Psychiatric Outcomes at 3 and 6 Months in Critically Ill SARS-CoV-2 Survivors: Prospective Study in a Portuguese Cohort

Prognóstico Psiquiátrico aos 3 e 6 Meses em Sobreviventes por Infeção SARS-CoV-2 Grave: Análise Prospectiva de uma Coorte Portuguesa

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Abstract:

Introduction: Although mid and long-term psychiatric sequelae are predicted, few studies have focused on critically ill SARS-CoV-2 survivors from Portugal.

We aimed to evaluate mid-term prevalence of psychiatric disease and respective predictors in COVID-19 survivors.

Methods: This is a longitudinal prospective study of critically ill COVID-19 survivors followed up at 3 (T3) and 6 (T6) months after discharge. A set of validated tools, including the GAD-7 for anxiety, PHQ-9 for depression, and PCL-V for PTSD was administered at both visits. Provisional diagnosis of anxiety, depression and PTSD was made if GAD-7≥10, PHQ-9≥10 and PCL-V≥31. Written informed consent was obtained.

Results: A total of 149 patients discharged after COVID-19 hospitalization, were recruited to an outpatient visit at T3 and T6. Of those, 117 completed the test battery. Participants' age ranged from 25 to 85 years with mean values 64.0±15.5, and 45 (38.5%) were female. Mean age-adjusted Charlson Comorbidity Index was 2.6±2.0 and 51 (43.6%) had at least one comorbidity. Twenty-nine patients (24.8%) presented with psychiatric comorbidities. Regarding education, 56.4% completed primary education, while 8.5% had university or postgraduate qualifications. Twenty patients (17.1%) were single, divorced or widowed.

Prevalence of psychiatric conditions at T3 and T6 was 22.2% *vs* 12.0% (p=0.012) for anxiety, 23.1% *vs* 11.1% (p=0.007) for depression and 7.7% vs 2.6% (p=0.031) for PTSD, respectively. Significant improvement between evaluations was noted in all mean PCL-V domains. Univariate analysis was conducted for anxiety and depression provisional diagnosis at T6. Female gender [OR 4.86 (CI 95% 1.42-16.60), p=0.012] and ferritin levels [OR 8.25 (CI 95% 1.04-65.60), p=0.046] seem to correlate with anxiety. Similarly, mMRC dyspnea scale [OR 1.62 (CI 95% 1.05-2.51), p=0.031] and psychiatric background [OR 3.44 (CI 95% 1.36-8.66), p=0.009] were correlated to depression. We did not find association between age, education, marital status, length of stay, do not intubate order, invasive mechanical ventilation and laboratory findings during hospitalization, and anxiety or depression.

Conclusion: Among critically ill SARS-CoV-2 survivors, clinically significant anxiety, depression and PTSD were observed 3 and 6 months after discharge. However substantial improvement over time was perceived. In our study, the risk of anxiety correlated with female gender and the risk of depression with mMRC dyspnea scale and psychiatric background.

Keywords: COVID-19/psychology; Depression; Mental Disorders; Mental Health; Stress Disorders, Post-Traumatic; Surveys and Questionnaires.

Resumo:

Introdução: Nos sobreviventes de infeção grave por SARS-CoV-2 as sequelas psiquiátricas a médio e longo prazo são expectáveis. Estudos portugueses a incidirem nesta temática são parcos.

O nosso objectivo foi fazer avaliação da prevalência a médio prazo e preditores de doenças psiquiátricas nos sobreviventes COVID-19.

Métodos: Estudo longitudinal e prospectivo com sobreviventes de infeção grave por SARS-CoV-2, avaliados aos 3 (T3) e 6 (T6) meses após a alta hospitalar. Foram aplicados instrumentos validados (GAD-7 para ansiedade, PHQ-9 para depressão e PCL-V para *stress* pós-traumático) e os diagnósticos provisórios foram estabelecidos com GAD-7 ≥ 10, PHQ-9 ≥ 10 e PCL-V ≥ 31. O consentimento informado foi obtido.

