Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full-length Article

Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up

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ABSTRACT

COVID-19 outbreak is associated with mental health implications during viral infection and at short-term follow-up. Data on psychiatric and cognitive sequelae at medium-term follow-up are still lacking. During an ongoing prospective cohort study, the psychopathological and cognitive status of 226 COVID-19 pneumonia survivors (149 male, mean age 58) were prospectively evaluated one and three months after hospital discharge. Psychiatric clinical interview, self-report questionnaires, and neuropsychological profiling of verbal memory, working memory, psychomotor coordination, executive functions, attention and information processing, and verbal fluency were performed.

Three months after discharge from the hospital, 35.8% still self-rated symptoms in the clinical range in at least one psychopathological dimension. We observed persistent depressive symptomatology, while PTSD, anxiety, and insomnia decreased during follow-up. Sex, previous psychiatric history, and the presence of depression at one month affected the depressive symptomatology at three months. Regardless of clinical physical severity, 78% of the sample showed poor performances in at least one cognitive domain, with executive functions and psychomotor coordination being impaired in 50% and 57% of the sample.

Baseline systemic immune-inflammation index (SII), which reflects the immune response and systemic inflammation based on peripheral lymphocyte, neutrophil, and platelet counts, predicted self-rated depressive symptomatology and cognitive impairment at three-months follow-up; and changes of SII predicted changes of depression during follow-up. Neurocognitive impairments associated with severity of depressive psychopathology, and processing speed, verbal memory and fluency, and psychomotor coordination were predicted by baseline SII.

We hypothesize that COVID-19 could result in prolonged systemic inflammation that predisposes patients to persistent depression and associated neurocognitive dysfunction. The linkage between inflammation, depression, and neurocognition in patients with COVID-19 should be investigated in long-term longitudinal studies, to better personalize treatment options for COVID-19 survivors.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has widely and rapidly spread worldwide in a matter of months. The COVID-19 pandemic continues to grow and, according to the World Health Organization, more than 99,300,000 confirmed cases and at least 2,130,000 death have been reported globally (WHO, 2020).

As the pandemic spread, there has been a growing recognition of mental health implications (Amsalem et al., 2020; The Lancet, 2020;

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Xiang et al., 2020). Emerging data show that COVID-19 outbreak is associated with delirium, fatigue, confusion, depression, anxiety, post-traumatic stress disorder (PTSD), obsessive–compulsive symptoms, and insomnia in the context of acute viral infection or at short-term follow-up after clinical recovery, with severity of psychiatric symptoms after virus clearance being proportional to the severity of systemic inflammation during the acute infection and significantly contributing to the quality of life of survivors (De Lorenzo et al., 2020; Ma et al., 2020; Mazza et al., 2020; Varatharaj et al., 2020).

The host immune response to SARS-CoV-2 infection, the persistent psychological stress before and during infection (Korman et al., 2020; Vai et al., 2020), and a possible direct viral infections of the central nervous system represent possible mechanisms to induce neuropsychiatric sequelae (Troyer et al., 2020). T helper (Th)-1 cytokines, including Interleukin (IL)-1β, IL-6, Interferon (IFN)-γ, Tumor Necrosis Factor (TNF)-α, CXCL10, and CCL2; and Th-2 cytokines, including IL-4, IL-10, and IL-1 receptor antagonist are all elevated in the serum of COVID-19 patients (Coperchini et al., 2020) in a "cytokine storm" typically associated with the illness.

Higher immune/inflammatory setpoints with higher circulating biomarkers of inflammation are observed in mood disorders in the absence of known triggering factors, and are currently investigated as underpinning pathogenetic mechanisms for depressive psychopathology (Gibney and Drexhage, 2013; Grosse et al., 2015; Poletti et al., 2020b). Peripheral cytokines involved in the host anti-viral response may elicit psychiatric symptoms by precipitating inflammation in the periphery and in central nervous system (CNS) (Dantzer, 2018). Moreover, significant stressors such as fear of severe and unknown disease, loneliness, stigma, and the denial contribute to widespread emotional distress and increased risk for psychiatric illness in COVID-19 patients (Pfefferbaum and North, 2020).

Beyond acute or sub-acute sequelae, the delayed or long-term incidence of neuropsychiatric complications in COVID-19 survivors are still unknown. Current knowledge suggests that viral infections can trigger chronic inflammation and aberrant immune responses, causing long-lasting neuropsychiatric syndromes involving cognitive, affective, and behavioural symptoms, over highly variable periods after infection (from weeks to years following acute infection) (Bechter, 2013; Kepinska et al., 2020; Lam et al., 2009; Rogers et al., 2020).

Considering the high prevalence of emergent psychiatric conditions that we have observed at one-month follow-up (Mazza et al., 2020) and surmising persistent delayed post-viral psychiatric and cognitive sequelae, here we aimed at studying psychopathological and neurocognitive impact of COVID-19 in survivors three-month after clinical recovery.

2. Material and methods

2.1. Design and study population

We prospectively evaluated the psychopathological and cognitive status of COVID-19 survivors three months (90.1 ± 13.4 days) after hospital discharge during an ongoing prospective cohort study at IRCCS San Raffaele Hospital in Milan. From an initial cohort of 402 COVID-19 survivors that were evaluated at one-month follow-up (see (Mazza et al., 2020)); 226 COVID-19 survivors were re-assessed at three months (149 male, mean age 58.5 ± 12.8, age range from 26 to 87 years). The three-month follow-up cohort did not differ from the drop-out group and from the initial cohort in terms of sociodemographic characteristics, clinical severity, and one-month psychopathology after False Discovery Rate (FDR) correction (See Supplementary material).

Inclusion criteria were clinical and radiological findings suggestive of COVID-19 pneumonia at the admission to the Emergency Department (ED). The infection was confirmed by positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal and/or throat swab. After ED evaluation, patients were hospitalized (n = 177, hospital stay 15.66 ± 10.1 days) or treated at home (n = 49).

To keep a naturalistic study design, exclusion criteria were limited to patients under 18 years.

