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DEPRESSION AND ANXIETY AMONG COVID-19 PATIENTS ADMITTED TO A "RED ZONE" INTENSIVE CARE UNIT: DO THE FACTORS OF SELF-AWARENESS OF SOMATIC HEALTH, ANXIETY, AND DEPRESSION CONTRIBUTE TO THE COURSE OF SARS-COV-2 INFECTION?

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SUMMARY

Background: *The prevalence of depressive disorders in the general population increased significantly during the COVID-19 pandemic. The aim of this study is to examine the relationship between history of anxiety and depressive disorders and COVID-19 outcome, hospitalization and severity of anxiety and depression, and whether such relationships are explicable by direct impact of the disease.*

Subjects and methods: *We conducted a questionnaire survey among 98 inpatients in the Department of Infectious Diseases of the Clinics of Samara State Medical University. The self-report questionnaire consisted of 120 items, including socio-demographic characteristics of participants, State-Trait Anxiety Inventory, and the Center for Epidemiologic Studies Depression Scale, with items reflecting subjective feelings about the COVID-19 pandemic. We used one-factor analysis of variance to compare between groups for those indicators that conformed to a normal distribution, and the chi-square test (χ^2) or Fisher's exact test to analyze group differences in the distribution of categorical variables was used.*

Results: *The mean (SD) total score on the STAI anxiety scale among hospitalized patients (51 (10.1)) significantly exceeded that of the COMET-G control group (44.9 (11.7) ($H=22.8$, $p<0.001$). There was a similar difference in the severity of depression as measured by the CES-D scale (23.4 (12.6) versus 18.0 (11.8), $H=15.2$ and $p<0.001$). In contrast to the general population, there were no statistically significant differences in anxiety and depression severity in the matched samples 52 subjects fulfilling the criteria of age, gender, and general perception of health condition.*

Conclusions: *Anxiety and depression scores among ICU (red zone) inpatients significantly exceeded the scores observed in the COMET-G general population group. Our study did not confirm expected relationship between symptoms of anxiety and depression (based on questionnaire response) and the risk of severe course of COVID-19 (e.g. hospitalization) in matched samples, but proved that the factor of self-awareness of health state may be related to the COVID-19 course severity. Future research would benefit from clinical interview of inpatients and follow-up monitoring of affective disorders to specify whether anxiety and particular type of depression (e.g., anxious) are selectively related to the severity of COVID-19 course and risks of affective disorders persistence after somatic recovery. The accumulation of mental disorders with age, and the bidirectional association of mood disorders and infectious diseases should be considered when assessing the risk factors.*

Key words: *anxiety – COMET-G - COVID-19 - depression - department of infectious diseases - intensive care unit - inpatients - red zone - self-perception of health - self-awareness of somatic health*

Abbreviations: *ABPM – ambulatory blood pressure monitoring; ANOVA – one-factor analysis of variance; ARR – Absolute risk reduction; CES-D – Center for Epidemiologic Studies Depression Scale; COMET-G – COVID-19 mental health international for the general population; COVID-19 – COronaVIrus Disease 2019; ICU – Intensive Care Unit; RASS – Risk Assessment Suicidality Scale; SARS – Severe acute respiratory syndrome; SD – standard deviation; STAI – State-Trait Anxiety Inventory; WHO – World Health Organization; WPA – World Psychiatric Association*

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INRODUCTION

According to the WHO, there had been as of December over 600 million cases of COVID-19 worldwide, and more than 6.5 million deaths (World Health Organization 2022a). During 2020 the onset of the alone COVID-19 pandemic brought 26% increases in the number of people living with anxiety, and a 28% increase in depressive disorders (World Health Organization 2022b). Fountoulakis et al. found that although the rate of probable depression was significantly higher in individuals with a history of psychiatric disorder (31.8% vs. 13.1%), there was an unexpectedly high proportion of individuals with depression without such a history (Fountoulakis et al. 2022). Thus, circumstances of the COVID-19 pandemic elicited a psycho-

logical response in the general population, and the post-COVID period also manifested an increased prevalence of psychiatric disorders (Taquet et al. 2021). In particular, the prevalence of depressive disorders increased significantly in the general population during the COVID-19 pandemic, with estimates ranging from 20.9 to 27.8% (Ettman et al. 2020, Kim et al. 2021).

