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Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors

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ABSTRACT

Infection-triggered perturbation of the immune system could induce psychopathology, and psychiatric sequelae were observed after previous coronavirus outbreaks. The spreading of the Severe Acute Respiratory Syndrome Coronavirus (COVID-19) pandemic could be associated with psychiatric implications. We investigated the psychopathological impact of COVID-19 in survivors, also considering the effect of clinical and inflammatory predictors.

We screened for psychiatric symptoms 402 adults surviving COVID-19 (265 male, mean age 58), at one month follow-up after hospital treatment. A clinical interview and a battery of self-report questionnaires were used to investigate post-traumatic stress disorder (PTSD), depression, anxiety, insomnia, and obsessive-compulsive (OC) symptomatology. We collected sociodemographic information, clinical data, baseline inflammatory markers and follow-up oxygen saturation levels.

A significant proportion of patients self-rated in the psychopathological range: 28% for PTSD, 31% for depression, 42% for anxiety, 20% for OC symptoms, and 40% for insomnia. Overall, 56% scored in the pathological range in at least one clinical dimension. Despite significantly lower levels of baseline inflammatory markers, females suffered more for both anxiety and depression. Patients with a positive previous psychiatric diagnosis showed increased scores on most psychopathological measures, with similar baseline inflammation. Baseline systemic immune-inflammation index (SII), which reflects the immune response and systemic inflammation based on peripheral lymphocyte, neutrophil, and platelet counts, positively associated with scores of depression and anxiety at follow-up.

PTSD, major depression, and anxiety, are all high-burden non-communicable conditions associated with years of life lived with disability. Considering the alarming impact of COVID-19 infection on mental health, the current insights on inflammation in psychiatry, and the present observation of worse inflammation leading to worse depression, we recommend to assess psychopathology of COVID-19 survivors and to deepen research on inflammatory biomarkers, in order to diagnose and treat emergent psychiatric conditions.

"After three weeks of treatments, I was healing from COVID, at home, had no fever, and just a little cough. But sometimes at night, my breath could go away all of a sudden, making me feel as if I was to die. I knew what it was because I had suffered from panic attacks in the past. I stayed there out on the balcony, for hours, trying to put fresh air into my lungs. It was terrible. Panic made me suffer more than COVID."
A patient's report at follow-up

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1. Introduction

Respiratory viral diseases are associated with both acute and long-lasting psychopathological consequences in the survivors (Bohmwald et al., 2018). Coronaviruses are negatively stranded RNA viruses, which cause infections ranging from common colds to severe acute respiratory syndrome (Peiris et al., 2003). Coronavirus exposure has also been implicated in neuropsychiatric diseases during and after Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks (Rogers et al., 2020). SARS survivors reported psychiatric symptoms, including post-traumatic stress disorder (PTSD), depression, panic disorder, and obsessive-compulsive disorder (OCD) at 1 to 50 months follow up (Wu et al., 2020; Cheng et al., 2004; Lam et al., 2009). Moreover, seropositivity for coronaviruses associated with suicide and psychosis persisting one year after SARS (Okusaga et al., 2011).

The recent spreading of the Severe Acute Respiratory Syndrome Coronavirus (COVID-19) pandemic seems yet to be associated with psychiatric implication (Troyer et al., 2020). Preliminary data suggest that patients with COVID-19 might experience delirium, depression, anxiety, and insomnia (Rogers et al., 2020). Coronaviruses could induce psychopathological sequelae through direct viral infection of the central nervous system (CNS) or indirectly via an immune response (Wu et al., 2020). Clinical, post-mortem, animal, in vitro, and cell culture studies demonstrated that coronaviruses are potentially neurotropic and can induce neuronal injuries (Desforges et al., 2019). Notwithstanding possible brain infiltration, “cytokines storm” involved in the immune response to coronaviruses may cause psychiatric symptoms by precipitating neuroinflammation (Dantzer, 2018; Netland et al., 2008).