Resultados: Foram recrutados 149 doentes após hospitalização por COVID-19, dos quais 117 completaram os questionários. A idade variou entre 25 e 85 anos (média de 64,0±15,5), sendo 45 (38,5%) mulheres. O Índice de Charlson ajustado à idade foi de 2,6±2,0, e 51 (43,6%) apresentaram comorbilidades. Vinte e nove doentes (24,8%) tinham comorbilidades psiquiátricas. Relativamente às habilitações literárias, 56,4% completaram o ensino básico e 8,5% tinham qualificações académicas.

A prevalência de condições psiquiátricas foi de 22,2% *vs* 12,0% (p=0,012) para ansiedade, 23,1% *vs* 11,1% (p=0,007) para depressão, e 7,7% vs 2,6% (p=0,031) para

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perturbação de *stress* pós-traumático, entre T3 e T6, com melhoria significativa entre as avaliações. A análise univariada mostrou que o género feminino [OR 4,86 (IC 95% 1,42-16,60), *p*=0,012] e níveis elevados de ferritina [OR 8,25 (IC 95% 1,04-65,60), *p*=0,046] correlacionaram-se com a ansiedade. A escala de dispneia mMRC [OR 1,62 (IC 95% 1,05-2,51), *p*=0,031] e antecedentes psiquiátricos [OR 3,44 (IC 95% 1,36-8,66), *p*=0,009] correlacionaram-se com a depressão. Não se identificou associação dos resultados com a idade, escolaridade, estado civil, tempo de internamento, ventilação mecânica ou outros achados laboratoriais.

Conclusão: Entre os sobreviventes por infeção grave por SARS-CoV-2, foram observados níveis significativos de ansiedade, depressão e stress pós-traumático aos 3 e 6 meses após a alta, com melhoria ao longo do tempo. O risco de ansiedade associou-se com o género feminino, e o risco de depressão com a escala de dispneia mMRC e os antecedentes psiquiátricos.

Palavras-Chave: COVID-19/psicologia; Depressão; Inquéritos e Questionários; Perturbações Mentais; Perturbações de Stress Pós-Traumático; Saúde Mental.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in December 2019 and rapidly spread around the world. On March 11, 2020, the World Health Organization (WHO) declared the outbreak of novel SARS-CoV-2 a global pandemic.[1] Portugal had the first confirmed case of COVID-19 on 2 March 2020.[2]

While SARS-CoV-2 primarily affects the respiratory system, the disease has resulted in systemic sequelae that remain poorly understood, posing a significant global public health challenge. Since the onset of the pandemic, evidence has highlighted an increased prevalence of psychiatric symptoms and diagnosis within the first three months following acute infection.[3]

Across European Union (EU) countries, an estimated 25 million people (5.4% of the population) live with anxiety disorders, and over 21 million with depression.[3] Portugal is the second European country with the highest rate of psychiatric disorders.[4] In 2019, Portugal had the highest share of population reporting chronic depression, 12.2%, among EU countries.[5] Anxiety disorders affected 16.5% of population.[4,6] The problem of mental health is serious and real with reports revealing that 1 in every 5 Portuguese suffers, or has suffered, from mental illness, thus placing our country at high risk.[4] Similar concerns have been raised regarding psychiatric sequelae of COVID-19, as survivors are at increased risk of mood and anxiety disorders.[7] These factors impact health- related quality of life (HRQoL) as it is recognized that COVID-19 may lead to poorer outcomes.[8-10]

This prospective study aimed to predict the psychiatric outcomes in critically ill SARS-CoV-2 survivors at 3 and 6 months after hospital discharge.

