WHITE PAPER

COVID-19: A focus on metabolic profiles and biomarker patterns

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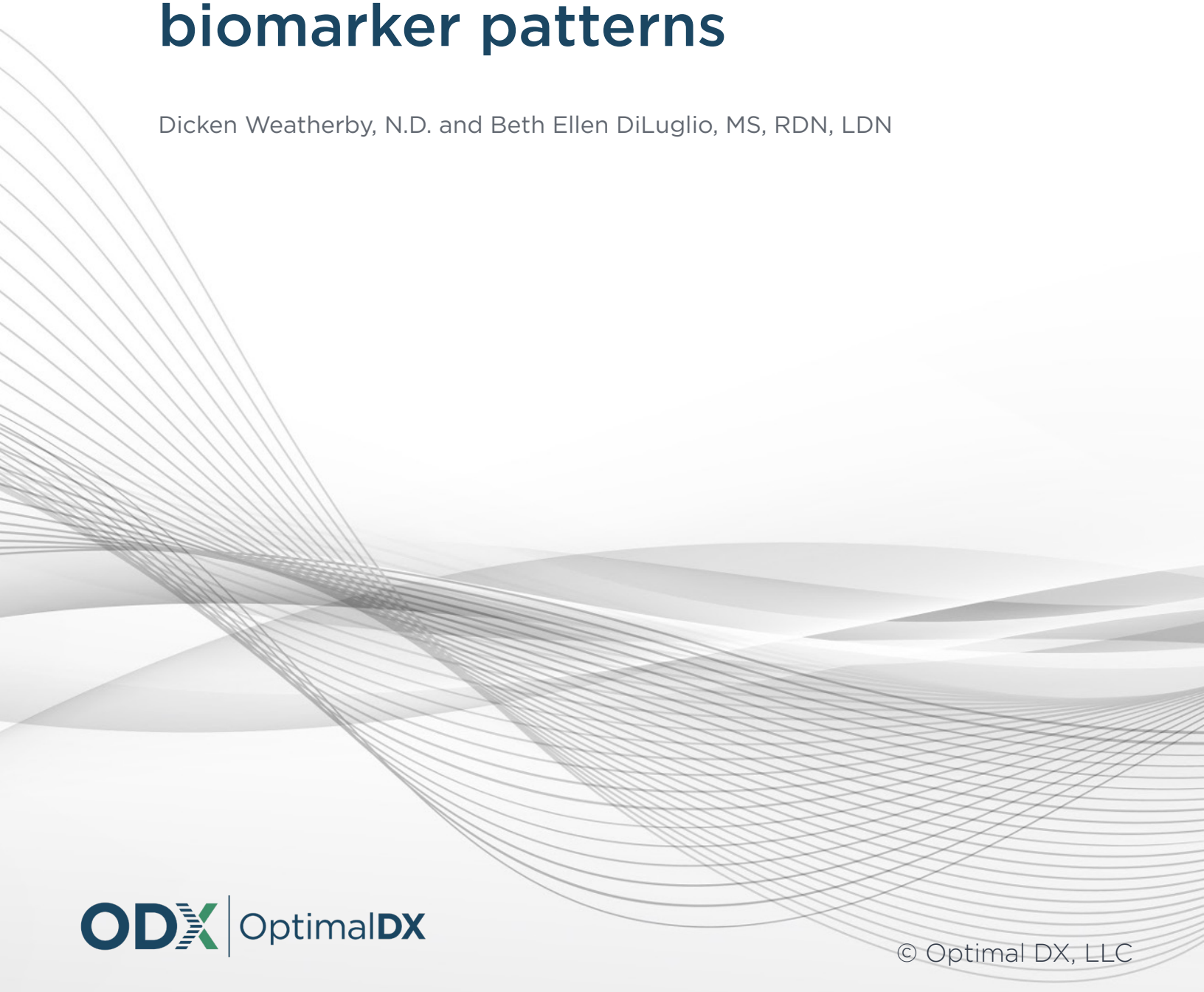

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Abstract

Coronavirus disease 2019 (COVID-19) is a highly contagious, potentially fatal viral infection caused by the severe respiratory syndrome coronavirus-2 (SARS-CoV-2 virus). As of June 22, 2021, there were 178,932,193 cases and 3,876,081 deaths worldwide caused by the COVID-19 pandemic.

Individuals most susceptible to severe disease are those who are older, and those with underlying chronic disorders such as cardiovascular disease, diabetes, hypertension, obesity, cancer, respiratory compromise, and lung, liver, or kidney disease. [1] [2] Notably, these same disorders are characterized by chronic inflammation, nutrient imbalances, and an unhealthy lifestyle.

Oxidative stress, inflammation, and immune activation are hallmark findings in COVID-19 and are reflected in routine blood chemistry results. Key markers to evaluate include IL-6, IL-10, hs-CRP, liver enzymes, alkaline phosphatase, ferritin, albumin, fasting glucose, hemoglobin A1C, LDH, omega-3 index, CBC with differential, neutrophil/lymphocyte ratio, vitamin C, vitamin D, selenium, and zinc.

Over time, emerging biomarker patterns provided clinicians with insight into the severity of metabolic dysfunction caused by the virus and the body's immune response to it. These patterns can be used to help predict the need for intensive care and evaluate the risk of morbidity and mortality. They can also help provide guidance for targeted nutrition support and intervention. A functional blood chemistry analysis helps identify biomarkers outside the optimal range as well as patterns that assist in creating a comprehensive assessment of COVID-19 and its severity.

Introduction

COVID-19 is an ongoing threat worldwide, especially to those most susceptible due to compromised immune function, suboptimal respiratory status, or comorbid conditions. Hygienic measures, social distancing, and vaccine initiatives can help reduce the spread of COVID-19. However, optimizing the health of the potential host is a prudent measure to not only reduce risk of severe COVID-19, but reduce the risk and severity of treatable comorbidities.

Early assessment of blood chemistry markers can identify metabolic imbalances and nutrient insufficiencies that worsen COVID-19 prognosis. This provides the clinician with an expanded toolbox to fight a potentially devastating disease. It also provides guidance for individuals to better protect themselves against this modern day pandemic.

This review will focus on biomarker characteristics associated with COVID-19 and:

- COVID-19 risk factors
- Common comorbidities
- Related blood chemistry biomarkers and patterns
- Optimal biomarker ranges for reducing metabolic disease and COVID-19 severity
- Nutrition intervention overview
- Optimal takeaways for the clinician

COVID-19 risk

Early in the COVID-19 pandemic, a systemic review and meta-analysis of studies from January 1 to April 6, 2020, revealed that severe disease occurs in approximately 23% of infected patients, who in turn had a mortality rate of ~6%.

Severity was statistically significantly higher in those with immunosuppression, malignancy, and chronic diseases such as diabetes, heart disease, hypertension, lung, liver, and kidney disease. Inflammatory markers were significantly higher in those with severe disease as well.[3]

In addition to the major chronic diseases, additional risk factors for severe disease include advanced age, darker skin, sickle cell disease, neurological disease, oxidative stress, pregnancy, exposure to pollution, smoking, excess alcohol, steroid use, medication use, lack of sunlight exposure, disadvantaged social or economic status, and vegetarian diet low in B12, zinc, copper, iron, selenium, vitamin D, and omega-3 EPA + DHA.[4 5 6 7 8 9 10 11 12 13 14]

Fatality rate for those with no comorbidities was less than 1% and increased with chronic disease to 10.5% with cardiovascular disease.[15]

Integrative practitioners recognize that many of the COVID-19 risk factors are modifiable risk factors that can be addressed and often resolved with lifestyle changes, nutrition intervention, and targeted supplementation.

A healthy, whole-food, plant-based diet rich in micronutrients, antioxidants, high-quality protein, and naturally occurring anti-inflammatory compounds can help reduce the risk and severity of common chronic diseases that increase risk of severe COVID-19. Stress management and minimization of toxin exposure is also crucial in promoting health instead of disease.

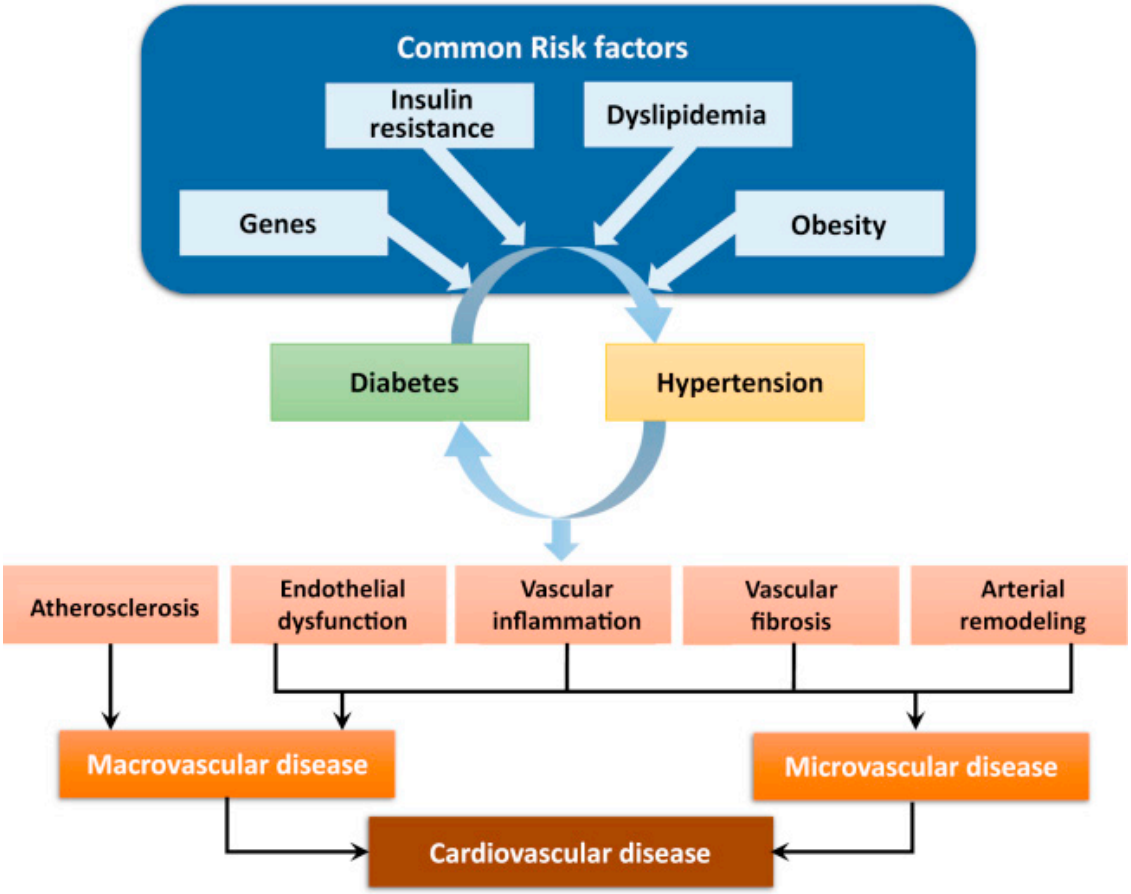
Ensuring optimal nutrition and health status must be a priority in the global approach to COVID-19 treatment and prevention as well.

Comorbidities and COVID-19

Many of the risk factors observed in more severe COVID-19 overlap those for chronic metabolic diseases and include: [16 17 18 19 20 21 22 23 24 25 26 27 28]

- Age
- Cardiovascular disease
- Dysbiosis
- Hyperglycemia
- Hypertension
- Immune system activation
- Inflammation
- Kidney disease
- Lack of fresh fruits and vegetables in the diet
- Obesity, especially abdominal/central obesity
- Oxidative stress
- Poverty
- Sedentary lifestyle, physical inactivity (also contribute to obesity)
- Toxin and pollution exposure
- Unhealthy Western-style diet

Risk factors and characteristics of common disorders that increase risk of severe COVID-19



Vascular processes whereby diabetes and hypertension predispose to cardiovascular disease. Common risk factors promote diabetes and hypertension, which are associated with atherosclerosis, vascular inflammation, endothelial dysfunction, and structural remodelling, which lead to macrovascular and microvascular disease. Vascular damage and endothelial dysfunction is amplified when diabetes and hypertension coexist.

Source: Petrie, John R et al. "Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms." The Canadian journal of cardiology vol. 34,5 (2018): 575-584. doi:10.1016/j.cjca.2017.12.005 [R] This is an open access article under the CC BY license ([R]).

COVID-19 blood chemistry biomarker patterns

Biomarker patterns can help differentiate between severe and moderate COVID-19 and help determine prognosis.

