Received: 8 April 2024 | Revised: 21 June 2024 | Accepted: 24 June 2024

https://doi.org/10.1016/j.rpth.2024.102534

ORIGINAL ARTICLE

Long-term course of ambulatory patients with COVID-19 initially treated with enoxaparin vs no anticoagulation: final analysis of the OVID (enoxaparin for outpatients with COVID-19) randomized trial

Riccardo M. Fumagalli[1,2] | Davide Voci[1] | Behnood Bikdeli[3,4] | Roland Bingisser[5] | Giuseppe Colucci[6,7,8] | Gabor Forgo[1] | Teresa Gerardi[9] | Bernhard Gerber[2,9] | Alexandru Grigorean[1] | Frederikus A. Klok[10] | Marc Righini[11] | Helia Robert-Ebadi[11] | Stefan Stortecky[12] | Silvia Ulrich[13] | Simon Wolf[1] | Dörte Wyss[1] | Lukas Hobohm[14,15] | Nils Kucher[1,2] | Stefano Barco[1,2,14] | the OVID investigators

[1]Department of Angiology, University Hospital Zurich, Zurich, Switzerland

[2]University of Zurich, Zurich, Switzerland

[3]Thrombosis Research Group, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[4]Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[5]Emergency Department, University Hospital Basel, Basel, Switzerland

[6]Service of Hematology, Clinica Luganese Moncucco, Lugano, Switzerland

[7]University of Basel, Basel, Switzerland

[8]Clinica Sant'Anna, Sorengo, Switzerland

[9]Clinic of Hematology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

[10]Department of Medicine, Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands

[11]Division of Angiology and Hemostasis, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[12]Department of Cardiology, Inselspital Bern, University of Bern, Bern, Switzerland

[13]Department of Pulmonology, University Hospital of Zurich, Zurich, Switzerland

[14]Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[15]Department of Cardiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Correspondence
Stefano Barco, Department of Angiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland.
Email: stefano.barco@usz.ch

Handling Editor: Dr Nick van Es

Abstract

Background: Early thromboprophylaxis does not prevent hospital admissions and death among outpatients with symptomatic COVID-19. Its impact on long-term outcomes, including long COVID symptoms and performance status, is unknown.

Objectives: To assess the long-term effects of thromboprophylaxis given at the time of acute COVID-19 in outpatients.

Methods: The OVID (enoxaparin for outpatients with COVID-19) trial randomized outpatients older than 50 years with acute COVID-19 to receive either subcutaneous enoxaparin 40 mg once daily for 14 days or standard of care (no thromboprophylaxis).

In this follow-up study, we assessed the 2-year outcomes, including all-cause hospitalization and death, cardiovascular events, long COVID symptoms, and functional limitations based on the Post–COVID-19 Functional Status (PCFS) scale and EuroQol-5 Dimensions-5 Levels scale.

Results: Of 469 potentially eligible patients, 468 survived, of whom 439 (mean age 59 years; 54% men) participated in the Post-OVID study. There was no difference in terms of hospitalization and death (8.3% in the treatment group vs 10% in controls; relative risk, 0.83; 95% CI, 0.5-1.5) and of cardiovascular events between groups. The risk of presenting with long COVID symptoms was similar in the 2 groups (44% in the treatment group vs 47% in the standard of care group), with no difference between groups also concerning individual symptoms. A PCFS grade of 1 to 3, indicating light-to-moderate functional limitation, was recorded in 15% of patients in each group (odds ratio, 0.98; 95% CI, 0.6-1.7). No patients reported severe limitations (PCFS grade 4). Median EuroQol visual analog scale score was 85 on 100 points (IQR, 80-90 for the standard of care group and 75-90 for the enoxaparin group).

Conclusion: Early thromboprophylaxis does not improve long-term, 2-year clinical and functional outcomes among symptomatic ambulatory patients with acute COVID-19.

KEYWORDS
COVID-19, heparin, long COVID, quality of life, thrombosis

Essentials

- The impact of thromboprophylaxis on long-term outcomes in COVID-19 outpatients is unknown.
- COVID-19 outpatients were randomized to receive thromboprophylaxis vs no thromboprophylaxis.
- There was no difference in hospitalization and death or in functional status after 2 years.
- Early thromboprophylaxis does not improve long-term outcomes in COVID-19 outpatients.

1 | INTRODUCTION

Patients with COVID-19 may experience long-term complications after the acute phase that may last months or years. Typical symptoms of the so-called "post-COVID condition" or "long COVID" [1,2] include fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia, and decline in quality of life [3–5].

Several trials have explored the efficacy and safety of anticoagulants for acute COVID-19 both during hospitalization and in outpatient settings. Among outpatients, no study could demonstrate a benefit in terms of early clinical outcomes [6–11]. These studies, however, were limited by far lower than expected outcome rates. The long-term effect of anticoagulation administered in the acute phase to symptomatic outpatients has never been investigated in dedicated trials, leaving the long-term impact of thromboprophylaxis unclear.

In the multicenter randomized controlled OVID (enoxaparin for outpatients with COVID-19) trial [8,12], we showed that prophylactic enoxaparin did not improve early clinical outcomes among patients with COVID-19 initially managed in the ambulatory setting. In the Post-OVID trial, we studied the association between early use of anticoagulation (vs no anticoagulation) and long-term outcomes, including clinical events, long COVID symptoms, functional performance status, and quality of life.

2 | METHODS

2.1 | Study setting

The Post-OVID study is the follow-up phase of the multicenter, randomized, open-label, controlled OVID study (BASEC-ID 2020-01157), an investigator-initiated, phase 3 trial conducted at 8 centers in Switzerland and Germany between August 2020 and January 2022 [13]. The Post-OVID protocol (BASEC-ID 2022-02141) was approved by the ethical commission during the conduction of the OVID trial and

before the start of the follow-up phase and data collection of the Post-OVID study. All patients provided separate written informed consent for the follow-up study.

