Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

Clinical and diagnostic significance of oxidative stress in post-COVID olfactory dysfunction associated with acute rhinosinusitis

Y. V. Svitlychna, A. V. Lupyr, N. O. Shushliapina

Kharkiv National Medical University, Kharkiv, Ukraine

Article info

Received 06.10.2025
Received in revised form 30.10.2025
Accepted 23.11.2025

Kharkiv National Medical University, Nauky av., 4, Kharkiv, 61022, Ukraine. Tel.: +38-099-521-88-29. E-mail: yvsvitlychna.po21@knmu.edu.ua

Svitlychna, Y. V., Lupyr, A. V., & Shushliapina, N. O. (2025). Clinical and diagnostic significance of oxidative stress in post-COVID olfactory dysfunction associated with acute rhinosinusitis. Regulatory Mechanisms in Biosystems, 16(4), e25188. doi:10.15421/0225188

Anosmia is a common long-term complication of COVID-19. Its development is poorly understood. In the current study, the impact of rhinosinusitis-associated olfactory dysfunction in post-COVID-19 patients on the redox metabolism of circulating blood cells was investigated. The patients enrolled for the study suffered from rhinosinusitis with post-COVID-19 olfactory dysfunction and were tested by the Sniffin' Sticks test to determine the olfactory function (normosmia, hyposmia, and anosmia). Thereafter, flow cytometry-based detection of reactive oxygen species (ROS) levels in circulating granulocytes, lymphocytes and erythrocytes was performed using a ROS-sensitive probe (2′,7′-dichlorodihydrofluorescein diacetate). The degree of eryptosis was additionally detected by analysis of phospholipid membrane scrambling (Annexin V-FITC staining). According to the results of olfactometry, anosmia was identified in 20 patients and hyposmia in 53 patients. Among the 57 patients who reported recovery of olfactory function, hyposmia was observed in 86% of cases on the threshold test and in 75% on the identification test. Our findings suggest that anosmia in post-COVID-19 patients is associated with elevated intracellular ROS levels in viable circulating granulocytes, lymphocytes and erythrocytes. Of note, elevation was found to be statistically significant compared to both normosmic and hyposmic patients. Notably, eryptosis induction was not observed in anosmic patients even on the background of oxidative damage to erythrocytes. Anosmia in post-COVID-19 promotes redox homeostasis imbalance in blood granulocytes, lymphocytes and erythrocytes, which might be of diagnostic significance.

Keywords: COVID-19; anosmia; eryptosis; erythrocytes; leukocytes; reactive oxygen species; rhinosinusitis.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus infectious disease-2019 (COVID-19) pandemic, is considered a highly contagious single-stranded RNA virus belonging to Coronaviridae family (Hillary & Ceasar, 2023; Li et al., 2023). According to the current estimates performed by the WHO, over 770 million verified cases of COVID-19 were reported by November 2023 with over 6 million lethal outcomes (Amer et al., 2024). Thus, COVID-19 is one of the most severe challenges to the healthcare systems worldwide in the 21st century, representing a huge medical, social and economic burden.

In addition to unprecedentedly high mortality rates, COVID-19 is characterized by a myriad of long-term effects (over 50 effects are reported), among which fatigue, headache, attention disorder, hair loss, and memory loss are the most common (Lopez-Leon et al., 2021). It is important to note that at least one out of the multiple described long-term complications of COVID-19 develops in over 80% of patients (Lenz et al., 2024). Importantly, anosmia, which is a loss of olfaction, is a frequent long-term effect of COVID-19 that has been reported to occur in 22–68% of patients (Carrillo-Larco & Altez-Fernandez, 2020). The mechanisms that underlie its development are still under scrutinous investigation. However, there is accumulating evidence that massive apoptosis of olfactory sensory neurons, expression of angiotensin-converting enzyme 2 (ACE2) on olfactory epithelial cells, which is required to provide entrance of SARS-CoV-2 into the cells, and local inflammation associated with excessive tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1) mediating tissue damage (Shamsundara & Jayalakshmi, 2023) play an important role in its development. Additionally, SARS-CoV-2 fuels inflammation in the olfactory epithelium binding to toll-like receptors (TLRs) promoting pyroptosis resulting in the release of IL-1β and IL-18 via the inflammasome/caspase-1-mediated pathway (Karimian et al., 2022). Thus, the pivotal role in COVID-19-associated anosmia is played by destruction of olfactory cells by the pathogen and related inflammation.

Notably, inflammation is widely promoted by oxidative stress associated with accumulation of reactive oxygen species (ROS) or reactive nitrogen species (RNS) against the background of the antioxidant system depletion (Biswas, 2016). Dysregulation of redox homeostasis has been widely reported for COVID-19 (Dos Santos et al., 2022). Moreover, severity of systemic oxidative stress has been reported to be a hallmark of COVID-19 (Bastin et al., 2023) and its prognostic significance has been emphasized (Uysal et al., 2023). It has been suggested that oxidative stress mediates long-term complications associated with post-COVID syndrome. For instance, elevation of circulating thiobarbituric acid-reactive substances (TBARS) in long COVID-19 has been demonstrated (Stufano et al., 2023). Moreover, post-COVID-19 fatigue is reported to be linked with superoxide anion elevation in blood samples and oxidative stress-induced DNA breaks (Hofmann et al., 2023). It is important to note that oxidative stress along with hyper-inflammation has been even suggested to be a major driver of long COVID-19 (Vollbracht & Kraft, 2022). Thus, systemic markers of oxidative stress might be of huge importance in determining development of post-COVID complications.

Anosmia as a neurological complication of COVID-19 is associated with neuroinflammation, which is commonly accompanied by redox imbalance triggered, in particular, by mitochondrial dysfunction with excessive mitochondrial ROS (mitROS) generation and fueled in a cytokine-dependent manner (Thakur et al., 2023). However, despite the current advances in our understanding of the factors contributing to anosmia development, the precise pathogenesis of this condition is still unknown and the role of oxidative stress is yet-to-be-elucidated. Moreover, it has become clear that a high percentage of COVID-19 patients faces post-COVID-19 syndrome, but the predisposing factors and prognostic criteria remain to be revealed (Maglietta et al., 2022). It is tempting to suggest that oxidative stress markers might be beneficial to identify populations at the highest risk of lack of olfactory function recovery. The aim of this study was to investigate the role of oxidative stress in the occurrence of post-COVID olfactory dysfunction in patients with acute rhinosinusitis.