WHO and WPA have indicated that persons with severe mental disorders are at risk of a complicated course upon falling ill with COVID-19 (Wang Q et al. 2021). Lee et al. showed that patients with severe mental illness had a slightly higher risk of severe clinical outcomes from COVID-19 compared to patients without history of mental illness (Lee et al. 2022). Severe mental illness can cause abnormal thoughts and perception, loss of connection to reality, delusions or even hallucinations, which can interfere in cognition and exacerbate social isolation. Such factors may lead to difficulty in obtaining medical care, or refusal to seek medical care and poor treatment adherence. Koyama et al. found that patients with depression had a significantly higher chance of re-hospitalization for COVID-19 and longer mean treatment times (Koyama et al. 2022). Among patients with psychiatric disorders, the risk of mortality from confirmed COVID-19 was significantly higher in than in patients without psychiatric disorder (Jeon et al. 2021). Ceban et al. found that individuals with pre-existing affective disorders were at higher risk of COVID-19 hospitalization and death and should consequently be categorized as at risk based on pre-existing condition (Ceban et al. 2021). A diagnosis of affective disorder was also associated with a greater likelihood of discharge to a skilled nursing facility or other rehabilitation facility rather than home (Castro et al. 2021). This association was also observed for psychotic disorders, mood disorders, substance use disorders, intellectual disability and developmental disorders, but not for anxiety disorders. Various mental disorders were associated with an increased risk of hospitalization, but with no significant associations with mortality during ICU hospitalization were found (Vai et al. 2021). The standardized ARR of the combined outcome (death from any cause or severe COVID-19 (COVID-19 with SARS, or hospitalization in the intensive care unit (ICU)) was significantly higher in patients with severe mental illness, including schizophrenic spectrum disorders, bipolar disorder, unipolar depression, and in patients receiving psychotropic medications and similar results have been reported for outcomes such as death or severe COVID-19 (Barcella et al. 2021). The COVID-19 affective disorder cohort recruited between February and December 2020 had a 2.76-fold increase in mortality compared to controls, and the anxiety disorder cohort had 2.39-fold greater mortality (Teixeira et al. 2021). Ranger et al. found that diagnosis and/or treatment of neuropsychiatric conditions other than dementia were associated with an increased likelihood of severe COVID-19 outcome, defined as as hospitalization, ICU admission, or death associated with COVID-19 infection (Ranger et al. 2022). It is obvious that the COVID-19-related somatic states, including those observed in patients admitted to ICU due to the severe forms of viral infection, have been shaped by people's "psychological, social, political and spiritual responses to them" (Jakovljevic 2021, p. 462). Moreover, "even a new normality (pathological normality or normal pathology) associated with COVID-19 pandemic and infodemic (epistemic hypervigilance and mistrust)", as well as the increased rates of mental disturbances on this flourishing information ground, have been presented across recent research data (Jakovljevic et al. 2020a,b, 2021 p. 462). According to the principles of biopsychosocial paradigm, any somatic state cannot be separated from the current human's mental well-being, and a person apparently reacts to the signals coming from his body in pain. Another way back, pre-existing mental disorders make a human-being significantly more vulnerable and some sort weak in relation to the immunity response to the external agents appearance (e.g. SARS-Cov-2 infection), such as the anxiety domain of mental symptoms was proved to be related to the oxidative stress increase which, in its turn, is causing the higher severity of COVID-19 course and other medical illnesses via biological mechanisms of hyperinflammation (Steenkamp et al. 2017, Vollbracht & Kraft 2022). Toubasi showed that pre-diagnosis of psychiatric disorders increased the risk of COVID-19 severity and mortality (Toubasi et al. 2021). In particular, higher mortality was observed in patients with schizophrenia, schizotypal and delusional disorders compared to patients with affective disorders.

Some studies also found an association between the presence of a pre-existing psychiatric disorder and the likelihood of infection, which might imply that pre-existing conditions increased the risk of falling ill from COVID-19. For example, Wang et al. found that patients with a recent diagnosis of a psychiatric disorder, particularly for the case of depression, had a significantly increased risk of subsequent COVID-19 infection (Wang et al. 2021). Yang et al. observed an increased risk of COVID-19 among individuals with pre-pandemic mental disorders compared to individuals without such disorders (Yang et al. 2020).

The aim of our study is to examine the relationship between history of anxiety and depressive disorders and COVID-19 outcome in the Samara region, in terms of hospitalization and severity of anxiety and depression. We further wish to establish whether the relationship between anxiety, depression and COVID-19 is explicable by a direct impact of the disease, or is due to other causes.

SUBJECTS AND METHODS

Participants

We conducted a questionnaire survey among 79 inpatients in the infectious diseases department of Clinics of the Federal State Budgetary Educational Institution of Higher Education «Samara State Medical University» of the Ministry of Healthcare of the Russian Federation, Samara from February 15 to April 23, 2021. All the recruited participants were definitively diagnosed with COVID-19. The relationship between hospitalization and history of anxiety and depressive disorders was assessed in the hospitalized population. The relationship between current COVID-19 severity and severity of depression and anxiety was assessed in comparison with the COMET-G population. To exclude the influence of additional factors, we identified a group matched for sex, age, and severity of perceived somatic health. All surveyed participants agreed to participate and provided verbal informed consent before their enrollment. Study approval was granted by the Ethical Committee of the Federal State Budgetary Educational Institution of Higher Education «Samara State Medical University» of the Ministry of Healthcare of the Russian Federation for Clinics and University Departments (N 98-n, 23.12.2020).

Study design

The study was a cross-sectional and observational survey within the framework of the multi-center cross-sectional study "COvid-19 and Mental health inTernational (COMET-G) study in General population" in 40 countries. However, the present survey was administered in an intensive care unit setting. The design of this study has been described in detail in the Supplementary Materials of our earlier publications (Fountoulakis et al. 2021, Smirnova et al. 2021).

Demographic and clinical data

Data includes sex, date of birth, place of residence, marital status, number of people in the household, number of children in the family, education, and employment (including employment in the health sector) during the period of the lockdown.

Questionnaires

The online self-report questionnaire consisted of 120 items, including (i) socio-demographic characteristics of participants, (ii) the Risk Assessment Suicidality Scale (RASS) (Fountoulakis et al. 2012), State-Trait Anxiety Inventory (STAI, STAI-S subscale for anxiety state) (Spielberger et al. 1970), Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 2016), (iii) the items reflecting subjective feelings about the COVID-19 pandemic, i.e., related worries and fears, recent changes in anxiety, depression and suicidality over the period of pandemic, as well as (iv) a history of mental disorders, somatic disorders, attitudes towards recommended protective behavior against COVID-19 virus, and (v) personal beliefs about the pandemic's origins, life habit changes such as changes in physical activity, eating behavior, sleep and sex quality, deviations in social media, and substance use.