The local ethical committee approved the study protocol in accordance with the principles in the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Clinical and neuropsychological assessment

Two trained psychiatrists in charge (MGM & FB) conducted the psychiatric unstructured clinical interview using the best estimation procedure to investigate the presence of current major psychiatric disorder (schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, obsessive–compulsive and related disorders, trauma- and stressor-related disorders, feeding and eating disorders, sleep-wake disorders, substance-related and addictive disorders) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Validated self-report questionnaires were used to assess psychopathology: Impact of Event 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), Women's Health Initiative Insomnia Rating Scale (WHIIRS) (Levine et al., 2003), and Obsessive-Compulsive Inventory (OCI) (Foa et al., 2002). Generally accepted standard cut-off scores were used to consider the presence of psychopathology (IES-R ≥ 33; PCL-5 ≥ 33; ZSDS index ≥ 50; BDI-13 ≥ 9; STAI-state ≥ 40; WHIIRS ≥ 9; OCI ≥ 21). The presence of psychopathology at one and three months was considered when the patient self-rated in the clinical range for depression, PTSD, anxiety, and obsessive–compulsive symptoms according to at least one questionnaire (ZSDS and/or BDI-13 and/or IES-R and/or PCL-5 and/or STAI-Y state and/or OCI), excluding the patients who self-rated in the pathological range only for insomnia in order to be more conservative as possible.

Inflammatory markers at hospital admission during acute COVID-19 were extracted from charts levels for the whole sample: C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) (SII = platelets X neutrophils / lymphocytes). In a subgroup of 45 patients out of the total sample, these markers were available also at the three-months follow-up.

In a subsample of 130 patients, we assessed cognitive functions through the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), a broad battery evaluating verbal memory, verbal fluency, working memory (digit sequencing), selective attention and processing speed (symbol coding), psychomotor coordination (token motor task), and executive functions (Tower of London). Considering that domain scores were adjusted according to normative Italian scores for the BACS subtests in patients aged 18–70 years, we did not perform cognitive assessment in patients older than 70 years (Anselmetti et al., 2008). To provide a standard metric for comparison across neurocognitive domains for each subtest an equivalent score, ranging from 0 to 4, has been obtained where scores 2, 3 or 4 reveal a good performance while score of 0 or 1 reveal a poor performance.

2.3. Statistical analyses

All the statistical analyses were performed with a commercially available software package (StatSoft Statistica 12, Tulsa, OK, USA) and following standard computational procedures (Dobson, 1990; Hill and Lewicki, 2006).

To account for the multiple covarying variables, we tested the effect of predictors on the outcomes in the context of the General Linear Model (GLM) and we calculated the statistical significance of the effect of the single independent factors on the dependent variables by parametric

estimates of predictor variables (least squares method). To investigate changes of psychopathology over time, repeated measures ANOVAs (according to sex and psychiatric history) were performed, considering ZSDS, BDI-13, IES-R, PCL-5, STAI-Y, OCI, and WHIIRS scores at one- and three-months follow-up. When appropriate, levels of significance were corrected for multiple comparisons with the method of the adaptive linear step-up procedures that control the FDR and q-values (FDR-adjusted p-value) were considered.

To test the effect of systemic inflammation on severity of psychopathology and neurocognitive performances, and considering the *a priori* expected significant interaction with other independent factors (age, sex, hospitalization) and the non-normal distribution of inflammatory biomarkers, independent variables were entered into a Generalized Linear Model (GLZM) analysis of homogeneity of variances with an identity link function (McCullagh and Nelder, 1989). Parameter estimates were obtained with iterative re-weighted least squares maximum likelihood procedures. The significance of the effects was calculated with the likelihood ratio (LR) statistic, which provides the most asymptotically efficient test known, by performing sequential tests for the effects in the model of the factors on the dependent variable, at each step adding an additional effect into the model contributing to incremental Chi-square statistic, thus providing a test of the increment in the log-likelihood attributable to each current estimated effect; or the Wald W^2 test as appropriate (Agresti, 1996; Dobson, 1990). The quality of the statistical model was checked using the entropy maximization principle of the Akaike information criterion (AIC) (Akaike, 1974).

3. Results

Clinical and demographic characteristics of participants are resumed in Table 1 (effects of sex and of previous DSM-V diagnosis) and Table 2 (effect of psychopathology at one and three months).

3.1. Psychopathology and need for treatment

Three months after hospital discharge 81/226 patients (35.8%) self-rated symptoms 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). Females, patients with a positive previous psychiatric diagnosis, and patients who already presented psychopathological symptoms one month after discharge suffered more in all psychopathological domains (Tables 1 and 2). Duration of hospitalization inversely correlated with three months ZSDS ($r = -0.23$, $p = 0.005$, $q = 0.01$), BDI-13 ($r = -0.21$, $p = 0.010$, $q = 0.015$), IES-R ($r = -0.20$, $p = 0.014$, $q = 0.017$), PCL-5 ($r = -0.26$, $p = 0.003$, $q = 0.01$), OCI ($r = -0.26$, $p = 0.004$, $q = 0.01$), and WHIIRS ($r = -0.17$, $p = 0.044$, $q = 0.044$). Age and setting of the care did not affect self-ratings psychopathology.

From the one-month to the three-month follow-up, patients showed a significant decrease over time of PTSD symptoms (IES-R: $F = 21.29$, $p = 0.001$; PCL-5: $F = 9.07$, $p = 0.003$), anxiety (STAI-state: $F = 11.28$, $p = 0.001$), and insomnia (WHIIRS: $F = 9.36$, $p = 0.003$), irrespectively of sex and previous psychiatric history (Table 3). In contrast, depression (according to ZSDS and BDI) did not significantly change; and obsessive–compulsive symptomatology significantly worsened ($F = 4.84$, $p = 0.030$) with no effect of sex and psychiatric history (Table 3). Interestingly, we found a statistical trend for the protective effect of previous psychiatric history on depressive symptoms over time (Time × psychiatric history $F = 3.36$, $p = 0.069$) (Table 3).