Methods

This prospective unicentric study was conducted in two phases and included all critically ill SARS-CoV-2 survivors admitted to a dedicated respiratory unit from November 2020 to November 2021. The inclusion criteria were patients aged over 18 years-old, with COVID-19 diagnosis by PCR on pharyngeal swab and admission to an advanced respiratory care unit (ARCU) for noninvasive respiratory support (NRS). One hundred and forty-nine eligible patients were recruited, at discharge, to an outpatient evaluation at 3 (T3) and 6 (T6) months. Patients with cognitive impairment (ICD 10: F01-F99, G80, Q00-Q07, Q90-Q99), who were unable to complete the questionnaires or refused to participate, were excluded at T3.

PHASE 1. HOSPITALIZATION

A general ward was converted to an ARCU dedicated to critically ill COVID-19 patients. All patients were admitted for treatment with NRS techniques such as high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV). Patients in need of invasive mechanical ventilation (IMV), vasopressor support or renal replacement therapy were transferred to ICU. All patients had access to rehabilitation in the ARCU and maintained treatment during all hospitalization.

Demographic and clinical information was prospectively obtained both during hospitalization and outpatient visits. Information regarding demographics, comorbidities [Charlson Comorbidity Index (CCI) and psychiatric background], education, marital status, NRS techniques, laboratory findings, length of stay and therapeutic ceiling concerning candidacy to IMV were collected during hospitalization. Laboratory findings considered included PaO2/FiO2 as a marker of disease severity; and C-reactive protein, procalcitonin, ferritin and interleukin-6 as markers of inflammation.

PHASE 2. OUTPATIENT VISIT

Outpatient evaluations were made at T3 and T6. In each evaluation, patients were asked to answer anxiety, depression, and post-traumatic stress disorder questionnaires.

QUESTIONNAIRES

Psychiatric morbidity was assessed with screening questionnaires validated for Portuguese population.

The Generalized Anxiety Disorder 7 (GAD-7)[11] is a seven-item self-report scale designed to assess generalized anxiety in primary care settings. Each of the seven items is scored from 0 (not at all) to 3 (nearly every day). The total GAD-7 scale score ranges from 0-21. Cut-offs can be used to classify anxiety symptoms severity as mild (5-9), moderate (10-14) and severe

(≥15). When formally validated against diagnostic psychiatric interviews, a GAD-7 score of ≥10 has a sensitivity of 89% and specificity of 82% to detect generalized anxiety disorder.[12]

The PHQ-9[13] is a nine-item self-report scale designed to assess symptoms of depression. Each of the nine items can be scored from 0 (not at all) to 3 (nearly every day), and the total scale score ranges from 0-27. Symptom severity can be assessed through the total score, where PHQ-9 scores of 5-9: mild, 10-14: moderate, 15-19: moderately severe, and ≥20: severe depressive symptoms. The PHQ-9 has been formally validated against structured diagnostic interviews administered by a mental health professional. PHQ-9 score ≥10 has a sensitivity of 88% and a specificity of 88% to detect major depression.[14]

PCL-5 is a tool that assesses the presence and severity of PTSD.[15] It is a 20-item 5-point Likert (0 = "Not at all" to 4 = "Extremely") scale assessing the 20 DSM-5 symptoms of PTSD. A provisional PTSD diagnosis was made according to the National Center for PTSD instructions, considering each item rated as 2 "Moderately" or higher as a symptom endorsed, then following the DSM-5 diagnostic rule which requires at least 1B item (intrusion symptoms associated with the traumatic event e.g. intrusive memories, dreams, flashbacks), 1C item (avoidance of trauma-related stimuli), 2D items (cognitive and mood symptoms e.g. distorted cognitions, diminished interests, feelings of detachment) and 2E items (alterations in arousal and reactivity e.g. angry outbursts, self-destructive behavior, sleep disorders). Patients with 3 criteria out of 4 were considered as affected by subthreshold PTSD. Prevalence was also reported using total scores with a cutoff of 30.

STATISTICAL ANALYSIS

No statistical sample size assessment was performed a priori, and sample size was the number of patients treated during the study period in the ARCU. Continuous variables are described using mean and standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables are reported frequency and percentages. The normality was checked using Kolmogorov-Smirnov test.

