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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

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Citation
Sadeghipour, P., Talasaz, A. H., Barco, S., Bakhshandeh, H., Rashidi, F., Rafiee, F., ... Bikdeli, B. (2022). 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. *European Journal Of Internal Medicine*, *103*, 76-83. doi:10.1016/j.ejim.2022.06.014

Version: Publisher's Version
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Downloaded from: https://hdl.handle.net/1887/3566758

Note: To cite this publication please use the final published version (if applicable).

European Journal of Internal Medicine 103 (2022) 76–83

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

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

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ARTICLE INFO

Keywords:
COVID-19
The post-COVID-19 functional status scale
Patient health questionnaire-2
Anticoagulation

ABSTRACT

Introduction: Patients affected with severe forms of coronavirus disease 2019 (COVID-19) suffer from a wide range of sequelae, from limited airway diseases to multiple organ failure. These sequelae may create exercise limitation, impair the daily activity and thus impact the mental health and the social life. However, the extent of functional limitations and depressive symptoms are understudied especially in patients with COVID-19 after intensive care unit (ICU) hospitalization.

Methods: The Intermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) was a clinical trial that randomized ICU patients with COVID-19 to intermediate-dose vs standard-dose anticoagulation. In the current study, we assessed the interval change in 30-day and 90-day functional limitations based on the post-COVID-19 functional status scale (PCFS) and depressive symptoms based on the Patient Health Questionnaire-2 (PHQ-2) in the trial participants. We also assessed the effect of intermediate-dose vs standard-dose prophylactic anticoagulation on the functional outcomes and depressive symptoms.

Results: Of 600 randomized patients in INSPIRATION, 375 (age: 62 years; 42% women) participated in the functional status study. 195 patients died during the 90-day follow up (191 by day 30). Among survivors, between day 30 and day 90, the proportion of patients with moderate-to-severe functional limitation (PCSF grade 3-or-4) decreased from 20.0% to 4.8% (P <0.001) and PHQ-2 $\geq$ 3 decreased from 25.5% to 16.6% (P = 0.05). The proportion of patients with no functional limitations (PCFS grade 0) increased (4.2% to 15.4%, P<0.001). Intermediate-dose compared with standard-dose prophylactic anticoagulation did not impact the 90-day proportion of patients with PCFS grade 3-or-4 (5.3% vs 4.2%; odds ratio (OR), 1.20, [95% CI, 0.46–3.11]; P = 0.80) or PHQ-2 $\geq$ 3 (17.9% vs 15.3%; OR, 1.14, [95% CI, 0.79–1.65]; P = 0.14), with similar results when accounting for study center.

Conclusion: In patients with COVID-19 admitted to the ICU, functional limitations and depressive symptoms were common at 30-day follow-up and had some improvement by 90-day follow-up among survivors. Intermediate-dose compared to standard-dose prophylactic anticoagulation did not improve functional outcomes.

1. Introduction

Coronavirus disease-2019 (COVID-19) has post-acute manifestations that may impact the everyday life functional and the mental health status of the affected patients [1]. In a cross-sectional global online survey on 735 COVID-19 survivors, 79.5% and 56.2% of the responders reported problems with their routine activities and mobility within 3 months after the diagnosis [2]. Similarly, in another online survey, only 5.3% of the participants reported to be symptom-free in 6-month follow up [3]. Tools such as the Post-COVID-19 Functional Status (PCFS) scale have been developed and validated to assess the chronic impact of COVID-19 on functional limitations [4,5]. COVID-19 can also cause depressive symptoms in recovered patients, which can impact the daily function and the return to normal activities [6]. In a survey of 3904

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https://doi.org/10.1016/j.ejim.2022.06.014
Received 1 April 2022; Received in revised form 11 June 2022; Accepted 17 June 2022
Available online 20 June 2022
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participants with various stages of prior COVID-19 severity, half had depressive symptoms during mean duration of 4 months post-infection [7].

Patients with COVID-19 who require ICU level of care may be at a particularly high risk for functional limitation and depression, although the severity is unknown [6,8]. It is possible that microvascular or macrovascular thrombosis and the associated thrombo-inflammation, common in the setting of COVID-19 [9-12], contribute to functional limitations among COVID-19 post-ICU survivors. This gap in knowledge is reflected by a lack of specific recommendations for physical and mental rehabilitation after the acute course of COVID-19.

The Intermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) trial was a multicenter randomized trial that compared the efficacy and safety of intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the ICU (13-15). Among the pre-specified goals of INSPIRATION were to evaluate the functional limitation (assessed by PCFS) and depressive symptoms (assessed by Patient Health Questionnaire-2 (PHQ-2) in the study participants. For the functional status study, since a direct treatment effect of short-term anticoagulation on 90-day functional and mood outcomes were believed to be unlikely, it was specified *a priori* to pool the study groups for the assessment of the changes in functional status and depressive symptoms between 30-day and 90-day follow-up, after excluding a significant beneficial or harmful treatment effect. This manuscript summarizes the results of the functional status study and reports the exploratory effect of treatment assignment on functional status and depressive symptoms.

2. Methods

2.1. Study design

INSPIRATION was a randomized clinical trial of patients with COVID-19 admitted to ICU. Patients were randomized to intermediate-dose vs standard-dose prophylactic anticoagulation. The present study assessed the interval change in functional impairment and depressive symptoms between the first and the third month of randomization, and assessed the potential treatment effect of assigned anticoagulation regimens on functional outcomes and depressive symptoms [14]. The trial was conducted in 10 academic centers in two cities of Tabriz and Tehran, Iran.