A multivariate GLM analysis of the effects of sex, previous psychiatric diagnosis, duration of hospitalization, and presence of psychopathology at one-month follow-up on the three months depressive symptomatology confirmed a significant multivariate effect of sex (Wilks' $\lambda = 0.92$; $F = 5.76$; $p = 0.003$), previous psychiatric diagnosis (Wilks' $\lambda = 0.93$; $F = 5.29$; $p = 0.006$), and presence of psychopathology at one-month (Wilks' $\lambda = 0.82$; $F = 15.16$; $p < 0.001$), all factors that predicted the persistence of psychopathology over time. Univariate testing showed significantly worse persistence of depressive symptomatology in females (ZSDS: $\beta = 0.21$, $F = 7.31$, $p = 0.008$; BDI-13: $\beta = 0.27$, $F = 11.12$; $p = 0.001$), in patients with previous lifetime psychiatric history (ZSDS: $\beta = 0.15$, $F = 4.66$, $p = 0.32$; BDI-13: $\beta = 0.23$, $F = 10.65$, $p = 0.001$), and in patients who showed psychopathology one month after discharge (ZSDS: $\beta = 0.41$, $F = 30.50$, $p < 0.001$; BDI-13: $\beta = 0.26$, $F = 11.92$, $p < 0.001$).

At the clinical interview 55/226 patients (24.3%) showed DSM-5 criteria for the diagnosis of current major psychiatric disorder (major depressive disorder ($n = 20$), anxiety disorders ($n = 20$), insomnia ($n = 7$), and other diagnoses ($n = 8$)). Of them, 34 patients were in need of a psychopharmacologic treatment, 10 patients were already taking drugs, while 24 patients started taking pharmacological treatment. Patients with positive previous psychiatric diagnosis were at higher risk to show DSM-5 criteria for the diagnosis of current major psychiatric disorder ($\chi^2 = 20.12$; $p < 0.001$ See Supplementary material). Overall, 9% of patients with no previous psychiatric history and 32% of patients with positive previous psychiatric history were prescribed psychotropic drugs (selective serotonin reuptake inhibitors alone, or combined with sleep-inducing benzodiazepines).

3.2. Neurocognitive functioning

Only 25 patients (19%) showed equivalent scores within the normal range in all domains, whereas 21 (16%) were poor performers in at least one function, 22 (17%) in two, 18 (14%) in three, 14 (11%) in four, 7 (5%) in five, and 2 (1.5%) showed no good performance at all.

Psychopathology influenced neurocognition. A GLM multivariate analysis of variance showed significant effects of any kind of psychopathology presented at one (Wilks' $\lambda = 0.81$; $F = 3.39$; $p = 0.004$) and three months (Wilks' $\lambda = 0.82$; $F = 2.32$; $p = 0.042$) after discharge; but not of sex, previous psychiatric diagnosis, and duration of hospitalization. Patients with psychopathology one-month after discharge performed worse on verbal fluency ($\beta = 0.349$, $p = 0.002$), information processing ($\beta = 0.348$, $p = 0.002$), and executive functions ($\beta = 0.353$, $p = 0.001$) at the three months assessment; whereas psychopathology at three months associated with worse information processing ($\beta = 0.355$, $p = 0.008$). In particular, severity of depressive symptoms (ZSDS scores) at one and three months follow-up predicted the performance in information processing (one month: Wald = 7.05, $p = 0.007$; three months: Wald = 8.37, $p = 0.003$).

Oxygen saturation level at admission and duration of hospitalization did not affect neurocognition.

3.3. Effect of inflammatory biomarkers

Systemic inflammation (SII level) predicted severity of depressive psychopathology at the three-months follow-up. A GLZM analysis of the effects of SII at hospital admission on severity of depression at three months, also considering sex, hospitalization, and age as factors, showed that best performing models according to AIC always included SII and significantly explained the variation of depression severity ($\chi^2 = 56.536$, $p < 0.0001$ for BDI; $\chi^2 = 42.417$, $p < 0.0001$ for ZSDS index scores). The significant effects were the main effect of sex (worse scores in females, BDI: $\chi^2 = 30.222$, $p < 0.0001$; ZSDS: $\chi^2 = 20.627$, $p < 0.0001$); the interaction of SII with hospitalization (BDI: $\chi^2 = 7.357$, $p = 0.0067$; ZSDS: $\chi^2 = 3.999$, $p = 0.0455$); the interaction of age and sex (BDI: $\chi^2 = 8.933$, $p = 0.0028$; ZSDS: $\chi^2 = 5.423$, $p = 0.0199$); and the triple interaction of SII with age and sex (BDI: $\chi^2 = 10.821$, $p = 0.0010$; ZSDS: $\chi^2 = 5.252$, $p = 0.0219$). Analysis of parameter estimates showed that in hospitalized patients, who had significantly worse inflammation (SII: 1480.61 ± 1395.47 vs 871.34 ± 711.27; Mann-Whitney $U = 1451.00$, $Z = 2.980$, $p = 0.0026$), but not in less severe patients treated at home, SII associated with worse BDI and ZSDS scores correcting for sex and age

Table 1
Psychiatric symptoms and neurocognition at three months in patients surviving COVID-19 infection, divided according to sex and psychiatric history, and levels of significance of the observed differences (Student's *t* test and Chi-square). Patients self-rated their symptoms on the Zung Self-rating Depression Scale (ZSDS); Beck's Depression Inventory (BDI); Impact of Event Scale – Revised (IES-R); PTSD Checklist for DSM-5 (PCL-5); State Anxiety Inventory (STAI); Women's Health Initiative Insomnia Rating Scale (WHIIRS); Obsessive-Compulsive Inventory (OCI).