Materials and methods

Ethics. The study was performed in accordance with the Declaration of Helsinki and approved by the Bioethics Commission of Kharkiv National Medical University (Protocol No. 8 dated 06.10.2021). All participants were fully informed about the study and provided written consent to participate.

Patients and groups. The study included 130 patients, aged 18–60 years (mean age 42.8 ± 1.2 years), who suffered from acute postviral rhinosinusitis with varying degrees of olfactory dysfunction after COVID-19. The patients were enrolled from the University Hospital of Kharkiv National Medical University (Kharkiv, Ukraine) from September 2021 to June 2024.

Diagnosis of acute rhinosinusitis was verified in accordance with EPOS 2020 guidelines (Fokkens et al., 2020) based on typical clinical manifestations such as nasal obstruction, nasal discharge, facial pain, and olfaction reduction or loss. Olfactory function was evaluated using the Sniffin' Sticks test (Rumeau et al., 2016; Vandersteen et al., 2022). The test is based on the ability to identify 16 odors such as peppermint, orange, fish, leather, rose, cloves, coffee, pineapple, licorice, anise, lemon, banana, cinnamon, apple, turpentine, and garlic. Smoking, eating and drinking was prohibited at least for 15 minutes before testing. Odors were presented to a blindfolded patient by an examiner wearing rubber gloves. The subtests were performed to evaluated olfactory threshold and identification with the time interval of 3–5 min between them. The threshold subset included three sticks, among which two contained exclusively a solvent, while one of them presented an odorant soaked in n-butanol. The test started with the red marker No. 1 presenting the highest concentration of the odorant. Then triplets of markers were offered sequentially with increasing concentration until the first correct answer was obtained. The patient's answers were recorded as either correctly identified (+) or not identified (−). The concentration at which the patient gave two consecutive correct answers (++) was considered a turning point. Thereafter, the examiner presented three matching sticks with lower concentrations until the first incorrect answer was provided (+−), which was considered the second turning point. Then a higher concentration of odorants was used until two correct answers were provided (++, the third turning point). The olfactory threshold score was defined as the average value of the turning points and was evaluated as follows: anosmia (1 point), hyposmia (2–6 points), and normosmia (7–16 points).

The identification subtest included 16 blue or 12 black markers. Each marker was introduced to a patient once with the time interval of at least 30 seconds to avoid olfactory desensitization. For each odorant, the patient was required to select among 4 answer options. The identification score corresponded to the number of correct answers and was assessed as follows: anosmia (0–6 points), hyposmia (7–10 points), and normosmia (11–12 points).

To determine ROS production in erythrocytes and various leukocyte subpopulations, as well as to assess eryptosis in circulating erythrocytes, patient blood samples were analyzed by flow cytometry.

ROS detection in circulating leukocytes of patients with post-COVID-19 anosmia. Leukocyte suspension was prepared from freshly collected blood delivered within 2 h in EDTA-containing vacutainer tubes. The commercially available lysing solution (BD FACS™ Lysing Solution, Becton Dickinson, San Jose, CA, USA) was employyed. An aliquot of 100 μL was mixed with 2 mL of the solution mentioned above. Following vortexing and incubation for 10 min at 24 °C, the samples were centrifuged during 5 min (500 g). The supernatant was discarded and the pellets were washed twice in phosphate-buffered saline (PBS) and resuspended in a working solution of 2′,7′-dichlorodihydrofluorescein diacetate (InvitrogenTM, Weltham, USA). The final probe concentration was 10 μM. Thereafter, 10 μL APC-CyTM 7-labelled mouse anti-human CD45 (BD Pharmingen, USA) was added. The samples were incubated for 30 min in the dark. The samples were washed with PBS and 10 μL 7-aminoactinomycin D (7-AAD, BD Pharmingen, USA) was added. The samples were incubated for 15 min in the dark.

ROS detection in circulating erythrocytes of patients with post-COVID-19 anosmia. To assess ROS production in erythrocytes, an aliquot of freshly collected blood samples (5 μL) was added to Ringer solution (5 mM glucose, 32 mM HEPES, 125 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 2 mM $MgCl_2$). The cells were washed twice (centrifugation at 1800 g for 5 min). Thereafter, an aliquot of the erythrocytes was resuspended in 2′,7′-dichlorodihydrofluorescein diacetate solution in PBS at the final dye concentration of 10 μM. Incubation with no exposure to light lasted for 30 min.

Phosphatidylserine externalization in circulating erythrocytes of patients with post-COVID-19 anosmia. Eryptosis was assessed by determining the degree of cell scrambling, i.e. phosphatidylserine externalization, by Annexin V-FITC staining. Erythrocyte suspensions were prepared as described above. Then, erythrocytes were stained with 5 μL FITC-labelled annexin V (BD Pharmingen™ FITC Annexin V, Becton Dickinson, USA) dissolved in 100 μL annexin-binding buffer (BD Pharmingen™ Annexin V Binding Buffer, Becton Dickinson, USA). The resuspended cells were incubated for 15 min in the dark.

Flow cytometry data acquisition and post-acquisition data analysis. Fluorescence of fluorescent dyes applied in the current study was acquired by BD FACSCantoTM II flow cytometer (BD Biosciences, Franklin Lakes, USA, 2020). Fluorescent dyes used for H2DCFDA and annexin V-FITC staining were excited by a 488 nm laser, and their emission was detected at 525 nm. 7-AAD emission was acquired at 650 nm following excitation by a 488 nm laser. APC-Cy7 emission was collected at 780 nm after excitation by a 633 laser.

The gating strategy included identification of CD45-positive cells based on APC-C7 fluorescence, populations of lymphocytes and granulocytes based on CD45 staining and side scatter (SSC) parameters. Viable cells were discriminated based on 7-AAD staining. 7-AAD-negative cells were considered live. Following this gating, 2′,7′-dichlorofluorescein (DCF) fluorescence was analyzed to quantify ROS production by detecting mean fluorescence intensity (MFI) parameters (Tkachenko et al., 2020; Onishchenko et al., 2022).

