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Original Research

The impact of healthcare setting on post-COVID mood disorders: a single-centre perspective from Southern Italy Respiratory Intensive Care Unit

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ABSTRACT

Background and objectives: Post-COVID syndrome includes several clinical identities, with both physical and mental alterations lasting several months from the acute phase of COVID-19 disease. However, to date, data concerning the relationship between healthcare settings during COVID-19 disease and post-COVID mood disorders are lacking.

Methods: We performed a prospective study enrolling 440 patients with post-COVID syndrome. Each patient underwent a complete clinical evaluation, along with blood and functional tests. Patients were divided according to the healthcare setting needed during COVID-19 disease.

Results: Patients admitted to RICU were more prone to develop mental alterations, even when compared to ICU-admitted patients. Other risk factors for mood disorders included female gender and some post-COVID symptoms.

Conclusions: Healthcare needs during COVID-19 can explain the higher incidence of mood disorders in post-COVID syndrome. RICU arises as an important but underexplored risk factor for post-COVID psychic sequelae.

1. Introduction

Patients who manage to recover from COVID-19 acute phase could experience several consequences defined with the term "Post-COVID-19 syndrome". This syndrome is characterized by the persistence of signs and symptoms after 4–12 weeks from the Severe Acute Respiratory Syndrome-COronaVirus 2 (SARS-CoV-2) infection and could affect many aspects of physical and mental health [1].

Literature provided evidence suggesting that Post-COVID-19 syndrome has several manifestation regardless the onset of the acute disease [2], although few studies defined the association between COVID-19 severity and Post-COVID symptoms. Moreover, data concerning the relationship between COVID-19 healthcare setting and the risk of post-COVID long-term consequences are still scanty. To date, the best described clinical scenario related to a specific healthcare setting is the Post Intensive Care Syndrome (PICS) [3,4]. In this term are embedded several aspects of physical, cognitive and mental health impairment, affecting ICU-treated patients for months after the discharge [3]. COVID-19 has worsened some of these conditions, resulting in a higher prevalence of PICS in COVID-19 survivors admitted in Intensive Care

Abbreviations: COVID-19, COronaVIrus Disease 19; SARS-COV2, Severe Acute Respiratory Syndrome-COronaVirus 2; PICS, Post Intensive Care Syndrome; ICU, Intensive Care Unit; RICU, Respiratory Intensive Care Units; ABG, Arterial Blood Gas analysis; 6MWT, 6 Minute Walking Test; RT-PCR, Real Time-Polymerase Chain Reaction; DLCO, Diffusing Capacity of Carbon Oxide; HRCT, High Resolution Computed Tomography; NPS, Naso-Pharyngeal Swab; ROC, Receiver Operating Characteristic; LMWH, Low Molecular Weight Heparin; HFNC, High Flow Nasal Cannula; NIV, Non-Invasive Ventilation; AIFA, Associazione Italiana del Farmaco; GW, General Ward; GGO, Ground Glass Opacities.

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Unit (ICU) [5]. Despite these data seem to suggest a strong connection between some long term COVID-19 symptoms and intensive healthcare settings, the impact of Respiratory Intensive Care Units (RICU) on post COVID-syndrome has not been established. In particular, it is still unknown whether RICU admission can be considered a real risk factor for the arise of mental alterations or mood disorders.

The aim of the study was to explore the relationships between RICU and long term COVID-19 symptoms, focusing on the risk of developing mood disorders according to healthcare setting of COVID-19 disease.

2. Material and methods

2.1. Study population

In our single-centre study, we enrolled a cohort of 440 consecutive patients attending our outpatient clinic in "Policlinico" University Hospital of Bari, Italy, for the Post-COVID follow-up visit June 2021 to April 2022. For each enrolled patient, we gathered anthropometric and anamnestic data, focusing on healthcare setting needed to overcome COVID-19 disease. Then, during each visit, several post-COVID signs and symptoms were investigated, considering each of them as a binary output (see Supplemental Material). As regard mood disorders, we asked our patients the following questions:

- *"Have you experienced a change in your mood after the acute phase of COVID-19 disease?*
- *"Have you experienced an increased anxiety, stress or depression after COVID-19 disease?"*

If the answer of at least one of these two question was "Yes", data was registered as "1" in our database, otherwise as "0".

For patients with a previous history of psychiatric disease we use the question:

- *"Have you experienced a worsening in your psychiatric disease after COVID-19 disease?"*
- *"Did you need a psychiatric consult after COVID-19 disease to overcome the burden of post-COVID mood disorders?"*

If the answer of at least one of these two question was "Yes", data was registered as "1" in our database, otherwise as "0".

