

NARRATIVE REVIEW

PERIOPERATIVE MEDICINE

Adverse clinical impact and outcome of inflammation and oxidative stress: Are the antioxidant properties of vitamin C helpful?

Ernest Herbert, PhD, FIBMS¹, Dominique Fournier, MSc²

Author addresses;

1. Ernest Herbert, Erdomo LLP, 22-Appletree Gardens, Whitley Bay, UK;
2. Dominique Fournier, 585, 71e rue Est, Québec (QC), G1H 1L9, Canada. E-mail: erdomo@erdomo.co.uk

Correspondence: Ernest Herbert, E-mail: ehbertdoc@gmail.com; Phone: 07933268173

Abstract

Inflammation and the oxidative stress are two main notorious driving forces behind the disease progression, deterioration and eventually the death of the individuals concerned. When these two aggravating factors have been effectively addressed, then the disorders affecting people can be under control and relief for the treating clinician. The patients can experience an improvement in health-related quality of life, or better total remission. This review evaluates the relation between oxidative stress in critically ill patients, vitamin C intake as an antioxidant and severity of illness. It also highlights the implications of these two processes in major disease areas, such as cancer, intensive care, sepsis, cardiology, rheumatology, and the damaging outcomes of the imbalance between the production of ROS and antioxidants.

Key words: Health impact assessment; Outcome measures; Inflammation; Oxidative stress injury; Dose-response relationship, Immunologic

Citation: Herbert E, Fournier D. Adverse clinical impact and outcome of inflammation and oxidative stress: Are the antioxidant properties of vitamin C helpful? *Anaesth. pain intensive care* 2022;26(4):710-719.

DOI: [10.35975/apic.v26i5.1993](https://doi.org/10.35975/apic.v26i5.1993)

Received: March 29, 2022; **Reviewed:** July 21, 2022; **Accepted:** August 17, 2022

1. Background

In a living system, Professor Moses Gomberg from the University of Michigan, USA first postulated the existence of free radicals in 1900, including triphenylmethyl (Ph_3C^*) radical.¹ In another development, Prof. Rebeca Gerschman came up in 1954 with the cause of oxygen toxicity, and that this chemical element can form free radicals.²

Oxidative stress comes from the imbalance between free radicals and antioxidants in the body, potentially leading to cell and tissue damage.³ It is a natural occurrence and affects the aging process. There are lots of scientific evidence suggesting that long-term oxidative stress has a tremendous impact on many chronic conditions, such as cancer, diabetes, rheumatoid arthritis, heart disease, Alzheimer and Parkinson's disease to mention but a few.⁴⁻⁶

Inflammation is a crucial response to the human immune system, but is an evolutionary conservative process involving the activation of immune and non-immune cells that protect the host from bacteria, viruses, toxins and infections, by eliminating pathogens and enhancing tissue repair and recovery.⁷ The intensity and degree of inflammatory response, whether systemic or localized, metabolic and neuroendocrine changes can occur for conservation of metabolic energy and allocation of nutrients to the activated immune system concerned.⁸

Though there are common mechanisms between acute and chronic systemic inflammation, the acute condition looks different from the systemic one. Typically, the acute response is triggered during infection through interactions between pattern recognition receptors expressed on innate immune cells and conserved structures arising from evolution on pathogens, known as pathogen-associated molecular patterns (PAMPs).

Activation of the acute inflammatory response can also be linked to damage-associated molecular patterns (DAMPs), which are derived relational responding to physical and chemical stimuli, or toxic and metabolic alterations – termed “sterile” agents during the course of cellular stress or damage.⁹ The systemic chronic inflammation (SCI) usually increases with age, meaning that older individuals have higher levels of cytokines, chemokines and acute phase proteins in circulation, and also greater expression of genes linked to inflammation.^{10,11}

It has been established that circumstances in infancy can immensely impact metabolic and immune response later in life, which invariably step up to SCI in adulthood.¹² Several human cancers are associated with chronic inflammation induced by biological, chemical, and physical risk factors. Through epidemiological and experimental data, an association between inflammation and cancer has been confirmed by anti-inflammatory therapies, showing efficacy in prevention and treatment.¹³ There is a large variety of sources where inflammation comes from; it comprises microbial and viral infections, exposure to allergens, radiation, toxic chemicals, autoimmune and chronic diseases, consumption of alcohol, tobacco use, and a high-calorie diet.¹⁴ Generally, the longer the duration of inflammation, the higher is the risk of cancer.¹⁵ There is recruitment of mast cells and leucocytes to the site of DNA damage during inflammation, leading to a “respiratory burst” due to an enhanced uptake of oxygen, thus a local increased release and accumulation of ROS.

Considerable evidence recently has shown that ROS are involved in chronic inflammation and cancer. In addition to induce genomic instability, ROS can specifically activate some signaling pathways and influence the development of tumors via regulation of cellular proliferation, angiogenesis, and metastasis.¹⁶ Cancer growth is a complicated process, which includes cellular and molecular changes mediated by different endogenous and exogenous stimuli. It has been expressed that oxidative DNA damage is a major feature of carcinogenesis.¹⁷

Oxidative stress caused by the imbalance between production of free radicals/ROS and antioxidant defence systems can activate different transcription factors, and further affecting their transcriptional pathways.¹⁸ It also plays a crucial role in the occurrence, development, treatment and prognosis of leukemia.¹⁹ Since there are still many limitations for conventionally treating it and other forms of cancer, new therapeutic approaches using antioxidants such as vitamin C infusions at a high dose have to be explored and added as a standard protocol in clinical practice.¹⁹ Antioxidants are considered to be the solution to these problems – substances that neutralize free radicals.