2.2. Patients

Briefly, patients with polymerase-chain-reaction confirmed COVID-19 admitted to the ICU within 7 days from the index hospitalization and life expectancy >24 h were considered for inclusion. Main exclusion criteria consisted of an established indication for therapeutic anticoagulation and overt bleeding. The assigned treatments were continued until 30 days from randomization or death or a thrombotic or hemorrhagic event, irrespective of hospital stay status [14]. Enoxaparin, was the primary anticoagulant agent in the present study. Patients assigned to intermediate-dose prophylactic anticoagulation received enoxaparin, 1 mg/kg daily. In the control group, enoxaparin 40 mg daily was the standard-dose prophylactic anticoagulation regimen. Predefined modifications according to body weight and creatinine clearance were applied. Unfractionated heparin was used for patients with severe renal insufficiency [14,15].Patient recruitment for INSPIRATION trial started from July 29, 2020.

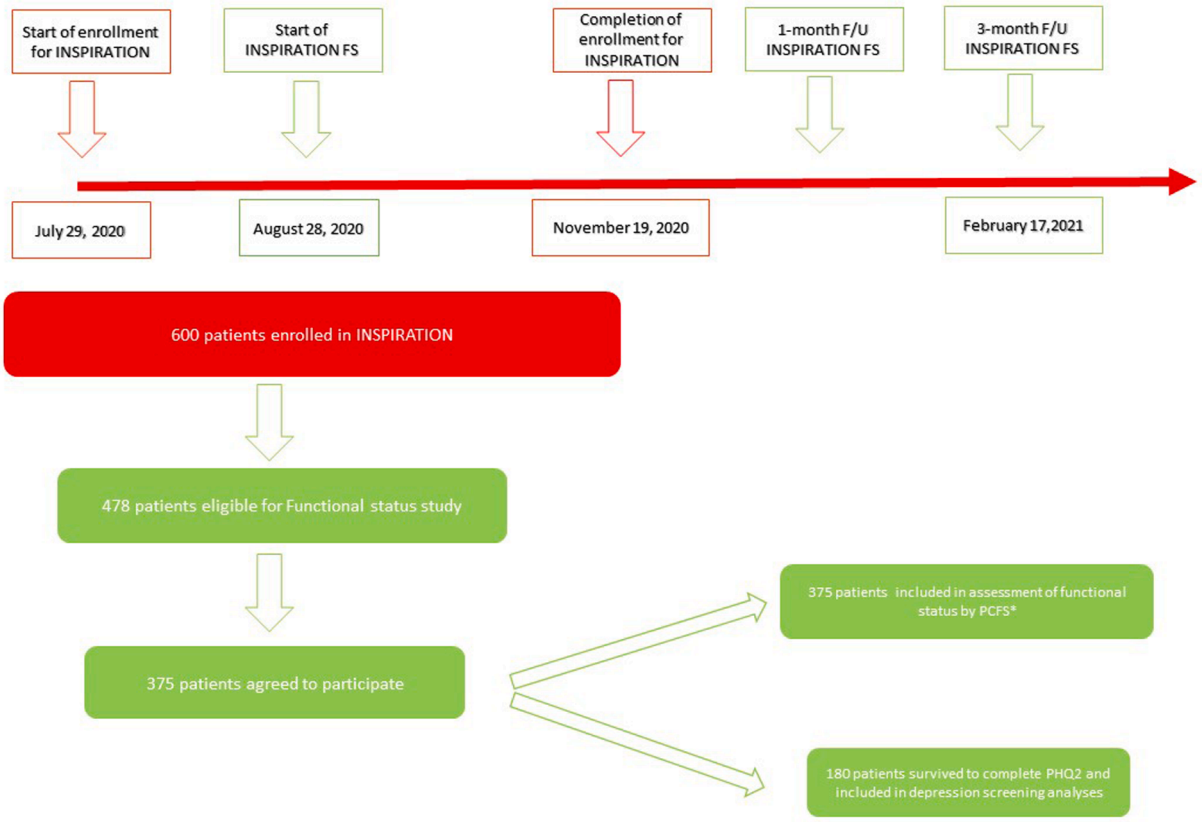

Fig. 1. Schematic representation of patient inclusion in INSPIRATION functional status(FS) cohort. *Since death is one of the pre-defined categories for PCFS, patients who died during follow-up were being considered for functional status analyses. However, for depression screening, patients needed to be alive to complete the questionnaire.

Inclusion of the PCFS and PHQ-2 data in INSPIRATION was started 1 month after the initiation of the trial (August 28, 2020). All patients who were enrolled between August 28, 2020 and November 19, 2020 (i.e., the date of completion of enrollment for INSPIRATION) and agreed to participate in the 30- and 90-days telephone-based follow ups, were included in the present study (Fig. 1). For depressed mood screening, only patients who survived up to 30-day and 90-day follow up were included, since the survey needs to be completed by patients.

