BMJ Open

Early prediction of long COVID-19 syndrome persistence at 12 months after hospitalisation: a prospective observational study from Ukraine

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To cite: Honchar O, Ashcheulova T, Chumachenko T, *et al*. Early prediction of long COVID-19 syndrome persistence at 12 months after hospitalisation: a prospective observational study from Ukraine. *BMJ Open* 2025;**15**:e084311. doi:10.1136/bmjopen-2024-084311

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084311).

Received 18 January 2024
Accepted 09 December 2024

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ABSTRACT

Objective To identify the early predictors of a self-reported persistence of long COVID syndrome (LCS) at 12 months after hospitalisation and to propose the prognostic model of its development.

Design A combined cross-sectional and prospective observational study.

Setting A tertiary care hospital.

Participants 221 patients hospitalised for COVID-19 who have undergone comprehensive clinical, sonographic and survey-based evaluation predischarge and at 1 month with subsequent 12-month follow-up. The final cohort included 166 patients who had completed the final visit at 12 months.

Main outcome measure A self-reported persistence of LCS at 12 months after discharge.

Results Self-reported LCS was detected in 76% of participants at 3 months and in 43% at 12 months after discharge. Patients who reported incomplete recovery at 1 year were characterised by a higher burden of comorbidities (Charlson index of 0.69±0.96 vs 0.31±0.51, p=0.001) and residual pulmonary consolidations (1.56±1.78 vs 0.98±1.56, p=0.034), worse blood pressure (BP) control (systolic BP of 138.1±16.2 vs 132.2±15.8 mm Hg, p=0.041), renal (estimated glomerular filtration rate of 59.5±14.7 vs 69.8±20.7 mL/min/1.73 m^2, p=0.007) and endothelial function (flow-mediated dilation of the brachial artery of 10.4±5.4 vs 12.4±5.6%, p=0.048), higher in-hospital levels of liver enzymes (alanine aminotransferase (ALT) of 76.3±60.8 vs 46.3±25.3 IU/L, p=0.002) and erythrocyte sedimentation rate (ESR) (34.3±12.1 vs 28.3±12.6 mm/h, p=0.008), slightly higher indices of ventricular longitudinal function (left ventricular (LV) global longitudinal strain (GLS) of 18.0±2.4 vs 17.0±2.3%, p=0011) and higher levels of Hospital Anxiety and Depression Scale anxiety (7.3±4.2 vs 5.6±3.8, p=0.011) and depression scores (6.4±3.9 vs 4.9±4.3, p=0.022) and EFTER-COVID study physical symptoms score (12.3±3.8 vs 9.2±4.2, p<0.001). At 1 month postdischarge, the persisting differences included marginally higher LV GLS, mitral E/e' ratio and significantly higher levels of both resting and exertional physical symptoms versus patients who reported complete recovery. Logistic regression and machine learning-based binary classification models have been developed to predict the persistence of LCS symptoms at 12 months after discharge.

Conclusions Compared with post-COVID-19 patients who have completely recovered by 12 months after hospital discharge, those who have subsequently developed 'very long' COVID were characterised by a variety of more pronounced residual predischarge abnormalities that had mostly subsided by 1 month, except for steady differences in the physical symptoms levels. A simple artificial neural networks-based binary classification model using peak ESR, creatinine, ALT and weight loss during the acute phase, predischarge 6-minute walk distance and complex survey-based symptoms assessment as inputs has shown a 92% accuracy with an area under receiver-operator characteristic curve 0.931 in prediction of LCS symptoms persistence at 12 months.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study presents a complex assessment of a wide range of predischarge predictors of Long COVID symptoms at 12 months beyond the traditionally used clinical and demographic data.
⇒ The prognostic value of identified predictors is being discussed in relation to the previously reported predictors of poor outcome at 1 and 3 months within the same cohort of patients.
⇒ The proposed framework of applying machine learning techniques to predict Long COVID may be used locally to account for differences in populations and currently prevailing virus variants.
⇒ Limitations of the study include a single-centre design, limited sample size, low COVID-19 vaccination coverage and different spectrum of prevailing SARS-CoV-2 variants at the time of recruitment.

BACKGROUND

Long COVID syndrome (LCS), also known as post-acute sequelae of SARS-CoV-2 infection (PASC), has emerged as a significant health concern following the global COVID-19 pandemic. Being characterised by symptoms lasting beyond the acute phase of the disease, it presents a multifaceted problem that affects a considerable proportion of individuals recovering from COVID-19, impeding

their return to preinfection levels of health and functionality.[1 2] Persistent symptoms reported in long COVID patients include fatigue, shortness of breath, cognitive impairment, chest pain, joint pain and neuropsychiatric disorders which can substantially hinder the quality of life.[3–5] The economic implications of long COVID should also be mentioned, as it may lead to substantial productivity loss and long-term disability in affected individuals, further adding to the overall societal impact.[1 6] Moreover, the prolonged course of LCS poses a substantial burden on healthcare systems by putting extra strain on the available resources.

LCS includes an extensive set of multisystemic manifestations, with more than 200 symptoms being described as attributable to its development.[7] Adding to difficulties in interpreting this spectrum, the underlying mechanisms of long COVID are also highly heterogenous and include, along with initial assumptions regarding possible virus persistence and residual morphological changes of the respiratory system,[8 9] systemic endothelial dysfunction and hypercoagulability,[10 11] chronic inflammation,[12] autoimmunisation[13] and autonomic dysregulation.[9 14] Importantly, both the incidence and severity of long COVID are significantly higher compared with what could be expected based on the observed prevalence of residual structural and functional impairment of the lungs.[15]

Whereas the current terminological framework only distinguishes cases lasting for more than 4 weeks (‘long COVID’ or PASC, postacute sequelae of COVID-19), 4–12 weeks (‘ongoing symptomatic COVID-19’) and more than 12 weeks (‘post-COVID’), there is a growing body of evidence pointing to the fact that an alarming number of individuals continue to experience symptoms after 1 year from the onset of disease,[16] with as many as 54% of patients reporting an absence or incomplete recovery on their follow-up self-completed questionnaire at 12 months[17] and the rate being even higher among those who required hospitalisation. Recently, the term ‘very long COVID’ has been aptly proposed by Ranucci *et al* to define the persistence of symptoms beyond 12–18 months after the onset of SARS-CoV-2 infection.[18]