Analysis of erythrocytes implied identification of Annexin V-positive cells, which were considered eryptotic (Yefimova et al., 2023; Prokopiuk et al., 2024). In addition, DCF fluorescence in erythrocytes was quantified to assess redox homeostasis of these cells (Tkachenko et al., 2021; Onishchenko et al., 2023).

FlowJo™ (v10, BD Biosciences, Franklin Lakes USA, 2012) software was used to process the obtained data.

The following exclusion criteria were applied: chronic rhinosinusitis with/without nasal polyps, exacerbation of chronic inflammatory diseases, acute Covid-19, obesity, hypertension, diabetes mellitus, pregnancy, smoking, cardiovascular diseases, atopic diseases, asthma, no informed consent provided.

Statistical analysis. Flow cytometry-based data were analyzed by applying the ANOVA test following by Bonferroni post-hoc analysis. Data are represented as mean ± SD. Differences were believed to be statistically significant at $P < 0.05$. Analysis was performed applying GraphPad Prism 5.0 software (GraphPad Software, Inc., USA, 2010).

Results

In the current study, 20 patients were identified as anosmic with the average of 0.9 ± 0.4 points for the threshold subtest and 4.4 ± 1.3 points for the identification subtest. Additionally, a total of 53 patients were classified as hyposmic (3.5 ± 1.3 and 7.1 ± 1.6 points, respectively). Of note, out of 57 patients self-reported as having recovery of olfactory function, 86% had hyposmia based on the threshold test (5.5 ± 1.1 points), while 75% of patients were hyposmic in accordance with the identification subtest (9.4 ± 1.4 points). Based on the outcome of the Sniffin' Sticks test, the patients were selected for further flow cytometry-based detection of redox homeostasis in circulating leukocytes and eryptosis markers.

Demographic data of patients selected for further flow cytometry-based research are summarized in Table 1. There were no differences in gender, age and body mass index (BMI) parameters of patients. Notably, circulating levels of C-reactive proteins were analyzed to allow comparison between groups. As illustrated in Figure 1a, analysis the association between olfaction disorders in post-COVID-19 pa-

tients with ROS levels in granulocytes revealed that anosmic patients had a statistically significant elevation of intracellular ROS compared with both normosmic and hyposmic individuals. The fluorescence intensity of a ROS level-reflecting dye was evaluated in the population of viable granulocytes (Figure 2), which mainly comprises neutrophils.

Table 1
Demographic data of patients with olfactory dysfunction after COVID-19

Parameters	Post-COVID-19 patients with restored olfactory function (n = 17)	Post-COVID-19 patients with reduced olfactory function (hyposmia) (n = 53)	Post-COVID with severely affected olfactory function (anosmia) (n = 20)	P-value
Gender (female/male)	8/9 (47.1% / 52.9%)	20/33 (37.7% / 62.3%)	8/12 (40.0% / 60.0%)	0.79
Average age, years	44.6 ± 11.8	45.6 ± 12.1	44.3 ± 11.6	0.83
BMI	22.7 ± 2.4	24.0 ± 1.7	22.4 ± 2.1	0.29
C-reactive protein, mg/L	7.6 ± 2.7	8.2 ± 1.9	7.9 ± 2.5	0.96

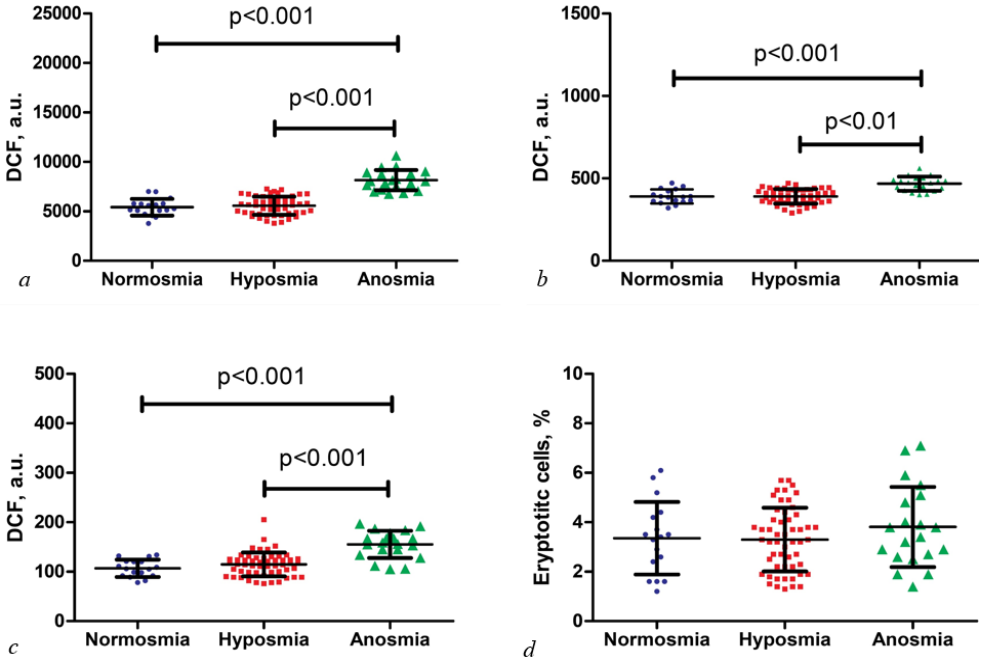

Fig. 1. Alterations of redox homeostasis in leukocytes and their subpopulations, as well as eryptosis parameters, in patients with COVID-19-associated rhinosinusitis with different degrees of olfaction disorders: ROS generation was investigated in viable granulocytes (*a*), lymphocytes (*b*), and erythrocytes (*c*); eryptosis degree was assessed by evaluating phosphatidylserine externalization following Annexin V-FITC staining (*d*); ANOVA test, Bonferroni post-hoc test, mean ± SD

