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Predicting the persistence of Long COVID 36 months after hospitalisation: a prospective Ukrainian cohort study

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ABSTRACT

Objective To determine early predictive markers and to develop prognostic models for self-reported persistence of Long COVID syndrome at 36 months after hospitalisation.

Design A prospective observational study with cross-sectional analyses at predefined follow-up points.

Setting A tertiary care hospital.

Participants 221 patients hospitalised for COVID-19 underwent detailed clinical, functional, imaging and survey-based symptom assessment prior to discharge and at 1 month, followed by a 3-year longitudinal follow-up on symptoms. 159 patients (mean age 53.1±13.6 years, 55% female) completed the 36-month assessment and were included in the final analysis.

Main outcome measure Self-reported persistence of Long COVID symptoms at 36 months after hospital discharge.

Results At 36 months after discharge, 66 (41%) patients reported persistent Long COVID symptoms. This group did not differ in age or sex structure, more frequently reported ongoing symptoms at 3 months (91% vs 59%, p<0.001) and 12 months (77% vs 13%, p<0.001), had longer time to hospitalisation (10.2±3.4 vs 5.2±3.9 days, p<0.001) and higher Charlson comorbidity index (0.61±0.96 vs 0.33±0.56, p=0.022), higher in-hospital creatinine (109 (100–119) vs 96 (85–105) µmol/L, p<0.001), aspartate aminotransferase (AST) (43 (37–55) vs 32 (21–47) IU/L, p=0.003), and alanine aminotransferase (47 (30–128) vs 42 (26–62) IU/L, p=0.011) and paradoxically lower Galectin-3 (8.6±0.7 vs 9.0±0.5 ng/mL, p<0.001) and sST2 (23.2±13.7 vs 29.7±15.8 ng/mL, p=0.012). No significant differences were found in inflammatory markers, minimal in-hospital peripheral capillary oxygen saturation, need for oxygen supplementation, pulmonary involvement on CT or lung ultrasound, and clinically negligible differences detected in cardiovascular evaluation, with a baseline tendency to minimal hypercontractility and lower flow-mediated dilation (10.1±5.1 vs 12.9%±5.9%, p=0.006) and marginally worse early dynamics of diastolic indices in Long COVID group. In 6-Minute Walking Test, no differences were observed at baseline but patients with Long COVID reported higher postexertional fatigue (3.3±2.1 vs 1.9±1.6, p<0.001) and dyspnoea (3.4±1.7 vs 2.5±1.8, p=0.027) despite lower blood oxygen desaturation (1.7±1.7 vs 2.8%±2.4%, p=0.014) at 1 month. In symptom assessment, longitudinal trajectories differed significantly for Medical Research Council Dyspnoea (p=0.004), post-COVID functional scale (p<0.001), EFTER-COVID study physical symptoms (p<0.001) and Symptom Burden Questionnaire for Long COVID Memory, Thinking and Communication (p<0.001) scores, reaching maximal differences by 3–12 months, while respiratory scores showed no sustained differences. A simple artificial neural network model combining predischarge variables (sex, age, creatinine, AST, weight loss, duration of hospitalisation and 6-Minute Walk Distance) with 3-month multidimensional symptom assessment achieved a 92% accuracy (area under the receiver operating characteristic, AUROC 0.902), consistently outperforming other machine learning classifiers. A simplified model using only 3-month survey data, age, sex and hospitalisation duration retained high discrimination accuracy (88%, AUROC 0.850).

Conclusions 41% of hospitalised COVID-19 patients reported persistent symptoms at 36 months, preceded by early divergence in patient-reported symptoms despite comparable recovery of objective functional parameters. Predictive models incorporating 3-month multidimensional symptom assessment and routine clinical variables accurately identified patients at risk, outperforming later reassessment strategies and supporting early risk stratification.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study employs a prospective design with an extended 36-month follow-up, integrating clinical, functional, imaging, vascular and patient-reported data for comprehensive phenotyping.
⇒ The predictive methodology systematically compares multiple machine learning approaches across different time points against a pragmatic clinical baseline to ensure model robustness.
⇒ While the extended 36-month observation period inherently introduces a risk of attrition bias, the study maintained a robust 72% retention rate despite profound external disruptions during the follow-up.
⇒ Key methodological limitations include a single-centre design, a moderate sample size, reliance on self-reported outcomes and a cohort reflecting early viral variants with low vaccination coverage.

BACKGROUND

Postacute sequelae of SARS-CoV-2 infection, commonly referred to as Long COVID, comprise a broad spectrum of persistent or newly emerging symptoms that extend well

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beyond the acute phase of the disease.[1 2] Fatigue, dyspnoea, cognitive dysfunction, followed by other signs of multisystem impairment, remain the most prevalent manifestations.[2 3] This broad clinical presentation is underpinned by profound pathophysiological heterogeneity, encompassing overlapping mechanisms such as persistent immune dysregulation, chronic inflammation, endothelial damage and coagulation abnormalities.[4] Although most individuals show gradual improvement within the first months, a substantial proportion continue to experience symptoms beyond that period. Recent prospective studies demonstrate that clinically relevant sequelae persist up to 36 months after infection, confirming the chronic nature of post-COVID conditions.[3 5 6]

Population-based and cohort studies consistently reveal that the risk of health deterioration remains elevated compared with uninfected controls 3 years after acute disease. In a nationwide electronic-health-record cohort, patients who survived the acute phase of COVID-19 maintained a 34% higher risk of experiencing ongoing health complications 3 years later compared with uninfected controls.[6] Among survivors of early-wave hospitalisations, 11%–54% report at least one persistent symptom 3 years later, and approximately one-third continue to demonstrate impaired pulmonary diffusion capacity or radiological abnormalities.[3 5 7] Multisystem consequences—neurological, cardiovascular, renal and metabolic—also contribute to the long-term burden, with 3-year mortality and major adverse cardiovascular events remaining higher among those with acute-phase neurological involvement.[8]

Across studies, several risk factors for persistent or relapsing symptoms recur with remarkable consistency. Greater acute-phase severity, including hospitalisation, oxygen therapy or intensive-care admission, confers the highest risk of long-term sequelae.[5 9] Chronic comorbidities such as diabetes, chronic kidney disease and cardiovascular or pulmonary disorders amplify this risk.[9 10] Baseline organ impairment—reduced diffusion capacity, lung consolidations, diminished functional capacity—predicts slower recovery and persistent disability.[7] Older age, female sex and higher levels of inflammatory markers during hospitalisation, including C reactive protein, erythrocyte sedimentation rate, alanine aminotransferase and creatinine, are independently linked to adverse trajectories.[6 9 11 12] Moreover, the presence of ongoing symptoms at 1–3 months markedly increases the probability of long-term persistence.[3 11]

Reliable prediction of such prolonged morbidity is essential for clinical practice, rehabilitation planning and health-system preparedness. Identification of high-risk patients enables targeted surveillance and early rehabilitation while informing allocation of resources to specialised services and social support. The continuing prevalence of long-term symptoms contributes to reduced work capacity, quality of life impairment and sustained healthcare utilisation.[9 13] Quantitative models that forecast persistence at extended time horizons are therefore instrumental for mitigating the human and economic toll of the pandemic.

Despite extensive epidemiological data, no validated prognostic model currently predicts Long COVID persistence at 36 months. Available research provides adjusted associations for specific outcomes but lacks integrated patient-level prediction.[9] A few studies have attempted predictive modelling at shorter horizons, including 24-month modelling studies in adults[14] and children[15] that demonstrated the feasibility of risk prediction for persistent Long COVID. Earlier analyses from the hospitalised cohort explored in the present study have also developed models for 3-month and 12-month outcomes with high internal accuracy.[11 12] The current study continues this trajectory by examining 36-month outcomes in the same cohort and directly comparing predictive strategies based on predischarge and postdischarge data. This approach aims to define the optimal timing and set of predictors for forecasting very-long-term persistence of Long COVID, addressing a major unmet need in postpandemic rehabilitation and healthcare planning.

METHODS

Study design

This was a prospective observational study that was conducted at the tertiary care hospital that served as a specialised COVID-19 treatment centre during the first wave of the pandemic for a population of approximately 2.4 million people in Kharkiv, Ukraine.

Participants

Between January and November 2021, adult patients (≥18 years) hospitalised with a confirmed diagnosis of COVID-19 pneumonia, verified via PCR testing, were screened for eligibility. Exclusion criteria included acute cerebrovascular events within the prior 6 months, history of myocardial infarction, acute or stage D chronic heart failure, permanent atrial fibrillation, uncontrolled severe hypertension (systolic pressure ≥180 mm Hg and/or diastolic pressure ≥110 mm Hg), significant valvular heart disease, active malignancy or systemic autoimmune disease, inability to provide informed consent or persistent need for supplemental oxygen at discharge.

The research team systematically approached eligible candidates on the inpatient wards prior to their hospital discharge. During this initial approach and prior to enrolment, patients were provided with comprehensive information regarding the study's aims, the nature of the longitudinal follow-up assessments, and their right to withdraw at any time without affecting their standard of care. Written informed consent was obtained from all participants prior to their formal inclusion in the study, in accordance with the ethical standards of the institutional review board.

