Psychological care reflecting the specifics of the course of viral infection in SARS-CoV-2 oncological patients with oxygenation disorder – a case series

Psychologická péče reflektující průběh a specifika virové infekce SARS-CoV-2 u onkologických pacientů s oxygenační poruchou – série kazuistik

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Summary

Background: During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, patients treated with acute coronavirus disease 2019 (COVID-19) in intensive care units (ICU) have suffered from neuropsychiatric complications such as anxiety, depression, and confusion. Conditions related to the environment have the potential to worsen these symptoms. In combination with virus-dependent neuroinflammation, they form a "toxic" mixture. Discussion and planning strategies for providing psychological care in the ICU during the pandemic have revealed a great current challenge. ***Case series:*** We share our experience concerning psychological interventions for oncological patients with oxygen saturation depletion. Our observation of two SARS-CoV-2 patients suggests a close time-related association between the increase in inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP) and intensive anxiety in the fast development of breath shortening in acute COVID-19 infection due to brain hypoxia and potential neuroinflammation. ***Conclusion:*** As cytokine IL-6 regulates induction of CRP gene expression, the changes in IL-6 concentrations associated with anxiety symptoms and breath shortening in the observed cluster can be detected hours earlier than changes in CRP levels, with a diagnostic implication for the clinicians. The SARS-CoV-2 patients with oncological diseases treated in our ICU asked for personal bedside contact with clinical psychologists, considered it irreplaceable and reported this psychological care as beneficial.

Key words

psychological care – SARS-CoV-2 – anxiety– interleukin 6 – C-reactive protein– neuroinflammation – brain hypoxia – intensive care unit

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Souhrn

Východiska: V průběhu pandemie virem SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) trpěli pacienti, léčení pro COVID-19 (coronavirus disease 2019) infekci na jednotkách intenzivní péče (JIP), neuropsychiatrickými problémy jako byla úzkost, deprese či zmatenost. Samotné prostřední JIP mělo tendenci výše zmíněné příznaky zhoršovat. Prostředí JIP tak spolu s neuroinflamací, vyvolanou virovou infekcí, může vést k „toxické" kombinaci. Diskuze a plánování strategií poskytování psychologické péče se tak ukázaly během pandemie COVID-19 jako nová velká výzva. ***Série případů:*** Autoři uvádějí vlastní zkušenosti s poskytováním psychologické péče na JIP u dvou onkologických pacientek s oxygenační poruchou při infekci SARS-CoV-2. Naše pozorování naznačuje těsnou časovou souvislost mezi elevací zánětlivých markerů interleukinu 6 (IL-6), resp. C-reaktivního proteinu (CRP) a rychlým rozvojem intenzivní úzkosti při progresi dechové tísně, asociované s mozkovou hypoxií a potenciální neuroinflamací. ***Závěr:*** Vzhledem k tomu, že IL-6 reguluje indukci exprese genu pro CRP, mohou být změny hladin IL-6, spojené s úzkostí při potenciální neuroinflamací detekovány řádově o několik hodin dříve oproti změnám hladin CRP, což může lékařům pomoci v diagnostice. Onkologičtí pacienti s infekcí virem SARS-CoV-2 léčeni na naší JIP žádali o osobní kontakt s klinickými psychology u lůžka a tento přístup považovali za nenahraditelný. Psychologickou péči vnímali pacienti jako přínosnou.

Klíčová slova

psychologická péče – SARS-CoV-2 – úzkost – interleukin-6 – C-reaktivní protein – neuroinflamace – hypoxie mozku – jednotka intenzivní péče