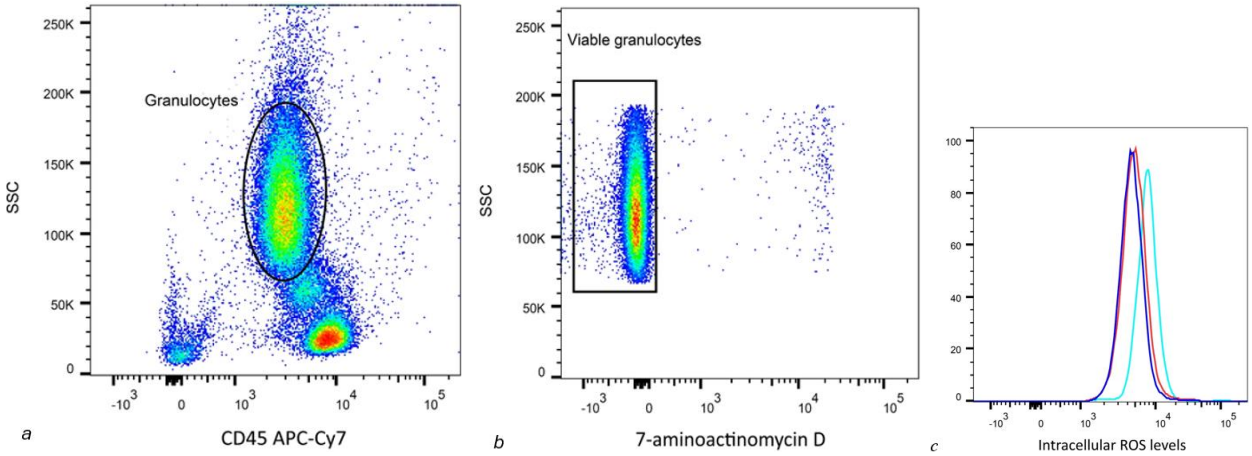

Fig. 2. Oxidative stress evaluation in blood granulocytes in COVID-19 rhinosinusitis patients with olfactory disorders: the gating strategy for selecting granulocytes was based on CD_{45} staining and side scatter (SSC) parameters (*a*); viable granulocytes were identified following 7-AAD staining (*b*); the content of ROS inside the cells was judged by 2′,7′-dichlorofluorescein fluorescence (*c*); light blue line – anosmia, red line – hyposmia, blue line – restored olfactory function

Figure 1b clearly demonstrates that anosmia is accompanied by a statistically significant elevation of intracellular ROS in circulating lymphocytes compared with the normosmic individuals. Importantly, ROS production in viable lymphocytes (Figure 3) of anosmic patients was higher than in hyposmic patients as well. It is important to note that elevation of lymphocytic ROS in anosmia was in line with data reported for granulocytes above. This is of particular interest due to the fact that ROS play a less significant role in biology of lymphocytes compared to neutrophils.

The same trend observed for circulating granulocytes and lymphocytes in this study was revealed for erythrocytes. As shown in Figure 4a, circulating erythrocytes in anosmic patients generated more ROS compared with normosmic and hyposmic patients.