A high-quality and approved high-dose intravenous vitamin C (7.5 g), otherwise known as Pascorbin® (the only therapy that received approval in Europe), a brand name that can provide a lasting solution to millions of patients around the world where inflammation and oxidative stress have rendered treatments ineffective or simply failed via conventional means.²⁰ Leading clinicians’ attitude must change to embrace this form of therapy. High-dose intravenous vitamin C is cost-effective, well tolerated, no side effects, and indicated for severe infections involving oncology, intensive care, sepsis in rheumatoid arthritis (RA) and COVID-19.²¹

Historically, physicians’ writing in Egypt from 3000 BC described patients who developed sepsis complications that have originated from traumatic wounds. The reports showed their understanding of sepsis refers to a systemic process with links to timing and systemic inflammation. With Hippocrates (460–370 BC), it was known in Ancient Greece as a condition causing “rotting” of the body.²² The Persian philosopher and physician Ibn Sina [Avicenna] (980–1037 AD) also outlined sepsis for the first time as a “decay” of blood and tissues accompanied by fever.²³ In contrast to ancient Egyptian and Greek colleagues, the modern-day physicians are provided with armamentarium of antibiotics, surgical procedures, and physiological devices in support delivered via intensive care that makes sepsis treatable if diagnosed in time.²⁴ However, there are an estimated 49 million cases of sepsis on a global scale and 11 million sepsis-related deaths annually. The most common cause of both in-hospital death and unplanned readmission among patients still remains associated with sepsis-related cases.^{25, 26}

For more than two years, the fight and dilemma in association with COVID-19 pandemic have paralyzed the global economy and jeopardized the capabilities of most healthcare systems. The capacity of intensive care units (ICUs) and limited resources have resulted in unprecedented bottlenecks for the management and containment of COVID-19 as well as millions of lives lost. Given the tantalizing circumstances that prevail with COVID-19, new treatment strategies including high-dose intravenous vitamin C are of crucial importance to be added to national protocols to mitigate against the notoriety of inflammation and oxidative stress in disease progression, deterioration, impaired quality of life and death among affected individuals.²¹

2. Interconnection of chronic inflammation and oxidative stress in oncology

Chronic inflammation and oxidative stress are interconnected pathological processes, which can result

Table 1: Biomarkers associated with oxidative stress and cancer pathology [Modified from Wigner et al. (2021); Neganova et al. (2021)].^{30, 83}

Gene	Enzyme	Gene Location
CAT	Catalase	11p13
COX-2	Prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2)	1q31.1
GPX3	Glutathione peroxidase 3	5q33.1
iNOS	Inducible nitric oxide synthase	17q11.2
NOX4	Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4	11q14.3
PON1	Serum paraoxonase/arylesterase 1	7q21.3
PON2	Serum paraoxonase/arylesterase 2	7q21.3
SOD1	Superoxide dismutase 1 (Cu-Zn)	21q22.11
SOD2	Superoxide dismutase 2/Manganese-dependent superoxide dismutase (MnSOD)	6q25

in cancer initiation and progression.²⁷ The increasing level of oxidative and inflammatory damage can lead to the severity of the cancer and corresponding tumor spread. On a global scale, cancer is the second cause of death after cardiovascular disorders according to the estimates of World Health Organization.²⁸ In 2020, the International Agency for Research on Cancer reported 19.3 million new cases and about 10 million cancer-related deaths associated with cancer worldwide. The prognosis by 2040 is that cancer cases in the world can rise to more than 28 million, which is an indication for clinicians to rather look for new treatment strategies than relying fully on conventional ones, particularly where those approaches failed or ineffective.²⁹

The major roles of oxidative stress and chronic inflammation have been confirmed from modern data, ranging from metastasis initiation to therapeutic resistance.³⁰ Disruption of the inherent antioxidant defence system caused by free radical overproduction could result in oxidative damage to various macromolecules, and in turn triggers genetic mutations that affect gene expression as well as modification of transcription factors.⁵ Furthermore, the production of pro-inflammatory cytokines, angiogenesis leading to the progression of tumors in bladder cancer patients could be catalyzed through excessive circulating oxygen species.³¹

3. Impact of inflammation and oxidative stress among patients including COVID-19 in ICU

Among critically ill trauma patients, there are numerous cellular processes involved such as lipid function, protein synthesis and inflammatory response, mainly due to increasing levels of oxidative stress.⁵ A significant

correlation exists between the fact of decreasing these levels by antioxidant substances, and better prognosis and outcomes in patients, including the improvement of coagulation, lipid profile, protein and inflammatory status.³²

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are prevalent among severely ill patients. Under normal circumstances, ROS/RNS are constantly being formed, but the critical condition can increase significantly their production. During critical illness, the pro-oxidant antioxidant balance is significantly functional because of their involvement in the pathogenesis of multiple organ failure. There is worsening oxidative stress associated with seriously ill patients admitted to ICU. Intake of antioxidant vitamins below 66% recommended dietary allowance (RDA) is linked to greater exacerbation of oxidative stress than those above. A reduced risk exists for worsening oxidative stress by 94%, with an antioxidant vitamin intake ranging from 66% to 100% as RDA.³³

Since COVID-19 outbreak, innumerable efforts are being made to understand the molecular mechanisms underlying the coronavirus disease 2019. The close relationship between this syndrome and sepsis has been highlighted, which indicates that most deaths in ICU can be because of SARS-CoV-2 infection triggering sepsis.³⁴ Severe COVID-19 patients exhibit some common features with sepsis, such as inflammation, elevated levels of systemic pro-inflammatory cytokines, immune dysregulation and microthrombosis.³⁵ In determining the severity of COVID-19, interconnection mechanisms such as inflammation and oxidative stress look extremely important. Severe COVID-19 illness has been affiliated with dysregulated innate immune response, an increased neutrophil-to-lymphocyte ratio level, and lymphopenia as well as cytokine storm.^{36, 37}

In the COVID-19 pandemic, the two critical processes involve assessing patients' needs in intensive care and

Table 2: Criteria for ICU admission and classification of COVID-19 (Modified from Daskaya et al. [2021])⁸⁴