Literature review reveals that COVID-19 patients with severe disease had significantly lower levels of lymphocytes, natural killer cells, B cells, and CD4+ and CD8+ T cells compared to those with mild or moderate disease. Increases in basophils and neutrophils reflected increased severity in some individuals as well.[29]

A significant correlation was found between mortality and[30]

- Increased WBC, neutrophil count, AST, ALT, creatinine, LDH, procalcitonin, CRP
- Decreased albumin and lymphocyte count

Additional patterns emerged that reflect a more severe COVID-19 presentation

Advanced COVID-19 pattern[31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50]	
Elevated	**Decreased**
• AST and ALT • BUN and creatinine may be elevated or decreased • C-reactive protein • Creatine kinase • Cytokines IL-6, IL-8, IL-10, IL-2R, IL-1β, and TNF-α • D-dimer • Erythrocyte sedimentation rate (ESR) • Ferritin • Fibrinogen • Glucose • Hemoglobin A1C, especially greater than 7.5% • LDH • Neutrophils • NLR Neutrophil to lymphocyte ratio • Procalcitonin • RDW-CV • Thrombin time • Total bilirubin	• Albumin • Basophils • Eosinophils • Lymphocytes • Monocytes • Omega-3 index • Prealbumin • Selenium • Superoxide dismutase (SOD) • Total protein • Total white blood cells • Vitamin C • Vitamin D • Zinc

Specific biomarker range clues for COVID-19

Biomarker	Relevant ranges	Background
Albumin	Below 3.5 mg/d associated with severe COVID-19 [51 52 53 54] 2.9 mg/dL Predicted ICU admission and 1.8 mg/dL or lower predicted mortality from COVID-19[55]	Albumin is a visceral carrier protein, It decreases with inflammation, critical illness, and severe malnutrition. Is a prognostic indicator for progression to pneumonia.[56]
LDH	388 u/L (6.48 ukat/L) Associated with positive PCR test for COVID-19[57] 731 U/L (12.2 ukat/L) and above predicted mortality from COVID-19[58]	Lactate dehydrogenase enzyme is found in many tissues, an increase in serum levels is associated with tissue and organ damage, including lung damage.
Hemoglobin A1C	HbA1C of greater than 7.5%	Elevated HbA1c is associated with hypercoagulation, inflammation, and high mortality[59]

Biomarker	Relevant ranges	Background
NLR	2.425 cutoff for COVID-19 [60] 3.0 Associated with clinical improvement[61] 3.27 Predicted severe disease and 5.72 predicted mortality[62]	Neutrophil/lymphocyte ratio (NLR) is a marker of inflammation. Elevated levels are associated with critical illness and more severe COVID-19.
Omega-3 Index (O3I)	An O3I of 5.7% or greater was associated with a 75% reduced risk of dying with COVID-19 than those with an O3I below 5.7%.[63] An O3I above 8% is considered optimal.	The O3I reflects percentage of EPA + DHA in red blood cell membranes, and mirrors levels in tissue. An optimal O3I is associated with reduced inflammation and chronic disease risk.
Vitamin C	0.19 mg/dL (11 umol/L) is deficient and 0.41 mg/dL (23 umol/L) insufficient[64] 1.3-4 mg/dL (73.8-227 umol/L) can be achieved with dietary intake[65]	Vitamin C is an important antioxidant that also exerts anti-inflammatory, anti-viral, and immune-modulating effects. [66] It protects epithelium, stimulates lymphocyte proliferation, reduces proinflammatory cytokines, and can reduce risk of ARDS. Critically ill may need 20-30 times more vitamin C.[67]
Vitamin D 25(OH)D	10 ng/mL (25 nmol/L) is severe deficiency 11.1 ng/mL (27.7 nmol/L) more likely to test positive for COVID-19[68] 20 ng/mL (50 nmol/L) insufficient[69] 30 ng/mL (75 nmol/L) reduced severity of COVID-19[70] 40-60 ng/mL (100-150 nmol/L) reduced risk of respiratory infection, COVID-19.[71] 50-70 ng/mL (125-175 nmol/L) reflects robust serum Vitamin D for disease prevention[72]	Vitamin D is converted in the body to an active hormone with anti-inflammatory, antifibrotic, antioxidant, and immune-modulating functions. [73] COVID-19 patients with serum 25(OH)D below 20 ng/mL (50 nmol/L) were more likely to be critically ill versus COVID-19 patients with serum levels above 20 ng/mL who were more likely to be asymptomatic. [74]
Selenium	Below 100 ug/L (1.27 umol/L) is indication for supplementation[75]	Selenium is a trace mineral required for innate immunity, normal T cell function, antibody production, and antioxidant, anti-inflammatory, and antimicrobial actions. [76]
Zinc	Below 60 ug/dL (9.2 umol/L) deficient,[77] associated with loss of sense of smell[78] Below 70 ug/dL (10.7 umol/L) increased risk of pneumonia in elderly[79] 80-120 ug/dL (12.24-18.4 umol/L) is common hospital reference range[80]	Zinc is a trace mineral required for antioxidant systems, immunity, activation of T-lymphocytes, and inhibition of viral replication. [81] Both zinc deficiency and excess can compromise immunity. [82]

Research identifies blood chemistry biomarkers and patterns

Several meta-analyses confirm biomarker patterns for severe COVID-19:

- Meta-analysis of data for 4663 COVID-19 patients indicated that elevated LDH and elevated CRP (the most prevalent finding), and decreased lymphocytes were associated significantly with severity of COVID-19. Elevations in erythrocyte sedimentation rate (ESR) and IL-6, and decreased levels of albumin and eosinophils were also associated with severe disease.[83]
- A 20-study meta-analysis confirmed that those with more severe disease displayed higher WBCs, ALT, AST, total bilirubin, CRP, procalcitonin, LDH, creatine kinase, and D-dimer and lower albumin values than less severe COVID-19. [84]
- Meta-analysis of 10 studies indicated that trends in blood chemistry marker patterns associated with COVID-19 include: [85]
    - Increased ALT, AST, total bilirubin, creatine kinase, LDH, and BUN and creatinine may be elevated or decreased
    - Decreased albumin
        - Changes in albumin may also be important to monitoring progression or improvement of COVID-19
- A 40-study meta-analysis of 5872 COVID-19 patients revealed that severe disease was associated with significantly: [86]
    - Lower: platelet count, lymphocyte count
    - Higher: CRP, LDH, WBC, procalcitonin, D-dimer, ALT, AST, creatinine, and average age
    - Researchers note that the higher levels of LDH, ALT, AST, and creatinine in the more severe or fatal groups likely represent more severe heart, liver, and kidney damage.
- Meta-analysis of 2401 patients found that of those who died of COVID-19:[87]
    - 66.6% were male
    - 38.6% had hypertension
    - 17.5% had chronic cardiovascular disease
    - 22.2% had diabetes
    - 15.6% had chronic cerebrovascular disease
    - Acute respiratory distress and shock were the most common complication
    - Decreased platelets and increased CRP and LDH were associated with mortality
- Meta-analysis of 13 studies, comprising 3027 cases of SARS-CoV-2 infection, revealed laboratory characteristics of disease progression: [88]

AST	greater than 40 U/L
Creatinine	1.5 mg/dL (133 umol/L) or greater
Hs-troponin	greater than 28 pg/mL
Procalcitonin	greater than 0.5 ng/mL
Lactate dehydrogenase	greater than 245 U/L
D-dimer	greater than 0.5 mg/L
WBC total	greater than 4×10^9/L

In a retrospective study of 2623 hospitalized adult COVID-19 patients, distinct progression of disease was reflected in blood chemistry biomarkers.[89]

		Non-critically ill	Critically ill	Death	P
ALT (median (IQR))	At admission test	21.00 (14.00, 37.00)	25.00 (15.00, 40.00)	28.00 (18.00, 43.00)	<0.001
	At second test	24.00 (16.00, 42.00)	28.00 (17.00, 46.00)	27.00 (17.00, 44.00)	<0.001
AST (median (IQR))	At admission test	24.00 (18.00, 34.00)	33.00 (23.00, 49.00)	41.00 (28.25, 60.50)	<0.001
	At second test	21.00 (16.00, 29.00)	25.00 (18.00, 37.00)	35.00 (24.00, 53.50)	<0.001
GGT (median (IQR))	At admission test	27.00 (18.00, 46.00)	37.00 (22.00, 70.00)	39.00 (25.00, 70.00)	<0.001
	At second test	29.00 (19.00, 49.00)	38.00 (22.00, 78.00)	43.00 (26.00, 75.50)	<0.001
ALT/AST (median (IQR))	At admission test	0.71 (0.56, 0.93)	0.67 (0.60, 1.08)	0.60 (0.53, 0.77)	0.558
	At second test	0.97 (0.66, 1.38)	1.05 (0.70, 1.33)	0.56 (0.56, 0.56)	0.455
TBIL (median (IQR))	At admission test	8.30 (6.20, 11.40)	10.00 (7.30, 14.50)	12.20 (8.60, 17.60)	<0.001
	At second test	8.20 (6.30, 11.30)	10.50 (7.62, 14.57)	13.70 (9.35, 20.30)	<0.001
DBIL (median (IQR))	At admission test	3.60 (2.60, 4.80)	4.70 (3.45, 6.70)	5.85 (4.20, 9.22)	<0.001
	At second test	3.40 (2.60, 4.60)	4.70 (3.50, 7.00)	6.90 (4.50, 11.00)	<0.001
IBIL (median (IQR))	At admission test	4.70 (3.40, 6.70)	5.10 (3.58, 7.73)	5.75 (4.10, 8.33)	<0.001
	At second test	4.80 (3.60, 6.70)	5.50 (3.90, 7.80)	6.20 (3.88, 9.62)	<0.001

Data are shown as median (IQR). P values were calculated by Kruskal-Wallis rank-sum test. The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), AST/ALT, total bilirubin (TBil), direct bilirubin (DBil), and indirect Bilirubin (IBiL) on admission and after admission were compared among non-critically ill, critically ill, and death groups. If the values of biomarkers were below the lower reference limit, half of the lower reference value was used.

Source: Huang, Wei et al. "Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases." Science China. Life sciences vol. 63,11 (2020): 1678-1687. doi:10.1007/s11427-020-1733-4 [R] [R] This article is made available via the PMC Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.

In retrospective evaluation of 413 COVID-19 patients (346 severe, 67 critical), significant differences in biomarker values were observed. When comparing the two groups, critically ill patients had significantly higher total WBCs, neutrophils, D-dimer, pro-calcitonin, CRP, IL-6, IL-10, and urea nitrogen.
Critically ill patients also had significantly lower lymphocytes, platelets, albumin, prealbumin, and albumin/globulin ratio.[90]
A study of 105 PCR-positive patients versus 102 PCR-negative for SARS-CoV-2 was conducted to compare routine blood test results. COVID-19 positive individuals had:[91]

- Significantly lower total WBC counts (6.47 vs 9.79 × 10^9/L) (though some studies found elevated WBC comparing moderate to severe COVID-19).
    - Neutrophils were most abundant of the WBCs present, lymphocytes were suppressed
- Significantly higher CRP (87.1 vs 63.1 mg/L)
- Significantly elevated vitamin B6-dependent AST and ALT (56.2 vs 38.1 U/L and 47.9 vs 33.1 U/L)
- Significantly elevated LDH 388 vs 275.4 U/L
    - Elevated LDH can be a marker of lung damage
- Researchers conclude that "Empirical thresholds for AST and LDH allowed the identification of 70% of either COVID-19-positive or COVID-19-negative patients on the basis of routine blood test results."

Routine blood tests may assist in early identification and assessment of COVID-19 patients. The following patterns were observed in emergency room patients, 105 of whom were COVID-19 positive versus 102 of whom were COVID-19 negative. The positive patients had: [92]

- WBC — Significantly higher
- Neutrophils — Significantly lower
- Lymphocytes — Significantly lower
- Monocytes — Significantly low
- Eosinophils — Significantly lower
- Basophils — Significantly lower
- Platelets — No significant difference
- CRP — Significantly higher
- AST — Significantly higher
- ALT — Significantly higher
- Alk phos — No significant difference
- GGT — No significant difference
- LDH — Significantly higher

A retrospective study of 227 pneumonia patients and 97 hospitalized COVID-19 patients found that 71.7% of those with COVID-19 had decreased eosinophils, a finding significant when compared to non-COVID-19 pneumonia patients. The association was strengthened when the neutrophil/lymphocyte ratio was considered, with an NLR cutoff value for COVID-19 of 2.425. [93]

Low levels of eosinophils on admission were associated with a greater incidence of fatigue, fever, shortness of breath, chest CT lesions, extended hospital stay, and disease course. An increase to normal levels of eosinophils occurred before PCR tests for COVID-19 converted to negative.