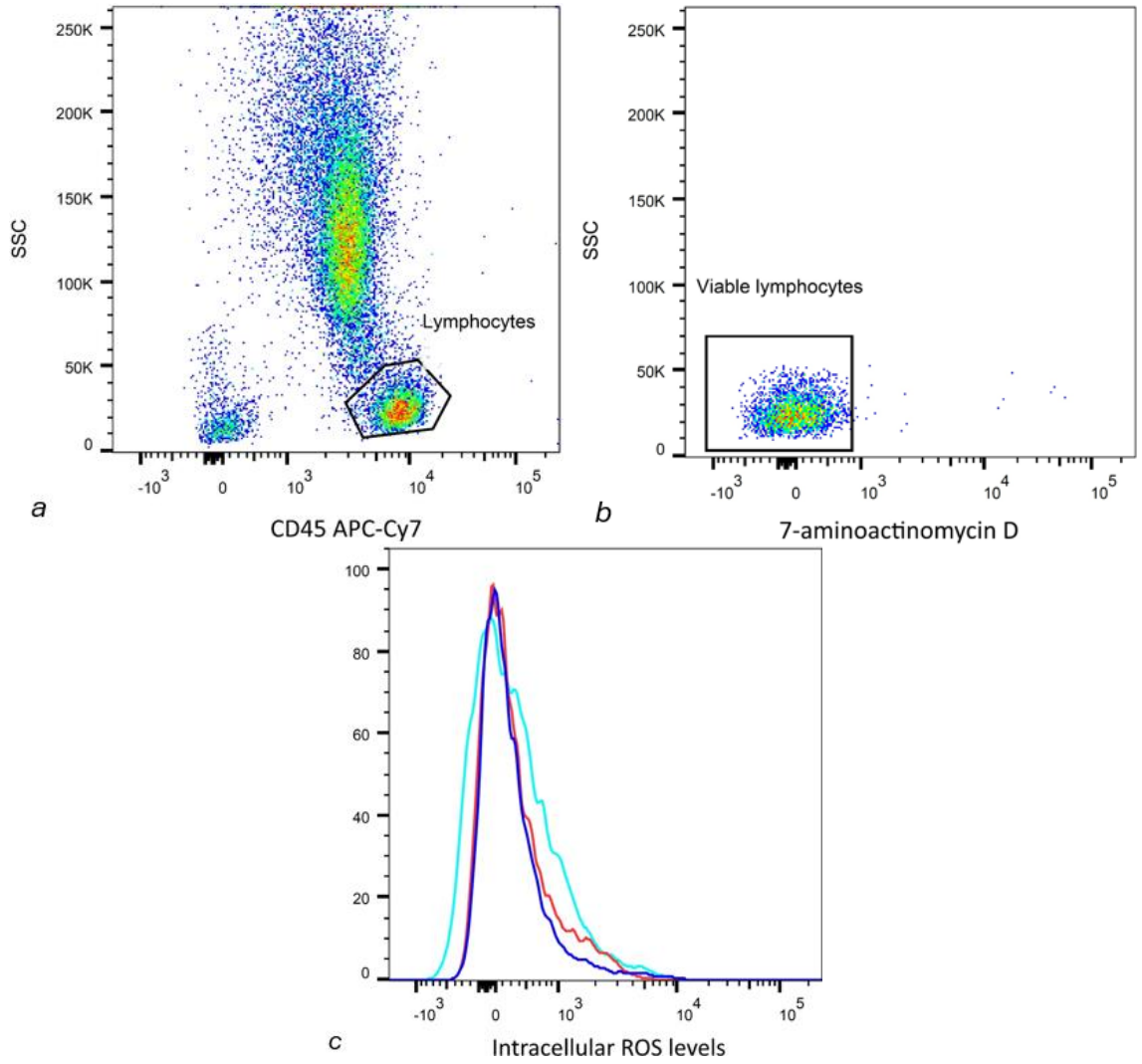

Fig. 3. Redox homeostasis was evaluated in circulating lymphocytes in COVID-19-associated rhinosinusitis with normal, reduced and lost olfaction: CD45-APC-Cy7 fluorescence and side scatter (SSC) signals were used to identify the subpopulation of lymphocytes (a); 7-AAD staining was applied to discriminate live and dead cells (*b*); ROS concentrations in lymphocytes were compared based on evaluation of 2′,7′-dichlorofluorescein fluorescence (*c*); light blue line – anosmia, red line – hyposmia, blue line – restored olfactory function

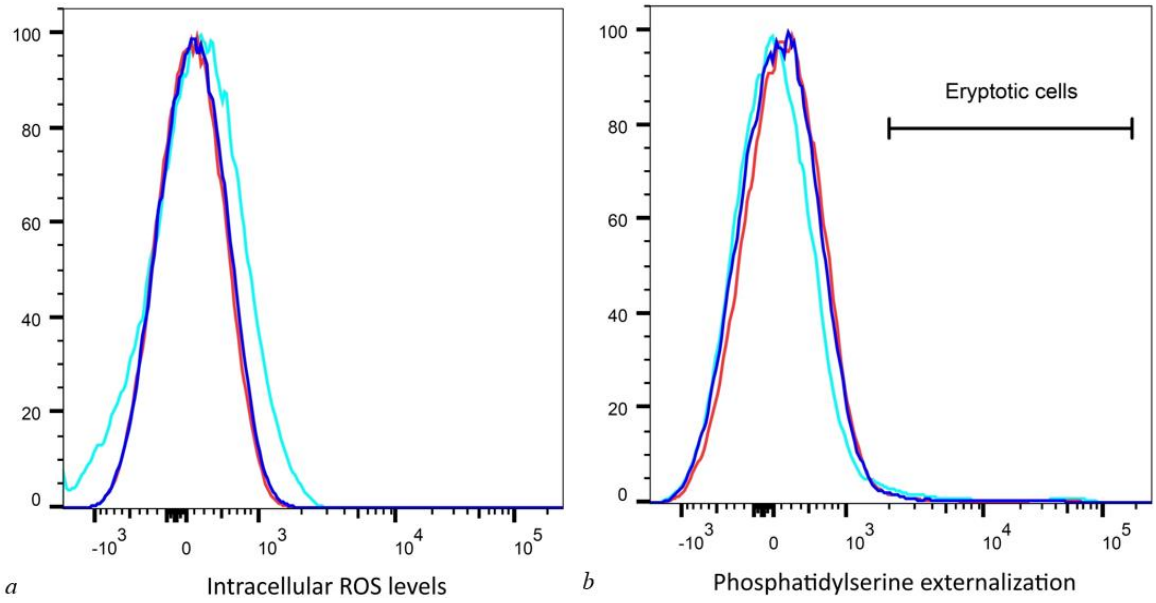

Fig. 4. Analysis of eryptosis parameters in COVID-19 rhinosinusitis patients with olfaction disorders was performed based on 2′,7′-dichlorodihydrofluorescein diacetate staining (*a*) and annexin V-FITC staining (*b*); light blue line – anosmia, red line – hyposmia, blue line – restored olfactory function

Oxidative stress is a widely reported trigger of eryptosis, which is defined as cell death of erythrocytes morphologically and functionally similar to apoptosis of nucleus-containing cells. Thus, the next step of our research was to detect the degree of this process in circulating erythrocytes. Unexpectedly, we revealed no statistically significant difference between the percentage of eryptotic cells in patients with no olfactory dysfunction, reduced olfactory function and its lack. As demonstrated in Figure 4b, eryptosis was evaluated by determining cell membrane scrambling, i.e. transfer of phosphatidylserine molecules from the inner leaflet of the phospholipid bilayer and their exposure on the surface of cells.

Discussion

In the current study, we investigated the impact of rhinosinusitis-associated olfactory dysfunction in post-COVID-19 patients in circulating cells to shed a light on the possible role of redox homeostasis imbalance and provide insights into new possible markers of the olfactory dysfunction. Indeed, we have revealed that anosmia is associated with ROS overproduction in granulocytes, lymphocytes, and erythrocytes. Of note, endogenous ROS in granulocytes, which primarily comprise the fraction of neutrophils, play a pivotal role in host defense mediating the oxidative burst due to the activity of NADPH oxidase in neutrophils (Chen & Junger, 2012). It is important to emphasize that excessive ROS generation in neutrophils has been reported for severe COVID-19 (Veenith et al., 2022). There is evidence that neutrophils participate in destruction of the olfactory epithelium in COVID-19 (Bourgon et al., 2022). Our findings are in line with this report, since overproduction of ROS indicates activation of neutrophils and the ability to destroy cells. It can be assumed that anosmia is secondary to activation of neutrophils. However, the cause-and-effect relationships between olfactory dysfunction and activation of neutrophils in post-COVID-19 should be further explored to deepen our knowledge in the field.

In contrast to neutrophils where ROS are crucial for the oxidative burst and macrophages where ROS regulate the involvement of inflammasomes and pyroptosis-associated cytokine release (Wang et al., 2019), the contribution of ROS to cellular biology of B-cells and T-lymphocytes is less studied. However, their importance for growth, differentiation and activation of lymphocytes is beyond doubt (Bassoy et al., 2021). Additionally, the role of lymphocytes-derived ROS in COVID-19 and long COVID-19 is poorly elucidated. In general, in COVID-19, anosmia is associated with a higher lymphocyte count (Talavera et al., 2020). Furthermore, local infiltration of the olfaction epithelium with CD3+ lymphocytes was reported in COVID-19-associated anosmia (Finlay et al., 2022). Our findings supplement these data indicating that oxidative stress in lymphocytes is observed at the systemic levels as well contributing to anosmia in post-COVID-19 patients.

