A longitudinal study of post-traumatic stress, depressive, and anxiety symptoms trajectories in subjects with bipolar disorder during the COVID-19 pandemic

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Abstract

Background. Bipolar disorder (BD) is recognized to be at high risk for developing negative psychopathological sequelae to potentially traumatic events. Nevertheless, scant data are still available about the effects of the COVID-19 emergency on the clinical course of BD. The present study examined prospectively the development and trajectories of post-traumatic stress, depressive, and anxiety symptoms among subjects with BD that were followed in an outpatient psychiatric clinic at the time of pandemic onset.

Methods. A cohort of 89 subjects with BD was enrolled during the first wave of the COVID-19 pandemic, and assessed at baseline (T0), 2-months (T1), and 6-months (T2) follow-up. A K-means cluster analysis was used to identify distinct trajectories of depressive, anxiety, and post-traumatic stress symptoms during the three time points.

Results. We identified three trajectories: the Acute reaction (13.5%); the Increasing severity (23.6%); and the Low symptoms (62.9%) groups, respectively. In the Acute reaction group a significant prevalence of female gender was reported with respect to the Low symptoms one. Subjects in the Increasing severity group reported significantly lower employment rate, and higher rate of relatives at risk for COVID-19 medical complications. Subjects in the Increasing Severity group reported higher rates of previous hospitalization and manic symptoms at baseline than those included in the Low symptoms one.

Conclusions. Our results describe three distinct symptom trajectories during the COVID-19 emergency in a cohort of subjects suffering from BD, suggesting the need of a long-term follow-up for detecting the impact of the COVID-19 pandemic in this vulnerable population.

Introduction

The COVID-19 pandemic, with its medical, social, economic, and cultural consequences, probably represents the most critical and complex global event of the recent history and this highly stressful situation has been stretching for more than 1 year to date [1]. This worldwide emergency, in fact, may imply exposure to a wide sort of stressful or traumatic events, such as social isolation, being quarantined or infected, loss of a loved-one, economic difficulties, or, more often, to a combination thereof [2,3]. Literature suggests the key role of individual vulnerability for the development of mental health consequences to the event “pandemic,” and the role of previous mental illness has been especially stressed [4–7]. However, despite a growing interest in this topic [8–12], the impact on the clinical course of psychiatric disorders, is still largely unexplored with scarce longitudinal clinical data. Furthermore, just a few studies were conducted on clinical samples [13–17], while other data come by subgroup analysis in the framework of online surveys with a cross-sectional design [18,19], which are burdened by several methodological limitations [20].

However, these studies suggest that individuals with psychiatric disorders may be more vulnerable to develop depressive, anxiety as well as post-traumatic stress symptoms [14–19,21,22], and there are well-grounded concerns that subjects suffering from bipolar disorder (BD) may be among the most vulnerable ones [23–25]. In the pandemic frame, subjects with BD may be at the crossroads of a range of individual risk factors, adverse environmental conditions and drastic changes in psychiatric assistance that may jeopardize treatment’s continuity and adherence to pharmacological therapy [26,27].

Moreover, negative life events can trigger or exacerbate mood episodes [28], and the Sars-CoV2 infection itself could lead to the development of a mood disorder and suicide behaviors.
During the first COVID-related national lockdown phase, in order to carry on the healthcare services for subjects suffering from BD, a specific service was introduced from March 1, 2020. This service was set-up during the acute phase of the COVID-19 pandemic, and it was conducted in the framework of the telepsychiatry visit as showed elsewhere. The study included a sample of 100 subjects with a DSM-5 diagnosis of BD and PTSD, as well as the detrimental prognostic significance of this co-occurrence, are widely acknowledged.

The interplay among enhanced trauma sensitivity, the persisting trauma exposure, and the intrinsic heterogeneity of longitudinal psychopathological trajectories after a traumatic event, makes the scenario highly complex. Indeed, previous studies have been demonstrating how post-traumatic stress symptoms evolve dynamically over time, depicting trajectories of delayed onset, recovery or resilience, or hesitating in a chronic course. Accordingly, the assessment of the COVID-19 pandemic impact on subjects with BD may be particularly challenging due to the prolonged duration and variability of the traumatic exposure, to the underlying episodic course of BD and to the interplay between post-traumatic stress, anxious and depressive symptoms that may overlap or influence each other. These factors clearly indicate the importance of performing longitudinal studies in which PTSD, depression or anxiety symptoms are jointly analyzed to identify predictive factors of aversive mental health consequences of traumatic events.

In light of these premises, aim of the present study was to examine prospectively the development and trajectories of post-traumatic stress, depressive and anxiety symptoms in a sample of subjects with BD that were followed in an outpatient psychiatric clinic, over a 6-month follow-up starting from the first national lockdown in Italy. Particular attention was devoted to the possible clustering of these symptoms in defining clinical subtypes at differential risk for worse outcomes. A further aim of the present study was to examine the sociodemographic and clinical factors associated with the different trajectories.

Materials and Methods

Study sample

The study included a sample of 100 subjects with a DSM-5 diagnosis of BD consecutively enrolled at the psychiatric outpatient service of the Azienda Ospedaliera Universitaria Pisana (AOUP, Pisa, Italy) when they were admitted to a telepsychiatry service, set-up during the acute phase of the COVID-19 pandemic. This specific service was introduced from March 1, 2020 to carry on the healthcare services for subjects suffering from BD, during the first COVID-related national lockdown phase, in which all outpatient facilities had been suspended according to the national norms adopted for the pandemic emergency. Researchers excluded from the telepsychiatric service the subjects with a current clinical diagnosis of Alcohol or Substance Use Disorder or Neurocognitive Disorder according to DSM-5 criteria. From an initial sample of 122 subjects assessed for eligibility in the telepsychiatry services, 6 subjects were excluded because affected by Alcohol or Substance Use Disorder, and 2 because affected by Neurocognitive Disorder. Finally, 14 subjects enrolled in the telepsychiatry service refused to participate to the study. The study assessments were conducted at three time points, namely T0, T1, and T2. The enrollment period and the first assessment (T0), occurred from April 1 to 30, 2020, during the first wave of the COVID-19 pandemic and the national lockdown in Italy; it was conducted in the framework of the telepsychiatry visit as showed elsewhere. The second time point (T1) was from June 1 to 30, 2020 (after 2 months from T0), during the following “reopening” phase of the COVID-19 emergency in Italy. The third time point (T2) was from October 1 to 31, 2020 (after 6 months from T0), at the beginning of the “second wave” of the pandemic in Italy. Hence, the study period was from April 1 to October 31, 2020. The T1 and T2 assessments were performed in the framework of a psychiatric visit. The percentage of dropout in participants between the three time points was 11%. Therefore, the final sample for the present study includes 89 subjects. During the study period, the sample presented a good adherence to a naturalistic treatment program.