Of 265 consecutive eligible patients, 44 declined participation, resulting in an initial cohort of 221 enrolled

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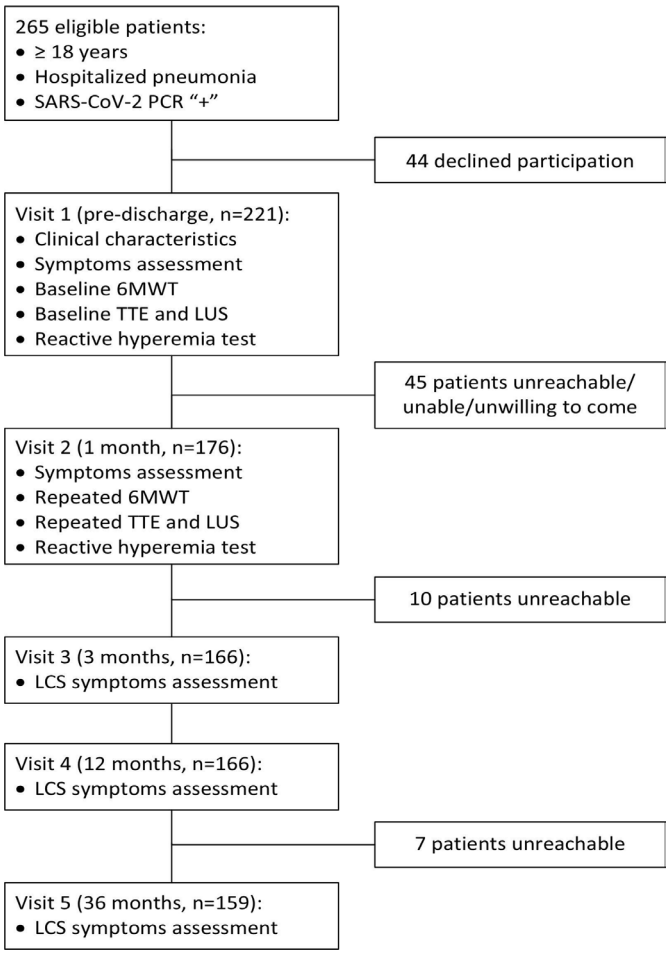


Figure 1 Study flow chart. 6MWT, 6-Minute Walk Test; LUS, lung ultrasound; TTE, transthoracic echocardiography.

individuals. The final analysis included 159 patients who completed follow-up assessments at 1, 3, 12 and 36 months postdischarge (see figure 1 for the study flow chart). A comprehensive comparative analysis was performed to evaluate potential attrition bias between the retained cohort (n=159) and patients lost to follow-up (n=62). The analysis indicated a largely non-differential attrition profile; statistically insignificant variations in baseline hypertensive profile did not translate into clinically meaningful functional disparities at the time of hospital discharge (see online supplemental table 1 for full comparative details). No fatalities were recorded among the contactable cohort.

Data collection

Baseline assessments were conducted 1–2 days prior to hospital discharge, when patients were clinically stable, with resting peripheral capillary oxygen saturation (SpO_2) ≥93% on room air, and free from acute respiratory symptoms for at least 3 days starting from the 10th day after symptom onset.[16] Demographic information, comorbidities, laboratory data, chest CT findings (quantified via the simplified RALE score[17]) and treatment details were extracted from medical records. Interviews were conducted to collect smoking status, symptom profiles, and comorbidities, alongside anthropometric measurements. Additional assessments included:

- Transthoracic echocardiography (TTE) was performed in 176 participants using the Radmir ULTIMA Expert system (Radmir Co., Ukraine) in accordance with American Society of Echocardiography / European Association of Cardiovascular Imaging guidelines[18 19]; ventricular global longitudinal strain (GLS) was quantified using a linear method as recently described.[20]
- Vascular reactivity: reactive hyperaemia of the brachial artery via upper arm occlusion.[21]
- Lung ultrasound (LUS): conducted at standard BLUE protocol points, with cumulative B-line and subpleural consolidation counts.[22 23]
- Functional capacity: 6-Minute Walk Test (6MWT) following ATS recommendations,[24] using a 20 m hallway and continuous SpO_2/heart rate monitoring.

Patients also completed standardised questionnaires: the chronic obstructive pulmonary disease (COPD) Assessment Test (CAT),[25] EFTER-COVID questionnaire physical symptom subscale,[26] Symptom Burden Questionnaire for Long COVID (SBQ-LC) Memory, Thinking and Communication subscale,[27] and Hospital Anxiety and Depression Scale (HADS).[28]

Follow-up at 1 month used the same in-person protocol. 3, 12 and 36-month assessments were conducted remotely, capturing self-reported persistence of Long COVID symptoms and reporting on the used questionnaires. The primary outcome was assessed using the specific prompt: 'Have you recovered completely, or do some symptoms persist?' (translated from the native language). This broad operational definition was used to capture the full spectrum of the syndrome and directly aligns with the WHO clinical case definition for post COVID-19 condition.[29] While symptoms were permitted to follow a relapsing and remitting course, patients were specifically required to link their ongoing symptom burden to an incomplete recovery from their index COVID-19 hospitalisation, excluding entirely new clinical events unrelated to the initial infection.

Patient and public involvement

Patients and public did not participate in the design, recruitment and conduct of the study.

Statistical analysis and prediction strategy

Data analysis was performed using StatSoft STATISTICA V.12. The distribution of continuous variables was assessed with the Shapiro-Wilk test. Normally distributed variables are reported as mean±SD and skewed data as median (IQR). Categorical variables are expressed as counts (percentages). Group comparisons used independent samples t-test for normally distributed variables, Mann-Whitney U test for skewed variables, χ^2 test for categorical data and Wilks test in repeated measures analysis

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of variance for variables with multiple assessment points. Statistical significance was set at p<0.05.

To predict persistent Long COVID symptoms at 36 months, we developed staged multivariable models incorporating predischarge and postdischarge data:

- Predischarge model included demographics, baseline comorbidities, in-hospital treatment, laboratory parameters, markers of the disease severity, predischarge LUS/echocardiography/6MWT metrics and symptom scores.
- 1, 3 and 12-month models: each included predischarge variables plus visit-specific clinical and symptom measures, capturing updated functional tests and symptom burden.
- Combined/dynamic models: time-updated models integrating the bulk of predischarge and postdischarge predictors available by the time of each visit, including self-assessed recovery status at 3 and 12 months.

Given the high-dimensional nature of the initial dataset relative to the sample size, we implemented a sequential, domain-constrained feature selection pipeline to mitigate the risk of the curse of dimensionality and algorithmic overfitting. Following an initial univariate screening to eliminate statistically non-informative variables (evaluated via Wald p values), the final predictor subsets were curated by harmonising statistical weights with clinical heuristics. Priority was assigned to markers demonstrating early temporal availability, alignment with the routine standard of care and logistical feasibility within a single clinical encounter, thereby anchoring the predictive feature space in clinical pragmatism.

Primary predictive modelling was conducted within a supervised learning framework using feed-forward multilayer perceptron (MLP) artificial neural networks. The study cohort was randomly partitioned into training, test and validation subsets (70:15:15 ratio). To constrain model capacity and minimise structural risk, the network topology was restricted to a shallow architecture comprising a single hidden layer of 4 to 14 neurons. Hyperparameter optimisation and network topology selection were executed via an automated neural architecture search, using the Broyden-Fletcher-Goldfarb-Shanno quasi-Newton optimisation algorithm to identify the most stable configuration. Predictive performance was quantified using classification accuracy and the area under the receiver operating characteristic (AUROC) curve. Sample size adequacy was evaluated post hoc using Cohen's d effect size and model accuracy metrics.[30]

To further validate model stability and ensure that the performance metrics were not artefacts of a stochastic data partition, the optimised network configurations were subsequently subjected to 10-fold cross-validation across the full study cohort. Throughout both stages, strict partition isolation was maintained; parameters for missing value imputation (median) were derived exclusively from the training folds/subsets and applied to the corresponding test sets to preclude data leakage. A schematic representation of the domain-constrained feature selection pipeline and modelling workflow is provided in online supplemental figure 1. Additionally, calibration for each of the final models was assessed within a Cox calibration framework using test and validation subsets.

To evaluate the incremental predictive value of the neural network approach, the optimised MLP models were benchmarked against a parsimonious baseline logistic regression model employing a main effects approach. This comparator used six predictors preselected through a combination of univariate screening and domain-specific knowledge. This specific configuration was restricted a priori to maximise predictive capacity while maintaining an events per variable ratio >10 (based on 66 outcome events) to prevent algorithmic overfitting. Apparent classification metrics were derived from the full dataset at the optimal probability threshold, while model discrimination was internally validated using 500 bootstrap resamples to calculate an optimism-corrected median AUROC. Additionally, an array of alternative machine learning (ML) classifiers was evaluated. To ensure a rigorous comparative analysis, the input feature spaces for these alternative models were stratified according to their respective algorithmic tolerances for high dimensionality. Specifically, support vector machine, naïve Bayes classifier and k-nearest neighbours models were trained using the full high-dimensional set of candidate predictors, and tree-based ensemble methods (random forest and boosted trees) were trained using the restricted predictor subsets identical to those isolated for the optimal MLP model. Finally, a pragmatic approach based on the assumption that no further changes in self-assessed recovery status (available at visit 4) would occur during the subsequent 12–36-month follow-up was used as a clinical comparator. Acknowledging the limitations inherent to a single-centre design and the lack of external validation, all resulting models are explicitly designated as exploratory prognostic screening tools rather than definitive diagnostic algorithms.