Current insight into inflammation in psychiatry suggests that infection-triggered perturbation of the immune system could specifically foster psychopathology, adding to the psychological stress of enduring a potentially fatal disease, and to stress-associated inflammation (Miller and Raison, 2016). The interaction between innate and adaptive immune systems and neurotransmitters emerged as a mechanism underpinning mood disorders, psychosis, and anxiety disorders (Najjar et al., 2013). In addition to the immunological mechanisms, fear of illness, uncertainty of the future, stigma, traumatic memories of severe illness, and social isolation experienced by patients during the COVID-19 are significant psychological stressors that may interact in defining psychopathological outcome (Brooks et al., 2020; Carvalho et al., 2020).

Taking into account the sparse preliminary studies on COVID-19 and considering the previous evidence about SARS and MERS outbreaks, we hypothesize that COVID-19 survivors will show a high prevalence of emergent psychiatric conditions including mood disorders, anxiety disorders, PTSD, and insomnia. Available data indicate that confusion and delirium are common features in the acute stage, while to date, no data exist on psychopathology in the post-illness phase (Rogers et al., 2020; Vindegaard and Eriksen Benros, 2020). Thus, the present study aims to investigate the psychopathological impact of COVID-19 in survivors at one month follow up, also considering the effect of possible risk factors.

2. Material and methods

2.1. Participants

We screened for psychiatric symptoms 402 patients surviving COVID-19 (265 male, mean age 57.8, age range from 18 to 87 years), from April 6 to June 9, 2020, during an ongoing prospective cohort study at IRCCS San Raffaele Hospital in Milan. All patients included in the present study had been first evaluated at the Emergency Department (ED), where they underwent clinical evaluation, electrocardiogram, hemogasanalysis, and hematological analysis (complete blood cell count including differential white blood cell count, and C-reactive protein (CRP)). After that, patients were admitted for severe pneumonia (n = 300, hospital stay 15.31 ± 10.32 days) or managed at home (n = 102). Psychiatric assessment was performed 31.29 ± 15.7 days after discharge, or 28.56 ± 11.73 days after ED. To keep a naturalistic study design, exclusion criteria were limited to patients under 18 years. Written informed consent was obtained from all participants, and the institutional review board approved the study in accordance with the principles in the Declaration of Helsinki.

2.2. Data collection and analysis

An unstructured clinical interview was conducted by well-trained psychiatrists in charge using the best estimation procedure, taking into account available charts, computerized medical records, and, if needed, the information provided by a relative. Sociodemographic and clinical data were collected using a data extraction form, including age, sex, psychiatric history, duration of hospitalization, baseline inflammatory markers, and follow-up oxygen saturation level. Baseline inflammatory markers during acute COVID-19 were extracted from ED charts: C-reactive Protein (CRP), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) (SII = platelets X neutrophils/lymphocytes) (Feng et al., 2020). Oxygen saturation level was recorded at the follow-up visit, soon after the psychiatric evaluation, to provide an index of respiratory efficiency.

Current psychopathology was measured using the following self-report questionnaire: Impact of Events Scale-Revised (IES-R) (Creamer et al., 2003), PTSD Checklist for DSM-5 (PCL-5) (Armour et al., 2016), Zung Self-Rating Depression Scale (ZSDS) (Zung, 1965), 13-item Beck’s Depression Inventory (BDI-13) (Beck and Steer, 1984), State-Trait Anxiety Inventory form Y (STAI-Y) (Vigneau and Cormier, 2008), Medical Outcomes Study Sleep Scale (MOS-SS) (Hays et al., 2005), Women’s Health Initiative Insomnia Rating Scale (WHIIRS) (Levine et al., 2003), and Obsessive-Compulsive Inventory (OCI) (Foa et al., 2002). Scores were considered in the pathological range when higher than generally accepted standard cutoff scores (IES-R ≥ 33; PCL-5 ≥ 33; ZSDS index ≥ 50; BDI-13 ≥ 9; STAI-state ≥ 40; STAI-trait ≥ 40; WHIIRS ≥ 9; OCI ≥ 21)