Then, each patient was tested for the most common biomarkers for the assessment residual inflammation or organ/tissue damage related to COVID-19 disease [6–8]. Visits also included Arterial Blood Gas analysis (ABG) and a 6 Minute Walking Test (6MWT). For patients with a negative SARS-CoV-2 Real Time-Polymerase Chain Reaction (RT-PCR) after at least 3 months from the infection, we also performed a body plethysmography with Diffusing Capacity of Carbon Oxide (DLCO), following national recommendations on safe lung functional tests during COVID-19 pandemic [9]. Finally, according to clinical judgement, respiratory physicians could demand chest High Resolution Computed Tomography (HRCT), in order to explore any potential residual lung damage. During the enrolment, only eight patients were excluded from the study due to the lack of precise information concerning COVID-19 healthcare setting.

The study was approved by the Institutional Ethics Committee (Ethical Committee number: 6717) and was conducted following the Helsinki Declaration of 1975 and the Good Clinical Practice standards. Patients signed written informed consent before the enrollment.

2.2. Statistical analysis

After assessing non-normal data distribution with Shapiro-Wilk test, we described quantitative variables as medians and confidence intervals, performing Mann-Whitney-U or Kruskal-Wallis test for comparison. Frequency distribution analysis was performed with Chi^2 or Fisher exact test. To assess cumulative risk for mood alterations, we performed Log-Rank test and Kaplan-Meier curves, considering "mood disorders" as a binary output and "days from negative Naso-Pharyngeal Swab (NPS) to visit" as the time variable. Then, we built up two Cox multivariate backward regression models (removal rule: $P > 0.1$), correcting the association between RICU admission and mood disorders development for all the most relevant anamnestic, anthropometric and clinical covariates. The first regression model was designed considering the overall population, while the second one excluded patients with a previous diagnosis of psychiatric disease, in order to avoid any possible confounding factor related to patients' past medical history. As covariates for the model, we considered the following elements: age, gender, admission ward [divided as "Home care", "General Ward (GW)", "RICU", "Intensive Care Unit (ICU)], respiratory support used during COVID-19 disease [divided as "No support", "Oxygen", "Non-Invasive Ventilation (NIV)", "Invasive Mechanical Ventilation (IMV)], post-COVID dyspnea, fatigue, cough, anosmia, ageusia, headache, muscle pain, memory loss, insomnia, Telogen Effluvium, days from first positive SARS-COV2 NPS to second consecutive negative test. These elements were chosen according to previous studies in literature [10,11].

Further details on statistical analysis are available in Supplemental Materials. Finally, we assessed the robustness of our regression models with Receiver Operating Characteristic (ROC) curves. Statistical analysis were performed using SPSS 26.0 (SPSS Inc, Chicago, Ill), considering a P value < 0.05 as statistically significant.

3. Results

3.1. Population analysis

Among the enrolled patients (see eTable 1), median age was 58 years, with a light tendency to male gender distribution (56.8% males vs 43.2 females). Every patient had a median of 2 previously diagnosed diseases, with a higher rate of arterial hypertension (42%), dyslipidemia (21.6%), thyroid dysfunction (14.8%) and type 2 diabetes mellitus (11.6%).

Median time for the first negative SARS-COV2 NPS was 23 days. On the other hand, 7% of our patients experienced a SARS-COV2 re-infection, with a significant shorter time needed for a complete NPS negativization compared to the first infectious episode (23 vs 10 days, $P < 0.0001$).

The vast majority of our population (98.6%) experienced symptoms during the acute phase of COVID-19 disease, such as fever (79.8%), fatigue (45.2%), cough (50%), dyspnea (56.1%), diarrhea (15.9%), ageusia (35%), anosmia (36.4%) and headache (23.9%). Therefore, half of them received home treatment with oral corticosteroids, while 58.2% were prescribed with antibiotics and 17.9% with Low Molecular Weight Heparin (LMWH). Finally, for patients with acute respiratory failure who cannot access to hospitals due to bed shortages, physicians prescribed liquid oxygen (17.9%).

As regard radiological exams, 52% of the studied patients performed a Chest X-ray or CT scan during COVID-19 disease. Among them, 76.8% showed a bilateral pneumonia, while pneumothorax (1.3%), pulmonary embolism (3.9%) and pleural effusions (3.5%) were less frequent.