RESULTS

Clinical characteristics

Among 159 participants who completed the 36-month follow-up (mean age 53.1±13.6 years, 55% female), 66 (41%) reported persistence of at least one Long COVID symptom, while 93 (59%) indicated complete recovery. Table 1 summarises the cross-sectional differences in baseline demographic characteristics, comorbidities, clinical severity indices, laboratory markers and treatment variables between patients with and without Long COVID symptoms at 36 months.

The two groups were comparable in terms of age, sex distribution, body mass index, smoking status, vaccination after the index episode and markers of acute respiratory disease severity, including the extent of pulmonary involvement on CT, minimal in-hospital oxygen saturation and need for oxygen supplementation or ventilatory

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Table 1 Baseline demographic and clinical characteristics of patients with and without persistent Long COVID symptoms at 36 months

Parameters	No Long COVID symptoms at 36 months	Long COVID symptoms at 36 months	Difference (95% CI)	Two-sided p value
Subjects, n (%)	93 (59)	66 (41)		
Female sex, n (%)	53 (57)	34 (52)		0.494
Age, years	51.8±14.3	55.0±12.5	3.2 (–1.1 to 7.5)	0.147
Long COVID symptoms at 3 months, n (%)	55 (59)	60 (91)		<0.001
Long COVID symptoms at 12 months, n (%)	12 (13)	51 (77)		<0.001
Vaccination following index episode, n (%)	53 (57)	37 (56)		0.907
BMI, kg/m^2	28.9±5.3	29.3±5.2	0.3 (–1.3 to 2.0)	0.691
Comorbidities, n (%)				
Hypertension	38 (41)	20 (30)		0.173
Obesity	34 (37)	25 (38)		0.865
Diabetes mellitus, type 2	10 (11)	6 (9)		0.731
History of peptic ulcer	4 (4)	7 (11)		0.123
History of cancer	4 (4)	3 (5)		0.941
History of stroke/TIA	1 (1)	2 (3)		0.372
Chronic kidney disease	0 (0)	2 (3)		0.091
Bronchial asthma	0 (0)	4 (6)		0.016
COPD	3 (3)	0 (0)		0.141
Angina pectoris	0 (0)	3 (4)		0.038
Chronic liver disease	0 (0)	2 (3)		0.091
Charlson comorbidity index	0.33±0.56	0.61±0.96	0.28 (0.04 to 0.52)	0.022
Active smoking status, n (%)	16 (17)	10 (15)		0.73
Hospitalisation period, days	14.3±3.5	15.8±5.7	1.5 (–0.3 to 3.2)	0.1
Time from disease onset to hospitalisation, days	5.2±3.9	10.2±3.4	5.0 (3.8 to 6.2)	<0.001
Pulmonary involvement by CT, %	32.4±22.2	29.1±17.4	–3.4 (–11.8 to 5.0)	0.425
Minimal in-hospital SpO2, %	88.8±7.7	87.4±7.6	–1.4 (–3.8 to 1.1)	0.264
Oxygen supplementation, n (%)				
Via nasal cannula	47 (51)	43 (65)		0.067
Non-invasive/invasive ventilation	4 (4)	2 (3)		0.679
Laboratory parameters				
Peak IL-6, pg/mL	11.3 (3.3; 45.0)	9.7 (3.1; 47.0)		0.222
Peak CRP, mg/L	17 (6; 48)	33 (7; 67)		0.321
Peak ESR, mm/hour	29.8±10.6	30.8±15.1	0.9 (–3.8 to 5.7)	0.699
Peak procalcitonin, ng/mL	0.06 (0.05; 0.07)	0.05 (0.03; 0.12)		0.534
Peak D-dimer, ng/mL	287 (179; 508)	179 (128; 628)		0.134
Peak ALT, IU/L	42 (26; 62)	47 (30; 128)		0.011
Peak AST, IU/L	32 (21; 47)	43 (37; 55)		0.003
Peak creatinine, µmol/L	96 (85; 105)	109 (100; 119)		<0.001
Lowest eGFR, mL/min/1.73 m^2	68.7±19.9	59.2±17.3	–9.5 (–17.6 to –1.4)	0.022
Haemoglobin, g/L	139±17	139±15	–1 (–7 to 5)	0.782
Cardiac troponin I, pg/mL	71.9 (65.9; 80.0)	74.9 (67.9; 83.5)		0.346
NT-proBNP, pg/mL	72.1 (45.3; 174.1)	72.1 (50.6; 238.4)		0.525
Galectin-3, ng/mL	9.0±0.5	8.6±0.7	–0.4 (–0.6 to –0.2)	<0.001
sST2, ng/mL	29.7±15.8	23.2±13.7	–6.5 (–11.5 to –1.5)	0.012

Continued

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Table 1 Continued

Parameters	No Long COVID symptoms at 36 months	Long COVID symptoms at 36 months	Difference (95% CI)	Two-sided p value
Treatment, n (%)				
Dexamethasone	81 (87)	60 (91)		0.455
Methylprednisolone	54 (58)	49 (74)		0.035
Remdesivir	38 (41)	30 (45)		0.564

Values are presented as mean±SD or median (IQR).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; eGFR, estimated glomerular filtration rate by CKD-EPI equation; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SpO2, peripheral capillary oxygen saturation; TIA, transient ischaemic attack.

support. Duration of hospitalisation did not differ significantly between groups. However, patients who later developed persistent symptoms were hospitalised later in the disease course, with a significantly longer interval between symptom onset and hospital admission.

The prevalence of common cardiometabolic comorbidities, most notably hypertension and obesity, was similar between groups. In contrast, patients with persistent Long COVID demonstrated a higher burden of less prevalent chronic conditions, including bronchial asthma and symptomatic coronary artery disease, translating into a significantly higher Charlson comorbidity index.

Inflammatory biomarkers during hospitalisation were largely comparable between groups, with no significant differences in peak interleukin-6, C reactive protein, procalcitonin, D-dimer concentrations or erythrocyte sedimentation rate. In contrast, markers of extrapulmonary organ involvement differed more clearly. Patients who later developed 'very long' COVID exhibited higher peak serum alanine and AST levels, higher peak creatinine concentrations and correspondingly lower estimated glomerular filtration rate, suggesting greater hepatic and renal involvement during the acute phase.

While standard cardiac biomarkers, including cardiac troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP), did not differ significantly between groups, circulating levels of galectin-3 and soluble ST2 were paradoxically higher during hospitalisation among patients who subsequently achieved complete recovery.

With regard to treatment, the use of dexamethasone and remdesivir was similar in both groups, while off-label pulse therapy with methylprednisolone was administered more frequently among patients who subsequently reported persistent symptoms.

Importantly, the persistence of symptoms at earlier follow-up points strongly differed between groups: patients with Long COVID at 36 months were substantially more likely to report ongoing symptoms at both 3 and 12 months, underscoring the continuity of symptom trajectories over time.

Sonographic assessment

Table 2 summarises cross-sectional and early longitudinal differences in echocardiographic, vascular and LUS parameters between patients with and without persistent Long COVID symptoms at 36 months, assessed predischarge and at 1 month after hospitalisation.

At the predischarge assessment, left ventricular (LV) and left atrial morphometric indices were largely comparable between patients who later reported complete recovery and those with persistent Long COVID symptoms at 36 months. Both groups demonstrated a tendency towards concentric LV geometry, reflected by similarly elevated relative wall thickness. Functionally, several systolic indices were modestly higher in patients who subsequently developed Long COVID. These differences reached statistical significance for mitral annular plane systolic excursion (both medial and lateral) and LV GLS, while LV ejection fraction and right ventricular free wall longitudinal strain showed similar but non-significant trends.

At the 1-month follow-up, patients without persistent symptoms at 36 months demonstrated mild reductions in right- and a similar trend in left atrial size, whereas no comparable decrease was observed among patients with Long COVID. In parallel, systolic function indices in the Long COVID group showed a tendency towards minimal decrease within normal range, manifested by a small decline in LV ejection fraction, mitral annular systolic velocities and excursion, and a similar trend for longitudinal strain of both ventricles, resulting in loss of the baseline intergroup differences.

LV diastolic parameters were similar between groups at discharge. During early follow-up, patients without subsequent 'very long' COVID exhibited more favourable changes, including increases in early diastolic tissue velocities and reductions in E/e′ ratio, both at rest and after the 6-Minute Walk Test. In contrast, these indices remained relatively unchanged in the Long COVID group, leading to marginally lower e′ values at 1 month despite similar baseline measurements.