Statistical analyses to compare group means and frequencies (Student’s *t*-test, Pearson χ^2 test) exploring effects of sex, hospitalization, or previous history of psychiatric illness on symptoms severity were performed, and Pearson’s correlation analysis was performed to explore the correlation between age, duration of hospitalization, time after discharge, baseline inflammatory marker, and oxygen saturation level and current psychopathology scores. To account for the multiple covarying variables, we also tested the effect of predictors (inflammatory markers, sex, previous psychiatric history) on the current psychopathological status (self-report scores) by modelling the influences of the predictors on the outcomes in the context of the General Linear Model (GLM) and calculating the statistical significance of the effect of the single independent factors on the dependent variables by parametric estimates of predictor variables (least squares method). Analyses of multivariate and univariate effects were perfomed by using a commercially available software package (StatSoft Statistica 12, Tulsa, OK, USA) and following standard computational procedures (Dobson, 1990; Hill and Lewicki, 2006).

3. Results

Psychiatric symptoms in COVID-19 survivors and measures of inflammation at first clinical contact (ED evaluation) are resumed in Table 1.

A significant proportion of patients self-rated symptoms in the pathological range: overall, 55.7% scored in the clinical range in at least one psychopathological dimension (PTSD according to IES-R and/or PCL-5, depression according to ZSDS and/or BDI-13, anxiety according to STAI-Y state, and OC symptomatology according to OCI), 36.8% in two, 20.6% in three, and 10% in four. Severity of depression also

Table 1
Psychiatric symptoms and measures of inflammation at first clinical contact in COVID-19 survivors, divided according to sex, previous psychiatric diagnosis, and setting of the care and levels of significance of the observed differences (Student's *t* test and Chi-square). Patients self-rated their symptoms on the Impact of Event Scale – Revised (IES-R), also yielding mean scores for intrusion, avoidance, and hyperarousal; PTSD Checklist for DSM-5 (PCL-5); Zung Self-rating Depression Scale (ZSDS); Beck's Depression Inventory (BDI); State-Trait Anxiety Inventory (STAI); Medical Outcomes Study Sleep Scale (MOS-SS); Women's Health Initiative Insomnia Rating Scale (WHIIRS); Obsessive-Compulsive Inventory (OCI).