A written informed consent was subjected to all eligible participants after receiving a detailed description of the study, with the opportunity to ask questions. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Area Vasta Nord-Ovest Toscana (Italy).

**Instruments and assessments**

Psychiatrists with clinical expertise in mood disorders performed clinical interviews and rating. Sociodemographic and clinical data were registered with a specific datasheet reporting information on the COVID-19 pandemic. The structured Clinical Interview for the Disorders of the DSM-5 (SCID-5) was utilized to determine the diagnosis of BD and to assess psychiatric comorbidity. At T0 participants were also investigated by means of: Impact of Event Scale-Revised (IES-R) to investigate PTSD symptoms; General Anxiety Disorder 7-Item (GAD-7) to evaluate anxiety symptoms; Patient Health Questionnaire-9 (PHQ-9) to examine depressive symptoms; and Young Mania Rating Scale (YMRS) to examine manic symptoms. At T1 and T2, the IES-R, GAD-7, and PHQ-9 were administered again. The IES-R is a 22-item scale measuring three core phenomena of PTSD: reexperiencing of traumatic events, avoidance, and hyperarousal. It refers to the last week. The IES-R total score is calculated adding the score of each item. According with the aim of the study, the items referred to the traumatic events that the subjects had experienced in the framework of the COVID-19 pandemic.

The GAD-7 is a self-assessment questionnaire used as a tool for screening and measuring the severity of anxious symptoms. Particularly, it investigates the frequency of anxious symptoms in the last 2 weeks using seven items with a score ranging from 0 (never) to 3 (almost every day).

The PHQ-9 represents one of the most used self-assessment tools for the screening of depressive symptoms. It consists of nine items that investigate the presence of depressive symptoms in the last 2 weeks, each evaluated on a scale from 0 (never) to 3 (almost every day).

The YMRS is the most widely clinician administered scale used for the assessment of the severity of manic symptoms. The scale is composed by 11-items: four items are graded on a 0–8 scale, while seven items are graded on a 0–4 scale. The score for each item is summed to obtain the YMRS total score.
Continuous variables were reported as mean ± standard deviation (SD), whereas categorical variables were reported as percentages. All tests were two-tailed and a p value < 0.05 was considered statistically significant. Kolmogorov–Smirnov and Shapiro–Wilk tests were computed to determine the normally distribution of the IES-R, GAD-7, and PHQ-9 scores.

We used a K-means cluster analysis based on the standardized IES-R, GAD-7, and PHQ-9 scores reported at T0, T1, and T2, to identify the peculiar trajectories of post-traumatic stress, anxiety, and depressive symptoms during the three time points. We used squared Euclidean Distance for the divergence measure between cases. To classify cases, the method of iterative updating of clustered centroids was chosen, with the new clusters centers to be calculated after all cases are assigned to a given cluster. To ensure maximum efficiency the final cluster centers estimated from a random sample were utilized as initial centers to classify the entire file. To assess the stability of a given solution, we compared results on data sorted in different ways. After comparing the results obtained for different K values, we identified as the most satisfactory solution the one that involves three clusters (K = 3). This solution ensured the minimum number of iterations before convergence criterion 0 was satisfied. Furthermore, it determined a small within-cluster variability compared to the difference between clusters, and the cluster sizes greater than 10% of the total sample size. We also calculated the power related to the dispersion analysis included in the cluster analysis.

Chi-square was computed to evaluate differences in categorical variables among the three groups. One-way ANOVA was utilized to compare continuous normally distributed variables among the three groups, while Kruskal–Wallis test was utilized for the nonparametric ones. Finally, Friedman test was computed to compare IES-R, GAD-7, and PHQ-9 scores among the T0, T1, and T2 in the total sample and in each group.

All statistical analyses were performed using the Statistical Package for Social Science, version 26.0 (SPSS Inc.). Power analyses were calculated by means of PASS 2008, 08.0.8 version.

Results

The sample included 34 (38.2%) males and 55 females (61.8%) at baseline. The mean age was 47.15 ± 16.12 (min 19, max 80) years. A total of 61 presented a BD-II (70.1%), and 36 (40.4%) individuals reported a comorbid disorder: 19 (21.3%) an anxiety disorder, 17 (19.1%) an obsessive–compulsive disorder, and 4 (4.5%) a feeding and eating disorder. Concerning the COVID-19 pandemic at the baseline evaluation, 28 subjects (31.5%) reported to be at risk for medical complications in the case of COVID-19 infection because of a chronic medical condition (e.g., diabetes mellitus or cardiovascular and respiratory diseases), only 1 (1.8%) was positive to COVID-19, and 28 (31.5%) referred occupational and economic difficulties (job loss, significantly lower earning, or financial losses) due to the lockdown. Furthermore, 29 individuals (32.6%) had a close one at risk for medical complications in the case of COVID-19 infection, 6 (6.7%) a relative infected by COVID-19 and 3 (3.4%) a loss of a relative or a close one by the COVID-19.