Assessment of endothelial function revealed significantly lower baseline flow-mediated dilation of the brachial artery in patients who reported ongoing symptoms at 36 months. This difference was no longer evident at 1 month, owing to improvement in the Long COVID group and relative stability in patients without persistent symptoms. LUS findings showed a comparable baseline

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Table 2 Echocardiographic, vascular and lung ultrasound parameters predischarge and at 1-month follow-up in patients with and without persistent Long COVID symptoms at 36 months

Parameters	Visit time	No Long COVID symptoms at 36 months n=93	Long COVID symptoms at 36 months n=66	Difference (95% CI)	Two-sided p value
Left chambers morphometry					
LA volume index, mL/m^2	0 months	28.2±6.8	29.3±6.5	1.1 (–1.0 to 3.3)	0.232
	1 month	26.8±6.4	28.4±6.1	1.5 (–0.8 to 3.8)	0.192
	P value	0.197	0.659		
LV end-diastolic volume index, mL/m^2	0 months	48.6±7.6	47.8±10.0	–0.8 (–3.6 to 2.0)	0.569
	1 month	46.9±8.4	46.9±10.2	0.0 (–3.4 to 3.3)	0.977
	P value	0.128	0.915		
LV end-systolic volume index, mL/m^2	0 months	16.8±4.0	16.1±5.5	–0.8 (–2.3 to 0.7)	0.308
	1 month	16.9±4.7	16.8±7.1	–0.1 (–2.2 to 1.9)	0.89
	P value	0.593	0.042		
LV relative wall thickness	0 months	0.44±0.07	0.46±0.08	0.02 (–0.01 to 0.04)	0.186
	1 month	0.44±0.07	0.46±0.09	0.01 (–0.01 to 0.05)	0.251
	P value	0.585	0.199		
LV mass index (height$^{2.7}$), g/m$^{2.7}$	0 months	37.7±10.5	37.7±5.6	0.1 (–2.9 to 2.7)	0.965
	1 month	35.3±7.8	37.5±5.8	2.2 (–0.4 to 4.7)	0.098
	P value	0.091	0.607		
Left ventricular function					
LV ejection fraction, %	0 months	65.3±6.3	66.7±7.2	1.5 (–0.7 to 3.6)	0.175
	1 month	64.4±6.2	65.3±7.7	1.0 (–1.5 to 3.5)	0.437
	P value	0.249	0.013		
Medial MAPSE, mm	0 months	12.7±1.7	13.5±2.3	0.8 (0.2 to 1.5)	0.015
	1 month	13.3±2.0	12.7±1.7	–0.5 (–1.2 to 0.2)	0.134
	P value	0.039	0.036		
Lateral MAPSE, mm	0 months	15.0±2.3	15.7±2.2	0.8 (0.0 to 1.5)	0.045
	1 month	15.2±2.5	14.7±2.4	–0.5 (–1.4 to 0.4)	0.297
	P value	0.339	0.075		
LV global longitudinal strain, %	0 months	17.2±2.2	18.0±2.5	0.8 (0.1 to 1.6)	0.036
	1 month	17.5±2.3	17.1±1.7	–0.4 (–1.2 to 0.4)	0.314
	P value	0.223	0.116		
LV s' mean, cm/s	0 months	9.7±2.0	9.9±1.2	0.2 (–0.3 to 0.8)	0.434
	1 month	9.4±1.6	9.1±1.8	–0.3 (–0.9 to 0.4)	0.392
	P value	0.123	0.002		
LV e' mean, cm/s	0 months	9.3±2.4	9.4±1.8	0.1 (–0.6 to 0.8)	0.8
	1 month	10.1±3.1	9.1±2.0	–1.0 (–2.0 to 0.0)	0.044
	P value	0.01	0.414		
LV E/e' ratio	0 months	7.8±2.0	7.1±1.4	–0.8 (–1.3 to –0.2)	0.01
	1 month	7.3±2.4	7.3±2.2	0.0 (–0.9 to 0.8)	0.959
	P value	0.041	0.571		
LV s' mean post-6MWT, cm/s	0 months	11.2±2.1	11.3±1.9	0.2 (–0.6 to 0.9)	0.673
	1 month	11.6±2.2	11.3±2.2	–0.3 (–1.2 to 0.6)	0.49
	P value	0.148	0.383		
LV e' mean post-6MWT, cm/s	0 months	10.7±2.6	10.7±2.3	0.0 (–0.9 to 1.0)	0.955
	1 month	12.1±2.4	11.3±2.2	–0.8 (–1.7 to 0.1)	0.082
	P value	<0.001	0.028		

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Table 2 Continued

Parameters	Visit time	No Long COVID symptoms at 36 months n=93	Long COVID symptoms at 36 months n=66	Difference (95% CI)	Two-sided p value
LV E/e' ratio post-6MWT	0 months	7.4±2.0	7.4±1.6	−0.1 (−0.8 to 0.7)	0.865
	1 month	7.0±2.2	7.7±1.4	0.7 (0.0 to 1.4)	0.066
	P value	0.02	0.211		
Right chambers evaluation					
RA area index, cm^2/m^2	0 months	8.4±2.5	7.7±1.4	−0.7 (−1.4 to 0.0)	0.05
	1 month	7.5±1.6	8.0±1.1	0.5 (−0.0 to 1.0)	0.039
	P value	0.013	0.896		
RV size (proximal outflow tract), mm	0 months	32.1±3.8	31.4±2.6	−0.7 (−2.0 to 0.5)	0.234
	1 month	32.6±4.5	31.1±3.3	−1.5 (−3.0 to 0.1)	0.059
	P value	0.337	0.526		
TAPSE, mm	0 months	25.0±4.2	24.9±4.2	−0.1 (−1.5 to 1.3)	0.886
	1 month	24.7±3.9	23.6±3.1	−1.1 (−2.4 to 0.2)	0.1
	P value	0.111	0.238		
RV free wall longitudinal strain, %	0 month	35.6±6.1	37.2±7.7	1.5 (−0.8 to 3.9)	0.195
	1 month	35.5±6.1	34.8±5.2	−0.8 (−2.8 to 1.4)	0.489
	P value	0.175	0.072		
Auxiliary sonographic evaluation					
Flow-mediated dilation of the brachial artery, %	0 months	12.9±5.9	10.1±5.1	−2.8 (−4.8 to −0.8)	0.006
	1 month	13.1±5.8	11.5±6.6	−1.6 (−4.0 to 0.8)	0.179
	P value	0.956	0.243		
Cumulative pulmonary B-lines score	0 months	23.0±12.1	22.5±11.0	−0.5 (−4.4 to 3.4)	0.793
	1 month	15.5±6.2	16.1±6.8	0.6 (−1.9 to 3.0)	0.649
	P value	<0.001	<0.001		
Cumulative pulmonary consolidations score	0 months	1.2±1.7	1.4±1.6	0.3 (−0.3 to 0.8)	0.346
	1 month	0.5±0.8	0.6±0.8	0.1 (−0.2 to 0.4)	0.571
	P value	<0.001	<0.001		

Values are presented as mean±SD. Values presented are from cross-sectional comparisons at 0 and 1 month and could be altered due to pairwise deletion of missing data in the paired t-test.
LA, left atrium; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; 6MWT, 6-Minute Walk Test; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

degree of residual subpleural consolidation burden as well as interstitial involvement (as reflected by cumulative B-line scores), with a marked reduction by 1 month in both groups.

6-Minute Walk Test

Table 3 presents comparisons of functional exercise capacity and symptom response during the 6-Minute Walk Test that was performed predischarge and at a 1-month visit between patients with and without persistent Long COVID symptoms at 36 months.

At the predischarge assessment, overall results of the 6-Minute Walk Test did not differ substantially between patients with persistent Long COVID symptoms and those who reported complete recovery at 36 months. Both absolute walking distance and distance indexed to predicted values were comparable between groups, indicating broadly preserved submaximal exercise capacity.

Baseline haemodynamic parameters measured before the test, including heart rate, systolic and diastolic blood pressure and peripheral oxygen saturation, were similar between groups. During exercise, both cohorts demonstrated appropriate chronotropic and blood pressure responses, with no clinically meaningful intergroup differences in peak heart rate or exercise-induced desaturation.

In contrast, patient-reported responses to exertion differed more clearly. Patients with persistent Long COVID symptoms reported higher levels of perceived dyspnoea and fatigue both at baseline and at the end of the walk test. Postexertional symptom scores remained elevated in this group despite comparable objective performance, whereas patients without Long COVID showed lower symptom intensity and more complete symptom resolution following exertion.