The Risk Assessment Suicidality Scale (RASS) has been developed as a self-report instrument with an emphasis on items describing suicide-related behavior (Fountoulakis et al. 2012). This scale consists of 12 items rated on a four-point Likert scale with responses ranging from 0 to 3 (Not at all, A little bit, Much, Very much, respectively) for assessing fear of death, intention regarding suicide, enjoyment gained from life, and a history of suicide attempts and self-harm behavior, with higher scores reflecting a greater tendency towards suicidality. According to the RASS scale developers' recommendations, we have also applied an item-based standardization procedure by summing specific scores to each response to calculate the total suicidality risk score (Fountoulakis et al. 2012).

Depression was measured using CES-D with cut-off in the total CES-D score of >23, as proposed by Fountoulakis et al. for clinically relevant depression (Fountoulakis et al. 2012); anxiety was measured using STAI, with a cut-off in the total STAI score of >39 for clinically relevant anxiety (Knight et al. 1983).

As we have previously described (Smirnova et al. 2021), the questionnaire was translated into Russian language and double checked by back translation into English by bilingual speakers.

Clinical and laboratory data

Clinical and laboratory parameters, days on ventilator, levels of ABPM, absolute cytotoxic T cells CD3-8+ and NK cells CD3-16+56+ values were recorded in patients.

Statistical analysis

We first characterized the participant sample and then compared its characteristics with a control population selected as part of the Russian arm of the larger COMET-G study, which had a similar design to the present study. To further control for bias in the study sample relative to the overall control population, we implemented a case-control matching approach in the approach we searched and selected cases from the COMET-G study database based on an exact match for sex and perceived health status, as well as age matching with a tolerance of ±5 years. This approach ensured the formation of balanced groups of cases and controls, which is essential for objective data analysis and reliable results.

Table 1. Socio-demographic characteristics of inpatients (hospitalized patients with COVID-19) study sample compared to Russian study sample of the COMET-G study

Socio-demographic characteristics	Definition	Hospitalized (n=79)	COMET-G (n=7777)	Hypothesis test
Age, Median (Q1, Q3)		31 (23, 41)	66 (58.5, 75.5)	H=186.047, p<0.001[1]
A1 (Sex), n (%)	Female	49 (62.0)	4,736 (60.9)	χ^2=2.148, df = 2, p=0.342[2]
	Male	30 (38.0)	2,836 (36.5)	
	Other	0 (0.0)	205 (2.6)	
A3 (Place of residence during this period), n (%)	Capital City	0 (0.0)	1,144 (14.7)	χ^2=99.876, df = 5, p<0.001[2]
	City (100,000-1 million population)	5 (6.3)	2,082 (26.8)	
	City > 1 million population	63 (79.8)	2,318 (29.8)	
	Rural area - Village	10 (12.7)	927 (11.9)	
	Town (20,000-100,000 inhabitants)	0 (0.0)	977 (12.6)	
	Town (<20,000 inhabitants)	1 (1.3)	329 (4.2)	
A4 (Marital Status), n (%)	Divorced (or estranged)	8 (10.1)	595 (7.7)	χ^2=106.518, df = 5, p<0.001[2]
	Live with someone without an official relationship	1 (1.3)	863 (11.1)	
	Married (or in a civil partnership)	54 (68.4)	3,231 (41.6)	
	Other	1 (1.3)	702 (9.0)	
	Single	5 (6.3)	2,278 (29.3)	
	Widower	10 (12.7)	108 (1.4)	
A5 (Number of people residing in the house during this period), n (%)	2	44 (55.7)	2,352 (30.2)	χ^2=40.534, df = 4, p<0.001[2]
	3	9 (11.4)	1,969 (25.3)	
	4	5 (6.3)	1,516 (19.5)	
	5+	2 (2.5)	858 (11.0)	
	Alone	19 (24.1)	1,082 (13.9)	
A6 (Number of children), n (%)	0	11 (13.9)	4,000 (51.4)	χ^2=47.327, df = 4, p<0.001[2]
	1	29 (36.7)	1,824 (23.5)	
	2	32 (40.5)	1,471 (18.9)	
	3	5 (6.3)	348 (4.5)	
	4+	2 (2.5)	134 (1.7)	
A7 (Education), n (%)	Bachelor's degree	24 (30.4)	1,377 (17.7)	χ^2 = 18.189, df = 4, p = 0.001[2]
	Basic school	9 (11.4)	701 (9.0)	
	High school	31 (39.2)	2,815 (36.2)	
	Master's degree	10 (12.7)	2,549 (32.8)	
	Scientific degree	5 (6.3)	335 (4.3)	
A9 (Employment), n (%)	Allowance due to health condition	1 (1.3)	68 (0.9)	χ^2=967.024, df = 11, p<0.001[2]
	Disability pension	0 (0.0)	49 (0.6)	
	Housekeeper	0 (0.0)	300 (3.9)	
	Not working by choice	2 (2.5)	105 (1.4)	
	Other	0 (0.0)	677 (8.7)	
	Retired	48 (60.8)	272 (3.5)	
	Self-employed	0 (0.0)	612 (7.9)	
	Student	0 (0.0)	1,166 (15.0)	
	Unemployed	0 (0.0)	858 (11.0)	
	Civil cervant	13 (16.5)	1,889 (24.3)	
	Private clerk	12 (15.2)	1,781 (22.9)	
	Unemployed	3 (3.8)	0 (0.0)	

