FSS; severe fatigue defined as FSS ≥36). Muscle strength and functional exercise capacity were evaluated using handgrip dynamometry and the six-minute walk test (6MWT), and psychological symptoms using the Hospital Anxiety and Depression Scale (HADS).

Generalized linear mixed models (GLMM) with time-lagged variables were used to examine whether clinical measures at one visit were associated with severe fatigue at the subsequent visit, including prior fatigue status to account for preceding fatigue burden.

Results

A total of 1,912 ICU survivors attended at least one follow-up visit, of whom 976 patients (51%) experienced severe fatigue at least once. The prevalence of severe fatigue was

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336/967 (34.7%) at 3 months, 628/1,522 (41.3%) at 6 months, 434/1,135 (38.2%) at 12 months, and 64/217 (29.5%) at 24 months. Persistent severe fatigue across multiple visits was observed in 655 patients (34.3%), and individual trajectories were heterogeneous over time.

In GLMM with time-lagged variable, prior fatigue status (OR 3.00, 95% CI 1.31–6.84), lower functional exercise capacity on the 6MWT (OR 0.77, 95% CI 0.61–0.95), and symptoms of anxiety (OR 6.76, 95% CI 2.01–22.68) and depression (OR 17.8, 95% CI 4.16–76.47), all measured at the preceding visit, were associated with severe fatigue at the subsequent visit.

Conclusions

Severe fatigue remained common up to 24 months after ICU discharge, with heterogeneous trajectories over time and persistent severe fatigue affecting approximately one-third of survivors. Prior fatigue status, lower functional exercise capacity, and psychological distress were associated with subsequent fatigue, supporting the value of multidimensional assessment of recovery within structured ICU follow-up programs.

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Keywords: fatigue, 6-minute walk test, functional exercise capacity, anxiety, depression, long-term outcome, follow-up.

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Statements and Declarations.

Author's contributions: NL, SP, and MB contributed to the conceptualization and design of the study. NL, SP, MB, and ML contributed to the development and amendment of the protocol. EP, SB, RC, GM, MP, PP, FR, FT, AL, SS, LQ, AC, and GC contributed to patient

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enrolment, study implementation, and data acquisition. ML contributed to data management. SP, NL, and SR contributed to data analysis. SP and NL drafted the initial manuscript of this article. NL, MB, and SP directly accessed and verified the data. SP has confirmed that all authors reviewed and approved the final manuscript. All authors had full access to the raw data and had final responsibility for the decision to submit for publication.

Conflict of interest: The authors declare no conflicts of interest related to this study.

Ethical Approval and Consent to participate: The study was approved by the Ethics Committee of Brescia (NP 3369) and by the local Ethics Committees of all participating centers, and was registered at ClinicalTrials.gov (NCT04608994). All patients provided informed consent to participate in the ICU survivor follow-up program at the time of the follow-up visit.

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Data Sharing Statement: Deidentified individual participant data that underlie the results reported in this article, together with the data dictionary defining each field in the dataset, will be made available. In addition, statistical R code will be available upon request. Data will be available upon publication and will remain accessible for 5 years thereafter. Data will be made available through DOI: 10.17632/3vnfg9tt5p.1. Access will be granted to researchers who provide a methodologically sound proposal for use in achieving the aims of their approved scientific project. Proposals should be directed to

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nicola.latronico@unibs.it. To gain access, data requestors will need to sign a data access agreement, and data will be shared following approval of the proposal.

INTRODUCTION

Fatigue is a subjective symptom characterized by an overwhelming sense of tiredness, lack of energy, and exhaustion that may limit an individual's ability to initiate or sustain physical and mental activities (1). In survivors of critical illness, fatigue represents one of the most frequent and persistent long-term complaints. Studies suggest that up to 70% of ICU survivors experience significant fatigue during the months following hospital discharge, often as part of the post-intensive care syndrome (PICS) (3). Fatigue may persist for 6 to 12 months or longer, and is associated with reduced functional and psychological health status, impaired health-related quality of life (HRQoL), and delayed return to work or normal daily activities (4, 5). Most studies of post-ICU fatigue have relied primarily on telephone interviews and self-reported questionnaires, which, although practical and scalable, provide limited opportunity to integrate objective assessments of muscle strength and functional exercise capacity (3–5). Structured ICU follow-up programs provide a unique clinical setting in which physical performance testing, psychological assessment, and patient-reported outcomes are assessed within a multidisciplinary framework. Within these programs, longitudinal in-person assessments conducted as part of routine clinical care may provide a comprehensive and clinically feasible characterization of fatigue trajectories and their relationship with recovery domains over time.

In this study, we adopted the International Classification of Functioning, Disability and Health (ICF) framework developed by the World Health Organization (WHO), which conceptualizes functioning and disability as the dynamic interaction between body functions, activities, and societal participation (6). The ICF framework was used as an organizational structure for multidimensional recovery assessments within the ICU follow-up program. This approach allowed fatigue to be examined alongside measures of physical

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function, functional exercise capacity, and psychological symptoms during recovery after critical illness (7).

The aim of this study was to describe the prevalence and longitudinal trajectories of fatigue after critical illness and to examine whether physical and psychological recovery domains were associated with subsequent fatigue over time, using a time-lagged approach.

METHODS

Study Design and Setting

This study was conducted within a structured ICU survivorship follow-up program, developed as part of the Long-Term Outcome (LOTO) project in Italy. The program represents a permanent clinical service providing standardized post-ICU evaluations to survivors of critical illness, aimed at identifying physical, cognitive, and psychological sequelae after ICU admission. As such, this study reflects routine clinical practice within an ongoing follow-up program rather than a one-time research cohort.

The clinical program operates in close collaboration with the “Alessandra Bono” Interdepartmental University Research Center for Long-Term Outcome in survivors of critical illness (LOTO), which coordinates a national multicenter network and supports research activities. Clinical data collected during routine follow-up visits are prospectively integrated into a research database. This infrastructure supports observational studies on long-term outcomes after critical illness.

For the present study, data were analyzed from six hospitals participating in the LOTO network. The protocol was approved by the Ethics Committee of Brescia (NP 3369) and by the local committees of all centers, registered at ClinicalTrials.gov (NCT04608994). Written informed consent was obtained from all participants. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Additional methodological details are provided in the Online Data Supplement.

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Participants

Consecutive adults (≥ 18 years) admitted to an intensive care unit (ICU) between January 1, 2016, and March 23, 2023, were screened. Inclusion criteria were survival to hospital discharge and an ICU stay of ≥72 hours. Patients were not excluded on the basis of pre-existing comorbidities, including neurological or degenerative conditions, nor for pre-existing physical dependence. Comorbidity burden was recorded using the Charlson Comorbidity Index and accounted for in the analyses. Patients were invited to attend in-person assessments at 3, 6, 12, and 24 months after ICU discharge.

ICU Data Collection

Demographic and clinical data, including age, sex, body mass index, comorbidities, admission diagnosis, illness severity (Simplified Acute Physiology Score II), and major treatments (mechanical ventilation duration, tracheostomy, catecholamine and steroid use, renal replacement therapy, ICU and hospital length of stay), were collected prospectively. Definitions of acute respiratory distress syndrome (ARDS) and COVID-19 followed established criteria (8, 9). Early mobilization followed the ABCDEF bundle (10).

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Follow-up Assessments

Patients were evaluated during standardized in-person visits conducted at predefined time points after hospital discharge as part of routine clinical follow-up.

Attendance to scheduled follow-up visits reflected routine clinical practice and was voluntary. Consequently, participation varied across visits and analyses were performed on patients who attended each assessment. No specific incentives were provided for participation, as visits were part of routine post-ICU clinical care.

Guided by the ICF framework, follow-up assessments captured complementary domains of post-critical illness recovery, including fatigue, muscle strength, functional exercise capacity, and symptoms of psychological distress.

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Fatigue was assessed using the Fatigue Severity Scale (FSS), a brief, standardized 9-item patient-reported outcome of the impact of fatigue on daily functioning (total score range, 9-63, with higher scores indicating greater fatigue impact) (11). The FSS was selected because it is brief, standardized, and feasible for repeated assessment within routine ICU follow-up visits, while capturing fatigue-related interference with daily activities. Severe fatigue was defined a priori as FSS >=36, corresponding to a mean item score >=4. Because this threshold was derived from non-ICU populations and no ICU-specific FSS cutoff has been established, it was used as an operational definition of high fatigue burden rather than a diagnostic threshold. Persistent fatigue was defined as severe fatigue present at two or more consecutive follow-up visits and was summarized descriptively.

The patient's functioning was evaluated by measuring (6):

a) muscle strength using the Medical Research Council Sum Score (MRCss) and handgrip dynamometry (HGD); for the MRCss, mild and significant ICUAW were defined as MRCss<55 and MRCss<48, respectively (12). Handgrip strength was expressed as percent-predicted values based on age- and sex-specific reference values, with lower values indicating reduced muscle strength;

b) functional exercise capacity using the 6-minute walk test (6MWT), which integrates multiple physiological and behavioral domains; predicted values were calculated using established equations (13).

c) basic activities of daily living using the Barthel Index (14).

Restrictions in participation were not directly measured using ICF-based participation instruments; however, selected SF-36 domains (including Role Physical and Social Functioning) capture aspects of participation and social roles (15).

Health-related quality of life was assessed with the SF-36 (15). Cognitive status was measured by the Montreal Cognitive Assessment (16). Symptoms of anxiety and depression were quantified with the Hospital Anxiety and Depression Scale (17); post-traumatic stress disorder with the PCL-5 (18); and insomnia with the Insomnia Severity Index (19). All

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instruments are validated and widely used in post-ICU research; further procedural details are provided in the Online Data Supplement.

Statistical Analysis

Continuous variables were summarized as mean ± SD or median [IQR], and categorical variables as counts (%). Percentages at each time point were calculated using the number of patients assessed at that visit as the denominator.

Candidate variables considered during model building included demographic variables, COVID-19 status, ICU severity variables, and follow-up measures of muscle strength, functional exercise capacity, psychological symptoms, and prior fatigue status. To reduce model complexity, candidate variables were first screened using Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression with 10-fold cross-validation (20). LASSO was used solely for variable selection, not for estimating final effect sizes. Variables retained by LASSO were subsequently included as fixed effects in a Generalized Linear Mixed Model (GLMM) with a patient-level random intercept to account for repeated observations within participants (21). Age, sex, follow-up time point, and prior fatigue status were retained a priori irrespective of LASSO selection. Final odds ratios and 95% confidence intervals were obtained from the GLMM and should be interpreted as conditional on the selected model.

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The primary multivariable analysis evaluated severe fatigue at the subsequent visit using time-lagged covariates. To strengthen temporal ordering and reduce the potential for reverse temporal associations, values measured at follow-up visit t–1 were used to estimate the odds of severe fatigue at visit t.