Among our 440 enrolled patients, 195 received home care during COVID-19 disease, while 245 were hospitalized due to a rapid clinical deterioration. After hospital admission, 33.5% of patients needed liquid oxygen only, while 6.1% were shifted to High Flow Nasal Cannula (HFNC) due to the worsening of their clinical condition. When respiratory failure became too intense to be treated with oxygen only, Non-Invasive Ventilation (NIV) was administered (37.9%), while a minor part of these patients needed orotracheal intubation (13.1%) or tracheostomy (11.7%). Finally, iv treatments used during COVID-19 disease included frequently corticosteroids (93.5%), antibiotics (91.4%) and LMWH (89%). On the contrary, convalescent plasma (6.1%) and Remdesivir (10%) were administered only in specific cases, according to

Table 1
Post COVID clinical and radiological features according to setting of care.

	Home care	GW[b]	RICU[c]	ICU[d]	P Value
Total patients (n)	195	104	77	64	
Age (Years, Median, IQR[a])	56 [48–64]	60.5 [55–71]	62 [56–68]	55 [49–61]	<0.0001
Number of Comorbidity (Median, IQR)	2 [1–3]	3 [1–4]	2 [1–3.5]	2 [1–3]	0.005
Days from negative NPS[e] to visit (Days, Median, IQR)	163 [113–234]	153 [87–243]	85 [48–146.5]	95.5 [55–173]	<0.0001
Days from positive to negative NPS (Days, Median, IQR)	20 [15–28]	25 [17–30]	27 [18.5–37]	28 [21–35]	<0.0001
COVID-19 vaccination status (n, %)					
• Pre-disease vaccination	15 (7.7)	9 (8.6)	11 (14.3)	5 (7.8)	
1 dose	7 (46.6)	5 (55.6)	3 (27.3)	3 (60)	
2 doses	4 (26.6)	4 (44.4)	7 (63.6)	2 (40)	
3 doses	4 (26.6)	0	1 (9.1)	0	
Long COVID symptoms (n, %)					
Dyspnea	97 (49.7)	53 (51)	45 (58.4)	34 (53.1)	
Fatigue	48 (24.6)	42 (40.3)	27 (35.1)	24 (37.5)	0.002
Cough	19 (9.7)	13 (12.5)	5 (6.5)	8 (12.5)	
Anosmia	5 (2.5)	1 (1)	4 (5.2)	3 (4.7)	
Ageusia	4 (2.1)	4 (3.8)	6 (7.8)	1 (1.6)	
Headache	13 (6.7)	5 (4.8)	6 (7.8)	5 (7.8)	
Muscle pain	21 (10.8)	17 (16.3)	17 (22.1)	10 (15.6)	0.03
Mood disorders	13 (6.7)	13 (12.5)	15 (19.5)	4 (6.2)	0.02
Memory Loss	19 (9.7)	6 (5.8)	10 (13)	6 (9.4)	
Insomnia	14 (7.1)	20 (19.2)	11 (14.3)	6 (9.4)	0.01
Telogen Effluvium	5 (2.6)	2 (1.9)	6 (7.8)	5 (7.8)	
Long COVID Chest CT (n, %)	48 (24.6)	56 (53.8)	42 (54.5)	36 (56.2)	<0.0001
Pneumothorax	0	0	0	1 (2.8)	
GGO[f]	15 (31.3)	28 (50)	27 (64.3)	15 (41.7)	<0.0001
Residual consolidation	3 (6.3)	3 (5.4)	4 (9.5)	5 (13.9)	
Septal thickening	3 (6.3)	10 (17.9)	7 (16.7)	6 (16.7)	
Lung scars	13 (27.1)	19 (33.9)	13 (31)	13 (36.1)	
Bronchiectasis	3 (6.3)	4 (7.1)	4 (9.5)	3 (8.3)	
Mosaic attenuation pattern	2 (4.1)	2 (3.6)	1 (2.4)	2 (5.5)	
Centrilobular nodules	10 (20.8)	3 (5.4)	2 (4.8)	1 (2.8)	0.001
"Tree-in-bud"	0	0	0	0	
Honeycombing	0	1 (1.9)	1 (2.4)	1 (2.8)	
Chest CT time from discharge (Months, Median, IQR)	6 [3–6]	6 [3–6]	3 [3–6]	3 [3–5.2]	0.0015
Treatment at discharge (n, %)					
Oral corticosteroids	6 (3.1)	1 (1)	7 (9.1)	1 (1.6)	0.002
Supplemental Oxygen	1 (0.5)	3 (2.9)	4 (5.2)	2 (3.1)	
Vitamin D	1 (0.5)	4 (3.8)	7 (9.2)	1 (1.6)	0.003
Oral multivitamins	14 (7.1)	12 (11.5)	8 (10.4)	5 (7.8)	
N-Acetilcysteine	0	2 (1.9)	1 (1.3)	2 (3.1)	
Antibiotic	0	0	0	0	
Respiratory Training	1 (0.5)	1 (1)	2 (2.6)	7 (10.9)	<0.0001

[a] IQR, InterQuartile Range.
[b] GW, General Ward.
[c] RICU, Respiratory Intensive Care Unit.
[d] ICU, Intensive Care Unit.
[e] NPS: NasoPharyngeal Swab.
[f] GGO, Ground Glass Opacity.

national Associazione Italiana del Farmaco (AIFA) recommendations [12].