2.3. Functional and mental health assessment

Functional status was assessed by PCFS. Briefly, PCFS is an ordinal outcome scale and is used for grading patients from 0 (no functional limitations) to 4 (severe functional limitations) and 5 (death) (e-Fig. 1) [4,5].The construct validity of the original version was proved in 1939 subjects 3-month after symptoms onset [5]. PCFS scale was selected for the present study since it has been designed for the assessment of long-term outcomes. This is distinct from other important scales that focus on short-term or in-hospital outcomes (such as the World Health Organization Ordinal Scale for Clinical Improvement) [5]. For the current study, we discussed the process of preparing a Farsi translation for the PCFS tool with the developers of this tool (FAK and BS). PCFS was first translated into Farsi (primary language in the study sites). Subsequently, it was back translated into English. The initial Farsi version was drafted by PS, BB (both cardiologists) and HB (clinical epidemiologist). All these authors are proficient in both English and Farsi. This version was back-translated, independently, to English by a cardiologist (AA), again proficient to both languages who was unaware of the primary English version, to ascertain fidelity to the original English version. Minor revisions were made in this process to ascertain preserving the content while attuning to language-specific intricacies. Following consensus-based revisions, the Farsi translation was sent to six clinicians (three cardiologists, one cardiac surgeon, one pediatrician and one social medicine specialist) who had contracted COVID-19 in the past, for pilot assessment and feedback and to one non-physician with expertise in Farsi and English literature. All participants found the questions to be easily understandable and noted an acceptable agreement between the original English version and the Farsi translation. The final Farsi version was reviewed for fluency by PS and BB. Finally, the same graphical design of the original English version was applied to the Faris version. This version, a user's manual, as well as >25 other translations and cultural adaptations can be found at: https://osf.io/qgpdv/ (CC-BY license).

The PHQ-2 questionnaire is a validated tool for screening depressive symptoms, which has been previously validated in Farsi [16] and is commonly used in COVID-19 [17]. PHQ-2 is scored from 0 to 6, with higher odds of major depressive disorder with a score ≥ 3 [18].

2.4. Study outcomes

The assessment of functional status and depressive symptoms between the two assigned anticoagulation regimens was set as a pre-specified exploratory outcome during the design of INSPIRATION trial. Also, the interval change in functional limitation and depressive symptoms between 30-day and 90-day post-randomization periods were assessed in the pooled cohort of patients. As explained before, patients with PCFS Grade 0, 1–2 and PCFS 3–4 were defined as no, minimal to mild, and moderate to severe functional limitation, respectively. Death before each interval was classified as PCFS Garde 5. In addition, patients screened with PHQ-2 ≥ 3, have higher odds of depressive symptoms. For 30-day and 90-day assessment of functional outcomes and depression screening, the day of randomization (while the patients were still in the ICU) was considered as day 1.

2.5. Statistical analysis

Data were described as median (interquartile range) for interval variables and frequency (percentage) for categorical variables.

As described previously, it was pre-specified to exclude a treatment effect for short-term intermediate-dose versus standard-dose prophylactic anticoagulation with respect to the 90-day functional and mood outcomes and to proceed with analyses for interval changes in functional and mood outcomes, from 30-day to 90-day follow-up in the pooled cohort. The treatment effects were subsequently analyzed in detail in exploratory analyses.

For comparisons of 90-day functional status and depressive symptoms between patients assigned to intermediate-dose and standard-dose prophylactic anticoagulation, a Mann Whitney U test was used for PCFS, followed by a mixed effects ordinal logistic regression model with random intercepts for centers resulting in odds ratios (ORs) and corresponding confidence interval (CIs). These ORs show the odds of ending up in a higher PCFS category under treatment. For comparison of PHQ-2 at 90-day follow-up between the anticoagulation strategies, a Pearson's chi square test (for PHQ-2 ≥ 3) was performed, followed by mixed effects logistic regression model with random intercept for centers.

Comparison of the changes in functional status and depressive symptoms (i.e., the proportion of patients with PCSF grade 3-or-4 and PHQ-2 ≥ 3, respectively) between the first and third months after the enrollment were performed with McNemar's test. Of note, patients who were enrolled after August 28, 2020 and died before completion of 30-day follow up were classified as PCFS grade 5 (death) and consequently included in the functional status analysis in order to prevent survival bias. In contrast, as stated earlier, for completion of PHQ-2, direct patient participation was required. Therefore, this analysis was performed in patients who survived to 90-day follow-up. Of note, only 4 patients died between days 31 and 90, thereby having little impact on the cohort being studied. A two-sided P-value < 0.05 was considered as statistically significant. No adjustment for multiplicity of comparison was pre-specified. Stata for MacOS (Stata Corp. 2013. *Stata Statistical Software: Release 13*. College Station, TX) was used for statistical analysis.

3. Results

Of 600 randomized patients, 478 were enrolled after initiation of the functional status study and were eligible for 90-day functional status analysis. Overall, 103 patients did not agree to participate. Therefore, 375 patients (median age, 62 years; 42% women) are included in the present analysis (Fig. 1). Baseline characteristics are summarized in Table 1. Considering the lack of the treatment effect between the two trial arms ($P = 0.80$ for PCFS and $P = 0.14$ for PHQ-2), the changes in functional status and depressive symptoms between 30-day and 90-day follow up are reported in the pooled cohort.