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Bilateral pneumonia resulting from respiratory failure with subsequent lung fibrosis represents the most severe complication of the disease [1,2]. The virus entry to a sensitive cell depends on the expression of angiotensin-converting enzyme 2 (ACE2) and human transmembrane protease serine 2 (TMPRSS2), which are required for the interaction with the SARS-CoV-2 spike protein in target cells [3]. The disease's severity depends on the infected person's age and health status, and it seems that women of fertile age are more protected from a severe course of the disease than men [4]. Because of SARS-CoV-2 mutations, the virus is under selection pressure, and its rapid evolution and formation of new variants are in progress [5,6]. The particular viral mutation influences the course of the disease, and it is well known that e. g. the delta variant is more dangerous than the omicron. Hyperactivation of immunity associated with the cytokine release syndrome/cytokine storm plays an essential role in the progression of COVID-19 disease. Active factors such as interleukin 6 (IL-6) seem to be at the centre of the etiopathogenesis of severe COVID-19 [7]. IL-6 is a multifunctional cytokine of early phase immune response produced by numerous cell types [8]. In addition to the serum elevation of IL-6 in severe COVID-19 in the course of cytokine storm, this interleukin is also elevated in the elderly (inflammaging), chronic inflammation, and cancer [9]. The inflammation-supporting cytokines, including IL-6, influence the metabolism of hepatocytes, adipocytes, and striated muscle, which in the case of cancer terminates the patient's life in the form of tumour wasting/cachexia, as was summarized by Brábek et al. [9]. Numerous patients after SARS-CoV-2 exhibit symptoms of neuroinflammation and many neurological problems can even be preserved several months after the recovery from the acute infection [10]. Subunit S1 of the viral spike protein seems to be an inductor of this neuroinflammation [11]. COVID-19 history is responsible for the deterioration of cognitive functions and psychiatric affections such as depression [12–14]. These problems are dependent on inflammation-supporting factors. IL-6 can cross the blood-brain barrier and participate in troubles with food intake, depression, and increased risk of suicide [15–17]. As a consequence of the topic of this article, lowered oxygen saturation, cytokine release syndrome, and elevated IL-6, tumour necrosis factor α (TNF-α), or interleukin 8 (IL-8) were defined as potential mediators of encephalitis and neuropsychiatric COVID-19 symptoms [18–21]. These data explain the evidence-based background of neuropsychiatric problems of COVID-19 patients and persons suffering from the postcovid syndrome and provide a severe platform for employing psychological approaches to treating acute COVID-19.

Case series

Psychological care was provided in the specially established ICU for COVID-19 patients led by physicians specialized in intensive care medicine in University Hospital Brno since January 2021 according to the indication of the attending physician after verbal agreement of the patient noted to the patient's medical record following the ethical standards of the Institutional and National Research Committee and according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We decided to offer psychological care to all patients with oncological comorbidities, as we assumed that these patients could have suffered from distress.

The first presented case is an 86-year-old woman, a widow with two adult sons. She has no previous history of mental illness. A series of seven crisis interventions were conducted. The first one was performed in the surgical ICU for post-operative subdepressive mood and anxiety. On February 16th, she was admitted with COVID-19 to the COVID ICU (Fig. 1), and on February 17th, psychological support was provided for intensive anxiety followed by delirium. She was aware of her disorientation, asked whether it was morning or evening, and called her sons in an attempt to get orientated. She suffered from fear of death and loss of her mind. She described the complex of her hallucinations – many dark specters trying to touch her. Her dreams were also disturbing; she was in prison with no

chance to escape. She recognized the psychologist from the previous contact and asked her to visit her again. At that time, she needed the touch of hands in gloves and supportive words. A young physician touched her hands and informed her about remdesivir treatment. The patient told the physician that the touches of living persons were the opposite of the touches of the dark side of her mind. She considered them as lights in the darkness. The next day, on February 18th, she felt better and was well oriented in time, person and situation. There was a change in her attitude to COVID-19 – she appeared with a fighting spirit, considering the possibility of surviving. On February 19th, she was exhausted – a CT scan was taken during the night shift, and the patient could not breathe well. She hoped she could get remdesivir. In the day, she was well oriented, but her mood was getting worse and depressive, with signs of intensive anxiety. The next contact followed after the weekend on Monday, February 22nd, when only a short visit and support were provided – the patient was still in a depressive state of mind, anxious, coughed frequently, and was exhausted. On February 23rd, she felt better – she wanted to survive and get home. She said she was trying not to be stressed with every cough and to stop pitying herself. She was not confused any longer. The next day, February 24th, the collaboration ended when she was without any signs of severe depression, anxiety, or confusion. Note that there is a time-related association between higher values of inflammatory markers (IL-6, C-reactive protein (CRP)), breath shortening, and symptoms of revealed psychopathology (Tab. 1) on February 19th, you can see an increase in IL-6, associated with the anxiety state and depressive mood according to psychological reports.