	Whole sample (n = 402)	Sex				Psychiatric history
		Females (n = 137)	Males (n = 265)	t or χ^2	p	Positive (n = 106)
Males n° (%)	264 (65.7)	–	–	–	–	52 (19.7)
Age	57.80 ± 13.33	55.90 ± 14.69	58.79 ± 12.49	−2.07	**0.040**	55.45 ± 12.47
Baseline C-reactive Protein (mg/L)	67.35 ± 40.80	45.52 ± 56.86	78.22 ± 72.60	−4.28	< **0.001**	69.24 ± 84.78
Baseline neutrophil/lymphocyte ratio	5.55 ± 3.09	4.17 ± 4.14	6.24 ± 5.58	−3.55	< **0.001**	5.68 ± 5.98
Baseline monocyte/lymphocyte ratio	0.52 ± 0.28	0.42 ± 0.31	0.57 ± 0.41	−3.32	< **0.001**	0.48 ± 0.33
Baseline systemic immune-inflammation index	1280.03 ± 1023.89	1020.82 ± 1011.24	1409.08 ± 1380.95	−2.70	**0.007**	1321.05 ± 1425.74
Follow-up oxygen saturation level	97.85 ± 1.34	97.87 ± 1.27	97.84 ± 1.38	0.17	0.868	97.98 ± 1.16
IES-R (n = 368, 91.5%)	23.83 ± 20.02	34.24 ± 16.58	18.30 ± 16.58	7.86	< **0.001**	35.76 ± 22.15
-Intrusion	1.12 ± 0.98	1.63 ± 0.81	0.85 ± 0.81	7.90	< **0.001**	1.68 ± 1.07
-Avoidance	1.18 ± 0.96	1.65 ± 0.82	0.93 ± 0.82	7.40	< **0.001**	1.74 ± 1.02
-Hyperarousal	1.10 ± 1.00	1.62 ± 0.86	0.83 ± 0.86	7.77	< **0.001**	1.74 ± 1.11
PCL-5 (n = 341, 84.8%)	14.49 ± 15.85	22.63 ± 12.39	10.29 ± 12.39	7.32	< **0.001**	23.30 ± 18.89
ZSDS (n = 368, 91.5%)	44.24 ± 11.40	51.20 ± 9.26	40.61 ± 9.26	9.41	< **0.001**	50.24 ± 13.09
BDI-13 (n = 372, 91.5%)	3.28 ± 4.40	5.08 ± 3.48	2.32 ± 3.48	6.03	< **0.001**	5.58 ± 5.87
STAI-state (n = 341, 84.8%)	38.19 ± 11.09	44.51 ± 9.55	34.84 ± 9.55	8.40	< **0.001**	44.61 ± 12.44
STAI-trait (n = 352, 87.6%)	35.99 ± 10.70	41.23 ± 9.52	33.21 ± 9.52	7.16	< **0.001**	41.88 ± 12.07
MOS (n = 328, 87.6%)	20.58 ± 5.82	23.46 ± 5.00	19.08 ± 5.00	6.94	< **0.001**	22.53 ± 6.68
WHIIRS (n = 367, 91.3%)	7.25 ± 5.03	9.25 ± 4.62	6.18 ± 4.62	5.83	< **0.001**	9.07 ± 5.29
OCI (n = 360, 89.5%)	11.82 ± 10.17	14.44 ± 9.40	10.41 ± 9.40	3.64	**0.001**	15.94 ± 11.55
IES-R ≥ 33 Yes (No)	105 (263)	64 (64)	41 (199)	54.06	< **0.001**	50 (51)
PCL-5 ≥ 33 Yes (No)	52 (289)	31 (85)	21 (204)	17.91	< **0.001**	27 (70)
ZSDS ≥ 50 Yes (No)	113 (255)	67 (59)	46 (196)	45.45	< **0.001**	50 (50)
BDI-13 ≥ 9 Yes (No)	42 (330)	26 (104)	16 (226)	15.13	< **0.001**	25 (78)
STAI-state ≥ 40 Yes (No)	144 (197)	78 (40)	66 (157)	42.15	< **0.001**	59 (35)
STAI-trait ≥ 40 Yes (No)	125 (227)	69 (53)	56 (174)	36.11	< **0.001**	54 (42)
WHIIRS ≥ 9 Yes (No)	147 (220)	69 (59)	78 (161)	15.7	< **0.001**	53 (47)
OCI ≥ 21 Yes (No)	74 (286)	33 (93)	41 (193)	3.77	0.052	34 (64)

	Psychiatric history			Setting			
	Negative (n = 296)	t or χ^2	p	Managed at home (n = 102)	Admitted (n = 300)	t or χ^2	p
Males n° (%)	212 (80.3)	18.03	< **0.001**	45 (17)	220 (83)	28.92	< **0.001**
Age	58.61 ± 13.56	−2.10	**0.036**	50.82 ± 14.43	60.18 ± 12.07	−6.42	< **0.001**
Baseline C-reactive Protein (mg/L)	66.67 ± 63.17	0.31	0.769	29.49 ± 40.80	79.46 ± 72.33	−6.10	< **0.001**
Baseline neutrophil/lymphocyte ratio	5.51 ± 4.95	0.27	0.796	3.77 ± 3.09	6.10 ± 5.62	−3.59	< **0.001**
Baseline monocyte/lymphocyte ratio	0.53 ± 0.40	−1.18	0.248	0.43 ± 0.28	0.55 ± 0.41	−2.55	**0.011**
Baseline systemic immune-inflammation index	1265.30 ± 1228.56	0.36	0.729	919.54 ± 1023.89	1389.51 ± 1332.79	−2.94	**0.004**
Follow-up oxygen saturation level	97.80 ± 1.40	1.01	0.313	98.24 ± 1.40	97.73 ± 1.31	2.82	**0.005**
IES-R (n = 368, 91.5%)	19.34 ± 17.16	7.54	< **0.001**	26.81 ± 20.35	22.83 ± 19.85	1.66	0.098
-Intrusion	0.91 ± 0.86	7.09	< **0.001**	1.26 ± 0.98	1.07 ± 0.98	1.59	0.112
-Avoidance	0.97 ± 0.86	7.31	< **0.001**	1.35 ± 1.01	1.12 ± 0.94	1.94	0.054
-Hyperarousal	0.86 ± 0.85	8.07	< **0.001**	1.26 ± 1.09	1.05 ± 0.97	1.79	0.075
PCL-5 (n = 341, 84.8%)	10.99 ± 12.93	6.90	< **0.001**	16.90 ± 15.91	13.74 ± 15.78	1.57	0.117
ZSDS (n = 368, 91.5%)	42.00 ± 9.83	6.50	< **0.001**	45.78 ± 11.04	43.71 ± 11.50	1.52	0.128

