COVID-19-related psychiatric manifestations requiring hospitalization: Analysis in older vs. younger patients

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Abstract. The complex manifestations of COVID-19 include psychiatric symptoms, having multifaceted profiles with varying severity during the acute phase and further during the recovery period. Limited data exist which have analyzed whether there are any age-related differences. A study lot of 89 COVID-19 patients with mild-to-moderate SARS-CoV-2 infection requiring hospitalization for mental issues provided comparative data from two age groups below and above 60 years. The majority of patients had new onset of a mental issue during COVID-19, 24.7% of the total lot being diagnosed with depressive disorder. The senior patient set had a significantly higher prevalence of sleep disorder vs. the younger study group (53.3 vs. 28.8%), depression (33.3 vs. 10.2%) and cognitive impairment (26.7 vs. 8.5%), while patients <60 years of age had a higher prevalence of hallucinations, delirium and bizarre behavior. Psychiatric manifestations are an important part of the symptomatology of COVID-19, sometimes requiring hospitalization. Age-related neuropsychiatric substrate could explain some of these differences between the two study subgroups. Further data are needed to complete the acute and long-term distinctive profiles of COVID-19-related mental illness in older and younger patients.

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Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; COVID-19, Coronavirus Disease 2019; WHO, World Health Organization; ACE-2, angiotensin-converting enzyme 2; RT-PCR, reverse transcription-polymerase chain reaction; ICD-10, International Classification of Diseases, 10th edition; MMSE, Mini Mental State Evaluation; MoCA, Montreal Cognitive Assessment; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; Ca^{2+}, calcium ion; OR, odds ratio; PASC, post-acute sequelae of COVID-19; PACS, post-acute COVID-19 syndrome; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CCL2, chemokine (C-C motif) ligand 2

Key words: COVID-19, elderly, psychiatric manifestations, sleep disorder, depression, cognitive impairment, immuno-senescence

Introduction

The COVID-19 pandemic, declared by the World Health Organization (WHO) on March 11, 2020, highly affected elderly fragile persons. The recently published data from the Global Burden of Disease Study 2019 forecasted the global prevalence of dementia in 2050 to 152.8 million globally, evolving from 57.4 million cases in 2019 (1). Age-related cognitive impairment, such as the decline in decision-making or in executive cognitive function, occur with the physiologic process of normal aging, but the number of people with age-associated neurodegenerative disorders is also increasing rapidly and there are age-related conditions that accelerate the rate of neuronal dysfunction, neuronal loss, and cognitive decline (2-4).

It was initially considered that COVID-19 clinical presentation primarily affects the respiratory system causing an interstitial pneumonia, but soon the medical body recognized

it as a systemic disease. The elderly are at a higher risk of developing severe forms of COVID-19 due to factors associated with aging (including the higher prevalence of medical comorbidities) (5,6). SARS-CoV2 attaches to healthy cell membranes primarily through the angiotensin-converting enzyme 2 (ACE-2) receptor present within many organs. There is widespread viral organ damage identified at the level of the lungs, brain, heart, kidney, liver, skin, endocrine system and gut (6-12), decreasing the bioavailability of ACE-2 receptors within the renin-angiotensin-aldosterone system. In individuals with pre-existing ACE-2 deficiencies (such as in hypertension, diabetes mellitus, and those of older age) the decrease in ACE-2 bioavailability as the infection spreads augments the risk of more severe symptoms (12,13).

There are multiple reports identifying psychiatric symptoms associated with COVID-19, such as: 'brain fog', insomnia, depressed mood, anxiety, behavioral or affective disorders, post-traumatic stress disorder, memory loss and cognitive impairment in a large proportion of patients (14,15). There are many hypotheses to explain the potential mechanisms underlying these symptoms and why there is such a variability of clinical phenotypes of the same disease. Most researchers tend to attribute them as multifactorial, considering direct viral neurotrophic effect of SARS-CoV-2, brain hypoxia, systemic inflammation, consequences of intensive care unit interventions, the use of mechanical ventilation and sedative drugs, secondary effects of medications used to treat COVID-19-all connected with dysfunction of peripheral organs triggering a cascade of neuronal and cerebral dysfunctions (3,5).

One strong theory of the severe evolution within the elder population relates to 'inflammaging', characterized as a 'low-grade, controlled, asymptomatic, chronic, systemic, inflammatory state that characterizes the aging process' (16). Alterations in biological functions of our body determine our biological age-distinct parameter against chronological age-which strongly impact our ability to react and to cope with the disease and also influence the effectiveness and safety of specific therapies, including the ones used for SARS-CoV-2 infection (3,17).