Patients' outcomes were compared, between timepoints, using Paired Student's t-tests or Wilcoxon for continuous variables or McNemar test for categorical variables.

The association between psychiatric provisional diagnosis at T6, and demographics and data from de hospitalization was calculated using a univariate logistic regression model and data is presented in odds ratio and 95% confidence interval.

Statistical analysis was performed using SPSS (version 27; SPSS, Chicago, IL, USA) and a p-value of ≤0.05 was considered statistically significant.

ETHICAL APPROVAL

Ethical approval for the study was granted by the ethics committee of Local Health Unit of Tâmega and Sousa (Portugal). Data from hospitalization were prospectively recorded after ethical approval (phase 1). For this purpose, informed consent was waived by the institution due to the heath care burden felt at the time. At the ambulatory evaluation all patients participated voluntarily and written informed consent was obtained from all study participants at T3 (phase 2). All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

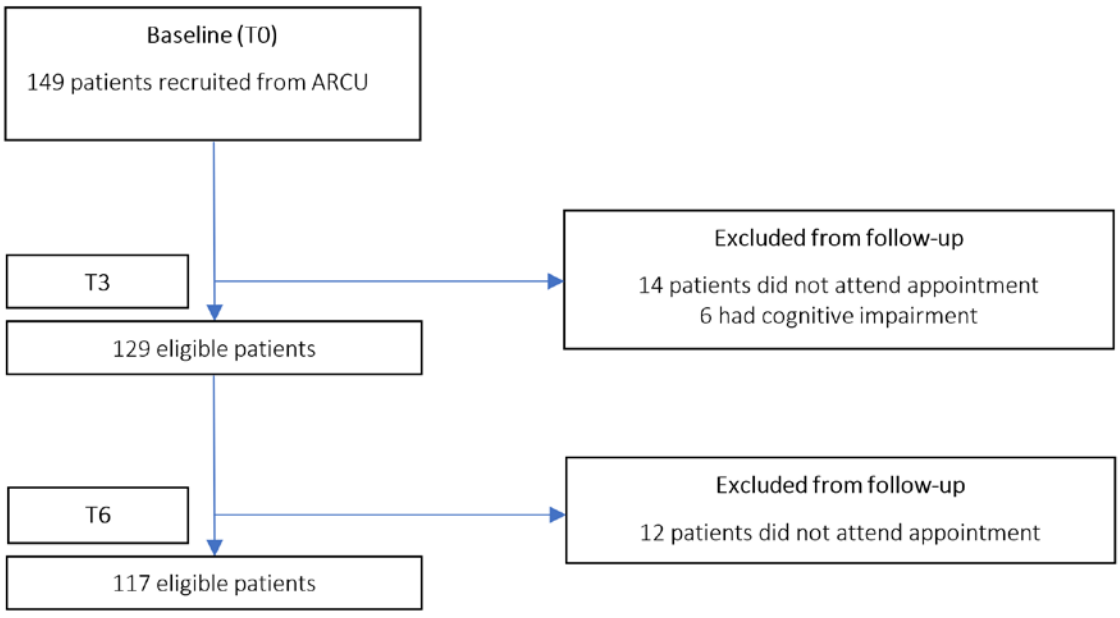

Figure 1: Flow diagram of participants.
ARCU: Advanced respiratory care unit

Table 1: Demographic and clinical characteristics of the study population.

