POOR SLEEP QUALITY MAY INDEPENDENTLY PREDICT SUICIDAL RISK IN COVID-19 SURVIVORS: A 2-YEAR LONGITUDINAL STUDY

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Abstract

Objective: Multiple symptoms of psychiatric, neurological, and physical illnesses may be part of Post-COVID conditions and may pose COVID-19 survivors a high suicidal risk. Accordingly, we aimed to study factors contributing to suicidal risk in Post COVID-19 patients.

Method: Consecutive patients with post COVID-19 conditions were followed for 2 years at the University Hospital of Ferrara at baseline (T0), 6 (T1), 12 (T2), and 24 (T3) months. Demographics, and clinical data for all patients included: disease severity, hospital length of stay, comorbidity, clinical complications, sleep quality, cognitive complaints, anxiety and stress-related symptoms, depressive symptoms, and suicidal ideation.

Results: The final sample included 81 patients with post COVID survivors. The mean age was 64 + 10,6 years, 35,8% were females, 65,4% had medical comorbidities, and 69,1% had WHO severe form of COVID forms. At T0 more than 90% of patients showed poor sleep quality, 59.3% reported moderate/severe depressive symptoms, and 51.% experienced anxiety, 25.9% experienced post-traumatic stress symptoms. At T0 suicidal ideation, interested 6.1% and at T3 it increased to 7.4%. In the regression analysis, suicidal ideation at baseline was best predicted by poor sleep quality (O.R. 1.71, p=0.044) and, after 2 years, suicidal ideation was best predicted by poor sleep quality experienced at baseline (OR 67.3, p=0.001).

Conclusions: Poor sleep quality may play as an independent predictor of suicidal risk in post-COVID survivors. Evaluating and targeting sleep disturbances in COVID survivors is important to prevent the consequences of disrupted sleep in mental health.

Key words: post-COVID survivors, poor sleep, suicidal ideation, depression, anxiety

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Introduction

Coronavirus Disease 2019 (COVID-19) survivors may suffer from multiple symptoms of psychiatric, neurological, and physical illnesses (Who 2021; Watanabe et al., 2022). According to WHO, the most common symptoms and complaints were fatigue (78%), shortness of breath (78%), cognitive dysfunction (74%), memory disturbances (65%), muscle pain (64%), and sleep disturbances (62%). (Watanabe et al., 2022). Persistent psychiatric symptoms among COVID-19 survivors such as depression, anxiety, and post-traumatic symptoms were also reported in post COVID-19 conditions (Premraj et al., 2022; Vanichkachorn et al., 2021).

Recently, Sher 2020, underlined that symptoms of psychiatric, neurological, and physical illnesses, as well as inflammatory damage to the brain in individuals with post-COVID conditions may pose COVID-19 survivors at high suicidal risk. Nevertheless, the literature focusing on the relationship between post-COVID-19 syndrome and suicidal risk is lacking, and to date, only three cross-

sectional studies have investigated this relationship. In these studies, cognitive complaints, physical symptoms and higher rates of psychopathology were correlated with greater suicidal risk (Gasnier et al., 2022; Simonetti et al., 2022; Woodward et al., 2022). Although sleep disturbances constitute a key feature of post COVID-19 conditions and are considered independent risk factors for suicidal risk (Geoffroy et al., 2021), they were not explored in relation to suicidal risk in post COVID-19 syndrome.

Accordingly, the present study aimed to explore the possible association between sleep quality, psychopathology and suicidal risk in patients post-COVID survivors in a 2 years longitudinal study.

Method

This was a longitudinal observational study. The protocol was approved by the local Ethical Committee Ferrara University Hospital Italy (EM66-2022_539/2020/Oss/AOUFe_EM1). Patients post COVID survivors during their hospitalization stay (between January 2020 and April 2021) at Ferrara University Hospital, were consecutively enrolled. Inclusion criteria were (a) men and women aged over 18 with a COVID-19 diagnosis (WHO criteria); (b) previous positivity to COVID-19; (c) capability of providing informed consent. Exclusion criteria were severe neurodevelopmental disorders, dementia, or other severe neurological disorders. Patients with severe cognitive impairments or inability to give informed consent were excluded. Informed consent was requested after explaining the study procedures and objectives. Patients were assessed after baseline (T0), 6 (T1), 12 (T2), and 24 (T3) months. The research team collected the following demographics, and clinical data for all the patients included: age, sex, symptoms' onset, disease severity (WHO criteria), hospital length of stay, comorbidity, clinical complications, sleep quality, cognitive complaints, anxiety and stress-related symptoms, depressive symptoms, and suicidal ideation.