[1]Do not fit normal distribution, Kruskal-Wallis test; [2]Pearson χ^2-test

Table 1. Continues

Socio-demographic characteristics	Definition	Hospitalized (n=79)	COMET-G (n=7777)	Hypothesis test
A10 (Employment in the Health Sector), n (%)	Doctor	3 (3.8)	722 (9.3)	χ^2=10.481, df = 5, p=0.063[2]
	Not a medical worker	74 (93.7)	6,201 (79.7)	
	Nurse	0 (0.0)	290 (3.7)	
	Other healthcare profession	0 (0.0)	241 (3.1)	
	Other hospital staff	1 (1.3)	213 (2.7)	
	Administrative staff in hospital	1 (1.3)	110 (1.4)	
B1 (Self-rated general health over the last month), n (%)	Bad	36 (45.6)	282 (3.6)	χ^2=400.868, df = 4, p<0.001[2]
	Good	9 (11.4)	2,508 (32.3)	
	Moderate	31 (39.2)	1,393 (17.9)	
	Perfect	2 (2.5)	2,381 (30.6)	
	Very good	1 (1.3)	1,213 (15.6)	
B2 (Presence of chronic medical conditions), n (%)	No	6 (7.6)	5,972 (76.8)	χ^2=202.061, df = 1, p<0.001[2]
	Yes	73 (92.4)	1,805 (23.2)	

[1]Do not fit normal distribution, Kruskal-Wallis test; [2]Pearson χ^2-test

Descriptive statistics were used to present the general characteristics of the sample, including demographics and baseline measures of the study. All variables were assessed for normality of distribution using the Shapiro-Wilk test. For variables with a distribution conforming to normality, we report mean values and standard deviations. This allowed for an accurate description of the central tendency and variability of the data within each group. One-factor analysis of variance (ANOVA) was used to compare between groups for indicators that conformed to a normal distribution. Where the distribution of variables deviated from normality, we present median values and interquartile ranges (first and third quartiles) were presented. In cases failing the normality test, we used the non-parametric Kruskal-Wallis test. Categorical variables are presented as frequencies and percentages. To analyze differences in the distribution of categorical variables between groups, the chi-square test (χ^2) or Fisher's exact test was used in cases where the expected frequencies in any of the cells of the contingency table were less than 5.

RESULTS

Sample characteristics

The study included 79 hospitalized patients. Their general characteristics in comparison with the COMET-G study control sample are summarized in Table 1. The median age of hospitalized patients was 66 years, thus significantly older than the COMET-G control group, for whom the median age was 31 years (H=186.047, p<0.001). Women predominated in both samples and accounted for 62.0% (49 of 79) of the hospitalized patients and 60.9% (4736 of 7783) for the general population of the Russian COMET-G study. As expected, we found differences by place of residence (χ^2=99.876, df=5, p<0.001). In the sample of hospitalized patients, 68.4% were married or in a common-law relationship, a significantly higher proportion than in the COMET-G control group (41.6%) (χ^2=106.518, df=5, p<0.001). Among hospitalized patients, 55.7% had 2 children, a significantly higher percentage than the 30.2% of the control sample (χ^2=40.534, df=4, p<0.001). 40.5% (X of 79) of the hospitalized patients lived in families of two, while the majority (51.4%) in the control group had no children (χ^2=47.327, df=4, p<0.001). The distributions of the samples by education and by employment also differed (χ^2=18.189, df=4, p=0.001 and χ^2=967.024, df=11, p<0.001, respectively). These data suggest significant demographic and socioeconomic differences between hospitalized patients and the control sample, highlighting the importance of considering these parameters when analyzing the association of COVID-19 course and mental health indicators.

COVID-19 clinical outcome

Outcome was recorded in 72 of 79 patients, whereas 7 patients were moved to another hospital. Among the 72 patients with recorded outcome, 7 patients died (X %). Table 2 shows the variables statistically significantly associated with outcome among hospitalized patients with COVID-19.

For depression history, 8.3% (6/72) had a history of depression, while 91.7% (66/72) did not. Among those with a depression history, 2 (33.3%) died and 4 (66.7%) recovered. In contrast, among those without a depression history, 5 (7.6%) died and 61 (92.4%) recovered. These outcomes did not differ significantly to Fisher's exact test (p=0.10, Fisher exact test).