2.2 | Study population

In brief, 475 adult outpatients aged 50 or older with acute COVID-19 and without other indications to anticoagulant therapy were randomized between August 2020 and January 2022 to receive either enoxaparin 40 mg once daily for a total of 14 days (enoxaparin group) or no treatment (standard of care group), provided that they had acute respiratory symptoms or body (tympanic) temperature higher than 37.5 °C. Participants were deemed eligible for inclusion if they were able to visit the study center for an initial assessment and lacked any medical conditions necessitating anticoagulation therapy. Main exclusion criteria involved contraindications to anticoagulant therapy, such as severe impairment of renal or hepatic function, severe anemia, a history of recent major bleeding, or concurrent use of dual antiplatelet therapy. The full list of eligibility criteria as well as the complete study design and procedures were reported previously [8,13]. The follow-up of OVID was 30 days for the primary outcomes and 90 days for secondary analyses.

In the Post-OVID study, the trial participants were contacted telephonically to assess clinical outcomes and symptoms of long COVID 24 months after the initial OVID enrollment.

2.3 | Primary and secondary outcomes

The primary outcome of the Post-OVID study was a composite of all-cause hospitalization and death within 24 months of randomization, which reflects the primary outcome of OVID. Secondary outcomes included (i) a composite of cardiovascular events encompassing deep vein thrombosis, pulmonary embolism, superficial vein thrombosis, myocardial infarction, critical limb ischemia, acute splanchnic vein thrombosis, and ischemic stroke or transient ischemic attack, (ii) health-related quality of life assessed through the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and EuroQol visual analog scale (EQ-VAS), (iii) post-COVID functional status assessed through the Post–COVID-19 Functional Status (PCFS) scale, and (iv) individual symptoms suggestive of long COVID. Furthermore, in the setting of Post-OVID, we performed a validation of the PCFS scale in 3 languages (German, Italian, and French).

The EQ-5D-5L scale is composed of a question descriptive system and a visual analog scale (EQ-VAS) [14–16]. This descriptive system comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety or depression, each graded in 5 levels of severity. The EQ-5D-5L generates a health profile using a 5-digit number, like 12231, which reflects the patient-reported 5 dimensions. These health profiles are then converted into a health utility score, applying a scoring algorithm based on a value set obtained from valuation tasks usually performed with samples from the general population. Since no validated set for Switzerland is currently available, we used the one of France, as suggested by Matter-Walstra et al. [17]. The EQ-5D-5L score is completed by the EQ-VAS, which records the patient's self-rated health on a vertical visual analog scale from 0 (worst possible health state) to 100 (best possible health state).

The PCFS scale is an ordinal outcome scale that grades patients from 0 (no functional limitations) to 4 (severe functional limitations) and 5 (death) [11,18–21].

These scales were administered in the patients' native languages, namely German, French, and Italian, to ensure comprehensibility and accurate responses. The PCFS scale, originally published in English, was translated by 2 bilingual authors (R.M.F. and S.W.) to ensure accuracy and consistency; a final version of the translations was then reviewed by a third independent author (S.B.).

As far as the EQ-5D-5L and EQ-VAS scales are concerned, validated translations were used.

All outcomes, including all-cause hospitalization and death, were adjudicated locally and by the sponsor, who had full access to the source medical documentation, and no independent adjudication was done.

2.4 | Statistical analysis

Median (quartile [Q] 1-Q3) or mean (SD) were calculated for continuous variables, while categorical variables were provided as numbers and percentages. Numerical and graphical analyses were used to describe the distribution of the clinical outcomes and symptoms. Clinical outcomes were provided separately for the first 90 days of follow-up, as per the OVID trial, and for the period elapsing from day 90 to month 24 of follow-up. Nonparametric statistical tests and linear logistic regression were used to test and visualize association between variables as appropriate. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for both primary and secondary outcomes. For comparison of the results of the 2 scales at 24-month follow-up between the 2 groups, a Mann–Whitney U-test followed by a linear regression model adjusted for age, sex, and language in which the scale was administered were used. In order to assess the construct validity of the PCFS scale in the 3 different languages, we compared the results with the ones obtained from EQ-VAS by performing a Jonckheere trend test [22]. All analyses were performed using the statistical software R, version 4.1.3 (R Foundation for Statistical Computing).

2.5 | Funding

The OVID (and Post-OVID) study, an independent, phase 3 trial initiated by investigators and sponsored academically by the University of Zurich, received funding from the Swiss National Science Foundation within the National Research Programme COVID-19 (NRP 78; #198352). Additionally, the study was supported with unrestricted financial aid from several public institutions and foundations: University Hospital Zurich (Innovation Pool), University of

TABLE 1 Baseline characteristics of the patients included in the long-term follow-up.

Characteristic	Total (*N* = 439)	Enoxaparin group (*n* = 218)	Control group (*n* = 221)
Age (y), mean (SD)	57 (9)	56 (10)	57 (9)
Men, *n* (%)	236 (54)	112 (51)	124 (56)
Race and ethnic group, *n* (%)			
Caucasian	419 (95)	210 (96)	209 (95)
Black	3 (0.7)	0 (0.0)	3 (1.4)
Asian	10 (2.3)	5 (2.3)	5 (2.3)
Others	7 (1.6)	3 (1.4)	4 (1.8)
Body mass index (kg/m^2), mean (SD)	25 (6)	25 (5)	25 (6)
Chronic obstructive pulmonary disease, *n* (%)	8 (1.8)	3 (1.4)	5 (2.3)
Chronic heart failure, *n* (%)	2 (0.5)	1 (0.5)	1 (0.5)
Atherosclerotic disease, *n* (%)	19 (4.3)	7 (3.2)	12 (5.4)
Arterial hypertension, *n* (%)	107 (24)	50 (23)	57 (26)
Diabetes mellitus, *n* (%)	37 (8.4)	18 (8.3)	19 (8.6)
History of smoking, *n* (%)	71 (16)	37 (17)	34 (15)
Renal insufficiency, *n* (%)	1 (0.2)	1 (0.5)	0 (0)
Hormonal treatment, *n* (%)	18 (4.1)	12 (5.5)	6 (2.7)
Respiratory rate (breaths/min), median (Q1-Q3)	16 (14-18)	16 (14-18)	16 (13-18)
Heart rate (beats/min), median (Q1-Q3)	76 (68-85)	76 (69-83)	76 (68-86)
Systolic blood pressure (mmHg), median (Q1-Q3)	131 (120-144)	130 (120-143)	132 (120-144)
Diastolic blood pressure (mmHg), median (Q1-Q3)	84 (78-92)	83 (77-92)	85 (78-91)
Body temperature (°C), median (Q1-Q3)	36.7 (36.4-37.1)	36.7 (36.4-37.1)	36.7 (36.4-37.1)
Oxygen saturation (%), median (Q1-Q3)	97 (96-98)	97 (97-98)	97 (96-98)
Dyspnea at rest, *n* (%)	5 (1.1)	4 (1.8)	1 (0.5)
Exertional dyspnea, *n* (%)	67 (15)	36 (17)	31 (14)
Cough, *n* (%)	282 (64)	135 (62)	147 (67)
Headache, *n* (%)	204 (46)	99 (45)	105 (48)

Q, quartile; SD, standard deviation.