(*continued on next page*)

Table 1 (*continued*)

	Psychiatric history			Setting			
	Negative (n = 296)	t or χ^2	p	Managed at home (n = 102)	Admitted (n = 300)	t or χ^2	p
BDI-13 (n = 372, 91.5%)	2.41 ± 3.29	6.58	**< 0.001**	4.04 ± 4.62	3.03 ± 4.30	1.93	0.055
STAI-state (n = 341, 84.8%)	35.74 ± 9.48	7.05	**< 0.001**	40.37 ± 11.69	37.44 ± 10.80	2.13	**0.033**
STAI-trait (n = 352, 87.6%)	33.78 ± 9.23	6.71	**< 0.001**	37.99 ± 10.48	35.25 ± 10.70	2.14	**0.032**
MOS (n = 328, 87.6%)	19.78 ± 5.23	3.98	**< 0.001**	22.18 ± 6.16	20.03 ± 5.60	2.97	**0.003**
WHIIRS (n = 367, 91.3%)	6.57 ± 4.76	4.35	**< 0.001**	7.81 ± 5.44	7.05 ± 4.87	1.25	0.210
OCI (n = 360, 89.5%)	10.28 ± 9.17	4.84	**< 0.001**	12.55 ± 10.34	11.56 ± 10.12	0.81	0.417
IES-R ≥ 33 Yes (No)	55 (212)	35.35	**< 0.001**	34 (59)	71 (204)	4.47	**0.034**
PCL-5 ≥ 33 Yes (No)	25 (219)	16.61	**< 0.001**	12 (69)	40 (220)	0.02	0.901
ZSDS ≥ 50 Yes (No)	63 (205)	24.02	**< 0.001**	34 (61)	79 (194)	1.55	0.212
BDI-13 ≥ 9 Yes (No)	17 (252)	23.96	**< 0.001**	14 (79)	28 (251)	1.75	0.185
STAI-state ≥ 40 Yes (No)	85 (162)	22.43	**< 0.001**	45 (42)	99 (155)	4.31	**0.037**
STAI-trait ≥ 40 Yes (No)	71 (185)	24.79	**< 0.001**	42 (53)	83 (174)	4.29	**0.038**
WHIIRS ≥ 9 Yes (No)	94 (173)	9.59	**0.002**	39 (55)	108 (165)	0.10	0.742
OCI ≥ 21 Yes (No)	40 (222)	16.48	**< 0.001**	22 (73)	52 (213)	0.53	0.464

included suicide ideation and planning, with 2.9% scoring 1 (suicidal ideation) at the BDI suicide item, 0.8% scoring 2 and 0.8% scoring 3 (suicidal planning).

Clinical and demographic characteristics of the patients influenced the severity of psychopathological sequelae of COVID-19. Females, patients with a positive previous psychiatric diagnosis, and patients who were managed at home showed an increased score on most measures (Table 1).