In a small study of 28 adults with mild and 15 patients with severe COVID-19, those with severe disease had significantly higher IL-6, glucose, fibrinogen, CRP, D-dimer, and thrombin time. The cutoff for IL-6 was 24.3 ug/L.[94] Notably, six out of seven patients with diabetes had severe versus mild COVID-19.

In a study of 9 ICU versus 58 non-ICU COVID-19 patients, those in the ICU had significantly lower lymphocytes and monocytes, and significantly higher neutrophils and peak LDH levels than non-ICU patients.[95]

In COVID-19 patients with ocular complications such as conjunctivitis and increased secretions, levels of WBCs, neutrophils, CRP, LDH, and procalcitonin were higher than in COVID-19 patients without ocular involvement. Researchers suggest that the virus may be transmitted via the eyes.[96]

In patients who recover from COVID-19, specific antibodies to SARS-CoV-2 are present, and CD4+ and CD8+ T cells, B cells, natural killer cells, and exhaustion markers on cytotoxic lymphocytes normalize.[97]

Albumin

Albumin is a key visceral protein that maintains capillary oncotic pressure and serves as a carrier for hormones, minerals, and fatty acids. It is a negative acute-phase protein, therefore variations in serum levels are dependent on clinical status.[98]

Low serum albumin is associated with critical illness, mortality, inflammation, and disease state (organ dysfunction, pancreatitis, burn, trauma, infection). Decreased levels are likely due to an increase in capillary permeability; decrease in protein synthesis; reduced total mass and half-

life of albumin; increased volume distribution; and increased vascular endothelial growth factor expression.[99] Inflammation, severe chronic malnutrition, malignancy, and fluid overload can also lead to hypoalbuminemia.[100]

A meta-analysis of 11 studies published through April 3, 2020, revealed that patients with severe COVID-19 had a significantly lower admission albumin (3.5 g/dL) than those with non-severe COVID-19 (4.05 g/dL).[101]

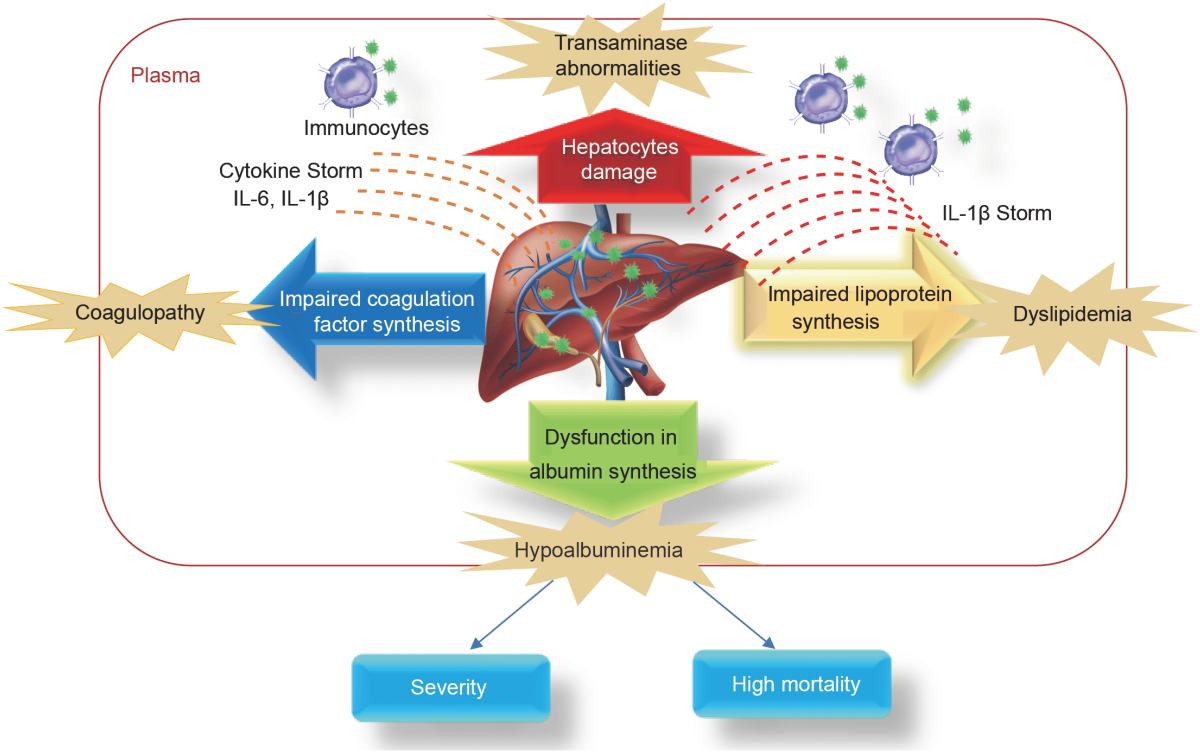
A retrospective study of 2623 adult COVID-19 patients revealed that production and serum levels of albumin, LDL, and HDL decreased with severity of COVID-19.[102]

- Median admission albumin was 3.66 mg/dL in non-critical cases, 3.22 in critical cases, and 3.11 in those who died of COVID-19.
- The second measurement revealed that median albumin significantly decreased: 3.55 in non-critical, 3.13 in critical, and 2.88 in those who died.
- Researchers attribute decreased albumin and lipoprotein synthesis to the negative effects of the cytokine storm characteristic of COVID-19.

COVID-19 patients showed a decline in albumin and lipid synthesis as the severity of the disease developed[103]

		Non-critically ill	Critically ill	Death	P
ALB (median (IQR))	At admission test	36.60 (33.18, 40.40)	32.20 (29.60, 35.75)	31.10 (27.85, 34.20)	<0.001
	At second test	35.50 (32.40, 38.50)	31.30 (28.80, 34.52)	28.80 (25.40, 31.35)	<0.001
GLO (median (IQR))	At admission test	31.70 (28.60, 35.40)	34.40 (30.55, 38.55)	36.05 (32.77, 39.20)	<0.001
	At second test	31.00 (27.80, 34.30)	33.00 (29.35, 37.70)	33.70 (30.70, 38.45)	<0.001
TP (median (IQR))	At admission test	68.70 (65.20, 72.20)	66.70 (63.10, 70.80)	67.05 (62.68, 71.03)	<0.001
	At second test	66.75 (63.20, 70.23)	65.10 (60.27, 69.53)	62.40 (58.30, 67.50)	<0.001
ALB/GLO (median (IQR))	At admission test	1.16 (0.96, 1.38)	0.93 (0.79, 1.10)	0.84 (0.74, 0.98)	0.558
	At second test	1.15 (0.97, 1.34)	0.94 (0.79, 1.10)	0.84 (0.71, 0.98)	<0.001
TG (median (IQR))	At admission test	1.25 (0.96, 1.77)	1.30 (0.99, 1.71)	1.55 (1.18, 2.21)	<0.001
	At second test	1.48 (1.09, 2.10)	1.48 (1.07, 2.02)	1.69 (1.25, 2.31)	<0.001
HDL-C (median (IQR))	At admission test	0.95 (0.80, 1.16)	0.86 (0.73, 1.05)	0.77 (0.56, 0.92)	<0.001
	At second test	0.99 (0.83, 1.20)	0.92 (0.74, 1.12)	0.72 (0.56, 0.87)	<0.001
LDL-C (median (IQR))	At admission test	2.44 (1.96, 2.97)	2.09 (1.60, 2.68)	1.92 (1.43, 2.52)	<0.001
	At second test	2.50 (2.02, 2.95)	2.29 (1.68, 2.83)	1.84 (1.36, 2.47)	<0.001

Data are shown as median (IQR). P values were calculated by Kruskal-Wallis rank-sum test. The plasma levels of albumin (ALB), globulin (GLO), total protein (TP), and ALB/GLO were included as serum protein and triglyceride (TG), cholesterol (TC), HDL-C, and LDL-C levels upon admission and after admission. P values were compared among non-critically ill, critically ill, and death groups. If the values of biomarkers were below the lower reference limit, half of the lower reference value was used.



Source: Huang, Wei et al. "Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases." Science China. Life sciences vol. 63,11 (2020): 1678-1687. Doi:10.1007/s11427-020-1733-4 [R] [R] This article is made available via the PMC Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.

Serum albumin was significantly lower in non-survivors (3.05 g/dL) versus survivors (3.76 g/dL) in a cohort of 299 adult COVID-19 patients. Albumin correlated inversely with total white blood cells count and neutrophil to lymphocyte ratio in these patients. Ultimately, in this cohort, hypoalbuminemia, lymphopenia, and co-morbidities were independently predictive of mortality.[104]

Another retrospective study of 134 COVID-19 patients revealed a significant difference in serum albumin between non-survivors (3.35 g/dL) and survivors (3.92 g/dL).[105]

Hypoalbuminemia associated with COVID-19 may be due to systemic inflammation which increases capillary permeability resulting in migration of albumin into interstitial spaces.[106]

Standard reference range albumin

Quest Diagnostics[107]	3.6-5.1 g/dL
Labcorp[108]	~3.9-5.2 g/dL

Ratio of fibrinogen to albumin (FAR)

The FAR value increases with severe infection and malignancy and is considered a marker of inflammation.

In a retrospective analysis of 113 patients, an elevated ratio of fibrinogen to albumin was considered an independent risk factor for predicting severity of COVID-19.[109] An optimal cutoff for FAR was 0.0883 or greater for severe COVID-19. The analysis also found that a platelet count of $135*10^9$/L or less was an independent predictor of severe disease.

Cytokines

Elevations in cytokines have been recognized as hallmark characteristics of COVID-19.

Serum levels of IL-6, IL-8, IL-10, IL-2R, IL-1β, and TNF-α were all significantly elevated whether patients fell into non-critical, critical, or mortality categories, reflecting the "cytokine storm" associated with COVID-19.[110] In this study, established normal ranges in pg/mL were below 7, 62, 9.1, 710, 5, and 8.1, respectively.

Table S1 Plasma inflammatory cytokine levels.

		Non-Critical	Critical	Death	P
IL-2R (median (IQR))	At admission test	466.00 (306.00, 696.00)	828.00 (539.00, 1201.75)	1091.00 (683.75, 1617.75)	<0.001
	At second test	628.50 (410.75, 853.75)	1016.50 (634.50, 1379.50)	1189.00 (827.00, 1524.00)	<0.001
IL-8 (median (IQR))	At admission test	9.90 (6.12, 17.30)	17.55 (10.38, 30.00)	24.30 (15.10, 65.10)	<0.001
	At second test	14.70 (9.60, 26.37)	21.90 (13.48, 35.70)	42.20 (21.90, 63.40)	<0.001
TNF-a (median (IQR))	At admission test	7.80 (6.00, 9.90)	9.30 (7.50, 12.72)	11.15 (8.45, 15.50)	<0.001
	At second test	8.00 (5.88, 10.35)	11.40 (8.62, 14.80)	13.20 (7.90, 19.90)	<0.001
IL-10 (median (IQR))	At admission test	2.50 (2.50, 5.10)	5.20 (2.50, 9.17)	10.30 (6.85, 17.90)	<0.001
	At second test	2.50 (2.50, 6.15)	6.35 (2.50, 12.77)	8.40 (5.30, 16.50)	<0.001
IL-6 (median (IQR))	At admission test	4.54 (2.00, 15.58)	25.96 (11.11, 52.17)	63.03 (38.33, 163.55)	<0.001
	At second test	9.96 (2.48, 30.63)	27.29 (8.71, 80.47)	77.65 (29.54, 180.37)	<0.001

Data are shown as median (IQR). p values were calculated by Kruskal–Wallis rank test. The cytokines including IL-6, IL-8, IL-10, IL-2R and TNF-a at the admission and after admission were compared among non-critical, critical and death groups. If the value of biomarkers below the lower reference limit, half of the lower reference value was used.