Zurich (Universität Zürich Forschungsförderung), Georg Pollert (Berlin), and the Johanna Dürmüller-Bol Foundation. The funders did not influence the design, data collection, management, analysis, interpretation, or drafting of the paper.

3 | RESULTS

A total of 439 (of 469 eligible) patients were included in the Post-OVID study at 6 centers (Supplementary Figure S1). The baseline characteristics are summarized in Table 1. Mean age was 57 (SD, 9) years, and 236 (54%) patients were men. No difference in the demographic and baseline characteristics was observed between the 2 groups. The mean follow-up time was 24 (SD, 4) months.

In Post-OVID, the primary outcome was recorded in a total of 18 (8.3%) patients in the enoxaparin group and 22 (10%) in the control group (relative risk, 0.83; 95% CI, 0.5-1.5), consisting of 39 all-cause hospitalizations and 1 death (glioblastoma; Table 2). The individual causes of primary outcomes are summarized in Supplementary Table S1. Events potentially related to long COVID, not listed among the secondary outcomes but resulting in hospitalization, included 1 case of thoracic pain in the control group and 1 case of depression in the enoxaparin group.

The absolute risk of new venous and arterial cardiovascular events was overall low, notably 1.6% (*n* = 7) in the period elapsing between day 90 and month 24, accounting for 4 (1.8%) events in the enoxaparin group and 3 (1.4%) events in the control group (relative risk, 1.35; 95% CI, 0.31-5.97). Events consisted primarily of arterial cardiovascular complications (1.1%; Table 2). When using HR as the effect measure, results for primary (HR, 0.78; 95% CI, 0.42-1.46) and secondary (HR, 1.3; 95% CI, 0.29-5.9) outcomes were fundamentally similar.

The risk of presenting with long COVID symptoms was similar in the 2 groups, approximately 45%, with no difference between groups

TABLE 2 Clinical outcomes.

Clinical outcome	Follow-up at 90 d (OVID trial)			Follow-up between 90 d and 24 mo (Post-OVID study)				
	Total (n = 472)	Enoxaparin group (n = 234)	Control group (n = 238)	Total (n = 439)	Enoxaparin group (n = 218)	Control group (n = 221)	RR (95% CI)	P value (Post-OVID)
All-cause hospitalization and death	22 (4.7%)	11 (4.7%)	11 (4.6%)	40 (9.1%)	18 (8.3%)	22 (9.9%)	0.83 (0.5-1.5)	.5
Hospitalization	22 (4.7%)	11 (4.7%)	11 (4.6%)	39 (8.9%)	17 (7.8%)	22 (10.0%)	0.78 (0.40-1.40)	.4
Death	0	0	0	1 (0.2%)	1 (0.5%)	0	-	.5
Venous and arterial cardiovascular events	6 (1.3%)	2 (0.9%)	4 (1.7%)	7 (1.6%)	4 (1.8%)	3 (1.4%)	1.35 (0.31-5.97)	.7
Venous thromboembolism	5 (1.1%)	1 (0.4%)	4 (1.7%)	2 (0.5%)	1 (0.5%)	1 (0.5%)	1.01 (0.06-16.11)	.99
Pulmonary embolism	5 (1.1%)	1 (0.4%)	4 (1.7%)	1 (0.2%)	0	1 (0.5%)	0.34 (0.01-8.25)	.5
Isolated deep vein thrombosis	0	0	0	0	0	0	-	-
Superficial vein thrombosis	0	0	0	1 (0.2%)	1 (0.5%)	0	3.04 (0.12-74.25)	.5
Acute coronary syndrome or coronary disease	0	0	0	3 (0.7%)	3 (1.4%)	0	-	.2
Ischemic stroke or transitory ischemic attack	1 (0.2%)	1 (0.4)	0	2 (0.5%)	0 (0%)	2 (0.9%)	-	.3

OVID, enoxaparin for outpatients with COVID-19; RR, relative risk.

TABLE 3 Prevalence of symptoms reported between day 90 and month 24 after SARS-CoV-2 infection.

Symptom	Total (n = 439)	Enoxaparin group (n = 218)	Control group (n = 221)
Any symptom (at least 1), *n* (%)	198 (45)	95 (44)	103 (47)
Cough, *n* (%)	56 (13)	33 (15)	23 (10)
Exertional dyspnea, *n* (%)	50 (11)	24 (11)	26 (12)
Anosmia, *n* (%)	42 (9.6)	23 (10)	19 (8.6)
Impaired concentration, *n* (%)	42 (9.6)	15 (6.9)	27 (12)
Headache, *n* (%)	39 (8.9)	21 (9.6)	18 (8.1)
Fatigue, *n* (%)	38 (8.8)	15 (6.9)	23 (10)
Ageusia, *n* (%)	36 (8.2)	17 (7.8)	19 (8.6)
Sore throat, *n* (%)	31 (7.1)	19 (8.7)	12 (5.4)
Palpitations, *n* (%)	27 (6.2)	13 (6.0)	14 (6.3)
Angina pectoris, *n* (%)	24 (5.5)	12 (5.5)	12 (5.4)
Sputum, *n* (%)	23 (5.2)	13 (6.0)	10 (4.5)
Dyspnea, *n* (%)	12 (2.7)	8 (3.7)	4 (1.8)
Abdominal pain, *n* (%)	8 (1.8)	4 (1.8)	4 (1.8)
Sleeping disorders, *n* (%)	2 (0.5)	1 (0.5)	1 (0.5)

also concerning individual symptoms, as illustrated in Table 3. The most prevalent ones were cough (13% of patients), exertional dyspnea (11%), impaired concentration (10%), anosmia (10%), and fatigue (9%). The intersections of the 4 most common symptoms are shown in Figure 1.