Oxidative stress induced by COVID-19 affects the functionality of cells resulting in the increased deformability of cells (Russo et al., 2022). It is important to mention that erythrocytes are sensitive to oxidative stress due to the imperfect antioxidant system and ROS are important regulators of their survival affecting primarily Ca^{2+} signaling, which is crucial for erythrocytes (Tkachenko, 2024). Of note, ROS production shown in this study for anosmic post-COVID-19 patients is a well-known trigger of eryptosis (Bissinger et al., 2019). Moreover, multiple studies have provided links between oxidative stress in erythrocytes and eryptosis in COVID-19 (Soma & Bester, 2022; Khedr et al., 2023). Therefore, we used a common hallmark of eryptosis, namely phosphatidylserine externalization, to detect whether olfactory dysfunction might induce this regulated cell death. No eryptosis induction observed in this study indicating that the elevation of ROS occurred at the subthreshold levels and might be compensated for. Of note, long COVID-19 has been known to be associated with anemia (Lechuga et al., 2023) and eryptosis frequently contributes to anemia development (Lang et al., 2017). However, in this case, this association was not established.

It is worth noting that the effectiveness of multiple oxidative stress markers in COVID-19 and post-COVID-19 patients for diagnostic purposes has been reported (Ahmed et al., 2023). However, to our knowledge, the diagnostic significance of links between olfactory dysfunction and oxidative stress in circulating leukocytes and erythrocytes has not been investigated. Our findings indicate that determination of ROS levels in circulating granulocytes, lymphocytes, and erythrocytes can be of diagnostic importance in patients with post-COVID-19 olfactory dysfunction.

Conclusions

According to the results, patients cannot always objectively assess their condition, but the use of diagnostic tests with a decrease in odor concentration makes it possible to detect disorders that tell us about the presence of ongoing degenerative disorders. In the current study, the association between intracellular ROS levels in circulating granulocytes, lymphocytes and erythrocytes and anosmia has been established in post-COVID-19 patients. There is no association between eryptosis degree with the severity of olfactory dysfunction. These findings might expand our knowledge about the pathogenesis of olfactory dysfunction in post-COVID-19 and add novel diagnostic tools.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare no conflicts of interest.

References

Ahmed, S. A., Alahmadi, Y. M., & Abdou, Y. A. (2023). The impact of serum levels of reactive oxygen and nitrogen species on the disease severity of COVID-19. International Journal of Molecular Sciences, 24(10), 8973.

Amer, S. A., Al-Zahrani, A., Imam, E. A., Ishteiwy, E. M., Djelleb, I. F., Abdullh, L. R., Ballaj, D., Amer, Y. A., El-Sokkary, R. H., Elshabrawy, A. M., Eskander, G., Shah, J., Raza, M. L., Alsafa, A. M. A. A., Ali, H. T., & Fawzy, H. M. (2024). Exploring the reported adverse effects of COVID-19 vaccines among vaccinated Arab populations: A multi-national survey study. Scientific Reports, 14(1), 4785.

Bassoy, E. Y., Walch, M., & Martinvalet, D. (2021) Reactive oxygen species: Do they play a role in adaptive immunity? Frontiers in Immunology, 12, 755856.

Bastin, A., Abbasi, F., Roustaei, N., Abdesheikhi, J., Karami, H., Gholamnezhad, M., Eftekhari, M., & Doustimotlagh, A. (2023). Severity of oxidative stress as a hallmark in COVID-19 patients. European Journal of Medical Research, 28(1), 558.

Bissinger, R., Bhuyan, A. A. M., Qadri, S. M., & Lang, F. (2019). Oxidative stress, eryptosis and anemia: a pivotal mechanistic nexus in systemic diseases. FEBS Journal, 286(5), 826–854.

Biswas, S. K. (2016). Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxidative Medicine and Cellular Longevity, 2016, 5698931.

Bourgon, C., Albin, A. S., Ando-Grard, O., Da Costa, B., Domain, R., Korkmaz, B., Klonjkowski, B., Le Poder S., & Meunier, N. (2022). Neutrophils play a major role in the destruction of the olfactory epithelium during SARS-CoV-2 infection in hamsters. Cellular and Molecular Life Sciences, 79(12), 616.

Carrillo-Larco, R. M., & Altez-Fernandez, C. (2020). Anosmia and dysgeusia in COVID-19: A systematic review. Wellcome Open Research, 5, 94.

Chen, Y., & Junger, W. G. (2012). Measurement of oxidative burst in neutrophils. Methods in Molecular Biology, 844, 115–124.

Dos Santos, A. A. C., Rodrigues, L. E., Alecrim-Zeza, A. L., de Araújo Ferreira, L., Trettel, C. D. S., Gimenes, G. M., da Silva, A. F., Sousa-Filho, C. P. B., Serdan, T. D. A., Levada-Pires, A. C,. Hatanaka, E., Borges, F. T., de Barros, M. P., Cury-Boaventura, M. F., Bertolini, G. L., Cassolla, P., Marzuca-Nassr, G. N., Vitzel, K. F., Pithon-Curi, T. C., Masi, L. N., Curi, R., Gorjao, R., & Hirabara, S. M. (2022). Molecular and cellular mechanisms involved in tissue-specific metabolic modulation by SARS-CoV-2. Frontiers in Microbiology, 13, 1037467.