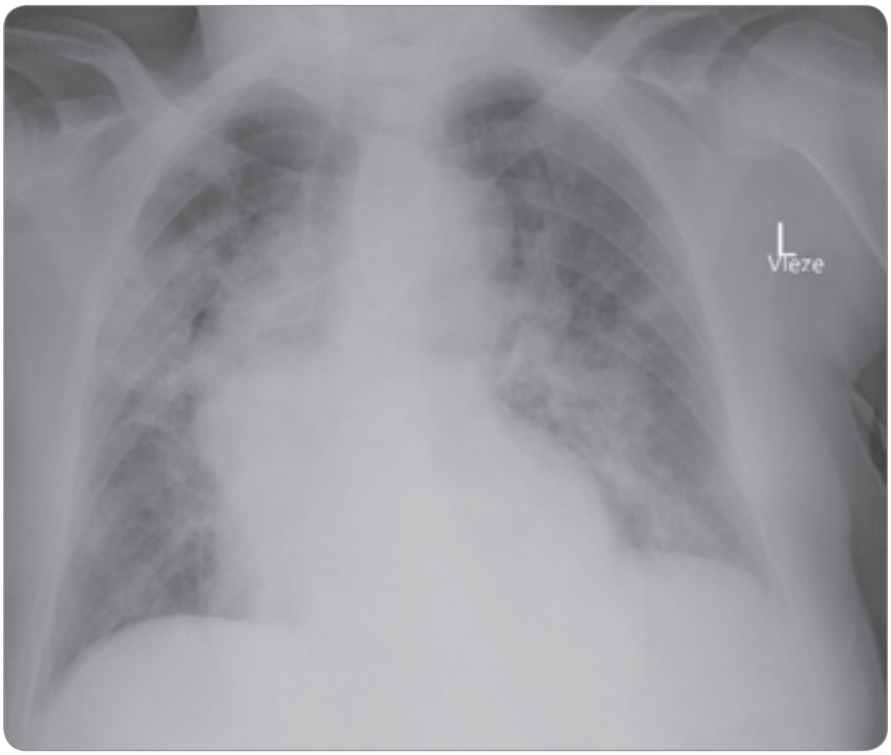

Fig. 1. Chest X-ray of patient 1.

Tab. 1. Characteristics of patient 1.

Date	Drugs				Oxygen saturation					Arterial astrup 6:00			
	paracetamol	trazodone	citalopram	quetiapine	8:00	9:00	10:00	11:00	12:00	pH	pO_2	pCO_2	HCO_3
16.2.2021	1 g à 8 h	×	×	×	×	×	×	×	×	×	×	×	×
17.2.2021	1 g à 8 h	×	×	×	97%	97%	96%	96%	98%	7,34	13,3	5,8	23,3
18.2.2021	1 g à 8 h	×	×	×	97%	99%	100%	94%	96%	7,36	9,8	5,4	22,8
19.2.2021	1 g à 8 h	75 mg/N	×	×	93%	92%	93%	95%	95%	7,43	8,5	5,2	25,9
20.2.2021	1 g à 8 h	75 mg/N	×	×	87%	88%	88%	87%	87%	7,49	9,1	5,3	30,1
21.2.2021	×	75 mg/N	×	×	92%	87%	82%	96%	94%	7,48	6,6	5,9	33,1
22.2.2021	×	75 mg/N	20 mg/N	×	95%	95%	97%	95%	95%	7,45	14,3	6,7	35,2
23.2.2021	×	75 mg/N	20 mg/N	25 mg à 8 h	90%	93%	94%	96%	95%	×	×	×	×
24.2.2021	×	75 mg/N	20 mg/N	25 mg à 8 h	94%	93%	95%	96%	97%	×	×	×	×
25.2.2021	×	75 mg/N	20 mg/N	25 mg à 8 h	96%	95%	95%	95%	97%	×	×	×	×
26.2.2021	×	75 mg/N	20 mg/N	25mg à 8 h	95%	96%	96%	95%	90%	×	×	×	×

CRP – C-reactive protein, IL-6 – interleukin 6, N – night

Tab. 1 – continuing. Characteristics of patient 1.