Cluster analysis

As initial clusters, we used the final centers estimated by a preliminary application of a K-means cluster analysis on a random sample of 50 subjects, to reduce the distance calculations and to select a good set of initial clusters. The second K-means cluster analysis applied to the entire data file met criterion 0 of convergence at the fifth iteration. We defined the three groups of subjects determined by the second K-means cluster analysis the Acute reaction group (N = 12, 13.5%), the Increasing severity group (N = 21, 23.6%) and the Low symptoms group (N = 56, 62.9%), respectively. Table 1 shows the initial cluster centers, the iteration history, the final cluster centers and the distances between the final cluster centers in the three groups, while in Figure 1 were reported the mean scores of IES-R, GAD-7, and PHQ-9 of the three groups at the three time points. The average distance of cases from their classification cluster center was 2.08 ± 0.82. Finally, in the dispersion analysis

| Table 1. K-means cluster analysis features. |
|---------------------------------------------|
| Acute reaction | Increasing severity | Low symptoms |
| **Initial cluster centers** | | | |
| IES-R T0 Z score | 1.32144 | −1.12671 | −1.20321 |
| IES-R T1 Z score | 3.52281 | −0.33156 | −0.66672 |
| IES-R T2 Z score | 3.57487 | −0.52903 | −0.60103 |
| GAD-7 T0 Z score | 1.92388 | 1.07737 | −1.46215 |
| GAD-7 T1 Z score | −1.21139 | 1.51593 | −1.21139 |
| GAD-7 T2 Z score | 0.56109 | 2.13011 | −1.00792 |
| PHQ-9 T0 Z score | 0.39925 | 2.47954 | −1.16097 |
| PHQ-9 T1 Z score | −1.18392 | 2.35138 | −0.84723 |
| PHQ-9 T2 Z score | −0.08055 | 2.73541 | −0.82159 |
| **Iteration history** | | | |
| 1 | 3.488 | 2.999 | 2.138 |
| 2 | 0.755 | 0.472 | 0.156 |
| 3 | 0.451 | 0.371 | 0.155 |
| 4 | 0.000 | 0.304 | 0.116 |
| 5 | 0.000 | 0.000 | 0.000 |
| **Final cluster centers** | | | |
| IES-R T0 Z score | 1.85698 | −0.15036 | −0.32477 |
| IES-R T1 Z score | 1.72829 | −0.05625 | −0.32557 |
| IES-R T2 Z score | 0.49094 | 0.62980 | −0.40432 |
| GAD-7 T0 Z score | 1.09501 | 0.59366 | −0.46448 |
| GAD-7 T1 Z score | 0.34458 | 0.95648 | −0.43965 |
| GAD-7 T2 Z score | −0.00114 | 1.40537 | −0.52041 |
| PHQ-9 T0 Z score | 0.48593 | 0.41576 | −0.38086 |
| PHQ-9 T1 Z score | 0.48552 | 1.00460 | −0.49851 |
| PHQ-9 T2 Z score | 0.12941 | 1.35213 | −0.54635 |
| **Final cluster distances** | | | |
| Acute reaction | − | 3.407 | 3.801 |
| Increasing severity | 3.407 | − | 3.908 |
| Low symptoms | 3.801 | 3.908 | − |

Note: Initial cluster centers, iteration history, final cluster centers, and distances between the final cluster centers in the Acute reaction (N = 12), Increasing severity (N = 21), and Low symptoms (N = 56) groups.
Figure 1. IES-R, GAD-7, and PHQ-9 mean scores among T0, T1, and T2 in the Acute reaction (N = 12), Increasing severity (N = 21), and Low symptoms (N = 56) groups.
Finally, at the T2 assessment, the GAD-7 and PHQ-9 scores than the group; the symptoms groups presented higher scores in the IES-R than the other two groups, and the Acute reaction and the increasing severity groups presented higher IES-R score than the other two groups. At T0, the Low symptoms group presented higher GAD-7 than the PHQ-9 score was higher at the T2 with respect to the T0.

Significant differences emerged in the following characteristics between the three groups. The Acute reaction group presented more females than the Low symptoms one. The Increasing severity group reported less employed subjects and more subjects with a relative at risk for COVID-19 medical complications than the other two groups, besides more subjects with a history of hospitalization than the Low symptoms group. Finally, the YMRS score was higher in the Increasing severity group with respect to the Low symptoms one (Table 3).

At T0, the Acute reaction group presented higher IES-R score than the other two groups, and the Acute reaction and the increasing severity groups presented higher scores in the GAD-7 and PHQ-9 than the Low symptoms group. At the T1 assessment the Acute reaction group presented higher IES-R score than the other two groups; the Acute reaction and the Increasing severity groups presented higher scores in the PHQ-9; the Increasing severity group presented higher score in the GAD-7 than the Low symptoms one. Finally, at the T2 assessment, the Acute reaction and the Increasing severity groups presented higher scores in the IES-R than the Low symptoms group; the Increasing severity group presented higher GAD-7 and PHQ-9 scores than the Acute reaction and Low symptoms ones; the Acute reaction group presented higher PHQ-9 score than the Low symptoms one (Table 4).

In the Acute reaction group, the IES-R and the GAD-7 scores were higher at the T0 than at the T2. In the Increasing severity group, the GAD-7 score at the T2 was higher than the T0 and T1 assessments, while the PHQ-9 score was higher at the T2 with respect to the T0. Finally, the Low symptoms group presented higher IES-R and PHQ-9 scores at the T0 than the T1 and the T2 (Table 4).

Discussion

To the best of our knowledge, this is the first study that prospectively examined the development and trajectories of post-traumatic stress, depressive, and anxiety symptoms among subjects with BD that were followed in an outpatient psychiatric unit at the time of pandemic onset. The results allowed us to detect different clusters based on depressive, anxiety, and post-traumatic stress symptoms trajectories, over a 6-month follow-up period, starting from the first national lockdown. Three clusters emerged: the Low symptoms group, including about two third of the sample, who showed limited psychopathological reactions to the event “pandemic”; the Increasing severity group, including about 23% of subjects who reported considerable symptoms that worsen over time; and the Acute reaction group, including about 10% of subjects, that showed a relevant acute reaction followed by a rapid improvement. As to specific features of the different clusters, female gender, work, and financial difficulties and a greater number of previous depressive episodes were mostly found in the Acute reaction group, while the presence of relatives or close ones at risk for COVID-19 related medical complications, resulted most strongly associated to the Increasing severity trajectory, along with low employment rate, previous psychiatric hospitalization, and manic symptoms at baseline.