3.2. Post-COVID syndrome features

Considering hospitalized patients, 42.4% of them were admitted into a General Ward (GW), 31.4% in a Respiratory Intensive Care Unit (RICU) and 26.1% in an ICU. In case of several ward admissions/discharges, we considered the ward with the highest level of healthcare support in which the patient spent at least three consecutive days.

As showed in Table 1, patients treated in RICU were older ($P < 0.0001$), with a longer median time for the NPS negativization than home-treated patients ($P < 0.0001$). Moreover, these patients reported more frequently muscular pain ($P = 0.03$) and mood disorder ($P = 0.02$) after the acute phase of COVID-19 disease. On the contrary, home-treated patients were less frequently affected by fatigue and insomnia.

Regarding radiological findings, hospitalized patients performed chest HRCT more frequently than home-treated patients, with residual Ground Glass Opacities (GGO) found in 64.3% of RICU-treated subgroup ($P < 0.0001$). On the other hand, centrilobular nodules were more frequently found in patients treated at home ($P = 0.001$), probably due to residual distal airways involvement or small mucus plugs.

After the clinical evaluation, every patient underwent blood sample collection and a complete lung function study (see eTable 2). Biomarkers dosages revealed higher levels of creatinine ($P = 0.04$) and NT-pro-BNP ($P = 0.001$) in patients admitted to GW, while RICU patients had increased LDH ($P = 0.001$) and Galectin-3 ($P < 0.0001$). Finally, ICU-treated patients had higher Interleukin 6 (IL-6, $P = 0.04$) plasma values compared to the rest of the cohort.

Lung function tests revealed a downtrend of lung volumes and diffusion according to the increasing healthcare needs of patients with COVID-19 disease. In fact, Forced Vital Capacity (FVC, $P = 0.0004$), Vital Capacity (VC, $P = 0.003$), Forced Expiratory Volume in the 1st second (FEV1, $P = 0.03$), Total Lung Capacity (TLC, $P < 0.0001$), Residual Volume (RV, $P = 0.03$), Diffusing Capacity of Lung for Carbon Monoxide (DLCO, $P < 0.0001$) showed a significant reduction in patients treated in RICU and ICU.

As regards 6MWT, hospitalized patients revealed lower pre-test ($P =$

Table 2
Multivariate Cox stepwise regression for mood disorders risk after of the overall population.

	Chi[2]	HR[a]	CI 95%[b]	P-Value
Cox regression model	97.4			<0.0001
Sex (Women)		2.1	1.07–4	0.03
Post-COVID19 symptoms				
Headache		2.9	1.4–6	0.005
Memory loss		6.6	3.4–12.8	<0.0001
Ward				
GW[c]		4.1	1.8–9.4	0.001
RICU[d]		5.1	2–12.8	0.001
Respiratory support				
NIV[e]		2.2	1.03–4.8	0.04

[a] HR, Hazard Ratio.
[b] CI, Confidence Interval.
[c] GW, General Ward.
[d] RICU, Respiratory Intensive Care Unit.
[e] NIV, Non-Invasive Ventilation.

0.02) and post-test (P = 0.004) SpO2, with an increased SpO2 variation (ΔSpO2) in patients admitted to RICU (P = 0.04). Moreover, GW-treated patients had the lowest median 6MWD in the entire cohort (P < 0.0001).

Lastly, ABG showed lower PaO2 (P = 0.006) and PaO2/FiO2 (P = 0.005) in the RICU group, despite the absence of a clear hypoxemia.

3.3. Healthcare COVID-19 setting and mood alterations

To better understand the relationship between mood disorders, COVID-19 disease healthcare setting and other post-COVID symptoms, we performed a Log-Rank analysis with Kaplan-Meier curves (See eTable 3). Patients admitted to RICU (P < 0.0001) showed a higher risk of mood disorders compared to all the other admission wards (See Fig. 1), while home-treated patients were less prone to develop mental alterations (P = 0.001). We also found a similar trend according to the need of respiratory support in the acute phase of COVID-19 disease. In fact, NIV-treated group showed a significant higher risk for mood disorders (P < 0.0001), while patients who did not receive any respiratory support had a lower risk (P = 0.001). Among post-COVID symptoms, patients reporting dyspnea (P = 0.01), fatigue (P = 0.003), headache (P < 0.0001), muscle pain (P = 0.001), memory loss (P < 0.0001), insomnia (P < 0.0001) and Telogen Effluvium (P < 0.0001) demonstrated an increased risk of having also mood disorders.