The cytokine storm and its manifestations have been observed in severe cases of COVID-19. Researchers liken it to the cytokine storm seen in Middle Eastern Respiratory Syndrome (MERS).[111] Research suggests that the spike protein characteristic of SARS-CoV-2 triggers increased IL-6 release and trans-signaling, leading to a hyperinflammatory response and cytokine storm.[112]

Cytokine storm can have a wide variety of manifestations with cardiovascular, cutaneous, gastrointestinal, hematological, and neurological consequences. Its severity may be categorized as mild, moderate, severe, or life-threatening.[113]

Interleukin-6

Interleukin-6 is member of the IL-6 family of cytokines which includes IL-11, IL-27, IL-31, and other metabolically active compounds.[114]

Several different cell types secrete IL-6 in response to pathological events and conditions including inflammation, infection, and cancer. Its expression is regulated by NF-IL-6, NF-kappa-B, and other activating nuclear factors. Bacterial LPS, viral infection, TNF-alpha, and IL-1 can all stimulate release of IL-6 due to their activation of NF-kappa-B.[115]

In one study of hospitalized COVID-19 patients, an IL-6 cutoff of 9.16 pg/mL was used to diagnose

severe COVID-19. One patient with moderate symptoms upon admission had initially elevated IL-6 of 24.64 pg/mL, IL-10 of 25.66 pg/mL, and CRP of 19.3 mg/L. That patient died within 14 days of admission despite having only "moderate symptoms."[116]

Elevated pro-inflammatory cytokines correlate with ARDS in severe COVID-19.[117]

Various cutoffs have been proposed for IL-6 as it relates to COVID-19:[118]

Healthy controls	0-10 pg/mL
Severe COVID-19	24.3 pg/mL
Respiratory failure in COVID-19	Greater than 80 pg/mL
Mortality from COVID-19	Greater than 100 pg/mL

Standard reference range serum IL-6

Quest Diagnostics[119]	Less than 5 pg/mL
Labcorp[120]	0-13 pg/mL

Labcorp statement:
"In an external study using Elecsys IL-6 on samples from 817 apparently healthy individuals, the upper limit of the reference range for IL-6 was 7 pg/mL (95th percentile). Based on the available clinical data, PCR-confirmed COVID-19 patients with IL-6 concentrations >35.0 pg/mL at presentation are at risk for mechanical ventilation during their hospitalization. IL-6 values should be used in conjunction with clinical findings and the results of other laboratory findings. IL-6 values alone are not indicative of the need for endotracheal intubation or mechanical ventilation."

Elevations in IL-6 during COVID-19 correlate with hepatic injury as reflected in increases in serum levels of AST, ALT, and GGT enzymes. Peak levels of IL-6 correlated with nadir albumin levels.[121]

Researchers warn against using IL-6 levels alone as a prognostic tool as levels can vary by time of day (a trough in the morning has been noted); variability between patients; presence of comorbidities such as obesity; pharmaceutical manipulation of levels; and variations in signaling which can determine whether IL-6 has pro- or anti-inflammatory effects.[122]

Both IL-6 and IL-10 can be elevated, reflecting the cytokine battle that rages during this potentially debilitating disease. The ratio of IL-6 to IL-10 provides further clues in the COVID-19 puzzle.

Interleukin-10

Interleukin-10 is an anti-inflammatory cytokine that curbs IL-6, TNF-alpha, and IL-8 pro-inflammatory activity.[123]

Research suggests that it is instrumental in controlling autoimmunity and angiogenesis,[124] resolving inflammation, and healing wounds.[125] IL-10 is also the "most widely studied anti-inflammatory and pro-resolution cytokine" in acute ARDS.[126]

During a cytokine storm, IL-10 induces an "immunoparalysis" that downregulates the function of neutrophils and monocytes. Short-term immunoparalysis may be beneficial but prolonged immunosuppression may contribute to mortality even in those who survive the initial cytokine storm.[127]

Standard reference range serum IL-10:

- Labcorp[128] 3.7-23.3 pg/mL
    - Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Ratio of IL-6 to IL-10

Research suggests that evaluating the ratio of IL-6 to IL-10 may be more clinically useful than measuring either cytokine alone.

Evaluation of the IL-6 to IL-10 ratio has been used to predict severity of injury in trauma patients. Early IL-6:IL-10 ratio of 3.11 correlated significantly with severity of injury and APACHI II scores.[129]

Calculation of the ratio of IL-6:IL-10 was integrated into the "Dublin-Boston score" and used to determine severity of infection for hospitalized COVID-19 patients. Both the day four change in IL-6:IL-10 ratio as well as the linear Dublin-Boston score were more valuable in predicting clinical outcome at day seven than measuring IL-6 alone. Each 0.1 unit increase in IL-6:IL-10 ratio day 1-4 increased the odds of a more severe clinical outcome.[130]

Neutrophil to lymphocyte ratio (NLR)

Neutrophils are the first white blood cell responders during an infection. Lymphocytes are the white blood cells that become B cells or T cells. Calculating the ratio between them provides important clues to inflammatory state and prognosis in COVID-19.

The neutrophil lymphocyte ratio serves as a biomarker of inflammation.

When comparing severe to non-severe COVID-19 cases, a meta-analysis of 15 studies revealed that individuals with severe COVID-19 presented with higher neutrophils and neutrophil to lymphocyte ratios, and lower lymphocyte counts.[131]

Meta-analysis of 13 studies comprising 1579 patients found that NLR provided good predictive value for assessing disease severity and mortality in COVID-19. For disease severity, the positive likelihood ratio was 3.6 (negative likelihood at NLR 0.2) and for mortality, the positive likelihood ratio was 4.8, though some studies established a "high cutoff value" of 6.5 or greater.[132]

In an Italian cohort of 74 hospitalized COVID-19 patients, a median NLR of 5.6 was associated with severe disease, and an NLR greater than 4 was associated with transfer to the ICU. An NLR below 3 was associated with clinical improvement.[133]

One study of 81 COVID-19 patients found that an NLR of greater than 9.8 was associated with significantly higher rates of acute respiratory distress syndrome and mechanical ventilation.[134]

A retrospective study of 139 hospitalized COVID-19 patients considered NLR values to be independent predictors of disease severity and mortality with optimal thresholds of 3.27 and 5.72, respectively. The study also found BUN/Creatinine ratios independently predicted severe disease and mortality with optimal thresholds of 33.5 and 51.7, respectively. A number of lab parameters differed significantly between severe and non-severe disease: [135]

	Severe	Non-severe
• BUN	46	23.8 mg/dL
• BUN/Cr	50.3	24.2
• CRP	53.6	14.2 mg/dL
• Lymphocyte count	1.16	1.48 10^9/L
• Monocyte/Lymphocyte ratio	0.4	0.27
• Neutrophil count	6.33	3.99 10^9/L
• NLR	6.1	2.46
• WBC	8.1	6 10^9/L

Standard reference range for NLR

Labcorp[136] 0-2.9

Published COVID-19 studies suggest: Low likelihood of severe COVID-19 disease progression 0.0-2.9 High likelihood of severe COVID-19 disease progression >4.9

Omega-3 Index

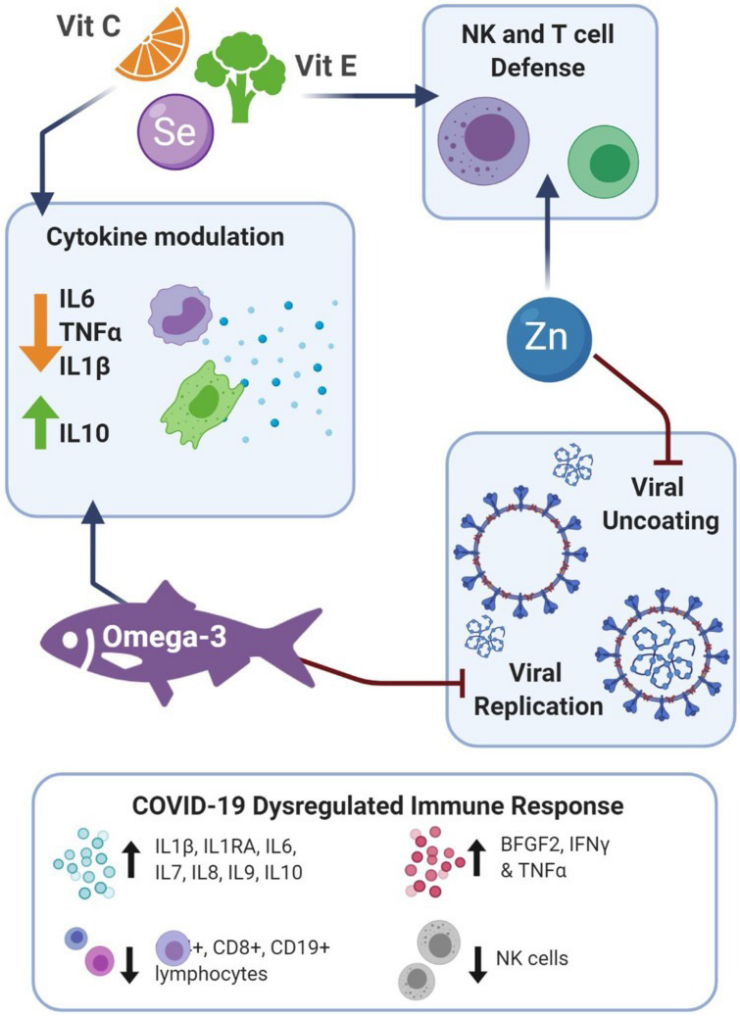
The omega-3 index (O3I) reflects the percentage of EPA and DHA found in red blood cell membranes. This measurement mirrors tissue concentrations, especially in the heart, brain, and gastrointestinal tract.

The incorporation of omega-3s into the phospholipid bilayer of cells provides a readily available source of anti-inflammatory precursors. Notably, the O3I maintains an inverse correlation with inflammatory biomarkers.[137]

Rapid progression of inflammation and "cytokine storm" is associated with increased mortality from COVID-19. Researchers suggest that omega-3s may decrease inflammatory markers and the cytokine storm, reduce cardiovascular complications, and reduce severity of acute respiratory distress syndrome (ARDS).[138]

A small pilot study of 100 hospitalized COVID-19 patients found that those with an O3I of 5.7% or above were 75% less likely to die than those with an O3I of less than 5.7%.[139] One double-blind, randomized clinical trial published in March of 2021 did report positive effects of omega-3 supplementation on acidosis and respiratory and renal function in critically ill COVID-19 patients. The study administered 400 mg EPA + 200 mg via enteral feeding for two weeks.[140]

Although a low O3I is associated with increased inflammation and more severe disease, supplementation with omega-3 fatty acids during COVID-19 is controversial and requires further study.[141]



Source: Shakoor, Hira et al. "Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?." Maturitas vol. 143 (2021): 1-9. doi:10.1016/j.maturitas.2020.08.003 [R]

Standard reference range Omega-3 Index[142]

Quest Diagnostics	1.4-4.9%
Optimal >3.2 %	
Moderate 2.2-3.2 %	
High <2.2 %	

Optimal Omega-3 Index >8%

Vitamin C

Unlike most mammals, humans cannot produce vitamin C (ascorbic acid), making it an essential nutrient that must be obtained exogenously.[143] Hepatic production of vitamin C increases under stress (except for humans, primates, and guinea pigs).[144]

Vitamin C possesses antiviral, anti-inflammatory, antioxidant, and immunomodulating effects, making it a focus of research in COVID-19. An insufficiency of vitamin C contributes to increased susceptibility to viral infection and the adverse effects of prolonged inflammation.[145]

A cross-sectional study of 14,519 adults participating in the NHANES III revealed that blood concentrations of vitamin C (and other antioxidants) were inversely correlated with CRP, likely a reflection of antioxidant depletion due to oxidative stress and inflammatory processes.[146]

Vitamin C: [147]

- Improves epithelial barrier integrity, natural killer cell activity, and neutrophil chemotaxis and phagocytosis
- Stimulates proliferation of lymphocytes and production of interferon
- Reduces release of proinflammatory cytokines
- Scavenges oxygen-free radicals and counteracts oxidative stress from the cytokine storm
- May help prevent ARDS which is characterized by oxidative damage to the lungs
- Deficiency is common in septic patients, with an inverse correlation between serum vitamin C and multi-organ dysfunction in sepsis
- Vitamin C levels in serum and in leukocytes decrease during the increased metabolic demands of infection.
- Supplementation can help replete serum and leukocyte vitamin C if provided in high enough doses.
- Meta-analysis of 1210 critically ill patients showed that providing 3-10 grams of IV vitamin C per day reduced mortality rate.
- Supplementation should be adjusted as needed as high concentrations may be pro-oxidative.
- Vitamin C may interfere with accuracy of glucometer readings due to it having a molecular structure similar to glucose.
- Note that differences in the vitamin C transporter system within the body may influence the efficacy of vitamin C supplementation in certain individuals.[148]
- High dose supplementation may be contraindicated in those with G6PD dehydrogenase deficiency, renal failure, or those prone to oxalate kidney stones.
- However, therapeutic doses of vitamin C below 16 gram/day may be tolerated in those with G6PD deficiency.[149]

Low serum vitamin C has been recognized as a factor in pneumonia and sepsis for decades and supplementation has been shown to be therapeutic. These benefits appear to translate into benefits for COVID-19 patients as well. [150]

- Critically ill patients may need 20-30 times more vitamin C than the general population and several gram doses to normalize serum levels.
- A randomized study of septic ARDS patients demonstrated that 200 mg/kg/day of vitamin C for four days was associated with a lower mortality rate of 30% versus 46% in the placebo group.