Of patients included in the study, 191/375 (50.9%) died during the 30-day follow-up (PCFS grade 5) and 168/375 (44.8%) patients reported any functional limitation (PCFS grade 1–4), including 75/375 (20.0%) who reported grade 3-or-4 limitation. Only 16/375 (4.2%) surviving patients did not report any functional limitations at 30-day follow-up. By 90-day follow up, a total of 195/375 (52.0%) patients died (four new deaths between days 31–90, all among patients with a 30-day PCFS grade 4) and 122/375 (32.5%) suffered from functional limitation (PCFS grades 1–4), of whom 18/375 (4.8%) had 90-day PCFS grade 3-or-4 limitations. Therefore, there was a decrease in the proportion of patients with PCSF grades 3-or-4 between the 30-day and 90-day follow ups (20.0% versus 4.8%, $P<0.001$). The PCFS changes between the two-time points is depicted in Fig. 2A. In addition, the proportion of patients with no functional limitations (PCFS grade 0) was improved from 16/375 (4.2%) to 58/375 (15.4%) ($P<0.001$).

A *post-hoc* multivariable analysis among 165 patients who survived to hospital discharged showed that only prolonged stay in the ICU (>7 days) was associated with increased odds of severe functional limitation

Table 1
Baseline characteristics between the two anticoagulation regimens and study population[a].

	Intermediate-dose prophylactic anticoagulation(n = 187)	Standard-dose prophylactic anticoagulation(n = 188)	Total participating patients (n = 375)
Age— years	63 (53 – 72)	62 (46 – 70.7)	62 (50 – 71)
Sex			
Women — no. (%)			159 (42.4)
	80 (42.8)	79 (42.0)	
Men — no. (%)			216 (57.6)
	107 (57.2)	109 (58.0)	
Body, mass index[b] —- kg/m^2	26.7 (24.4 – 29.6)	27.3 (25.2 – 30.4)	27 (24.7 – 30)
Current smokers— no. (%)	20 (10.7)	13 (6.9)	33 (8.8)
Coexisting Conditions— no. (%)			
Hypertension	91 (48.9)	72 (38.5)	163 (43.7)
Diabetes	53 (28.3)	46 (24.5)	99 (26.4)
Hyperlipidemia	49 (26.2)	44 (23.4)	93 (24.8)
Coronary artery disease	32 (17.1)	17 (9.0)	49 (13.1)
Obstructive airway disease	15 (8.0)	11 (5.9)	26 (6.9)
Ischemic cerebrovascular accidents	4 (2.1)	8 (4.3)	12 (3.2)
Heart failure	4 (2.1)	4 (2.1)	8 (2.1)
Hemorrhagic stroke	0	0	0
Duration of symptoms prior to hospitalization— days	7 (4 – 8)	7 (5 – 10)	5 (7 – 9)
Duration of hospitalization before randomization — days	4 (3 – 6)	4 (3 – 6)	4 (3 – 6)
Baseline Indicators of Illness Severity			
Vasopressor agent support within 72-hour of enrollment— no. (%)	6 (3.3)	8 (4.3)	14 (3.8)
Acute Physiology and Chronic Health Evaluation II at the time of randomization[c]	8 (5 – 11)	8 (5 – 10)	8 (5 – 11)
Acute respiratory support— no. (%)			
Nasal cannula	7 (3.8)	12 (6.5)	19 (5.1)
Face mask	18 (9.8)	12 (6.5)	30 (8.1)
Reservoir mask	57 (31.0)	57 (30.6)	114 (30.8)
High flow nasal cannula	6 (3.3)	4 (2.2)	10 (2.7)
Non-invasive positive pressure ventilation	63 (34.2)	60 (32.3)	123 (33.2)
Invasive positive pressure ventilation (endotracheal intubation)	36 (19.3)	42 (22.3)	78 (20.8)
Drug history — no. (%)			
Baseline medication			
Aspirin	64 (34.2)	48 (25.5)	112 (29.9)
Co-treatment			
Antiviral therapy	157 (84.0)	145 (77.1)	302 (80.5)
Corticosteroid use	177 (94.7)	173 (92)	350 (93.3)
Renin–angiotensin–aldosterone system inhibitors	54 (28.9)	44 (23.4)	98 (26.1)
Median laboratory values at baseline			
Creatinine— mg/dl	1.1 (0.9 – 1.3)	1 (0.9 – 1.2)	1.08 (0.9 – 1.25)
White blood cells count—cells/mm^3	10,100 (6900 – 13,900)	10,350 (7, 647 – 13,090)	10,300 (7400 – 13,500)
Hemoglobin level—g/dL	13.2 (11.9 – 14.7)	13.5 (11.9 – 14.5)	13.3 (11.9 – 14.6)
Platelet count—10^3/fL	241 (176 – 302)	228.5 (173 – 298.7)	230 (173 – 301)
D-dimer level—ng/ml	950 (397 – 2601.5)	840 (320 – 1622)	860 (359 – 2086.5)
Prothrombin time—seconds	13.9 (12.7 – 15)	13.6 (12.5 – 15)	13.7 (12.6 – 15)
International normalized ratio	1.1 (1.01 – 1.2)	1.1 (1 – 1.2)	1.1 (1 – 1.2)
Activated partial thromboplastin time—seconds	32 (28 – 38)	30.9 (27 – 35.7)	31 (27.7 – 36)

[a] All data are median (Q1,Q3) unless stated otherwise.
[b] The body-mass index is the weight in kilograms divided by the square of the height in meter.
[c] Acute Physiology and Chronic Health Evaluation II is an index for the severity of the disease, and range from 0 to 71, and compose of three components: Acute Physiology Score, age, and chronic health status. Higher score indicates poorer outcome.