Our results show considerable, although widely ranging, rates of depressive, anxiety, and post-traumatic stress symptoms in subjects BD during the first 6 months of the COVID-19 pandemic. Available data on this issue are far from being univocal. Indeed, while some studies suggest a good resilience level in clinical samples of subjects suffering from BD [16], other ones report a greater psychological burden with respect to healthy controls [13,19]. Previous studies show that life events, as well as traumatic exposure, may play a major role in BD course [23,56,57].Remarkably, subjects with BD are at risk of developing psychopathological reactions even after indirect exposure to traumatic event [46,58]. Accordingly, Pollack et al. [58] previously reported a marked increase in distress among subjects with BD exposed to September 11 events through media. In this regard, despite subjects we enrolled belongs to a relatively low-incidence infection area, they have been extensively exposed to indirect consequences of the pandemic, such as fear of contagion, social isolation, financial constraints, and abrupt routine changes. Consistently, a previous study on BD subjects during the Italian national lockdown showed clinically significant PTSD symptoms in 17% of the sample [50].

As mentioned above, the cluster analysis outlines three different clusters, namely Low symptoms, Increasing severity, and Acute reaction groups. Previous longitudinal studies on PTSD symptoms showed similar patterns [44,59–61]. Data from long-term longitudinal studies on large samples of war veterans outline a wide majority of resilient subjects to traumatic exposure; a pattern characterized by high severity in the aftermath of trauma with a subsequent recovery; and subgroups that endure aversive effects of the trauma in the long term [44]. As already mentioned, assessing the impact of the COVID-19 pandemic on subjects with BD can be particularly challenging because of the interplay among the onset of trauma-related symptomatology, the co-occurring anxiety and mood symptoms, the potential impact on the course of BD itself [46,47,62]. Indeed, the combined analysis of the three symptomatological dimensions highlights a consensual trend in anxiety, depressive and post-traumatic symptoms among the three groups. This is in line with a great amount of literature highlighting high
Table 3. Sociodemographic, clinical, and COVID-19 characteristics in the total sample (N = 89) and in the Acute reaction (N = 12), Increasing severity (N = 21), and Low symptoms (N = 56) groups.