- Meta-analysis revealed that vitamin C supplementation resulted in reduced mechanical ventilation and length of ICU stay
- Serum vitamin C levels of 0.41 mg/dL (23 umol/L) are considered hypovitaminosis C and levels below 0.19 mg/dL (11 umol/L) were considered vitamin C deficient
- The World Health Organization recognized adjunctive vitamin C as an intervention with biologic plausibility.
- Several clinical trials are currently investigating the efficacy of vitamin C in the treatment of COVID-19

A small study of critically ill COVID-19 adults with ARDS revealed underlying vitamin C deficiency. The study found that 17 of 18 patients had undetectable serum vitamin C using a detection limit of 0.15 mg/dL (8.5 umol/L), while one patient had a deficient level of 0.24 mg/dL (13.5 umol/L).[151]

Vitamin C insufficiency was detected in 21 critically ill COVID-19 ICU patients with a mean serum level of 0.39 mg/dL (22.2 umol/L), well below the standard hospital reference value of 0.51 mg/dL (29.1 umol/L). Mean vitamin D levels of 22 ng/mL (55 nmol/L) were also below normal hospital values of 30–100 ng/mL (75-250 nmol/L). Researchers strongly recommend assessing for and correcting insufficiencies of vitamins C and D.[152]

Standard reference range vitamin C

Quest Diagnostics[153]	Males 0.2-2.1	Females 0.3-2.7 mg/dL
Labcorp[154]	0.4-2 mg/dL	

Optimal ranges of vitamin C[155]

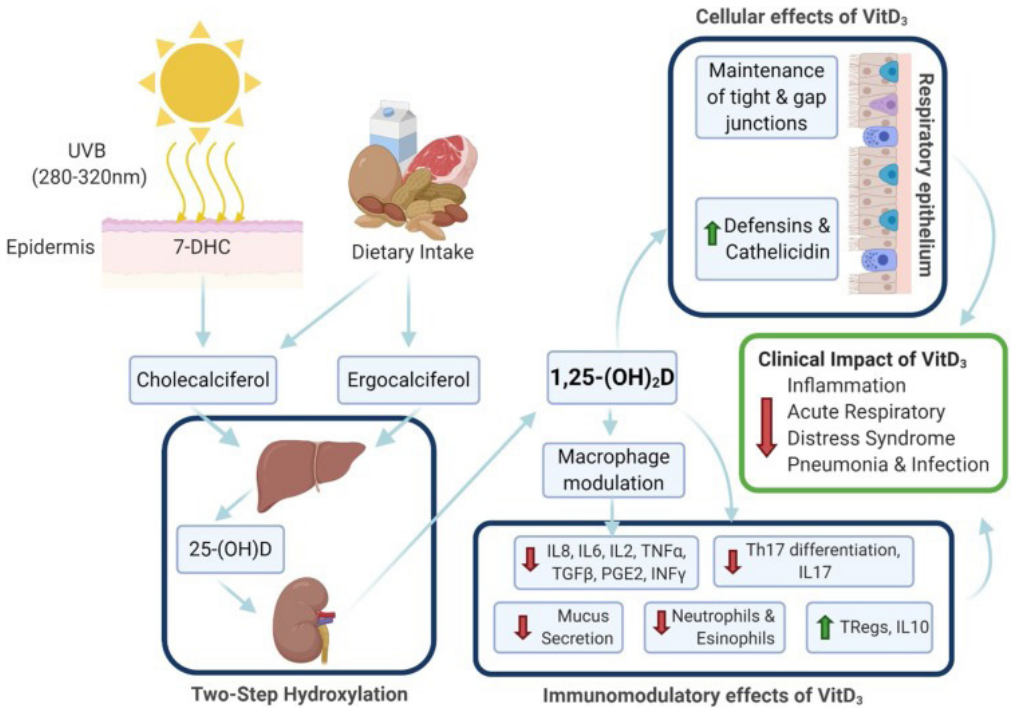
Vitamin C status	Serum vitamin C
• Oral intake of vitamin C from foods	1.3-4 mg/dL (73.8-227 umol/L)
• Maximal free radical scavenging	17.5 mg/dL (1000 umol/L)
• IV vitamin C therapy	Greater than 350 mg/dL (20000-49000 umol/L)

Vitamin D

Vitamin D3 (cholecalciferol), is produced in the skin from the cholesterol compound 7-dehydrocholesterol when exposed to UVB light from the sun. Cholecalciferol is then converted mainly by the liver to 25(OH) vitamin D and then by the kidney to active 1,25(OH)2D. Total 25(OH) D is commonly measured in blood to assess vitamin D status.[156]

Sun exposure, which could provide 80-100% of vitamin D requirements under optimal conditions, is often insufficient due to latitude, winter season, clothing, indoor living, weather, dark skin (melanin in dark skin blocks UV light and vitamin D production), etc. Also, cutaneous production of vitamin D may decline with age.[157]

Historically, exposure to sunlight during spring and summer months would lead to an accumulation of vitamin D in adipose tissue. Subsequently in the winter when food was scarce and weight loss ensued, stored vitamin D was released, helping to maintain adequate serum levels. In modern times an overabundance of food prevents that weight loss and endogenous release of vitamin D, contributing to deficiency.[158]



Immunomodulatory actions of vitamin D.IL: interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Th: T-Helper; 7-DHC: 7-Dehydrocholesterol; PGE2: Prostaglandin E2.

Source: Shakoor, Hira et al. "Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?." Maturitas vol. 143 (2021): 1-9. doi:10.1016/j.maturitas.2020.08.003 [R]

Vitamin D insufficiency is emerging as a significant factor in COVID-19 susceptibility and progression due to its various roles as an anti-inflammatory, antifibrotic, antioxidant, and immune modulating compound.[159] Research suggests that a 25(OH)D level of 30 ng/mL (75 nmol/L) or greater was associated with reduced disease severity and mortality.[160]

African Americans have been disproportionately affected by COVID-19 and have seen a six-fold increase in death rate from this grievous disease.[161] In Chicago alone, more than 50% of COVID-19 cases, and 70% of related deaths occurred in African Americans, an ethnic group also at greater risk of vitamin D deficiency. Insufficiency of vitamin D translates into a critical insufficiency of its most vital benefits including immunomodulatory, antioxidant, and anti-inflammatory properties, setting the stage for infectious disease.[162]

Insufficiency or deficiency of vitamin D:

- Impairs innate immunity and increases vulnerability to viral disease
- Increases renin-angiotensin system and susceptibility to COVID-19 cytokine storm
- Groups at higher risk for vitamin D deficiency are the same groups at higher risk for severe COVID-19:[163]
    - Chronic disease: cardiovascular disease, diabetes, hypertension)
    - Dark-skinned (high in melanin)
    - Elderly
    - Hypertension

- Institutional living
- Lack of sun exposure
- Males
- Obesity
- COVID-19 fatality parallels rate of vitamin D deficiency
- Symptomatic patients who were Vitamin D deficient (11.1 ng/mL) were significantly likely to test PCR positive for SARS-Co-V-2 compared to symptomatic patients with vitamin D levels of 24.6 ng/mL who ultimately tested negative.

A hospital study of 134 COVID-19 patients noted that only 19% of ICU COVID patients had a vitamin D level above 20 ng/mL (50 nmol/L). Researchers note that vitamin D deficiency is common in critically ill patients and is associated with acute respiratory distress syndrome due to exacerbation of lung inflammation.[164]

A study of 50 hospitalized mild to severe COVID-19 patients revealed vitamin D levels significantly lower than those of controls. Approximately 76% of patients presented with vitamin D insufficiency with levels of 20 ng/mL (50 nmol/L) or less. Severe vitamin D deficiency with levels 10 ng/mL (25 nmol/L) or less was observed in 24% of patients versus 7.3% of controls. Selenium deficiency was also observed in 42% of patients with mean levels of 103.2 ug/L (1.31 umol/L) in males and 96.7 ug/L (1.23 umol/L) in females.[165]

Researchers emphasize the importance of assessing and addressing insufficiencies in micronutrients including vitamin C, vitamin D, and selenium in in COVID-19 patients.[166]

Inflammatory markers in relation to Vitamin D[167]

Parameter	**Patients with Serum 25 (OH) D level) >20 ng/mL n=64 [X]**	**Patients with Serum 25 (OH) D level) <20 ng/mL n=90 [Y]**	'p' value [X] vs [Y]
Group A Asymptomatic COVID-19	62	29	NA
Group B Critically Ill COVID-19	2	61	NA
Serum IL-6 in pg/mL (mean ± 2SD)	12.18 ± 4.29	19.34 ± 6.17	0.03*
Serum TNF α in pg/mL (mean ± 2SD)	11.87 ± 3.15	13.26 ± 5.64	0.06*
Serum ferritin in ng/mL (mean ± 2SD)	186.83 ± 20.18	319.17 ± 38.21	0.0003*

*Chi-square test. SD Standard deviation.

The mean concentration (in ng/mL) of 25 (OH)D in Group A was 27.89 ± 6.21where as in Group B the mean level was 14.35 ± 5.79.

The analysis of serum level of inflammatory markers reveals mean IL-6 level (in pg/mL) of 19.34 ± 6.17 in patients with vitamin D deficiency (serum 25 (OH)D < 20 ng/mL) and 12.18 ± 4.29 in patients with normal vitamin D level, the difference was found to be statistically significant. Serum ferritin level was also significantly high in patients with vitamin D deficiency (319.17 ± 38.21 ng/mL vs 186.83 ± 20.18 ng/mL) than in patients with normal vitamin D. Serum TNFα level (in pg/mL) was also high in vitamin D deficient COVID-19 patients (13.26 ± 5.64 vs 11.87 ± 3.15) but the difference was not significant. Among both the groups diabetes was the commonest co-morbidity followed by hypertension.

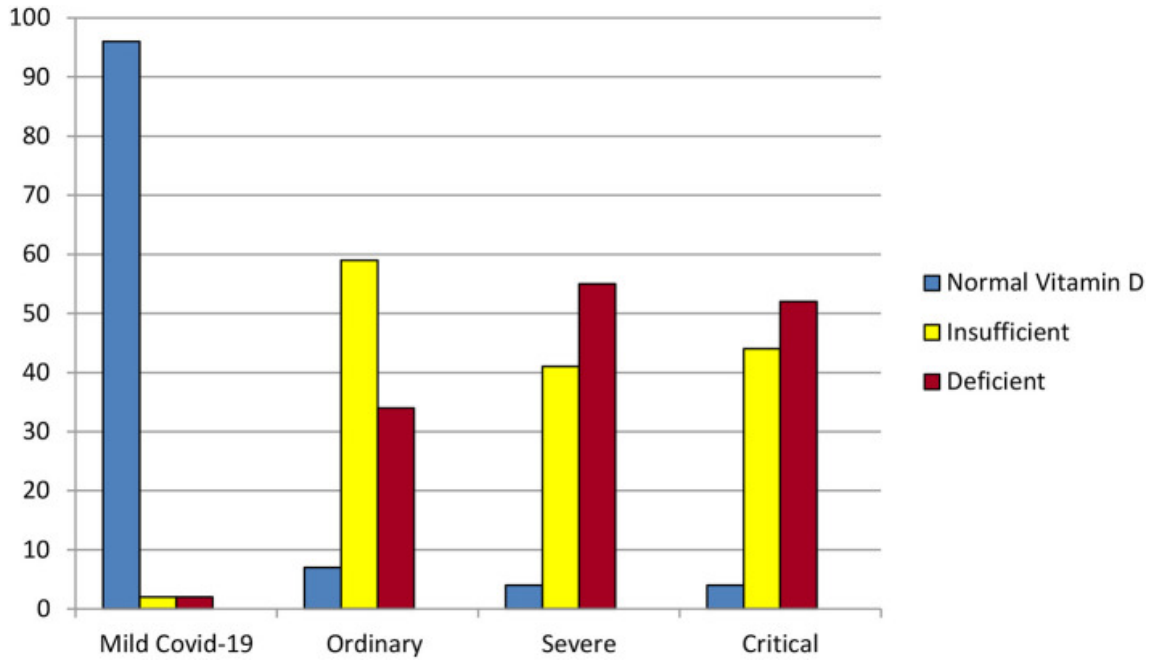
Source: Jain, Anshul et al. "Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers." Scientific reports vol. 10,1 20191. 19 Nov. 2020, doi:10.1038/s41598-020-77093-z [R] Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. [R].