Consistent with known gender effects we found a 2.9:1F:M ratio ($\chi^2 = 54.98$, p = < 0.001) according to IES-R and 2.8:1 ($\chi^2 = 17.91$, p = < 0.001) according to PCL-5 for clinical PTSD; 2.8:1 ($\chi^2 = 45.45$, p < 0.001) according to ZSDS and 3:1 ($\chi^2 = 15.13$, p < 0.001) according to BDI for clinical depression; 2.2:1 for clinical state anxiety ($\chi^2 = 42.15$, p = < 0.001) and 2.3:1for clinical trait anxiety ($\chi^2 = 36.11$, p = < 0.001); and finally 1,7:1 ($\chi^2 = 15.70$, p = < 0.001) for sleep disturbances according to WHIIRS.

Considering the previous need for psychiatric interventions, prior of COVID-19, 36 patients had been diagnosed with major depressive disorder, 28 with generalized anxiety disorder, 20 with panic attack disorder, 5 with bipolar disorder, 5 with social phobia, 3 with eating disorders, and 4 with other disorders. These patients suffered a more significant impact on mental health, as rated on most measures (Table 1).

Duration of hospitalization inversely correlated with PCL-5 (r = −0.15, p = 0.019), ZSDS (r = −0.16, p = 0.009), BDI-13 (r = −0.13, p = 0.036), STAI-Y state (r = −0.18, p = 0.003), and OCI (r = −0.12, p = 0.044). Age inversely correlated with BDI (r = −0.12, p = 0.018), and MOS (r = −0.18, p = 0.001).

A multivariate GLM analysis of the effects of sex, previous psychiatric diagnosis, and hospitalization, on the current psychopathological status confirmed a significant multivariate effect of sex (Wilks' λ = 0.78; F = 9.55; d.f. 8,266; p < 0.0001) and previous psychiatric history (Wilks' λ = 0.89; F = 4.07; d.f. 8,266; p < 0.0001), but not of hospitalization (Wilks' λ = 0.98; F = 0.84; d.f. 8,266; p = 0.570). Univariate testing showed significantly worse effects on all measures of current psychopathological status in females (IES-R: β = 0.389, F = 45.84, d.f. 1,273, p < 0.0001; PCL-5: β = 0.371, F = 40.93, p < 0.0001; ZSDS: β = 0.396, F = 47.33, p < 0.0001; BDI: β = 0.293, F = 22.90, p < 0.0001; STAI-Y: β = 0.396, F = 47.27, p < 0.0001; OCI: β = 0.195, F = 9.29, p = 0.0025; IRS: β = 0.292, F = 21.37, p < 0.0001; MOS: β = 0.346, F = 31.93, p < 0.0001) and in patients with a previous positive psychiatric history, except for MOS (IES-R: β = 0.274, F = 25.86, d.f. 1,273, p < 0.0001; PCL-5: β = 0.267, F = 24.11, p < 0.0001; ZSDS: β = 0.237, F = 19.25, p < 0.0001; BDI: β = 0.221, F = 14.74, p = 0.0002; STAI-Y: β = 0.238, F = 19.39, p < 0.0001; OCI: β = 0.190, F = 9.98, p = 0.0018; IRS: β = 0.123, F = 4.29, p = 0.0393; MOS: β = 0.099, F = 0.96, p = 0.329).

Baseline inflammatory markers (CRP, NLR, MLR, and SII) were higher in males and in patients that were treated as inpatients, while follow-up oxygen saturation level was higher in patients that were managed at home (Table 1). Baseline inflammatory marker as well as follow up oxygen saturation levels did not correlate with psychopathological scores except for a nominal direct correlation between OCI and baseline MLR, not surviving correction for multiple comparisons (Table 2). A comparison (Student's *t* test) of mean baseline inflammatory markers between patients who showed or not psychopathological scores in the clinical range did not show significant effects.