Table 2. Demographic variables, clinical and laboratory data, associated with clinical outcome in hospitalized patients with COVID-19

Demographic variables, clinical and laboratory data	Definition	Recovery (n = 65)	Death (n=7)	Hypothesis test
Age, Median (Q1, Q3)	-	65.0 (58.0, 75.0)	76.0 (71.5, 81.5)	H = 5.209, p = 0.022[1]
A5 (Number of people residing in the house during this period), Median (Q1, Q3)	-	2.0 (2.0, 2.0)	1.0 (1.0, 2.0)	H = 4.411, p = 0.036[1]
B1 (Self-rated general health over the last month), Median (Q1, Q3)	-	0.0 (1.0, 1.0)	0.0 (0.0, 0.0)	H = 9.147, p = 0.002[1]
C3 (Fear of family member contracting coronavirus and dying), Median (Q1, Q3)	-	2.0 (1.0, 3.0)	0.0 (0.0, 1.5)	H = 5.686, p = 0.017[1]
F20 (STAI State Anxiety Inventory), Median (Q1, Q3)	-	3.0 (3.0, 3.0)	4.0 (3.5, 4.0)	H = 7.189, p = 0.007[1]
G14 (CES-D Center for Epidemiologic Studies Depression Scale), Median (Q1, Q3)	-	1.0 (0.0, 1.0)	3.0 (1.5, 3.0)	H = 6.864, p = 0.009[1]
K2 (Most internet sources regarding COVID-19 are misinforming/misleading), Median (Q1, Q3)	-	1.0 (0.0, 2.0)	0.0 (0.0, 0.0)	H = 3.904, p = 0.048[1]
K3 (Internet takes up more time than usual due to the conditions), Median (Q1, Q3)	-	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	H = 5.263, p = 0.022[1]
M5 (Alcohol use during lockdown compared to before), Median (Q1, Q3)	-	0.0 (0.0, 0.0)	0.0 (0.0, 0.5)	H = 3.921, p = 0.048[1]
N3 (Pleasure and satisfaction from current sex life), Median (Q1, Q3)	-	2.0 (0.0, 2.0)	0.0 (0.0, 0.5)	H = 4.194, p = 0.041[1]
N4 (Sex helps deal with daily stress and anxiety), Median (Q1, Q3)	-	2.0 (1.0, 3.0)	0.0 (0.0, 0.5)	H = 5.403, p = 0.020[1]
O9 (RASS-revised Adult Suicidal Ideation Scale), Median (Q1, Q3)	-	3.0 (1.0, 3.0)	1.0 (1.0, 1.0)	H = 5.301, p = 0.021[1]
Ambulatory blood pressure monitoring, s, Mean (SD)	-	44.260 (8.591)	61.733 (58.588)	F = 5.155, p = 0.026[2]
Cytotoxic T cells CD3-8+(abs) standard 0.06-0.28 boundary 0.01-1, Mean (SD)	-	0.069 (0.048)	0.108 (0.062)	F = 3.990, p = 0.050[2]
NK cells CD3-16+56+ (abs) 0,17-0,40 boundary 0,05-2,0, Mean (SD)	-	0.232 (0.135)	0.350 (0.235)	F = 3.996, p = 0.050[2]
Days on ventilator, Mean (SD)	-	0.000 (0.000)	4.167 (3.430)	F = 65.982, p < 0.001[2]
A4 (Marital Status), n (%)	Married (or in a civil partnership)	47 (65.28%)	2 (2.78%)	χ^2 = 15.059, p = 0.010[3]
	Divorced (or estranged)	6 (8.33%)	1 (1.39%)	χ^2 = 15.059, p = 0.010[3]
	Single	5 (6.94%)		χ^2 = 15.059, p = 0.010[3]
	Widower	5 (6.94%)	4 (5.56%)	χ^2 = 15.059, p = 0.010[3]
	Live with someone without an official relationship	1 (1.39%)	-	χ^2 = 15.059, p = 0.010[3]
	Other	1 (1.39%)	-	χ^2 = 15.059, p = 0.010[3]

[1]Do not fit normal distribution, Kruskal-Wallis test; [2]Fit normal distribution, One-way ANOVA; [3]Pearson χ^2-test

Similarly, for anxiety history, 6 of 72 individuals (8.3%) had a history of anxiety, while 66 (91.7%) did not. Among those with an anxiety history, 1 (16.7%) died and 5 (83.3%) recovered. In the group without an anxiety history, 6 (9.1%) died and 60 (90.9%) recovered. These observed outcomes did not differ between the two groups (p=0.47, Fisher exact test).

Analysis of data from Table 2 revealed statistically significant differences between COVID-19 outcomes (recovery and death) among hospitalized patients, which were associated with several key variables. The age of patients who died was significantly higher compared to those who recovered, with median values of 76 (interquartile range 71.5-81.5) and 65 (interquartile range 58-75)

Table 3. Anxiety and Depression severity among hospitalized patients with COVID-19 compared to Russian study sample of the COMET-G project

Scales total score	Statistics	Hospitalized (n=79)	COMET-G (n=7777)	Hypothesis test
STAI total score	Median (Q1, Q3)	50 (45, 56)	45 (36, 52)	H = 22.780, p < 0.001[1]
	Mean (SD)	51.051 (10.122)	44.946 (11.749)	
CES-D total score	Median (Q1, Q3)	23 (13.5, 32.5)	15 (9, 26)	H = 15.170, p < 0.001[1]
	Mean (SD)	23.430 (12.609)	18.019 (11.827)	
RASS total score	Median (Q1, Q3)	7.000 (5.000, 10.000)	9.000 (7.000, 13.000)	H = 17.875, p < 0.001[1]
	Mean (SD)	10.642 (5.484)	8.392 (4.606)	

[1] Do not fit normal distribution, Kruskal-Wallis test

years, respectively (H=5.209, p=0.022). The number of children and self-rated physical fitness were also found to be associated with outcomes, with statistically significant group differences observed in number of children (H=4.411, p=0.036) and self-rated physical fitness (H=9.147, p=0.002). Thus, we selected the subjective perception of own health as a control variable to compare anxiety and depression scores between hospitalized and COMET-G sample.