Classification of vitamin D levels (serum 25(OH)D levels):

Classification	Nanograms	Nanomoles	Recommended D intake
Danger of toxicity	>100 ng/ml*	>250 nmol/l	
Normal or optimal	>30 ng/ml	>75 nmol/l	400–4,000 IU/day
Insufficient	21–29 ng/ml	51–74 nmol/l	4,000–6,000 IU/day
Deficient	11–20 ng/ml	26–50 nmol/l	7,000 IU/day
Severely deficient (often not distinguished from deficient)	<10 ng/ml	25 nmol/l	10,000 IU/day x 1 month or 500,000 IU x 1
NIH target	30 ng/ml	75 nmol/l	2000 IU/day
Prevention of respiratory infection	40-60 ng/ml	100-150 nmol/l	6000 IU/day normal weight until goal 7000-8000/day obese
Reduce risk CVD, hypertension	50-80 ng/ml	125-200 nmol/l	4000-10000 IU/day until goal
COVID-19	40-60 ng/ml	100-150 nmol/l	5000-10000 IU/day until goal

*some sources found that 150 ng/ml was not harmful.

Source: Benskin, Linda L. "A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is Increased in Vitamin D Deficiency." Frontiers in public health vol. 8 513. 10 Sep. 2020, doi:10.3389/fpubh.2020.00513 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.



Some of the results of the retrospective chart review by Alipio et al. (3). Of the 212 hospitalized COVID-19 patients, 96% of those with mild COVID-19 had normal vitamin D levels (above 30 ng/ml). In contrast, over 50% of the patients with severe or critical COVID-19 were vitamin D deficient (level 20 ng/ml or lower).

Source: Benskin, Linda L. "A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is Increased in Vitamin D Deficiency." Frontiers in public health vol. 8 513. 10 Sep. 2020, doi:10.3389/fpubh.2020.00513 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A prospective observational study assessed serum levels of 25(OH) vitamin D, as well as markers of inflammation (IL-6, ferritin, TNF-alpha) in Indian COVID-19 patients. Of 154 patients, 91 patients were asymptomatic (Group A) and 63 patients were severely ill and required ICU care (Group B).[168] Data indicates that vitamin D deficiency was significantly related to severe COVID-19, and also correlated with elevations in IL-6, ferritin, TNF-a, and fatality rates:

Mild vs severe COVID-19:	Group A (asymptomatic)	Group B (symptomatic)
Vitamin D, mean	27.89 ng/mL	14.35 ng/mL highly significant
Vitamin D deficiency	32.96%	96.82%

Vitamin D deficient vs sufficient:

	Vitamin D deficient	Vitamin D sufficient
IL-6	19.34 pg/mL	12.18 pg/mL
Ferritin	319.17 ng/mL	186.83 ng/mL
TNF-a	13.26 pg/mL	11.87 pg/mL
Fatality	21%	3.1%

As pointed out by Grant et al. 2020, the goal of vitamin D therapy should be to maintain serum 25(OH)D concentrations of at least 40-60 ng/mL (100-150 nmol/L). For those at risk of COVID-19 or influenza, 10,000 IU/day of vitamin D3 may be indicated for two weeks followed by 5,000 IU/day until goals are reached.[169] Researchers note that higher levels of supplementation may be useful for those already infected with the virus.

A literature review of randomized trials, systematic reviews, meta-analyses, and international consensus conferences confirms maintenance of robust serum vitamin 25(OH)D levels in the range of 50-70 ng/mL (125-175 nmol/L).[170]

Standard reference range 25(OH) vitamin D

Quest Diagnostics[171]	30-100 ng/mL (75-250 nmol/L)
Labcorp[172]	30-100 ng/mL (75-250 nmol/L)
Optimal Vitamin D	50-90 ng/mL (125-225 nmol/L)

Zinc

Zinc is only needed in trace amounts in the body, but it participates in a wide range of metabolic processes. These include antioxidant reactions, neurobehavioral development, cellular growth, immunity, development and activation of T-lymphocytes, and inhibition of viral replication.[173]

Zinc supports the integrity and barrier function of epithelial cells (e.g., skin and mucous membranes) which are compromised in zinc deficiency. Fortunately, supplementation can improve epithelial barrier integrity.[174]

Zinc can also help reduce the cytokine storm characteristic of severe COVID-19 due to its modulation of T cell activity.[175]

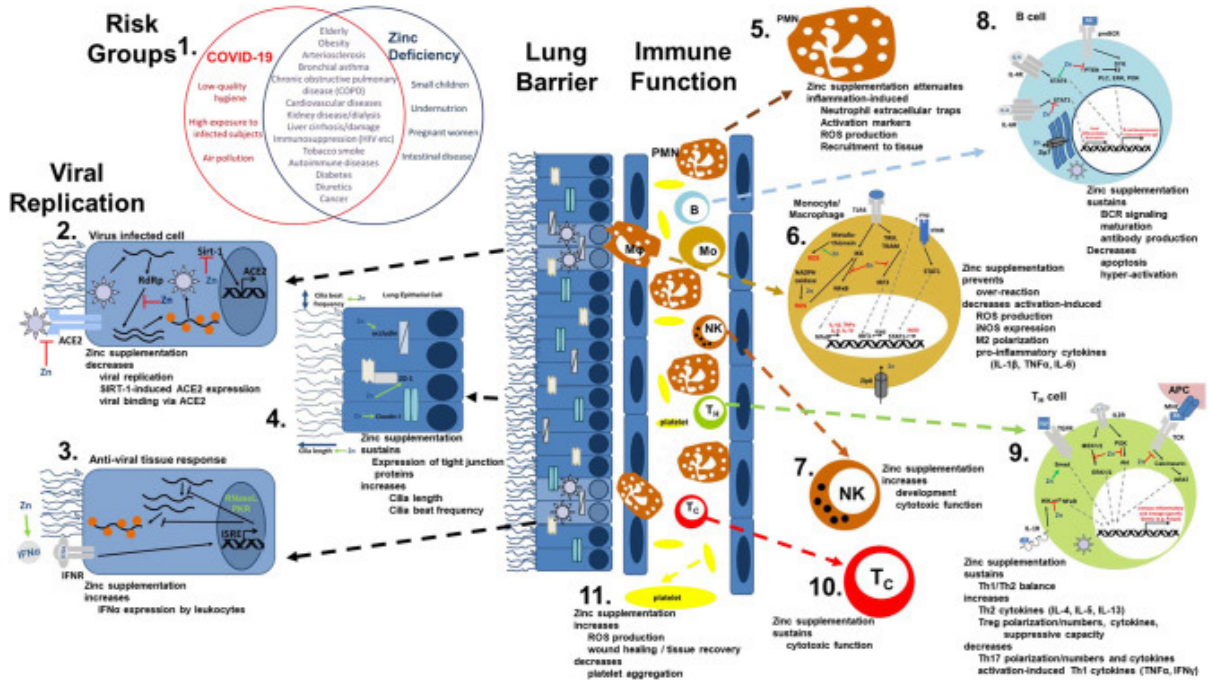
Zinc deficiency will have notably negative effects on immunity:[176]

- Reduced activity of immune cells, e.g., impaired phagocytosis.
- Decreased critical neutrophil functions.
- Weakened natural killer cell function.
- Reduced lymphocyte number and activation.

- Diminished antibody production.
- Imbalanced T helper cell cytokine secretion with decreased IFN-gamma production.
    - IFNs are immunostimulatory cytokines with antiviral activity.
- Increased thymic atrophy and consequent risk of infection.
- Zinc is crucial to counteract excessive inflammatory reactions…resulting in a reduced production of pro–inflammatory cytokines.
- Drugs can deplete zinc. For example, long–term use of some ACE–inhibitors like captopril, verapamil, and ramipril can significantly lower serum zinc levels.
- On the other hand, excess of zinc can also impair immune response by inhibiting T–lymphocyte and B–lymphocyte function, reducing intracellular pathogen destruction in macrophages or inducing an overload of regulatory T cells,
    - This demonstrates that a balanced zinc homeostasis is critical for adequate immune functions.

An estimated 16% of all deep respiratory infections are caused by zinc deficiency worldwide. Zinc deficiency is commonly observed in immunosuppression, asthma, COPD, pneumonia, cystic fibrosis, autoimmune disorders, diabetes, CVD, obesity, cancer, kidney disease, liver damage and cirrhosis, and in the elderly. Symptoms of zinc deficiency include[177 178]

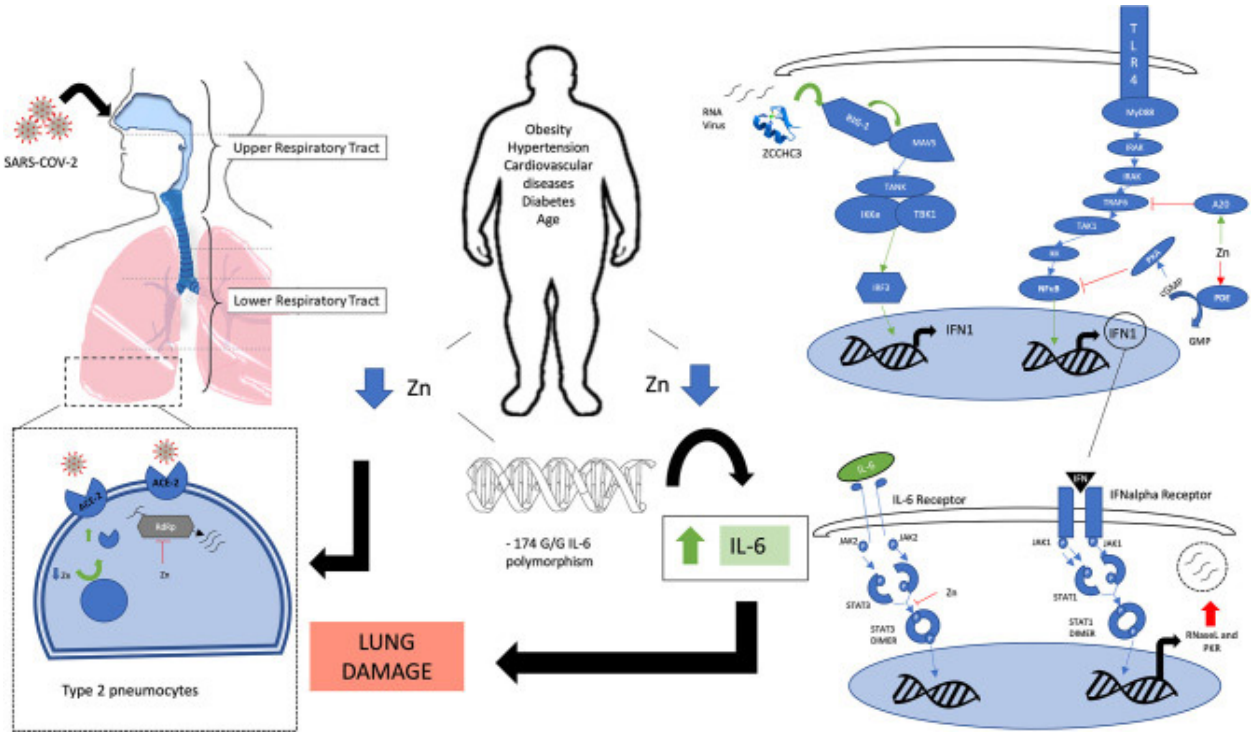
- Aching and pain in limbs
- Cough
- Diarrhea
- Fever
- Gastrointestinal disorders
- General weakness
- Growth retardation
- Immune system imbalance
- Impaired smell and taste
- Runny nose
- Skin disorders
- Sore throat
- Susceptibility to infections
- Weight loss



Source: Wessels, Inga et al. "The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis." Frontiers in immunology vol. 11 1712. 10 Jul. 2020, doi:10.3389/fimmu.2020.01712 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Zinc and COVID-19 key points[179]

- Zinc deficiency may be common and associated with severe infection.
- Zinc helps to enhance the interferon type 1 response to the virus and participates in many regulatory pathways.
- Low levels of zinc have been associated with higher IL-6 responses.
- IL-6 plays an important role in severe lung injury due to COVID-19 infection.
- Zinc inhibits SARS-CoV RNA polymerase, and thus its replication capacity.
- Zinc may increase the efficacy of antimalarial agents, since they are zinc ionophores.
- Differences in mortality due to COVID-19 infection may be explained to some degree by−174 IL-6 gene polymorphism
- Homeostasis maintains a constant intracellular zinc concentration and a plasma concentration within the reference range of 70-160 ug/dL (11–25 umol/L). Low plasma zinc was defined as less than 60 ug/dL (less than 9.2 umol/L)