A multivariate GLM analysis of the effects of baseline inflammatory markers (CRP, NLR, MLR, and SII) on the current psychopathological status revealed however a significant effect of SII (Wilks' λ = 0.92; F = 2.12; d.f. 8,185; p = 0.0357), with no effect of the other markers surviving the statistical threshold. Univariate testing showed that SII significantly and positively influenced ZSDS (β = 0.411, F = 5.18, p = 0.0238), STAI-Y (β = 0.372, F = 4.26, p = 0.0404), and MOS (β = 0.572, F = 10.49, p = 0.0014).

Table 2
Pearson correlation analysis between psychiatric symptoms and baseline and follow up marker of phisical ilness. Event Scale – Revised (IES-R); PTSD Checklist for DSM-5 (PCL-5); Zung Self-rating Depression Scale (ZSDS); Beck's Depression Inventory (BDI); State-Trait Anxiety Inventory (STAI); Medical Outcomes Study Sleep Scale (MOS-SS); Women's Health Initiative Insomnia Rating Scale (WHIIRS); Obsessive-Compulsive Inventory (OCI).

	IES-R		PCL-5		BDI-13		ZSDS		STAI-state		MOS		WHIIRS		OCI	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Baseline																
C-reactive Protein (mg/L)	−0.081	0.147	−0.061	0.288	−0.091	0.098	−0.099	0.076	−0.093	0.107	−0.113	0.053	−0.069	0.215	−0.012	0.829
Neutrophil/lymphocyte ratio	−0.055	0.323	−0.029	0.613	−0.084	0.130	−0.009	0.860	−0.049	0.394	−0.110	0.063	−0.043	0.443	0.109	0.053
Monocyte/lymphocyte ratio	−0.064	0.246	−0.049	0.399	−0.090	0.103	−0.017	0.761	−0.008	0.889	−0.109	0.064	−0.034	0.536	0.115	**0.042**
Systemic immune-inflammation index	−0.001	0.981	0.015	0.791	−0.009	0.864	0.023	0.678	0.001	0.998	−0.025	0.664	0.007	0.895	0.107	0.057
Follow-up																
Oxygen saturation level	0.006	0.924	0.026	0.669	−0.001	0.999	0.067	0.289	−0.051	0.407	0.044	0.486	0.059	0.322	−0.003	0.959

4. Discussion

This is the first study that investigates psychopathology in a sample of COVID-19 survivors at one month follow-up after hospital treatment. We reported high rates of PTSD, depression, anxiety, insomnia, and OC symptomatology. Our findings mirror the results from previous coronaviruses outbreak studies, where the psychiatric morbidities ranged from 10% to 35% in the post-illness stage (Rogers et al., 2020; Sheng et al., 2005).

Psychiatric consequences to SARS-CoV-2 infection can be caused both, by the immune response to the virus itself, or by psychological stressors such as social isolation, psychological impact of a novel severe and potentially fatal illness, concerns about infecting others, and stigma. The immune response to coronaviruses induces local and systemic production of cytokines, chemokines, and other inflammatory mediators (Cameron et al., 2008). COVID-19 patients, such as SARS and MERS patients, show high levels of Interleukin (IL)-1β, IL-6, Interferon (IFN)-γ, CXCL10, and CCL2 suggesting an activation of T-helper-1 cell function. Moreover, in COVID-19, unlike in SARS and MERS, elevated levels of T-helper-2 cell-secreted cytokines (such as IL-4 and IL-10) were found (Ye et al., 2020; Channappanavar and Perlman, 2017). Higher concentrations of these cytokines seem to suggest a more severe clinical course (Huang et al., 2020). Cytokines dysregulation (especially IL-1β, IL-6, IL-10, IFN-γ, TNF-α, and transforming growth factor-β (TGF-β)) are known to involve factors that others and we associated with psychiatric disorders (Kohler et al., 2017; Miller et al., 2011; Renna et al., 2018; Poletti et al., 2019; Benedetti et al., 2017; Benedetti et al., 2020). Neuroinflammation, blood-brain-barrier disruption, peripheral immune cell invasion into the CNS, neurotransmission impairment, hypothalamic-pituitary adrenal (HPA) axis dysfunction, microglia activation and indoleamine 2,3-dioxygenase (IDO) induction, all represent interaction pathways between immune systems and psychopathological mechanism underpinning psychiatric disorders (Dantzer, 2018; Najjar et al., 2013; Benedetti et al., 2020; Jones and Thomsen, 2013).