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI was designed to evaluate overall sleep quality in clinical populations. Each of the questionnaire's 19 self-reported items belongs to one of seven subcategories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each item is weighted on a 0–3 interval scale. The global PSQI score is then calculated by totalling the seven component scores, providing an overall score ranging from 0 to 21, with poor sleep quality denoted from a cut-off of ≥ 5.

Cognitive impairment was evaluated with the Montreal Cognitive Assessment MoCA. It evaluates visuospatial skills, attention, language, abstract reasoning, delayed recall, executive function, and orientation. A cut-off ≤ 12 is considered pathologic (Nasreddine et al., 2005).

Symptoms of anxiety were assessed with the Beck Anxiety Inventory (BAI). *The* BAI items are scored on a scale between 0 and 3 and have a maximum score of 63. A total score of 0–7 is considered a minimal range, 8–15 is mild, 16–25 is moderate, and 26–63 is severe anxiety (Beck, 1988).

Post-traumatic stress symptoms were assessed with the Impact of Event Scale–Revised (IES-R) (Weiss & Marmar, 1997). The revised version of the Impact of Event Scale (IES-r) has 22 items and a scoring range

of 0 to 88; a score of 33 and above are indicating post-traumatic stress symptoms.

Depressive symptoms were assessed with the Patient Health Questionnaire – 9 (PHQ-9) (Kroenke et al., 2001). The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression consists of 9 items. Total scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe, and severe depression, respectively.

Suicidal ideation was assessed with PHQ-9 item 9 asking: "Thoughts that you would be better off dead or of hurting yourself in some way" and possible answers were not at all (0), several days (1), more than half the days (2) and nearly every day (3). A score of 1, 2,3 was considered positive for suicidal ideation.

At T3, suicidal ideation was also assessed with the Suicidal Ideation Scale (SSI). The Scale for Suicide Ideation (SSI) is a 19-item instrument of the current intensity of specific attitudes, behaviors, and plans to commit suicide (Beck et al., 1979). Each item consists of three options graded according to the intensity of the suicidality and rated on a 3-point scale ranging from 0 to 2 (no ideation to strong ideation). The ratings are then summed to yield a total score, which ranges from 0 to 38. The best cut-off to indicate high/low risk was >3.

Statistical analysis

The statistical analyses were performed using SPSS 22.0 for Windows. Results were expressed as mean + standard deviation (SD) and/or percent values. The Shapiro-Wilk Test was used to check the normality of the variables.

We conducted a repeated ANOVA analyses on PSQI, MoCA, BAI, IES-R, PHQ-9 total score and PHQ Item 9 including T0, T1, T2, and T3. For the purpose of the study linear and multiple regression and logistic models were then built with suicidal ideation at T0, T1, T2 (item 9 PHQ) and T3 (SSI total score) as dependent variables while taking into account age, sex, symptoms' onset, disease severity (WHO criteria), hospital length of stay, comorbidities and clinical complications. A mediation analysis using the Sobel Test (Sobel, 1982) was performed in order to study the potential processes that may underlie the relationships between these variables. All pathways of the mediation were tested.

Results

Descriptive statistic

The final sample included 81 patients with post COVID survivors. The mean age was 64 $\pm$ 10,6 years, N° 29, 35,8% were females. The mean length of hospital stay was 81$\pm$ 23 days, N° 53, 65,4% had medical comorbidities; N° 56, 69,1% had WHO severe form of COVID-19. Some patients were recruited during the first wave (n°16, 18,7%), and others during the second and third wave (**table 1**). The majority of patients (98.7%) showed respiratory distress and 17,3% showed Acute respiratory distress syndrome (ARDS) (**table 1**).