Source: Mayor-Ibarguren, Ander et al. "A Hypothesis for the Possible Role of Zinc in the Immunological Pathways Related to COVID-19 Infection." Frontiers in immunology vol. 11 1736. 10 Jul. 2020, doi:10.3389/fimmu.2020.01736 [R]

A prospective study found significantly lower fasting serum zinc levels in 47 hospitalized COVID-19 patients with median serum levels of 74.5 ug/dL versus a median of 105. ug/dL in healthy controls. More than 57% of patients were blatantly zinc deficient with an odds ratio of 5.54 for developing complications including ARDS and prolonged hospital stay. Zinc deficiency was only observed in 11% of healthy controls with levels 71.8-79.6 ug/dL. Hospital reference ranges for zinc were 80-120 ug/dL (12.24-18.4 umol/L).[180]

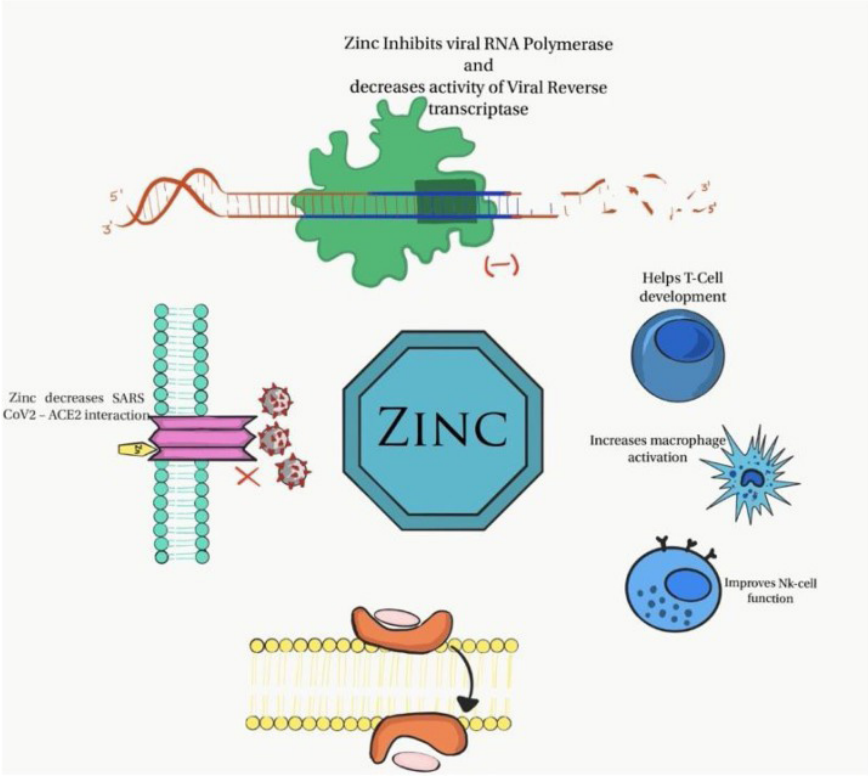


Illustration of antiviral and immunomodulatory properties of zinc in COVID-19

Zinc, along with vitamins C and D can have a synergistic effect in helping maintain the crucial first-line barriers of skin and mucous membranes. Insufficiency or marginal deficiency will disrupt metabolism and compromise immunity.[181]

Zinc insufficiency, especially within immune cells, may be directly related to dysregulation of immune responses in the elderly who are at greater risk of zinc deficiency and COVID-19 morbidity.[182]

Researchers note that a serum zinc below 70 ug/dL (10.7 umol/L) is considered a risk factor for pneumonia in the elderly. Reduced zinc also correlates with increased levels of IL-6, IL-8, and TNF-alpha. A daily preventative dose of 25 mg or less should be adequate. Intake of more than 25 mg/day may disrupt copper balance and warrant increased copper intake. Researchers also recommend selenium supplementation of 100-200 ug/day if serum levels are below 100 ug/L (1.27 umol/L).[183]

Up to 79% of COVID-19 patients present with acute gastrointestinal complications including abdominal pain, vomiting, diarrhea, or gastrointestinal bleeding. Research suggests that supplementation with zinc amino acid chelate may help restore gastrointestinal integrity, resolve diarrhea, and replete zinc lost via the GI tract.[184]

Researchers suggest that zinc supplementation may be beneficial to healing tissue damage caused by inflammation and the related cytokine storm seen during COVID-19.[185]

Hypogeusia (loss of taste) and hyposmia/anosmia (loss of smell) are significant findings in COVID-19 patients with 71-89% experiencing loss of taste and 68-85% experiencing olfactory

dysfunction. These are recognized signs of zinc insufficiency as well. A study of 134 COVID-19 patients revealed that 78.4% of them had loss of smell. Serum zinc levels in those with olfactory dysfunction was 57-59 ug/dL compared to 61-63 ug/dL in those without olfactory dysfunction, a non-statistically significant difference. However, zinc therapy with 50 mg elemental zinc twice daily did reduce duration of olfactory dysfunction.[186]

It is notable that the range of serum zinc for all patients in this study (57-63 ug/dL) was below the optimal range of 80-100 ug/dL needed for maintenance of homeostasis.[187]

Researchers note that hypogeusia may occur without accompanying olfactory disturbances and may occur prior to organ or lung involvement in COVID-19, prompting calls for early supplementation with oral zinc lozenges in these patients.[188]

A suboptimal level of alkaline phosphatase indicates an underlying zinc (or magnesium) deficiency and should be part of a comprehensive nutrition assessment.[189]

Standard reference range serum zinc

Quest Diagnostics[190]	50-130 ug/dL (7.6-20 umol/L)
Labcorp[191]	56-135 ug/dL(8.6-21 umol/L)
Optimal serum zinc	80-100 ug/dL (12-15 umol/L)

Biomarker clues to COVID-19 severity lie in their specific characteristics:[192]

- ✓ Albumin levels correlate with hepatic and renal function and may reflect long-term nutrition status
- ✓ Serum albumin of less than 2.9 mg/dL (29 g/L) was the best predictor for ICU admission in a retrospective study of 427 COVID-19 patients. [albumin levels decrease with inflammation]
- ✓ Cardiac troponin levels may reveal cardiovascular compromise
- ✓ D-dimer may reveal blood clotting dysfunction
- ✓ Ferritin and CRP elevations may reflect an increased inflammatory state
- ✓ LDH increases may reflect lung damage or widespread tissue damage
- ✓ The best cutoffs for predicting mortality from COVID-19 were LDH above 731 U/L (12.2 ukat/L), and an albumin of 1.8 mg/dL (18 g/L) or lower.
- ✓ Cutoffs for COVID-19 severity also included a ferritin of greater than 2824 ng/mL (6.3 nmol/L) and CRP greater than 30.3 mg/dL (303 mg/L).
- ✓ D-dimer may be useful in patient triage as levels of 1 ug/mL or greater on admission were associated with increased mortality.[193]

Blood type was assessed as a factor in susceptibility and severity of COVID-19. Research suggests that blood type may have an association with testing positive but did not correlate with severity of COVID-19.[194] [195] Blood type did not correlate with intubation or risk of death.

- Type O blood was less likely to test positive
- Type A blood had no association with testing positive
- Type B and type AB had higher odds of testing positive
- Rh+ status increased odds of testing positive

A prospective study of 164 COVID-19 positive patients with hypertension assessed inflammatory and thrombotic status, and clinical outcomes with regard to blood type: 92 had non-O-type blood and 72 had O-type blood. Results indicated that[196]

- Non-O-type individuals had significantly higher pro-thrombotic indices

- Non-O-type blood was an independent predictor of cardiac injury and death
    - Rates of cardiac injury were significantly higher in the non-O-type blood group (29.3% vs 13.9%).
    - Rates of death were significantly higher in the non-O-blood type group (19.6% vs 8.3%)
- IL-6 levels were independent predictors of cardiac injury and mortality
- D-dimer levels were also independent predictors of mortality

Targeted nutrition support strategies

In general, critically ill COVID-19 patients benefit from balanced nutrition support:[197]

- Total Calories 20-30 kcal/kg, adjust for tolerance, morbidity, refeeding if underweight
- Protein 1.3-1.5 grams/kg, up to 50% branched chain amino acids
- Carbohydrate 2 grams carbohydrate/kg body weight/d up to 150 grams/d
  Adjust as needed
- Fat 1.5 grams/kg body weight, incorporate medium and long-chain fatty acids
    - Note that supplementation with omega-3 fatty acids during viral infection and treatment is controversial and must be considered on a case-by-case basis.[198] [199] [200] [201]

Vitamin C supplementation

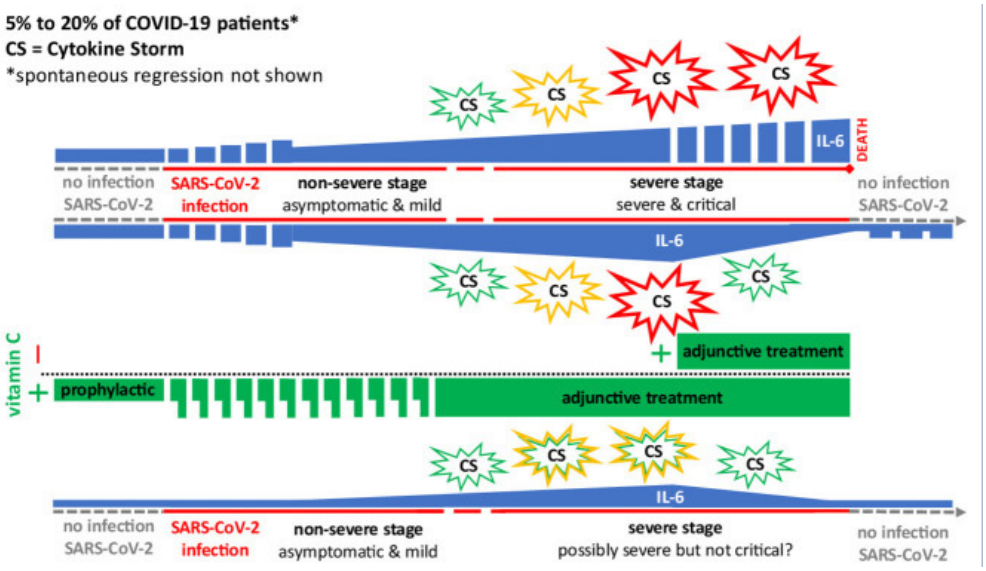
Supplemental vitamin C has been found to reduce incidence of pneumonia, reduce ICU length of stay and duration of mechanical ventilation, reduce IL-6, and may be effective at modulating the cytokine storm associated with COVID-19.[202]

Vitamin C has promising potential in the fight against COVID-19 as it: [203]

- Prevents an increase of IL-6 and other cytokines in inflammatory conditions
- May inhibit neutrophils from creating neutrophil extracellular traps that contribute to organ damage and mortality
- May positively affect thrombosis
- Randomized placebo-controlled research demonstrated that even lower doses of 500 mg twice daily reduced IL-6 and CRP in in patients with diabetes and/or hypertension.
- Higher doses appear to be needed for COVID-19, especially for ARDS in those patients, and several clinical trials are underway including the use of 6-12 grams of vitamin C per day.
- Researchers suggest that increased oral doses may be given as bowel tolerance will increase with severity of disease. Some patients may tolerate up to 200 grams per day.
- Interestingly high-dose vitamin C has been tolerated in chemotherapy patients at doses of up to 1.5 g/kg administered up to 1 g/min.