Our analysis focused on the prevalence and manifestations of psychiatric disorders in relation to the COVID-19 acute phase and further reviewed the results in elder vs. younger patients, comparing the two study subgroups split by the 60 year age cut-off. The added value of this study to the wealth of research data on COVID-19 is to provide detail on the psychiatric dimension of the acute COVID-19 setting and to compare side by side two age groups, with different morbidity/disease profiles, in order to understand whether different age-associated long-term effects may be expected.

Patients and methods

A study lot of 89 patients diagnosed with COVID-19 and admitted during a 12-month period (09/2020-09/2021) to the 'Elisabeta Doamna' Psychiatric Hospital was analyzed with regards to psychiatric diagnosis, specific manifestations and the moment of their onset. All patients were in the acute infectious phase testing positive for SARS-CoV2 ARN (RT-PCR laboratory tests).

Diagnosis used the standard common International Classification of Diseases, 10th edition (ICD-10) coding (18). The admittance to psychiatric hospital was determined by the severity of the symptomatology and/or the potential self-harming risk. The psychiatric clinical manifestations were prevailing; only mild to moderate respiratory COVID-19 forms were included in the study. Cognitive assessment was based on Mini Mental State Evaluation (MMSE) (19), Clock-Drawing Test (20) and Montreal Cognitive Assessment (MoCA) (21).

In the study lot, we comparatively assessed two subgroups of patients, split by the 60 year age cut-off. The relative risk (RR) of psychiatric symptomatology and the prevalence of comorbidities were measured within the two subgroups using MedCalc software (version 20.110; MedCalc Software Ltd.). A descriptive statistical analysis was applied for this retrospective study.

Results

Demographics. The demographic analysis of the population in the study lot exhibited a median age of 51.3 years (with an age interval of 19 to 91 years), the split between age groups being 66.3/33.7% for patients in the <60 years of age group and respectively 60-91 years of age. A balanced sex ratio was considered and most of the patients lived in an urban area. Median hospitalization duration was 21.7 days (shortest 2 days, longest 111 days) (Table I).

Moment of psychiatric diagnosis in relation to COVID-19. Out of the 89 patients included in the analysis, 27% were registered and previously treated for a psychiatric condition before the onset of the SARS-CoV-2 infection; in the context of COVID-19, their disease was aggravated or presented new symptoms which required hospitalization. The majority of the hospital admissions were related to newly occurring psychiatric manifestations within the COVID-19 acute phase (73%), with different prevalence in the two study subgroups (first psychiatric symptoms during COVID-19 acute phase occurred in 63.3% of the patients ≥60 years of age and in 78% of the patients <60 years of age).

Psychiatric disorders during the acute phase of COVID-19. The most prevalent type of diagnosis was of a depressive disorder type, 24.7% in the general lot of all ages, whereas the situation was different when analyzed by age subgroup. For younger patients <60 years, the highest prevalence (30.5%) was for paranoid/schizophrenic type of diagnosis (ICD-10 codes: F21, Schizotypal personality disorder; F20.0, Paranoid schizophrenia; F25, Schizoaffective disorder). For the older patient subgroup (≥60 years) the most frequent diagnosis was for depressive disorder, but occurring in a significantly higher percentage vs. the study set (33.3%); the elderly patients received ICD-10 diagnoses such as F33, Recurrent depressive disorder; F32.2/F32.3, Severe depressive episode with/without psychotic symptoms (Table II).

The RR of depression was 1.64 for the elderly COVID-19 patients when compared with younger subjects; for this older age group there was a significantly lower prevalence of psychotic disorders, all types of alcohol dependence disorders and paranoid/schizophrenic disorders. Affective disorders were found to be more frequent in older COVID-19 patients when compared with the younger subgroup (RR, 2.95).

Table I. Demographics and hospital stay analysis: Total lot and subgroup split in the study lot.

Items	Total study set	Patients <60 years of age	Patients ≥60 years of age
Study lot, no. of patients (n)	89 (%)	59 (%)	30 (%)
Area of residence			
Urban area, n (%)	52 (58.4)	32 (54.2)	20 (66.7)
Rural area, n (%)	37 (41.6)	27 (45.8)	10 (33.3)
Sex			
Female, n (%)	41 (46.1)	24 (40.7)	17 (56.7)
Male, n (%)	48 (53.9)	35 (59.3)	13 (43.3)
Median period of hospitalization (days)	21.7	21	22.1

Table II. Types of psychiatric ICD-10 diagnoses in the study lot.

