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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 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

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) [2, 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 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.

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 h. 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.

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.

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 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.

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 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 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

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)
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 6 mg/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

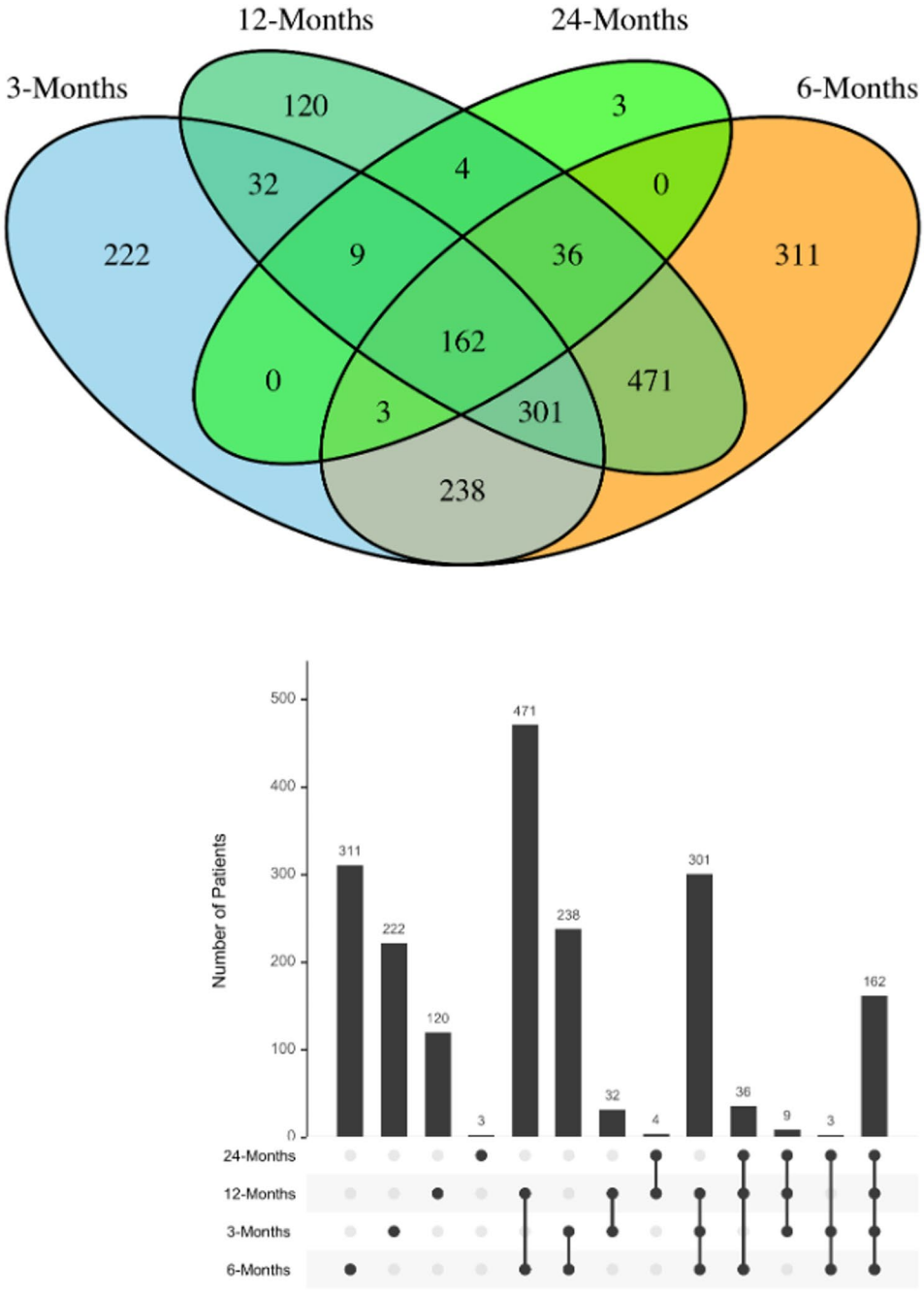


Fig. 1 Follow-up attendance patterns across study visits. The upper panel shows a Venn diagram of follow-up attendance at 3, 6, 12, and 24 months. Each coloured ellipse represents one follow-up time point, and overlapping regions indicate patients who attended multiple visits. Numbers within each region 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 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