|                                | Total sample N (%) | (a) Acute reaction N (%) | (b) Increasing severity N (%) | (c) Low symptoms N (%) | p     | Post hoc |
|--------------------------------|--------------------|--------------------------|------------------------------|------------------------|-------|----------|
| Females                        | 55 (61.8%)         | 11 (91.70%)              | 15 (71.4%)                   | 29 (51.80%)            | 0.021 * a > c |
| Married/cohabiting             | 35 (39.3%)         | 4 (33.3%)                | 8 (38.1%)                    | 23 (41.1%)             | 0.876 *          |
| Living with family             | 69 (77.5%)         | 10 (83.3%)               | 16 (76.2%)                   | 43 (78.8%)             | -     | -        |
| University degree              | 14 (15.7%)         | 2 (16.7%)                | 3 (143%)                     | 9 (16.1%)              | 0.977 *          |
| Employed                       | 42 (47.2%)         | 7 (58.3%)                | 4 (19.0%)                    | 31 (55.4%)             | 0.012 * a > b, c > b |
| Age (years)                    | 47.15 ± 16.12      | 45.33 ± 13.77            | 49.90 ± 16.74                | 46.49 ± 16.50          | 0.656 *          |
| Bipolar disorder characteristics|                    |                          |                              |                        |                   |
| Psychiatric family history     | 70 (78.7%)         | 11 (91.7%)               | 16 (76.2%)                   | 43 (76.8%)             | 0.496 *          |
| Previous psychiatric hospitalization | 40 (46.0%) | 5 (45.5%)                | 15 (75.0%)                   | 20 (35.7%)             | 0.010 * b > c    |
| Bipolar disorder type II       | 61 (70.1%)         | 8 (72.7%)                | 14 (70.0%)                   | 39 (69.6%)             | 0.979 *          |
| Manic polarity onset           | 16 (18.6%)         | 1 (9.1%)                 | 4 (20.0%)                    | 11 (20.0%)             | -     | -        |
| Age of onset (years)           | 27.45 ± 13.58      | 22.18 ± 10.17            | 28.95 ± 15.51                | 27.96 ± 13.41          | 0.376 **         |
| Previous any mood episodes     | 10.04 ± 6.89       | 13.00 ± 7.67             | 11.95 ± 8.17                 | 8.74 ± 5.94            | 0.115 ***        |
| Previous depressive episodes   | 5.96 ± 4.01        | 8.73 ± 5.20              | 7.05 ± 4.35                  | 5.00 ± 3.26            | 0.033 ***        |
| Previous manic episodes        | 4.00 ± 3.49        | 4.71 ± 5.04              | 3.64 ± 3.62                  | 3.94 ± 3.96            | 0.510 ***        |
| Time since the last episode (weeks) | 16.90 ± 19.07 | 16.09 ± 14.74            | 10.05 ± 12.20                | 19.53 ± 21.36          | 0.081 ***        |
| YMRS at T0                     | 2.52 ± 3.41        | 2.33 ± 3.39              | 3.81 ± 3.56                  | 2.07 ± 3.29            | 0.024 *** b > c  |
| Psychiatric comorbidities      |                    |                          |                              |                        |                   |
| Any comorbid disorder          | 36 (40.4%)         | 5 (41.7%)                | 9 (42.9%)                    | 22 (39.3%)             | 0.956 *          |
| Anxiety disorder               | 19 (21.3%)         | 2 (16.7%)                | 4 (19.0%)                    | 13 (23.2%)             | -     | -        |
| Obsessive–compulsive disorder  | 17 (19.1%)         | 1 (8.3%)                 | 5 (23.8%)                    | 11 (19.6%)             | -     | -        |
| Feeding and eating disorder    | 4 (4.5%)           | 2 (16.7%)                | 1 (4.8%)                     | 1 (1.8%)               | -     | -        |
| Psychiatric treatment          |                    |                          |                              |                        |                   |
| Antidepressant                 | 53 (60.2%)         | 7 (63.6%)                | 14 (66.7%)                   | 22 (57.1%)             | 0.726 *          |
| Lithium                        | 37 (42.0%)         | 5 (45.5%)                | 11 (52.4%)                   | 21 (37.5%)             | 0.485 *          |
| Antiepileptic mood stabilizers | 72 (81.8%)         | 9 (81.8%)                | 16 (76.2%)                   | 57 (83.9%)             | -     | -        |
| Antipsychotic                  | 38 (43.2%)         | 5 (45.5%)                | 11 (52.4%)                   | 22 (39.3%)             | 0.579 *          |
| Benzodiazepine                 | 16 (18.8%)         | 2 (18.2%)                | 6 (30.0%)                    | 8 (14.8%)              | -     | -        |
| COVID-19 related variables     |                    |                          |                              |                        |                   |
| Work or financial difficulties due to lockdown | 28 (31.5%) | 8 (66.7%)                | 4 (19.0%)                    | 16 (28.6%)             | 0.013 * a, b > c  |
| Being at risk for medical complications related to COVID-19 infection | 51 (68.5%) | 6 (50.0%)                | 12 (57.1%)                   | 43 (76.8%)             | 0.084 *          |
| Positive to COVID-19 T0        | 1 (1.1%)           | 0 (0%)                   | 0 (0%)                       | 1 (1.8%)               | -     | -        |
| Positive to COVID-19 T1        | 3 (3.4%)           | 0 (0%)                   | 0 (0%)                       | 3 (5.4%)               | -     | -        |
| Positive to COVID-19 T2        | 4 (4.5%)           | 0 (0%)                   | 1 (4.8%)                     | 3 (5.5%)               | -     | -        |
| A relative at risk for medical complications related to COVID-19 | 60 (67.4%) | 5 (41.7%)                | 19 (90.5%)                   | 36 (64.3%)             | 0.011 * b > a, b > c |
| A relative positive for COVID-19 T0 | 6 (6.7%) | 1 (8.3%)                 | 2 (9.5%)                     | 3 (5.4%)               | -     | -        |
| A relative positive for COVID-19 T1 | 7 (7.9%) | 2 (16.7%)                | 2 (9.5%)                     | 3 (5.4%)               | -     | -        |
| A relative positive for COVID-19 T2 | 9 (10.1%) | 2 (16.7%)                | 2 (9.5%)                     | 5 (8.9%)               | -     | -        |
| Loss of a relative for the COVID-19 T0 | 3 (3.4%) | 1 (8.3%)                 | 0 (0%)                       | 2 (3.6%)               | -     | -        |
comorbidity rates between PTSD, depression, and anxiety in trauma-exposed populations [63,64]. Some aspects emerging from our analysis of sociodemographic information are worthy of a more focused discussion. First, the sharply higher burden of symptoms reported at baseline evaluation by the Acute reaction group, which is characterized by a marked female prevalence, financial hardships, and more previous depressive episodes. Female gender represents a risk factor for acute psychopathological reaction to traumatic events [64], as confirmed by recent studies conducted in the frame of COVID-19 pandemic [65,66]. Furthermore, recent studies corroborated the prominent role of ongoing economical difficulties in determining psychological distress in subjects suffering from BD during the current pandemic [13,19,50]. Finally, the higher number of previous bipolar illness episodes may suggest an increased mood instability that can predispose to the onset of not only depressive symptoms but also anxiety and post-traumatic stress ones. On the other hand, subjects from the Increasing severity group presented more frequently unfavorable sociodemographic features, such as a lower occupational rate or a relative at risk for medical complications related to COVID-19. The association between low socioeconomic status and poor mental health had been repeatedly reported [67]. Consequently, it could be supposed that people in this group were both exposed to a relatively higher stress-dose and be more vulnerable. They, in fact, had higher rates of previous hospitalizations, suggesting a more severe course of the underlying disorder, and reported higher manic symptoms at baseline. This is in line with literature, since previous studies reported that PTSD rates were significantly associated with manic, hypomanic, or mixed mood states at the time of trauma. We also corroborated the findings that manic symptoms in the framework of the traumatic event are related to the development of depressive and anxiety symptoms too [37,38,46,49,58]. Some limitations should be taken into account. First, the small sample size. However, in this regards it is important to acknowledge that the present study represents one of the few longitudinal effects.

### Table 3. Continued

|                                | (a) Acute reaction N (%) | (b) Increasing severity N (%) | (c) Low symptoms N (%) | p       | Post hoc |
|--------------------------------|--------------------------|-----------------------------|------------------------|---------|----------|
| Loss of a relative for the COVID-19 T1 | 5 (5.6%)                | 1 (8.3%)                    | 1 (4.8%)               | 3 (5.4%) | –        |
| Loss of a relative for the COVID-19 T2 | 5 (5.6%)                | 1 (8.3%)                    | 1 (4.8%)               | 3 (5.4%) | –        |

*Referred to a chi-square test.
**Referred to a ANOVA test.
***Referred to a Kruskal–Wallis test.

### Table 4. Comparison of IES-R, GAD-7, and PHQ-9, scores among T0, T1, and T2 in the total sample (N = 89) and in the Acute reaction (N = 12), Increasing severity (N = 21), and Low symptoms (N = 56) groups.