Prior fatigue status at visit t–1 was included to account for preceding fatigue burden and to distinguish persistence from new or recurrent fatigue. Consecutive visit pairs (3→6 months, 6→12 months, and 12→24 months) contributed to the analyses. Patients whose first observed follow-up visit occurred at 6 or 12 months could contribute lagged pairs from

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their first observed visit onward; no unobserved prior fatigue status was imputed. Available attendance pairs were defined as consecutive visit pairs in which the patient attended both visits, whereas complete-case analytic pairs were defined as attendance pairs with non-missing outcome and covariate data for the corresponding model. We report both the number of available attendance pairs and the number of complete-case analytic pairs contributing to each model. The time-lagged LASSO-GLMM was performed as a complete-case analysis, requiring non-missing values for the outcome, the lagged outcome, and all candidate variables entered into the penalized selection step. This complete-case requirement resulted in an analytic sample of 622 consecutive visit pairs, all derived from patients without COVID-19; therefore, COVID-19 status could not be retained in the final model or tested as an interaction term because there was no residual variation in COVID-19 status within the analytic sample. Accordingly, odds ratios should be interpreted as associations between clinical status at the preceding observed visit and severe fatigue at the subsequent observed visit, conditional on prior fatigue status and other covariates. Mixed-effects models allowed participants with complete follow-up to contribute all eligible complete-case visit pairs while accounting for within-patient correlation. Multicollinearity among covariates included in the multivariable models was assessed using variance inflation factors (VIFs), with VIF values <5 considered to indicate no problematic multicollinearity. Because the study was embedded in a real-world clinical follow-up program, incomplete attendance across visits was expected. To explore potential differences associated with follow-up participation, characteristics measured at the 3-month visit were compared across groups defined by subsequent follow-up attendance (≥2 subsequent visits, 1 subsequent visit, or no visit beyond 3 months). Continuous variables were compared using the Kruskal-Wallis test and categorical variables using the χ^2 test. To evaluate the potential impact of differential follow-up attendance, a sensitivity analysis using inverse probability weighting (IPW) was performed. The probability of attending follow-up visits at 6, 12, and 24 months was estimated using logistic regression models including demographic characteristics, ICU severity variables, and clinical status at the

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preceding visit. Stabilized weights were calculated using a numerator model that included age, sex, and visit time point, and a denominator model that additionally included baseline severity and prior-visit clinical variables. Weights were truncated at the 5th and 95th percentiles and applied in weighted logistic regression models with patient-level cluster-robust standard errors. All tests were two-sided ($\alpha = 0.05$) and performed in R v4.5.0 (22).

RESULTS

We evaluated 1,912 ICU survivors in six centers, of whom 500 (26%) were patients with COVID-19, with a median age of 59 years (IQR 48-69), a median ICU length of stay of 9 days (IQR 6-15), and a substantial burden of critical illness, including high rates of ARDS and mechanical ventilation. **Table 1** presents their main characteristics at ICU admission.

Figure 1 presents follow-up visit attendance across the study time points. Based on visit attendance, the number of possible consecutive visit pairs was 704 for 3-to-6 months, 970 for 6-to-12 months, and 211 for 12-to-24 months. After requiring non-missing outcome, lagged outcome, and candidate-variable data for the LASSO selection step, 622 consecutive visit pairs contributed to the complete-case time-lagged LASSO-GLMM analysis. All visit pairs in this analytic sample were derived from patients without COVID-19; therefore, COVID-19 status had no residual variability and could not be evaluated as either an independent variable or an interaction term in the final time-lagged model. Overall, 976 of 1,912 patients (51%) experienced severe fatigue at least once during follow-up. The prevalence of severe fatigue at each visit was 336/967 (34.7%) at three months, 628/1522 (41.3%) at six months, 434/1135 (38.2%) at 12 months, and 64/217 (29.5%) at 24 months, as shown in Table S1. The prevalence of impairments across fatigue, physical, cognitive, and psychological domains at each follow-up time point is summarized in **Table S1**.

Figure 2 illustrates transitions between fatigue and non-fatigue states, including patterns of early fatigue, recurrent fatigue, and late-onset fatigue, among patients who were initially fatigue-free. Persistent fatigue was observed in 655 of 1,912 patients (34.3%).

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Age-, sex-, and follow-up time-adjusted associations between baseline and ICU characteristics, as well as physical, mental, and cognitive status, and severe fatigue are shown in **Tables S2 and S3.** Severe fatigue was significantly associated with increasing age, female sex, comorbidities, non-COVID-19 diagnosis, absence of steroid therapy, tracheostomy, longer ICU length of stay, and impairments across the PICS domains.

The results of the 622 complete-case LASSO-GLMM analysis are shown in **Figure 3**. Severe fatigue at the preceding visit (OR = 3.0, 95% CI 1.31 to 6.84, p = 0.009), lower functional exercise capacity on the 6MWT (OR = 0.77, 95% CI 0.61 to 0.95, p = 0.017), and clinically relevant symptoms of anxiety (OR 6.76, 95% CI 2.01–22.68) and depression (OR 17.8, 95% CI 4.16–76.47), all measured at the preceding visit, were independently associated with severe fatigue at the subsequent visit.

Pairwise correlations were low, and variance inflation factors (VIFs) for fixed effects were all close to 1, indicating no evidence of problematic multicollinearity in the model (**Table S4**).

At the 3-month visit, baseline characteristics differed across groups defined by subsequent follow-up attendance, with patients who attended ≥2 subsequent visits generally showing greater illness severity and resource use (e.g., longer ICU length of stay, longer duration of mechanical ventilation, and higher SAPS II scores (**Table S5**). However, in sensitivity analyses using IPW to account for potential bias due to differential follow-up attendance, the estimates from the multivariable model remained consistent with the primary analysis (**Table S6**).

DISCUSSION

In this large multicenter prospective study of ICU survivors followed for up to 24 months, we identified four main findings. First, fatigue was highly prevalent, with more than one-third of participants affected at each follow-up visit and over half experiencing severe fatigue at least once during the study period. Second, individual trajectories of severe

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fatigue were heterogeneous, with approximately one-third of patients showing persistent fatigue across multiple visits. This descriptive estimate should be interpreted in the context of variable visit attendance in this real-world follow-up program. Third, lower functional exercise capacity and psychological distress were associated with subsequent fatigue, even after accounting for prior fatigue status. Finally, prior fatigue was associated with subsequent fatigue, while ICU-related clinical variables, cognitive function, and sleep disturbances were not retained in the final multivariable model. These findings highlight the long-term burden of fatigue after critical illness and identify recovery domains that may warrant attention during follow-up and rehabilitation.

The high prevalence and persistence of fatigue in our cohort align with previous reports identifying fatigue as a core feature of PICS (3–5). Our findings indicate that fatigue remains both prevalent and fluctuating long after hospital discharge, reinforcing the need for prolonged surveillance and support.

The longitudinal structure of our follow-up assessments highlights the dynamic nature of fatigue during recovery after critical illness. Individual transition patterns revealed heterogeneous fatigue trajectories, with some patients experiencing persistent fatigue, others recovering over time, and others developing recurrent or late-onset fatigue during follow-up. These findings suggest that fatigue after critical illness is not a static condition but rather a dynamic component of recovery that may evolve over months or years, with important implications for longitudinal monitoring and multidisciplinary follow-up care.

Together, these findings support a multidimensional view of post-ICU fatigue, in which functional exercise capacity and psychological distress represent complementary recovery domains associated with subsequent fatigue rather than a single underlying mechanism. This interpretation is consistent with the use of structured follow-up clinics to integrate patient-reported outcomes with objective functional testing and psychological assessment.

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Our time-lagged modelling approach extends prior cross-sectional findings by showing that lower functional exercise capacity at one visit was associated with severe fatigue at the subsequent visit. This supports the relevance of temporal ordering in the relationship between functional capacity and fatigue, although it does not imply a unidirectional causal relationship. Fatigue may represent a downstream consequence of impaired physical capacity, a parallel manifestation of systemic dysfunction, such as underlying biological or physiological dysregulation, or a bidirectional process in which fatigue and reduced activity reinforce one another over time.

The observed associations between depressive and anxiety symptoms and subsequent fatigue reinforce the importance of psychological burden in ICU survivors. Psychological distress remained associated with subsequent fatigue after accounting for prior fatigue status, although causal relationships cannot be established. This observation underscores the need for integrated follow-up strategies that address both physical and mental health domains.

A major strength of our study lies in its comprehensive and patient-centered approach. All evaluations were conducted through structured, in-person follow-up visits, allowing for standardized testing and consistent longitudinal data collection. Importantly, the study was embedded in a continuous ICU follow-up program, allowing the assessment of fatigue within routine clinical care rather than a one-time research cohort. The prospective, multicenter design involving a large and diverse patient population supports the relevance of our findings across structured ICU follow-up settings. Unlike many previous studies relying primarily on telephone interviews or self-reported questionnaires, this follow-up program integrates standardized in-person clinical assessments with patient-reported outcomes, allowing a combined evaluation of physical performance, functional capacity, and psychological symptoms during routine follow-up.

This study also has several limitations. First, the FSS ≥36 cutoff used to define severe fatigue was extrapolated from non-ICU populations. Therefore, absolute prevalence

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estimates should be interpreted as threshold-dependent and may differ from studies using other instruments or cutoffs. However, the longitudinal analyses focus on associations and trajectories within a consistently applied operational definition.

Second, the two-stage modeling approach, in which LASSO was used for variable selection before the GLMM, does not fully account for the uncertainty introduced by the variable-selection step. Accordingly, confidence intervals and p-values from the final models should be interpreted as conditional on the selected model and may underestimate statistical uncertainty. This consideration is particularly relevant for depressive symptoms, for which the confidence interval was wide, indicating limited precision despite an association in the expected direction. The multivariable findings should therefore be interpreted primarily as exploratory time-lagged associations rather than as definitive prognostic estimates.

Third, because the study was embedded in a real-world clinical follow-up program, attendance varied across visits, and later time points included fewer patients. Patients who continued follow-up differed from those with fewer visits, suggesting potential selection bias. Although IPW sensitivity analyses yielded estimates consistent with the primary model, weighting cannot account for unmeasured factors influencing attendance; estimates at later time points, particularly 24 months, should therefore be interpreted with greater caution. Accordingly, the 24-month prevalence estimate should be regarded as exploratory rather than confirmatory.

Fourth, residual confounding cannot be excluded, particularly given the lack of pre-ICU functional and psychological assessments and data on post-discharge rehabilitation exposure. The directionality between fatigue and psychological distress remains uncertain, and the observed time-lagged associations should not be interpreted as evidence of causal relationships. Although the ICF framework was used to organize the multidimensional assessment strategy, it was only partially operationalized. In particular, participation was not directly measured using a dedicated ICF-based instrument; therefore, the ICF should

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be interpreted as an organizational framework rather than as a fully specified analytical model.