	Total (n=117)
Female gender, n (%)	45 (38.5)
Age, median (IQR), years	64.0 (15.5)
Age distribution, n (%) <50, years 50-70, years >70, years	 20 (17.1) 69 (59.0) 28 (23.9)
Education, median (IQR), years	4.0 (5.0)
Psychiatric background, n (%)	29 (24.8)
Single, divorced or widowed, n (%)	20 (17.1)
PaO2/FiO2, mmHg, median (IQR)	100.0 (48.5)
Do not intubate order, n (%)	22 (18.8)
NIRS, n (%) HFNC NIV IMV	 108 (92.3) 18 (15.4) 11 (9.4)
Length of stay, median (IQR), days	13.0 (13.0)

Results

One hundred forty-nine patients were discharged to ambulatory follow-up. Of those, 117 patients were included in the analysis (Fig. 1). Four patients were excluded due to dementia and 2 due to Down syndrome at T3. No patient refused to participate or withdraw informed consent during the study period.

Demographic characteristics of the study population are shown in Table 1. Participants' age ranged from 25 to 85 years. The majority were men. Forty-five percent had at least one comorbidity included in Charlson comorbidity index and and mean Charlson comorbidity-index was 2.6 ± 2.0 points. The most frequent were diabetes (30.8%), heart failure (12.0%), myocardial infarction and cerebrovascular disease (4.3%), peripheral artery disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease and solid tumor (2.6%). Twenty-nine patients (24.8%) had previous psychiatric comorbidities: 19 reported depression, 7 anxiety, 4 sleep disorders, 2 psychotic disorder, 2 bipolar disease and 2 PTSD.

Concerning education, 56.4%, 24.8%, 10.3% and 8.5% had 1st cycle-basic education, 2nd and 3rd cycles – basic education, secondary education and university/ postgraduate education, respectively. Twenty patients (17.1%) were single, divorced, or widowed.

More than 90% of patients were treated with HFNC. Eleven patients were transferred to ICU for IMV.

Table 2 presents GAD-7 and PHQ-9 and PCL-V scores evolution over time. At T3 evaluation, 26 and 27 patients were provisional diagnosed with generalized anxiety disorder and major depression, respectively. Only 9 patients scored for PTSD at T3. At T6, about half of the patients showed mood and anxiety improvements. This was equally noticed in all PTSD domains.

Predictors of psychiatric outcomes were evaluated for anxiety and depression (Table 3). This analysis was not conducted for PTSD due to the low number of diagnosis 6 months after discharge. Female gender and serum ferritin levels were associated with increased risk of anxiety. The likelihood of depression disorder was correlated with the psychiatric background and mMRC dyspnea scale. Interestingly, an association between psychiatric outcomes and age, marital status, education, length of stay, invasive mechanical ventilation, *do not intubate* order, severity of acute respiratory distress syndrome, was not found.

Overall, 10.3% of patients were referred for further psychiatric or psychological evaluation.

Discussion

This study aimed to examine the mid-term psychiatric outcomes among critically ill SARS-CoV-2 Portuguese survivors treated outside ICU. To our knowledge this is the first

Table 2: Outcomes 3 and 6 months after discharge

	T3	T6	*p*-value
GAD-7 ≥10, n (%)	26 (22.2)	14 (12.0)	0.012
GAD-7, mean (SD)	5.5 (6.1)	3.7 (4.8)	<0.001
PHQ-9, ≥10, n (%)	27 (23.1)	13 (11.1)	0.007
PHQ-9, mean (SD)	5.7 (5.6)	3.6 (4.7)	<0.001
PCL-V, ≥31, n (%)	9 (7.7)	3 (2.6)	0.031
PCL-V, mean (SD) Re-experiencing Avoidance Negative impact in cognition and mood Hyper-arousal	11.2 (13.1) 2.8 (4.3) 1.6 (2.4) 2.6 (3.7) 4.2 (5.0)	6.1 (13.1) 1.5 (2.8) 0.7 (1.3) 1.7 (3.3) 2.2 (3.2)	<0.001 <0.001 <0.001 <0.001 <0.001

Table 3: Analysis of association between patient's characteristics and psychiatric outcomes