|                                | T0 Mean ± SD | T1 (3 months) Mean ± SD | T2 (6 months) Mean ± SD | p       | Post hoc |
|--------------------------------|--------------|--------------------------|-------------------------|---------|----------|
| **IES-R**                      |              |                          |                         |         |          |
| Total sample                   | 17.86 ± 13.13| 8.13 ± 12.14             | 7.80 ± 13.43            | <0.001  | T0 > T1, T > T2 |
| (a) Acute reaction group       | 42.00 ± 8.59 | 28.58 ± 18.69            | 15.17 ± 19.31           | 0.009   | T0 > T2 |
| (b) Increasing severity group  | 15.76 ± 10.00| 7.28 ± 9.77              | 17.09 ± 17.49           | 0.079   | –        |
| (c) Low symptoms group         | 13.48 ± 8.73 | 4.07 ± 4.78              | 2.73 ± 5.66             | <0.001  | T0 > T1, T0 > T2 |
| p***                           | <0.001       | <0.001                   | <0.001                  |         |          |
| Post hoc*                      | a > b, a > c | a > b, a > c             | a > c, b > c            |         |          |
| **GAD-7**                      |              |                          |                         |         |          |
| Total sample                   | 6.89 ± 4.68  | 5.75 ± 4.85              | 7.45 ± 6.36             | 0.066   | –        |
| (a) Acute reaction group       | 12.08 ± 5.38 | 7.42 ± 5.30              | 7.42 ± 4.12             | 0.016   | T0 > T2 |
| (b) Increasing severity group  | 9.71 ± 4.39  | 10.33 ± 5.45             | 16.38 ± 3.77            | 0.002   | T0 < T2, T1 < T2 |
| (c) Low symptoms group         | 4.71 ± 2.91  | 3.68 ± 2.88              | 4.11 ± 3.77             | 0.122   | –        |
| p***                           | <0.001       | <0.001                   | <0.001                  |         |          |
| Post hoc*                      | a > c, b > c | b > c                    | b > a, b > c            |         |          |
| **PHQ-9**                      |              |                          |                         |         |          |
| Total sample                   | 8.26 ± 5.51  | 6.97 ± 6.01              | 7.49 ± 6.82             | 0.012   | T0 > T1 |
| (a) Acute reaction group       | 11.50 ± 4.56 | 9.92 ± 6.73              | 8.42 ± 5.51             | 0.401   | –        |
| (b) Increasing severity group  | 11.09 ± 6.11 | 13.00 ± 6.17             | 16.67 ± 5.10            | 0.042   | T0 < T2 |
| (c) Low symptoms group         | 6.50 ± 4.72  | 4.07 ± 3.25              | 3.86 ± 3.63             | <0.001  | T0 > T1, T0 > T2 |
| p***                           | <0.001       | <0.001                   | <0.001                  |         |          |
| Post hoc*                      | a > c, b > c | a > c, b > c             | b > a > c               |         |          |

*p < 0.05 in post hoc pair-wise comparison adjusted for Bonferroni inequalities.
**Related to a Friedman test.
***Related to a Kruskal–Wallis test.
research conducted on a clinical sample of subject with BD assessed by clinicians, during the COVID-19 pandemic. Second, the use of self-report instruments could be considered less accurate that a clinician assessment. Moreover, the telepsychiatry setting at baseline may have influenced in some way the results of the assessments. Third, cautiousness should be adopted when comparing our results with previous studies on trajectories after a traumatic event because of major methodological differences, such as different sample characteristics or timing of assessment. Fourth, in the present study, the three time points corresponded to three different environmental conditions related to COVID-19, and it might influence the psychopathological status of the sample. Finally, possible protective factors, such as social support or coping styles, besides different treatments, which may have influenced the emergence of symptoms, were not evaluated in the study.

In conclusion, we observed three distinct symptom trajectories during the COVID-19 emergency in subjects suffering from BD. While most individuals regularly followed in a psychiatric setting reported a mild reaction, others presented acute or even enduring psychopathological response. In BD female gender, low socioeconomic status, numerous previous episodes, and manic/hypomanic symptoms during the Lockdown appear possible predictive factors of unfavorable outcome after a traumatic event; in this sense, the present findings will be useful for the development of further studies focusing on specific therapeutic strategies for BD in the framework of a traumatic event.

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

**Author Contributions.** Conceptualization: C.C.; Data curation: A.Co., C.A.B., A.Ca.; Formal analysis: C.C., C.A.B., G.M., V.D.; Investigation: C.C., A.Co., C.A.B., V.P.; Methodology: C.C., A.Co., C.A.B., V.D.; Project administration: C.C.; Supervision: C.C., C.A.B., L.D.; Writing—original draft: C.C., A.Co., C.A.B.; Writing—review and editing: C.C., A.Co., A.B., A.Ca., V.P., G.S., V.D.