(PCFS Grade ≥3). Also, among 180 patients who completed both the 30-day and 90-day PHQ-2 questionnaires, female sex was associated with a higher odds of depressive symptoms (PHQ-2 ≥ 3) at three-month. Our *post-hoc* multivariable analysis among 168 patients with at least minimum of functional limitation (PCFS Grade 1–4) at 30-day, showed that younger age at the time of enrollment was a predictor of functional limitation recovery at 90-day. Also, the *post-hoc* multivariable analysis among 47 patients with high odds of depressive symptoms (PHQ-2 ≥ 3) at the first-month, was unable to find any predictors for depressive symptoms improvement at third-month evaluation (Supplement).

The median PHQ-2 total score was 2 (IQR, 0–3) at 30-day follow-up. It declined to 0 (IQR, 0–2) at 90-day follow-up (P<0.001). The proportion of patients with PHQ-2 ≥ 3, decreased from 47/180 (26.1%) patients at 30-day to 30/180 (16.6%) patients at 90-day follow up (P = 0.05) (Fig. 2B).

The treatment effect for intermediate-dose versus standard-dose prophylactic anticoagulation was evaluated at the 90-day follow up; a total of 187 and 188 patients were assigned in the intermediate-dose and standard-dose anticoagulation regimens, respectively, of whom 98 (intermediate-dose group) and 97 (standard-dose group) patients died (i.e., PCFS grade 5). PCFS grading did not show a difference between the two anticoagulation regimens, at 90-day follow-up, with a median PCFS grade of 0–3 (IQR,1–5) in both groups (P = 0.90) (Fig. 3A). In addition, the proportion of patients with PCSF grade 3-or-4 was not different between the two study groups (10/187 (5.3%) versus 8/188 (4.2%); OR_{binary}, 1.20, [95% CI, 0.46 to 3.11], P = 0.80). In the mixed effects ordinal regression model with random intercept for centers, there was no association between the assigned anticoagulation regimen and PCFS grading at 90-day follow-up ($OR_{ordinal}$, 1.07, [95% CI, 0.75 to 1.53], P = 0.68).

Assessment of the treatment effect on depressive symptoms in the two study groups indicted that the proportion of patients with 90-day PHQ-2 score ≥ 3 was not different in those assigned to intermediate-dose versus standard-dose prophylactic anticoagulation (16/89

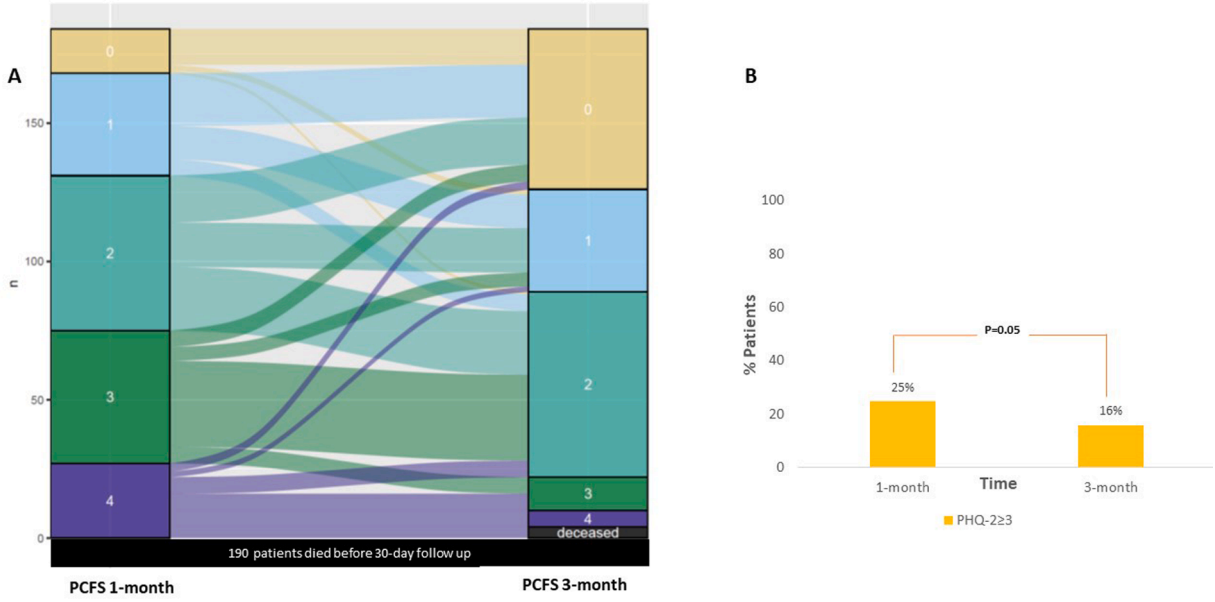

Fig. 2. PCFS and PHQ-2 changes in 1-and 3-month follow up. *Panel A.* Perceived change in PCFS at 1- and 3-month intervals (Sankey plot). Notably, only four patients (all categorized by PCFS grade 4 at Day 30) died between days 31 and 90. The proportion of patients with severe functional limitation decreased over time. The proportion of patients with severe functional limitation (PCFS grade 3-or-4) decreased by 3-month follow-up. *Panel B,* the proportion of patients with PHQ-2 $\geq$ 3 decreased over time. PCFS denotes for Post-COVID-19 functional scale, PHQ-2, Patient Health Questionnaire-2.