Criteria	Mild	Common	Severe	Critically severe
	Mild clinical manifestations, no imaging performed	Fever, respiratory symptoms, pneumonia on X-ray or CT	a) Respiratory distress, RR \geq 30 breaths/min b) Oxygen saturation \leq 93% at rest c) Arterial partial pressure of oxygen (PaO ₂)/fraction of inspired O ₂ (FiO ₂) \leq 300 mmHg, 1 mmHg = 0.133 KPa	a) Respiratory failure b) Shock c) Combined with organ failure, need for ICU treatment
Oxygen saturation < 93% despite nasal oxygen support of 5 l/min and above				
Partial oxygen pressure < 60 mmHg despite nasal oxygen support of 5 l/min and above				
PaO ₂ /FiO ₂ < 300				
Bilateral/multilobar infiltration on chest radiography or computed tomography (CT) with clinical deterioration or increase in infiltration compared with previous imaging				
Hypotension (systolic blood pressure < 90 mmHg, drop in usual systolic blood pressure > 40 mmHg, mean arterial pressure < 65 mmHg) or vasopressor requirement				
Signs of hypoperfusion in the skin, lactate > 2 mmol/L, increase in SOFA score (> 2)				
Elevation in cardiac enzymes (troponin) or arrhythmia				
Kidney and liver abnormalities, thrombocytopenia				
Development of MAS				
<i>ICU: Intensive care unit; PaO₂/FiO₂: partial pressure of arterial oxygen/fraction of inspired oxygen; SOFA: Sequential Organ Failure Assessment; MAS: macrophage activation syndrome</i>				

predicting disease progression during their stay in the ICU. The most crucial point in the clinical trajectory for COVID-19 is to figure out patient deterioration and emergence of the need for ICU admission.³⁸ Though the criteria for the last can vary depending on the severity of infection and resources at disposal, the major ones are hypoxia (oxygen saturation <90% even with a support of 6 l/minute), hemodynamic instability needing vasoactive agents, presence of acute respiratory distress syndrome (ARDS), and necessity for mechanical ventilation.³⁹⁻⁴¹ Besides these conditions, some laboratory parameters

have also been considered, such as increased inflammatory or coagulation markers (D-dimer level > 1 ug/ml, elevated fibrin degradation products, prolonged activated partial thromboplastin time and prothrombin time, worsening lymphopenia, neutrophil count, high levels of troponin, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase.⁴²⁻⁴⁴

Markers of ROS generation and antioxidant activity have been associated with many critical illnesses. Severely ill patients can have increased levels of ROS as well as

decreased antioxidant defenses.³³ In seriously ill patients, long-term mortality is of vital importance, and one of the influencing factors is the frailty of the patient concerned. According to Ayala et al. (2021),⁴⁵ incrementing ROS levels, especially the superoxide anion in the first 24 h of ICU admission is a significant indicator of long-term mortality in non-obese elderly people without morbidity, which means that oxidative stress is the hallmark of the aging process. The main feature of frailty is oxidative stress, which is the brain behind the promotion of inflammation, particularly the increased CRP and IL-6 among these patients.¹⁰

As acute inflammation associated with critical illness is not totally resolved in some ICU survivors, persistent inflammation can be responsible for driving frailty-related outcome as disability and mortality, and the cornerstone of this inflammatory state can be basal oxidative stress ratio in affected individuals.⁴⁶

4. Vascular inflammation and oxidative stress in cardiovascular disorders

According to the latest data from the Global Burden of Disease Study, cardiovascular conditions are the leading cause of death and reducing the quality of life worldwide.⁴⁷ Both inflammation and oxidative stress are important players in chronic cardiovascular diseases.⁴⁸ Due to the near-ubiquitous presence of oxidative stress in this condition, a major association has been forged between it and the cardiovascular prognosis.

Inflammatory processes have a clear connection with vascular dysfunction and cardiovascular diseases, such as arterial hypertension, hypercholesterolemia, and coronary artery disease.⁴⁹ Both inflammation and oxidative stress are enhanced in chronic heart failure.⁵⁰ Mitochondrial dysfunction, a strong impairment in heart failure and a leading cause of oxidative stress, which in turn exerts damaging impact on cellular components with mitochondria inclusive, thus generating a chain reaction.⁵¹

Oxidative stress and inflammation have drawn some attention recently as significant pathophysiological factors of heart failure and potential influencing contributors to this syndrome progression.⁵² Both are closely connected with each other, whether in the acute phase after myocardial infarction or during chronic cardiac remodeling.⁵³ In dysfunctional cardiomyocytes, the increased levels of ROS get to severe oxidative DNA damage, and consequently stimulate nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP-1).⁵⁴ The expression of inflammatory mediators, such as TNF α and IL-6, does lead to develop a subclinical inflammatory state, which invariably contributes to

cardiac remodeling, and heart failure is the result of PARP-1 overactivation, and the impairment of several cellular metabolic pathways.⁵⁵ Overexpression of TNF α damages mitochondrial DNA, inhibits antioxidants, and alters the functional activities of mitochondrial complex III, thereby increasing ROS generation.⁵⁶

Based on history, the first proposed biomarker of heart failure was CRP, and sub-analysis of the Valsartan Heart Failure Trial (Val-HeFT) suggested that high-sensitivity CRP (hs-CRP) increasing levels are linked to features of more severe heart failure, mortality and corresponding morbidity.⁵⁷ Several elements contribute to the cause of oxidative stress in this syndrome, which promotes a local subclinical inflammatory response.

5. Clinical outcomes of high-dose intravenous vitamin C in combatting inflammation and oxidative stress

As it is well established that inflammation and oxidative stress can be treated effectively using an antioxidant, such as vitamin C infusion at a high dose, it is about time this therapy is enshrined in healthcare protocols to put an end to the dilemma of ineffective or failure in tackling these processes head-on.⁵ Since we, as humans, lost the vitamin C biosynthesis in the course of our evolution more than 60 million years ago due to the inactivation of an important enzyme, we have no other choice than to acquire it from external means unless we can reverse the evolutionary trend through technological know-how.⁵⁸

High-dose vitamin C (HDVC) is a safe, highly effective therapy, which is indispensable from intensive care, biochemical and inflammatory reaction kinetic viewpoints.⁵⁹ Mainstream clinicians should embrace this treatment, especially where conventional strategies have failed or partially effective. If HDVC is given to severely ill or patients with chronic conditions as early as possible after the injurious event, or before if feasible, it seems most effective.⁶⁰ In the critically ill, short-term use of intravenous vitamin C as a resuscitation drug could help to intervene at the earliest in the oxidative cascade as to optimize both micro- and macrocirculation and reduce cellular injury.⁶¹