To confirm these findings, we performed two multivariate Cox regressions.

In the first model (overall population, see Table 2), female gender (P = 0.03), RICU (P = 0.001) and GW admission (P = 0.001), headache (P = 0.005), memory loss (P < 0.0001) and NIV use (P = 0.04) were all associated with an increased cumulative risk of developing mood disorders.

Table 3
Multivariate Cox stepwise regression for mood disorders risk after excluding patients with history of diagnosed mood disorders.

	Chi[2]	HR[a]	CI 95%[b]	p-value
Cox regression model	83.7			<0.0001
Sex (Women)		3.1	1.4–6.8	0.004
Age		1.05	1.01–1.08	0.006
Post-COVID19 symptoms				
Headache		3.5	1.5–8	0.003
Memory loss		5.1	2.3–11.3	<0.0001
Insomnia		3.8	1.8–8.1	<0.0001
Ward				<0.0001
Homepatients		0.126	0.04–0.36	<0.0001
RICU[c]		2.5	1.1–5.3	0.02

[a] HR, Hazard Ratio.
[b] CI, Confidence Interval.
[c] RICU, Respiratory Intensive Care Unit.

On the other hand, the second regression model (no previous psychic diseases, See Table 3) revealed that female gender (P = 0.004), age (P = 0.006), RICU admission (P = 0.02), headache (P = 0.003), memory loss (P < 0.0001) and insomnia (P < 0.0001) were all risk factors for mood disorders. On the contrary, home treatments resulted to be protective from mental alterations due to COVID-19 disease (P < 0.0001).

Finally, we tested both first (AUC = 0.75, P < 0.0001) and second (AUC = 0.87, P < 0.0001) model's accuracy using ROC curves, confirming the robustness and the accuracy of our analysis (See eFig. 1).

4. Discussion

Our study identified four different groups based on the intensity of healthcare needs during the acute phase of COVID-19 disease. Considering patients' reported symptoms, RICU admission arises as an important risk factor for developing mental alterations, even if compared with ICU patients, usually more prone to develop mental problem after the discharge. To date, this is the first study addressing the role of COVID-19 RICU admission on the development of mood alterations. Previously, only PICS [13] has been related to COVID-19 disease [4,5,14]. We believe that the reason for such increased risk for mental disorders in RICU subgroup was deeply related to the organization of this kind of ward. RICU is a specialist respiratory unit for the treatment and monitoring of patients with acute respiratory failure, usually requiring higher level of respiratory supports (high flow oxygen, mechanical ventilation) and continuous monitoring of several vital parameters (heart rate, blood pressure, respiratory rate and oxygen saturation). In particular, our COVID-19 RICU, since March 2021, has been built precisely for COVID-19 emergency, with the purpose to offer the best clinical support to the huge number of patients dealing with respiratory failure due to COVID-19 pneumonia. Logistics of our RICU resemble the usual setting of an ICU, with an open space accommodating up to 16 patients continuously monitored. In this setting, patients lacked of personal privacy, saw other patient's deaths and sufferings, heard healthcare professional's speech, all without any filter protecting them from such stimuli. Moreover, the lack of windows and natural light altered patients' circadian rhythm, exposing them to the development of mental alterations [5]. Finally, our patients were not usually fully sedated, being exposed to several trigger such as physical pain, positional discomfort (awake prone positioning), noise (alarms from monitors and respiratory equipment) and visual stimuli (permanent artificial light, monitors' flashing lights). All these circumstances negatively emphasized the experience of the RICU admission, with an important impact on patients' return to normal life. In our regression model, not only patients admitted in RICU but also GW patients were more prone to develop mood disorders, as well as patients who received NIV treatment during the hospitalization. However, considering GW and NIV loss of significance in the model excluding patients with previous diagnosis of mental diseases, we believe that past medical history could have affect these results. In particular, a positive history of psychic disease could have influenced the decision about the proper admission ward. In fact, since patients with psychiatric diseases have worse COVID-19-related outcomes [15], we reasonably believe that such patients could have been intentionally admitted in RICU or ICU for a better monitoring. Similarly, excluding patients with previous psychiatric diseases from the regression analysis could mean the drop out of some patients who underwent mechanical ventilation, causing NIV loss of significance in the model. On the other hand, home-treated patients seem to be protected from the development of post-COVID mental alterations. In fact, the lack of the traumatic effect of the hospitalization could explain this finding. Nevertheless, this data should be considered with caution, as this variable appeared to be deeply time-dependent. In other terms, the difference in time from negative SARS-COV2 NPS to the post-COVID visit could have influenced this result. As expressed in Table 1, median time to visit was higher in home-treated patients, probably due to the less intense COVID-19 syndrome experienced. This latency could have