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,

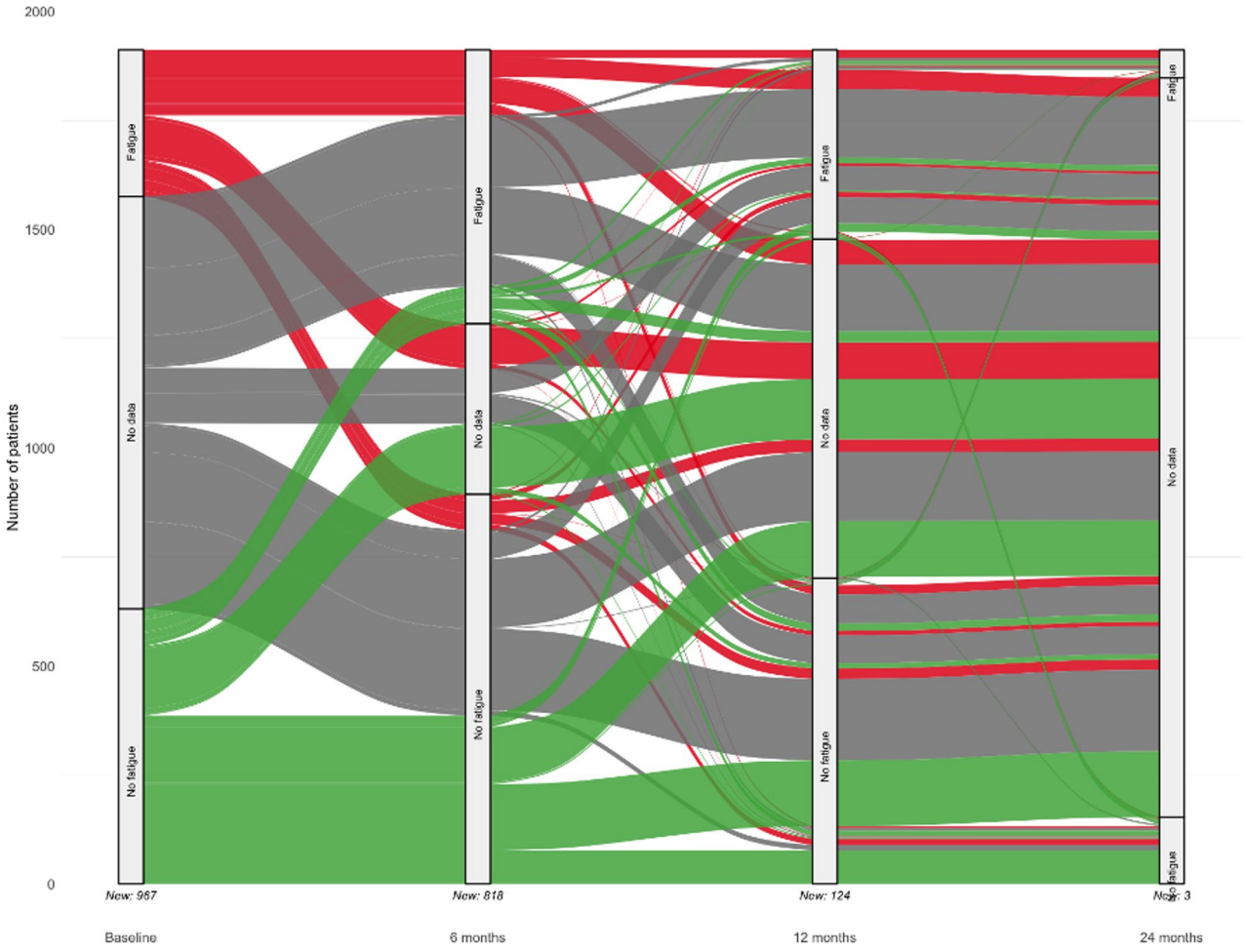


Fig. 2 Long-term trajectories of post-ICU fatigue. Alluvial (Sankey) diagram showing how individual patients moved between "No fatigue" (green) and "Fatigue" (red) from the first post-discharge assessment (Baseline, 3 months) through 6 months, 12 months, and 24 months. Ribbon width is proportional to 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