Vitamin C and antioxidant supplementation[204]

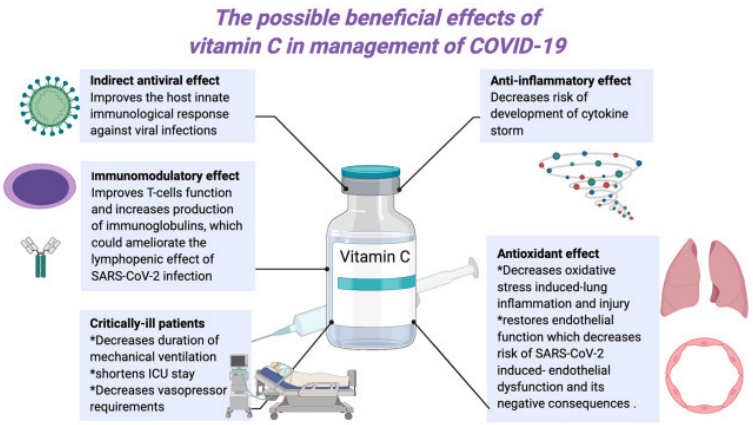
- Prevention: 2000 mg/day oral vitamin C, ideally split into 2-4 doses per day
- Acute treatment of sepsis, ARDS 10,000 mg/day intravenously
- IV vitamin C 50 mg/kg every 6 hours for 4 days, extended as needed
- Adequate hydration before and after treatment can help reduce or prevent potential side effect of high dose therapy which include dry mouth, dizziness, nausea, perspiration, and weakness.
- Additional antioxidant supplementation with tocopherols, alpha-lipoic acid, N-acetylcysteine, glutathione, L-carnitine [if TMAO not elevated], coenzyme Q10, zinc, and selenium compounds.
- Several ongoing clinical trials are in place to closely the examine the efficacy of micronutrient supplementation in the prophylaxis and treatment of COVID-19



Source: Feyaerts, Adam F, and Walter Luyten. "Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19?." Nutrition (Burbank, Los Angeles County, Calif.) vol. 79-80 (2020): 110948. doi:10.1016/j.nut.2020.110948 [R] Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website. Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Researchers suggest that high dose vitamin C (typically up to 16 grams per day intravenously) can: [205]

- Favorably impact patients with viral pneumonia and ARDS in severe SARS-CoV-2 infection by decreasing inflammation and pathogen infectiveness and virulence
- Optimize immune defense
- Reduce tissue and organ injury
- Improve overall outcome of the disease.
- Dramatically reduce the need for treatment with high doses of corticosteroids, antibacterials and antiviral drugs.
- Can be effective for primary prevention of viral infections by boosting the innate immune response.
- In infected patients, vitamin C therapy may shorten the disease course and prevent complications of the disease.



Source: Abobaker, Anis et al. "Overview of the possible role of vitamin C in management of COVID-19." Pharmacological reports : PR vol. 72,6 (2020): 1517-1528. doi:10.1007/s43440-020-00176-1 [R] This article is made available via the PMC Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.

Zinc supplementation

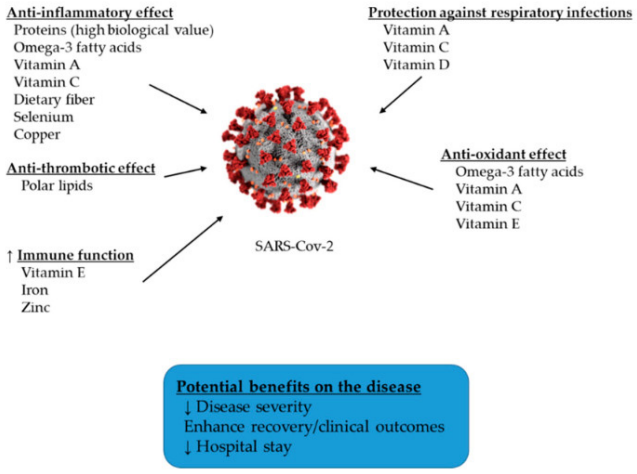
Zinc is able to inhibit coronavirus replication and may have some therapeutic benefit if administered early in the infection.[206] Zinc may also be efficacious as adjuvant therapy to chloroquine-based drugs which help increase intracellular zinc where zinc, in turn, drug efficacy. However, long-term high-dose zinc is not recommended due to potential side effects including copper deficiency, anemia, reduction of HDL, and potential genitourinary consequences.[207]

A 2000 randomized double-blind placebo-controlled trial involving 48 subjects evaluated the effect of ~80 mg of elemental zinc on cold symptom duration. A dose of 12.8 mg of elemental zinc in the form of zinc acetate lozenges was taken every 2-3 hours while awake for 4-5 days. The supplemented group experienced significantly fewer days with symptoms, with an average duration of 4.5 days versus 8.1 days in the unsupplemented group.[208]

Researchers reviewed a number of studies utilizing nutrition or phytochemical prevention or intervention for COVID-19 with the most promising compounds being:[209]

- Catechin gallate and gallocatechin gallate
- Elderberry
- Fiber
- Forsythoside
- Melatonin
- Polyphenols
- Probiotics
- Propolis
- Quercetin
- Selenium
- Vitamins A, C, E, D
- Zinc

Effects of several nutrients on aspects of COVID-19 infection. ↑: increase, ↓: decrease



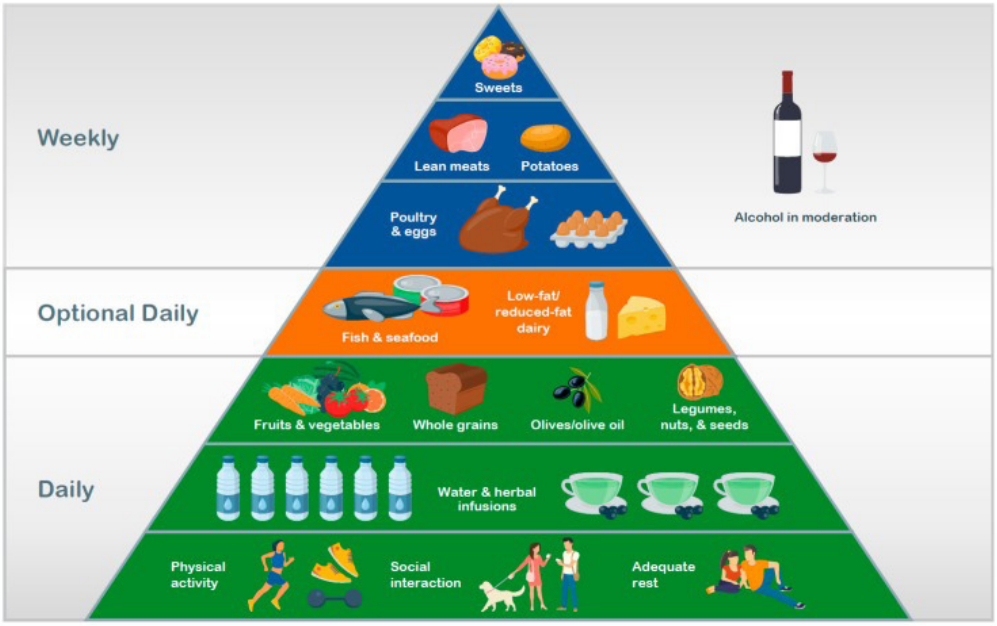
Source: Fernández-Quintela, Alfredo et al. "Key Aspects in Nutritional Management of COVID-19 Patients." Journal of clinical medicine vol. 9,8 2589. 10 Aug. 2020, doi:10.3390/jcm9082589 [R] This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

Recommended intakes of certain nutrients with key roles in disease susceptibility and the maintenance of an adequate immune function. [210]

Nutrient	Immune Function	Recommendation		References
		Healthy Individuals	Diseased/Infected Patients	
Vitamin C	Maintenance of functional and structural integrity of mucosal cells in innate barriers Normal functioning of T cells Antimicrobial, anti-inflammatory and antioxidant effects Antibody production Reduction of respiratory tract and lung infection risk	200 mg/day	1–2 g/day	[R,R]
Vitamin D	Maintenance of functional and structural integrity of mucosal cells in innate barriers Normal functioning of T cells Antimicrobial, anti-inflammatory and antioxidant effects Antibody production and antigen responses Reduction of respiratory tract and lung infection risk Alleviation of the inflammatory response	2000 IU/day (50 µg/day)	10,000 IU during few weeks, followed by 5000 IU (until 25-hydroxyvitamin D concentrations rise above 40–60 ng/mL (equivalent to 100–150 nmol/L))	[R,R,R]
Vitamin E	Maintenance of functional and structural integrity of mucosal cells in innate barriers Differentiation, and functioning of innate immune cells Anti-inflammatory and antioxidant effects Antibody production and antigen responses Reduction of respiratory tract and lung infection risk Support of T cell-mediated immunity	15 mg/day (RDA)	200 IU/day	[R]
Selenium	Differentiation, and functioning, of innate immune cells Normal functioning of T cells Antibody production Antimicrobial, anti-inflammatory and antioxidant effects	50 µg/day	Up to 200 µg/day	[R,R]
Zinc	Maintenance of functional and structural integrity of mucosal cells in innate barriers. Differentiation, and functioning, of innate immune cells. Antimicrobial, anti-inflammatory and antioxidant effects. Antibody production and antigen response. Support of lymphocyte and cytokine functions, and innate immunity overall. Inhibits the activity and replication of coronavirus (SARS-CoV which caused an outbreak in 2002)	Men: 8 mg/day Women: 11 mg/day (RDA)	Zinc lozenges: over 75 mg/day administered within 24 h (divided into 6–8 doses, each separated by 2–3 h when awake) Zinc gluconate: 13.3 mg/day within 3 days (at least)	[R,R,R,R,R,R]
Iron	Maintenance of functional and structural integrity of mucosal cells in innate barriers Differentiation, and functioning, of innate immune cells Normal functioning of T cells. Antimicrobial, anti-inflammatory and antioxidant effects	Men: 8 mg/day Women age 19–50: 18 mg/day Women age > 51: 8 mg/day (RDA)	Ferrous iron salts (ferrous sulfate and ferrous gluconate): 60 mg Fe/day (taken with food to avoid gastric discomfort)	[R,R]
Omega-3 fatty acids (EPA + DHA)	Conversion to specialized pro-resolving mediators (SPMs) such as, protectins, resolvins and maresins to relieve the inflammation and enhance lung injury	250–300 mg/day of EPA + DHA	1500–3000 mg/day EPA + DHA	[R,R]
Multivitamin supplements including vitamins (A, B6, B12, C, D, E and folate) and trace elements (Zn, Fe, Se, Mg and Cu)	Support of the cells and tissues of the immune system overall Maintenance and development of in innate barriers Growth and differentiation of innate cells Antibody production and generation of memory cells Production and activity of antimicrobial proteins Phagocytic activities of neutrophils and macrophages	Supplying nutrient requirements according to the 100% RDA for age and gender This is in addition to a well-balanced diet		[R,R,R]

Source: Fernández-Quintela, Alfredo et al. "Key Aspects in Nutritional Management of COVID-19 Patients." Journal of clinical medicine vol. 9,8 2589. 10 Aug. 2020, doi:10.3390/jcm9082589 [R] This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

Healthy diet and lifestyle pyramid



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Optimal Takeaways

- Diet, nutritional status, and lifestyle are modifiable risk factors for COVID-19 and its comorbidities. These factors should be highlighted in public messaging about the COVID-19 pandemic.
- Biomarker clues can provide insight into severity of COVID-19 as well as underlying nutrient insufficiencies and deficiencies.
- It is imperative that assessment of key biomarkers and nutrients be part of COVID-19 evaluation, monitoring, and therapy, especially:
  - ✓ Inflammatory markers
  - ✓ Transaminase enzymes
  - ✓ LDH
  - ✓ Fibrinogen
  - ✓ WBC differential
  - ✓ Neutrophil: lymphocyte ratio
  - ✓ IL-6, IL-10
  - ✓ Albumin
  - ✓ Prealbumin
  - ✓ Vitamin C
  - ✓ Vitamin D
  - ✓ Selenium
  - ✓ Zinc
  - ✓ Omega-3 Index
- Remember that optimal lab ranges are narrower than standard lab ranges and may give earlier clues to imbalance or deficiency.
- A healthy dietary pattern modeled on the Mediterranean diet or DASH diet can help reduce the risk of chronic metabolic diseases and in turn, reduce risk of severe COVID-19:
  - Minimum of 4 servings of fruit, 5 servings of vegetables during COVID and beyond
  - Adequate whole grains, meats, beans, dairy, protein, whey protein
  - Incorporate herbs, spices, tea, coffee daily
  - Minimum of 35 grams of fiber daily, ideally from whole foods, can supplement with psyllium
  - Include fermented foods, probiotic-containing foods

    - Adequate micronutrient intake particularly vitamins A, Bs, C, D, E, zinc, and selenium
    - Minimize or eliminate highly processed foods, added sugars and salt, excessive saturated fats, fatty processed meats
    - Targeted nutrition support should be utilized
        - A high-potency multivitamin-mineral supplement can provide a foundation with additional micronutrient supplementation as needed
- Other factors should be considered in the fight to prevent and treat COVID-19 including
    - Sleep hygiene
    - Stress management
    - Mental health
    - Social connections
    - Environmental factors, clean air, clean water, clean food
    - Health literacy

A Traditional, Complementary and Integrative Health and Medicine Support Registry has been developed to collect longitudinal data "aiming to capture key case, treatment/supportive care, and outcome variables related to the use of traditional, complementary, and integrative health and medicine products and practices in response to the COVID-19 crisis."[211]

Several organizations from a variety of disciplines have joined the registry and provided an integrated path for improving COVID-19 treatment and resolution.

Additional references[212]

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