At the 1-month follow-up, objective functional performance demonstrated a parallel increase in both groups,

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Table 3 Six-Minute Walk Test in patients with and without persistent Long COVID symptoms at 36 months

Parameters	Visit time	No Long COVID symptoms at 36 months n=93	Long COVID symptoms at 36 months n=66	Difference (95% CI)	Two-sided p value
6-Minute Walk Distance, m	0 months	404±69	386±70	−18 (−45 to 8)	0.171
	1 month	467±53	454±76	−13 (−38 to 12)	0.308
	P value	<0.001	<0.001		
6-Minute Walk Distance, % of predicted	0 months	62.3±9.4	62.4±10.1	0.1 (−3.6 to 3.8)	0.961
	1 month	72.2±9.0	74.9±12.1	2.8 (−1.3 to 6.8)	0.178
	P value	<0.001	<0.001		
Baseline heart rate, bpm	0 months	84.0±13.6	81.5±11.0	−2.5 (−7.2 to 2.2)	0.298
	1 month	80.7±14.8	82.0±13.6	1.2 (−4.3 to 6.7)	0.663
	P value	0.08	0.367		
Maximal heart rate, bpm	0 months	107.7±14.6	104.8±13.9	−3.0 (−8.5 to 2.6)	0.29
	1 month	110.6±14.7	109.2±13.1	−1.4 (−6.9 to 4.2)	0.621
	P value	0.103	0.007		
Maximal heart rate, % of the individual maximum	0 months	62.2±7.8	61.2±8.3	−1.0 (−4.0 to 2.1)	0.218
	1 month	64.1±8.2	64.4±8.0	0.3 (−2.9 to 3.5)	0.847
	P value	0.041	0.006		
Heart rate increment, bpm	0 months	22.8±11.2	23.1±12.1	0.3 (−4.2 to 4.8)	0.896
	1 month	29.5±11.6	26.2±11.7	−3.4 (−7.9 to 1.2)	0.15
	P value	<0.001	0.02		
Baseline SpO2, %	0 months	95.1±5.2	95.1±5.7	0.0 (−1.8 to 1.9)	0.969
	1 month	98.1±0.8	97.9±0.7	−0.2 (−0.5 to 0.1)	0.216
	P value	<0.001	0.001		
Minimal SpO2, %	0 months	93.8±4.8	95.0±2.7	1.2 (−0.2 to 2.7)	0.1
	1 month	95.3±2.6	96.3±1.7	0.9 (0.0 to 1.8)	0.039
	P value	0.002	0.003		
Peak O2 desaturation, %	0 months	3.1±2.8	2.3±1.7	−0.7 (−1.6 to 0.2)	0.13
	1 month	2.8±2.4	1.7±1.7	−1.0 (−1.9 to −0.2)	0.014
	P value	0.196	0.05		
Baseline systolic BP, mm Hg	0 months	131.9±17.2	137.8±15.1	5.9 (−0.1 to 11.8)	0.052
	1 month	131.4±15.2	138.1±17.7	6.7 (0.5 to 13.0)	0.034
	P value	0.925	0.53		
Baseline diastolic BP, mm Hg	0 months	84.2±13.4	83.9±8.5	−0.2 (−4.4 to 4.0)	0.907
	1 month	80.5±10.9	84.3±10.5	3.8 (−0.3 to 7.9)	0.067
	P value	0.06	0.606		
Dyspnoea at start, pts (modified Borg scale)	0 months	1.1±1.4	1.6±1.7	0.5 (−0.1 to 1.0)	0.11
	1 month	0.6±0.9	1.0±1.3	0.3 (−0.1 to 0.7)	0.145
	P value	0.015	0.009		
Fatigue at start, pts (modified Borg scale)	0 months	2.4±2.5	2.6±1.6	0.2 (−0.6 to 1.0)	0.591
	1 month	1.0±1.2	1.7±1.4	0.8 (0.3 to 1.3)	0.002
	P value	<0.001	0.012		
Dyspnoea at finish, pts (modified Borg scale)	0 months	3.1±2.2	3.5±1.5	0.4 (−0.7 to 1.5)	0.496
	1 month	2.5±1.8	3.4±1.7	0.9 (0.1 to 1.7)	0.027
	P value	0.008	0.348		

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Table 3 Continued

Parameters	Visit time	No Long COVID symptoms at 36 months n=93	Long COVID symptoms at 36 months n=66	Difference (95% CI)	Two-sided p value
Fatigue at finish, pts (modified Borg scale)	0 months	3.3±2.3	3.3±1.4	−0.0 (−1.1 to 1.1)	0.984
	1 month	1.9±1.6	3.3±2.1	1.4 (0.6 to 2.2)	<0.001
	P value	<0.001	0.451		

Values are presented as mean±SD. Values presented are from cross-sectional comparisons at 0 and 1 month and could be altered due to pairwise deletion of missing data in the paired t-test.
BP, blood pressure; SpO2, peripheral capillary oxygen saturation.

showing no significant differences between patients with and without ongoing symptoms at 36 months and evidenced by increased absolute and indexed 6MWD and mildly higher chronotropic recruitment compared with predischarge values. Both baseline and peak haemodynamic responses to exercise at 1 month continued to be similar between groups, indicating stable submaximal exercise capacity during early recovery. Interestingly, nadir SpO2 values during exertion were slightly higher in patients of the persistent Long COVID group despite identical resting values.

In contrast, symptom dynamics over time differed between groups. Patients without persistent Long COVID demonstrated a larger reduction in baseline fatigue as well as postexertional fatigue and dyspnoea scores between discharge and the 1-month visit. At the same time, patients with persistent Long COVID showed smaller decrease in baseline fatigue and no improvement in postexertional symptoms intensity during the early follow-up period, resulting in significant intergroup differences at 1 month.

Symptoms

Longitudinal multiquestionnaire assessments revealed significant divergence in symptom recovery trajectories between the two groups (table 4).

At the predischarge assessment, patient-reported outcomes across respiratory, general physical, cognitive and emotional domains were largely comparable between patients who later reported complete recovery and those with persistent Long COVID symptoms at 36 months. Respiratory symptoms burden, assessed using CAT, CCQ, and MRC Dyspnoea scores, as well as post-COVID functional scale reflecting general functioning and both HADS subscales scores did not differ significantly between groups at baseline. In contrast, measures of physical (EFTER-COVID study physical symptoms score) and cognitive well-being (SBQ-LC Memory, Thinking and Communication scale) demonstrated early separation, with patients who subsequently developed Long COVID reporting higher symptom burden already at the predischarge assessment.

At the 1-month follow-up, differences across multiple symptom domains became more apparent. Respiratory symptom scores began to show the trend towards higher values among patients who later developed persistent Long COVID, resulting in a higher MRC Dyspnoea score. General physical symptom burden remained significantly higher in the Long COVID group, accompanied by divergence in the trajectory of the functional capacity as assessed by Post-COVID-19 Functional Status scale (PCFS). SBQ-LC Memory, Thinking and Communication score at this point in time has temporarily lost its discriminatory significance, while HADS Anxiety score paradoxically demonstrated higher value in the non-Long COVID group.

By the 3-month visit, intergroup differences were evident across all questionnaire clusters with the exception of the emotional one. Respiratory, physical, cognitive and general functional scores consistently remained higher in patients with persistent Long COVID, while patients without Long COVID showed further improvement across domains. These differences largely persisted at the 12-month assessment, with the exception being the attenuation of inter-group differences in CAT and CCQ.

Longitudinal analyses demonstrated markedly different recovery trajectories. Patients without persistent Long COVID exhibited a more significant improvement over time in dyspnoea, physical, cognitive and general functional domains compared with patients with Long COVID at 36 months who showed more modest improvement across most symptom domains, resulting in sustained symptom burden and significant divergence in longitudinal trajectories between groups.

Prognosis

To address the high-dimensional nature of the initial dataset and mitigate the risk of algorithmic overfitting, we employed a preliminary feature-pruning stage to the 299 candidate predischarge and postdischarge predictors that included baseline characteristics of the patients, in-hospital clinical and laboratory parameters, expert exploratory TTE and 6MWT at 0 and 1 month, and multiple scale-based assessment of symptoms at 0, 1, 3 and 12 months. Of the initial pool, 63 parameters demonstrated significant marginal effects and were retained for subsequent modelling. Self-assessed symptom persistence at 12 months showed the highest individual association (Somers' D=0.624), closely followed by duration of hospitalisation (D=0.619), EFTER-COVID physical symptoms score at 3 and 12 months (D=0.526 and 0.479),

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Table 4 Longitudinal multiquestionnaire based symptom assessment in patients with and without persistent Long COVID symptoms at 36 months

Parameters	Visit time	No Long COVID symptoms at 36 months n=93	Long COVID symptoms at 36 months n=66	Difference (95% CI)	P value
CAT score	0 months	16.3±7.7	17.0±7.7	0.8 (–1.8 to 3.3)	0.552
	1 month	11.0±6.5	13.1±7.0	2.1 (–0.3 to 4.5)	0.092
	3 months	8.5±7.0	11.7±8.2	3.2 (0.7 to 5.8)	0.012
	12 months	6.0±5.1	7.4±5.2	1.4 (–0.3 to 3.2)	0.102
					0.336*
CCQ score	0 months	20.3±11.9	22.3±14.0	2.0 (–2.1 to 6.2)	0.335
	1 month	13.2±7.5	15.4±10.3	2.2 (–0.9 to 5.4)	0.161
	3 months	7.9±6.4	10.9±7.6	3.0 (0.7 to 5.4)	0.011
	12 months	4.8±4.9	6.5±6.5	1.7 (–0.2 to 3.6)	0.077
					0.360*
MRC Dyspnoea score	0 months	2.3±1.0	2.5±1.3	0.2 (–0.2 to 0.6)	0.249
	1 month	1.5±0.7	2.0±0.9	0.5 (0.2 to 0.8)	<0.001
	3 months	1.3±0.7	1.6±0.7	0.3 (0.1 to 0.5)	0.009
	12 months	1.3±0.5	1.5±0.7	0.3 (0.1 to 0.5)	0.004
					0.004*
HADS Anxiety score	0 months	6.2±4.2	6.6±3.6	0.4 (–0.3 to 1.2)	0.290
	1 month	6.2±3.8	4.8±3.3	–1.4 (–2.7 to –0.1)	0.034
	3 months	3.9±3.3	3.9±3.0	0.0 (–1.3 to 1.4)	0.965
	12 months	NA†	NA†		
					0.016*
HADS Depression score	0 months	5.1±4.1	5.8±4.1	0.7 (–0.7 to 2.0)	0.322
	1 month	4.5±3.6	4.7±3.9	0.1 (–1.1 to 1.6)	0.717
	3 months	4.2±3.7	4.4±3.8	0.2 (–1.5 to 1.8)	0.814
	12 months	NA†	NA†		
					0.921*
EFTER-COVID study physical symptoms score	0 months	9.5±4.5	11.4±4.0	1.9 (0.5 to 3.3)	0.01
	1 month	5.4±3.6	7.9±4.1	2.5 (1.3 to 3.8)	<0.001
	3 months	2.9±3.0	6.2±3.5	3.3 (2.2 to 4.4)	<0.001
	12 months	2.1±2.9	4.7±3.4	2.5 (1.5 to 3.6)	<0.001
					<0.001*
SBQ-LC Memory, Thinking and Communication score	0 months	2.3±3.2	3.6±3.1	1.3 (0.2 to 2.4)	0.019
	1 month	1.8±3.2	2.5±2.5	0.7 (–0.3 to 1.7)	0.146
	3 months	1.1±2.3	2.2±2.5	1.1 (0.3 to 1.9)	0.008
	12 months	0.9±1.3	2.0±2.5	1.2 (0.5 to 1.8)	<0.001
					<0.001*
PCFS score	0 months	2.2±0.7	2.4±0.7	0.2 (–0.2 to 0.4)	0.143
	1 month	1.5±0.7	1.8±0.6	0.3 (0.1 to 0.5)	0.008
	3 months	0.8±0.8	1.5±0.7	0.7 (0.4 to 0.9)	<0.001
	12 months	0.4±0.7	1.1±0.7	0.7 (0.5 to 0.9)	<0.001
					<0.001*