Considering the scope of the problem and the range of its possible clinical presentations (with a high prevalence of potentially limiting symptoms), the ability to predict the development of long and ‘very long’ COVID-19 could have major benefits, with potential implications for the selection of treatment (limited to date to pulmonary rehabilitation), follow-up strategy and patients’ self-management of lifestyle and occupation. At the same time, despite the increasingly recognised importance and continued extensive studies on symptomology at different time points, to date there is a lack of effective tools to forecast the trajectory of long-term symptoms in COVID-19 convalescents. Possible ways to improve the prognostic accuracy include assessing a wider spectrum of potential predictors by expanding the evaluation of patients beyond the standard of care as well as phenotyping of the heterogeneous population of convalescents using the readily available clinical and anamnestic markers.[9]

Thus, the objective of the current study was to identify the early predictors of a self-reported persistence of LCS at 12 months after hospitalisation and to propose the prognostic model of its development.

METHODS

Study design

This was a single-centre prospective observational study that was conducted at the pulmonological department of a specialised COVID-19 treatment centre serving a population of approximately 2.4 million people in Kharkiv, Ukraine.

Participants

Between January and November 2021, hospitalised patients were evaluated for eligibility criteria that included the age of 18 years or older, the diagnosis of pneumonia and a positive PCR test confirming the SARS-CoV-2 aetiology. Exclusion criteria that were applied included stroke within the past 6 months, history of myocardial infarction, acute heart failure, stage D chronic heart failure, permanent atrial fibrillation, severe uncontrolled hypertension (defined as systolic blood pressure (BP)≥180 mm Hg and/or diastolic BP≥110 mm Hg), significant valvular heart disease, active cancer or systemic autoimmune pathology, inability to provide informed consent and continued dependence on supplemental oxygen at the time of discharge.

Overall, 265 consecutive eligible patients were identified and invited to participate in the study; 44 of those declined to participate and 221 patients were enrolled. The final cohort included 166 patients who successfully completed the follow-up visits at 1, 3 and 12 months post-discharge (see online supplemental figure 1 for the study flowchart).

Data collection

The first visit took place at the end of the hospitalisation period, typically 1–2 days before discharge. All patients were in stable clinical condition, with resting capillary blood oxygen saturation (SpO2) over 93% on room air and were meeting the clinical criteria of epidemic safety, including normalisation of body temperature and absence of acute respiratory disease symptoms for at least 3 days, starting from the 10th day after symptoms onset.[19]

During the first visit, baseline demographic characteristics such as age and gender were recorded and information regarding laboratory parameters, CT findings (using the simplified Radiographic Assessment of Lung Edema (RALE) score as proposed by Wong *et al*[20]) and treatment regimens were extracted from medical records. Data on symptoms, smoking status and comorbidities was collected through interviews and anthropometric measurements were taken. Transthoracic echocardiography (TTE) was performed in 176 participants using the Radmir ULTIMA

Expert ultrasound system (Radmir, Ukraine), with the measurements performed in accordance with the guidelines by the American Society of Echocardiography and European Association of Cardiovascular Imaging.[21–23] Ventricular global longitudinal strain (GLS) was assessed using the recently proposed linear method.[24–26] Additional sonographic evaluation included a reactive hyperaemia test of the brachial artery using an upper arm occlusion[27] and lung ultrasound (LUS) in the standard Bedside Lung Ultrasound Examination (BLUE) protocol points[28] (cumulative numbers of B-lines and subpleural consolidations were calculated and taken for analysis). 6-minute walk test (6MWT) was conducted in the same cohort of patients by the standardised protocol as recommended by the American Thoracic Society;[29] a 20 m hallway was used, heart rate (HR) and SpO2 were monitored throughout the test via Bluetooth-connected pulse oximeter. At the end of the visit, patients were given time to fill out the questionnaires on symptoms that included the chronic obstructive pulmonary disease assessment test, EFTER-COVID study subscale on physical symptoms, Symptom Burden Questionnaire for Long COVID Memory, Thinking and Communication subscale and Hospital Anxiety and Depression Scale (HADS).[30–34]

Follow-up

The first postdischarge visit at 1 month followed an identical protocol. The follow-up visit at 3 months and the final visit that was scheduled at 12 months were conducted remotely via telephone, email or text messengers. During these, the presence of LCS was determined, being defined as a self-reported perception of worsened health status compared with the pre-COVID-19 state or persistence of post-COVID-related symptoms during the month preceding the visit.

Patient and public involvement

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

Statistical analysis

Data analysis was performed using the StatSoft Statistica V.12 software package. The assessment of data distribution was conducted using the Shapiro-Wilk test. Descriptive statistics for continuous variables are presented as mean±SD or median (IQR) for normally distributed and skewed continuous variables, respectively. Categorical variables are reported as counts (percentages). Independent samples t-test was employed to compare normally distributed continuous variables and the Mann-Whitney U-test for skewed parameters. Binary and categorical variables were compared using χ^2 test. Longitudinal comparisons were conducted through paired samples t-test or Wilcoxon signed-rank test. Statistical significance was established at $p<0.05$. Logistic regression analysis was performed employing all effects method to assess the marginal effects of potential predictors and an all effects method to build a predictive model; resulting models were evaluated using Somers' D, Kolmogorov-Smirnov statistic, receiver-operator characteristic (ROC) analysis and Brier score. The significance of the included predictors was assessed using Wald p value.