Regarding PSQI total score, it decreased across evaluations with statistical differences (F 39,635< p < 0,017), except for T1 vs T2 (p =0,607). At T0 more than 90% of patients showed poor sleep quality and after 2 years still, 24.7% reported poor sleep quality (**table 1**, **figure 1**).

Regarding PHQ-9 total score, it decreased across

Table 1. *Clinical and demographic data. Acute respiratory distress syndrome (ARDS), BAI: Beck Anxiety Inventory, IES-R : Impact of Event Scale – Revised, Montreal Cognitive Assessment MoCA, Scale of Suicide Ideation (SSI), Patient Health Questionnaire – 9 (PHQ-9), Item 9 PHQ= suicidal risk, Pittsburgh Sleep Quality Index (PSQI)*

	T0		T1 6 months	T2 12 months	T3 24 months	F, p
Age years	64 ± 10,6					
hospital length of stay days	81± 23					
	N°	**%**				
Famale sex	29	35.8				
Comorbidities	53	65.4				
Critic Severe forms	56	69.1				
First wave	16	19.7				
Second wave	25	30.9				
Third wave	40	49.4				
Respiratory distress	80	98.7				
ARDS	14	17.3				
PSQI mean±SD	12.89± 5.53		10.34 ±6.49	9.93± 6.27	4.0 ±3.45	39.635 p < 0,017
Poor sleep quality	91.4%		79%	75.3%	24.7%	
PHQ-9 mean±SD	6.52± 4.71		5.02± 4.74	4.44± 3.44	3.98± 3.64	14.888, p<0.001
Moderate/severe depressive symptoms	59.3%		37.3%	35.8%	25.9%	
PHQ item 9 suicidal ideation	N°5	6.1%	N°4 4.9%	N°1 1.2%	N°6 7.4%	4.896, p=0.003
BAI mean±SD	8.76± 6.92		7.86± 10.20	7.33± 6.63	7. 69± 8.03	F=0.424 p=0,736
Anxiety symptoms	51.9%		33.3%	28.4%	29.6%	
IES-R mean±SD	22.71± 17		18.44 ±16.61	17.71± 15.16	14.56± 11.57	F=4,671 p=0.004
Post-traumatic stress symptoms	25.9%		17.3%	13.6%	13.6%	
Cognitive complains MoCA	69.1 %		67.9%	50.6 %		F=2,047 p=0.133
SSI total score					N °8 9.9%	

evaluations with statistical differences (F: 14,888, p<0.001): T1, T2, and T3 scores were statistically reduced compared to those of T0. At T0 59.3% reported moderate/severe depressive symptoms, at T1 37.3%, at T2 35.8% and at T3 25.9% were still experiencing depressive symptoms (**table 1**, **figure 1**).

Regarding suicidal Ideation, PHQ item 9, there were significant differences across evaluations. In particular, it resulted decrease from T0 to T1 and T2, and then at T3 it was increased (4.896,p=0.003) (**table 1**, **figure 1**). At T3 Suicidal ideation scale was additionally administered and it resulted that 8 subjects 9.9% experienced suicidal ideation.

The BAI total score was not significantly decreased across evaluations (F=0.424 p=0,736). At T0 almost 52% reported anxiety symptoms and at T3 almost 30% were still experiencing anxiety symptoms (**table 1**, **figure 1**).

Regarding IES-R total score, there was a significant decrease when comparing T0 to T3 only (F=4,671 p=0.004). At T0 25.9% experienced post-traumatic symptoms, and after 2 years 13.6% were still experiencing symptoms (**table 1**, **figure 1**).

Cognitive complaints (MoCA total score) remained

similar across evaluations (F=2,047 p=0.133).

Logistic regressions

Linear logistic regression model on suicidal ideation at T0 (item 9 PHQ-9) revealed that poor sleep quality, anxiety symptoms, post-traumatic stress symptoms, and depressive symptoms at T0 predicted suicidal ideation at T0. In the multivariate models, only poor sleep quality at T0 remained significant (O.R. 1.71, p=0.044). Other variables including COVID severity, comorbidities, or cognitive complaints did not result in significant.