3.1 | Scales

After 2 years of follow-up, only a small proportion of patients experienced functional limitations, as indicated by the PCFS grading (Table 4 and Figure 2), or impaired quality of life, as shown by the EQ-VAS scale (Figure 3) and the EQ-5D-5L scale (Figure 4 and Supplementary Table S2) assessment. All patients included in the study completed the questionnaires. A total of 65 (14.8%) patients reported any functional limitations measured with the PCFS scale. The majority of them (n = 58; 13.2% of total) described their limitations as negligible or minor, corresponding to a PCFS 1 to 2 grade, and none reported severe functional limitations (corresponding to grade 4 of the PCFS scale). There was no significant difference in the proportion of patients reporting a PCFS grade of 1 to 3 between the groups (15% in each group; odds ratio, 0.98; 95% CI, 0.6-1.7; $P > .99$). The same results were found after adjusting for age, sex, and language in which the scale was administered.

The results obtained from the EQ-VAS (Figure 3) and the EQ-5D-5L (Figure 4 and Supplementary Table S2) scales indicated a

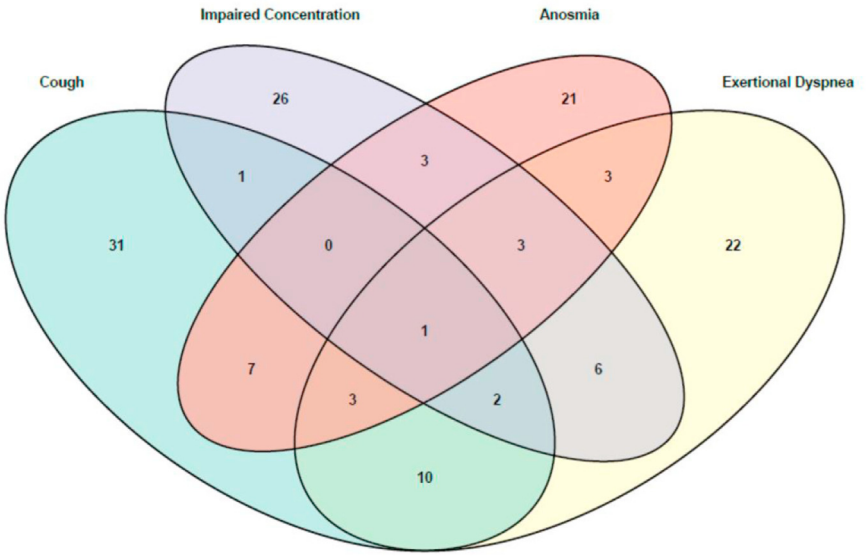

FIGURE 1 Most common persisting symptoms reported between day 90 and month 24 after SARS-CoV-2 infection.

highly functioning population with few limitations across all 5 dimensions considered. The median EQ-VAS score was 85 out of 100 in both groups (IQR, 80-90 for the standard of care group and 75-90 for the enoxaparin group). After adjusting for age, sex, and language in a linear regression model, no association between group of randomization and higher score of EQ-VAS was found (P = .3).

Among the 5 health dimensions assessed by the EQ-5D-5L, the most affected one was anxiety, with 52 (12%) patients reporting anxiety issues, 10% in the enoxaparin group vs 13% in controls, followed by pain, 10% vs 11%, respectively. The median utility index derived from the 5 dimensions of the EQ-5D-5L scale showed no difference between the 2 treatment groups (1.00 [IQR, 1.00-1.00] in both groups; Supplementary Table S2).

A multivariable analysis aimed to assess association between baseline characteristics and increased odds of functional impairment at 2 years showed that hypertension at baseline was associated with higher odds of presenting functional limitations according to the PCFS scale (PCFS grade, >0). Similarly, a linear regression model showed that hypertension, higher body mass index, and female sex correlated with a lower EQ-VAS score.

Finally, given the lack of validation of the PCFS scale in German, Italian, and French, we showed the association between PCFS and EQ-VAS, as depicted in Figure 5. The PCFS scale showed an inverse correlation with the EQ-VAS score, which was consistent across all 3 languages. This inverse relationship indicates that higher degrees of functional impairment (as per PCFS grade) are associated with lower self-perceived health status (EQ-VAS score). Statistical trend analysis confirmed the correlation of the 2 scales in each language with significant P values (German, $P < .001$; Italian, $P = .03$; French, $P < .001$).

4 | DISCUSSION

In Post-OVID, the follow-up data analysis of the multinational, phase 3, randomized controlled OVID trial, we showed that prophylactic enoxaparin administered during the acute phase of illness in

TABLE 4 Post–COVID-19 Functional Status scale results.

PCFS grade	Total (N = 439)	Enoxaparin group (n = 218)	Control group (n = 221)
0 (no functional limitations)	373 (85%)	186 (85%)	188 (85%)
1 (negligible functional limitations)	38 (8.7%)	19 (8.7%)	19 (8.6%)
2 (slight functional limitations)	20 (4.6%)	11 (5.0%)	9 (4.1%)
3 (moderate functional limitations)	7 (1.6%)	2 (0.9%)	5 (2.3%)
4 (severe functional limitations)	0	0	0
5 (death)	1 (0.2%)	1 (0.5%)	0

PCFS, Post–COVID-19 Functional Status.

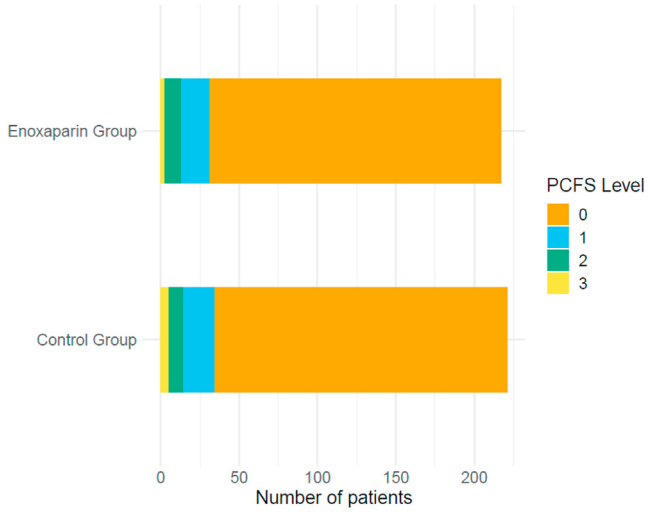

FIGURE 2 Distribution of Post–COVID-19 Functional Status (PCFS) scale levels by treatment group. PCFS grading among the enoxaparin group and the control group (no anticoagulation) 24 months after acute COVID-19 disease. PCFS grading classifies patients from 0 (no functional limitations) to 4 (severe functional limitations) and 5 (death).