An unsupervised machine learning (ML) approach was employed to develop binary classification models based on simple artificial neural networks (SANN). The study cohort was randomly divided into training, test and validation subsets, with a proportional split of 70:15:15, respectively. Each set of input variables was used to train 1000 predictive models. Missing data were imputed using class median values. The training process used an automated neural architecture search strategy and the Broyden-Fletcher-Goldfarb-Shanno optimisation algorithm. Subsequently, the obtained models were automatically ranged based on their predictive performance, assessed by calculating the percentage of correctly classified cases from the test and validation subsets. The predictive performance of the models was assessed based on the area under ROC (AUROC) curves, Brier score and accuracy which was calculated as the percentage of correctly classified cases from the test and validation subsets. The final predictive model underwent 10-fold cross-validation. To evaluate the adequacy of the sample size, a post hoc approach incorporating an assessment of the model accuracy and the data set effect size using Cohen's d statistic was performed.[35]

RESULTS

Clinical characteristics

The average time from the onset of symptoms to the initiation visit was 22.6±7.1 days. The mean age of the final cohort participants was 53.7±13.3 years and did not differ significantly between patients with and without ongoing long COVID symptoms at 12 months (see table 1). The proportion of female and male subjects was also equal between clinical groups and adequately reflected the sex structure of the general study population.

Prevalence of the main comorbidities (with hypertension and obesity being by far the most frequent ones with rates of 36–40%) was similar among long COVID patients and those who were reporting complete recovery. At the same time, there was a tendency to higher rates of less frequent concomitant conditions that were reaching statistical significance for chronic kidney disease, bronchial asthma and symptomatic coronary artery disease and resulted in a higher cumulative burden of comorbidities in the LCS cohort as assessed by Charlson index. There were no intergroup differences in the extent of pulmonary involvement by CT, levels of SpO2 on admission or the treatment used.

Surprisingly, patients of both groups were characterised by similar levels of inflammatory biomarkers during hospitalisation, except for slightly higher values of erythrocyte sedimentation rate (ESR). At the same time, participants with LCS at 12 months had higher in-hospital serum levels of liver enzymes and creatinine, with the latter resulting

Table 1 Demographics and predischarge clinical characteristics of the study participants with and without persisting long COVID syndrome at 12 months

Parameters	No long COVID symptoms at 12 months	Long COVID symptoms at 12 months	Difference (95% CI)	2-sided p value
Subjects	95 (57)	71 (43)		
Female sex	51 (54)	39 (55)		0.873
Age, years	52.9±14.5	54.7±12.8	1.8 (–2.5; 6.1)	0.409
Long COVID symptoms at 3 months	55 (58)	71 (100)		<0.001
BMI, kg/m^2	28.8±5.3	29.3±5.0	0.5 (–1.1; 2.1)	0.529
Comorbidities				
Hypertension	38 (40)	27 (38)		0.797
Obesity	34 (36)	27 (38)		0.767
Diabetes mellitus, type 2	9 (9)	8 (11)		0.706
History of peptic ulcer	4 (4)	8 (11)		0.082
History of cancer	2 (2)	5 (7)		0.117
History of stroke/TIA	3 (3)	3 (4)		0.715
Chronic kidney disease	0 (0)	4 (6)		0.019
Bronchial asthma	0 (0)	4 (6)		0.019
COPD	3 (3)	0 (0)		0.131
Angina pectoris	0 (0)	3 (4)		0.043
Chronic liver disease	0 (0)	2 (3)		0.100
Charlson Comorbidity Index	0.31±0.51	0.69±0.96	0.37 (0.15; 0.60)	0.001
Active smoking status	17 (18)	6 (8)		0.081
Hospitalisation period, days	14.6±4.1	15.8±5.1		0.106
Pulmonary involvement by CT, %	34.0±21.9	30.1±18.8	–3.9 (–12.1; 4.3)	0.344
Minimal in-hospital SpO2, %	88.7±7.5	87.4±7.8	–1.3 (–3.7; 1.1)	0.277
Oxygen supplementation				
Via nasal cannula	48 (51)	45 (63)		0.099
Non-invasive/invasive ventilation	6 (6)	3 (4)		0.556
Laboratory parameters				
Peak IL-6, pg/mL	10.0 (3.2–25.2)	9.7 (3.1–47.0)		0.843
Peak CRP, mg/L	16 (6–48)	33 (7–67)		0.412
Peak ESR, mm/hour	28.3±12.6	34.3±12.1	6.1 (1.6; 10.5)	0.008
Peak procalcitonin, ng/mL	0.06 (0.05–0.08)	0.05 (0.03–0.12)		0.521
Peak D-dimer, ng/mL	287 (199–494)	179 (128–628)		0.197
Peak ALT, IU/L	46.3±25.3	76.3±60.8	30.0 (11.0; 49.0)	0.002
Peak AST, IU/L	33.0±17.6	52.5±38.9	19.5 (7.2; 31.9)	0.002
Peak creatinine, µmol/L	97.4±17.0	109.7±26.2	12.3 (3.5; 21.2)	0.007
Lowest eGFR, mL/min/1.73 m^2	69.8±20.7	59.5±14.7	–10.3 (–17.7; –2.9)	0.007
Haemoglobin, g/dL	13.9±1.7	13.9±1.3	–3.1 (–9.4; 3.3)	0.760
Treatment				
Dexamethasone	85 (89)	62 (87)		0.667
Methylprednisolone	64 (67)	47 (66)		0.874
Remdesivir	42 (44)	32 (45)		0.912

Values 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; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; SpO2, peripheral capillary oxygen saturation; TIA, transient ischaemic attack.

in significantly lower estimated glomerular filtration rate (eGFR).

Sonographic assessment

A comprehensive echocardiographic evaluation of observed patients has revealed minor differences between groups. Patients who had completely recovered by 12 months had similar cardiac morphometry at the baseline evaluation but were characterised by a mild decrease in the size of both atria during the first-month postdischarge which was not observed in the LCS cohort. Both groups had a persistent tendency to concentric left ventricular (LV) geometry, manifested as a higher-than-normal relative wall thickness. Functionally, patients with LCS at the baseline were characterised by slightly higher values of most systolic indices, with the differences reaching statistical significance for mitral annular plane systolic excursion and both left and right ventricular longitudinal strain. These changes mostly disappeared by 1 month due to the tendency to a somewhat more significant reduction among the patients with LCS, manifested by a decrease in the LV ejection fraction (through an increase in end-systolic volume), mitral s' velocity and right ventricular free wall strain. LV diastolic parameters were similar at the baseline but characterised by slightly better dynamics in the LCS-free cohort and resulted in the marginally lower E/e' ratio at 1 month despite initially equal values (see table 2 for details).