Fifth, because inclusion required an ICU stay of at least 72 hours, our cohort represents a more severely ill subset of ICU survivors, which may limit generalizability. In addition, although the overall cohort included both COVID-19 and non-COVID ICU survivors across a long enrolment period, the final complete-case time-lagged LASSO-GLMM sample consisted exclusively of non-COVID patients. Therefore, the main multivariable time-lagged findings should be interpreted as primarily applicable to the non-COVID complete-case population. Pandemic-era differences in ICU care, rehabilitation practices, and follow-up engagement may have introduced heterogeneity in the broader cohort, but COVID-19 interaction effects could not be formally assessed within the time-lagged model because COVID-19 status had no residual variability in the analytic sample. This should be considered when interpreting the generalizability of the findings.

Our findings have important implications for clinical practice and research. Objective measures of functional capacity and systematic psychological screening may help identify ICU survivors more likely to experience severe fatigue during follow-up. Given that physical impairment, psychological distress, and prior fatigue status were associated with subsequent fatigue, early rehabilitation and timely mental health support may represent important components of multidisciplinary follow-up programs. Future studies should determine whether interventions targeting physical and psychological recovery domains can modify fatigue trajectories.

Figures

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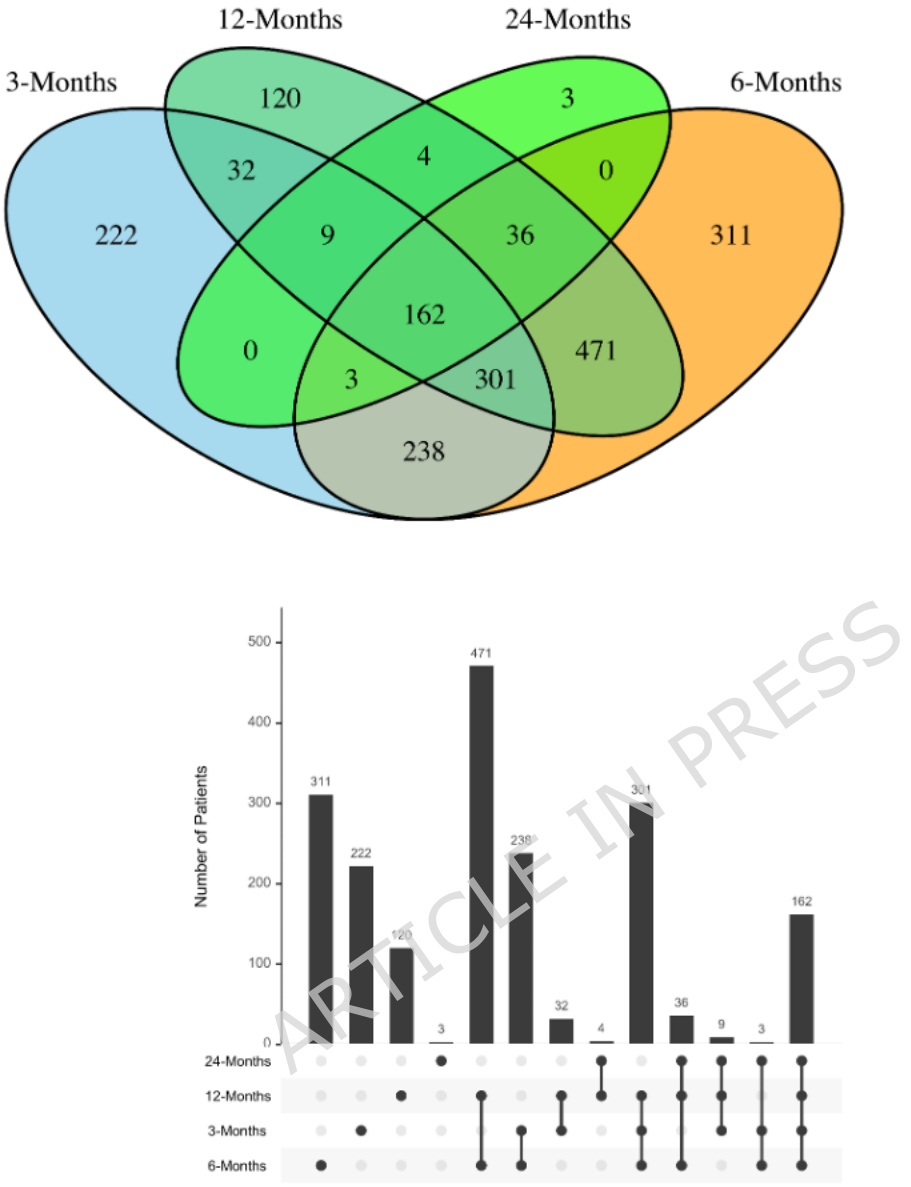


Figure 1: Follow-up attendance patterns across study visits

The upper panel shows a Venn diagram of follow-up attendance at 3, 6, 12, and 24 months. Each coloured ellipse represents one follow-up time point, and overlapping regions indicate patients who attended multiple visits. Numbers within each region indicate the number of patients with that specific combination of completed visits. The lower panel shows the same information using an UpSet plot. In the UpSet plot, vertical bars indicate the number

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of patients in each attendance pattern, while the black dots and connecting lines below each bar identify the specific visit combination represented by that bar; grey dots indicate visits not included in that combination. Together, these visualizations summarize overall follow-up coverage and the heterogeneity of visit attendance across the study period.

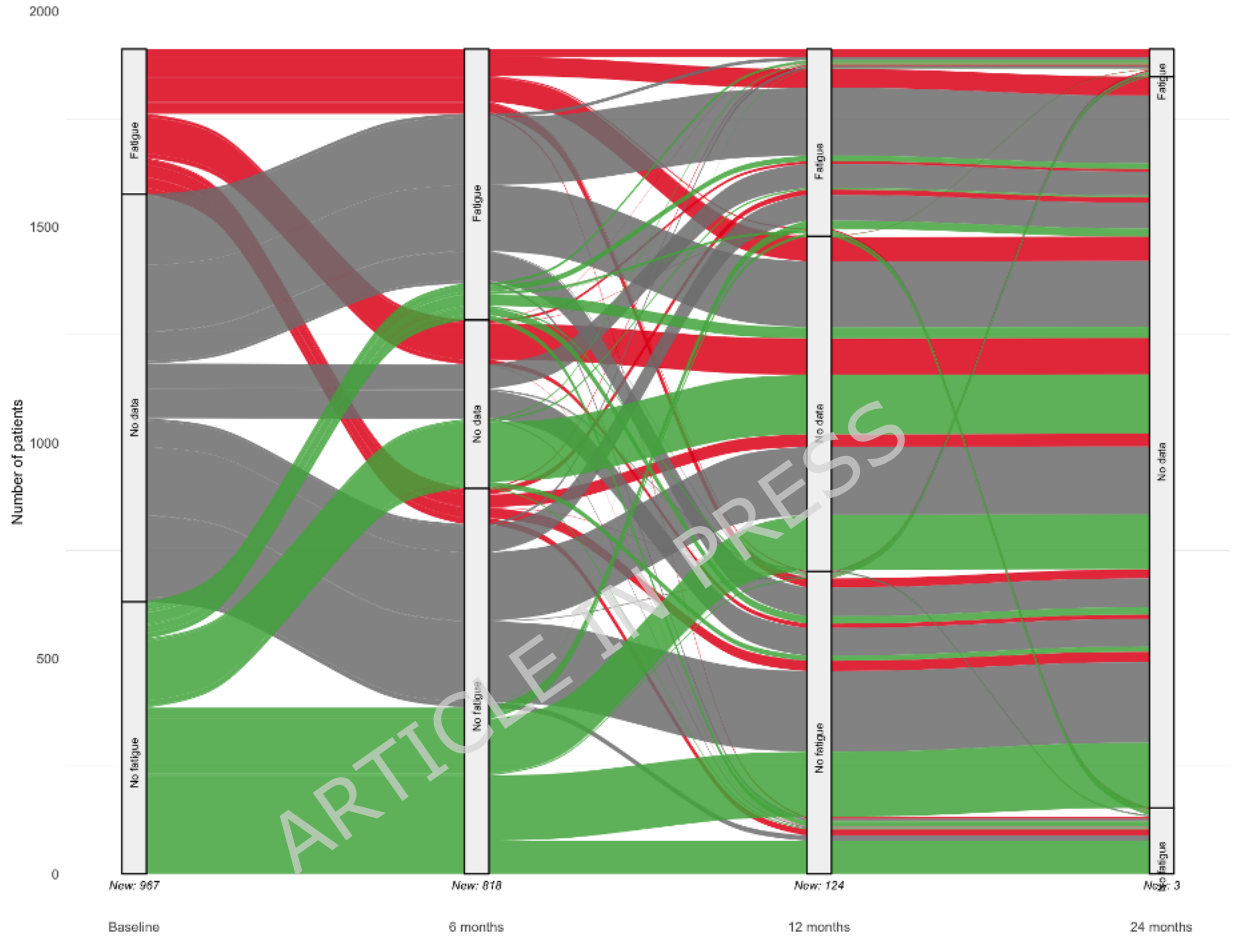
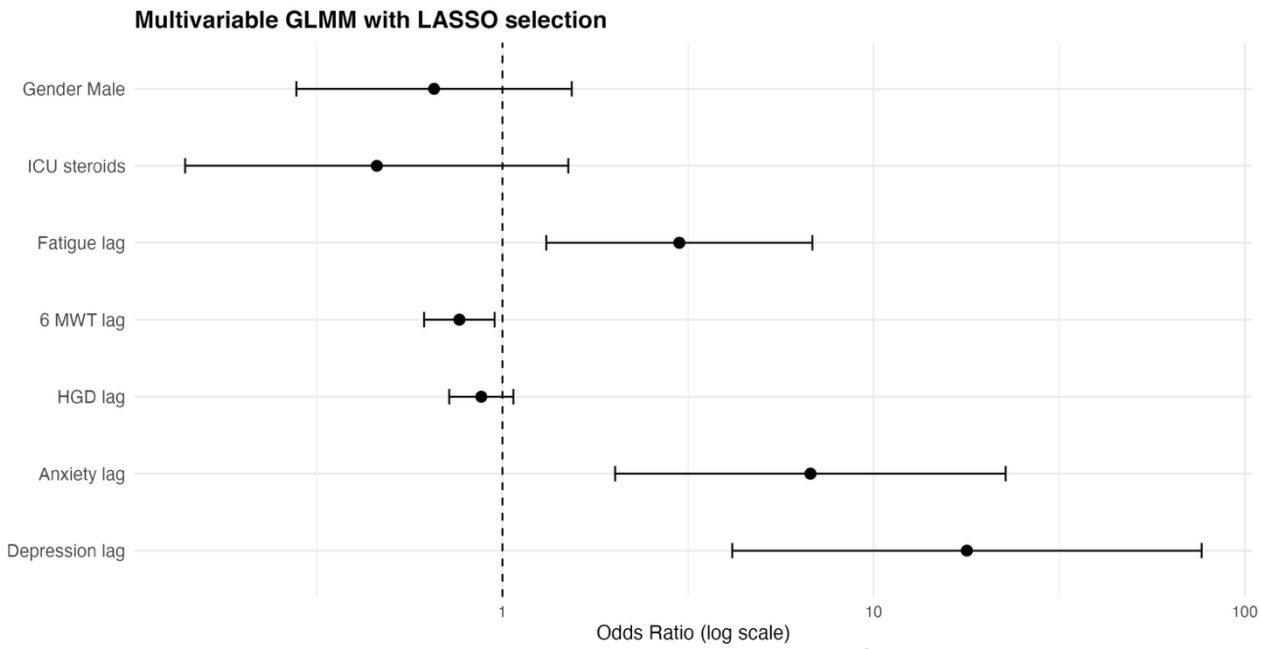


Figure 2: Long-term trajectories of post-ICU fatigue

Alluvial (Sankey) diagram showing how individual patients moved between “No fatigue” (green) and “Fatigue” (red) from the first post-discharge assessment (Baseline, 3 months) through 6 months, 12 months, and 24 months. Ribbon width is proportional to the number of patients following each trajectory; vertical bars display the total number assessed at each visit. Grey ribbons indicate patients who did not attend the follow-up visit. The diagram illustrates patterns of persistence, remission, and late-onset fatigue over time.