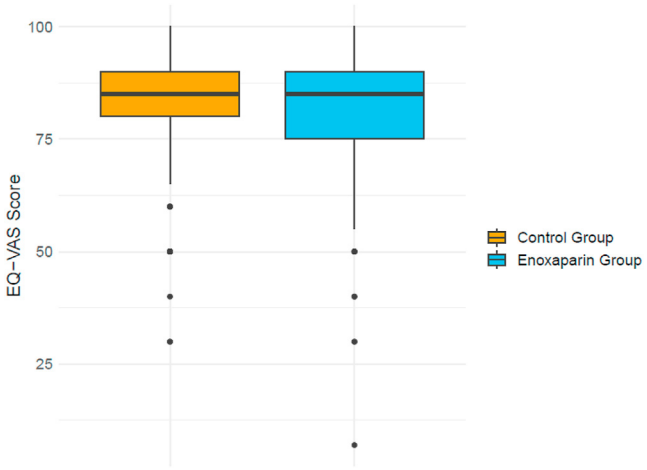

FIGURE 3 Distribution of the results of the EuroQol visual analog scale (EQ-VAS) by treatment group. EQ-VAS grading among the enoxaparin group and the control group (no anticoagulation) 24 months after acute COVID-19 disease. EQ-VAS is a standardized instrument for measuring an individual's self-rated health on a vertical visual analog scale ranging from 0 to 100, where 0 represents the "worst imaginable health state" and 100 represents the "best imaginable health state".

outpatients with symptomatic COVID-19 did not influence long-term clinical and functional outcomes. These included 2-year all-cause death, hospitalization, cardiovascular events, persistent symptoms, functional dysfunction, and quality of life. Although these aspects have already been studied in patients with COVID-19 requiring hospitalization [23], no trial focusing on early anticoagulation for the prevention of long-term outcomes has been conducted thus far.

Nearly half of all unplanned all-cause hospitalizations within 2 years from randomization occurred within the first 90 days following randomization, notably hospital admissions due to pneumonia diagnosed in the first 10 days after enrollment in the study [12]. The possibility of recall bias influencing this result cannot be overlooked since the assessment of outcomes during the first 90 days involved patient contact at 3, 7, 14, 30, and 90 days, whereas the assessment of outcomes between day 90 and month 24 was conducted in a single interview. However, this distribution pattern becomes even more evident when examining venous and arterial cardiovascular events, with a nearly equal number of events occurring in the first 90 days compared with the subsequent 21 months (6 [1.3%] vs 7 [1.6%], respectively), stating an excess of events reflecting the prothrombotic state of the acute phase [24,25], as also described in population-wide cohort studies [26]

The prevalence of persistent symptoms reported by the patients after a median follow-up of 2 years was overall not negligible but similar in both groups for all the symptoms considered. Indeed, the incidence of the most common persistent symptoms, including exertional dyspnea, anosmia, impaired concentration, and fatigue in our cohort, appears to be lower than those reported in meta-analyses published earlier during the pandemic [27–29]. It must be acknowledged, however, that these studies included primarily patients who were hospitalized. A recent registry-based study from Norway [30], which incorporated data from over 53,000 COVID-19 outpatients, revealed a lower symptom prevalence compared with earlier reports, similar to our findings. By then comparing our results with these ones, we found higher instances of persisting cough (13% compared with 2.0% in the Norwegian register), persistent anosmia (9.6% vs 0.4%), and memory issues (9.6% vs 0.6%), while the rates of fatigue (8.8% vs 6.0%) and dyspnea (2.7% vs 2.6%) were similar.

In order to further investigate the potential benefit of an early prophylaxis with anticoagulation in the setting of long COVID, we made an assessment of the health status of the patients using 2 validated performance scales, rather than relying on the less measurable definition of long COVID provided by the World Health Organization [31]. Both the PCFS scale and EQ-VAS or EQ-5D-5L scale showed that only a minor proportion of patients had persistent functional limitations. Again, there was no significant difference between the 2 study groups. This observation further suggests that early thromboprophylaxis with enoxaparin does not markedly affect long-term functional status or quality of life in COVID-19 patients. Also, our findings show that 14.8% of patients scored above 0 on the PCFS scale (with no cases of severe functional limitations), and the median EQ-VAS scale score was 85 (Q1-Q3, 80-90), indicating that while a significant number of outpatients continue to experience persistent problems, these issues are generally mild in their manifestation and have a minimal impact on daily functional abilities.

Our results also suggest that certain baseline characteristics, including arterial hypertension and being female, may be associated with an increased likelihood of experiencing functional impairment or a reduced quality of life, as assessed by one or both of the utilized scales. It