*P value in repeated measures ANOVA.
†Data were not collected at 12 months due to the onset of a full-scale war being a significant confounding factor.
ANOVA, analysis of variance; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; MRC, Medical Research Council; PCFS, Post-COVID-19 Functional Status scale; SBQ-LC, Symptoms Burden Questionnaire- Long COVID.

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post-COVID functional scale score at 12 and 3 months (D=0.512 and 0.443) and peak in-hospital creatinine (D=0.451). The complete results of this pruning process are provided in online supplemental table S2, and the flow chart summarising the modelling workflow and feature-selection pipeline is provided in online supplemental figure S1.

To establish a rigorous clinical benchmark for evaluating the ML approaches, we developed a parsimonious baseline logistic regression model. This comparator used a restricted set of six predictors, curated by harmonising the strongest results of the univariate screening with clinical heuristics to ensure a robust events-per-variable ratio (>11). This baseline model achieved an internally validated, bootstrapped median AUROC of 0.82 (95% CI 0.73 to 0.90)—refer to online supplemental table S3 for model parameters.

Subsequently, a suite of ML classification models was developed using staged predictor sets to reflect real-world data availability at baseline and follow-up. Initial inputs comprised the 63 parameters identified during the preliminary pruning stage, supplemented by age and sex as universally recognised prognostic markers.[14 31 32] To optimise model parsimony, redundant predictors were iteratively eliminated based on global sensitivity analysis of the trained architectures and the pragmatic goal of minimising required diagnostic procedures beyond the standard of care. Performance metrics for the resulting ML models, including comparisons against the baseline logistic regression, alternative ML approaches and the pragmatic assumption that self-assessed recovery remains unchanged between 12 and 36 months, are presented in table 5, with corresponding receiver operating characteristic (ROC) curves illustrated in figure 2.

As shown in table 5, the use of a set of in-hospital parameters complemented by predischarge 6MWD and questionnaire-based symptom assessment allowed the development of a predischarge model with reasonable predictive capacity for the 36-month outcome. Postponing the auxiliary assessment until the 1-month visit resulted in only a marginal increase in predictive metrics (which may be partially data-driven, given the absence of a concomitant increase in AUROC) at the expense of an additional visit and the need to extend both the survey and 6MWT protocols; performing the latter appeared mandatory in order to preserve the model performance.

Assessment at 3 months was the most informative time point for predicting persistence of Long COVID symptoms at 36 months. While combining predischarge data and 6MWD with a multidimensional survey at 3 months yielded the highest predictive performance among all developed models (accuracy=91.7%, sensitivity=92.9%, specificity=91.2%, AUROC=0.902 in the test/validation cohort), focusing on survey data at 3 months complemented by age, sex and duration of the index hospitalisation enabled development of a second high-performance model that eliminated the need to include any in-hospital parameters beyond those available anamnestically or not included in the standard of care (accuracy=87.5%, sensitivity=79.0%, specificity=93.1%, AUROC=0.850).

Use of survey results at 12 months paradoxically resulted in a mild decrease in predictive performance of the acquired model. Importantly, it failed to improve the predictive performance beyond a major reference comparator, namely, the assumption that no further changes in self-assessed recovery status (available at visit 4) would occur during the subsequent 12-month to 36-month follow-up.

Comparative evaluation of prognostic performance demonstrated that the optimal SANN-based models exhibited superior predictive ability for the 36-month outcome compared with both the parsimonious logistic regression (serving as the traditional clinical benchmark) and the suite of alternative ML approaches, including support vector machine, naïve Bayes, k-nearest neighbours, random forest and boosted trees methods. To ensure the robustness of these findings, we performed 10-fold cross-validation, consistently achieving stable predictive performance across all validation folds. Calibration assessment on the test and validation subsets demonstrated conservative predictions without evidence of overfitting, with slope parameters >1 (online supplemental figure S2).

To assess models performance against a stricter clinical threshold, a proxy sensitivity analysis was conducted evaluating the primary models' ability to predict a PCFS score of ≥2 at the 12-month follow-up. Applied to the full follow-up cohort (n=159), the optimally performing 3-month SANN model achieved an overall accuracy of 73.6% (sensitivity 63.8%, specificity 79.2%, positive predictive value (PPV) 63.8%, negative predictive value (NPV) 79.2%). Comparatively, the model exclusively using 3-month data achieved an accuracy of 69.2% (sensitivity 67.2%, specificity 70.3%, PPV 56.5%, NPV 78.9%) (see Online supplemental material and online supplemental table S4 for further details).

The resulting set of optimally performing prognostic models incorporating universally available in-hospital predictors and the results of questionnaire-based survey at 3 months (with and without predischarge 6MWD) are available in open access at https://doi.org/10.5281/zenodo.18403825, online supplemental figure S3 for technical parameters of the model performance and online supplemental table S5-S6 for network architecture.

DISCUSSION

This study concludes a long-term observational project initiated in 2021 to investigate the persistence and predictability of Long COVID following hospitalisation for acute SARS-CoV-2 infection, integrating data across multiple follow-up points and culminating in a 36 month assessment. Building on our previously reported 3-month and 12-month analyses,[11 12] the present findings provide a detailed view of extended symptom trajectories and prognostic determinants of a 3-year outcome.

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Table 5 Comparison of prognostic performance of developed models to predict Long COVID at 36 months versus baseline logistic regression, alternative machine learning methods and a pragmatic prognostic approach

Models	Accuracy, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Baseline logistic regression model (3 months+predischarge)					
Age, sex, duration of hospitalisation (0 month), creatinine (0 months), EFTER-COVID (3 months), SBQ-LC (3 months)	80.5	77.3	82.8	76.1	83.7
SANN models using predictors available by different time points					
SANN 11–8–2 (predischarge): Duration of hospitalisation (0 months), SBQ-LC (0 months), weight loss (0 months), age (0 months), 6MWD (0 months), EFTER-COVID (0 months), creatinine (0 months), sex, AST (0 months), pulse BP (0 months)	81.2	72.2	86.7	76.5	83.9
SANN 16–7–2 (1 month+predischarge + 6 MWT): sex, duration of hospitalisation (0 months), peak SpO2 dip in 6MWT (1 month), creatinine (0 months), EFTER-COVID (1 month), PCFS (1 month), AST (0 months), age (0 months), fatigue at 6' in 6MWT (1 month), mean BP (1 month), SBQ-LC (1 month), baseline fatigue (1 month), weight loss (0 months), dyspnoea at 6' in 6MWT (1 month), MRC Dyspnoea (1 month)	85.4	75	92.9	88.2	83.9
SANN 13–12–2 (3 months+predischarge): sex, SBQ-LC (3 months), MRC Dyspnoea (3 months), creatinine (0 months), EFTER-COVID (3 months), CCQ (3 months), duration of hospitalisation (0 months), weight loss (0 months), PCFS (3 months), AST, CAT (3 months), age (0 months)	87.5	86.7	87.9	76.5	93.6
SANN 14–14–2 (3 months+predischarge+6 MWT): weight loss (0 months), creatinine (0 months), PCFS (3 months), AST (0 months), SBQ-LC (3 months), EFTER-COVID (3 months), 6MWD (0 months), age (0 months), CCQ (3 months), sex, MRC Dyspnoea (3 months), duration of hospitalisation (0 months), CAT (3 months)	91.7	92.9	91.2	81.3	96.9
SANN 10–6–2 (3 months only): sex, duration of hospitalisation (0 months), CAT (3 months), CCQ (3 months), age (0 months), MRC Dyspnoea (3 months), EFTER-COVID (3 months), PCFS (3 months), SBQ-LC (3 months)	87.5	78.9	93.1	88.2	87.1
SANN 14–4–2 (12 months+predischarge+6 MWT): Long COVID at 12 months, sex, duration of hospitalisation (0 months), MRC Dyspnoea (12 months), 6MWD (0 months), age (0 months), SBQ-LC (12 months), AST (0 months), creatinine (0 months), weight loss (0 months), EFTER-COVID (12 months), PCFS (12 months)	77.1	78.6	76.5	57.9	89.7
Alternative machine learning methods-based models (0 months, 1 month, 3 months, 12 months+6 MWT at 0 months)					
Support vector machine*	31.4	80	11.1	27.3	57.1
Naïve Bayes classifier*	72.9	83.3	69.4	47.6	92.6
K-nearest neighbours*	70.9	66.7	73.3	60	78.6
Random forest†	77.1	63.6	88.5	82.4	74.2
Boosted trees†	78.5	75.8	80.4	73.5	82.2
Assumption that no changes in symptoms will occur during 12–36-month follow-up					
Long COVID at 12 months=Long COVID at 36 months	83	77.3	87.1	81	84.4