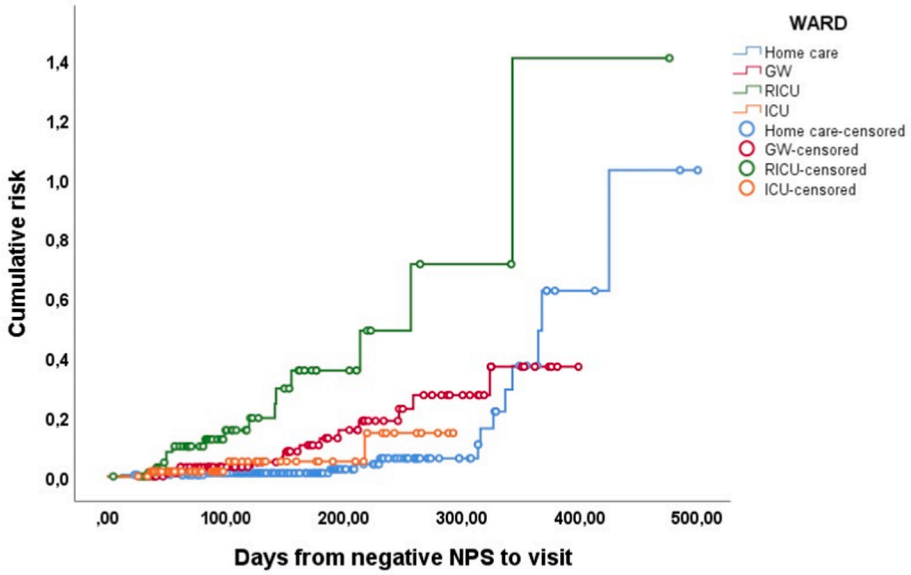

Fig. 1. Patients admitted in RICU shows a higher cumulative risk for mood disorder development.

diluted the impact of mood disorders reported during post-COVID visit.

Considering post-COVID symptoms, only headache, memory loss and insomnia resulted statistically significant in our models. All these factors are known to be highly related to the onset and the development of mood disorders [16–19]. In our cohort (see Table 4), patients reporting post-COVID mood alterations had also a higher frequency of headache ($P < 0.0001$), memory impairment ($P < 0.0001$) and insomnia ($P < 0.0001$). Considering our data, it seems reasonable to think that these three symptoms could have triggered or powered the onset of mood disorders related to post-COVID syndrome. Surprisingly, differences between RICU-admitted patients and ICU-admitted patients were evident only considering mood disorders. In fact, the frequency of mood disorders in RICU-treated patients is higher than in ICU patients (eTable 5). Despite this, neither insomnia, memory loss nor headache showed this trend. On the other hand, as showed in Fig. 2, Kaplan-Meier curves and Log-Rank analysis assessing cumulative risk for mood disorders in RICU vs ICU patients showed statistically significant results only for mood disorders. Consequently, while in the entire enrolled population some post-COVID symptoms could have strengthen the development of mood disorders, the direct comparison between RICU and ICU admitted patients did not show such findings. As stated before, it is reasonable to think that RICU structure along with the lack of patients' full sedation could explain these results.

Table 4
Post COVID features in patients with referred mood disorders.