Diagnostic class	Total lot (%)	Patients <60 years of age (%)	Patients ≥60 years of age (%)
Psychotic disorder, n (%)	9 (10.1)	8 (13.6)	1 (3.3)
Alcohol dependence and related, n (%)	7 (7.9)	6 (10.2)	1 (3.3)
Dementia, n (%)	7 (7.9)	0 (0)	7 (23.3)
Depressive disorder, n (%)	22 (24.7)	12 (20.3)	10 (33.3)
Behavioral/personality disorder, n (%)	16 (18.0)	11 (18.6)	5 (16.7)
Schizophrenic/paranoid disorder, n (%)	18 (20.2)	18 (30.5)	0 (0)
Affective disorder, n (%)	10 (11.2)	4 (6.8)	6 (20.0)

ICD-10, International Classification of Diseases, 10th edition.

Psychiatric manifestations during the acute phase of COVID-19. The most frequent symptom which occurred during COVID-19 in our study group was anxiety (in 78.7% of the patients of all ages, with similar prevalence in the two study subgroups). Clinical manifestations such as psychomotor agitation, hallucinations, sleep disorders or delirium were presented by a third of the patients in the general study set, but the prevalence was different when analyzed by age split. Significantly more patients ≥60 years showed cognitive impairment and subjective memory deficits, as well as depression, sleep disorders and psychomotor agitation as compared with the younger patient group (Fig. 1).

Comorbidities as associated diagnosis for the psychiatric manifestations during the acute phase of COVID-19. A total of 68.5% of all study patients had at least 1 comorbidity: 80% in the older patient group as compared to 62.7% in the younger group. The most prevalent were metabolic disorders (29.2% of all patients had dyslipidemia or diabetes mellitus) in the total study lot, significantly different when measured in each age group; most patients ≥60 years of age had a cardiovascular disorder-hypertension, angina pectoris, cardiac rhythm disorders or arrhythmias, while in the <60 year subgroup the most frequent comorbidity was metabolic (30.5% of younger patients) (Table III).

There was no correlation identified between the type of comorbidity and the moment or the type of psychiatric manifestations in relation to COVID-19, within any of the study groups.

Discussion

It was demonstrated that SARS-CoV-2 is an opportunistic pathogen of the nervous system, with ACE-2 expression in the brain being a determinant for the viral tropism and psychiatric manifestations associated with COVID-19, generated either through direct neurotoxicity or immune-reactivity of the host (22). Available data show that COVID-19 is associated with cerebral oxidative stress, neuroinflammation, deterioration within the white matter, brain vessel endothelium and blood-brain barrier, cerebral hypoperfusion and demyelination (23,24).

In addition, research focusing on the immediate impact of COVID-19 on ageing has highlighted a consistently accelerated biological age gap of 5.22 years and a significant shortening of their telomeres (a known marker of ageing) in COVID-19 survivors as compared with COVID-19 naïve individuals (25). On medium to long term this may trigger earlier and/or accelerated onset of age-related neurodegenerative disorders which, together with direct cerebral consequences of SARS-CoV-2 infection, may affect the

Table III. Types of comorbidities in the study lot.

Type of associated diagnosis	Total study lot (%)	Patients <60 years of age (%)	Patients ≥60 years of age (%)
Metabolic comorbidities, n (%)	26 (29.2)	18 (30.5)	8 (26.7)
Cardiovascular comorbidities, n (%)	24 (27.0)	8 (13.6)	16 (53.3)
Neurologic comorbidities, n (%)	1 (1.1)	1 (1.7)	0
Respiratory comorbidities, n (%)	16 (18.0)	9 (15.3)	7 (23.3)