Date	Ventilation support	Parameters	Arterial astrup 2:00				Inflammatory markers		Status praesens psychicus – dominant symptomatology
			pH	pO_2	pCO_2	HCO_3	CRP (mg/L)	IL-6 (ng/L)	
16.2.2021	×	×	7,4	8,7	5,2	24,1	237,8	119	no intervention
17.2.2021	nasal cannula	2 L	7,33	11,6	5,5	21,7	269,5		anxiety signs in confusion, "giving up"
18.2.2021	nasal cannula	2 L	×	×	×	×	216,9	43,7	without signs of confusin, subdepressive mood (but fighting spirit)
19.2.2021	nasal cannula	2 L	×	×	×	×	142	136	anxiety, depressive mood (cough, breathlessness)
20.2.2021	nasal cannula	7 L	×	×	×	×	152,5	7,6	no intervention
21.2.2021	O_2 mask	5 L	7,49	9,3	5,5	31,3	67,5	27,6	no intervention
22.2.2021	nasal cannula	5 L	×	×	×	×	49,3	57	anxiety, depressive mood (cough, breathlessness)
23.2.2021	nasal cannula	8 L	×	×	×	×	51,4	23,7	less anxious, depressive mood (but stenic quality appeared)
24.2.2021	nasal cannula	4 L	×	×	×	×	27,7	10,8	without signs of confusin, serious anxiety or serious depressive symptoms
25.2.2021	nasal cannula	3 L	×	×	×	×	15,3	21,1	no intervention
26.2.2021	nasal cannula	3 L	×	×	×	×	10,9	47,2	no intervention

CRP – C-reactive protein, IL-6 – interleukin 6, N – night

The second presented case is a 49-year-old married woman with two adult children and no previous history of mental illness. She takes a disability pension for oncology illness. A series of eight psychological interventions were conducted. On March 11th, psychological support was provided when she came to the COVID ICU with fever and breath shortening (Fig. 2); despite her somatic state, she showed no signs of anxiety, depression, or confusion. The next day, March 12th, she felt worse and was worried about her father and daughter being infected with SARS-CoV-2 as well. She was very anxious on Monday morning, March 15th, with low oxygen saturation (60–70%). Probably because of opiates, her psychomotor rate was getting slow. She reported fears from intubation. The next day, March 16th, she still revealed signs of anxiety, her mood was subdepressive, and she verbalized ruminating thoughts about the threat of intubation. That day, she tried to speak more extensively and change the direction of her mind, looking forward to arranging her son's wedding plans in May. She tried to imagine the picture of a complete family on a wedding day, including herself, her father, and her daughter. This "wedding imagination" was very helpful in her crisis. After that, her blood oxygen saturation increased from 70 to 90%. She

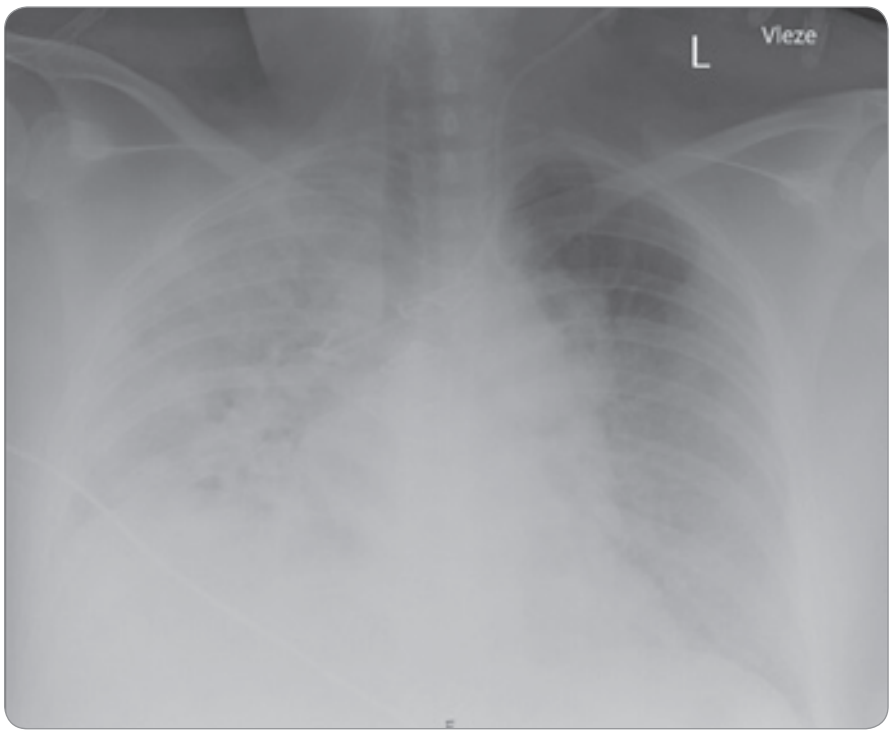

Fig. 2. Chest X-ray of patient 2.

Tab. 2. Characteristics of patient 2.