	Total	Anxiety			Depression		
		GAD7≥10	OR (CI 95%)	*p*-value	GAD7≥10	OR (CI 95%)	*p*-value
Female gender, n (%)	45 (38.5)	10 (22.2)	4.86 (1.42-16.60)	0.012	6 (13.3)	1.43 (0.45-4.56)	0.547
Age, median (IQR), years	64.0 (15.5)	61.5 (18.5)	0.99 (0.95-1.05)	0.972	61.0 (15.5)	1.01 (0.96-1.06)	0.723
Education, median (IQR), years	4.0 (5.0)	5.0 (8.0)	1.07 (0.93-1.23)	0.345	4.0 (4.0)	0.96 (0.81-1.13)	0.602
Psychiatric background, n (%)	29 (24.8)	7 (24.1)	2.37 (0.93-6.05)	0.072	8 (61.5)	3.44 (1.36-8.66)	0.009
Single, divorced or widowed, n (%)	20 (17.1)	0 (0.0)	0.33 (0.07-1.54)	0.160	1 (7.7)	1.53 (0.52-4.47)	0.436
Length of stay, median (IQR), days	13.0 (13.0)	16.5 (23.0)	1.01 (0.98-1.04)	0.513	12.0 (12.5)	0.98 (0.94-1.03)	0.502
***Do not intubate*,** n (%)	22 (18.8)	4 (18.2)	0.53 (0.15-1.88)	0.325	2 (9.1)	1.31 (0.27-6.38)	0.739
IMV, n (%)	11 (9.4)	1 (7.1)	0.72 (0.09-6.06)	0.759	0 (0.0)	-	-
mMRC, median (IQR)	2.0 (1.0)	2.0 (0.0)	1.47 (0.95-2.27)	0.085	2.0 (0.0)	1.62 (1.05-2.51)	0.031
Laboratory findings, median (IQR)							
PaO2/FiO2, mmHg	100.0 (48.5)	98.4 (68.5)	1.00 (0.99-1.02)	0.805	93.8 (71.8)	1.00 (0.99-1.02)	0.720
C-reactive protein, mg/L	155.0 (119.5)	149.9 (179.8)	1.00 (1.00-1.01)	0.506	158.5 (130.7)	1.00 (0.99-1.01)	0.653
Procalcitonin, ng/mL	0.2 (0.5)	0.2 (0.16)	1.00 (0.99-1.01)	0.409	0.1 (0.1)	0.99 (0.99-1.00)	0.257
Ferritin>1500 ng/mL	41 (35.0)	1 (7.1)	8.25 (1.04-65.60)	0.046	2 (15.4)	3.3 (0.70-15.67)	0.133
Interleukin-6, pg/mL	62.0 (111.0)	57.4 (110.0)	1.00 (0.99-1.01)	0.409	56.5 (103.0)	0.99 (0.99-1.00)	0.257

inquiry conducted on patients admitted to an ARCU. We report a significant improvement in anxiety, depression and PTSD rates over time.

About one quarter of patients reported moderate to severe symptoms of generalized anxiety and major depression, at 3 months outpatient evaluation. This translated into anxiety and depression prevalence rates of 22.2% and 23.1%, respectively. After 6 months, a substantial improvement was noticed with rates of 12.0% for anxiety and 11.1% for depression. These values are slightly lower than anxiety and depression rates noted in studies of the general adult population in Portugal.[4-6] Psychiatric outcomes vary widely across the world. A review that included 16 research papers on this subject during COVID-19 pandemic in different countries, found that in China depression rates ranged between 8.3%-48.3%, in Italy between 15.4%-17.0% and in Spain ranged from 1.7% for severe depression and 8.7% for mild depressive symptoms.[16] We believe that our favorable outcomes result from several factors. Firstly, several studies showed that sociodemographic, economic and health-related factors, such as gender, age, education, income, pre-COVID-19 mental health, have impact on mental health outcomes.[17,18] Higher levels of psychiatric disorders were reported in younger persons with high income, who also tended to perceive a greater pandemic interference in their daily lives.[19] More than 80% of our patients had 50 years-old or more and was retired, a condition that might have limited the impact of pandemics in patients daily habits. Moreover, the majority lived in rural areas, where the access to agricultural and livestock goods might have limited the economic burden.