	Whole sample (n = 226)	Sex				Psychiatric history			
		Males (n = 149)	Females (n = 77)	t or χ^2	p	Negative (n = 164)	Positive (n = 62)	t or χ^2	p
Males (females)	149 (77)	–	–	–	–	120 (44)	29 (33)	13.95	**<0.001**
Age	58.52 ± 12.79	59.71 ± 11.55	56.17 ± 14.72	1.97	**0.049**	59.41 ± 13.15	56.17 ± 11.57	1.71	0.091
Education (years)	12.58 ± 3.68	12.64 ± 3.64	12.52 ± 3.77	0.16	0.866	12.46 ± 3.84	12.84 ± 3.36	−0.51	0.609
Baseline C reactive protein (mg/l)	74.27 ± 81.1	89.34 ± 81.1	46.03 ± 61.61	3.93	**<0.001**	70.78 ± 68.32	83.05 ± 97.13	−1.02	0.3092
Baseline neutrophil/ lymphocyte ratio	5.73 ± 5.98	6.66 ± 5.98	3.92 ± 3.14	3.54	**<0.001**	5.32 ± 4.43	6.78 ± 7.13	−1.75	0.0815
Baseline monocyte/ lymphocyte ratio	0.51 ± 0.42	0.55 ± 0.42	0.43 ± 0.35	1.96	0.051	0.5 ± 0.41	0.53 ± 0.37	−0.53	0.5983
Baseline systemic immune-inflammatory index	1312.87 ± 1388.19	1479.29 ± 1388.19	1002.38 ± 830.95	2.57	**0.010**	1234.98 ± 1125.98	1497.34 ± 1474.8	−1.34	0.1817
ZSDS index (n = 188)	43.56 ± 11.62	40.04 ± 9.16	50.56 ± 12.82	−6.47	**<0.001**	41.35 ± 10.55	48.77 ± 12.43	−4.18	**<0.001**
BDI-13 (n = 186)	3.05 ± 4.55	1.68 ± 2.57	5.73 ± 6.15	−6.31	**<0.001**	1.93 ± 2.98	5.66 ± 6.24	−5.52	**<0.001**
IES-R (n = 187)	21.05 ± 19.78	16.86 ± 17.59	29.29 ± 21.36	−4.24	**<0.001**	17.57 ± 18.28	29.18 ± 20.93	−3.81	**<0.001**
PCL-5 (n = 174)	12.7 ± 15.84	8.11 ± 12.34	20.79 ± 18.06	−5.49	**<0.001**	8.77 ± 12.82	21.20 ± 18.37	−5.15	**<0.001**
STAI-Y state (n = 177)	36.19 ± 11.47	32.70 ± 9.58	43.54 ± 11.72	−6.54	**<0.001**	33.66 ± 9.78	42.27 ± 12.96	−4.83	**<0.001**
OCI (n = 134)	14.04 ± 11.71	11.37 ± 10.22	19.70 ± 12.74	−4.06	**<0.001**	11.87 ± 10.82	18.65 ± 12.29	−3.24	**0.002**
WHIIRS (n = 173)	6.16 ± 4.73	5.32 ± 4.56	7.72 ± 4.7	−3.27	**0.001**	5.76 ± 4.7	7.07 ± 4.75	1.7	0.090
ZSDS index ≥ 50 Yes (%)	51 (28%)	20 (16%)	31 (49%)	23.36	**0.001**	28 (23%)	23 (40%)	7.84	**0.005**
BDI-13 ≥ 8 Yes (%)	20 (9%)	4 (2%)	16 (26%)	21.28	**<0.001**	5 (5%)	15 (26%)	21.46	**<0.001**
IES-R ≥ 33 Yes (%)	39 (22%)	20 (16%)	19 (31%)	12.93	**0.001**	19 (15%)	20 (36%)	17.87	**<0.001**
PCL-5 ≥ 33 Yes (%)	22 (13%)	6 (5%)	16 (26%)	14.54	**<0.001**	7 (6%)	15 (27%)	15.58	**<0.001**
STAI-Y state ≥ 40 Yes (%)	51 (30%)	21 (18%)	30 (54%)	23.25	**<0.001**	25 (21%)	26 (50%)	16.11	**<0.001**
OCI ≥ 21 Yes (%)	33 (26%)	14 (16%)	19 (44%)	13.05	**<0.001**	16 (18%)	17 (39%)	7.58	**0.005**
WHIIRS ≥ 9 Yes (%)	43 (24%)	20 (18%)	23 (37%)	8.33	**0.003**	25 (22%)	18 (33%)	3.02	0.082
Verbal memory (n = 130)	41.20 ± 10.28	39.49 ± 10.00	43.67 ± 10.27	2.32	**0.022**	40.67 ± 9.99	42.34 ± 10.93	0.86	0.392
Verbal fluency (n = 130)	45.42 ± 12.05	46.61 ± 13.31	43.69 ± 9.81	1.36	0.176	45.59 ± 11.88	45.05 ± 12.56	0.23	0.811
Working memory (n = 126)	20.32 ± 4.93	21.50 ± 4.74	18.68 ± 4.75	3.28	**0.001**	20.29 ± 5.13	20.39 ± 4.53	−0.1	0.918
Attention and Information processing (n = 130)	46.61 ± 11.68	46.00 ± 11.85	47.49 ± 11.44	0.71	0.476	46.12 ± 12.67	47.65 ± 9.22	−0.69	0.488
Psychomotor coordination (n = 130)	68.33 ± 18.33	68.15 ± 19.83	68.60 ± 16.07	0.13	0.891	68.69 ± 18.24	67.56 ± 18.72	0.32	0.744
Executive functions (n = 130)	13.99 ± 4.50	14.15 ± 4.53	13.75 ± 4.49	0.49	0.619	13.86 ± 4.62	14.5 ± 4.41	−0.7	0.48
Verbal memory poor performance (%)	11 (10%)	7 (10%)	4 (9%)	0.14	0.708	7 (9%)	4 (11%)	0.03	0.871
Verbal fluency poor performance (%)	39 (32%)	22 (32%)	17 (33%)	0.05	0.824	26 (32%)	13 (32%)	0.01	0.929
Working Memory poor performance (%)	30 (24%)	11 (15%)	19 (37%)	7.67	**0.005**	21 (26%)	9 (22%)	0.14	0.708
Attention and Information Processing poor performance (%)	43 (33%)	29 (38%)	14 (27%)	1.61	0.204	32 (36%)	11 (27%)	1.14	0.284
Psychomotor coordination poor performance (%)	72 (57%)	43 (59%)	29 (56%)	0.12	0.727	49 (59%)	23 (56%)	0.05	0.812
Executive Functions poor performance (%)	60 (50%)	32 (46%)	28 (56%)	1.23	0.266	40 (51%)	20 (49%)	0.03	0.847

Table 2
Psychiatric symptoms and neurocognition in patients surviving COVID-19 infection, divided according to the presence of psychopathology at one and three months and levels of significance of the observed differences (Student's *t* test and Chi-square). Patients self-rated their symptoms on the Zung Self-rating Depression Scale (ZSDS); Beck's Depression Inventory (BDI); Impact of Event Scale – Revised (IES-R); PTSD Checklist for DSM-5 (PCL-5); State Anxiety Inventory (STAI); Women's Health Initiative Insomnia Rating Scale (WHIIRS); Obsessive-Compulsive Inventory (OCI).