*The whole set of revealed predictors at 0, 1, 3, 12 months was used as inputs.
†Given a limited number of cases, the set of predictors was reduced to those included in the SANN (3 months+predischarge+6MWT) model; parameters included into each model are presented in the order of decreasing predictive value, the time of parameter registration is provided in parentheses.
AST, aspartate transferase; BP, blood pressure; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; EFTER-COVID, EFTER-COVID study physical symptoms score; 6MWD, 6-Minute Walking Distance; 6MWT, 6-Minute Walking Test; NPV, negative predictive value; PCFS, Post-COVID functional scale; PPV, positive predictive value; SANN, simple artificial neural network; SBQ-LC, Symptoms Burden Questionnaire- Long COVID; SpO2, capillary blood oxygen saturation.

At 36 months after discharge, 41% of previously hospitalised patients continued to report persistent symptoms consistent with Long COVID. Our results align with data from the large multicentre Dutch CO-FLOW cohort up to 36 months, where postexertional malaise was reported by 36% of previously hospitalised patients, and fatigue and cognitive problems in approximately 60% without trend for improvement between year 2 and year 3.[33] A recent

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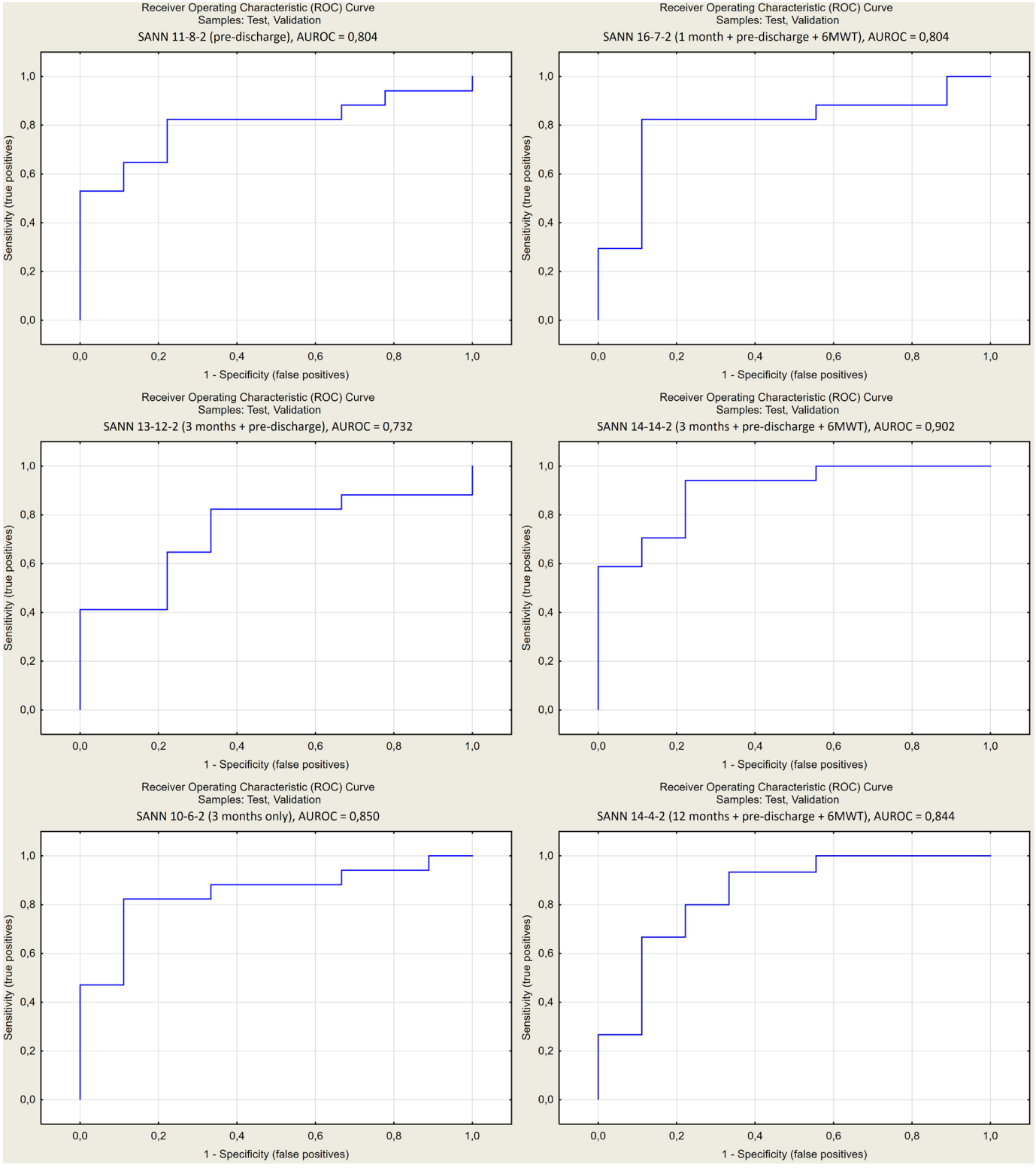


Figure 2 Receiver-operator curves of developed SANN models to predict Long COVID at 36 months. 6MWT, 6-Minute Walk Test; AUROC, area under the receiver operating characteristic curve; SANN, simple artificial neural network.

3.5-year follow-up study reported that approximately one-quarter of participants continued to experience fatigue, sleep disturbance and postexertional symptoms, particularly among those with more severe initial disease.[34] A broader meta-analysis that included both hospitalised and ambulatory patients has also reported that approximately 20% (95% CI 8% to 43%) of COVID-19 survivors report at least one unresolved symptom at 3 years after

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infection, most commonly fatigue, dyspnoea and sleep disturbances.[9] The similarity in symptom prevalence between independent cohorts from different healthcare systems strengthens the evidence that a substantial proportion of hospitalised COVID-19 survivors experience durable symptom persistence well beyond the first year of recovery. Our findings are also consistent with population-level analyses demonstrating long-lasting health impacts after severe COVID-19. Using large US healthcare databases, Cai *et al* showed that although the excess risk of many postacute sequelae declines over time, individuals hospitalised during acute infection retain a measurable burden of disability and excess mortality at 3 years.[6] While that study focused on composite health outcomes rather than symptom-defined Long COVID, it supports the notion that hospitalisation marks a subgroup with prolonged vulnerability.

When interpreting long-term epidemiological findings, the potential impact of attrition on prevalence estimates and generalisability must be considered. In extended longitudinal cohorts, systematic dropout, whether driven by severe functional decline or rapid clinical recovery, can skew subsequent prevalence estimates and limit the generalisability of predictive models. To assess this risk, we conducted a comparative attrition analysis (online supplemental table S1). While patients lost to follow-up exhibited an insignificantly higher baseline prevalence of hypertension, their functional status at hospital discharge, including PCFS scores and 6-Minute Walk Distance, was clinically comparable to the retained cohort, suggesting a largely non-differential attrition profile. Consequently, we consider the retained cohort to be a representative sample of the initial surviving population, preserving the validity of the reported prevalence estimates and the developed predictive tools.

Patients with persistent symptoms at 36 months in our cohort were characterised by a higher burden of pre-existing comorbidities, delayed hospitalisation and greater multisystem involvement during the acute phase. These observations are concordant with a large electronic health record based analysis identifying baseline health status, comorbidity clusters and acute disease severity as key determinants of Long COVID risk.[35] Importantly, our data suggest that these associations remain relevant over very long follow-up periods, not only during the first postacute year.

In contrast to the studies emphasising systemic inflammation (particularly elevated IL-6, TNF-α and CRP levels)[36 37] as a central mechanism of symptom persistence during the first months after acute infection, inflammatory markers were not strong discriminators of the outcomes in our cohort. Indeed, the pathophysiological landscape of Long COVID is highly heterogeneous, encompassing overlapping immunological drivers, endothelial damage and complex multisystem sequelae.[4] Taken together, these data suggest that while inflammatory dysregulation may be relevant in early or intermediate phases, 'very long-term'[38] symptom persistence appears more closely linked to markers of organ vulnerability and impaired recovery capacity than to sustained systemic inflammation. An unexpected finding was the inverse association between in-hospital levels of Galectin-3 and sST2 and the persistence of Long COVID at 36 months. While both biomarkers are established predictors of acute SARS-CoV-2 severity,[39–41] literature regarding their long-term prognostic trajectory remains fragmented and occasionally contradictory.[42] Given our observational design, extrapolating isolated mechanistic findings to explain these long-term clinical trajectories would be highly speculative; further targeted studies are required to elucidate their biological role in Long COVID.