Linear logistic regression model on suicidal ideation at T1 (item 9 PHQ-9) revealed that poor sleep quality, anxiety symptoms, post-traumatic stress symptoms, and depressive symptoms at T1 predicted suicidal ideation at T1. In the multivariate models, no variables remained significant. Other variables including T0 conditions did not show any significance.

Since suicidal ideation at T2 interested one subject, analyses were not performed.

Linear logistic regression model on suicidal ideation at T3 (SSI total score) revealed that poor sleep quality

Figure 1. *Sleep and psychiatric variables across evaluations*
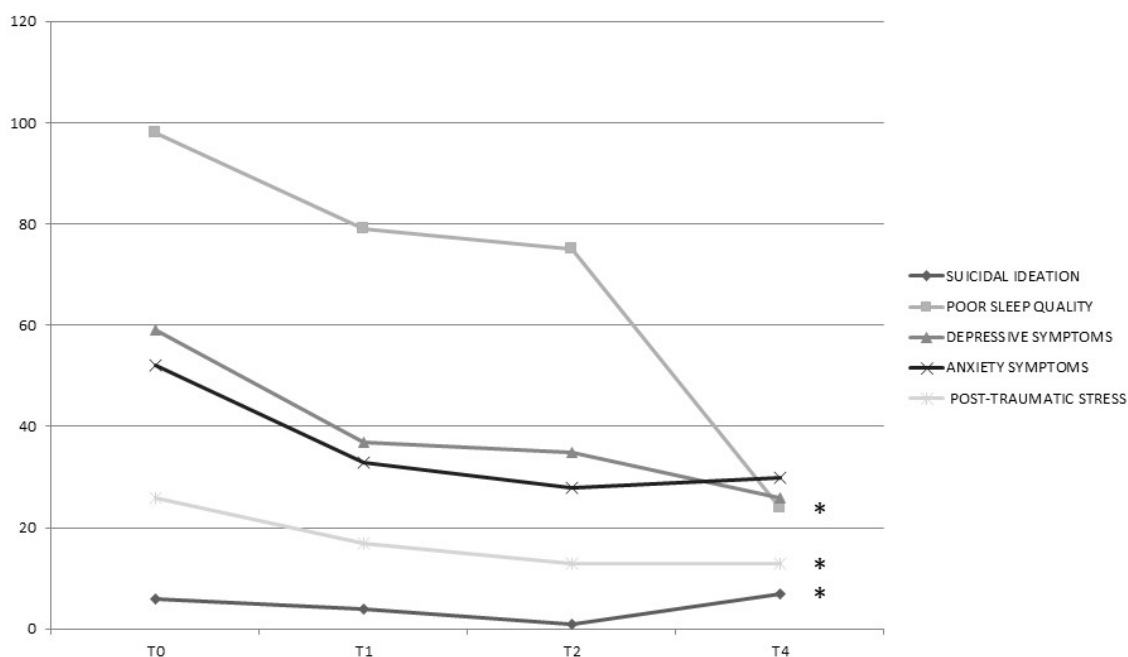
T0. Baseline, T1 after 6 months, T2 after 12 months, T3 after 24 months.
Poor sleep quality (Pittsburgh Sleep Quality Index , PSQI) decrease across evaluations with statistical differences At T0 more than 90% of patients showed poor sleep quality and after 2 years still 24.7% reported poor sleep quality. Depressive symptoms (Patient Health Questionnaire – 9 PHQ-9 totals core) decreased across evaluations with statistical differences (p<0.001). At T0 59.3% reported moderate/severe depressive symptoms, and at T4 25.9% were still experiencing depressive symptoms. Post traumatic stress symptoms (IES-R: Impact of Event Scale) were significantly decreased when comparing T0 to T4 only (p=0.004). At T0 25.9% experienced post-traumatic symptoms, and after 2 years 13.6% were still experiencing symptoms.

and, post-traumatic stress symptoms at T0, anxiety symptoms at T0, post-traumatic stress symptoms, and depressive symptoms at T3, predicted suicidal ideation at T3. In the multivariate models, only poor sleep quality at T0 remained significant (p=0.010).