In the context of clinical and laboratory parameters, days on ventilator, levels of ABPM, and absolute CD3-8+ and CD3-16+56+ values showed highly significant statistical differences (F=65.982, p=0.000 for the case of days on ventilator, more detailed information in the Table 2), emphasizing the seriousness of the deceased patients' condition. Analysis of marital status revealed a positive association with disease outcomes (χ^2=15.059, p=0.010), indicating the potential impact of social support.

Thus, the results illustrate the importance of considering age, marital status, physical status, and clinical and laboratory parameters when assessing outcomes for hospitalized patients with COVID-19. Overall, the results of the analysis highlight the multifactorial nature of COVID-19 outcomes, including the relationship between demographics, clinical status, laboratory parameters, and socioeconomic aspects. These findings highlight the need for a comprehensive approach to the assessment and management of hospitalized patients with COVID-19, especially those in high-risk groups.

Population comparison of anxiety and depression severity

A comparison of the severity of anxiety, depression and suicide risk between hospitalized patients and the COMET-G Russian population sample is shown in Table 3. The mean (SD) total score on the STAI anxiety scale among hospitalized patients was 51.05 (10.12), which significantly exceeded that of the COMET-G control group, i.e. 44.95 (11.75) (H=22.78, p<0.001). A similar trend was observed in the severity of depression as measured by the CES-D scale (23.43 (12.61) compared to 18.02 (11.83), H=15.170 and p<0.001). Regarding suicidal risk as measured by the RASS scale, we saw the opposite relationship: hospitalized patients showed lower scores compared to controls (10.64 (5.48) vs. 8.39 (4.61), H=17.88, p<0.001).

Analysis of matched samples

Case-control matching identified 52 subjects fulfilling the criteria of age, gender, and general perception of health condition. Table 4 compares the severity of anxiety and depression and demographic variables between samples of hospitalized patients and the matched control group. In contrast to the general population, there were no statistically significant differences in anxiety and depression severity in the matched samples. The mean (SD) of the STAI anxiety scale was 51.05 (10.12) for the total sample of hospitalized patients compared to 44.95 (11.75 in the total COMET-G sample. In the matched samples, corresponding scores were 50.23 (9.49) and 49.17 (12.03) respectively (F=0.248 and p=0.62). The median (Q1, Q3) values of the CES-D depression scale in the total samples of hospitalized patients and controls were 23 (13.5, 32.5) and 15 (9, 26), as compared to 21 (10.5, 35.5) and 18 (1, 30.5) with matching (H=0.672 and p=0.41).

DISCUSSION

Our study results do not support firm conclusions about the association of anxiety and depression levels in ICU (red-zone units) inpatients with the indicators of severity of COVID-19 course or outcome in their cases. However, study results highlight the finding on the severity of affective disorders (anxiety and depression) being significantly higher in COVID-19 inpatients' population compared to the general population of COMET-G study respondents (Fountoulakis et al. 2022). The design of the study should be clarified to check these important interrelationships but was limited by the standartized COMET-G study protocol, aiming the datasets comparability procedures.

Table 4. Comparison of Anxiety and Depression severity and demographic variables in hospitalized patients and Russian COMET-G samples matched by gender, age, and general health perception

Socio-demographic characteristics	Definition	Hospitalized n = 52	COMET-G n = 52	Hypothesis test
Age, Median (Q1, Q3)		61.000 (55.000, 71.000)	59.000 (53.000, 68.500)	H = 1.004, p = 0.316[1]
STAI, Mean (SD)		50.231 (9.486)	49.173 (12.032)	F = 0.248, p = 0.620[2]
CES_D, Median (Q1, Q3)		21.000 (10.500, 35.500)	18.000 (11.000, 30.500)	H = 0.672, p = 0.412[1]
A1 (Sex), n (%)	Female	34 (65.38%)	34 (65.38%)	χ^2 = 0.000, p = 1.000[3]
	Male	18 (34.62%)	18 (34.62%)	
A3 (Place of residence during this period), n (%)	City (100.000 – 1 million population)	16 (30.77%)	1 (1.92%)	χ^2 = 50.341, p < 0.001[3]
	City > 1 million population	12 (23.08%)	5 (9.62%)	
	Capital City	12 (23.08%)	0 (0.00%)	
	Town (20.000 – 100.000 inhabitants)	6 (11.54%)	0 (0.00%)	
	Rural area - Village	5 (9.62%)	5 (9.62%)	
	Town (<20.000 inhabitants)	1 (1.92%)	1 (1.92%)	
A4 (Marital Status), n (%)	Married (or in a civil partnership)	20 (38.46%)	37 (71.15%)	χ^2 = 11.754, p = 0.038[3]
	Single	9 (17.31%)	5 (9.62%)	
	Widower	9 (17.31%)	4 (7.69%)	
	Divorced (or estranged)	7 (13.46%)	4 (7.69%)	
	Live with someone without an official relationship	4 (7.69%)	1 (1.92%)	
	Other	3 (5.77%)	1 (1.92%)	
A5 (Number of people residing in the house during this period), n (%)	Alone	25 (48.08%)	27 (51.92%)	χ^2 = 1.683, p = 0.794[3]
	2	17 (32.69%)	12 (23.08%)	
	3	6 (11.54%)	7 (13.46%)	
	4	2 (3.85%)	2 (3.85%)	
	5+	2 (3.85%)	4 (7.69%)	
A6 (Number of children), n (%)	0	13 (25.00%)	9 (17.31%)	χ^2 = 1.833, p = 0.767[3]
	1	19 (36.54%)	19 (36.54%)	
	2	18 (34.62%)	20 (38.46%)	
	3	1 (1.92%)	3 (5.77%)	
	4+	1 (1.92%)	1 (1.92%)	
A7 (Education), n (%)	Basic school	2 (3.85%)	2 (3.85%)	χ^2 = 31.323, p < 0.001[3]
	High school	17 (32.69%)	21 (40.38%)	
	Bachelor	(0.00%)	17 (32.69%)	
	Magister / Msci	32 (61.54%)	9 (17.31%)	
	PhD	1 (1.92%)	3 (5.77%)	
A9 (Employment), (%)	Pension	20 (38.46%)	0 (0.00%)	χ^2 = 59.752, p < 0.001[3]
	Private clerk	10 (19.23%)	7 (13.46%)	
	Civil servant	7 (13.46%)	11 (21.15%)	
	Allowance for health reasons	4 (7.69%)	1 (1.92%)	
	Self-employed	4 (7.69%)	0 (0.00%)	
	Other	3 (5.77%)	0 (0.00%)	
	Retired	2 (3.85%)	28 (53.85%)	
	Unemployed	1 (1.92%)	3 (5.77%)	
	Housekeeper	1 (1.92%)	0 (0.00%)	
	Not working by choice (e.g. living via corporate earnings etc.)	(0.00%)	2 (3.85%)	