	Psychopathology at one month follow-up					Psychopathology at three months follow-up				
	Negative (n = 113)	Positive (n = 113)	t or χ^2	p	q	Negative (n = 145)	Positive (n = 80)	t or χ^2	p	q
Males (females)	96 (17)	53 (60)	36.42	**<0.001**	**<0.001**	110 (35)	39 (42)	17.76	**<0.001**	**<0.001**
Age	58.72 ± 12.26	58.32 ± 13.36	0.23	0.817	0.862	59.24 ± 12.6	57.21 ± 13.11	1.14	0.256	0.304
Education (years)	13.05 ± 3.6	12.18 ± 3.74	1.29	0.200	0.237	12.62 ± 3.63	12.53 ± 3.79	0.13	0.896	0.945
ZSDS index (n = 188)	36.55 ± 5.86	53.13 ± 11.31	−13.29	**<0.001**	**<0.001**	36.71 ± 5.94	53.44 ± 10.65	−13.76	**<0.001**	**<0.001**
BDI-13 (n = 186)	1.01 ± 1.28	5.96 ± 5.79	−8.36	**<0.001**	**<0.001**	0.78 ± 1.19	6.34 ± 5.52	−10.22	**<0.001**	**<0.001**
IES-R (n = 187)	11.61 ± 9	39.44 ± 19.89	−12.76	**<0.001**	**<0.001**	18.54 ± 17.30	38.92 ± 20.39	−7.59	**<0.001**	**<0.001**
PCL-5 (n = 174)	4.45 ± 4.48	25.62 ± 17.47	−11.11	**<0.001**	**<0.001**	3.47 ± 4.05	25.47 ± 17.19	−12.39	**<0.001**	**<0.001**
STAI-Y state (n = 177)	29.33 ± 6.26	43.92 ± 9.68	−12.74	**<0.001**	**<0.001**	29.51 ± 5.63	45.93 ± 10.84	−13.15	**<0.001**	**<0.001**
OCI (n = 134)	6.31 ± 4.81	18.5 ± 10.55	−10.60	**<0.001**	**<0.001**	7.33 ± 5.38	23.10 ± 11.86	−10.32	**<0.001**	**<0.001**
WHIIRS (n = 173)	5.18 ± 3.98	9.25 ± 5.2	−6.32	**<0.001**	**<0.001**	4.2 ± 3.50	8.93 ± 4.89	−7.38	**<0.001**	**<0.001**
Verbal memory (n = 130)	48.95 ± 8.8	48.99 ± 10.92	−0.02	0.982	0.982	40.37 ± 10.73	42.52 ± 9.49	−1.15	0.249	0.304
Verbal fluency (n = 130)	48.74 ± 14.14	43.54 ± 10.08	2.31	**0.023**	**0.034**	46.41 ± 12.53	42.52 ± 9.49	1.18	0.237	0.304
Working memory (n = 126)	22.32 ± 4.66	19.81 ± 4.94	2.82	**0.006**	**0.010**	20.71 ± 4.75	19.71 ± 5.19	1.11	0.286	0.319
Attention and Information processing (n = 130)	53.29 ± 10.95	48.06 ± 11.22	2.60	**0.011**	**0.017**	48.08 ± 11.41	44.24 ± 11.81	1.84	0.067	0.098
Psychomotor coordination (n = 130)	74.49 ± 17.59	69.92 ± 17.82	1.39	0.166	0.210	68.37 ± 18.47	68.28 ± 18.29	0.02	0.977	0.977
Executive functions (n = 130)	15.66 ± 4.46	13.78 ± 4.49	2.27	**0.025**	**0.040**	14.57 ± 4.37	13.06 ± 4.59	1.88	0.061	0.096

Table 3
Changes of psychopathology over time according to sex and psychiatric history (repeated measures ANOVA). Zung Self-rating Depression Scale (ZSDS); Beck's Depression Inventory (BDI); Impact of Event Scale – Revised (IES-R); PTSD Checklist for DSM-5 (PCL-5); State Anxiety Inventory (STAI); Obsessive-Compulsive Inventory (OCI); Women's Health Initiative Insomnia Rating Scale (WHIIRS).

	One month follow-up	Three months follow-up	Time		Time × sex		Time × psychiatric history	
			F	p	F	p	F	p
ZSDS index (n = 178)	43.88 ± 11.74	43.38 ± 11.62	2.095	0.15	0.627	0.43	3.358	0.069
BDI-13 (n = 173)	3.23 ± 4.06	2.94 ± 4.5	1.203	0.274	0.783	0.378	0.758	0.385
IES-R (n = 175)	25.27 ± 20.6	20.59 ± 19.86	21.286	**0.001**	1.759	0.187	2.661	0.105
PCL-5 (n = 150)	15.81 ± 16.52	12.65 ± 15.86	9.069	**0.003**	0.001	0.97	0.356	0.552
STAI-Y state (n = 158)	37.7 ± 11.27	35.53 ± 11.26	11.276	**0.001**	2.244	0.136	0.183	0.67
OCI (n = 124)	12.52 ± 9.45	14.07 ± 12.1	4.836	**0.03**	2.151	0.145	0.008	0.93
WHIIRS (n = 163)	7.22 ± 5.07	6.12 ± 4.64	9.364	**0.003**	3.753	0.154	0.139	0.71

(BDI: Wald $W^2 = 19.635$, $p < 0.0001$; ZSDS; Wald $W^2 = 18.217$, $p < 0.0001$). Inspection of data (Fig. 1) shows highly dispersed depression ratings at low levels of inflammation, with more severe symptoms at higher levels of inflammation.