Mediation analyses

Results of the mediation analyses for suicidal ideation at 24 months (SSI total score) highlighted that post-traumatic stress symptoms at 24 months (IES-R total score at T3) acted as mediators between poor sleep quality at T0 (PSQI total score T0) and suicidal risk after 24 months (Z=2.74, SE=0.05, p=0.006). Other pathways were explored but did not reach significance.

Discussion

The present study aimed to explore the possible association between sleep quality, psychopathology, and suicidal risk in patients hospitalized for COVID-19 in a 2 years longitudinal follow-up. The study showed that across 2 years poor sleep, anxiety, stress-related symptoms, and depressive symptoms tended to decrease in Post-COVID survivors. Indeed, more than 20% still experienced poor sleep, anxiety, and depression, and almost 13% still experienced post-traumatic symptoms. In particular, suicidal ideation interested 6.15% of the sample at baseline, tended to decrease within 1 year, and then increased between 1 and 2 years from the diagnosis reaching 9.9%. Predictors of suicidal ideation

at baseline were especially sleep and psychiatric symptoms and among them, poor sleep emerged as the stronger predictor. Similarly, suicidal ideation after 2 years was correlated to sleep and psychiatric disturbances, but the stronger predictor resulted in poor sleep experienced at baseline.

Since disturbed sleep is considered an independent predictor of suicidal risk (Geoffroy et al., 2021; Romier et al., 2023), it seems that this could be confirmed in Post-COVID survivors. This is the first longitudinal study about suicidal ideation in Post-COVID survivors taking into account medical, sleep, and psychiatric factors, and it showed that especially sleep disruption experienced at the beginning may affect suicidal ideation.

In this study 81 patients with moderate/severe Post-COVID survivors were followed for 2 years, for the majority they had medical comorbidities, were hospitalized for more than 40 days, and had respiratory distress. These patients at baseline experienced poor sleep quality in more than 90% of the cases, experienced moderate/severe depressive symptoms in 59.3%, anxiety symptoms in 52%, experienced post-traumatic symptoms in 25.9%, and suicidal ideation in 6.1%. In the present study, after 2 years more than 20% of patients still experienced sleep and psychiatric symptoms, and especially suicidal risk was even higher than at baseline.

These data are in line with previous works showing high rates of anxiety, depression, sleep and post-traumatic symptoms and higher suicidal risk in Post-COVID patients (Gasnier et al., 2022; Mazza

Table 2. *Suicidal ideation at baseline logistic regression analyses. Suicidal Ideation item 9 Patient Health Questionnaire – 9 at baseline. O.R.= Odd ratio, Acute respiratory distress syndrome (ARDS)*

Suicidal Ideation T0	Linear logistic regression		Multivariate logistic regression	
	OR	p	OR	p
Sex	1.2	0.84	-	-
Comorbidities	0.32	0.23	-	-
COVID-severity	0.27	0.16	-	-
Hospital length stay	0.16	0.112	-	-
Respiratory distress	0.23	0.98	-	-
ARDS	0.99	0.15	-	-
Poor sleep quality	**1.60** 1.138-2.27	**0.007**	**1.71** 1.016-2.910	**0.044**
Anxiety symptoms	**1.76** 1.04-1.32	**0.009**	1.17	0.459
Post-traumatic stress symptoms	**1.096** 1.025-1,172,	**0.007**	1.09	0.158
Depressive symptoms	**1.152** 0.985-1.348	**0.077**	1.08	0.433
Cognitive impairment	0.88	0.511	-	-

Table 3. *Suicidal ideation after 6 months logistic regression analyses. Linear and multivariate logistic regression on Suicidal Ideation item 9 Patient Health Questionnaire – 9 at baseline. O.R.= Odd ratio, p= significance, Acute respiratory distress syndrome (ARDS)*