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**References**

1. Fiorillo A, Gorwood P. The consequences of the COVID-19 pandemic on mental health and implications for clinical practice. Eur Psychiatry. 2020; 63(1):e52. doi:10.1016/j.eurpsy.2020.35.
2. Holmes EA, O’Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry. 2020;7(6): 547–60. doi:10.1016/S2215-3963(20)30168-1.
3. Giallonardo V, Sampogna G, Del Vecchio V, Luciano M, Albert U, Carmassi C, et al. The impact of quarantine and physical distancing following COVID-19 on mental health: study protocol of a multicentric Italian population trial. Front Psychiatry. 2020;11:533. doi:10.3389/fpsyt.2020.00533.
4. Pfefferbaum B, North CS. Mental health and the COVID-19 pandemic. N Engl J Med. 2020;383(6):510–2. doi:10.1056/NEJMmp2008017.
5. Adhanom Ghebreyesus T. Addressing mental health needs: an integral part of COVID-19 response. World Psychiatry. 2020;19(2):129–30. doi:10.1002/wps.20768.
6. Unutzer J, Kimmel BJ, Snowden M. Psychiatry in the age of COVID-19. World Psychiatry. 2020;19(2):130–1. doi:10.1002/wps.20766.
7. Stewart DE, Appelbaum PS. COVID-19 and psychiatrists’ responsibilities: a WPA position paper. World Psychiatry. 2020;19(3):406–7. doi:10.1002/wps.20803.
8. McCracken LM, Badinou F, Buhrman M, Brocki KC. Psychological impact of COVID-19 in the Swedish population: depression, anxiety, and insomnia and their associations to risk and vulnerability factors. Eur Psychiatry. 2020; 63(1):e81. doi:10.1016/j.eurpsy.2020.81.
9. Fiorillo A, Sampogna G, Giallonardo V, Del Vecchio V, Luciano M, Albert U, et al. Effects of the lockdown on the mental health of the general population during the COVID-19 pandemic in Italy: results from the COMET collaborative network. Eur Psychiatry. 2020;63(1):e87. doi: 10.1016/j.eurpsy.2020.89.
10. Buselli R, Corsi M, Baldanzi S, Chiumiento M, Del Lupo E, Dell’Oste V, et al. Professional quality of life and mental health outcomes among health care workers exposed to Sars-Cov-2 (COVID-19). Int J Environ Res Public Health. 2020;17(17):6180. doi:10.3390/ijerph17176180.
11. Chen JA, Chung WJ, Young SK, Tuttle MC, Collins MB, Darghouth SL, et al. COVID-19 and telepsychiatry: early outpatient experiences and implications for the future. Gen Hosp Psychiatry. 2020;66:89–95. doi:10.1016/j.genhosppsych.2020.07.002.
12. Gorwood P, Fiorillo A. One year after the COVID-19: what have we learnt, what shall we do next? Eur Psychiatry. 2021;64(1):e15. doi:10.1192/eurpsy.2021.9.
13. Yocum AK, Zhai Y, McInnis MG, Han P. Covid-19 pandemic and lockdown impacts: a description in a longitudinal study of bipolar disorder. J Affect Disord. 2021;282:1226–33. doi:10.1016/j.jad.2021.01.028.
14. Hao F, Tan W, Jiang L, Zhang L, Zhao X, Zou Y, et al. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. Brain Behav Immun. 2020;87:100–6. doi:10.1016/j.bbi.2020.04.069.
15. Di Nicola M, Dattoli L, Moccia L, Pepe M, Janiri D, Fiorillo A, et al. Serum 25-hydroxyvitamin D levels and psychological distress symptoms in patients with affective disorders during the COVID-19 pandemic. Psychoneuroendocrinology. 2020;122:104869. doi:10.1016/j.psyneuen.2020.104869.
16. Tundo A, Beto S, Necci R. What is the impact of COVID-19 pandemic on patients with pre-existing mood or anxiety disorder? An observational prospective study. Medicina (Kaunas). 2021;57(4):304. doi:10.3390/medicina57040304.
17. Carta MG, Ouali U, Perra A, Ben Cheikh Ahmed A, Boe L, Aissa A, et al. Living with bipolar disorder in the time of Covid-19: biorhythms during the severe lockdown in Cagliari, Italy, and the moderate lockdown in Tunisia. Front Psychiatry. 2021;12:634765. doi:10.3389/fpsyt.2021.634765.
18. García-Álvarez L, de la Fuente-Tomás L, García-Portilla MP, Sáiz PA, Lacasa CM, Dal Santo F, et al. Early psychological impact of the 2019 coronavirus disease (COVID-19) pandemic and lockdown in a large Spanish sample. J Glob Health. 2020;10(2):020505. doi:10.7189/jogh.10.020505.
19. Van Rheemen TE, Meyer D, Neill E, Phillippou A, Tan EL, Toh WL, et al. Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: initial results from the COLLATE project. J Affect Disord. 2020;275:69–77. doi:10.1016/j.jad.2020.06.037.
20. Holman EA, Thompson RR, Garfin DR, Silver BC. The unfolding COVID-19 pandemic: a probability-based, nationally representative study of mental health in the United States. Sci Adv. 2020;6(42):eabd5390. doi:10.1126/sciadv.abd5390.
21. Kuzman M, Curkovic M, Wasserman D. Principles of mental health care during the COVID-19 pandemic. Eur Psychiatry. 2020;63(1):e45. doi:10.1192/eurpsy.2020.54.
22. Thome J, Coogan A, Simon F, Fischer M, Tucha O, Faltraco F, et al. The impact of the COVID-19 outbreak on the medico-legal and human rights of psychiatric patients. Eur Psychiatry. 2020;63(1):e50. doi:10.1192/j.eurpsy.2020.54.
23. Lex C, Bäzner E, Meyer TD. Does stress play a significant role in bipolar disorders? A meta-analysis. J Affect Disord. 2017;208:298–308. doi:10.1016/j.jad.2016.08.057.
24. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health
records in the United States. World Psychiatry. 2021;20(1):124–30. doi: 10.1002/wps.20806.

25. De Hert M, Mazereel V, Detraux J, Van Assegh K. Prioritizing COVID-19 vaccination for people with severe mental illness. World Psychiatry. 2021;20(1):34–55. doi: 10.1002/wps.20826.

26. Stefana A, Youngstrom EA, Chen J, Hinshaw S, Maxwell V, Michalak E, et al. The COVID-19 pandemic is a crisis and opportunity for bipolar disorder. Bipolar Disord. 2020;22(6):641–3. doi:10.1111/bip.13499.

27. Vieta E, Pérez V, Arango C. Psychiatry in the aftermath of COVID-19. Rev Psiquiatr Salud Ment (Engl Ed). 2020;3(2):105–10. doi:10.1016/j.rpsm.2020.04.004.

28. Maguire C, McCusker CG, Meenagh C, Mulholland C, Shannon C. Effects of trauma on bipolar disorder: the mediational role of interpersonal difficulties and alcohol dependence. Bipolar Disord. 2008;10(2):293–302. doi:10.1111/j.1399-5618.2007.00504.x.

29. Lu S, Wei N, Jiang J, Wu L, Sheng J, Zhou J, et al. First report of manic-like symptoms in a COVID-19 patient with no previous history of a psychiatric disorder. J Affect Disord. 2020;277:337–40. doi:10.1016/j.jad.2020.08.031.

30. Noone R, Cabassa JA, Gardner L, Schwartz B, Alpert JE, Gabay V. Letter to the editor: new onset psychosis and mania following COVID-19 infection. J Psychiatr Res. 2020;150:177–7. doi:10.1016/j.jpsychires.2020.07.042.

31. Gillett G, Jordan J. Severe psychiatric disturbance and attempted suicide in a patient with COVID-19 and no psychiatric history. BMJ Case Rep. 2020;13(10):e239191. doi:10.1136/bcr-2020-239191.

32. Rajkumar RP. COVID-19 and mental health: a review of the existing literature. Asian J Psychiatr. 2020;52:102066. doi: 10.1016/j.ajp.2020.102066.

33. Lowe SR, Ratanatharathorn A, Lai BS, van der Mei W, Barbano AC, Bryant R, et al. Posttraumatic stress disorder symptom trajectories within the first year following emergency department admissions: pooled results from the International Consortium to predict PTSD. Psychol Med. 2021;51:1129–39. doi:10.1017/S0033291719004088.