Date	Drugs					Oxygen saturation					Arterial astrup 6:00			
	morphine	quetiapine	codeine	tofisopam	trazodone	8:00	9:00	10:00	11:00	12:00	pH	pO_2	pCO_2	HCO_3
11.3.2021	2 mg/h	×	×	×	×	96%	95%	96%	90%	92%	7,46	4,3	5,5	23
12.3.2021	2 mg/h	×	×	×	×	80%	84%	80%	82%	94%	7,41	7,1	6,3	×
13.3.2021	4 mg/h	×	×	50 mg 14:00	×	76%	77%	70%	60%	64%	7,42	5,2	6,8	33,3
14.3.2021	4 mg/h	25 mg 3×/D	×	×	×	60%	63%	63%	64%	62%	7,41	5,2	7,3	34,1
15.3.2021	2 mg/h	25 mg 3×/D	×	×	75 mg tbl	81%	70%	85%	85%	85%	7,49	6,1	6,2	35,5
16.3.2021	2 mg/h	25 mg 3×/D	×	×	75 mg tbl	89%	85%	90%	88%	88%	7,49	6,5	6,3	37,2
17.3.2021	2 mg/h	25 mg 3×/D	×	×	×	86%	91%	89%	88%	90%	7,49	7,1	6,4	36,3
18.3.2021	2 mg/h	50 mg/N	×	×	×	86%	80%	92%	86%	85%	7,51	6,6	5,9	35
19.3.2021	1 mg/h	50 mg/N	×	×	×	93%	87%	86%	86%	87%	7,49	6,8	5,8	33,1
20.3.2021	1 mg/h	50 mg/N	30 mg 4×/D	×	×	95%	94%	92%	94%	96%	7,45	6,2	8,9	32,2
21.3.2021	×	50 mg/N	30 mg 4×/D	×	×	90%	90%	96%	96%	96%	7,48	8	5,5	30,3
22.3.2021	×	25 mg/N	30 mg 3×/D	×	×	95%	95%	96%	90%	93%	7,44	9,1	5,7	29,1
23.3.2021	×	×	30 mg/N	×	×	92%	94%	93%	91%	90%	7,44	12,1	5,9	29,9
24.3.2021	×	×	30 mg/N	×	×	94%	94%	95%	96%	93%	×	×	×	×
25.3.2021	×	×	30 mg/N	×	×	94%	93%	93%	95%	×	×	×	×	×

Date	Ventilation support	Parameters	Arterial astrup 14:00				Inflammatory markers		Status praesens psychicus – dominant symptomatology
			pH	pO_2	pCO_2	HCO_3	CRP (mg/L)	IL-6 (ng/L)	
11.3.2021	HFNO, O_2 mask	Q 60 L/92%; 15 L	7,42	7,5	5,1	24,8	184,9	111	without any signs of psychopathology
12.3.2021	HFNO, O_2 mask	Q 60 L/92%; 15 L	7,4	4,95	6,71	31,2	149,7	7	slightly anxious mood
13.3.2021	HFNO, O_2 mask	Q 60 L/95%; 15 L	7,4	4,5	7	32,7	60,1	9,6	no intervention
14.3.2021	HFNO, O_2 mask	Q 60 L/95%; 15 L	7,39	4,8	7,6	34,1	43	31,2	no intervention
15.3.2021	HFNO, O_2 mask	Q 60 L/95%; 15 L	7,48	6	5,7	33,9	76,4	13	slow PM rate, intensive anxiety signs
16.3.2021	HFNO, O_2 mask	Q 60 L/95%; 15 L	7,49	6,4	6,3	35,7	61,6	8,7	anxiety – subdepressive symptoms, but stenic attitude appeared – "the breaking point in coping with the ilness"
17.3.2021	HFNO	Q 60 L/95%	7,45	3,7	6,99	36,4	29	13,2	slightly anxious mood
18.3.2021	HFNO	Q 60 L/90%	7,49	6,9	5,8	32,8	39,8	15,6	slightly anxious mood
19.3.2021	HFNO	Q 50 L/80%	7,49	6,8	5,3	30,5	61,9	11,4	no intervention
20.3.2021	HFNO	Q 50 L/80%	7,48	6,4	5,1	28,5	23,7	2,5	no intervention
21.3.2021	HFNO	Q 45 L/45%	7,47	9,1	5,3	29	8,5	2,3	no intervention
22.3.2021	O_2 mask	Q 10–15 L	7,43	10,1	5,6	27,5	6,2	14,7	without signs of serious psychopathology
23.3.2021	O_2 mask	Q 3–5 L	×	×	×	×	7,5	15,3	no intervention
24.3.2021	O_2 mask	Q 3–5 L	×	×	×	×	7,9	7,2	no intervention
25.3.2021	O_2 mask	Q 3–5 L	×	×	×	×	4,9	3,7	