Flow-mediated vasodilation (FMD) at the baseline was significantly impaired in the general study cohort but was even lower in LCS-positive participants compared with patients who were symptom-free at 12 months. On re-evaluation at 1 month, no intergroup difference was observed (see figure 1).

Cumulative pulmonary B-lines score at both visits was similar between patients with and without symptoms at 12 months, showing a significant decrease during an early follow-up. Residual pulmonary consolidations score by the moment of discharge was significantly higher in patients with LCS who were at the same time demonstrating faster recovery with no significant difference left by the moment of re-evaluation at 1 month.

6-minute walk test

Assessment of the general physical functional status in the 6MWT has revealed some peculiar differences between the study groups (see table 3). Patients who subsequently reported long-lasting symptoms had performed slightly worse at the baseline (with observed minor difference in the distance walked disappearing when adjusting for age using sex-specific regression equations) but were showing results at 1 month that were similar to those in the LCS-free cohort. There were no significant differences in the resting and exertional HR; HR increment during the test was improving quicker in LCS participants on the background of the low base effect and was reaching equal values versus symptom-free cohort by 1 month. Systolic BP in the LCS group was higher at both visits.

LCS participants predischarge were exhibiting higher resting levels of dyspnoea, but no difference in symptoms was observed at the end of the 6MWT. After 1 month, exertional symptoms improved significantly in patients that were free of LCS at 1 year but failed to do so in the long COVID cohort, resulting in higher scores of both pretest and post-test fatigue and dyspnoea. O2 saturation parameters at rest and throughout the test were similar in both groups at the baseline evaluation; at 1 month, patients who later reported complete recovery were reaching somewhat lower minimal SpO2/higher values of O2 desaturation during the test.

Symptoms

More detailed assessment of the symptom levels using self-completed questionnaires dedicated to both physical and emotional symptoms has revealed significant improvement in the LCS group ($p<0.001$ on all the scales used) during the early postdischarge convalescence period (see figure 2). In patients who have recovered by 12 months, a similar rate of improvement was observed for physical symptoms, but no significant decrease between visits was revealed for anxiety and depression on the background of the initially lower scores. Medical Research Council (MRC) Dyspnoea score was higher both at the baseline and at 1 month among patients who subsequently developed LCS, thus corroborating Borg scale reporting obtained during the 6MWT. The cumulative burden of heterogeneous physical symptoms as assessed by the appropriate subscale of the EFTER-COVID study questionnaire was also significantly higher in the LCS group at both visits. HADS scores were higher in the long COVID cohort at the baseline with the differences ameliorating by the time of reassessment at 1 month.

Prognosis

To develop a tool for predicting the persistence of long COVID symptoms at 12 months, we used a two-step approach. As a preliminary step, logistic regression analysis was applied to assess the predictive value of available predischarge clinical data. Among the parameters included in the baseline marginal analysis, the EFTER-COVID physical symptoms score exhibited the highest independent predictive value, followed by serum creatinine, 6-minute walk distance, weight loss during the acute COVID-19 phase, ESR, eGFR, HADS scores, systolic BP and LV GLS (refer to supplementary material for the resulting logistic regression model and online supplemental table 1-3 for the complete list of predictors, parameters and the bootstrap protocol of the model).

As a second step, all significant predictors identified earlier in the baseline logistic regression marginal analysis were used as initial input variables to develop SANN-based binary classification models. Subsequently, stepwise deletion of excessive inputs was performed based on the results of global sensitivity analysis of the current network version to develop a model that would use a necessary minimum of easily available clinical parameters.

Table 2 Echocardiographic characteristics of hospitalised COVID-19 patients during the first month of follow-up

Parameters	Visit time	No long COVID symptoms at 12 months n=95	Long COVID symptoms at 12 months n=71	Difference (95% CI)	2-sided p value
Left chambers morphometry					
LA volume index, mL/m^2	0 month 1 month p	28.3±6.7 26.6±5.9 0.041	29.3±6.7 28.6±6.8 0.884	1.0 (–1.1; 3.1) 2.0 (–0.3; 4.2)	0.359 0.090
LV end-diastolic volume index, mL/m^2	0 month 1 month p	48.2±8.2 46.9±9.3 0.551	48.7±10.3 47.1±8.8 0.398	0.5 (–2.4; 3.3) 0.2 (–3.1; 3.5)	0.732 0.910
LV end-systolic volume index, mL/m^2	0 month 1 month p	16.9±4.4 16.7±5.2 0.776	16.6±5.4 17.1±6.5 0.008	–0.3 (–1.8; 1.2) 0.5 (–1.6; 2.5)	0.660 0.650
LV relative wall thickness	0 month 1 month p	0.45±0.07 0.45±0.08 0.999	0.46±0.08 0.45±0.08 0.211	0.00 (–0.02; 0.03) 0.00 (–0.05; 0.05)	0.682 0.689
LV mass index (height$^{2.7}$), g/m$^{2.7}$	0 month 1 month p	37.9±9.5 35.8±6.7 0.297	38.3±8.8 36.9±7.6 0.161	0.4 (–2.5; 3.3) 1.2 (–1.3; 3.7)	0.787 0.354
Left ventricular function					
LV ejection fraction, %	0 month 1 month p	65.0±6.6 64.9±6.5 0.828	66.1±7.1 64.3±7.3 0.013	1.1 (–1.0; 3.3) –0.5 (–3.0; 1.9)	0.293 0.667
Lateral MAPSE, mm	0 month 1 month p	14.7±2.3 14.8±1.9 0.533	15.7±2.2 15.3±3.1 0.238	1.0 (0.3; 1.7) 0.5 (–0.4; 1.4)	0.006 0.271
LV global longitudinal strain, %	0 month 1 month p	17.0±2.3 17.0±1.9 0.938	18.0±2.4 17.8±2.2 0.890	1.0 (0.2; 1.7) 0.8 (0.0; 1.5)	0.011 0.045
LV s' mean, cm/s	0 month 1 month p	9.7±1.7 9.4±1.5 0.046	9.7±1.7 9.1±2.0 0.008	0.0 (–0.5; 0.6) –0.3 (–0.9; 0.3)	0.965 0.303
LV e' mean, cm/s	0 month 1 month p	9.2±2.1 9.8±2.7 0.045	9.2±2.4 9.7±2.9 0.729	0.1 (–0.6; 0.8) –0.1 (–1.1; 0.9)	0.854 0.792
LV E/e' ratio	0 month 1 month p	7.5±1.8 7.0±1.9 0.044	7.4±1.8 7.8±2.7 0.599	0.0 (–0.6; 0.5) 0.8 (0.0; 1.6)	0.873 0.053
Right chambers evaluation					
RA area index, cm^2/m^2	0 month 1 month p	8.4±2.5 7.6±1.6 0.024	7.8±1.4 8.0±1.1 0.323	–0.6 (–1.3; 0.1) 0.4 (–0.1; 0.9)	0.080 0.116
RV size (proximal outflow tract), mm	0 month 1 month p	31.7±3.7 32.3±4.4 0.142	31.9±2.8 31.5±3.4 0.180	0.2 (–1.0; 1.3) –0.8 (–2.3; 0.7)	0.766 0.304
TAPSE, mm	0 month 1 month p	24.5±4.4 24.2±3.7 0.053	25.3±4.2 24.1±3.4 0.194	0.8 (–0.6; 2.2) –0.1 (–1.4; 1.2)	0.766 0.931
RV free wall longitudinal strain, %	0 month 1 month p	35.3±6.1 35.1±6.3 0.135	37.6±7.5 35.2±5.0 0.034	2.4 (0.1; 4.6) 0.1 (–2.0; 2.2)	0.039 0.910