[1]Do not fit normal distribution, Kruskal-Wallis test; [2]Fit normal distribution, One-way ANOVA; [3]Pearson χ^2-test

Table 4. Continues

Socio-demographic characteristics	Definition	Hospitalized n = 52	COMET-G n = 52	Hypothesis test
B1 (Self-rated general health over the last month), n (%)	Bad	14 (26.92%)	14 (26.92%)	$\chi^2 = 0.000$, $p = 1.000$[3]
	Moderate	27 (51.92%)	27 (51.92%)	
	Good	8 (15.38%)	8 (15.38%)	
	Very good	1 (1.92%)	1 (1.92%)	
	Perfect	2 (3.85%)	2 (3.85%)	
B2 (Presence of chronic medical conditions), n (%)	Yes	29 (55.77%)	46 (88.46%)	$\chi^2 = 12.241$, $p < 0.001$[3]
	No	23 (44.23%)	6 (11.54%)	
F21 (Anxiety change), n (%)	The same	25 (48.08%)	18 (34.62%)	$\chi^2 = 2.098$, $p = 0.350$[3]
	A little worse	18 (34.62%)	21 (40.38%)	
	Much worse	9 (17.31%)	13 (25.00%)	
G21 (Depression change), n (%)	The same	32 (61.54%)	21 (40.38%)	$\chi^2 = 7.218$, $p = 0.125$[3]
	A little worse	10 (19.23%)	18 (34.62%)	
	Much worse	7 (13.46%)	12 (23.08%)	
	A little better	2 (3.85%)	1 (1.92%)	
	Much better	1 (1.92%)	0 (0.00%)	

[1]Do not fit normal distribution, Kruskal-Wallis test; [2]Fit normal distribution, One-way ANOVA; [3]Pearson χ^2-test

Nevertheless, we cannot deny an obvious finding of our study which demonstrated that the STAI anxiety scale scores and CES-D depression scale scores among inpatients (patients hospitalized to the red zones due to severity of SARS-Cov-2 infection) significantly exceeded those scores registered in the COMET-G general population control group. Moreover, anxiety and depression scores were higher among ICU-inpatients, even if we take into account that our COMET-G control group could potentially include both outpatients and inpatients (this question was not registered in the primary protocol of the COMET-G study, so we cannot proceed with the straight answer). This finding goes in relation to previous data on affective disorders cohort and anxiety disorders cohort being associated with higher severity of COVID-19 outcome, higher hospitalization rates, ICU admission chances and higher amount of mortality cases due to the SARS-Cov-2 infection (Ranger et al. 2022, Teixeira et al. 2021).

Suicidal risk as measured via the RASS scale discovered the opposite interrelationships, such as hospitalized patients demonstrated lower suicidality scores compared to COMET-G general population respondents.

- However, this fact could be interpreted in the context of severity of physical state of ICU inpatients and their basic feeling of death fear related to the instinct of self-preservation, which means that anxiety (with intentions for future) was a more prominent symptom rather than self-harm behaviour or suicidal ideations, which usually appear in the context of depressive state.
- Though, in addition to prominent anxiety scores, depression scores among inpatients were also higher compared to COMET-G study group, we might also speculate that depression among inpatients should be qualified either as anxious clinical type of depression (with symptoms of fear about future, bad clinical outcome, death from COVID-19, etc.) or asthenic-hypodynamic clinical type of depression (with symptoms of lack of energy for planning and actions, including suicidal activities, etc.) rather than melancholic clinical type, as far the melancholic depression is often related to suicidal and self-harm behavior compared to the first two clinical types of depression described above.