With regard to the risk factor related to psychopathology, consistently with previous epidemiological studies, we have found that females, and patients with positive previous psychiatric diagnoses, suffered more in all psychopathological dimensions (Vindegaard and Eriksen Benros, 2020; Ozamiz-Etxebarria et al., 2020; Pappa et al., 2020). Moreover, outpatients showed increased anxiety and sleep disturbances, while the duration of hospitalization inversely correlated with PTSD, depression, anxiety, and OC symptomatology. Also considering the worse severity of COVID-19 in hospitalized patients, this observation suggests that less healthcare support could have increased the social isolation and loneliness typical of COVID-19 pandemics, thus inducing more psychopathology after remission (Ozbay et al., 2007; Leigh-Hunt et al., 2017). Finally, younger patients showed higher levels of depression and sleep disturbances, in agreement with previous studies describing a worse psychological impact of COVID-19 pandemic in younger people (Wang et al., 2020).

Neither oxygen saturation level at follow up nor baseline inflammatory markers associated with depression, anxiety, PTSD nor insomnia, suggesting that psychiatric symptomatology was not a manifestation of physical symptoms, with the exception of baseline SII that positively associated with measures of anxiety and depression at follow-up. The SII is an objective marker of the balance between host systemic inflammation and immune response status considering together neutrophil, platelet, and lymphocyte all of them involved in different pathway of immune/inflammatory response (Huang et al., 2019). Higher levels have been associated with worse prognosis in several medical diseases, in particular in the field of oncology. In a single study, higher SII levels were associated with major depressive disorder (MDD) (Zhou et al., 2020), suggesting that it could be a marker of the low-grade inflammation observed in mood disorders (Benedetti et al., 2020; Arteaga-Henríquez et al., 2019). Interestingly, we also found a direct correlation between OCI and MLR and a trend for a direct correlation between OCI and NLR and SII, suggesting that higher baseline inflammation could be associated whit later OC symptomatology. Recent evidence, in agreement with our observation, suggests an impact of COVID-19 on OCD related both to an immune and inflammatory dysregulation both to an increased perceived risk about contamination (Shafran et al., 2020; Banerjee, 2020; Teixeira et al., 2014). Moreover, baseline inflammatory parameters where higher among males and inpatients, who showed less psychopathology at follow-up, corroborating the complexity of the interaction between psychopathology and physical status.

In the light of the above, interest to deepen research on biomarkers of inflammation is warranted, to investigate the possible association between possible persistent low-grade inflammation as observed in mood disorders (Benedetti et al., 2020; Arteaga-Henríquez et al., 2019), and psychopathological symptoms at follow-up in COVID-19 survivors. This approach could also allow to identify possible new specific targets for the treatment of inflammation-related neuropsychiatric conditions (Capuron and Miller, 2011).

The main limitation of the present study is its cross-sectional nature that does not allow interpretation for causality.

5. Conclusions

In conclusion, our study hypotheses were supported by the present results based on a cohort of 402 patients. As predicted, COVID-19 survivors presented a high prevalence of emergent psychiatric sequelae,

with 55% of the sample presenting a pathological score for at least one disorder. Higher than average incidence of PTSD, major depression, and anxiety, all high-burden non-communicable conditions associated with years of life lived with disability, is expected in survivors. Moreover, depression associates with a markedly increased risk of all-cause and cause-specific mortality (Cuijpers et al., 2014). Considering the alarming impact of COVID-19 infection on mental health, we now suggest assessing psychopathology of COVID-19 survivors, to diagnose and treat emergent psychiatric conditions, monitoring their changes over time, with the aim of reducing the disease burden, which is expected to be very high in patients with psychiatric conditions (Williams, 2016). This will also allow investigating how the immune-inflammatory response translates into psychiatric illness improving our knowledge in the etiopathogenesis of these disorders.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.07.037.

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