	Mood disorders	Control	P-Value
Total patients (n)	45	395	
Age (Years, Median, IQR§)	60 [56–69]	58 [50–66]	0.04
Number of Comorbidity (Median, IQR)	2 [2–4]	2 [1–3]	0.01
Days from negative NPS® to visit (Days, Median, IQR)	163 [72–286]	128 [85–208]	
Days from positive to negative NPS (Days, Median, IQR)	27 [18.5–34]	23 [17–31]	0.03
Healtcare setting (n, %)			0.009
Home care	13 (6.7)	182 (46.1)	
GW‡	13 (12.5)	91 (23)	
RICU#	15 (19.5)	62 (15.7)	
ICU*	4 (6.3)	60 (15.2)	
Respiratory support (n, %)			0.03
No support	15 (6.8)	204 (51.6)	
Oxygen	12 (12.6)	83 (21)	
NIV§	16 (17.2)	77 (19.5)	
IMV¶	2 (6.1)	31 (7.8(	
Long COVID symptoms (n, %)			
Dyspnea	31 (68.9)	198 (50.1)	0.02
Fatigue	24 (53.3)	117 (29.6)	0.002
Cough	7 (15.6)	38 (9.6)	
Anosmia	2 (4.4)	11 (2.8)	
Ageusia	2 (4.4)	13 (3.3)	
Headache	12 (26.7)	17 (4.3)	<0.0001
Muscle pain	13 (28.9)	52 (13.2)	0.01
Memory Loss	19 (42.2)	22 (5.6)	<0.0001
Insomnia	15 (33.3)	36 (9.1)	<0.0001
Telogen Effluvium	8 (17.8)	10 (2.5)	<0.0001

‡GW, General Ward.
#RICU, Respiratory Intensive Care Unit.
*ICU, Intensive Care Unit.
§IQR, InterQuartile Range.
§NIV, Non-Invasive Ventilation.
¶IMV, Invasive Mechanical Ventilation.

To date, few studies identified reliable predictors of the possible onset of long-term consequences of COVID-19 disease [1]. The PHOSP-COVID study identified some risk factor (female gender, middle age, ≥2 comorbidities, use of mechanical ventilation) that could affect the full recovery after discharge. Moreover, severity of physical consequences seems to be strictly connected with mental health alteration, while cognitive impairments were independent [20].

Moreno-Perez et al., on the other hand, confirmed the presence of neurological consequences after COVID-19 diseases, without focusing on post-COVID mood disorders [21].

Huang and colleagues observed a higher prevalence of depression and anxiety in post-COVID patients after 6 months from hospital discharge [10]. In particular, women had increased odds not only for mood disorders but also for fatigue and muscle fatigue. Our results are consistent with these findings, confirming the increased risk for women to develop psychic consequences after COVID-19 disease. Moreover, the association between gender and mood disorders is well described in literature [22,23], even after SARS epidemic [24]. As a matter of fact, Coronaviruses seem to frequently cause neurologic and psychiatric alterations, both during the acute and the post-acute phases of the infection [25].

Our study has some limitations. First, we did not administer any specific questionnaire regarding mental or mood disorders. However, considering the purpose of the study, we felt confident to treat the variable "mood disorders" only as binary, since we were not interested in quantitative measures to assess the relationship with healthcare