Moreover, changes of systemic inflammation over time influenced the pattern of change of depressive symptoms (Fig. 1). The decrease of SII from hospital admission to three months after discharge significantly influenced the change of depressive symptoms at follow-up, as rated both at BDI-13 (Wald $W^2 = 14.304$, $p = 0.0002$) and at ZSDS (Wald $W^2 = 6.881$, $p = 0.0087$), with no effects of sex, age, and hospitalization: patients who showed a marked decrease of SII also showed a decrease of depression severity, while patients who showed minor changes of SII showed persistent or worsening depression. A GLM repeated measures analysis of variance confirmed a significant interaction of delta SII with time on the pattern of change of both BDI-13 ($F = 12.37$, d.f. 1,32, $p = 0.0013$) and ZSDS ($F = 5.95$, d.f. 1,32, $p = 0.0204$).

Systemic inflammation also predicted neurocognitive performance. A GLZM analysis of the effects of SII at hospital admission on BACS scores, also considering sex, hospitalization, and age as factors, showed a significant negative main effect of age on all measures, and a significant interaction of SII and age on verbal memory ($\chi^2 = 4.908$, $p = 0.0267$), verbal fluency ($\chi^2 = 4.273$, $p = 0.0387$), speed of information processing (symbol coding, $\chi^2 = 5.544$, $p = 0.0185$), and psychomotor coordination ($\chi^2 = 6.680$, $p = 0.0097$), the latter also influenced by the main effect of SII ($\chi^2 = 7.636$, $p = 0.0057$). Analysis of parameter estimates showed a negative effect of SII on performance (Fig. 2).

No association was found between other inflammatory markers (CRP, NLR, and MLR) at baseline and three months follow-up and depression.

4. Discussion

This is the first study to prospectively investigate the psychiatric and neurocognitive sequelae at a medium-term follow-up in COVID-19 survivors. Our main finding is the presence of isolated persistent depressive symptomatology at three months follow-up after SARS-CoV-2 infection, which is predicted by systemic inflammation during acute infection, and by its pattern of change over time. A parallel decrease of PTSD, anxiety and insomnia over time suggests specific long lasting depressive sequelae in COVID-19 survivors. Moreover, we observed dysfunctions in attention and information processing that were strictly related to the presence of depressive symptomatology both at one and three months, and to systemic inflammation.

Several mechanisms could underpin the impact of COVID-19 on mood and cognition, including both biological and psychological factors. COVID-19 induces a robust immune response characterized by a hyperinflammatory state with high levels of IL-1β, IL-4, IL-6, IL-10, TNF-α CXCL10, and CCL2 (Mehta et al., 2020; Ye et al., 2020). Inflammation is known to be associated to depression inducing brain-blood-barrier

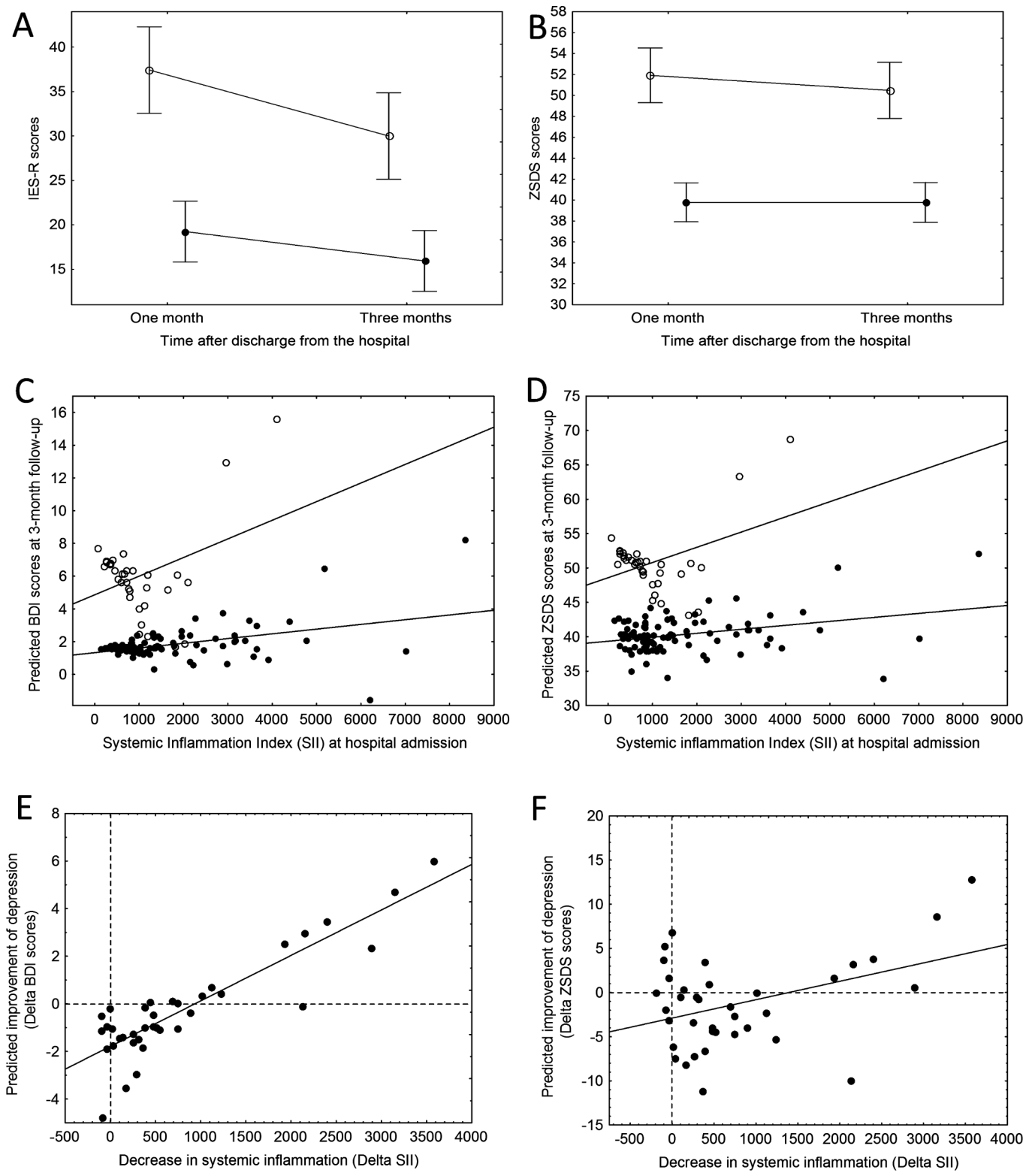

Fig. 1. Changes of psychopathology over time, and its relationship with systemic inflammation. Top: Significant decrease of PTSD symptoms (IES-R scores) over time (A), with persistence of depressive symptoms (ZSDS scores) (B); black dots are males, white are females. Middle: Effect of systemic inflammation (SII) at hospital admission, on depressive symptoms at three-month follow-up as measured by BDI-13 (C) or ZSDS (D); black dots are males, white are females. Bottom: Effect of the decrease of systemic inflammation from hospital admission to 3 months after hospital discharge, on the pattern of change of depressive symptoms during follow-up as measured by BDI-13 (E) or ZSDS (F).