Finlay, J. B., Brann, D. H., Abi Hachem, R., Jang, D. W., Oliva, A. D., Ko, T., Gupta, R., Wellford, S. A., Moseman, E. A., Jang, S. S., Yan, C. H., Matsunami, H., Tsukahara, T., Datta, S. R., & Goldstein, B. J. (2022). Persistent post-COVID-19 smell loss is associated with immune cell infiltra-

tion and altered gene expression in olfactory epithelium. Science Translational Medicine, 14(676), eadd0484.
Fokkens, W. J., Lund, V. J., Hopkins, C., Hellings, P. W., Kern, R., Reitsma, S., Toppila-Salmi, S., Bernal-Sprekelsen, M., Mullol, J., Alobid, I., Terezinha Anselmo-Lima, W., Bachert, C., Baroody, F., von Buchwald, C., Cervin, A., Cohen, N., Constantinidis, J., De Gabory, L., Desrosiers, M., Diamant, Z., Douglas, R. G., Gevaert, P. H., Hafner, A., Harvey, R. J., Joos, G. F., Kalogjera, L., Knill, A., Kocks, J. H., Landis, B. N., Limpens, J., Lebeer, S., Lourenco, O., Meco, C., Matricardi, P. M., O'Mahony, L., Philpott, C. M., Ryan, D., Schlosser, R., Senior, B., Smith, T. L., Teeling, T., Tomazic, P. V., Wang, D. Y., Wang, D., Zhang, L., Agius, A. M., Ahlstrom-Emanuelsson, C., Alabri, R., Albu, S., Alhabash, S., Aleksic, A., Aloulah, M. Al-Qudah, M., Alsaleh, S., Baban, M. A., Baudoin, T., Balvers, T., Battaglia, P., Bedoya, J. D., Beule, A., Bofares, K. M., Braverman, I., Brozek-Madry, E., Richard, B., Callejas, C., Carrie, S., Caulley, L., Chussi, D., de Corso, E., Coste, A., El Hadi, U., Elfarouk, A., Eloy, P. H., Farrokhi, S., Felisati, G., Ferrari, M. D., Fishchuk, R., Grayson, W., Goncalves, P. M., Grdinic, B., Grgic, V., Hamizan, A. W., Heinichen, J. V., Husain, S., Ping, T. I., Ivaska, J., Jakimovska, F., Jovancevic, L., Kakande, E., Kamel, R., Karpischenko, S., Kariyawasam, H. H., Kawauchi, H., Kjeldsen, A., Klimek, L., Krzeski, A., Kopacheva Barsova, G., Kim, S. W., Lal, D., Letort, J. J., Lopatin, A., Mahdjoubi, A., Mesbahi, A., Netkovski, J., Nyenbue Tshipukane, D., Obando-Valverde, A., Okano, M., Onerci, M., Ong, Y. K., Orlandi, R., Otori, N., Ouennoughy, K., Ozkan, M., Peric, A., Plzak, J., Prokopakis, E., Prepageran, N., Psaltis, A., Pugin, B., Raftopulos, M., Rombaux, P., Riechelmann, H., Sahtout, S., Sarafoleanu, C. C., Searyoh, K., Rhee, C. S., Shi, J., Shkoukani, M., Shukuryan, A. K., Sicak, M., Smyth, D., Sindvongs, K., Soklic Kosak, T., Stjarne, P., Sutikno, B., Steinsvag, S., Tantilipikorn, P., Thanaviratananich, S., Tran, T., Urbancic, J., Valiulius, A., Vasquez de Aparicio, C., Vicheva, D., Virkkula, P. M., Vicente, G., Voegels, R., Wagenmann, M. M., Wardani, R. S., Welge-Lussen, A., Witterick, I., Wright, E., Zabolotniy, D., Zsolt, B., & Zwetsloot, C. P. (2020). European position paper on rhinosinusitis and nasal polyps 2020. Rhinology, 58(29), 1–464.
Hillary, V. E., & Ceasar, S. A. (2023). An update on COVID-19: SARS-CoV-2 variants, antiviral drugs, and vaccines. Heliyon, 9(3), e13952.
Hofmann, H., Önder, A., Becker, J., Gröger, M., Müller, M. M., Zink, F., Stein, B., Radermacher, P., & Waller, C. (2023). Markers of oxidative stress during post-COVID-19 fatigue: A hypothesis-generating, exploratory pilot study on hospital employees. Frontiers in Medicine, 10, 1305009.
Karimian, A., Behjati, M., & Karimian, M. (2022). Molecular mechanisms involved in anosmia induced by SARS-CoV-2, with a focus on the transmembrane serine protease TMPRSS2. Archives of Virology, 167(10), 1931–1946.
Khedr, A., Khayat, M. T., Khayyat, A. N., Asfour, H. Z., Alsilmi, R. A., & Kammoun, A. K. (2023). Accumulation of oxysterols in the erythrocytes of COVID-19 patients as a biomarker for case severity. Respiratory Research, 24(1), 206.
Lang, F., Bissinger, R., Abed M., & Artunc F. (2017). Eryptosis – the neglected cause of anemia in end stage renal disease. Kidney and Blood Pressure Research, 42(4), 749–760.
Lechuga, G. C., Morel, C. M., & De-Simone, S. G. (2023). Hematological alterations associated with long COVID-19. Frontiers in Physiology, 14, 1203472.
Lenz, C., Slack, M. P. E., Shea, K. M., Reinert, R. R., Taysi, B. N., & Swerdlow, D. L. (2024). Long-term effects of COVID-19: A review of current perspectives and mechanistic insights. Critical Reviews in Microbiology, 50(3), 315–328.
Li, G., Hilgenfeld, R., Whitley, R., & De Clercq, E. (2023). Therapeutic strategies for COVID-19: Progress and lessons learned. Nature Reviews Drug Discovery, 22(6), 449–475.
Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (2021). More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. Scientific Reports, 11(1), 16144.
Maglietta, G., Diodati, F., Puntoni, M., Lazzarelli, S., Marcomini, B., Patrizi, L., & Caminiti, C. (2022). Prognostic factors for post-COVID-19 syndrome: A systematic review and meta-analysis. Journal of Clinical Medicine, 11(6), 1541.
Onishchenko, A. I., Prokopiuk, V. Y., Chumachenko, V. A., Virych, P. A., Tryfonyuk, L. Y., Kutsevol, N. V., & Tkachenko, A. S. (2023). Hemocompatibility of dextran-graft-polyacrylamide/zinc oxide nanosystems: Hemolysis or eryptosis? Nanotechnology, 35(3), 035102.
Onishchenko, A., Myasoedov, V., Yefimova, S., Nakonechna, O., Prokopyuk, V., Butov, D., Kökbaş, U., Klochkov, V., Maksimchuk, P., Kavok, N., & Tkachenko, A. (2022). UV light-activated GdYVO(4):Eu(3+) nanoparticles induce reactive oxygen species generation in leukocytes without affecting erythrocytes *in vitro*. Biological Trace Element Research, 200(6), 2777–2792.