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Term	OR	CI	p
Gender Male	0.65	0.28–1.54	0.330
ICU steroids	0.46	0.14–1.51	0.199
Fatigue lag	3.00	1.31–6.84	0.009
6 MWT lag	0.77	0.61–0.95	0.017
HGD lag	0.88	0.72–1.07	0.195
Anxiety lag	6.76	2.01–22.68	0.002
Depression lag	17.83	4.16–76.47	0.000

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Figure 3: Time-lagged factors associated with severe fatigue during follow-up after ICU discharge

Lagged variables were measured at the preceding visit (t-1), and the outcome was severe fatigue at the subsequent visit (t). Odds ratios were estimated using mixed-effects logistic regression with a patient-level random intercept. 6MWT and HGD were expressed as percent-predicted values and scaled per 10-unit increase unless otherwise stated.

Panel A: Forest plot of odds ratios (log scale) from the mixed-effects logistic model with time-lagged variables.

The error bars show 95% confidence intervals.

Panel B: corresponding odds-ratio table.

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6MWT = 6-minute walk test. HGD = Handgrip Dynamometry. HADS = Hospital Anxiety and Depression Scale.

*Variables have been scaled by 10.

Table 1: Baseline demographic and clinical ICU characteristics.

	N=1912
Age, years mean (IQR)	59 (48 – 69)
Sex, Male number (percentage)	1275/1732 (73.6%)
Reason for Admission number (percentage) or median (IQR)	
Sepsis	143 / 1 912 (7.5%)
Acute neurological disorder	448 / 1 912 (23%)
ARDS	710 / 1 912 (37%)
Trauma	283 / 1 912 (15%)
Post-operative	68 / 1 912 (3.6%)
Others	260 / 1 912 (14%)
COVID-19	500 / 1 912 (26%)
BMI at ICU admission, kg/m²	26.7 (23.7-30.6)
SAPS II	26.6 (23.6-30.2)

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MV Duration	6 (2-11)
Tracheostomy	346 / 1 635 (21%)
Use of Steroids*	640 / 1 607 (40%)
Use of catecholamine**	830 / 1 637 (51%)
Number of comorbidities (percentage)**	
0	439 / 1 646 (27%)
1	389 / 1 646 (24%)
2	293 / 1 646 (18%)
3	235 / 1 646 (14%)
More than 3	290 / 1 646 (18%)
ICU LOS days median (IQR)	9 (6 - 15)
H LOS days median (IQR)	27 (18 - 40)

Number reflects the number of patients with non-missing data for that variable.

* Steroid use is intended as either dexamethasone 6mg/day for 10 days (in case of COVID-19) or methylprednisolone 1-2 mg/Kg for 7-15 die (in case of ARDS).

** Refer to the comorbidities listed in the Charlson Comorbidity Index.

ARDS = Acute Respiratory Distress Syndrome. BMI = Body Mass Index. COVID-19= Coronavirus Disease 2019. H = Hospital. ICU = Intensive Care Unit. IQR = interquartile range. LOS = Length of stay. MV = Mechanical Ventilation. SAPS II = Simplified Acute Physiology Score II. SD = Standard deviation.

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References

1. Gruet M, Temesi J, Rupp T, Levy P, Millet GY, Verges S. Stimulation of the motor cortex and corticospinal tract to assess human muscle fatigue. *Neuroscience* 2013;231:384–399.

2. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, *et al.* Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;40:502–509.

3. Neufeld KJ, Leoutsakos J-MS, Yan H, Lin S, Zabinski JS, Dinglas VD, *et al.* Fatigue Symptoms During the First Year Following ARDS. *Chest* 2020;158:999–1007.

4. Morel J, Infantino P, Gergelé L, Lapole T, Souron R, Millet GY. Prevalence of self-reported fatigue in intensive care unit survivors 6 months-5 years after discharge. *Sci Rep* 2022;12:5631.

5. Kennouche D, Foschia C, Brownstein CG, Lapole T, Rimaud D, Royer N, *et al.* Factors associated with fatigue in COVID-19 ICU survivors. *Med Sci Sports Exerc* 2024;56:1563–1573.

6. Buñuales J, Diego G, Moreno M. International classification of functioning, disability and health (ICF). *Rev Esp Salud Publica* 2001;76:271–279.

7. Latronico N, Rasulo FA, Eikermann M, Piva S. Illness Weakness, Polyneuropathy and Myopathy: Diagnosis, treatment, and long-term outcomes. *Crit Care* 2023;27:1–13.

8. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, *et al.* Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.

9. Coronavirus Disease 2019 (COVID-19) 2020 interim case definition, approved April 5, 2020. 2025;at <https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2020/>.

10. Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF bundle in critical care. *Crit Care Clin* 2017;33:225–243.

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11. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–1123.

12. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, *et al.* The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med* 2017;43:1270–1281.

13. Gimeno-Santos E, Vilaró J, Arbilllaga-Etxarri A, Herrero-Cortina B, Ramon MA, Corberó AB, *et al.* Development and comparison of reference equations for the six-minute walk test in Spanish healthy adults aged 45-85 years. *Arch Bronconeumol* 2025;61:459–466.

14. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:61–65.

15. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. *J Clin Epidemiol* 1998;51:1025–1036.

16. McDicken JA, Elliott E, Blayney G, Makin S, Ali M, Larner AJ, *et al.* Accuracy of the short-form Montreal Cognitive Assessment: Systematic review and validation. *Int J Geriatr Psychiatry* 2019;34:1515–1525.

17. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:69–77.

18. Bovin MJ, Marx BP, Weathers FW, Gallagher MW, Rodriguez P, Schnurr PP, *et al.* Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess* 11 2016;28:1379–1391.

19. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601–608.

20. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010;33:1–22.

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ARTICLE IN PRESS

21. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models Usinglme4. *J Stat Softw* 2015;67:.

22. *_R: Language Environment Statistical Computing_. R Foundation Statistical Computing*. Vienna, Austria: 2025.

23. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Shanholtz C, Husain N, *et al.* Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med* 2012;185:517–524.

24. Hosey MM, Needham DM, Kudchadkar SR. Fatigue in critical care survivors: multidisciplinary and self-management strategies. *Anaesthesia* 2021;76:1163–1166.

25. Egger M, Wimmer C, Stummer S, Reitelbach J, Bergmann J, Müller F, *et al.* Reduced health-related quality of life, fatigue, anxiety and depression affect COVID-19 patients in the long-term after chronic critical illness. *Sci Rep* 2024;14:3016.

26. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. *Am J Respir Crit Care Med* 2010;182:446–454.

27. Prescott HC, Angus DC. Enhancing recovery from sepsis. *JAMA* 2018;319:62.

28. Marra A, Pandharipande PP, Girard TD, Patel MB, Hughes CG, Jackson JC, *et al.* Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. *Crit Care Med* 2018;46:1393–1401.

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Fatigue after critical illness: prevalence, trajectories, and longitudinal associations in a multicenter ICU survivor follow-up program

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ABSTRACT

Background

Fatigue is a common and disabling sequela among survivors of critical illness, yet its long-term trajectory and clinical correlates during recovery remain poorly understood,

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particularly its dynamic evolution over time and its relationship with physical and psychological domains of recovery.

Methods

We conducted a prospective multicenter observational study embedded in a structured ICU follow-up program across six Italian hospitals. Outcomes were assessed during standardized in-person visits at 3, 6, 12, and 24 months after ICU discharge.

Fatigue was assessed using the Fatigue Severity Scale (FSS; severe fatigue defined as FSS ≥36). Muscle strength and functional exercise capacity were evaluated using handgrip dynamometry and the six-minute walk test (6MWT), and psychological symptoms using the Hospital Anxiety and Depression Scale (HADS).

~~Mixed-effects logistic regression models with time-lagged predictors~~ Generalized linear mixed models (GLMM) with time-lagged variables were used to examine whether clinical measures at one visit were associated with severe fatigue at the subsequent visit, including prior fatigue status to account for ~~baseline symptom~~ preceding fatigue burden.

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Results

A total of 1,912 ICU survivors attended at least one follow-up visit, of whom 976 patients (51%) experienced severe fatigue at least once. The prevalence of severe fatigue was 336/967 (34.7%) at 3 months, 628/1,522 (41.3%) at 6 months, 434/1,135 (38.2%) at 12 months, and 64/217 (29.5%) at 24 months~~, with no consistent decline over time~~. Persistent severe fatigue across multiple visits was observed in 655 patients (34.3%), and individual trajectories were heterogeneous over time.

In ~~multivariable~~ GLMM with time-lagged ~~analyses~~ variable, ~~fatigue~~ prior fatigue status (OR 3.00, 95% CI 1.31–6.84), lower functional exercise capacity on the 6MWT (OR 0.77, 95% CI 0.61–0.95), and symptoms of anxiety (OR 6.76, 95% CI 2.01–22.68) and depression (OR

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17.8, 95% CI 4.16–76.47), all measured at the preceding visit, were ~~independently~~ associated with ~~higher odds of~~ severe fatigue at the subsequent visit.

Conclusions

Severe fatigue remained common up to 24 months after ICU discharge, with heterogeneous trajectories over time and persistent severe fatigue affecting approximately one-third of survivors. ~~Measures of physical impairment and psychological distress, together with prior fatigue status,~~ Prior fatigue status, lower functional exercise capacity, and psychological distress were ~~independently~~ associated with subsequent fatigue, ~~suggesting that fatigue after critical illness emerges at the intersection of these recovery domains and represents a dynamic component of long-term recovery.~~ supporting the value of multidimensional assessment of recovery within structured ICU follow-up programs.

Keywords: fatigue, 6-minute walk test, functional exercise capacity, anxiety, depression, long-term outcome, follow-up.