We strongly aware that this particular data interpretation is not clearly proved in terms of evidence-based approach, due to the study limitations of the clinical interview unavailability for ICU inpatients. Clinical interview, managed by psychiatrists, would potentially clarify this psychopathology part of our hypothesis. Despite the study limitations, we would like to give a notice to the researchers' audience that clinical typology of depression, including pre-existing affective disorders, deserves special attention. The context of clinical psychopathology of affective disorders is important when we describe current infection-related states and the risks of being infected, as well as when we predict COVID-19-related somatic outcomes, in agreement with previous COVID-19-related research (Koyama et al. 2022, Lee et al. 2022, Toubasi et al. 2021, Vai et al. 2021, Wang et al. 2022, Yang et al. 2020), according to the literature of clinical (descriptive) psychopathology (Kasper 2001, Vertogradova 1980, Vertogradova & Voloshin 1983, Xu & Sun 2022) and key research finding about anxiety domain of symptoms being related

to the oxidative stress via mechanisms of hyperinflammation causing the higher severity of COVID-19 course and other medical illnesses (Steenkamp et al. 2017, Vollbracht & Kraft 2022).

We note that our study is confined to a rather specific population (Table 1) of median age 66 years, living in a city > 1 million population (79.8%), married or in a common-law relationship (68.4%), having 2 children (55.7%), living in 2-person households (40.5%), having a Bachelor's degree (30.4%) or high school graduate, (39.2%), and retired (60.8%). It was therefore necessary to compare the sample of hospitalized patients with a similar sample from the general population by matching samples by gender, age, and general health perceptions. After matching the samples, the differences between the scores on the STAI anxiety scale and the CES-D depression scale in the hospitalized patient group and the control group were eliminated (Table 4). Since the corresponding sample from the general population also showed increased scores on the STAI and CES-D scales, they are not related to the course and outcomes of COVID-19, but rather to the characteristics of the population - older age, and understanding of the severity of their health status. Thus, understanding the presence of COVID-19 overlaps with the assessment of health status, perhaps resulting in interaction leading to increased anxiety.

Other factors were associated with negative outcomes of COVID-19 in our patient group of median age 66 years. In one epidemiological study, global prevalence of depression among older adults was 35.1% (Cai et al. 2023), which is close to findings of a previous meta-analyses in India (34.4%) (Pilania et al. 2019), but higher than in China (23.6%) (Li et al. 2014) and lower than in South Asian countries (42.0%) (Assariparambil et al. 2021). Diseases, physical ailments, and chronic use of certain medications are factors that influence the development of depression in the elderly (Rathod et al. 2019). Age is an independent and important variable that may affect the occurrence of depression and its symptoms (Deshpande et al. 2014). In our study social factors associated with lack of care (fewer relatives in the family, widowhood) lead to a more severe outcome of COVID-19 as well as specific features of the course of COVID-19 (days on ventilator, blood coagulation indices, immune response indices). Although multivariable logistic regression models showed no association between diagnosis of depression and the risk of mechanical ventilation, depression was associated with a reduced risk of mortality in Germany (Kostev et al. 2022).

As expected, our hospitalized individuals had higher anxiety and depression scores than the general population. However, when we controlled for sex, age, and perceived health status, these differences disappeared. We may interpret this to mean that it is not COVID-19 disease or hospitalization per se that determine the severity of anxiety and depression, but rather the perception of one's health in the context of the risks inherent in the disease However, when adjusting for sex, symptom perception, and age (to ± 5-years tolerance), the differences between the samples disappeared, suggesting that the severity of symptoms of depression and anxiety in our hospitalized patient population was determined not by hospitalization per se, but by their awareness of the severity of symptoms.

CONCLUSION

- Anxiety and depression scores among inpatients (patients hospitalized to the red-zone ICU due to severity of SARS-Cov-2 infection) significantly exceeded the scores observed in the COMET-G general population control group. Suicidality risk scores were, on the contrary, lower among hospitalized patients compared to COMET-G respondents. These findings rise a question for future research, whether anxiety states and clinical type of depression (e.g., hypothetically, anxious depression) are selectively related to the severity of the viral infection-associated medical conditions and risks of developing affective disorders after somatic recovery.
- Our study did not confirm expected relationship between symptoms of anxiety and depression based on questionnaire responses and the risk of severe course of COVID-19 (e.g. hospitalization) when matched by age, gender and other socio-demographic variables but the self-awareness of somatic health did matter; clinical interview of ICU inpatients would provide a clarification of our hypothesis.
- The increasing burden of mental disorders with age, and the bidirectional association of affective disorders and infectious diseases should be considered when assessing risk factors. Moreover, screening of anxiety and depressive symptoms, as well as identifying clinical type of depression, may contribute to reduction of risks and improvement of COVID-19-related affective complications.

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Limitations of the study:

Our sample was small and limited to patients at one center. We obtained data using a self-questionnaire, which may be apt to produce bias.

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Contribution of individual authors:

Darya Astafeva wrote the first draft of the manuscript with the supervision from PI Daria Smirnova.

Dmitrii Konstantinov & Daria Smirnova formulated the primary concept, elaborated the research hypothesis, and defined the keywords search algorithm.

Dmitrii Konstantinov, Aleksander Kolsanov, Igor Davydkin, Elena Avdeeva, Natalia Kuvshinova managed the university research group to study COVID-19-associated somatic and mental disorders, as well as data collection protocols in "red-zone" intensive care units.

Timur Syunyakov analyzed the data.

Konstantinos N Fountoulakis & Daria Smirnova share senior authorship of this manuscript.

Larisa Popova, Elena Konstantinova & Tatiana Konnova collected the data.

All authors contributed to the detailed revision, and all approved the final version of the article prior to its submission.

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