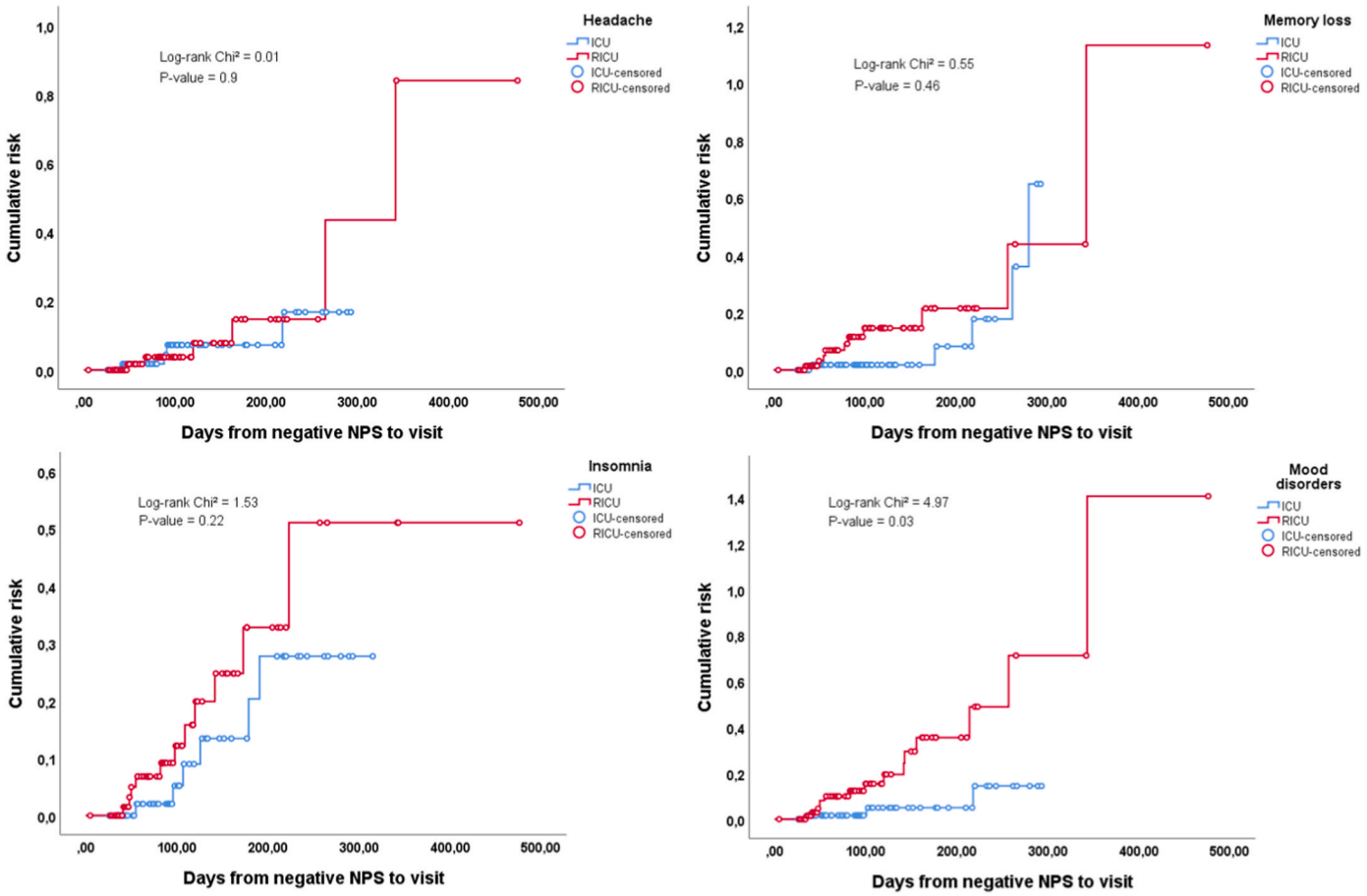

Fig. 2. Kaplan-Meier curves for headache, memory loss, insomnia and mood disorders for RICU vs ICU admitted patients. Among these variables, only mood disorders showed statistically significant results (Log-rank $Chi^2 = 4.97$, $P = 0.03$).

settings. Second, radiological and functional findings were available only for a part of our cohort. Moreover, as regard chest CT-scans, no quantitative analysis concerning extension or severity of post-COVID radiological alterations was performed. Nevertheless, our findings are in line with those previously described in literature [1]. Third, we were not able to collect information about delirium episodes during COVID-19 disease, which could be a cause of long term mood disorders. In fact, since patients attending our outpatient clinic came from different healthcare settings, it was difficult to obtain reliable data on COVID-related delirium episodes. Finally, a wider follow up time would be useful to describe long term mood sequelae related to COVID-19 healthcare settings.

5. Conclusions

In conclusion, COVID-19 healthcare settings seems to have a strong impact in the development of mood disorders. In particular, RICU may represent a potential risk factor for this post-COVID manifestation, exposing patients to several negative stimuli which can trigger or exacerbate psychologic disorders.

Author's contributions

- Dr Andrea Portacci participated in the design of the study, in the sequence of alignment, in the statistical analysis and drafted the manuscript
- Dr Vitaliano Nicola Quaranta participated in the literature research, in the statistical analysis and in the final draft of the manuscript
- Dr Ilaria Iorillo participated in the design of the study, in the literature research and drafted the manuscript
- Dr Enrico Buonamico partecipated in the literature research and in data acquisition
- Dr Fabrizio Diaferia partecipated in the literature research and data acquisition
- Dr Sara Quaranta participated in the literature research and in data collection/interpretation
- Dr Cristian Locorotondo participated in the literature research and in data collection/interpretation
- Prof Silvano Dragonieri partecipated in data acquisition and in the final revision of the manuscript
- Prof Giovanna Elisiana Carpagnano partecipated participated in the design of the study, in the interpetation of the results and in the final revision ot the manuscript
- All authors read and approved the final manuscript.
- All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Andrea Portacci: Conceptualization, Methodology, Software, Writing – original draft. **Vitaliano Nicola Quaranta:** Data curation, Formal analysis, Software, Writing – review & editing. **Ilaria Iorillo:** Conceptualization, Investigation, Writing – original draft. **Enrico Buonamico:** Writing – review & editing, Visualization. **Fabrizio Diaferia:** Investigation, Data curation. **Sara Quaranta:** Conceptualization, Investigation, Data curation. **Cristian Locorotondo:** Formal analysis, Software. **Silvano Dragonieri:** Writing – review & editing, Supervision, Visualization. **Giovanna Elisiana Carpagnano:** Conceptualization, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.107006.

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