Prokopiuk, V., Onishchenko, A., Tryfonyuk, L., Posokhov, Y., Gorbach, T., Kot, Y., Kot, K., Maksimchuk, P., Nakonechna, O., & Tkachenko, A. (2024). Marine polysaccharides carrageenans enhance eryptosis and alter lipid order of cell membranes in erythrocytes. Cell Biochemistry and Biophysics, 82, 747–766.
Rumeau, C., Nguyen, D. T., & Jankowski, R. (2016). How to assess olfactory performance with the Sniffin' Sticks test(®). European Annals of Otorhinolaryngology, Head and Neck Diseases, 133(3), 203–206.
Russo, A., Tellone, E., Barreca, D., Ficarra, S., & Laganà, G. (2022). Implication of COVID-19 on erythrocytes functionality: Red blood cell biochemical implications and morpho-functional aspects. International Journal of Molecular Sciences, 23(4), 2171.
Shamsundara, M., & Jayalakshmi, L. (2023). Anosmia – an effect of COVID-19 infection – review. Indian Journal of Otolaryngology and Head and Neck Surgery, 75(1), 815–821.
Soma, P., & Bester, J. (2022). Pathophysiological changes in erythrocytes contributing to complications of inflammation and coagulation in COVID-19. Frontiers in Physiology, 13, 899629.
Stufano, A., Isgrò, C., Palese, L. L., Caretta, P., De Maria, L., Lovreglio, P., & Sardanelli, A. M. (2023). Oxidative damage and post-COVID syndrome: A cross-sectional study in a cohort of Italian workers. International Journal of Molecular Sciences, 4(8), 7445.
Talavera, B., García-Azorín, D., Martínez-Pías, E., Trigo, J., Hernández-Pérez, I., Valle-Peñacoba, G., Simón-Campo, P., de Lera, M., Chavarría-Miranda, A., López-Sanz, C., Gutiérrez-Sánchez, M., Martínez-Velasco, E., Pedraza, M., Sierra, Á., Gómez-Vicente, B., Guerrero, Á., & Arenillas, J. F. (2020). Anosmia is associated with lower in-hospital mortality in COVID-19. Journal of the Neurological Sciences, 419, 117163.
Thakur, A., Sharma, V., Averbek, S., Liang, L., Pandya, N., Kumar, G., Cili, A., & Zhang, K. (2023). Immune landscape and redox imbalance during neurological disorders in COVID-19. Cell Death and Disease, 14(9), 593.
Tkachenko, A. (2024). Apoptosis and eryptosis: Similarities and differences. Apoptosis, 29(3–4), 482–502.
Tkachenko, A. S., Klochkov, V. K., Lesovoy, V. N., Myasoedov, V. V., Kavok, N. S., Onishchenko, A. I., Yefimova, S. L., & Posokhov, Y. O. (2020). Orally administered gadolinium orthovanadate GdVO(4):Eu(3+) nanoparticles do not affect the hydrophobic region of cell membranes of leukocytes. Wiener Medizinische Wochenschrift, 170(7–8), 189–195.
Tkachenko, A., Kot, Y., Prokopyuk, V., Onishchenko, A., Bondareva, A., Kapustnik, V., Chumachenko, T., Perskiy, Y., Butov, D., & Nakonechna, O. (2021). Food additive E407a stimulates eryptosis in a dose-dependent manner. Wiener Medizinische Wochenschrift, 172, 135–143.
Trentin, S., Oliveira, B. S. F., Borges, Y. F. F., & Rieder, C. R. M. (2022). Evaluation of the complete Sniffin sticks test versus its subtests in differentiating Parkinson's disease patients from healthy controls. Arquivos de Neuro-Psiquiatria, 80(9), 908–913.
Uysal, P., Yüksel, A., Durmus, S., Cuhadaroglu, Ç., Gelisgen, R., & Uzun, H. (2023). Can circulating oxidative stress-related biomarkers be used as an early prognostic marker for COVID-19? Frontiers in Medicine, 10, 1041115.
Vandersteen, C., Payne, M., Dumas, L.-É., Plonka, A., D'Andréa, G., Chirio, D., Demonchy, É., Risso, K., Robert, P., Fernandez, X., Askenazy-Gittard, F., Savoldelli, C., Guevara, N., Castillo, L., Manera, V., & Gros, A. (2022). What about using sniffin' sticks 12 items test to screen post-COVID-19 olfactory disorders? European Archives of Oto-Rhino-Laryngology, 279(7), 3477–3484.
Veenith, T., Martin, H., Le Breuilly, M., Whitehouse, T., Gao-Smith, F., Duggal, N., Lord, J. M., Mian, R., Sarphie, D., & Moss, P. (2022). High generation of reactive oxygen species from neutrophils in patients with severe COVID-19. Scientific Reports, 12(1), 10484.
Vollbracht, C., & Kraft, K. (2022). Oxidative stress and hyper-inflammation as major drivers of severe COVID-19 and long COVID: Implications for the benefit of high-dose intravenous vitamin C. Frontiers in Pharmacology, 13, 899198.
Wang, Y., Shi, P., Chen, Q., Huang, Z., Zou, D., Zhang, J., Gao, X., & Lin, Z. (2019). Mitochondrial ROS promote macrophage pyroptosis by inducing GSDMD oxidation. Journal of Molecular Cell Biology, 11(12), 1069–1082.
Yefimova, S., Klochkov, V., Kavok, N., Tkachenko, A., Onishchenko, A., Chumachenko, T., Dizge, N., Özdemir, S., Gonca, S., & Ocakoglu, K. (2023). Antimicrobial activity and cytotoxicity study of cerium oxide nanoparticles with two different sizes. Journal of Biomedical Materials Research – Part B Applied Biomaterials, 111(4), 872–880.
Yefimova, S., Onishchenko, A., Klochkov, V., Myasoedov, V., Kot, Y., Tryfonyuk, L., Knigavko, O., Maksimchuk, P., Kökbaş, U., Kalashnyk-Vakulenko, Y., Arkatov, A., Khanzhyn, V., Prokopyuk, V., Vyshnytska, I., & Tkachenko, A. (2023). Rare-earth orthovanadate nanoparticles trigger Ca(2+)-dependent eryptosis. Nanotechnology, 34(20), 205101.