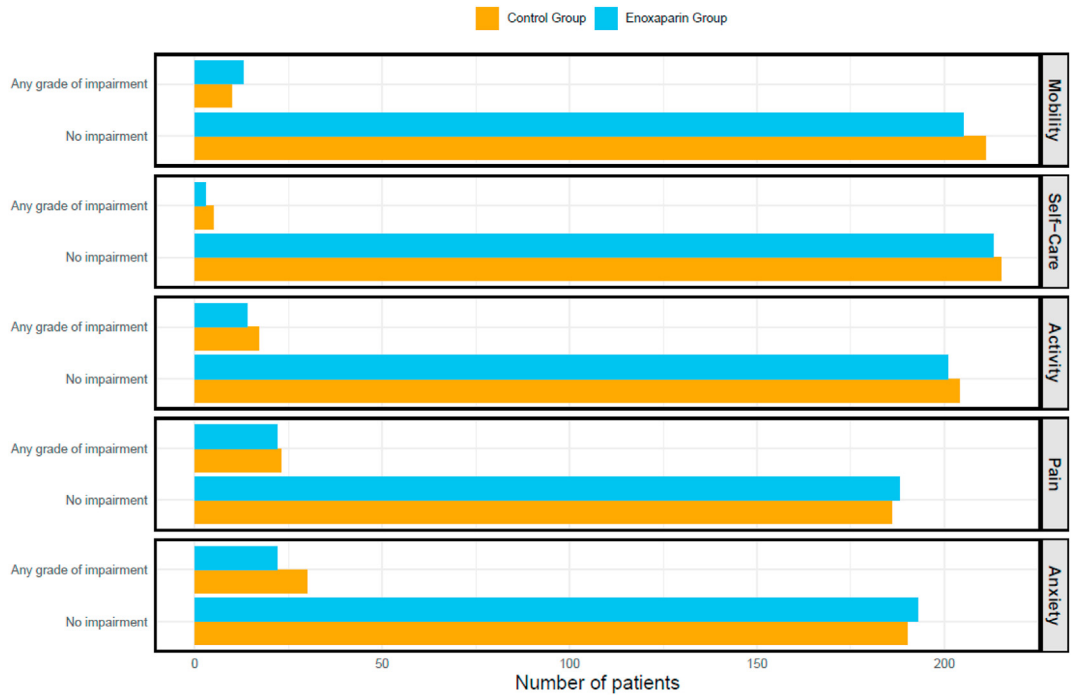

FIGURE 4 Dichotomized results of the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) scale by treatment group. EQ-5D-5L grading among the enoxaparin group and the control group (no anticoagulation) 24 months after acute COVID-19 disease. A standardized instrument for measuring generic health status, EQ-5D-5L assesses health in 5 dimensions: mobility, self-care, usual activities, pain, and anxiety. Each dimension has 5 levels of severity, ranging from no impairment to extreme impairment. Since the patients were highly functioning and had few limitations, the results of the scale were dichotomized into "no impairment" (level 1) vs "Any grade of impairment" (levels 2-5).

is important to note that hypertension also represented the most prevalent comorbidity at baseline, having thus a higher likelihood of being statistically significant. Nonetheless, these findings are consistent with existing literature that identifies these factors as established risk factors for post-COVID syndrome in both inpatient and outpatient settings [23,32–34].

The expectations that initially anticoagulated COVID-19 outpatients might show better long-term outcomes were based on potential for reducing *in situ* thromboses and venous thromboembolism (VTE) complications. Early in the pandemic, this has been a common theme, and there have been soon reports of various private clinics promoting unproven therapies, including a mix of antithrombotic

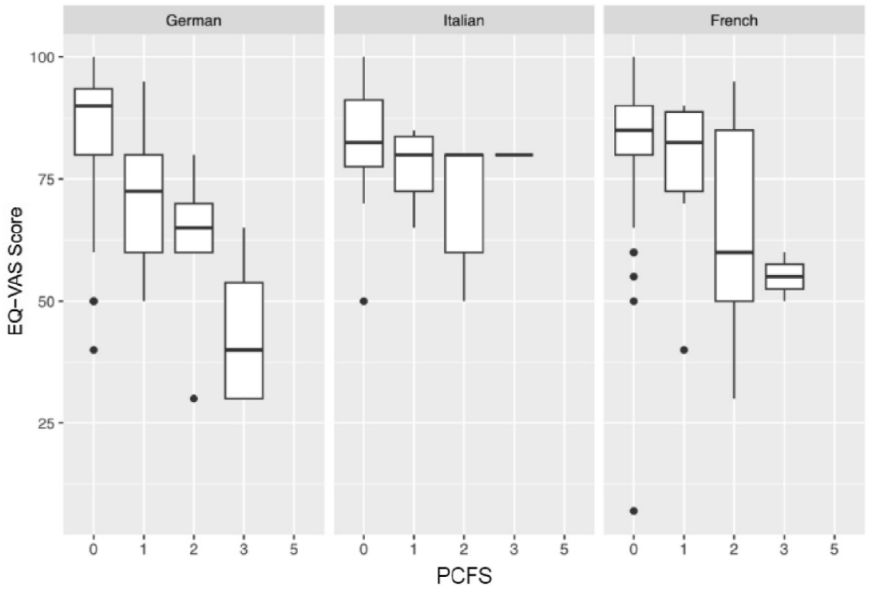

FIGURE 5 Correlation between the results of the Post–COVID-19 Functional Status (PCFS) scale and the EuroQol visual analog scale (EQ-VAS). The results of the PCFS and the EQ-VAS were stratified by the language group in which the questionnaires were administered to study participants. Higher degrees of functional impairment (as indicated by PCFS grade) were associated with lower self-perceived health status (EQ-VAS score).

agents, oxygen, and vitamins to prevent or treat long COVID. In our 90-day analysis [12] and in the current study, we found no tendency or trends toward an improvement of symptoms with enoxaparin thromboprophylaxis. We believe that any potential benefit would have been contingent on VTE prevention, but only within a subgroup of outpatients characterized by a significantly higher VTE risk, similar to that of hospitalized patients.

Regarding the translation of the assessment tools, while validated translations of the EQ-VAS and EQ-5D-5L scales are available in the 3 Swiss national languages (German, Italian, and French), a validated translation of the PCFS scale is not yet available. Since this absence could potentially introduce bias, we conducted a trend analysis, revealing a strong correlation between the results of the EQ-VAS and PCFS scales. These findings further underscore the PCFS scale's effectiveness and reliability across different linguistic contexts.

4.1 | Limitations

While this study prospectively assessed the prevalence of persistent symptoms 2 years after acute COVID infection based on a randomized clinical trial, it is important to acknowledge a number of limitations associated with our research. First, the rate of SARS-CoV-2 reinfection during the follow-up period was unknown. Second, we lacked information about the prerandomization functional status, as expressed by the EQ-5D-5L and EQ-VAS scales, as well as of the functional status at the time of randomization, thus preventing us from performing a time analysis of the functional status changes during the considered period. However, our data being derived from a randomized controlled trial implies that by virtue of random assignment, the baseline functional status was likely to be balanced between the 2 groups. Furthermore, in order to assess the functional status, we relied on patients' subjective reports without further confirming it through objective assessment, such as cardiopulmonary exercise testing. Lastly, our study included patients from the first 3 COVID-19 waves in Europe; thus, it remains uncertain whether thromboprophylaxis would affect outcomes related to current and future variants of COVID-19.

5 | CONCLUSIONS

In conclusion, our results indicate that early thromboprophylaxis with enoxaparin does not improve the long-term clinical and functional outcomes among patients who received initial ambulatory care for acute COVID-19.