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Statements and Declarations.

Author's contributions: NL, SP, and MB contributed to the conceptualization and design of the study. NL, SP, MB, and ML contributed to the development and amendment of the protocol. EP, SB, RC, GM, MP, PP, FR, FT, AL, SS, LQ, AC, and GC contributed to patient enrolment, study implementation, and data acquisition. ML contributed to data management. SP, NL, and SR contributed to data analysis. SP and NL drafted the initial manuscript of this article. NL, MB, and SP directly accessed and verified the data. SP has confirmed that all authors reviewed and approved the final manuscript. All authors had full

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Data Sharing Statement: Deidentified individual participant data that underlie the results reported in this article, together with the data dictionary defining each field in the dataset, will be made available. In addition, statistical R code will be available upon request. Data will be available upon publication and will remain accessible for 5 years thereafter. Data will be made available through DOI: 10.17632/3vnfg9tt5p.1. Access will be granted to researchers who provide a methodologically sound proposal for use in achieving the aims of their approved scientific project. Proposals should be directed to nicola.latronico@unibs.it. To gain access, data requestors will need to sign a data access agreement, and data will be shared following approval of the proposal.

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INTRODUCTION

Fatigue is a subjective symptom characterized by an overwhelming sense of tiredness, lack of energy, and exhaustion that may limit an individual's ability to initiate or sustain physical and mental activities (1). In survivors of critical illness, fatigue represents one of the most frequent and persistent long-term complaints. Studies suggest that up to 70% of ICU survivors experience significant fatigue during the months following hospital discharge, often as part of the post-intensive care syndrome (PICS) (3). Fatigue may persist for 6 to 12 months or longer, and is associated with reduced functional and psychological health status, impaired health-related quality of life (HRQoL), and delayed return to work or normal daily activities (4, 5). Most studies of post-ICU fatigue have relied primarily on telephone interviews and self-reported questionnaires, which, although practical and scalable, provide limited opportunity to integrate objective assessments of muscle strength and functional exercise capacity (3–5). Structured ICU follow-up programs provide a unique clinical setting in which physical performance testing, psychological assessment, and patient-reported outcomes are assessed within a multidisciplinary framework. Within these programs, longitudinal in-person assessments conducted as part of routine clinical care may provide a comprehensive and clinically feasible characterization of fatigue trajectories and their relationship with recovery domains over time.

In this study, we adopted the International Classification of Functioning, Disability and Health (ICF) framework developed by the World Health Organization (WHO), which conceptualizes functioning and disability as the dynamic interaction between body functions, activities, and societal participation (6). The ICF framework was used as an organizational structure for multidimensional recovery assessments within the ICU follow-up program. This approach allowed fatigue to be examined alongside measures of physical function, functional exercise capacity, and psychological symptoms during recovery after critical illness (7). ~~The ICF framework provides a comprehensive model to evaluate recovery after critical illness, given the multidimensional nature of PICS (7). In this~~

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~~context, longitudinal data integrating objective physical performance and psychological assessments are essential to better characterize the evolution and clinical correlates of fatigue after critical illness.~~

The aim of this study was to describe the prevalence and longitudinal trajectories of fatigue after critical illness and to examine whether ~~impairments in~~ physical and psychological recovery domains ~~are~~ were associated with subsequent fatigue over time, using a time-lagged approach~~, leveraging longitudinal assessments from a real-world ICU follow-up program~~.

METHODS

Study Design and Setting

This study was conducted within a structured ICU survivorship follow-up program, developed as part of the Long-Term Outcome (LOTO) project in Italy. The program represents a permanent clinical service providing standardized post-ICU evaluations to survivors of critical illness, aimed at identifying physical, cognitive, and psychological sequelae after ICU admission. As such, this study reflects routine clinical practice within an ongoing follow-up program rather than a one-time research cohort.

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The clinical program operates in close collaboration with the “Alessandra Bono” Interdepartmental University Research Center for Long-Term Outcome in survivors of critical illness (LOTO), which coordinates a national multicenter network and supports research activities. Clinical data collected during routine follow-up visits are prospectively integrated into a research database. This infrastructure supports observational studies on long-term outcomes after critical illness.

For the present study, data were analyzed from six hospitals participating in the LOTO network. The protocol was approved by the Ethics Committee of Brescia (NP 3369) and by the local committees of all centers, registered at ClinicalTrials.gov (NCT04608994).

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Written informed consent was obtained from all participants. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Additional methodological details are provided in the Online Data Supplement.

Participants

Consecutive adults (≥ 18 years) admitted to an intensive care unit (ICU) between January 1, 2016, and March 23, 2023, were screened. Inclusion criteria were survival to hospital discharge and an ICU stay of ≥72 hours. Patients were not excluded on the basis of pre-existing comorbidities, including neurological or degenerative conditions, nor for pre-existing physical dependence. Comorbidity burden was recorded using the Charlson Comorbidity Index and accounted for in the analyses. Patients were invited to attend in-person assessments at 3, 6, 12, and 24 months after ICU discharge.

ICU Data Collection

Demographic and clinical data, including age, sex, body mass index, comorbidities, admission diagnosis, illness severity (Simplified Acute Physiology Score II), and major treatments (mechanical ventilation duration, tracheostomy, catecholamine and steroid use, renal replacement therapy, ICU and hospital length of stay), were collected prospectively. Definitions of acute respiratory distress syndrome (ARDS) and COVID-19 followed established criteria (8, 9). Early mobilization followed the ABCDEF bundle (10).

Follow-up Assessments

Patients were evaluated during standardized in-person visits conducted at predefined time points after hospital discharge as part of routine clinical follow-up.

Attendance to scheduled follow-up visits reflected routine clinical practice and was voluntary. Consequently, participation varied across visits and analyses were performed on patients who attended each assessment. No specific incentives were provided for participation, as visits were part of routine post-ICU clinical care.

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Guided by the ICF framework, follow-up assessments captured complementary domains of post-critical illness recovery,~~. Measures included patient-reported~~ including fatigue, muscle strength ~~as an indicator of body function~~, functional exercise ~~capacity reflecting activity limitations~~, and symptoms of psychological distress ~~representing mental health status~~.

Fatigue was assessed using the Fatigue Severity Scale (FSS), a brief, standardized 9-item patient-reported measure of the impact of fatigue on daily functioning (total score range, 9-63, with higher scores indicating greater fatigue impact) (11). The FSS was selected because it is brief, standardized, and feasible for repeated assessment within routine ICU follow-up visits, while capturing fatigue-related interference with daily activities. Severe fatigue was defined a priori as FSS >=36, corresponding to a mean item score >=4. Because this threshold was derived from non-ICU populations and no ICU-specific FSS cutoff has been established, it was used as an operational definition of high fatigue burden rather than a diagnostic threshold.~~Severe fatigue was defined as FSS ≥ 36 (11).~~ Persistent fatigue was defined as severe fatigue present at two or more consecutive follow-up visits and was summarized descriptively.

The patient's functioning was evaluated by measuring (6):

a) muscle strength using the Medical Research Council Sum Score (MRCss) and handgrip dynamometry (HGD); for the MRCss, mild and significant ICUAW were defined as MRCss<55 and MRCss<48, respectively (12). Handgrip strength was expressed as percent-predicted values based on age- and sex-specific reference values, with lower values indicating reduced muscle strength ~~significant ICUAW was defined as a force value of less than 11 kg (IQR 10-40) in men and less than 7 kg (IQR 0-7.3) in women~~;

b) functional exercise capacity using the 6-minute walk test (6MWT), which integrates multiple physiological and behavioral domains; predicted values were calculated using established equations (13).

c) basic activities of daily living using the Barthel Index (14).

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Restrictions in participation were not directly measured using ICF-based participation instruments; however, selected SF-36 domains (including Role Physical and Social Functioning) capture aspects of participation and social roles (15).

Health-related quality of life was assessed with the SF-36 (15). Cognitive status was measured by the Montreal Cognitive Assessment (16). Symptoms of anxiety and depression were quantified with the Hospital Anxiety and Depression Scale (17); post-traumatic stress disorder with the PCL-5 (18); and insomnia with the Insomnia Severity Index (19). All instruments are validated and widely used in post-ICU research; further procedural details are provided in the Online Data Supplement.

Statistical Analysis

Continuous variables were summarized as mean ± SD or median [IQR], and categorical variables as counts (%). Percentages at each time point were calculated using the number of patients assessed at that visit as the denominator.

Candidate variables ~~predictors, including~~ considered during model building included demographic variables, COVID-19 status, ICU severity variables, and follow-up measures of muscle strength, functional exercise capacity, ~~and~~ psychological symptoms, ~~as well as~~ and prior fatigue status. ~~were first evaluated using~~ To reduce model complexity, candidate variables were first screened using Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression with 10-fold cross-validation (20). LASSO was used solely for variable selection, not for estimating final effect sizes. Variables ~~identified~~ retained by LASSO were subsequently included as fixed effects in a Generalized Linear Mixed Model (GLMM) ~~multivariable mixed-effects logistic regression models~~ with a patient-level random intercept to account for repeated observations within participants (21). Age, sex, follow-up time point, and prior fatigue status were retained a priori irrespective of LASSO selection. ~~and fixed effects for time point, age (per 10 years), sex, ICU severity variables, and time-lagged measures of muscle strength, functional exercise capacity, psychological symptoms,~~

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and prior fatigue status (21). Final effect estimates odds ratios and 95% confidence intervals were therefore obtained from the GLMM mixed-effects models and should be interpreted as conditional on the selected model. accounting for within-patient correlation. Clinically relevant variables (age, sex, and time point) were retained irrespective of the LASSO selection.

The primary multivariable analysis evaluated severe fatigue at the subsequent visit using time-lagged covariates. To strengthen temporal ordering and reduce the potential for reverse temporal associations, predictors were entered as time-lagged covariates, such that values measured at follow-up visit t–1 were used to estimate the odds of severe fatigue at visit t.