34. van der Wal SJ, Vermetten E, Elbert G. Long-term development of post-traumatic stress symptoms and associated risk factors in military service members deployed to Afghanistan: results from the PRISMO 10-year follow-up. Eur Psychiatry. 2020;64(1):e10. doi:10.1016/j.eurpsy.2020.113.

35. Dickstein BD, Suvak M, Litz BT, Adler AB. Heterogeneity in the course of posttraumatic stress disorder: trajectories of symptomatology. J Trauma Stress. 2010;23(3):331–9. doi:10.1002/jts.20523.

36. Hernandez JM, Cordova MJ, Ruzek J, Reiser R, Gwizdowski IS, Suppes T, et al. Presentation and prevalence of PTSD in a bipolar disorder population: a STEP-BD examination. J Affect Disord. 2013;150(2):450–5. doi:10.1016/j.jad.2013.04.038.

37. Carmassi C, Bertelloni CA, Gesi C, Conversano C, Stratta P, Massimetti G, et al. New DSM-5 PTSD guilt and shame symptoms among Italian earthquake survivors: impact on maladaptive behaviors. Psychiatry Res. 2017;251:142–7. doi:10.1016/j.psychres.2016.11.026.

38. Dell’Oso L, Da Pozzo E, Carmassi C, Trincavelli ML, Ciapparelli A, Martini C. Lifetime manic-hypomanic symptoms in post-traumatic stress disorder: relationship with the 18 kDa mitochondrial translocator protein density. Psychiatr Res. 2010;177(1–2):139–43. doi:10.1016/j.psychres.2008.07.019.

39. Dell’Oso L, Carmassi C, Mussetti L, Socci C, Shear MK, Conversano C, et al. Lifetime mood symptoms and adult separation anxiety in patients with complicated grief and/or post-traumatic stress disorder: a preliminary report. Psychiatry Res. 2012;198(3):436–40. doi:10.1016/j.psychres.2011.12.020.

40. Carmassi C, Bertelloni CA, Dell’Oste V, Barberi FM, Maglio A, Bucchinelli B, et al. Tele-psychiatry assessment of post-traumatic stress symptoms in 100 patients with bipolar disorder during the COVID-19 pandemic social-distancing measures in Italy. Front Psychiatry. 2020;11:580736. doi:10.3389/fpsyg.2020.580736.

41. First MB, Williams JBW, Karg RS, Spitzer RL. Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV). Arlington, TX: American Psychiatric Association; 2016.

42. Weiss DS, Marmar CR. The impact of event scale—revised. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD. New York: Guildford Press; 1996. p. 399–411.

43. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7. doi:10.1001/archinte.166.10.1092.

44. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. JAMA. 1999;282(18):1737–44. doi:10.1001/jama.282.18.1737.

45. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–35. doi:10.1192/bjp.133.5.429.

46. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. Psychiatry Clin Neurosci. 2017;71(1):6–17. doi:10.1111/pcn.12433.

47. Dell’Oso L, Carmassi C, Carlini M, Rucci P, Torri P, Cesari D, et al. Sexual dysfunctions and suicidality in patients with bipolar disorder and unipolar depression. J Sex Med. 2006;11(10):3063–70. doi:10.1016/j.jsxm.2011.03.010.

48. Pollack MH, Simon NM, Fogliani A, Pitman R, McNally RJ, Nierenberg AA, et al. Persistent posttraumatic stress disorder following September 11 in patients with bipolar disorder. J Clin Psychiatry. 2006;67(3):394–9. doi:10.1097/00004880-200603000-00009.

49. Bonnanno GA, Mancini AD. Beyond resilience and PTSD: mapping the heterogeneity of responses to potential trauma. Psychological Trauma: Theory, Research, Practice, and Policy. 2012;4(1):74–83. doi:10.1037/a0017829.

50. Donoho CJ, Bonanno GA, Porter B, Kearney L, Powell TM. A decade of war: prospective trajectories of posttraumatic stress disorder symptoms among deployed US military personnel and the influence of combat exposure. Am J Epidemiol. 2017;186(12):1310–8. doi:10.1093/aje/kwx318.

51. Porter B, Bonanno GA, Frasco MA, Dursa EK, Boyko EJ. Prospective post-traumatic stress disorder symptom trajectories in active duty and separated military personnel. J Psychiatr Res. 2017;89:55–64. doi:10.1016/j.jpsychires.2017.01.016.
62. Dell’osso L, Carmassi C, Rucci P, Ciapparelli A, Paggini R, Ramacciotti CE, et al. Lifetime subthreshold mania is related to suicidality in posttraumatic stress disorder. CNS Spectr. 2009;14(5):2626. doi:10.1017/s1092852900025426.

63. Albert U, Carmassi C, Cosci F, De Cori D, Di Nicola M, Ferrari S, et al. Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: a systematized review. Int Clin Psychopharmacol. 2016;31(5):249–58. doi:10.1097/YIC.0000000000000127.

64. Carmassi C, Gesi C, Corsi M, Cremone IM, Bertelloni CA, Massimetti E, et al. Exploring PTSD in emergency operators of a major University Hospital in Italy: a preliminary report on the role of gender, age, and education. Ann Gen Psychiatry. 2018;17:17. doi:10.1186/s12991-018-0184-4.

65. Liu CH, Zhang E, Wong GTF, Hyun S, Hahm HC. Factors associated with depression, anxiety, and PTSD symptomatology during the COVID-19 pandemic: clinical implications for U.S. young adult mental health. Psychiatry Res. 2020;290:113172. doi:10.1016/j.psychres.2020.113172.

66. Gesi C, Carmassi C, Cerveri G, Carpita B, Cremone IM, Dell’Osso L. Complicated Grief: What to Expect After the Coronavirus Pandemic. Front Psychiatry. 2020 May 26;11:489. doi: 10.3389/fpsyt.2020.00489.

67. MacIntyre A, Ferris D, Gonçalves B, Quinn N. What has economics got to do with it? The impact of socioeconomic factors on mental health and the case for collective action. Palgrave Commun. 2018;4:10. doi:10.1057/s41599-018-0063-2.