Administering vitamin C intravenously produces substantially higher plasma levels compared with oral intake.⁶² Through intravenous (IV) administration straight into the bloodstream, it bypasses all the “control” mechanisms, which virtually removes the upper limit of achievable plasma concentration.⁶³ Several pharmacokinetic studies indicate that these levels are attained for a longer period of time, some suggest up to 12–16 hours.^{62, 64, 65}

Many studies have reported favorable results of HDVC in critically ill patients.⁶⁶⁻⁶⁸ The major health outcomes include reduction in respiratory morbidity and new organ failure, less mechanical ventilation for days and shorter length of stay in ICU and/or hospital. Because oxidative stress is emerging as a critical factor in COVID-19 physiopathology, antioxidants can be feasible agents as co-adjutant therapy to attenuate its disease severity.⁶⁹

The first scientist who experimented with intravenous vitamin C was Linus Pauling; he found that it may be a great therapeutic tool in the treatment of some chronic diseases, especially in supporting those with cancer.⁷⁰ The response of cancer cells to IV administration of vitamin C is different when compared to the body's normal cells.⁷¹ For instance, a malignant cell makes a rather rapid and sustained increase in hydrogen peroxide in response to vitamin C, resulting in a "rusting effect" known as oxidative damage. Normal or healthy cells do not react in this way to vitamin C. This phenomenon makes intravenous vitamin C (IVC) a unique and targeted treatment, unlike any other chemotherapy-like medication.⁷²

Many studies have demonstrated evidence of a good safety profile for IVC therapy with relatively few adverse events.^{73, 74} Vitamin C treatment in amounts of at least 10 g/day has been shown to improve quality of life, reduce pain and increase life expectancy, potentially survival time by several years, in a number of cases and clinical studies.⁷⁵ It is vital that each IV therapy is tailored to the needs of the individual patient and particular situation. Protocols can be adjusted based on how she/he is feeling, the type of chronic disease or cancer, conventional treatments currently being received, and what is financially feasible over time as well.

The therapy with high-dose vitamin C given by IV is highly beneficial and effective for those individuals under a greater than usual stress level, experience symptoms of extreme fatigue, require a boost to their immune system to fight acute and/or chronic viral and/or bacterial infections, who have damaged the skin because of the sun and surgery, and to help in mitigating side effects associated with chemo- and radiation therapy.⁷⁶

6. Conclusion

As a rule, all critically ill patients, the cellular processes will trigger the inflammation response and increase the oxidative stress. There is a strong association between inflammation and oxidative stress, which is evidently seen even including COVID-19.⁶⁹ Both are significant risk factors for cancer, intensive care, sepsis, cardiology and rheumatology, and post-acute COVID-19 syndrome or "long COVID." Clinical strategies for tackling these two processes during treatment are crucial for clinicians

to improve health-related quality of life (HRQoL), mitigate disease progression, ineffective therapy, deterioration and eventual death of affected persons.⁷⁷

Pathogenesis is driven by vitamin C deficiency, which aggravates the disease progression while its infusion at a high dose might be one way to dysfunctional epigenetic regulation.⁷⁸ Viruses activate NF- κ b (a protein that responds to infection), and vitamin C has been found to inhibit it, helping lower inflammation and their ability to replicate.⁷⁹ Emerging evidence suggests that high-dose vitamin C therapy may be useful to reduce COVID-19 symptoms, and it has been found to improve overall health outcomes.²¹

While expecting a new normal life after COVID-19, many millions of people will undoubtedly experience morbidity and mortality coupled with broadening of health inequalities, and trillions of economic losses worldwide.⁸⁰ As COVID-19 will remain for the foreseeable future just like flu, the global challenge is how to manage or contain it moving forward.⁸¹ This new reality includes vaccine with one-year efficacy and treating patients suffering from long- or post-COVID with a credible therapeutic option like an antioxidant (vitamin C infusion at a high dose). Therefore, we strongly urged a high-quality high-dose IVC of 7.5 g (otherwise known as Pascorbin[®], as a brand name), which is cost-effective; it can be explored and adopted by clinicians in their protocol similar to China's and India's.²⁰ Moreover, it will enhance HRQoL of patients, provide effective therapeutic assistance to physicians, and alleviate the mayhem associated with notorious processes far before the emergence of the pandemic.⁸²

Vitamin C infusion at a high dose is expected to be one of the challenging therapies to combat inflammation and oxidative stress in a critically ill individual. Antioxidant balance is of functional relevance during critical illness because it is involved in the pathogenesis of multi-organ failures. Alteration in endogenous substance levels with antioxidant capacity is related to a redox imbalance in critically ill patients. Therefore, intake of antioxidant vitamins should be carefully monitored to be as close as possible to RDA. In immune functions attacking joints, L-ascorbic acid could benefit patients with arthritis. An increasing body of research indicates that the vitamin may help relieve pain, reduce inflammation, protect against cartilage damage, development and progression caused by rheumatoid arthritis (RA) and osteoarthritis (OA). In addition, vitamin C appears to moderate the autoimmune response in RA and can prevent a worsening of the chronic condition. There is no denial that L-ascorbic acid works for everyone whether they have arthritis or not.

Vitamin C can scavenge free radicals, quenching ROS and organic peroxides. It impedes oxidation at high

concentrations (> 1000 mg/kg) by scavenging oxygen. Furthermore, L-ascorbic acid uses direct or cooperative regeneration of oxidized vitamin E, carotenoids and GSH to quench ROS.

Aging is a progressive or sequential change in anatomical tissues and organs, as well as in their structures and functions, which might lead to general debility and death. The human body produces antioxidants and free radical scavengers in order to inhibit or delay cell damage. Reinforcing the antioxidant defence system and/or counteracting the effects of immoderate ROS and nitrogen species is crucial and may reduce the progression of aging and chronic degenerative disorders. As a therapeutic approach involving antioxidants at the target site of oxidative stress, efficient concentrations that translate into clinical indications are required to boost confidence among healthcare professionals in using them to treat affected individuals.