Prior fatigue status at visit t–1 was included as a predictor to account for baseline preceding symptom fatigue burden and to distinguish persistence from new or recurrent fatigue. Consecutive visit pairs (3→6 months, 6→12 months, and 12→24 months) contributed to the analyses. Patients whose first observed follow-up visit occurred at 6 or 12 months could contribute lagged pairs from their first observed visit onward; no unobserved prior fatigue status was imputed. Patients were not excluded if severe fatigue had been reported at earlier follow-up visits. All available visit pairs were included regardless of prior fatigue status, allowing the models to capture both persistence and recurrence of fatigue over time. Available attendance pairs were defined as consecutive visit pairs in which the patient attended both visits, whereas complete-case analytic pairs were defined as attendance pairs with non-missing outcome and covariate data for the corresponding model. We report both the number of available attendance pairs and the number of complete-case analytic pairs contributing to each model. The time-lagged LASSO-GLMM was performed as a complete-case analysis, requiring non-missing values for the outcome, the lagged outcome, and all candidate variables entered into the penalized selection step. This complete-case requirement resulted in an analytic sample of 622 consecutive visit pairs, all derived from patients without COVID-19; therefore, COVID-19 status could not be

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retained in the final model or tested as an interaction term because there was no residual variation in COVID-19 status within the analytic sample. Accordingly, odds ratios should be interpreted as associations between clinical status at the preceding observed visit and severe fatigue at the subsequent observed visit, conditional on prior fatigue status and other covariates. ~~Thus, odds ratios reflect the association between clinical status at a preceding visit and the odds of severe fatigue at the subsequent visit, conditional on prior fatigue status and other covariates.~~ Mixed-effects models allowed ~~inclusion of participants with incomplete follow-up while accounting~~ participants with complete follow-up to contribute all eligible complete-case visit pairs while accounting for within-patient correlation. Multicollinearity among covariates included in the multivariable models was assessed using variance inflation factors (VIFs), ~~with all VIFs close to 1~~ with VIF values <5 considered to indicate no problematic multicollinearity. Because the study was embedded in a real-world clinical follow-up program, incomplete attendance across visits was expected. To explore potential differences associated with follow-up participation, ~~baseline~~ characteristics measured at the 3-month visit were compared across groups defined by subsequent follow-up attendance (≥2 subsequent visits, 1 subsequent visit, or no visit beyond 3 months). Continuous variables were compared using the Kruskal-Wallis test and categorical variables using the χ^2 test. To evaluate the potential impact of ~~loss to follow-up,~~ differential follow-up attendance, a sensitivity analysis using inverse probability weighting (IPW) was performed. The probability of attending follow-up visits at 6, 12, and 24 months was estimated using logistic regression models including ~~baseline~~ demographic characteristics, ICU severity variables, and clinical status at the preceding visit. Stabilized weights were calculated using a numerator model that included age, sex, and visit time point, and a denominator model that additionally included baseline severity and prior-visit clinical variables. Weights were truncated at the 5th and 95th percentiles and applied in weighted logistic regression models with patient-level cluster-robust standard errors.

All tests were two-sided ($\alpha = 0.05$) and performed in R v4.5.0 (22).

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RESULTS

We evaluated 1,912 ICU survivors in six centers, of whom 500 (26%) were patients with COVID-19 ~~patients~~, with a median age of 59 years (IQR 48-69), a median ICU length of stay of 9 days (IQR 6-15), and a substantial burden of critical illness, including high rates of ARDS and mechanical ventilation. **Table 1** presents their main characteristics at ICU admission.

Figure 1 presents follow-up visit attendance across the study time points. Based on visit attendance, the number of possible consecutive visit pairs was 704 for 3-to-6 months, 970 for 6-to-12 months, and 211 for 12-to-24 months. After requiring non-missing outcome, lagged outcome, and candidate-variable data for the LASSO selection step, 622 consecutive visit pairs contributed to the complete-case time-lagged LASSO-GLMM analysis. All visit pairs in this analytic sample were derived from patients without COVID-19; therefore, COVID-19 status had no residual variability and could not be evaluated as either an independent variable or an interaction term in the final time-lagged model. Overall, 976 of 1,912 patients (51%) experienced severe fatigue at least once during follow-up. The prevalence of severe fatigue at each visit was 336/967 (34.7%) at three months, 628/1522 (41.3%) at six months, 434/1135 (38.2%) at 12 months, and 64/217 (29.5%) at 24 months, as shown in Table S1. The prevalence of impairments across fatigue, physical, cognitive, and psychological domains at each follow-up time point is summarized in **Table S1**.

~~The prevalence of severe fatigue did not show a significant reduction over time. However, individual fatigue trajectories were heterogeneous.~~ **Figure 2** illustrates transitions between fatigue and non-fatigue states ~~from 3 to 24 months after ICU discharge~~ across follow-up visits, ~~revealing diverse patterns,~~ ~~recovery~~ ~~from~~ including patterns of early fatigue, recurrent fatigue, and late-onset fatigue, among patients who were initially fatigue-free. Persistent fatigue was observed in 655 of 1,912 patients (34.3%).

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Age-, sex-, and follow-up time-adjusted associations between baseline and ICU characteristics, as well as physical, mental, and cognitive status, and severe fatigue are shown in **Tables S2 and S3.** Severe fatigue was significantly associated with increasing age, female sex, comorbidities, non-COVID-19 diagnosis, absence of steroid therapy, tracheostomy, longer ICU length of stay, and impairments across the PICS domains.

The results of the 622 complete-case LASSO-GLMM analysis ~~of the multivariable mixed-effects logistic regression model, informed by LASSO-based variable selection,~~ are shown in **Figure 3**. Severe fatigue at the preceding visit (OR = 3.0, 95% CI 1.31 to 6.84, p = 0.009), ~~as well as~~ lower functional exercise capacity on the 6MWT (OR = 0.77, 95% CI 0.61 to 0.95, p = 0.017), and clinically relevant symptoms of anxiety (OR 6.76, 95% CI 2.01–22.68) and depression (OR 17.8, 95% CI 4.16–76.47), all measured at the preceding visit, were ~~independently~~ associated with ~~higher odds of~~ severe fatigue at the subsequent visit.

Pairwise correlations were low, and variance inflation factors (VIFs) for fixed effects were all close to 1, indicating no evidence of problematic multicollinearity in the model (**Table S4**).

At the 3-month visit, baseline characteristics differed across groups defined by subsequent follow-up attendance, with patients who attended ≥2 subsequent visits generally showing greater illness severity and resource use (e.g., longer ICU length of stay, longer duration of mechanical ventilation, and higher SAPS II scores) (**Table S5**). However, in sensitivity analyses using inverse probability weighting to account for potential bias due to ~~missing follow-up~~ differential follow-up attendance, the estimates from the multivariable model remained consistent with the primary analysis (**Table S6**).

DISCUSSION

In this large multicenter prospective study of ICU survivors followed for up to 24 months, we identified four main findings. First, fatigue was highly prevalent, with more than one-third of participants affected at each follow-up visit and over half experiencing severe

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fatigue at least once during the study period. Second, individual trajectories of severe fatigue were heterogeneous, with approximately one-third of patients showing persistent fatigue across multiple visits. This descriptive estimate should be interpreted in the context of variable visit attendance in this real-world follow-up program. Third, lower functional exercise capacity and psychological distress were associated with subsequent fatigue, even after accounting for prior fatigue status. Finally, prior fatigue ~~emerged as a strong correlate of~~ was associated with subsequent fatigue, while ICU-related clinical variables, cognitive function, and sleep disturbances ~~were not associated with later fatigue~~ were not retained in the final multivariable model. These findings highlight the long-term burden of fatigue after critical illness and ~~suggest actionable targets for follow-up and rehabilitation~~ identify recovery domains that may warrant attention during follow-up and rehabilitation.

The high prevalence and persistence of fatigue in our cohort align with previous reports identifying fatigue as a core feature of PICS (3–5). Our findings ~~confirm~~ indicate that fatigue remains both prevalent and fluctuating long after hospital discharge, reinforcing the need for prolonged surveillance and support.

~~Our findings support the conceptualization of fatigue as emerging at the intersection of multiple domains of recovery, consistent with the a multidimensional framework proposed by the ICF~~.

~~The observed associations of functional impairment and psychological distress with subsequent fatigue support the view that fatigue reflects the combined impact of impairments across these domains rather than a single underlying mechanism.~~

The longitudinal structure of our follow-up assessments highlights the dynamic nature of fatigue during recovery after critical illness. Individual transition patterns revealed heterogeneous fatigue trajectories, with some patients experiencing persistent fatigue, others recovering over time, and others developing recurrent or late-onset fatigue during follow-up. These findings suggest that fatigue after critical illness is not a static condition

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but rather a dynamic component of recovery that may evolve over months or years, with important implications for longitudinal monitoring and multidisciplinary follow-up care.

Together, these findings support a multidimensional view of post-ICU fatigue, in which functional exercise capacity and psychological distress represent complementary recovery domains associated with subsequent fatigue rather than a single underlying mechanism. This interpretation is consistent with the use of structured follow-up clinics to integrate patient-reported outcomes with objective functional testing and psychological assessment.

Our time-lagged modelling approach extends prior cross-sectional findings by ~~suggesting that impairments in functional exercise capacity may precede fatigue rather than merely coexisting with it~~ showing that lower functional exercise capacity at one visit was associated with severe fatigue at the subsequent visit. ~~suggesting that these domains are temporally related rather than merely cross-sectionally associated~~. This supports the relevance of temporal ordering in the relationship between functional capacity and fatigue, although it does not imply a unidirectional causal relationship. However, this temporal association does not imply a unidirectional causal relationship. Fatigue may represent a downstream consequence of impaired physical capacity, a parallel manifestation of systemic dysfunction, such as underlying biological or physiological dysregulation, or a bidirectional process in which fatigue and reduced activity reinforce one another over time.

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~~The strong association between depressive and anxiety symptoms and subsequent fatigue reinforces the importance of the psychological burden in ICU survivors.~~ The observed associations between depressive and anxiety symptoms and subsequent fatigue reinforce the importance of psychological burden in ICU survivors. ~~Our findings suggest that psychological distress may contribute to subsequent fatigue independent of prior fatigue status,~~ Psychological distress remained associated with subsequent fatigue after accounting for prior fatigue status, although causal relationships cannot be established. This observation underscores the need for integrated follow-up strategies that address both physical and mental health domains.

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~~The longitudinal structure of our follow-up assessments also highlights the dynamic nature of fatigue during recovery after critical illness. More than half of patients experienced severe fatigue at least once, yet only about one-third showed persistent fatigue, indicating substantial variability in fatigue trajectories over time. As illustrated by transition patterns between visits, some patients experienced sustained fatigue, whereas others improved or developed fatigue at later time points. These findings suggest that fatigue after critical illness is not a static condition but rather a fluctuating component of recovery that may evolve over months or years, with important implications for long-term follow-up and care planning.~~

A major strength of our study lies in its comprehensive and patient-centered approach. All evaluations were conducted through structured, in-person follow-up visits, allowing for standardized testing and consistent longitudinal data collection. Importantly, the study was embedded in a continuous ICU follow-up program, allowing the assessment of fatigue within routine clinical care rather than a one-time research cohort. The prospective, multicenter design involving a large and diverse patient population ~~enhances the generalizability of our findings~~ supports the relevance of our findings across structured ICU follow-up settings. Unlike many previous studies relying primarily on telephone interviews or self-reported questionnaires, this follow-up program integrates standardized in-person clinical assessments with patient-reported outcomes, allowing a combined evaluation of physical performance, functional capacity, and psychological symptoms during routine follow-up.

This study also has several limitations. First, the FSS ≥36 cutoff used to define severe fatigue was extrapolated from non-ICU populations. Therefore, absolute prevalence estimates should be interpreted as threshold-dependent and may differ from studies using other instruments or cutoffs. However, the longitudinal analyses focus on associations and trajectories within a consistently applied operational definition.