APPENDICES

OVID (enoxaparin for outpatients with COVID-19) investigators

Stefano Barco (Zürich, Switzerland), Davide Voci (Zürich, Switzerland), Ulrike Held (Zürich, Switzerland), Tim Sebastian (Zürich, Switzerland), Roland Bingisser (Basel, Switzerland), Giuseppe Colucci (Lugano, Switzerland), Daniel Duerschmied (Mannheim, Germany), André Frenk (Bern, Switzerland), Bernhard Gerber (Bellinzona, Switzerland), Andrea Götschi (Zürich, Switzerland), Stavros V. Konstantinides (Mainz, Germany), François Mach (Geneve, Switzerland), Helia Robert-Ebadi (Geneve, Switzerland), Thomas Rosemann (Zürich, Switzerland), Noemi R Simon (Basel, Switzerland), Hervé Spechbach (Geneve, Switzerland), David Spirk (Zürich, Switzerland), Stefan Stortecky (Bern, Switzerland), Lukas Vaisnora (Bern, Switzerland), Marc Righini (Geneve, Switzerland), Nils Kucher (Zürich, Switzerland), Stéphanie Roth Zetzsche (Zürich, Switzerland), Rebecca Spescha (Zürich, Switzerland), Claudia Leeger (Zürich, Switzerland), Yulia Butscheid (Zürich, Switzerland), Eliane Probst (Zürich, Switzerland), Evy Micieli (Zürich, Switzerland), Gabor Forgo (Zürich, Switzerland), Fabian Johner (Zürich, Switzerland), Alexandru Grigorean (Zürich, Switzerland), Georgios Vatsakis (Zürich, Switzerland), Dagmar Keller Lang (Zürich, Switzerland), Silvana Rampini Speck (Zürich, Switzerland), Barbara Hasse (Zürich, Switzerland), Marco Rueegg (Zürich, Switzerland), Isabelle Arnold (Zürich, Switzerland), Christian Nickel (Basel, Switzerland), Jeannette Busch (Basel, Switzerland), Marc Blondon (Geneve, Switzerland), Frédéric Glauser (Geneve, Switzerland), Micol G. Cittone (Bellinzona, Switzerland), Chiara Kessler (Basel, Switzerland), Diona Gjermeni (Freiburg in Breisgau, Germany), Christoph B. Olivier (Freiburg in Breisgau, Germany), Nadine Gauchel (Freiburg in Breisgau, Germany), Paul Biever (Freiburg in Breisgau, Germany), Lukas Hobohm (Mainz, Germany), Dorothea Becker (Mainz, Germany), Marc Schindewolf (Bern, Switzerland), Arnaud Kuenzi (Bern, Switzerland), and Silvia Ulrich (Zürich, Switzerland).

ACKNOWLEDGMENTS

We thank all patients for having agreed to participate in the OVID study and in the present follow-up study.

FUNDING

The OVID study was an independent, investigator-initiated, phase 3 trial with an academic sponsor (University of Zurich) and was primarily funded by the Swiss National Science Foundation (SNF) in the frame of the National Research Programme COVID-19 (NRP 78; #198352). Additionally, the sponsor received unrestricted financial support for the conduct of the study from the following public institutions or foundations: University Hospital Zurich (Innovation Pool), University of Zurich (Universität Zürich Forschungsförderung), Georg Pollert (Berlin), and Johanna Dürmüller-Bol Foundation.

AUTHOR CONTRIBUTIONS

R.M.F.: methodology, software, formal analysis, writing—original draft, writing—review and editing, and visualization. D.V.: data curation, writing—review and editing, and project administration. B.B.: methodology and writing—review and editing. R.B.: data curation and writing—review and editing. G.C.: data curation and writing—review and editing. G.F.: data curation. T.G.: data curation. B.G.: data curation

and writing—review and editing. A.G.: data curation and writing—review and editing. F.A.K.: writing—review and editing. M.R.: data curation and writing—review and editing. H.R.-E.: data curation. S.S.: data curation and writing—review and editing. S.U.: writing—review and editing. S.W.: writing—review and editing. D.W.: writing—review and editing. L.H.: writing—review and editing. N.K.: conceptualization and methodology. S.B.: data curation, investigation, methodology, project administration, writing—review & editing, and supervision.

RELATIONSHIP DISCLOSURE

R.M.F., D.V., R.B., G.C., G.F., B.G., F.A.K., M.R., H.R.-E., S.S., S.U., S.W., D.W., L.H., N.K., and S.B. have nothing to disclose. B.B. is supported by a Career Development Award from the American Heart Association and VIVA Physicians (#938814). B.B. was supported by the Scott Schoen and Nancy Adams IGNITE Award and is supported by the Mary Ann Tynan Research Scientist award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital and the Heart and Vascular Center Junior Faculty Award from Brigham and Women's Hospital. B.B. reports that he was a consulting expert, on behalf of the plaintiff, for litigation related to 2 specific brand models of inferior vena cava filters. B.B. has neither been involved in the litigation in 2022-2024 nor has he received any compensation in 2022-2024. B.B. reports that he is a member of the Medical Advisory Board for the North American Thrombosis Forum and serves in the Data Safety and Monitory Board of the NAIL-IT trial funded by the National Heart, Lung, and Blood Institute and Translational Sciences.

ORCID

Riccardo M. Fumagalli https://orcid.org/0000-0002-6794-1986

REFERENCES

[1] Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21:133–46.

[2] Lai CC, Hsu CK, Yen MY, Lee PI, Ko WC, Hsueh PR. Long COVID: an inevitable sequela of SARS-CoV-2 infection. *J Microbiol Immunol Infect*. 2023;56:1–9.

[3] Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Chron Respir Dis*. 2021;18:14799731211002240. https://doi.org/10.1177/14799731211002240

[4] Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. 2020;370:m3026. https://doi.org/10.1136/bmj.m3026

[5] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27:601–15.

[6] Ananworanich J, Mogg R, Dunne MW, Bassyouni M, David CV, Gonzalez E, et al. Randomized study of rivaroxaban vs placebo on disease progression and symptoms resolution in high-risk adults with mild coronavirus disease 2019. *Clin Infect Dis*. 2022;75:e473–81.

[7] Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. *JAMA*. 2021;326:1703–12.