7. Conflict of interest

The study did not require any grant, and no external or industry funding was involved.

8. Authors' contribution

Both authors took equal part in the concept, search and collection of data and manuscript writing.

9. References

- Gomberg M. An instance of trivalent carbon: triphenylmethyl. *J Am Chem Soc.* 1900;22(11):757-71. DOI: [10.1021/ja02049a006](https://doi.org/10.1021/ja02049a006)
- Gerschman R, Gilbert DL, Nye SW, Dwyer P, Fenn WO. Oxygen poisoning and x-irradiation: a mechanism in common. *Science.* 1954;119(3097):623-6. [PubMed] DOI: [10.1126/science.119.3097.623](https://doi.org/10.1126/science.119.3097.623)
- Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev.* 2017;2017:8416763. [PubMed] DOI: [10.1155/2017/8416763](https://doi.org/10.1155/2017/8416763)
- Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. *Clin Interv Aging.* 2018;13:757-72. [PubMed] DOI: [10.2147/CIA.S158513](https://doi.org/10.2147/CIA.S158513)
- Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L, Panzarini E, et al. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. *Front Physiol.* 2020;11:694. [PubMed] DOI: [10.3389/fphys.2020.00694](https://doi.org/10.3389/fphys.2020.00694)
- Garcia-Sanchez A, Miranda-Diaz AG, Cardona-Munoz EG. The role of oxidative stress in physiopathology and pharmacological treatment with pro- and antioxidant properties in chronic diseases. *Oxid Med Cell Longev.* 2020;2020:2082145. [PubMed] DOI: [10.1155/2020/2082145](https://doi.org/10.1155/2020/2082145)
- Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S3-23. [PubMed] DOI: [10.1016/j.jaci.2009.12.980](https://doi.org/10.1016/j.jaci.2009.12.980)
- Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med.* 2019;25(12):1822-32. [PubMed] DOI: [10.1038/s41591-019-0675-0](https://doi.org/10.1038/s41591-019-0675-0)
- Herwald H, Egesten A. On PAMPs and DAMPs. *J Innate Immun.* 2016;8(5):427-8. [PubMed] DOI: [10.1159/000448437](https://doi.org/10.1159/000448437)
- Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol.* 2018;15(9):505-22. [PubMed] DOI: [10.1038/s41569-018-0064-2](https://doi.org/10.1038/s41569-018-0064-2)
- Franceschi C, Garagnani P, Vitale G, Capri M, Salvioi S. Inflammaging and 'garb-aging'. *Trends Endocrinol Metab.* 2017;28(3):199-212. [PubMed] DOI: [10.1016/j.tem.2016.09.005](https://doi.org/10.1016/j.tem.2016.09.005)
- Singer K, Lumeng CN. The initiation of metabolic inflammation in childhood obesity. *The J Clin Invest.* 2017;127(1):65-73. [PubMed] DOI: [10.1172/JCI88882](https://doi.org/10.1172/JCI88882)
- Gonda TA, Tu S, Wang TC. Chronic inflammation, the tumor microenvironment and carcinogenesis. *Cell Cycle.* 2009;8(13):2005-13. [PubMed] DOI: [10.4161/cc.8.13.8985](https://doi.org/10.4161/cc.8.13.8985)
- Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res.* 2009;15(2):425-30. [PubMed] DOI: [10.1158/1078-0432.CCR-08-0149](https://doi.org/10.1158/1078-0432.CCR-08-0149)
- Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002;420(6917):860-7. [PubMed] DOI: [10.1038/nature01322](https://doi.org/10.1038/nature01322)
- Storz P. Reactive oxygen species in tumor progression. *Front Biosci.* 2005;10:1881-96. [PubMed] DOI: [10.2741/1667](https://doi.org/10.2741/1667)
- Mishra AP, Salehi B, Sharifi-Rad M, Pezzani R, Kobarfard F, Sharifi-Rad J, et al. Programmed cell death, from a cancer perspective: an overview. *Mol Diagn Ther.* 2018;22(3):281-95. [PubMed] DOI: [10.1007/s40291-018-0329-9](https://doi.org/10.1007/s40291-018-0329-9)
- Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. *World Allergy Organ J.* 2012;5(1):9-19. [PubMed] DOI: [10.1097/WOX.0b013e3182439613](https://doi.org/10.1097/WOX.0b013e3182439613)
- Dong C, Zhang NJ, Zhang LJ. Oxidative stress in leukemia and antioxidant treatment. *Chin Med J (Engl).* 2021;134(16):1897-907. [PubMed] DOI: [10.1097/CM9.0000000000001628](https://doi.org/10.1097/CM9.0000000000001628)
- Vollbracht C, Raithel M, Krick B, Kraft K, Hagel AF. Intravenous vitamin C in the treatment of allergies: an interim subgroup analysis of a long-term observational study. *J Int Med Res.* 2018;46(9):3640-55. [PubMed] DOI: [10.1177/0300060518777044](https://doi.org/10.1177/0300060518777044)
- Kwak SG, Choo YJ, Chang MC. The effectiveness of high-dose intravenous vitamin C for patients with coronavirus disease 2019: A systematic review and meta-analysis. *Complement Ther Med.* 2022;64:102797. [PubMed] DOI: [10.1016/j.ctim.2021.102797](https://doi.org/10.1016/j.ctim.2021.102797)
- Sygitowicz G, Sitkiewicz D. Organ damage in sepsis: molecular mechanisms. In: Neri V, Huang L, Li J, editors. *Infections and Sepsis Development*. IntechOpen; 2021. DOI: [10.5772/intechopen.98302](https://doi.org/10.5772/intechopen.98302)
- Botero JSH, Pérez MCF, editors. *The history of sepsis from Ancient Egypt to the XIX century*. London: IntechOpen; 2012. DOI: [10.5772/2958](https://doi.org/10.5772/2958)