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Second, the two-stage modeling approach, in which LASSO was used for variable selection before the GLMM, does not fully account for the uncertainty introduced by the variable-selection step. Accordingly, confidence intervals and p-values from the final models should be interpreted as conditional on the selected model and may underestimate statistical uncertainty. This consideration is particularly relevant for depressive symptoms, for which the confidence interval was wide, indicating limited precision despite an association in the expected direction. The multivariable findings should therefore be interpreted primarily as exploratory time-lagged associations rather than as definitive prognostic estimates.

Third, because the study was embedded in a real-world clinical follow-up program, attendance varied across visits, and later time points included fewer patients. Patients who continued follow-up differed from those with fewer visits, suggesting potential selection bias. Although IPW sensitivity analyses yielded estimates consistent with the primary model, weighting cannot account for unmeasured factors influencing attendance; estimates at later time points, particularly 24 months, should therefore be interpreted with greater caution. Accordingly, the 24-month prevalence estimate should be regarded as exploratory rather than confirmatory.

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Fourth, residual confounding cannot be excluded, particularly given the lack of pre-ICU functional and psychological assessments and data on post-discharge rehabilitation exposure. The directionality between fatigue and psychological distress remains uncertain, and the observed time-lagged associations should not be interpreted as evidence of causal relationships. Although the ICF framework was used to organize the multidimensional assessment strategy, it was only partially operationalized. In particular, participation was not directly measured using a dedicated ICF-based instrument; therefore, the ICF should be interpreted as an organizational framework rather than as a fully specified analytical model.

Fifth, because inclusion required an ICU stay of at least 72 hours, our cohort represents a more severely ill subset of ICU survivors, which may limit generalizability. In addition,

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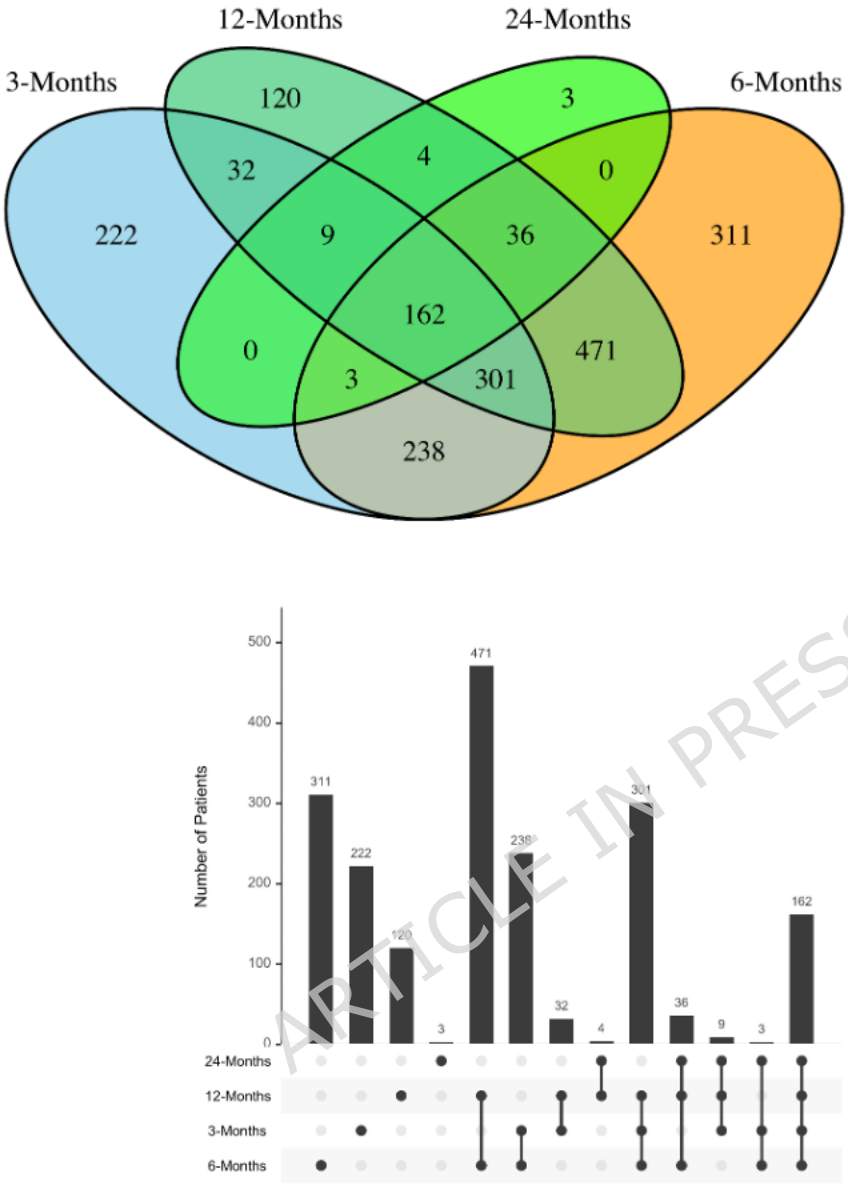
although the overall cohort included both COVID-19 and non-COVID ICU survivors across a long enrolment period, the final complete-case time-lagged LASSO-GLMM sample consisted exclusively of non-COVID patients. Therefore, the main multivariable time-lagged findings should be interpreted as primarily applicable to the non-COVID complete-case population. Pandemic-era differences in ICU care, rehabilitation practices, and follow-up engagement may have introduced heterogeneity in the broader cohort, but COVID-19 interaction effects could not be formally assessed within the time-lagged model because COVID-19 status had no residual variability in the analytic sample. This should be considered when interpreting the generalizability of the findings.

~~Incomplete follow-up could have introduced selection bias, as patients who attended multiple visits tended to have greater illness severity and resource use at baseline. However, sensitivity analyses using IPW yielded results consistent with the primary analysis, supporting the robustness of our finding despite differential follow-up attendance~~. ~~The lack of data on post-discharge rehabilitation exposure precluded adjustment for its potential impact on fatigue trajectories.~~

Our findings have important implications for clinical practice and research. Objective measures of functional capacity and systematic psychological screening ~~should be integrated to~~ may help identify ICU survivors more likely to experience severe fatigue during follow-up~~identify patients at risk and guide targeted interventions~~. Given that physical impairment, psychological distress, and prior fatigue status were ~~independently~~ associated with subsequent fatigue, early rehabilitation and timely mental health support may represent important components of multidisciplinary follow-up programs. ~~represent follow-up programs key strategies, ideally delivered within multidisciplinary programs~~. ~~Future studies should assess whether targeted interventions on these modifiable factors can alter fatigue trajectories~~. Future studies should determine whether interventions targeting physical and psychological recovery domains can modify fatigue trajectories.

Figures

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Figure 1: ~~Follow-up visit attendance and overlap across time points~~ Follow-up attendance patterns across study visits

~~The upper panel shows a Venn diagram of patients who completed follow-up visits at 3, 6, and 12 months, illustrating the overlap across these three time points.~~

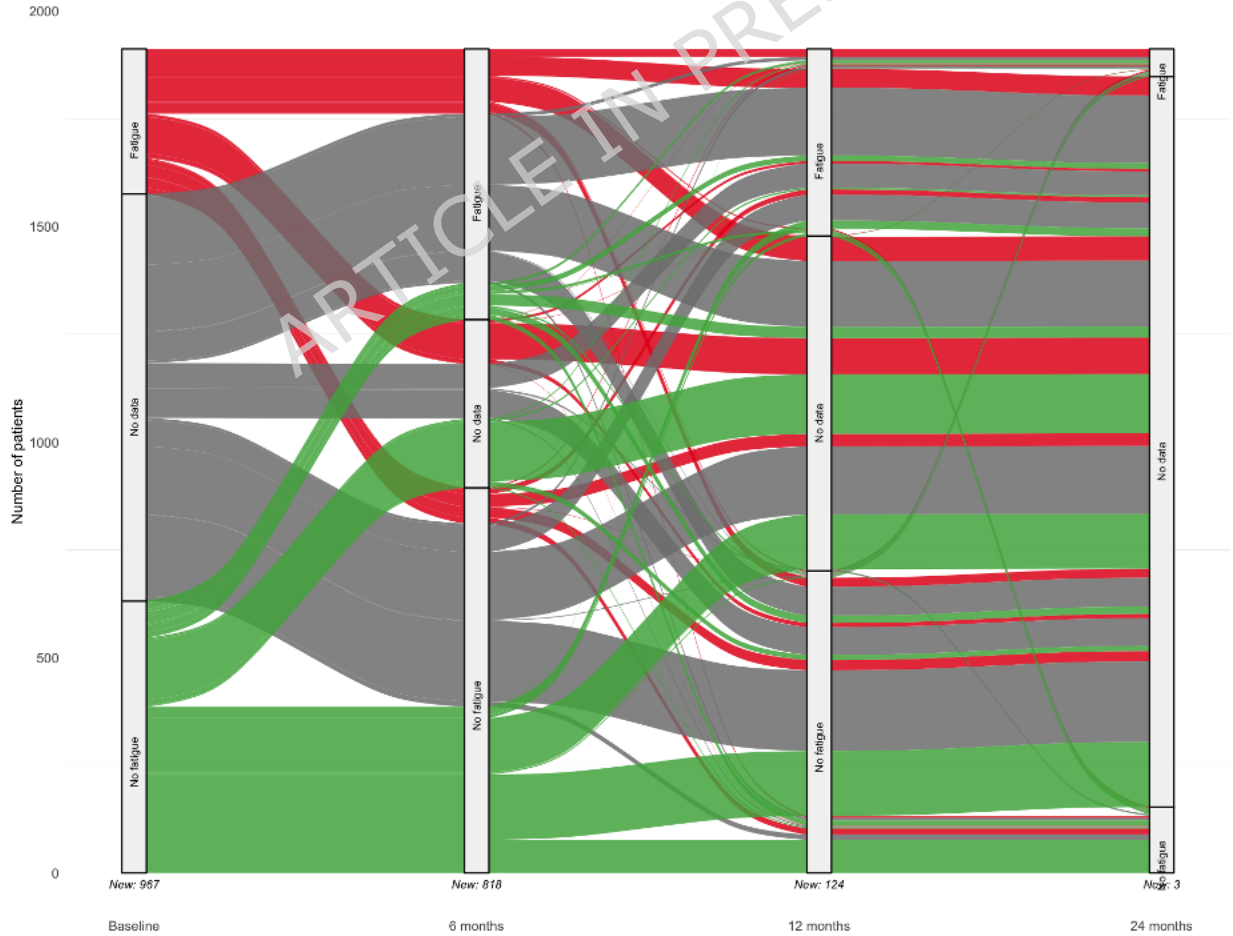
~~The bottom panel displays an UpSet plot representing all combinations of time point attendance (including 24-month visits). vertical bars indicating the number of patients in~~

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~~each attendance pattern. and the horizontal dots indicating the time points attended. Together, these visualizations illustrate overall follow-up coverage and patterns of visit attendance across the study period.~~

The upper panel shows a Venn diagram of follow-up attendance at 3, 6, 12, and 24 months. Each coloured ellipse represents one follow-up time point, and overlapping regions indicate patients who attended multiple visits. Numbers within each region indicate the number of patients with that specific combination of completed visits. The lower panel shows the same information using an UpSet plot. In the UpSet plot, vertical bars indicate the number of patients in each attendance pattern, while the black dots and connecting lines below each bar identify the specific visit combination represented by that bar; grey dots indicate visits not included in that combination. Together, these visualizations summarize overall follow-up coverage and the heterogeneity of visit attendance across the study period.