Perhaps the most consistent and clinically relevant signal throughout the study was the dissociation between objective functional recovery and subjective symptom experience. Six-Minute Walk Distance and haemodynamic responses improved comparably in both groups during early convalescence, yet patients who ultimately developed very Long COVID reported persistently higher baseline and postexertional dyspnoea and fatigue. This pattern mirrors observations from physiological studies, where objective exercise capacity did not differ between symptom-defined groups despite marked differences in exertional intolerance[43] at 1 year after acute infection, and resting physiological parameters were often comparable between symptomatic and recovered individuals despite the differences in objective exercise parameters at 3 months.[44] The persistence of postexertional symptoms despite normalised objective performance supports contemporary models implicating altered central symptom processing and autonomic dysregulation rather than fixed organ damage.[45–48] Importantly, early failure of symptom improvement, particularly fatigue and exertional intolerance, emerged as one of the strongest longitudinal signals preceding their very long-term persistence in our cohort.

Predischarge cardiovascular and pulmonary imaging revealed only subtle differences between outcome groups, with echocardiographic disparities largely limited to indices of longitudinal systolic function that were paradoxically slightly higher among patients who later developed persistent symptoms. These differences resolved by the one month follow-up, suggesting that they likely reflected transient loading conditions or compensatory myocardial responses rather than structural injury (refer to Honchar *et al*[49] for more detailed characterisation of the observed cohort). In contrast, measures more closely related to vascular and microcirculatory function, including diastolic indices and brachial artery flow-mediated dilation, demonstrated patterns of greater prognostic relevance: patients who ultimately recovered showed early functional improvement, whereas those with persistent Long COVID exhibited relative stagnation.

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These observations align with the concept of endothelial dysfunction being a key feature and driving mechanism of both acute and long COVID-19.[50–53] LUS abnormalities, including the B-lines score and residual consolidations burden, improved over time in both groups and did not meaningfully discriminate long-term outcomes, aligned with the lack of robust evidence supporting their standalone predictive value for the very long-term persistence of symptoms despite known associations with disease severity and prognosis during acute SARS-CoV-2 infection[54 55] and evidence on stable residual structural and functional pulmonary abnormalities at 3 years.[56]

An important component of the present study was the development and validation of predictive models for Long COVID persistence at 36 months after hospitalisation. While numerous studies have addressed risk factors for Long COVID, relatively few have attempted formal prediction beyond one year, and even fewer have evaluated model performance at multiyear horizons. Existing long-term analyses generally rely on baseline demographic and acute illness characteristics, often achieving only moderate discrimination. For example, the CORFU study developed a regression-based model predicting Long COVID at 2 years using sex, body mass index, comorbidities and markers of acute disease severity, with an AUC of 0.71.[14] Similarly, large-scale EHR-based ML approaches from the RECOVER consortium demonstrated heterogeneous predictive performance across Long COVID phenotypes, with particularly limited accuracy for fatigue-dominant symptom clusters.[35] While these efforts highlight the feasibility of long-term risk stratification, they also underscore the limitations of models that rely predominantly on static baseline variables.

In contrast, our optimally performing model integrates baseline and acute phase clinical parameters (including sex, age, duration of hospitalisation, resulting weight loss, in-hospital creatinine, AST and predischarge 6MWD) with postacute multidimensional patient-reported symptom assessment at 3 months. This design reflects growing evidence from longitudinal cohorts, including the CO-FLOW study, that long-term symptom persistence at 3 years is characterised less by residual structural organ damage and more by sustained postexertional and functional limitations.[33] By explicitly incorporating early postacute symptom burden and functional status, our approach captures prognostically relevant information that is not fully represented by acute-phase severity or comorbidity profiles alone. Compared with models focused exclusively on baseline predictors, this strategy appears better suited to discriminating very long-term outcomes, particularly for symptom-driven phenotypes such as fatigue, exertional intolerance and cognitive complaints, resulting in superior predictive performance.

When compared with our previously published 12-month predictive model,[11] the most notable difference was the diminishing prognostic role of ESR, whereas creatinine, liver aminotransferase levels and weight loss preserved their significance. Importantly, multidimensional symptom profile obtained at 3 months emerged as the most stable long-term predictor, also requiring widening the spectrum of used questionnaires. This shift supports a dynamic view of Long COVID risk prediction, in which prognostically informative features evolve over time and models intended for multiyear horizons must incorporate postacute functional and patient-reported domains rather than relying solely on baseline characteristics. Similarly to the 12-month outcome in our cohort,[57] persistence of symptoms at 3 years could also be reasonably well predicted when only complementing the multidimensional survey data by age, sex and length of hospital stay.

Taken together, our findings underscore the clinical utility of early risk stratification. Notably, our optimal 3-month neural network models demonstrated superior predictive capacity compared with a pragmatic clinical heuristic (the assumption that symptom status at 12 months would persist to 36 months) within the study cohort. By identifying high-risk trajectories 9 months earlier, and with greater accuracy, this approach offers meaningful incremental value over simple longitudinal symptom tracking.

From a practical implementation standpoint, this early identification facilitates a shift from reactive to proactive care. While pharmacological cures for Long COVID remain elusive, specific downstream interventions for patients flagged as high-risk might include early referral to multidisciplinary Long COVID clinics, targeted cardiopulmonary rehabilitation programmes and prioritisation for therapeutic clinical trials. Conversely, identifying patients with a high probability of spontaneous recovery provides clinical reassurance and limits the over-utilisation of advanced diagnostic resources. While the presented models require external validation, they highlight the feasibility of developing locally calibrated tools that account for population characteristics, healthcare pathways and circulating viral variants, in order to optimise healthcare resource allocation.

Strengths and limitations

The strengths of this study include its prospective design, extended 3-year follow-up and comprehensive predischarge phenotyping, incorporating functional testing, advanced cardiovascular and pulmonary imaging, and vascular assessment, with multidimensional longitudinal symptom evaluation. To our knowledge, this is the first study to develop predictive models for Long COVID persistence at 36 months after hospitalisation, integrating acute-phase clinical data with early postacute functional and patient-reported

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measures. Systematic comparison of multiple modelling approaches further strengthens the robustness of the findings and supports their potential relevance for clinical risk stratification.

However, several limitations warrant consideration. The single-centre design and moderate sample size limit generalisability and inherently increase the risk of overfitting. Although we employed rigorous internal validation techniques (including domain-constrained feature selection and 10-fold cross-validation) to mitigate structural risk, in the absence of external validation, our reported performance metrics should be viewed as an optimistic upper bound. Consequently, we explicitly frame these predictive models not as definitive diagnostic products ready for immediate clinical deployment, but rather as exploratory prognostic screening tools. The lack of external validation in independent cohorts remains a primary limitation regarding immediate clinical applicability.

Furthermore, given the observational nature of this study, the models presented are strictly prognostic; the identified predictors represent predictive associations rather than established causal pathways. Given the extended observation period, our study is susceptible to attrition bias; however, our comparative attrition analysis (online supplemental table S1) suggests a low likelihood of systematic, severity-driven dropout. The primary outcome at 36 months (the self-reported persistence of incomplete recovery) is inherently broad and captures cases of heterogeneous clinical significance, limiting the precision of our predictive modelling for severe disease. Nevertheless, our models maintained a high negative predictive value in the sensitivity analysis, functioning reasonably well within the study cohort as rule-out screening tools for clinically meaningful impairment. Follow-up beyond the early convalescent period relied primarily on self-reported outcomes without repeated objective imaging or physiological testing, precluding the assessment of late subclinical organ changes. Furthermore, reliance on self-reported symptom persistence over a 36-month period may be influenced by evolving psychosocial and contextual factors, particularly given the severe external stressors experienced by the cohort. Additionally, the exclusion of individuals with severe pre-existing conditions or need for oxygen supplementation may introduce selection bias, although the prevalence of major comorbidities in our cohort was comparable to that reported in similar studies.

Finally, the primary value of this modelling strategy lies in its ability to serve as a proof-of-concept for personalised risk stratification. However, the study cohort reflects early-pandemic SARS-CoV-2 variants, historical treatment protocols and low vaccination coverage. Before these algorithms can be safely integrated into routine clinical practice, they require prospective validation in independent, contemporary local cohorts. Given the dynamic nature of the pandemic, such validation is strictly necessary to ensure the models adequately reflect the current SARS-CoV-2 epidemiological landscape, shifting treatment paradigms and specific population characteristics.

CONCLUSIONS

In this prospective cohort of previously hospitalised COVID-19 patients, 41% continued to report Long COVID symptoms 36 months after acute infection, which was preceded by early divergence in patient-reported exertional, general physical and cognitive symptoms trajectories despite comparable recovery of objective functional capacity and comparable parameters of cardiovascular and pulmonary visualisation. Symptom status at 3 months after discharge carried strong prognostic value for very long-term outcomes, enabling accurate prediction of symptom persistence at 36 months when combined with routine clinical and laboratory variables. These findings support early postacute risk stratification to guide long-term follow-up and targeted management strategies.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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