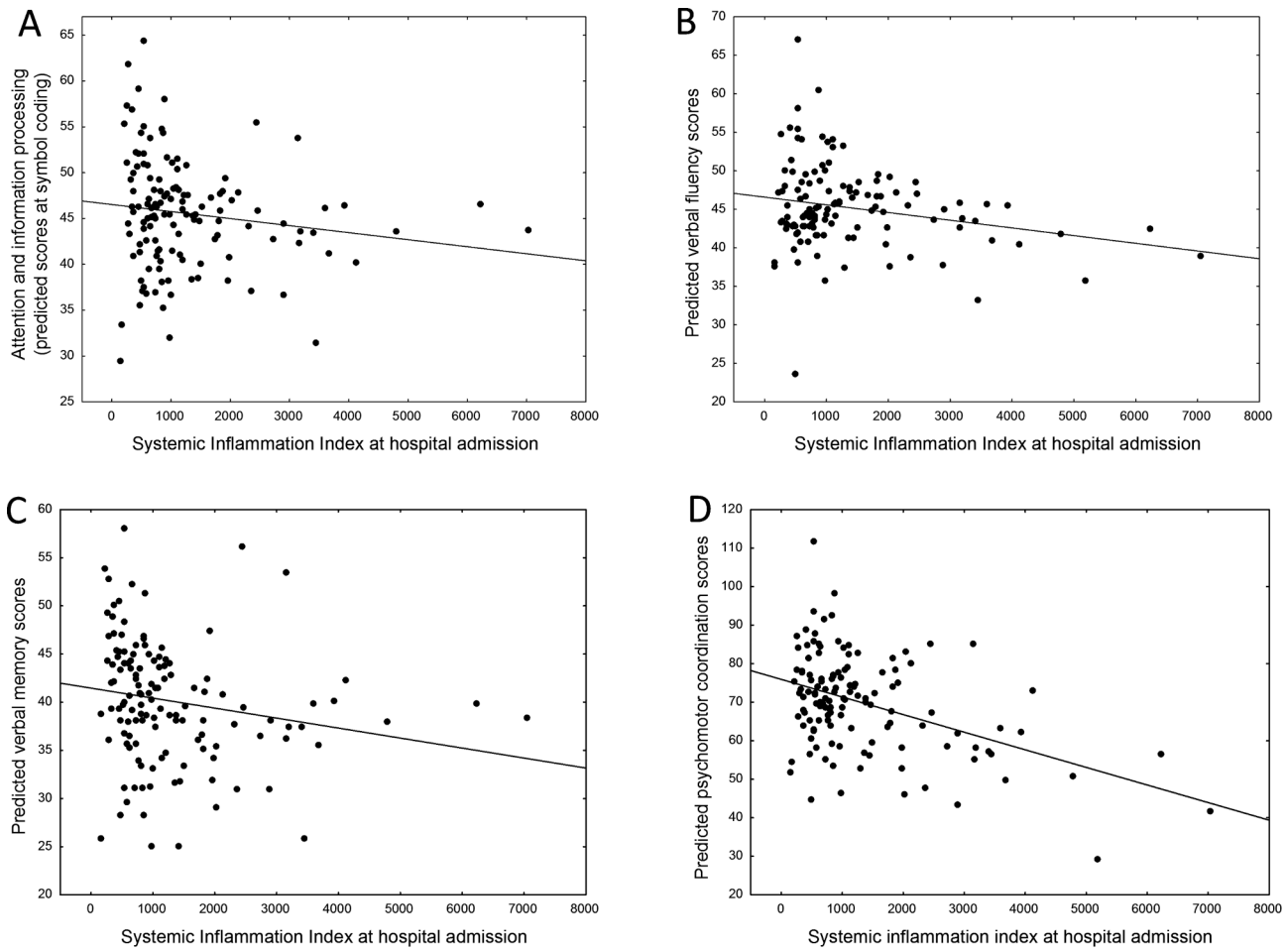

Fig. 2. Effect of systemic inflammation (SII) at hospital admission, on neurocognitive performances at three-month follow-up as measured with BACS. A: Attention and speed of information processing (symbol coding). B: Verbal fluency. C: Verbal memory. D: Psychomotor coordination.

disruption, microglia activation, neurotransmission alteration, indoleamine 2,3-dioxygenase 1 (IDO) activation, and oxidative stress (Benedetti et al., 2020a; Miller and Raison, 2016). Depressed patients are characterized by higher levels of cytokines when compared to healthy controls with consistent results in literature when considering IL-1β, IL-6, IL-10, CCL2, TNF-α, and transforming growth factor-β (TGF-β) (Enache et al., 2019; Eyre et al., 2016; Howren et al., 2009; Kohler et al., 2017; Poletti et al., 2020b). NLR, MLR and SII are low-cost, suitable for clinical routine analysis, and reproducible markers of the systemic inflammatory response, which can be easily derived from blood cell essay and determined under simple laboratory conditions (Balta et al., 2013). Several studies have proven that these inflammatory ratios can be used as inflammatory biomarkers in depression (Mazza et al., 2018; Wang et al., 2021; Zhou et al., 2020b). In the present study, we have found that baseline SII predicted severity of depressive psychopathology and neurocognitive performance at the three-months follow-up. In this context, we have previously found that higher inflammation, quantified by SII, is associated with higher depression in COVID-19 survivors (Mazza et al., 2020). This finding is consistent with the reported higher depression in convalescent COVID-19 patients with higher NLR (Yuan et al., 2020). We also observed a protective effect against depression of cytokine-blocking agents (anakinra, a recombinant version of the human IL-1β receptor antagonist, and tocilizumab, a monoclonal antibody targeting the IL-6 receptor), possibly associated with their effect in dampening SII, in hospitalized male patients surviving severe, life-threatening COVID-19 (Benedetti et al., 2020b). SII, considering together neutrophil, platelet, and lymphocyte, is an objective marker of the balance between host systemic inflammation and immune response (Huang et al., 2019). Neutrophils are critical for starting and regulating the innate immune defense through phagocytosis, apoptotic action, chemotactic role, oxidative stress, and secretion of inflammatory mediators (Nathan, 2006). Platelets are an aspecific first line inflammatory marker that mediate endothelial permeability and recruitment of neutrophils and macrophages and their effector functions. Platelet activation is mediated by serotonin, dopamine, glutamate, cytokines and P-selectin, all of them plays an important role in psychiatric disorders (Dietrich-Muszalska and Wachowicz, 2017). Finally, lymphocytes are primarily involved in adaptive immunity, with a regulatory or protective function (Alberts, 2008). Considering together three complementary cells mediating different immune or inflammatory pathways, SII is less affected by confounding conditions, and more predictive in evaluating chronic systemic inflammatory status than neutrophils, platelets or lymphocytes separately (Gibson et al., 2007).