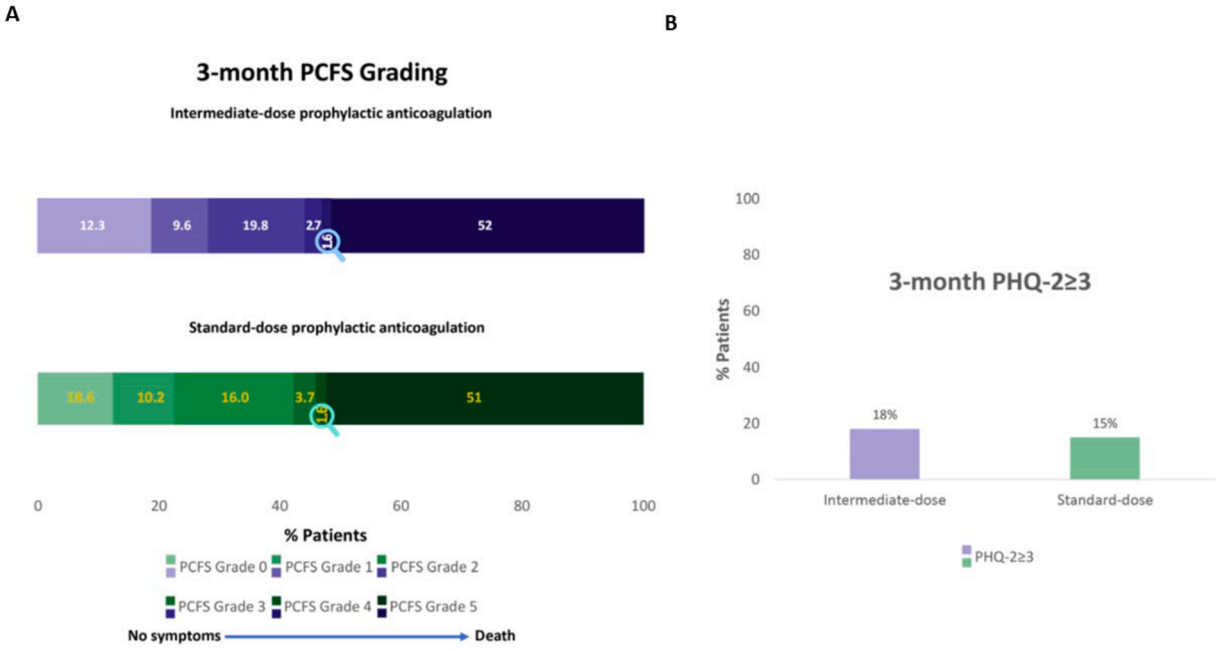

Fig. 3. Three-month PCFS Grading (Panel A) and proportion of patients PHQ-2 $\geq$ 3 (Panel B) between the two anticoagulation regimens (Intermediate-dose versus standard-dose prophylactic anticoagulation). PCFS grading classified patients from 0 (no functional limitations) to 4 (severe functional limitations) and 5 (death). PHQ-2 $\geq$ 3 shows higher odds of major depressive disorder. PCFS denotes for Post-COVID-19 functional scale, PHQ-2, Patient Health Questionnaire-2.

[17.9%] versus 14 /91 [15.3%]; OR_{binary}, 1.14, [95% CI, 0.79 to 1.65], $P = 0.14$) (Fig. 3B). In the mixed effect logistic regression model with random intercept for centers, there was no significant association between the assigned anticoagulant regimen and PHQ-2 $\geq$ 3 at 90-day follow-up (OR_{binary}, 0.74, 95% CI: 0.36 to 1.53, $P = 0.42$).

4. Discussion

In this analysis from the INSPIRATION trial, we noted that fewer than half of the patients with COVID-19 admitted to the ICU died by 30-day follow-up and one in five of the survivors had severe functional limitations (PCFS grade 3-or-4) at 30-day follow up. In addition, nearly 5% had persistent severe functional limitation by 90-day follow-up.

Only a small but increasing minority became completely free from functional limitations during follow-up. The severity of depressive symptoms decreased over the 3-month study period. However, one sixth of the patients had a positive depression screen at the 90-day follow up, suggesting a high probability of major depression. Importantly, intermediate-dose versus standard-dose prophylactic anticoagulation did not impact the functional limitations. These results, along with findings from other analyses from short-term clinical outcomes [15,19,20], do not support the use of intermediate-dose prophylactic anticoagulation in patients with COVID-19 admitted to the ICU.

SARS-CoV-2 entrance into endothelial cells of brain vasculature through angiotensin-converting enzyme 2 receptors can lead to inflammation, thrombin production, promoting microthrombi deposition. Furthermore, systemic inflammation results in decreased monoamines and trophic factors and activation of microglia, leading to an increase in the glutamate, N-methyl-D-aspartate and excitotoxicity. These changes can cause new-onset or exacerbation of preexisting neuropsychiatric problems including depression and functional limitation [21,22]. This study complements the findings about functional recovery in COVID-19 from prior investigations. A large national survey on 508,707 participants in the community in England, reported a weighted prevalence of chronic symptoms of 5.75% (5.68, 5.81) for one and 2.22% (2.1, 2.26) for three or more symptoms [23]. In nearly one-third of participants with at least one persistent symptom, the post-COVID manifestations have severely impaired their daily life. Taboada et al. in a prospective observational study of 91 patients with COVID-19 discharged from ICU, reported a 63% decrease in quality of life (assessed by EuroQol Group Association five-domain, three-level questionnaire) at 6-month follow up, compared to pre-COVID-19 involvement [24]. To our knowledge, no studies evaluating the post-COVID-19 functional limitation based on PCFS in critically-ill population have been published, yet.