Values 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 the missing data in the paired t-test.
LA, left atrium; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

The resulting set of predictors included weight loss during acute COVID-19, in-hospital peak ESR, creatinine and alanine transferase, predischarge 6-minute walk distance and self-completed HADS and EFTER-COVID physical symptoms scores. The final network adopted an 8-8-2 SANN architecture and exhibited a 92%

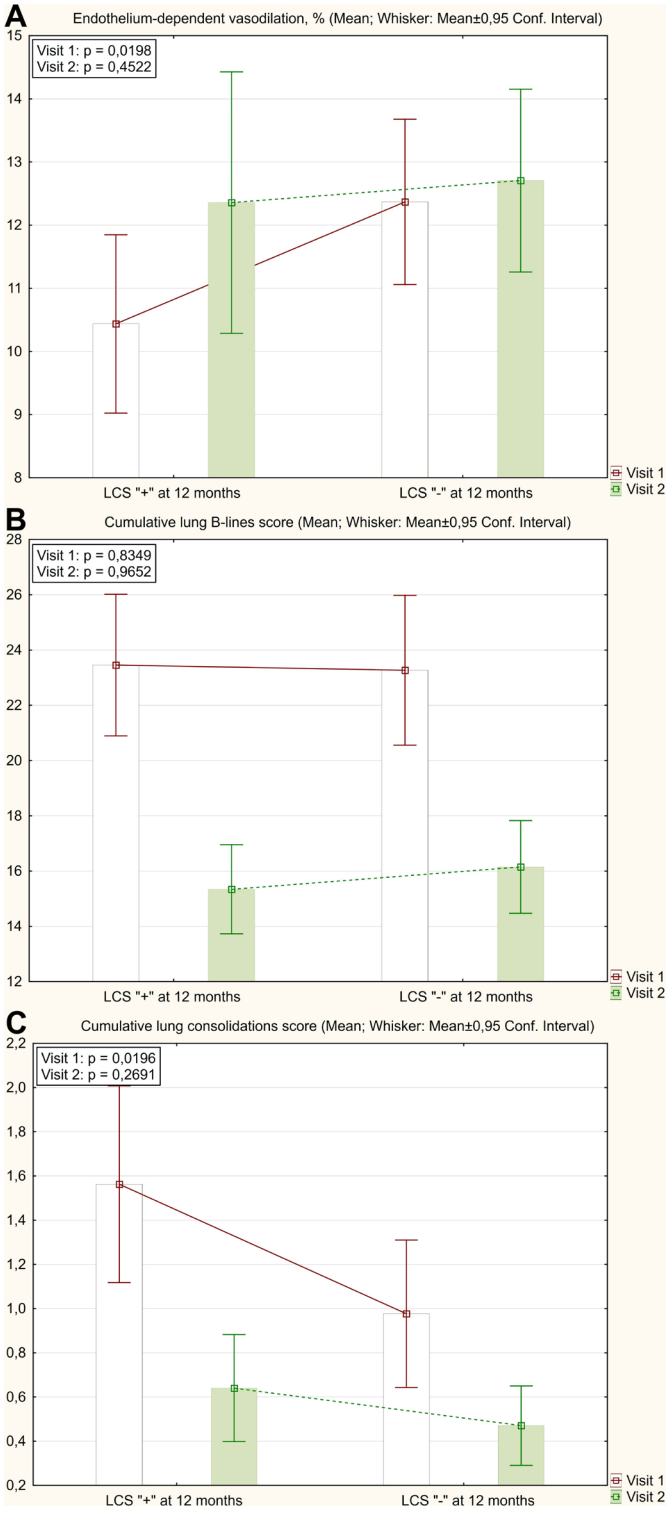

Figure 1 Sonographic assessment of observed patients with COVID-19 during the 1 month postdischarge follow-up. (A) Flow-mediated dilation of the brachial artery. (B) Cumulative lung B-lines score. (C) Cumulative lung consolidations score. LCS, long COVID syndrome.

predictive accuracy (89% for sensitivity, 94% for specificity), AUROC of 0.931 and Brier score of 0.127 in the randomly selected test and validation subsets of the study cases (source file available in open access at https://doi.org/10.5281/zenodo.8147049; refer to supplementary material for instructions for use, online supplemental figure 2 for technical parameters of the model training and performance and online supplemental table 4 for network weights and connections). To ensure the robustness of the final model, we performed a 10-fold cross-validation by retraining the neural networks using alternative sampling, consistently achieving non-inferior predictive performance in the test/validation subsets (refer to online supplemental table 5 for the protocol of cross-validation).