Neurocognitive impairment has been commonly reported in patients with a viral infection. In SARS and MERS, after recovery from the infection, impairment of memory, attention, concentration, or mental processing speed were reported in more than 15% of patients at a follow-up period ranging between 6 weeks and 39 months (Hopkins et al., 1999; Sheng et al., 2005). In COVID-19, a dysexecutive syndrome in a third of survivors was described (Helms et al., 2020), as well as cognitive dysfunction in sustained attention domain possibly linked to the underlying inflammatory processes measured with CRP (Zhou et al., 2020a). Consistently with previous literature, we observed a high rate of cognitive deficits in COVID-19 survivors at three months, irrespective of medical severity of the illness, with only 22% of the sample showing a good performance in all the investigated domains. Executive functions

and psychomotor coordination were the most involved domain being impaired in 50% and 57% of the sample; information processing, verbal fluency, and working memory were impaired in around 30% of the sample.

These effects were influenced both, by the presence of psychopathology, and by systemic inflammation, thus confirming the connection between depression, inflammation, and cognition. Many studies have implied that inflammation activation is inextricably linked to cognitive dysfunction suggesting a primary role of IL-1β, IL-6, IL-18, and TNF-α (Beydoun et al., 2019; Gorelick, 2010; McAfoose and Baune, 2009). Recently, elevated NLR was described in mild cognitive impairment, while platelet/lymphocyte ratio and SII associated with risk of dementia in the general population (An et al., 2019; van der Willik et al., 2019).

In patients with a depressive episode in course of Major Depressive Disorder (MDD) or Bipolar Disorder (BD), we have previously reported an association of peripheral IL-8, TNF-α, CCL2, CCL4 with cortical thickness (Poletti et al., 2019); of IL-1β, IL-9, CCL5 with brain glutamate, N-acetylaspartate, and Myo-Inositol levels (Poletti et al., 2020a); and of IL-8, IL-10, TNF-α, IFN-γ with white matter (WM) microstructure, with levels of inflammatory cytokines being inversely related with measures of WM integrity (Benedetti et al., 2016). We also associated this WM phenotype with neurocognitive dysfunctions (Poletti et al., 2015), an effect proportional to illness duration (Melloni et al., 2019). Consistent with the present findings, attention and information processing, verbal memory, and psychomotor coordination were among the affected domains, and given that the lifetime speed of information processing closely associates with WM microstructure in humans and in animal models (Bartzokis et al., 2012; Kochunov et al., 2007; Lu et al., 2013), we can surmise that subtle effects on structural and functional brain connectivity could mediate the detrimental effects of COVID-19 on neurocognition.

The potential linkage between inflammatory status, depressive symptomatology, and associated neurocognitive dysfunction in patients with COVID-19 should then be investigated in long-term longitudinal studies, to better personalize treatment options (Benedetti et al., 2020b). As such, we hypothesize that COVID-19 could result in prolonged systemic inflammation that could lead to the development of persistent depression. We found at three months follow-up that 20 patients (8.9% of the total) met the criteria for the diagnosis of a depressive episode. When considering self-report assessment, 28% of the whole sample scored in the pathological range for depression according to ZSDS index and 9% according to the more conservative BDI-13 (Shafer, 2006), the latter showing higher consistency with the clinical interview findings. According to literature and consistent with our findings at one-month follow-up study, we observed that females, patients with positive psychiatric history, patients with shorter hospitalization, and patients who presented psychopathology at one-month follow-up showed higher depressive symptomatology (Mazza et al., 2020). Overall, thirty-four patients needed psychopharmacological treatment, and interestingly in 9% of patients with no previous psychiatric history were started a pharmacological treatment. Considering this percentage, and given the global burden of COVID-19 infection, the public health implications of such effects will be significant and demanding for the psychiatric services.

The present results must be viewed in light of some limitations. The subgroup of patients with assessment of the inflammatory state at three months is too small to generalize our findings over time; thus, further studies are needed to better investigate the interaction between inflammation, depression, and neurocognition in COVID-19 patients. The limited health care resources and patient's compliance related to the clinical setting forced us to choose an unstructured interview format instead of a structured clinical interview. Moreover, we were not able to assess the neurocognition in all patients but only in a subsample. Recruitment was in a single center, thus raising the possibility of population stratification; the study needs to be replicated in larger multicentric studies with a more heterogeneous population.

5. Conclusions

In conclusion, we observed that COVID-19 survivors remain clinically depressed three months after hospital discharge while other symptoms probably more related to acute psychological stressors such as PTSD, insomnia, and anxiety decrease over time. Depression also affects neurocognitive performances, possibly sharing the same inflammatory triggers. Considering that, depression associates with a markedly increased risk of all-cause and cause-specific mortality, and given the global burden of COVID-19 infection, timely and longitudinal investigations of the trajectory and characteristics of COVID-19 associated neuropsychiatric outcomes are critical for the personalized treatment of survivors in the following months and years.

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

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