Suicidal Ideation T1		Linear logistic regression		Multivariate logistic regression	
		OR	p	OR	p
Sex		0.58	0.83	-	-
Comorbidities		1.362	0.33	-	-
COVID-severity		5.27	0.566	-	-
Hospital length stay		2.26	0.232	-	-
Respiratory distress		1.23	0.967	-	-
ARDS		1.86	0.234	-	-
Poor sleep quality T0		0.88	0.778		
Poor sleep quality T1		**1.24** 1.052-1.466	**0.011**	1.142	0.334
Anxiety symptoms T0		1.030	0.680		
Anxiety symptoms T1		**1.26** 1.072-1.491	**0.005**	1.12	0.564
Post-traumatic stress symptoms	T0	1.03	0.355		
Post-traumatic stress symptoms	T1	**1.114** 1.030-1206	**0.007**	1.09	0.158
Depressive symptoms T0		0.88	0.567		
Depressive symptoms T1		**1.32** 1.095-1603	**0.004**	1.08	0.433
Cognitive impairment T0		0.77	0.344	-	-
Cognitive impairment T1		0.88	0.345		

et al., 2020; Premraj et al., 2022; Simonetti et al., 2022; Vanichkachorn et al., 2021). Mazza et al., 2020 argued that psychiatric consequences of SARS-CoV-2 infection can be caused both, by the immune response to the virus itself, or by psychological stressors such as social isolation and the psychological impact of a novel severe medical illness. Similarly, there is a bidirectional relationship between sleep, stress, and inflammation (Akkaoui et al., 2023; Irwin, 2019; Elder et al., 2023; Lo Martire et al., 2020). It is possible that disturbed sleep may be related to the state of hyper-inflammation and activation of the stress system but it can also be an additional factor favouring psychiatric disorders and contributing to hyper-inflammatory state in Post-COVID survivors. A hyper-inflammatory state might represent a common mechanism linking post-COVID-19 syndrome, psychopathology, sleep disturbances, and suicide.

In the present study, suicidal ideation at baseline

Table 4. *Suicidal ideation after 24 months logistic regression analyses. Linear and multivariate analyses on Suicidal Ideation was measured with the Suicidal Ideation Scale. O.R.= Odd ratio, Acute respiratory distress syndrome (ARDS)*

Suicidal ideation T3 SSI score	Linear logistic regression		Multivariate logistic regression	
	OR	p	OR	p
Sex	2.58	0.456	-	-
Comorbidities	0.88	0.789	-	-
COVID-severity	0.85	0.456	-	-
Hospital length stay	1.60	0.590	-	-
ARDS	1.87	0.324	-	-
Poor sleep quality T0	**7.33** **1.234-62.175**	**0.046**	**67.73** **2.692-170.476**	**0.010**
Anxiety symptoms T2	**6.20** **1.116-34.449**	0.037	0.241	0.674
Post-traumatic stress symptoms T0	**4.77** **1.011-22.821**	**0.43**	0.28	0.250
Post-traumatic stress symptoms T4	**13.66** **2.482-75.268**	**0.003**	0.82	0.064
Depressive symptoms T4	**6.00** **1.079-33.378**	**0.041**	0.24	0.304

Figure 2. *Mediation analyses*
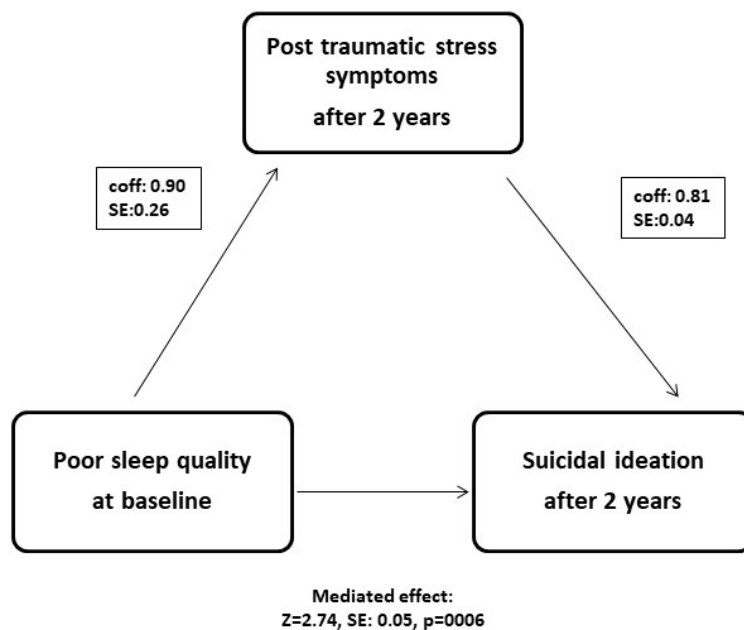
Poor sleep quality at baseline (T0) showed a direct effect on higher suicidal risk after 2 years (T3). Post-traumatic symptoms after 2 years acted as a mediator in their relationship (Z=2.74, SE=0.05, p=0.006), SE=Standard Error