Although PCFS captures some elements about anxiety and depression, in this study we opted for ad-hoc data collection on depression screening using PHQ-2, as well. In a recent study of 73 mechanically-ventilated patients due to severe respiratory failure with COVID-19, Olanipekun et al. reported that 44% of survivors screened positive for a probable major depression disorder at 90-day follow up based on PHQ-2 questionnaire. We have reported a lower incidence of patients with high likelihood of severe depression in this study (16.6%). These differences should be assessed as additional evidence accrues from ongoing studies [15].

Limited evidence exists about potential predictors for persistent functional limitation and depressive symptoms and factors leading to their improvement. Our post-hoc analysis showed that prolonged ICU stay (>7 days) was associated with increased odds for severe functional limitation at three-month follow up and, and younger age as a predictor of improvement in functional status over time. Also, female sex was associated with higher odds of depressive symptoms at three-month evaluation, although no statistically meaningful predictors were found for depressive symptoms improvement over time. It should be considered, however, that our analyses were post-hoc and not powered for the above purposes. Other studies, albeit small, have suggested advanced age, male sex, need for mechanical ventilation, duration of mechanical ventilation and length of ICU stay as potential predictors for persistent impaired quality of life in patients with COVID-19 [24]. Of note, pre-COVID-19 experience showed weak correlations between quality of care during ICU stay and quality of life impairment in *ARDS survivors* [25].

This study has several strengths. PCFS and PHQ-2 questionnaires were completed prospectively and through structured telephone interview on a considerable sample of consecutively enrolled patients, which minimize the recall bias compared with online surveys. Both questionnaires were evaluated in 2 time intervals, which allowed for the assessment of the change in functional and depressive symptoms over time. Finally, being built on the background of a randomized trial, we had the opportunity to evaluate the effect of escalated-dose versus standard-dose anticoagulation on functional status measures.

5. Limitations

The study has several limitations. First, 103 patients did not agree to participate in the present survey. Their objection might relate to their limited functional status, mental health or cognitive status, and might influence the final results [26]. However, the baseline characteristics between the participating (375 patients) and non-participating (103 patients) population were balanced, which decreases the risk of selection bias (e-Table 1). It is not feasible to engage patients without consent in prospective research studies. Future large-scale routine care studies based on electronic records, with appropriate institutional review board approval, can share complementary information about the external validity of our findings. Second, many of the study participants were enrolled during the earlier months of the pandemic. As effective therapies and experience of health systems for management of COVID-19 lead into lower mortality rates over time, it is possible that a larger proportion of survivors experience some form of durable functional impairment. Third, the pre-COVID-19 functional and mood status in the INSPIRATION participants was unknown and therefore comparison with pre-COVID-19 levels is not possible. Some inferences can be made from general data from Iran, which indicate that 0.3% and 2.1% of the general population complained about the severe functional limitation and severe anxiety/depressed mood, respectively [27]. Finally, since follow up interviews were telephonic, application of more detailed questionnaires such as PHQ-9 for confirmation of major depression were not feasible and warrant attention in future studies.

In conclusion, disturbed functional status is a common feature at 30-day follow-up after ICU admission with COVID-19, with a minority having severe persistent functional limitations even at 3-month follow-up. Severity of depressive symptoms among survivors decreased over time. However, a considerable number of patients expressed depressive symptoms even at 3-month follow-up. Intermediate-dose compared with standard-dose prophylactic anticoagulation did not impact the 3-month functional status or depressive symptoms. Larger studies are needed to understand the predictors of functional and mental impairment. Identification of valid predictors would help the design of RCTs which intended to test different therapeutic strategies (from non-pharmacological interventions such as rehabilitation program or building resilience and coping behaviors to pharmacotherapy) for quality-of-life and mental health improvement of patients with COVID-19 after hospital discharge. Considering the current knowledge gap, individualized approach should be ponder based on available resources and patients' compliance

Ethical statement

Participating patients or their healthcare proxies provided written informed consent for participation. The ethics committee at the Rajaie Cardiovascular Medical and Research Center approved the study protocol, which was accepted by all other study sites.

Funding

This study was funded by the Rajaie Cardiovascular Medical and Research Center.

Financial/nonfinancial disclosures

Dr. Barco reports institutional grants from Boston Scientific, Sanofi, Concept Medical, and Bard; personal fee from Bayer and Boston Scientific; non-financial support from Daiichi Sankyo. Dr. Jimenez has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo

Pharma, Pfizer, ROVI and Sanofi; served as a speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, ROVI and Sanofi; received grants for clinical research from Daiichi Sankyo, Sanofi and ROVI. Dr. Piazza has received research grant support to Brigham and Women's Hospital from EKOS, a BTG International Group company, Bayer, the Bristol Myers Squibb/Pfizer Alliance, Portola, and Janssen. He has received consulting fees from Amgen, Pfizer, Boston Scientific Corporation and Thrombolex. Dr Parikh reported receiving grants from Abbott Vascular, Boston Scientific, Surmodics, and TriReme Medical; nonfinancial support from Cordis, Medtronic, Philips, and Cardiovascular Systems Inc; and personal fees from Terumo, Abiomed, Inari, and Penumbra outside the submitted work. Dr Kirtane reported receiving institutional funding to Columbia University and/or the Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, Cardiovascular Systems Inc, CathWorks, Siemens, Philips, and ReCor Medical, including fees paid to Columbia University and/or the Cardiovascular Research Foundation for speaking engagements and/or consulting; consulting fees from Neurotronic; and travel expenses/meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, Cardiovascular Systems Inc, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr. Van Tassell has received research support from Novartis, Swedish Orphan Biovitrum, Olatec Therapeutics, and Serpin Pharma and has been a consultant for R-Pharm and Serpin Pharma. Dr. Lip reports consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Dr. Goldhaber has received research support from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Boston Scientific, Daiichi-Sankyo, Janssen, the National Heart, Lung, and Blood Institute, and the Thrombosis Research Institute; and has received consulting fees from Bayer, Agile, Boston Scientific, and Boehringer Ingelheim. FK reports research grants from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, MSD, The Netherlands organisation for Health Research and Development, Actelion, the Dutch Heart foundation and the Dutch Thrombosis association, all outside the submitted work. Dr Krumholz reported receiving personal fees from UnitedHealth, IBM Watson Health, Element Science, Aetna, Facebook, Siegfried & Jensen Law Firm, Arnold & Porter Law Firm, Martin/Baughman Law Firm, F-Prime, and the National Center for Cardiovascular Diseases, Beijing; being the cofounder of HugoHealth, a personal health information platform, and Refactor Health, an enterprise health care artificial intelligence–augmented data management company; receiving contracts from the Centers for Medicare & Medicaid Services, through Yale New Haven Hospital, to develop and maintain measures of hospital performance; and receiving grants from Medtronic, the US Food and Drug Administration, Johnson & Johnson, and the Shenzhen Center for Health Information outside the submitted work. Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. All other authors have no disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.06.014.

Appendix

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References

[1] Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med 2021:1–15.

[2] Shah R, Ali FM, Nixon SJ, Ingram JR, Salek SM, Finlay AY. Measuring the impact of COVID-19 on the quality of life of the survivors, partners and family members: a cross-sectional international online survey. BMJ Open 2021;11:e047680.

[3] Vaes AW, Goërtz YMJ, Van Herck M, et al. Recovery from COVID-19: a sprint or marathon? 6-month follow-up data from online long COVID-19 support group members. ERJ Open Res 2021;7.
[4] Klok FA, Boon GJ, Barco 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.
[5] Machado FV, Meys R, Delbressine JM, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. Health Qual Outcomes 2021;19:1–10.
[6] Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2021;174:576–8.
[7] Perlis RH, Ognyanova K, Santillana M, et al. Association of acute symptoms of COVID-19 and symptoms of depression in adults. JAMA Netw Open 2021;4. e213223-e213223.
[8] Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324:603–5.
[9] Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:2950–73.
[10] Hashemi A, Madhavan MV, Bikdeli B. Pharmacotherapy for prevention and management of thrombosis in COVID-19. Semin Thromb Hemost 2020;46:789–95.
[11] Favaloro EJ, Lippi G. Maintaining hemostasis and preventing thrombosis in coronavirus disease 2019 (COVID-19)-part III. Semin Thromb Hemost 2022;48:3–7.
[12] Poredos P, Poredos P. Involvement of inflammation in venous thromboembolic disease: an update in the age of COVID-19. Semin Thromb Hemost 2022;48:93–9.
[13] Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate vs standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to ICU: ninety-day results from the INSPIRATION trial. Thromb Haemost 2021.
[14] Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: rationale and design of the INSPIRATION/INSPIRATION-S studies. Thromb Res 2020;196:382–94.
[15] Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the inspiration randomized clinical trial. JAMA 2021;325:1620–30.
[16] Ghazisaeedi M, Mahmoodi H, Arpaci I, Mehrdar S, Validity Barzegari S. Reliability, and optimal cut-off scores of the WHO-5, PHQ-9, and PHQ-2 to screen depression among university students in Iran. Int J Ment Health Addict 2021:1–10.
[17] Barzilay R, Moore TM, Greenberg DM, et al. Resilience, COVID-19-related stress, anxiety and depression during the pandemic in a large population enriched for healthcare providers. Transl Psychiatry 2020;10:291.
[18] Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003;41:1284–92.
[19] Moores LK, Tritschler T, Brosnahan S, et al. Thromboprophylaxis in patients with COVID-19. A brief update to the chest guideline and expert panel report. Chest 2022.
[20] Perepu US, Chambers I, Wahab A, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomized controlled trial. J Thromb Haemost 2021;19:2225–34.
[21] Boldrini M, Canoll PD, Klein RS. How COVID-19 affects the brain. JAMA Psychiatry 2021;78:682–3.
[22] Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain 2021;144:3576–88.
[23] Whitaker M., Elliott J., Chadeau-Hyam M. et al. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people.
[24] Taboada M, Moreno E, Cariñena A, et al. Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. Br J Anaesth 2021;126:e110–3.
[25] Apfelbacher C, Brandstetter S, Blecha S, et al. Influence of quality of intensive care on quality of life/return to work in survivors of the acute respiratory distress syndrome: prospective observational patient cohort study (DACAPO). BMC Public Health 2020;20:861.
[26] Brintnall-Karabelas J, Sung S, Cadman ME, Squires C, Whorton K, Pao M. Improving recruitment in clinical trials: why eligible participants decline. J Empir Res Hum Res Ethics 2011;6:69–74.
[27] Emrani Z, Akbari Sari A, Zeraati H, Olyaeemanesh A, Daroudi R. Health-related quality of life measured using the EQ-5D-5 L: population norms for the capital of Iran. Health Qual Life Outcomes 2020;18:108.