[8] Barco S, Voci D, Held U, Sebastian T, Bingisser R, Colucci G, et al. Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (OVID): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet Haematol*. 2022;9:e585–93.

[9] Cools F, Virdone S, Sawhney J, Lopes RD, Jacobson B, Arcelus JI, et al. Thromboprophylactic low-molecular-weight heparin versus standard of care in unvaccinated, at-risk outpatients with COVID-19 (ETHIC): an open-label, multicentre, randomised, controlled, phase 3b trial. *Lancet Haematol*. 2022;9:e594–604.

[10] Piazza G, Spyropoulos AC, Hsia J, Goldin M, Towner WJ, Go AS, et al. Rivaroxaban for prevention of thrombotic events, hospitalization, and death in outpatients with COVID-19: a randomized clinical trial. *Circulation*. 2023;147:1891–901.

[11] Avezum Á, Oliveira Junior HA, Neves PDMM, Alves LBO, Cavalcanti AB, Rosa RG, et al. Rivaroxaban to prevent major clinical outcomes in non-hospitalised patients with COVID-19: the CARE - COALITION VIII randomised clinical trial. *EClinicalMedicine*. 2023;60:102004. https://doi.org/10.1016/j.eclinm.2023.102004

[12] Voci D, Götschi A, Held U, Bingisser R, Colucci G, Duerschmied D, et al. Enoxaparin for outpatients with COVID-19: 90-day results from the randomised, open-label, parallel-group, multinational, phase III OVID trial. *Thromb Res*. 2023;221:157–63.

[13] Barco S, Bingisser R, Colucci G, Frenk A, Gerber B, Held U, et al. Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus disease-2019 (the OVID study): a structured summary of a study protocol for a randomized controlled trial. *Trials*. 2020;21:770. https://doi.org/10.1186/s13063-020-04678-4

[14] Human Research Act (HRA). https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjC8qHgsPCHAxU4gP0HHaShAaQQFnoECC8QAQ&url=https%3A%2F%2Fwww.swissmedic.ch%2Fdam%2Fswissmedic%2Fen%2Fdokumente%2Fbewilligungen%2Fklv%2Ffederal_act_on_researchinvolvinghumanbeingshumanresearchacthra.pdf.download.pdf%2Ffederal_act_on_researchinvolvinghumanbeingshumanresearchacthra.pdf&usg=AOvVaw1ID40xYmjAtm3JISrmRo3A&opi=89978449. [accessed February 1, 2024].

[15] Devlin N, Pickard S, Busschbach J. The development of the EQ-5D-5L and its value sets. In: Devlin N, Roudijk B, Ludwig K, eds. *Value sets for EQ-5D-5L: a compendium, comparative review & user guide*. Cham (CH): Springer; 2022:1–12.

[16] Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. *Appl Health Econ Health Policy*. 2017;15:127–37.

[17] Matter-Walstra K, Klingbiel D, Szucs T, Pestalozzi BC, Schwenkglenks M. Using the EuroQol EQ-5D in Swiss cancer patients, which value set should be applied? *Pharmacoeconomics*. 2014;32:591–9.

[18] Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J*. 2020;56:2001494. https://doi.org/10.1183/13993003.01494-2020

[19] Machado FVC, Meys R, Delbressine JM, Vaes AW, Goërtz YMJ, van Herck M, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. *Health Qual Life Outcomes*. 2021;19:40. https://doi.org/10.1186/s12955-021-01691-2

[20] de Jong CMM, Boon GJAM, Le YNJ, Barco S, Siegerink B, Klok FA. The Post-Venous Thromboembolism Functional Status Scale: from call to action to application in research, extension to COVID-19 patients, and its use in clinical practice. *Semin Thromb Hemost*. 2023;49:764–73.

[21] de Jong CMM, Le YNJ, Boon GJAM, Barco S, Klok FA, Siegerink B. Eight lessons from 2 years of use of the Post-COVID-19 Functional Status scale. *Eur Respir J*. 2023;61:2300416. https://doi.org/10.1183/13993003.00416-2023

[22] DescTools: Tools for descriptive statistics. R package version 0.99. 23. http://cran.nexr.com/web/packages/DescTools/DescTools.pdf; 2017 [accessed February 1, 2024].

[23] Inspiration Investigators. Durable functional limitation in patients with coronavirus disease-2019 admitted to intensive care and the effect of intermediate-dose vs standard-dose anticoagulation on functional outcomes. *Eur J Intern Med*. 2022;103:76–83.

[24] Gupta A, Satapathy AK, Bahinipati P. Delayed catastrophic thrombotic events in post-acute COVID-19. *Thromb Res*. 2022;220:60–4.

[25] Willems LH, Nagy M, Ten Cate H, Spronk HMH, Groh LA, Leentjens J, et al. Sustained inflammation, coagulation activation and elevated endothelin-1 levels without macrovascular dysfunction at 3 months after COVID-19. *Thromb Res*. 2022;209:106–14.

[26] Knight R, Walker V, Ip S, Cooper JA, Bolton T, Keene S, et al. Association of COVID-19 with major arterial and venous thrombotic diseases: a population-wide cohort study of 48 million adults in England and Wales. *Circulation*. 2022;146:892–906.

[27] Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. *J Infect Dis*. 2022;226:1593–607.

[28] Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens*. 2022;11:269. https://doi.org/10.3390/pathogens11020269

[29] Malik P, Patel K, Pinto C, Jaiswal R, Tirupathi R, Pillai S, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-a systematic review and meta-analysis. *J Med Virol*. 2022;94:253–62.

[30] Hetlevik Ø, Wensaas KA, Baste V, Emberland KE, Özgümüs T, Håberg SE, et al. Prevalence and predictors of post-COVID-19 symptoms in general practice - a registry-based nationwide study. *BMC Infect Dis*. 2023;23:721. https://doi.org/10.1186/s12879-023-08727-6

[31] World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus. https://iris.who.int/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf?sequence=1; 2021 [accessed February 1, 2024].

[32] Davis HE, McCorkell L, Vogel JM, Topol EJ. Author correction: long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21:408. https://doi.org/10.1038/s41579-023-00896-0

[33] Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, Gokhale KM, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med*. 2022;28:1706–14.

[34] Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat Commun*. 2022;13:3528. https://doi.org/10.1038/s41467-022-30836-0

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102534