was particularly associated with sleep and psychiatric symptoms. In our study, sleep and psychiatric disturbances were more potently correlated with suicidal ideation than medical comorbidities or other COVID-related disorders.

These data are in line with two studies addressing psychiatric disorders and suicidal ideation in Post-COVID syndrome (Gasnier et al., 2022; Simonetti et al., 2022). Indeed, in one study a role for medical comorbidities emerged. The new observation of the present study regarded the potential role of poor sleep quality. In our logistic regression, it emerged that disrupted sleep was the most important factor favouring suicidal ideation at the beginning, during the diagnostic period of Post-COVID Syndrome. Most importantly, this early sleep disruption emerged as the most potent causal factor for suicidal ideation after 2 years after the infection.

Interestingly, the mediation analyses showed that anxiety symptoms after 1 year and post-traumatic symptoms at 2 years mediated the association between poor sleep quality at baseline and suicidal risk after 2 years. These data are in line con accumulating evidence about the role of disturbed sleep as a risk factor for psychopathology (Riemann et al., 2022). It is possible that the impairment of the sleep system may affect regulatory processes on emotions, cognition, and stress response favouring, even in the long term, psychopathology which may contribute as a proximal factor to suicidal risk.

In this framework, several neurobiological pathways may explain the link between poor sleep and increased suicidal risk (McCall & Black, 2013). While sleep has important regulatory functions, disturbed sleep is associated with the hyperactivation of stress and inflammatory systems leading to a state of cognitive, somatic, and physiological hyperarousal (Riemann et al., 2022). The overload of stress and inflammatory systems has in fact already been hypothesized as a factor possibly correlated with suicidal risk (McCall & Black, 2013). While sleep has important regulatory functions for cognition and emotions, poor sleep may favor hopelessness and rumination, impairment of executive decision-making process and a tendency to impulsivity, emotional reactivity, and aggressive behaviours hence contributing to suicidal risk (McCall & Black, 2013).

While sleep is essential to brain homeostasis and brain plasticity and to mental and physical health, disrupted sleep may act as a stressor and may contribute to mental disorders which may contribute to suicidal risk including anxiety and post-traumatic stress symptoms hence contributing to suicidal risk even in the long term. It is possible that when the sleep system is disturbed it may have long-term consequences on cognition and emotions thus contributing to negative trajectories of mental disturbances including suicidal risk.

Limitations

These results should be interpreted considering several limitations. Longitudinal studies are needed in larger samples of patients with Post-COVID syndrome and analyzing the effects of therapeutic approaches for sleep and psychiatric disorders. It could be also interesting to examine patients who attempted suicide to better examine the direction of risk and be able to generalize these findings.

Conclusion

Post-COVID survivors may be at high suicidal risk, both at the beginning of the disorder and in the long term. Multiple factors may contribute to this increased risk, indeed even after considering disease severity, medical comorbidities, and psychiatric symptoms, disturbed sleep emerged as a strong factor potentially contributing to suicidal risk, even in the long term. Since sleep disturbances impair sleep functions, it is possible that disturbed sleep may emerge not only as a proximal precipitating factor for suicidal risk but also as mediating or distal factor. It is also possible that it may contribute to the development of mental disturbances which may precipitate suicidal risk. Assessing and treating sleep disturbance in post-COVID survivor patients should be a priority in order to prevent the negative consequences of impaired sleep.

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