Lanciano *et al* 2020,[20] found that despite educational qualifications have been classified has a protective factor against perception of worst health, people with a higher education realizes the socioeconomic and political impact of COVID-19 pandemic as more severe, which can exacerbate their mental health. A study conducted during COVID-19 pandemic showed that individuals with high education experienced higher levels of anxiety and depression.[21] Over 80% of our sample had only basic education, a factor that might have contributed to our lower depression and anxiety rates.

Second, social support and interaction influence health behaviors and outcomes.[22] Due to the pandemic, most people were forced to change their routines, leading to remote work and contact eviction with consequently social isolation. Our study population lived primarily in rural areas near neighbors and relatives and had access to gardens and backyards allowing a safe social interaction, limiting isolation impact arising from COVID-19 restrictions. Additionally, our sample's marital status is a factor to consider, as only 17.1% were single, divorced or widowed. Having a partner may help cope with mood and anxiety symptoms.

We noticed that female gender has a higher probability of reporting mild to moderate levels of anxiety. Several mental illnesses are more common amongst women, including anxiety and depressive disorders.[23] The gender difference in mental diseases is linked to steroid hormones and genes and to a greater propensity for women to report these problems.[23,24]

Several studies postulate that the psychiatric consequences of COVID-19 might be related to the immune response to the virus. Local and systemic production of

cytokines, chemokine, and other inflammatory mediators are induced in response to SARS-CoV-2 acute infection.[25] The role of inflammatory markers such ferritin, interleukin-6 and C-reactive protein and in psychiatric outcomes remains an important topic in developing literature. In our population, laboratorial results did not correlate with anxiety or depression. However, the risk of anxiety seems to be associated to higher ferritin levels, although these results must be carefully interpreted due to the wide confidence interval and disperse values founded.

This study has some limitations. First, it is a small convenience sample recruited from a single center in Portugal. It's uncertain whether our findings can be generalized to the Portuguese population. Larger studies are needed to confirm this data. Second, we do not have information about mental health questionnaires from our cohort previous to SARS-CoV-2 infection, limiting the attribution of psychiatric symptoms/diagnosis to post- COVID-19 sequelae. Third, provisional psychiatric diagnosis was not validated by a psychiatric team, although 10.3% of our patients were referred to a mental health appointment.

Conclusion

Regardless of the severity of SARS-CoV-2 infection, anxiety, depression a post-traumatic stress symptoms improvement was noted during follow-up, demonstrating a positive trajectory in mental health outcomes among survivors. Nevertheless, risk factors such as female gender, psychiatric background and mMRC scale emphasize the importance of specific determinants to better understand mental health vulnerabilities. Further researches with larger and more diverse cohorts are needed to better understand the temporal associations between mental health symptoms and their determinants, offering a broader and more comprehensive understanding.

Ultimately, it is imperative that mental health professionals implement proactive interventions aimed to prevent the emergence of long-term psychological disorders. Such strategies should focus on the early identification of at-risk individuals and the effective management of associated factors, contributing to the sustained promotion of mental well-being within the population. ■

Apresentações Anteriores/Previews Presentations

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Contributorship Statement

CA - Data collection and article writing.
HV - Study design and article writing.
MM - Study design, statistical analysis, drafting and review.
BS, FC, AR, TC - Data collection.
AC - Study design, review and data collection.
All authors approved the final version to be published.

Declaração de Contribuição

CA – Recolha de dados e redação do artigo.
HV – Desenho do estudo e redação do artigo.
MM – Desenho do estudo, análise estatística, redação e revisão.
BS, FC, AR, TC – Recolha de dados.
AC – Desenho do estudo, revisão e recolha de dados.
Todos os autores aprovaram a versão final a ser publicada.

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