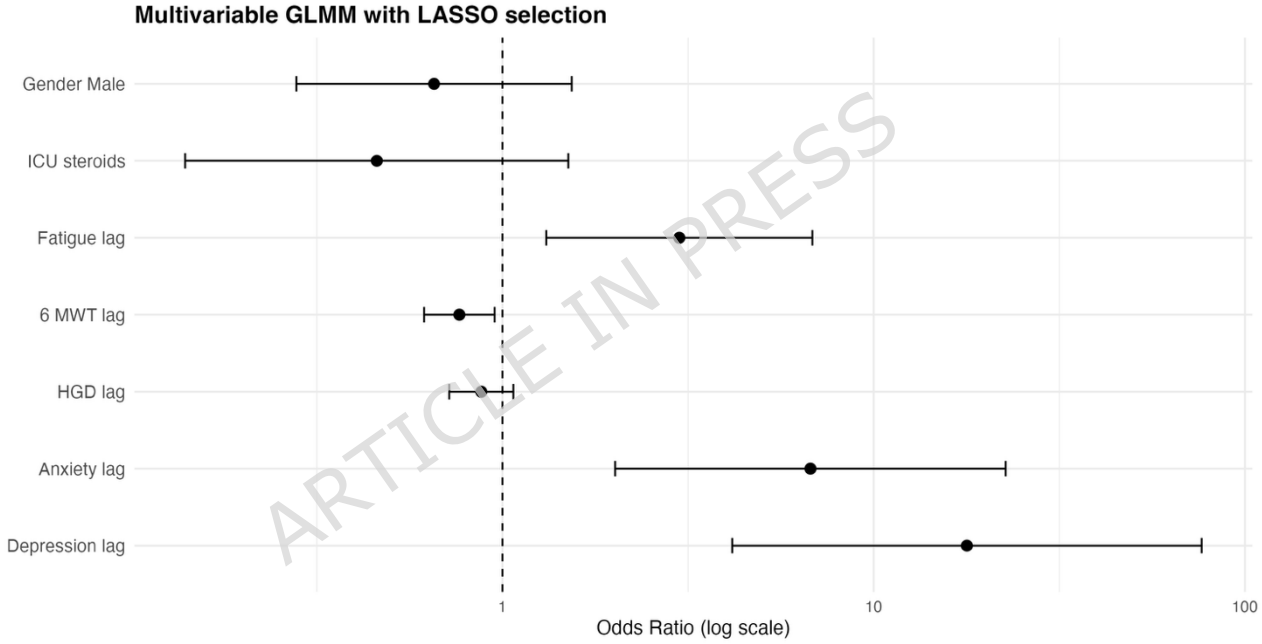
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Figure 2: Long-term trajectories of post-ICU fatigue

Alluvial (Sankey) diagram showing how individual patients moved between “No fatigue” (green) and “Fatigue” (red) from the first post-discharge assessment (Baseline, 3 months) through 6 months, 12 months, and 24 months. Ribbon width is proportional to the number of patients following each trajectory; vertical bars display the total number assessed at each visit. Grey ribbons indicate patients who did not attend the follow-up visit. ~~were alive but had no fatigue assessment recorded at that time point (missing)~~. The diagram illustrates patterns of persistence, remission, and late-onset fatigue over time.



Term	OR	CI	p
Gender Male	0.65	0.28–1.54	0.330
ICU steroids	0.46	0.14–1.51	0.199
Fatigue lag	3.00	1.31–6.84	0.009
6 MWT lag	0.77	0.61–0.95	0.017
HGD lag	0.88	0.72–1.07	0.195
Anxiety lag	6.76	2.01–22.68	0.002
Depression lag	17.83	4.16–76.47	0.000

Figure 3: Time-lagged factors associated with severe fatigue during follow-up after ICU discharge

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Lagged variables were measured at the preceding visit (t-1), and the outcome was severe fatigue at the subsequent visit (t). Odds ratios were estimated using mixed-effects logistic regression with a patient-level random intercept. 6MWT and HGD were expressed as percent-predicted values and scaled per 10-unit increase unless otherwise stated.

Panel A: Forest plot of odds ratios (log scale) from the mixed-effects logistic model with time-lagged ~~predictors~~ variables.

The error bars show 95% confidence intervals.

Panel B: corresponding odds-ratio table.

~~Note: all predictors were measured at the preceding visit.~~

6MWT = 6-minute walk test. HGD = Handgrip Dynamometry. HADS = Hospital Anxiety and Depression Scale.

*Variables have been scaled by 10.

Table 1: Baseline demographic and clinical ICU characteristics.

	N=1912
Age, years mean (IQR)	59 (48 – 69)
Sex, Male number (percentage)	1275/1732 (73.6%)
Reason for Admission number (percentage) or median (IQR)	
Sepsis	143 / 1 912 (7.5%)
Acute neurological disorder	448 / 1 912 (23%)
ARDS	710 / 1 912 (37%)

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Trauma	283 / 1 912 (15%)
Post-operative	68 / 1 912 (3.6%)
Others	260 / 1 912 (14%)
COVID-19	500 / 1 912 (26%)
BMI at ICU admission, kg/m^2	26.7 (23.7-30.6)
SAPS II	26.6 (23.6-30.2)
MV Duration	6 (2-11)
Tracheostomy	346 / 1 635 (21%)
Use of Steroids*	640 / 1 607 (40%)
Use of catecholamine**	830 / 1 637 (51%)
Number of comorbidities (percentage)**	
0	439 / 1 646 (27%)
1	389 / 1 646 (24%)
2	293 / 1 646 (18%)
3	235 / 1 646 (14%)

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More than 3	290 / 1 646 (18%)
ICU LOS days median (IQR)	9 (6 - 15)
H LOS days median (IQR)	27 (18 - 40)

Number reflects the number of patients with non-missing data for that variable.

* Steroid use is intended as either dexamethasone 6mg/day for 10 days (in case of COVID-19) or methylprednisolone 1-2 mg/Kg for 7-15 die (in case of ARDS).

** Refer to the comorbidities listed in the Charlson Comorbidity index.[31]

ARDS = Acute Respiratory Distress Syndrome. BMI= Body Mass Index. COVID-19= Coronavirus Disease 2019. H= Hospital. ICU= Intensive Care Unit. IQR= interquartile range. LOS= Length of stay. MV= Mechanical Ventilation. SAPS II= Simplified Acute Physiology Score II. SD= Standard deviation.

References

1. Gruet M, Temesi J, Rupp T, Levy P, Millet GY, Verges S. Stimulation of the motor cortex and corticospinal tract to assess human muscle fatigue. *Neuroscience* 2013;231:384–399.

2. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, *et al.* Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;40:502–509.

3. Neufeld KJ, Leoutsakos J-MS, Yan H, Lin S, Zabinski JS, Dinglas VD, *et al.* Fatigue Symptoms During the First Year Following ARDS. *Chest* 2020;158:999–1007.

4. Morel J, Infantino P, Gergelé L, Lapole T, Souron R, Millet GY. Prevalence of self-reported fatigue in intensive care unit survivors 6 months-5 years after discharge. *Sci Rep* 2022;12:5631.

5. Kennouche D, Foschia C, Brownstein CG, Lapole T, Rimaud D, Royer N, *et al.* Factors associated with fatigue in COVID-19 ICU survivors. *Med Sci Sports Exerc* 2024;56:1563–1573.

ARTICLE IN PRESS

ARTICLE IN PRESS

6. Buñuales J, Diego G, Moreno M. International classification of functioning, disability and health (ICF). *Rev Esp Salud Publica* 2001;76:271–279.

7. Latronico N, Rasulo FA, Eikermann M, Piva S. Illness Weakness, Polyneuropathy and Myopathy: Diagnosis, treatment, and long-term outcomes. *Crit Care* 2023;27:1–13.

8. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, *et al.* Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.

9. Coronavirus Disease 2019 (COVID-19) 2020 interim case definition, approved April 5, 2020. 2025;at <https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2020/>.

10. Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF bundle in critical care. *Crit Care Clin* 2017;33:225–243.

11. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–1123.

12. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, *et al.* The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med* 2017;43:1270–1281.

13. Gimeno-Santos E, Vilaró J, Arbilllaga-Etxarri A, Herrero-Cortina B, Ramon MA, Corberó AB, *et al.* Development and comparison of reference equations for the six-minute walk test in Spanish healthy adults aged 45-85 years. *Arch Bronconeumol* 2025;61:459–466.

14. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:61–65.

15. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. *J Clin Epidemiol* 1998;51:1025–1036.

16. McDicken JA, Elliott E, Blayney G, Makin S, Ali M, Larner AJ, *et al.* Accuracy of the short-form Montreal Cognitive Assessment: Systematic review and validation. *Int J Geriatr Psychiatry* 2019;34:1515–1525.

ARTICLE IN PRESS

ARTICLE IN PRESS

17. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:69–77.
18. Bovin MJ, Marx BP, Weathers FW, Gallagher MW, Rodriguez P, Schnurr PP, *et al.* Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess* 11 2016;28:1379–1391.
19. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601–608.
20. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010;33:1–22.
21. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models Usinglme4. *J Stat Softw* 2015;67:.
22. _*R: Language Environment Statistical Computing*_. *R Foundation Statistical Computing*. Vienna, Austria: 2025.
23. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Shanholtz C, Husain N, *et al.* Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med* 2012;185:517–524.
24. Hosey MM, Needham DM, Kudchadkar SR. Fatigue in critical care survivors: multidisciplinary and self-management strategies. *Anaesthesia* 2021;76:1163–1166.
25. Egger M, Wimmer C, Stummer S, Reitelbach J, Bergmann J, Müller F, *et al.* Reduced health-related quality of life, fatigue, anxiety and depression affect COVID-19 patients in the long-term after chronic critical illness. *Sci Rep* 2024;14:3016.
26. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. *Am J Respir Crit Care Med* 2010;182:446–454.
27. Prescott HC, Angus DC. Enhancing recovery from sepsis. *JAMA* 2018;319:62.

ARTICLE IN PRESS

ARTICLE IN PRESS

28. Marra A, Pandharipande PP, Girard TD, Patel MB, Hughes CG, Jackson JC, *et al.* Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. *Crit Care Med* 2018;46:1393–1401.

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