24. Jarczак D, Kluge S, Nierhaus A. Sepsis-pathophysiology and therapeutic concepts. *Front Med (Lausanne)*. 2021;8:628302. [PubMed] DOI: [10.3389/fmed.2021.628302](https://doi.org/10.3389/fmed.2021.628302)
25. Angus DC, Bindman AB. Achieving diagnostic excellence for sepsis. *JAMA*. 2022;327(2):117-8. [PubMed] DOI: [10.1001/jama.2021.23916](https://doi.org/10.1001/jama.2021.23916)
26. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA*. 2014;312(1):90-2. [PubMed] DOI: [10.1001/jama.2014.5804](https://doi.org/10.1001/jama.2014.5804)
27. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med*. 2010;49(11):1603-16. [PubMed] DOI: [10.1016/j.freeradbiomed.2010.09.006](https://doi.org/10.1016/j.freeradbiomed.2010.09.006)
28. World Health Organization. Global health estimates: leading causes of death [Internet]. 2019. Available from: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghle-leading-causes-of-death>
29. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-49. [PubMed] DOI: [10.3322/caac.21660](https://doi.org/10.3322/caac.21660)
30. Neganova M, Liu J, Aleksandrova Y, Klochkov S, Fan R. Therapeutic influence on important targets associated with chronic inflammation and oxidative stress in cancer treatment. *Cancers*. 2021;13(23). [PubMed] DOI: [10.3390/cancers1323062](https://doi.org/10.3390/cancers1323062)
31. Yang D, Elnor SG, Bian ZM, Till GO, Petty HR, Elnor VM. Pro-inflammatory cytokines increase reactive oxygen species through mitochondria and NADPH oxidase in cultured RPE cells. *Exp Eye Res*. 2007;85(4):462-72. [PubMed] DOI: [10.1016/j.exer.2007.06.013](https://doi.org/10.1016/j.exer.2007.06.013)
32. Tan BL, Norhaizan ME, Liew WP, Sulaiman Rahman H. Antioxidant and oxidative stress: a mutual interplay in age-related diseases. *Front Pharmacol*. 2018;9:1162. [PubMed] DOI: [10.3389/fphar.2018.01162](https://doi.org/10.3389/fphar.2018.01162)
33. Abiles J, de la Cruz AP, Castano J, Rodriguez-Elvira M, Aguayo E, Moreno-Torres R, et al. Oxidative stress is increased in critically ill patients according to antioxidant vitamins intake, independent of severity: a cohort study. *Crit Care*. 2006;10(5):R146. [PubMed] DOI: [10.1186/cc5068](https://doi.org/10.1186/cc5068)
34. Ren C, Yao RQ, Ren D, Li JX, Li Y, Liu XY, et al. The clinical features and prognostic assessment of SARS-CoV-2 infection-induced sepsis among COVID-19 patients in Shenzhen, China. *Front Med (Lausanne)*. 2020;7:570853. [PubMed] DOI: [10.3389/fmed.2020.570853](https://doi.org/10.3389/fmed.2020.570853)
35. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J Exp Med*. 2020;217(6). [PubMed] DOI: [10.1084/jem.20200652](https://doi.org/10.1084/jem.20200652)
36. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell*. 2020;181(5):1036-45 e9. [PubMed] DOI: [10.1016/j.cell.2020.04.026](https://doi.org/10.1016/j.cell.2020.04.026)
37. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. *J Exp Med*. 2020;217(6). [PubMed] DOI: [10.1084/jem.20200678](https://doi.org/10.1084/jem.20200678)
38. Hajjar LA, Costa I, Rizk SI, Biselli B, Gomes BR, Bittar CS, et al. Intensive care management of patients with COVID-19: a practical approach. *Ann Intensive Care*. 2021;11(1):36. [PubMed] DOI: [10.1186/s13613-021-00820-w](https://doi.org/10.1186/s13613-021-00820-w)
39. Mansab F, Donnelly H, Kussner A, Neil J, Bhatti S, Goyal DK. Oxygen and mortality in COVID-19 pneumonia: a comparative analysis of supplemental oxygen policies and health outcomes across 26 countries. *Front Public Health*. 2021;9:580585. [PubMed] DOI: [10.3389/fpubh.2021.580585](https://doi.org/10.3389/fpubh.2021.580585)
40. Ohshimo S. Oxygen administration for patients with ARDS. *J Intensive Care*. 2021;9(1):17. [PubMed] DOI: [10.1186/s40560-021-00532-0](https://doi.org/10.1186/s40560-021-00532-0)
41. Akhavan AR, Habboushe JP, Gulati R, Iheagwara O, Watterson J, Thomas S, et al. Risk stratification of COVID-19 patients using ambulatory oxygen saturation in the emergency department. *West J Emerg Med*. 2020;21(6):5-14. [PubMed] DOI: [10.5811/westjem.2020.8.48701](https://doi.org/10.5811/westjem.2020.8.48701)
42. Abu-Farha M, Al-Sabah S, Hammad MM, Hebbar P, Channanath AM, John SE, et al. Prognostic genetic markers for thrombosis in COVID-19 patients: a focused analysis on D-dimer, homocysteine and thromboembolism. *Front Pharmacol*. 2020;11:587451. [PubMed] DOI: [10.3389/fphar.2020.587451](https://doi.org/10.3389/fphar.2020.587451)
43. Queisser KA, Mellema RA, Middleton EA, Portier I, Manne BK, Denorme F, et al. COVID-19 generates hyaluronan fragments that directly induce endothelial barrier dysfunction. *JCI Insight*. 2021;6(17). [PubMed] DOI: [10.1172/jci.insight.147472](https://doi.org/10.1172/jci.insight.147472)
44. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – a systematic review. *Life Sci*. 2020;254:117788. [PubMed] DOI: [10.1016/j.lfs.2020.117788](https://doi.org/10.1016/j.lfs.2020.117788)
45. Ayala JC, Grimaldo A, Sequeda-Castaneda LG, Aristizabal-Pachon AF, Morales L. Oxidative stress in ICU patients: ROS as mortality long-term predictor. *Antioxidants (Basel)*. 2021;10(12)1912. [PubMed] DOI: [10.3390/antiox10121912](https://doi.org/10.3390/antiox10121912)
46. Paul JA, Whittington RA, Baldwin MR. Critical illness and the frailty syndrome: mechanisms and potential therapeutic targets. *Anesth Analg*. 2020;130(6):1545-55. [PubMed] DOI: [10.1213/ANE.0000000000004792](https://doi.org/10.1213/ANE.0000000000004792)
47. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982-3021. [PubMed] DOI: [10.1016/j.jacc.2020.11.010](https://doi.org/10.1016/j.jacc.2020.11.010)
48. Steven S, Frenis K, Oelze M, Kalinovic S, Kuntic M, Bayo Jimenez MT, et al. Vascular inflammation and oxidative stress: major triggers for cardiovascular disease. *Oxid Med Cell Longev*. 2019;2019:7092151. [PubMed] DOI: [10.1155/2019/7092151](https://doi.org/10.1155/2019/7092151)
49. Ruparelina N, Chai JT, Fisher EA, Choudhury RP. Inflammatory processes in cardiovascular disease: a route to targeted therapies. *Nat Rev Cardiol*. 2017;14(3):133-44. [PubMed] DOI: [10.1038/nrcardio.2016.185](https://doi.org/10.1038/nrcardio.2016.185)
50. Ayoub KF, Pothineni NVK, Rutland J, Ding Z, Mehta JL. Immunity, inflammation, and oxidative stress in heart failure:

- emerging molecular targets. *Cardiovasc Drugs Ther.* 2017;31(5-6):593-608. [PubMed] DOI: [10.1007/s10557-017-6752-z](https://doi.org/10.1007/s10557-017-6752-z)
51. Zhou B, Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. *J Clin Invest.* 2018;128(9):3716-26. [PubMed] DOI: [10.1172/JCI120849](https://doi.org/10.1172/JCI120849)
 52. Aimo A, Castiglione V, Borrelli C, Saccaro LF, Franzini M, Masi S, et al. Oxidative stress and inflammation in the evolution of heart failure: from pathophysiology to therapeutic strategies. *Eur J Prev Cardiol.* 2020;27(5):494-510. [PubMed] DOI: [10.1177/2047487319870344](https://doi.org/10.1177/2047487319870344)
 53. Grieve DJ, Byrne JA, Cave AC, Shah AM. Role of oxidative stress in cardiac remodelling after myocardial infarction. *Heart Lung Circ.* 2004;13(2):132-8. [PubMed] DOI: [10.1016/j.hlc.2004.02.008](https://doi.org/10.1016/j.hlc.2004.02.008)
 54. Wang C, Xu W, Zhang Y, Zhang F, Huang K. PARP1 promote autophagy in cardiomyocytes via modulating FoxO3a transcription. *Cell Death Dis.* 2018;9(11):1047. [PubMed] DOI: [10.1038/s41419-018-1108-6](https://doi.org/10.1038/s41419-018-1108-6)
 55. Pacher P, Szabo C. Role of poly(ADP-ribose) polymerase 1 (PARP-1) in cardiovascular diseases: the therapeutic potential of PARP inhibitors. *Cardiovasc Drug Rev.* 2007;25(3):235-60. [PubMed] DOI: [10.1111/j.1527-3466.2007.00018.x](https://doi.org/10.1111/j.1527-3466.2007.00018.x)
 56. Morgan MJ, Liu ZG. Reactive oxygen species in TNF α -induced signaling and cell death. *Mol Cells.* 2010;30(1):1-12. [PubMed] DOI: [10.1007/s10059-010-0105-0](https://doi.org/10.1007/s10059-010-0105-0)
 57. Anand IS, Rector TS, Kuskowski M, Snider J, Cohn JN. Prognostic value of soluble ST2 in the Valsartan Heart Failure Trial. *Circ Heart Fail.* 2014;7(3):418-26. [PubMed] DOI: [10.1161/CIRCHEARTFAILURE.113.001036](https://doi.org/10.1161/CIRCHEARTFAILURE.113.001036)
 58. Hornung TC, Biesalski HK. Glut-1 explains the evolutionary advantage of the loss of endogenous vitamin C-synthesis: the electron transfer hypothesis. *Evol Med Public Health.* 2019;2019(1):221-31. [PubMed] DOI: [10.1093/emph/eoz024](https://doi.org/10.1093/emph/eoz024)
 59. Schoenfeld JD, Sibenaller ZA, Mapuskar KA, Wagner BA, Cramer-Morales KL, Furqan M, et al. O₂(-) and H₂O₂-mediated disruption of Fe metabolism causes the differential susceptibility of NSCLC and GBM cancer cells to pharmacological ascorbate. *Cancer Cell.* 2017;31(4):487-500.e8. [PubMed] DOI: [10.1016/j.ccell.2017.02.018](https://doi.org/10.1016/j.ccell.2017.02.018)
 60. Hemila H. Vitamin C and infections. *Nutrients.* 2017;9(4). [PubMed] DOI: [10.3390/nu9040339](https://doi.org/10.3390/nu9040339)
 61. Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. *Crit Care.* 2014;18(4):460. [PubMed] DOI: [10.1186/s13054-014-0460-x](https://doi.org/10.1186/s13054-014-0460-x)
 62. Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med.* 2004;140(7):533-7. [PubMed] DOI: [10.7326/0003-4819-140-7-200404060-00010](https://doi.org/10.7326/0003-4819-140-7-200404060-00010)
 63. Mikirova N, Casciari J, Riordan N, Hunninghake R. Clinical experience with intravenous administration of ascorbic acid: achievable levels in blood for different states of inflammation and disease in cancer patients. *J Transl Med.* 2013;11:191. [PubMed] DOI: [10.1186/1479-5876-11-191](https://doi.org/10.1186/1479-5876-11-191)
 64. Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of vitamin C. *Nutrients.* 2019;11(10):2412. [PubMed] DOI: [10.3390/nu11102412](https://doi.org/10.3390/nu11102412)
 65. Duconge J, Miranda-Massari JR, Gonzalez MJ, Jackson JA, Warnock W, Riordan NH. Pharmacokinetics of vitamin C: insights into the oral and intravenous administration of ascorbate. *P R Health Sci J.* 2008;27(1):7-19. [PubMed]
 66. Zhang M, Jatava DF. Vitamin C supplementation in the critically ill: a systematic review and meta-analysis. *SAGE Open Med.* 2018;6:2050312118807615. [PubMed] DOI: [10.1177/2050312118807615](https://doi.org/10.1177/2050312118807615)
 67. Mathew ST, Patel J, Joseph S. Atrial fibrillation: mechanistic insights and treatment options. *Eur J Intern Med.* 2009;20(7):672-81. [PubMed] DOI: [10.1016/j.ejim.2009.07.011](https://doi.org/10.1016/j.ejim.2009.07.011)
 68. Shrestha DB, Budhathoki P, Sedhai YR, Mandal SK, Shikhrakar S, Karki S, et al. Vitamin C in critically ill patients: an updated systematic review and meta-analysis. *Nutrients.* 2021;13(10). [PubMed] DOI: [10.3390/nu13103564](https://doi.org/10.3390/nu13103564)
 69. Beltran-Garcia J, Osca-Verdegal R, Pallardo FV, Ferreres J, Rodriguez M, Mulet S, et al. Oxidative stress and inflammation in COVID-19-associated sepsis: the potential role of anti-oxidant therapy in avoiding disease progression. *Antioxidants (Basel).* 2020;9(10). [PubMed] DOI: [10.3390/antiox9100936](https://doi.org/10.3390/antiox9100936)
 70. Frei B, Lawson S. Vitamin C and cancer revisited. *Proc Natl Acad Sci U S A.* 2008;105(32):11037-8. [PubMed] DOI: [10.1073/pnas.0806433105](https://doi.org/10.1073/pnas.0806433105)
 71. Carr AC, Cook J. Intravenous vitamin C for cancer therapy – identifying the current gaps in our knowledge. *Front Physiol.* 2018;9:1182. [PubMed] DOI: [10.3389/fphys.2018.01182](https://doi.org/10.3389/fphys.2018.01182)
 72. Bottger F, Valles-Marti A, Cahn L, Jimenez CR. High-dose intravenous vitamin C, a promising multi-targeting agent in the treatment of cancer. *J Exp Clin Cancer Res.* 2021;40(1):343. [PubMed] DOI: [10.1186/s13046-021-02134-y](https://doi.org/10.1186/s13046-021-02134-y)
 73. Honore PM, Spapen HD, Marik P, Boer W, Oudemans-van Straaten H. Dosing vitamin C in critically ill patients with special attention to renal replacement therapy: a narrative review. *Ann Intensive Care.* 2020;10(1):23. [PubMed] DOI: [10.1186/s13613-020-0640-6](https://doi.org/10.1186/s13613-020-0640-6)
 74. Klimant E, Wright H, Rubin D, Seely D, Markman M. Intravenous vitamin C in the supportive care of cancer patients: a review and rational approach. *Curr Oncol.* 2018;25(2):139-48. [PubMed] DOI: [10.3747/co.25.3790](https://doi.org/10.3747/co.25.3790)
 75. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci U S A.* 1978;75(9):4538-42. [PubMed] DOI: [10.1073/pnas.75.9.4538](https://doi.org/10.1073/pnas.75.9.4538)
 76. Suh SY, Bae WK, Ahn HY, Choi SE, Jung GC, Yeom CH. Intravenous vitamin C administration reduces fatigue in office workers: a double-blind randomized controlled trial. *Nutr J.* 2012;11:7. [PubMed] DOI: [10.1186/1475-2891-11-7](https://doi.org/10.1186/1475-2891-11-7)
 77. Munguia L, Rubio-Gayosso I, Ramirez-Sanchez I, Ortiz A, Hidalgo I, Gonzalez C, et al. High flavonoid cocoa supplement ameliorates plasma oxidative stress and inflammation levels while improving mobility and quality of life in older subjects: a double-blind randomized clinical trial. *J Gerontol A Biol Sci Med Sci.* 2019;74(10):1620-7. [PubMed] DOI: [10.1093/gerona/glz107](https://doi.org/10.1093/gerona/glz107)
 78. Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in disease prevention and cure: an overview. *Indian J Clin*