The inclusion of the parameters obtained 1 month after discharge did not improve the predictive performance of the logistic regression-based nor the ML-based models (see online supplemental table 6 for marginal effects of Visit 2 variables).

DISCUSSION

The current study reports on the results of a 1 year follow-up of hospitalised COVID-19 survivors that included a comprehensive clinical, sonographic and survey-based evaluation predischarge and at 1 month, followed by assessment of a self-reported recovery to pre-COVID state that was performed at 3 and 12 months after discharge.

Univariate analysis of the baseline in-hospital parameters of the study participants has revealed similar demographics, clinical presentation and the treatment used among those who remained symptomatic and who reported complete recovery by 12 months; at the same time, patients with LCS were characterised by higher burden of comorbidities, somewhat worse BP control and renal function and higher levels of liver enzymes and ESR (but not C-reactive protein or interleukin-6), which, to our knowledge, has not been reported before; one has to mention that caution is needed in interpreting these associations, as the results could be confounded with other variables. Our findings did not confirm the previously reported role of the female sex as a risk factor for LCS at 1 year.[36–38] Similar to data presented in,[39] we did not find confirmation of the positive[36 38] or negative[37] association of age with persisting symptoms at 12 months. Similar to most of the mentioned sources, our study did not find body mass index (BMI) to be predictive of LCS at 1 year as reported in.[40] Smoking status in our cohort also was not associated with the risk of very long COVID, being in line with previously reported data.[36 41] Unlike some previously reported studies,[36 38 39 42 43] we have not found significant prognostic value of clinical markers of the acute phase severity, including the length of hospital stay, use of corticosteroids, need for oxygen supplementation or invasive ventilation in predicting the persistence of LCS at 1 year.

Comprehensive TTE has revealed slightly better 1-month dynamics of diastolic indices and both atria's size in LCS-free participants, while their counterparts were characterised by a partial reversal of the previously reported tendency to a minimal hypercontractility on the background of a slightly higher cardiac output versus

Table 3 Parameters of the 6-minute walk test in hospitalised COVID-19 patients predischarge and after 1 month of follow-up

Parameters	Visit time	No long COVID symptoms at 12 months n=95	Long COVID symptoms at 12 months n=71	Difference (95% CI)	2-sided p value
6-minute walk distance, metre	0 month 1 month p	411±69 469±58 <0.001	376±61 453±73 <0.001	–35 (–60; –11) –16 (–42; 9)	0.005 0.199
6-minute walk distance, % of predicted	0 month 1 month p	63.2±9.2 73.1±9.7 <0.001	61.6±10.1 73.9±11.5 <0.001	–1.6 (–5.1; 2.0) 0.8 (–3.2; 4.9)	0.379 0.685
Baseline heart rate, bpm	0 month 1 month p	81.9±11.3 82.4±14.2 0.831	83.7±14.3 79.6±13.9 0.127	1.8 (–2.8; 6.3) –2.8 (–8.2; 2.7)	0.445 0.317
Maximal heart rate, bpm	0 month 1 month p	106.8±13.7 110.5±13.5 0.022	104.8±15.4 109.0±14.5 0.029	–2.0 (–7.4; 3.4) –1.5 (–7.0; 4.0)	0.470 0.592
Maximal heart rate, % of the individual maximum	0 month 1 month p	61.7±7.4 64.5±7.9 0.007	59.1±14.8 63.7±8.2 0.030	–2.6 (–6.7; 1.6) –0.7 (–3.9; 2.4)	0.218 0.643
Heart rate increment, bpm	0 month 1 month p	24.3±10.9 27.8±10.9 0.013	20.8±11.6 28.4±12.7 < 0.001	–3.5 (–7.7; 0.8) 0.6 (–4.0; 5.2)	0.107 0.790
Baseline SpO2, %	0 month 1 month p	97.0±4.9 98.0±0.7 < 0.001	97.2±5.8 98.1±0.8 0.001	0.2 (–1.5; 1.9) 0.1 (–0.2; 0.4)	0.802 0.544
Minimal SpO2, %	0 month 1 month p	94.0±4.4 95.3±2.7 0.003	94.2±3.8 96.4±1.3 < 0.001	0.2 (–1.3; 1.7) 1.1 (0.2; 2.0)	0.805 0.017
Peak O2 desaturation, %	0 month 1 month p	2.9±2.7 2.7±2.4 0.279	3.0±2.5 1.8±1.5 0.007	0.2 (–0.8; 1.1) –0.9 (–1.7; –0.1)	0.749 0.035
Baseline systolic BP, mm Hg	0 month 1 month p	132.2±15.8 130.0±12.7 0.399	138.1±16.2 140.0±19.5 0.921	5.9 (0.2; 11.6) 10.0 (4.0; 16.0)	0.041 0.001
Baseline diastolic BP, mm Hg	0 month 1 month p	84.5±12.2 80.8±9.7 0.052	83.0±9.9 83.6±12.3 0.602	–1.4 (–5.5; 2.6) 2.8 (–1.4; 6.9)	0.475 0.186
Dyspnoea at start, points (modified Borg scale)	0 month 1 month p	1.0±1.4 0.5±0.9 0.015	1.8±1.7 1.1±1.2 0.001	0.7 (0.2; 1.3) 0.6 (0.2; 1.0)	0.010 0.006
Fatigue at start, points (modified Borg scale)	0 month 1 month p	2.3±2.3 1.0±1.0 <0.001	2.6±2.0 1.8±1.6 0.005	0.3 (–0.4; 1.1) 0.9 (0.4; 1.4)	0.383 <0.001
Dyspnoea at finish, points (modified Borg scale)	0 month 1 month p	3.2±2.3 2.4±1.8 0.025	3.5±1.4 3.4±1.5 0.756	0.3 (–0.8; 1.4) 1.0 (0.3; 1.8)	0.560 0.008
Fatigue at finish, points (modified Borg scale)	0 month 1 month p	3.3±2.4 2.0±1.6 < 0.001	3.6±1.2 3.2±2.1 0.878	–0.3 (–0.7; 1.4) 1.2 (0.4; 2.0)	0.551 0.003

Values 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 the missing data in the paired t-test.
BP, blood pressure; bpm, beats per minute; SpO2, peripheral capillary oxygen saturation.

matched controls[44] that was initially more pronounced in the LCS group. Both groups were characterised by a significant persistent shift to concentric LV geometry and a high prevalence of type I diastolic dysfunction. The existing data on the post-COVID-19 evolution of echocardiographic parameters is scarce and at times conflicting. While the obtained results indirectly confirm the data from some of the prominent papers in the field,[45–47] we found no studies assessing the prognostic role of observed changes in the context of 'very long' COVID.