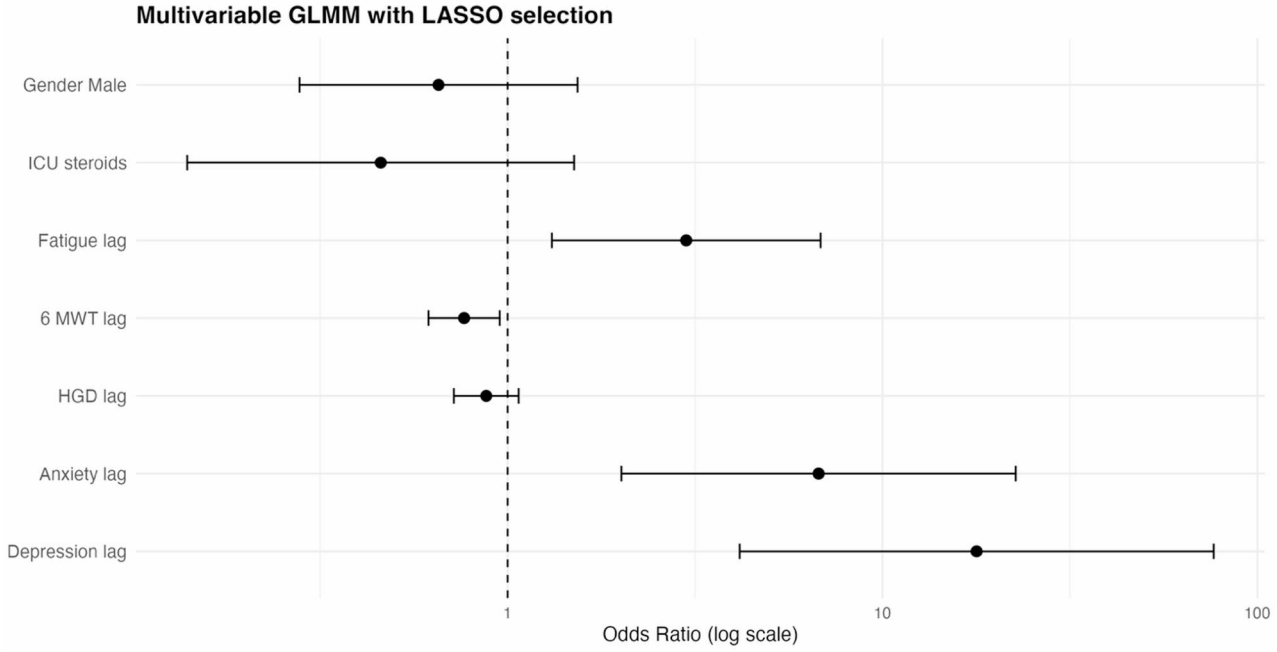
recurrent fatigue, and late-onset fatigue, among patients who were initially fatigue-free. Persistent fatigue was observed in 655 of 1,912 patients (34.3%).

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 Fig. 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).



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

Fig. 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. 6MWT = 6-minute walk test. HGD = Handgrip Dynamometry. HADS = Hospital Anxiety and Depression Scale. *Variables have been scaled by 10

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 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.

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 [23]. 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 [24, 25]. 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[26–28].

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 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 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 h, 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.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-026-06130-6.

Supplementary Material 1.

Acknowledgements
Not applicable.

Author contributions
N.L., S.P., and M.B. contributed to the conceptualization and design of the study. N.L., S.P., M.B., and M.L. contributed to the development and amendment of the protocol. E.P., S.B., R.C., G.M., M.P., P.P., F.R., F.T., A.L., S.S., L.Q., A.C., and G.C. contributed to patient enrolment, study implementation, and data acquisition. M.L. contributed to data management. S.P., N.L., and S.R. contributed to data analysis. S.P. and N.L. drafted the initial manuscript of this article. N.L., M.B., and S.P. directly accessed and verified the data. S.P. 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.

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Data availability
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.

Declarations

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.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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