- Biochem. 2013;28(4):314-28. [PubMed] DOI: [10.1007/s12291-013-0375-3](https://doi.org/10.1007/s12291-013-0375-3)
79. Liu T, Zhang L, Joo D, Sun SC. NF-kappaB signaling in inflammation. *Signal Transduct Target Ther.* 2017;2. [PubMed] DOI: [10.1038/sigtrans.2017.23](https://doi.org/10.1038/sigtrans.2017.23)
 80. Bamba C, Riordan R, Ford J, Matthews F. The COVID-19 pandemic and health inequalities. *J Epidemiol Community Health.* 2020;74(11):964-8. [PubMed] DOI: [10.1136/jech-2020-214401](https://doi.org/10.1136/jech-2020-214401)
 81. Bertolino L, Vitrone M, Durante-Mangoni E. Does this patient have COVID-19? A practical guide for the internist. *Intern Emerg Med.* 2020;15(5):791-800. [PubMed] DOI: [10.1007/s11739-020-02377-1](https://doi.org/10.1007/s11739-020-02377-1)
 82. Almhdawi KA, Alrabbaie H, Arabiat A, Alhammouri AT, Hamadneh M, Obeidat D, et al. Physicians' health-related quality of life and its associated factors during COVID-19 pandemic in Jordan: a cross-sectional study. *Eval Health Prof.* 2022 Mar;45(1):76-85. [PubMed] DOI: [10.1177/01632787211068899](https://doi.org/10.1177/01632787211068899)
 83. Wigner P, Grebowski R, Bijak M, Saluk-Bijak J, Szemraj J. The interplay between oxidative stress, inflammation and angiogenesis in bladder cancer development. *Int J Mol Sci.* 2021;22(9). [PubMed] DOI: [10.3390/ijms22094483](https://doi.org/10.3390/ijms22094483)
 84. Daskaya H, Yilmaz S, Uysal H, Calim M, Sumbul B, Yurtsever I, et al. Usefulness of oxidative stress marker evaluation at admission to the intensive care unit in patients with COVID-19. *J Int Med Res.* 2021;49(7):3000605211027733. [PubMed] DOI: [10.1177/03000605211027733](https://doi.org/10.1177/03000605211027733)