Auxiliary sonographic assessment has allowed for the detection of worse baseline FMD of the brachial artery and higher cumulative lung consolidations score (but no differences in B-lines score) among patients with LCS, with the differences subsiding due to faster positive dynamics by the time of re-evaluation at 1 month. The

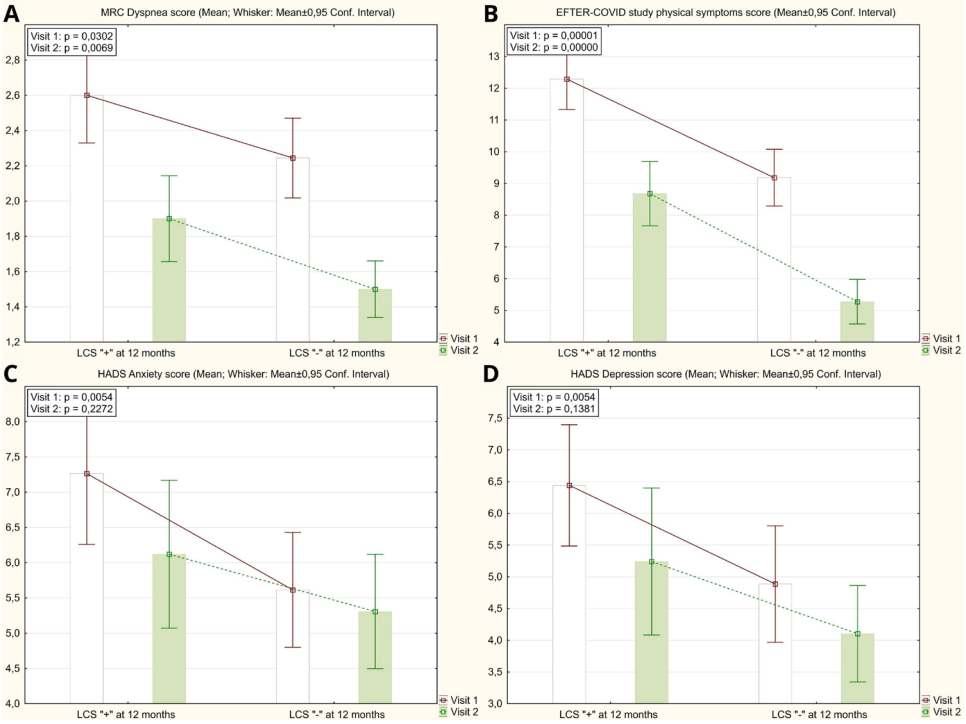

Figure 2 Self-completed survey of symptoms level in hospitalised patients with COVID-19 predischarge and after a 1 month follow-up. (A) MRC Dyspnoea score. (B) EFTER-COVID study physical symptoms score. (C) HADS Anxiety score. (D) HADS Depression score. HADS, Hospital Anxiety and Depression Scale; LCS, long COVID syndrome; MRC, Medical Research Council.

observed FMD changes were in line with available data on its profile in the context of LCS,[48] thus supporting the well-established concept of significant endothelial involvement during both acute and chronic phases of COVID-19.[10 12 49] Whereas data exists on the prognostic role of FMD[50 51] and LUS[52 53] during acute SARS-CoV-2 infection, no robust evidence was identified regarding its predictive value for LCS development and long-term persistence.

The subtle differences in 6MWT parameters were mainly bound to subjective symptom levels on the background of overall similar physical performance. Being only marginally more symptomatic at the baseline, patients with LCS had retained higher levels of both fatigue and dyspnoea at 1 month while showing no improvement in the level of exertional symptoms. Most likely, this was the factor that allowed the patients with complete recovery at 12 months to develop slightly higher levels of exertion manifested by somewhat lower exertional SpO2. Analysis of the applied survey data has confirmed higher levels of physical symptoms in the LCS cohort, including self-reported MRC Dyspnoea score and cumulative burden of physical symptoms by the appropriate subscale of the EFTER-COVID study questionnaire, whereas initially higher levels of anxiety and depression as assessed by HADS were ameliorated by 1 month. The findings of our study were in line with the map of symptoms most typically identified in patients with PASC.[1 54 55]

To create a tool to predict the long-term persistence of long COVID symptoms, we adopted a two-step approach that allowed us to mitigate the risk of overfitting due to the relatively small sample size. First, a set of significant predictors has been identified based on the univariate marginal effects in logistic regression analysis and a regression model has been built (refer to supplementary material for details). Considering that logistic regression models derived from samples<500 cases are innately vulnerable to overfitting and random effects,[56] no internal validation of the obtained model has been performed, as that would require reserving a holdout subsample, hence further downsizing the number of training cases.

As a more robust alternative, a ML approach was subsequently used to develop SANN-based binary classification models. Of the networks trained, the one that was characterised by optimal performance was using weight loss during acute COVID-19, in-hospital peak ESR and alanine aminotransferase (ALT, predischarge 6-minute walk distance and self-completed HADS and EFTER-COVID physical symptoms scores as inputs. The model was characterised by 92% accuracy (89% for sensitivity, 94% for specificity) and an AUROC curve of 0.931 in the validation subset; given a 43% prevalence of 'very long' COVID-19 in the study cohort, it translated into 7.1 times lower rate of misclassified cases compared with the blunt assumption that all patients did and 5.4 times less—that they did not have LCS symptoms at 12 months. The combination of predictive accuracy>0.8 and the mean intergroup effect size of 0.52 for the selected set of inputs attested to the robustness of the model in the post hoc analysis using the method proposed in;[35] considering the

binary classification task, the observed rates of missing data (see online supplemental table 7) should not have significantly influenced the model performance.[57]

The proposed model was tailored to include the most easily available parameters from the extensive list of potential predictors derived in our study while at the same time minimising the necessary spectrum of additional investigations that were not part of the standard of care during hospitalisation for COVID-19. Considering the lack of significant improvement in the model's performance on inclusion of parameters obtained at Visit 2, the benefit of earlier risk stratification and logistical challenges associated with the potential need for reassessment 1 month after discharge, the model only includes parameters available before and during the hospitalisation period.