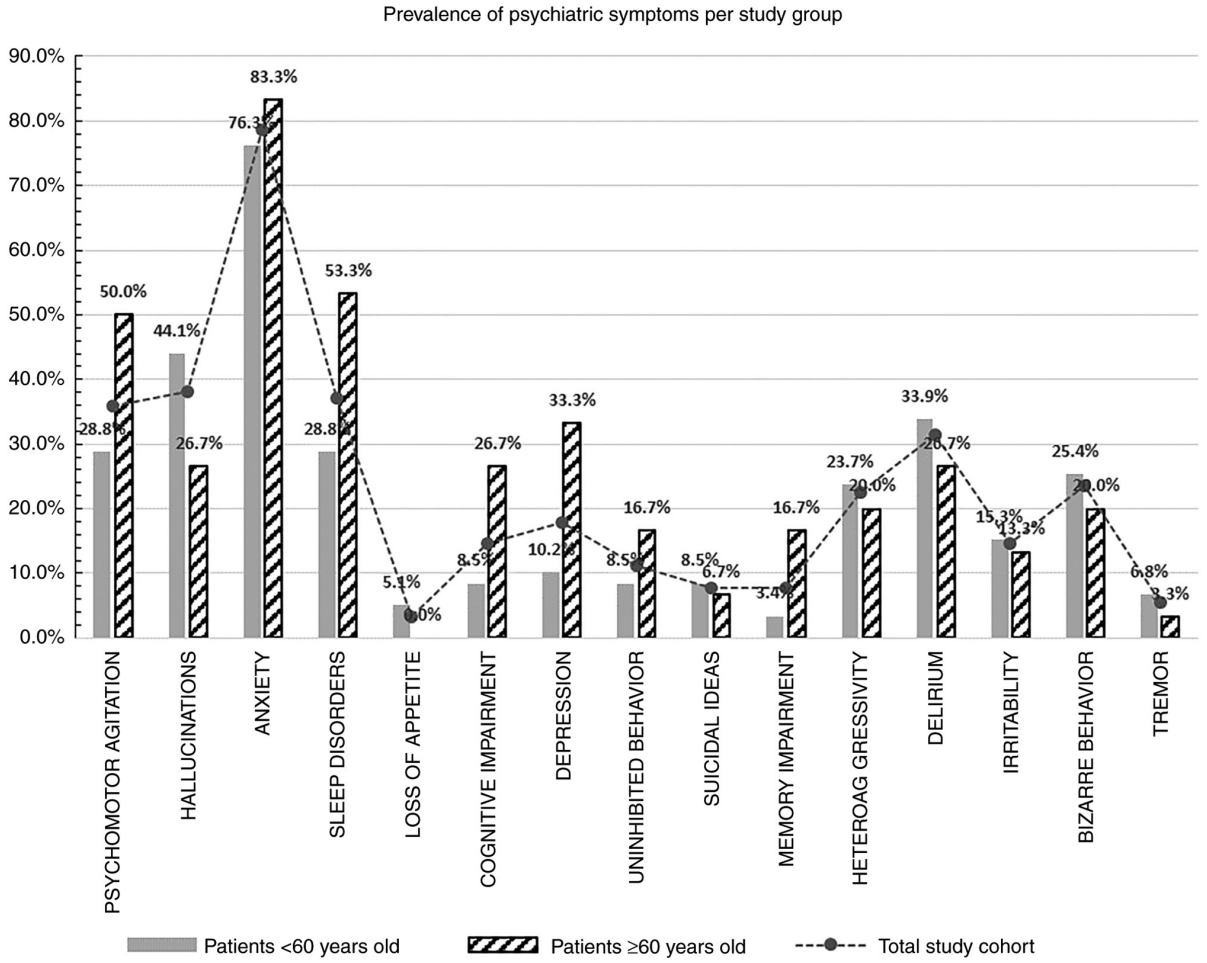

Figure 1. Analysis of the psychiatric manifestations for each study group, showing distinct psychiatric manifestations in older vs. younger patients.

evolution of dementia prevalence and manifestations in the future (26,27).

Neuropsychological assessment during acute COVID-19 is difficult, especially in medium and severe cases (22). Our study focused on a group of 89 COVID-19 patients that required hospitalization because of the severity of their psychiatric symptoms and not related to the respiratory syndrome or other manifestations of the disease. We analyzed comparatively two sub-groups of patients based on an age cut-off (<60 years and ≥60 years of age) in order to assess whether geriatric patients, with a demonstrated higher risk of morbidity and mortality due to COVID-19, have psychiatric manifestations similar to younger patients suffering from a comparable clinical form of the infectious disease: mild to moderate.

Related to the frequency of a new psychiatric diagnosis during the acute COVID-19 phase, in our study lot there was no significant difference between the two age groups. Regarding available data, there is no consistency between studies. A literature review regarding correlations between psychiatric disorders and COVID-19 showed that the infectious disease may act as a trigger for a new onset of psychiatric dysfunctions and may also aggravate the severity of previously diagnosed mental disorders (7,28,29). This may have multiple causes and studies published previously to the pandemic period demonstrate that self-isolation and stress are determining a special form of inflammatory syndrome (30). Reports from Italy analyzing the prevalence of psychiatric disorders in the database of COVID-19 deaths (where the median age at death

was 80 years with an interval of 72-86 years in the analyzed group) presented a frequency of 6.5% of the patients with a psychiatric diagnosis prior to the infection (31,32).