CRP – C-reactive protein, D – day, HFNO – high flow nasal oxygenation, IL-6 – interleukin 6, N – night, PM – vysvětlení zkratky

took a monitor picture using her phone and sent the picture home. She reported relief and a better mood immediately after that. She said to the clinical psychologist, "My family is the sense of my life, and I want to return to them. My approach is to be active in my attitude to the COVID treatment – so, visit me daily, train my mind and my breathing during the conversation, and stay a bit longer daily. I will move my legs in the bed and walk with a rehabilitation nurse. The plan of visits of all the healthcare providers means the promise of the next days." On March 17th and 18th, she felt better with a retreat of anxiety and mood clearing. The collaboration ended on March 22nd, when she was without any signs of severe depression or anxiety. Note that there is a time-related association between the increase in IL-6 (day 4) and CRP (day 5) and an intense anxiety state followed by breath shortening and low blood oxygen saturation values (Tab. 2).

Discussion

Depression and anxiety symptoms were more common among COVID-19 patients than in normal controls in a study conducted by Guo et al. [22]. The presence of mood and anxiety disorders may be highly correlated to the severity of physiological status, mainly as it is reflected in blood levels of peripheral inflammation markers [22]. Guo and his co-workers found the associations between the severity of depression symptoms and the level of CRP and suggested them as an indication where the virus could affect the central nervous system and induce neuropsychiatric symptoms by activation of immune-inflammatory response [22]. In addition, the improvement in CRP concentration strongly correlated with the levels of depression at the time of their observation [22]. Our observation in two SARS-COV-2 treated patients suggests a close time-related association between inflammatory markers (IL-6, CRP) and intense anxiety in the fast development of breath shortening in acute COVID-19 infection. Rapid detection of the cluster of symptoms related to blood inflammation markers could have a significant impact on the strategy of diagnostic decision-making and on effective multidisciplinary treatment of acute COVID-19 infection when the acute distress respiratory syndrome accompanied by the cytokine storm [7,23] could be a severe threat to patients with oxygenation disorder. As cytokine IL-6 regulates induction of CRP gene expression [24], the changes in IL-6 concentrations associated with anxiety symptoms and breath shortening in the observed cluster can be detected hours earlier than changes in CRP levels, with a diagnostic implication for the clinicians, e.g. diagnostic accounts about the potential progression of viral infection or intensive bacterial colonization of the surgical wounds in operated SARS-CoV-2 oncological patients.

Conclusion

Our observations in two oncological patients with oxygenation disorder suggest a close time-related association between inflammatory markers (IL-6, CRP) and intense anxiety in the fast development of breath shortening in acute COVID-19 infection due to brain hypoxia and potential neuroinflammation. Our SARS-CoV-2-positive oncological patients with oxygenation disorder reported psychological care in bedside contact as beneficial and were capable of conversation and imagination. Our preliminary psycho-neuro-immunological findings need to be verified by other research studies.

Authors' contribution

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Concept and design: Kateřina Skřivanová, Vladimír Procházka, Karel Smetana Jr
Acquisition, analysis, or interpretation of data: Kateřina Skřivanová, Tomáš Korbička, Jan Hudec, Martin Jaborník
Drafting of the manuscript: Kateřina Skřivanová, Tomáš Korbička, Jan Hudec, Martin Jaborník, Karel Smetana Jr
Critical revision of the manuscript for important intellectual content: Vladimír Procházka, Karel Smetana Jr
Administrative, technical, or material support: Martin Jaborník, Kateřina Skřivanová, Karel Smetana Jr
Supervision: Vladimír Procházka, Karel Smetana Jr
All authors contributed to the critical revision of the manuscript and approved the final version of the manuscript.

Competing interests

Karel Smetana Jr is a co-inventor of U.S. patent No. 11,246,874 B1 and cooperates with Oxygen Biotech LLC 108 W 13th St. Wilmington DE 19801. This company had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results. Other authors declare no conflict of interest.

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