We have previously proposed models to forecast the early dynamics of spontaneous physical functional recovery following hospitalisation for COVID-19[58] as well as the persistence of LCS symptoms at 3 months after discharge.[59] Compared with the sets of predictors of poor outcome at 1 and 3 months, age, sex and BMI have lost their predictive value for LCS at 1 year, whereas the burden of comorbidities, in-hospital ESR and eGFR and predischarge 6-minute walk distance were consistently identified as significant prognostic markers. The values of minimal and predischarge SpO2, as well as in-hospital need for oxygen supplementation, were characterised by the gradual decrease of significance along the described timeline and were losing their predictive value by 12 months. Predischarge systolic BP values were consistently predictive of LCS both at 3 and 12 months, as was the RV free wall strain, whereas LV GLS, mitral annular plane systolic excursion and liver enzymes were only becoming prognostically significant for 1-year outcome. Interestingly, the predischarge residual burden of pulmonary consolidations was identified as a significant predictor of outcome at 12 months, whereas LUS/CT markers of interstitial involvement were losing their prognostic value which was most evident early after discharge. Both at 3 and 12 months, predischarge scores on self-completed physical symptoms surveys (that have not performed well in predicting poor early physical recovery) remained powerful prognostic markers of LCS persistence, with their predictive value naturally getting even higher on follow-up reassessments.

The ability to predict the development of LCS has the potential to improve patient care and healthcare planning. Early identification of individuals at higher risk for developing LCS could enable timely intervention strategies, ensuring prompt initiation of targeted rehabilitation programmes, individual support and emerging dedicated therapies. This forecasting capability could potentially allow healthcare providers to more effectively allocate available resources by taking into account the individualised risk profiles while tailoring care plans for postacute COVID-19 patients.

Strengths and limitations

To our knowledge, this is the first study dedicated to the complex assessment of predictors of long COVID symptoms persistence at 12 months that evaluates the prognostic role of predischarge 6MWT, comprehensive echocardiography, LUS, flow-mediated dilation of the brachial artery and survey-based assessment of symptoms in addition to the traditional clinical and demographic data. It is also the first study proposing a set of binary classification models that can be used to predict 'very long' COVID syndrome following the acute phase hospitalisation. This prognostic capability might be highly beneficial for healthcare providers and policymakers in the context of forecasting the expected need for rehabilitation and support programmes as well as disability-related economic burden and hence contribute to the optimised allocation of available resources.

Limitations of the study include possible centre-related effects; however, no significant associations were observed between the study outcomes and administration of methylprednisolone pulse therapy, which was the sole notable difference compared with the commonly applied standards of acute COVID-19 care. Individuals with severe underlying pathologies were excluded from the study to minimise the potential confounding effects, thereby introducing a source of selection bias. At the same time, the prevalence of major comorbidities in our study cohort aligned with previous reports, suggesting that the overall picture was unlikely to be significantly affected by this factor. A limited sample size and incomplete data set could contribute to the risk of overfitting the logistic regression model and affect the performance of the ML model. Lastly, it should be noted that the spectrum of prevailing SARS-CoV-2 variants has evolved since the enrolment period and a larger proportion of patients have been vaccinated. Hence, caution must be exercised when extrapolating the findings of our study to the current landscape of long COVID care.

CONCLUSIONS

Compared with post-COVID-19 patients who had completely recovered by 12 months after hospital discharge, those who subsequently developed 'very long' COVID were characterised by a variety of more pronounced residual predischarge abnormalities that had mostly subsided by 1 month, except for steady differences in the physical symptoms levels. A SANN-based binary classification model using peak ESR, ALT and weight loss during the acute phase, predischarge 6-minute walk distance and complex survey-based symptoms assessment as inputs has shown a 92% accuracy in predicting the LCS symptoms at 12 months.

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Acknowledgements The authors would like to thank M Yerzina for the technical support in the data collection and to acknowledge the work of the hospital administration and staff: A Bobeyko, V Byzov, V Blazhko, E Khodosh, N Matyash, O Morozova, L Kolisnyk, I Talalay, V Kozlov, L Avdeyeva, who have set conditions for the proper functioning of the clinic.

Contributors Transparency: OH accepts responsibility for the overall content of the article as a guarantor and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained. Authors contribution: OH—study design (SD), literature search (LS), data collection (DC), analysis (DA) and interpretation (DI), writing (WM) and revision (RM) of the manuscript. TA—SD, DI and RM. TC—DI and RM. DC—DA, DI and RM. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. An unsupervised machine learning (ML) approach was employed to develop binary classification models based on simple artificial neural networks (SANN). The study cohort was randomly divided into training, test and validation subsets, with a proportional split of 70:15:15, respectively. Each set of input variables was used to train 1000 predictive models. Missing data were imputed using class median values. The training process used an automated neural architecture search strategy and the Broyden-Fletcher-Goldfarb-Shanno optimisation algorithm. Subsequently, the obtained models were automatically ranged based on their predictive performance, assessed by calculating the percentage of correctly classified cases from the test and validation subsets. The predictive performance of the models was assessed based on the area under receiver-operator characteristic (ROC) curves, Brier score and accuracy which was calculated as the percentage of correctly classified cases from the test and validation subsets. The final predictive model underwent 10-fold cross-validation. A resulting SANN-based binary classification model using peak erythrocyte sedimentation rate, creatinine, alanine aminotransferase and weight loss during the acute phase, predischarge 6-minute walk distance and complex survey-based symptoms assessment as inputs has shown a 92% accuracy with an area under ROC curve 0.931 in prediction of long COVID syndrome symptoms persistence at 12 months.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethical Committee of Kharkiv National Medical University (No. 3/2021). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Individual patients' data is protected due to privacy concerns. The supporting data might be provided upon reasonable request.

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