Immuno-senescence is a risk factor for more severe manifestations of COVID-19 and is adding to the neuropsychiatric damage that is directly induced by the viral infection (5).

From early pandemic phases, reports on psychiatric symptomatology associated with COVID-19 have identified delirium, agitation, depression, anxiety, insomnia or memory/cognitive impairment (3,28,29). The prevalence of these is not yet established, nor is the longer term consequence of these types of complications; recent data revealed a high incidence of 33.6% for neurologic and psychiatric morbidity in the 6 months following COVID-19 (33). In addition, it was demonstrated that neurologic and psychiatric manifestations during COVID-19 acute phase could act as predictors of disease severity and mortality (34).

In a meta-analysis published early in 2020, the authors found that 63% of patients were affected by psychiatric symptoms during acute SARS and MERS infections (including anxiety, insomnia, confusion, depression, psychoses) (24). The prevalence of mental health issues ranged from 20-36% in the general public and healthcare workers during acute COVID-19 (29), and a study from Wuhan reported a high prevalence of anxiety (38.5%) and depression (35.9%) (35).

These findings are much lower in prevalence than our reported data, but the major difference is that the present study withdraws information regarding psychiatric issues requiring hospitalization of acute COVID-19 patients. There is much detailed research concerning post-acute neuropsychiatric sequelae of the SARS-CoV-2 infection, with estimates up to 18.1% for the incidence of first and recurrent psychiatric illness in the 90 days post COVID-19 diagnosis (36,37).

We found significant differences between studies coming from heterogeneous patient populations and study designs, and scarce data regarding the variation in older vs. younger COVID-19 patients manifesting psychiatric symptomatology in the acute phase. Generally anxiety and depression have a high incidence, also delirium is frequently mentioned as a symptom during acute SARS-CoV-2 infection (30,32).

The underlying pathophysiological mechanisms of the psychiatric spectrum of COVID-19 include direct viral damage of the neuronal network, hypoxic injury and immune-mediated damage. The elevation of biomarkers of inflammation strongly correlates with neuro-cognitive impairment, as dysregulation in cytokine function (a known phenomenon of this infectious disease) is associated with psychiatric disorders (38,39). Depression, presented by a third of the older patients in our set, is linked with increased levels of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and chemokine (C-C motif) ligand 2 (CCL2), which are also increased in COVID-19 patients and are correlated with the severity of the disease (8,40-42). In addition, other major psychiatric disorders including schizophrenia, bipolar disorders, suicide or sleeping disorder have been significantly associated with alterations of certain immunomediators (43). Corroborating these data with the research on immuno-senescence and the immunologic substrate of the age-related neurocognitive dysfunction, we can hypothesize that this may be the link explaining higher incidence of some psychiatric COVID-19 manifestations in older vs. younger patients (psycho-motor agitation, sleep disorders, depression, cognitive impairment) (Fig. 1).

A high percentage of the psychiatric hospitalized patients in our lot had at least one other diagnosis associated with mental dysfunction and SARS-CoV-2 infection. The only significant difference between our two study subgroups regarding comorbidities is the prevalence of cardiovascular disorders, with a relative risk (RR) of 3.93 for the senior group vs. patients <60 years of age. It is considered that there is a complex and bidirectional relationship between cardiovascular disease and mental illnesses such as depression, anxiety, schizophrenia or bipolar disorder. Our study did not provide enough statistical power to determine whether there is any correlation linking psychiatric manifestations of COVID-19 with the difference in the comorbidity prevalence within the two age subgroups.

After more than 2.5 years of living with the pandemic, there are sufficient data to demonstrate that older individuals are more prone to aggravated infections of SARS-CoV-2, with more severe manifestations of pulmonary disease, heart failure, hepatic and kidney dysfunction, neurocognitive damage; all triggered by the direct viral invasion and cytokine storm with microvascular coagulation among the main pathogenic mechanisms (6,30). These initial alterations continue in the majority of affected senior individuals beyond the acute phase, and we still have to evaluate and develop strategies for long term psychological and neuropsychiatric sequelae of the pandemic. For example, it has been demonstrated that the Ca^{2+} dysregulation in Alzheimer's disease is also a mechanism for SARS-CoV-2 infection pathogenicity and it was hypothesized that it may facilitate the viral lifecycle at the brain level, together with the increased ACE-2 expression and other common neuro-inflammatory substrates (6,43,44).

As data exist suggesting that COVID-19 may promote the initiation and progression of dementia (including Alzheimer's disease), contributing significantly to cognitive impairment especially in the elderly, it is probable that the pandemic will accelerate the already high trends of increasing dementia prevalence (1,14,37). In a recent report from Wuhan, China, at one year after being discharged, senior COVID-19 survivors were associated with an increased risk of longitudinal cognitive decline when compared with uninfected control individuals; severe COVID-19 was associated with a higher risk of early-onset [odds ratio (OR)=4.87], late-onset (OR=7.58) or progressive (OR=19.00) cognitive decline (45).

Beyond direct disease consequences, COVID pandemic restrictions also had a significant impact on the general population, especially the elderly, due to social isolation, fear of being infected and for the uncertain future, limited physical activity and exposure to sunlight, complications of anxiety and depression (2,29,44). Therefore, healthcare systems need to adjust their dementia risk reduction strategies in order to adjust for the post-pandemic evolution in population's mental health and growing needs (15,46).

COVID-19 consequences on mental health are significant and this is demonstrated by numerous studies, most of them analyzing the clinical entity defined as Long COVID or Post-acute sequelae of COVID (PASC) or Post-acute COVID-19 Syndrome (PACS). Probably in the next years we

may be able to further explore long term implications for both COVID-19 survivors and patients having an impact due to the pandemic reshaping of their lives (22,47).

The limitations of the present study relate to the small sample size which, in the context of scarce data in the literature regarding differences between older vs. younger patients with psychiatric manifestations of SARS-CoV-2 infection, need extended data from broader cohorts to support our hypothesis and complete the long-term projections and prognostic variables for COVID-19 survivors. Another perspective is looking into comparative data regarding the moment of psychiatric illness onset in order to observe differences of manifestations in patients with previous vs. new psychiatric disorder; the present study did not have a large enough sample lot to provide relevant conclusions, thus, a broader patient group may be considered for future research.

Relevant data identified a wide range of psychiatric symptoms exhibited by COVID-19 patients during their acute disease, with a severity which may decrease during the recovery period. In addition to the direct results of the infectious disease, it is also important to recognize the stress, fear of death, and anxiety concerning the consequences of COVID-19 on their own health and their family members (48).

In conclusion, an altered mental status is a frequent manifestation of COVID-19. Our study assessed the prevalence of the most often occurring manifestation and compared two study subgroups of younger vs. older patients (60 year old age cut-off). Common psychiatric disorders triggered by SARS-CoV-2 infection include depression, schizophrenic or paranoid disorders and behavioral illness, but there is a different symptomatic profile in older when compared with younger patients.

Anxiety is the most prevalent symptom during COVID-19 acute phase (presented by 78.7% of all patients in our research) and both elder and young adults are affected in similar ratios. Our data showed that apart from anxiety, patients ≥60 years of age suffer mostly from cognitive and memory impairment, depression, sleep disorder and psychomotor agitation, while younger patients present more frequently delirium, bizarre behavior, hallucinations or hetero-aggressivity.

Age-related neuropsychiatric substrate could explain some of these differences between the two study subgroups. Furthermore, it is important to gather additional data on the correlations between inflammation, cytokine involvement and psychiatric disorders; a deeper understanding of the pathological mechanisms could help develop new clinical algorithms and even new therapeutic targets for a more custom approach.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Conceptualization of the study was accomplished by FS and AR, methodology design was the responsibility of FS and VDO. Validation of the data was the responsibility of AR, CS, EPD and GO. Formal analysis was conducted by FS; data curation and statistical analysis was conducted by FS, AN, EPD and ALT. GO, CS and AR substantially contributed to the interpretation of the results; writing-original draft preparation was conducted by FS; writing-review and editing were conducted by AR and AN. Data representation was the responsibility of FS; supervision was conducted by AR; project administration was the responsibility of FS and GO; FS, CS and GO contributed equally to this research. FS and VDO had full access to the database; EPD and GO confirm the authenticity of all the raw data. All authors have discussed the results, and read and approved the final manuscript.

Ethics approval and consent to participate

The retrospective study publication was approved by the Medical Ethics Committee of 'Elisabeta Doamna' Psychiatric Hospital of Galati, Romania as comprehensive doctoral research (no. 4/11.03.2019) and according to the Helsinki Declaration (49). Due to the retrospective nature of this study individual patient consent for use of their data was not necessary.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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