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Determination of Indoleamine 2,3 Dioxygenase Enzyme (IDO-1) Activity Levels in COVID-19 Patients According to Disease Severity, and Relationship with Inflammatory Markers

COVID-19 Hastalarında Hastalık Ciddiyetine Göre İndolamin 2,3 Dioksijenaz Enzimi (IDO-1) Aktivite Düzeylerinin Belirlenmesi

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ABSTRACT

Introduction: *The novel coronavirus (COVID-19) infection continues to impact the world, and its full effects on the immune system remain unknown. According to recent research, indoleamine dioxygenase (IDO) is crucial for viral infections such hepatitis B, C, HIV, and influenza. This study measured IDO-1 activity levels in COVID-19 patients to evaluate the influence of acute phase reactants and IDO-1 activity on disease severity.*

Materials and Methods: *The study is a prospective cross-sectional study. Between 15 March 2020 and 5 April 2020, adult patients who were hospitalised in the infectious diseases clinic of the hospital and diagnosed with COVID-19 infection with SARS-CoV-2 PCR test positivity were included in the study. Patients were categorised according to World Health Organization COVID-19 disease severity. On the first day of hospitalisation, C-reactive protein (CRP), D-dimer, ferritin, fibrinogen, procalcitonin, leukocyte and IDO-1 levels were analysed.*

Results: *The group with severe-critical pneumonia was older and had significantly higher levels of D-dimer, ferritin, and CRP ($p< 0.001$, $p= 0.039$, $p= 0.008$, and $p< 0.001$, respectively). IDO-1 levels were detected in both groups. The group with mild-moderate pneumonia had a higher mean IDO-1 level, although the difference was not statistically significant.*

Conclusion: *Although no statistically significant difference was found, elevated IDO-1 levels were observed in the serum of patients with mild to moderate COVID-19 pneumonia. This is consistent with findings from other studies that reported high IDO-1 levels at the histopathological level in patients with mild to moderate COVID-19 pneumonia.*

Key Words: *COVID-19; IDO-1; IDO-1-kynurenine-ahr pathway*

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ÖZ

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Giriş: *Yeni koronavirüs (COVID-19) infeksiyonunun dünya genelinde etkisi devam etmektedir ve bağışıklık sistemi üzerindeki etkileri tam olarak anlaşılmamıştır. Son veriler, indolamin 2,3 dioksijenaz enziminin (İDO) HIV, influenza, hepatit B ve C gibi viral infeksiyonlarda önemli bir rol oynadığını göstermiştir. Bu çalışmada, COVID-19 hastalarında İDO-1 aktivite düzeyinin ölçülmesi ve İDO-1 aktivitesiyle inflamatuvar belirteçlerin hastalığın ciddiyeti ile ilişkisinin değerlendirilmesi amaçlanmıştır.*

Materyal ve Metod: *Çalışma prospektif kesitsel bir çalışmadır. Çalışmada 15 Mart 2020 - 5 Nisan 2020 tarihleri arasında hastanenin infeksiyon hastalıkları kliniğinde yatan ve SARS-CoV-2 PCR testi pozitifliği ile COVID-19 infeksiyonu tanısı koyulan yetişkin hastalar Dünya Sağlık Örgütü COVID-19 hastalık ciddiyetine göre kategorize edilmiştir. Hastaneye yatışın ilk gününde C-reaktif protein (CRP), D-dimer, ferritin, fibrinojen, prokalsitonin, lökosit ve İDO-1 seviyeleri analiz edilmiştir.*

Bulgular: *Ağır-kritik pnömoni grubu hafif-orta pnömoni grubuna kıyasla daha ileri yaştaydı ve daha yüksek CRP, ferritin ve D-dimer seviyeleri mevcuttu ($p< 0.001$, sırasıyla $p= 0.039$, $p= 0.008$, $p< 0.001$). Her iki grupta da serumda İDO-1 düzeyleri tespit edildi. İstatistiksel olarak anlamlı farklılık olmamasına rağmen, ortalama İDO-1 düzeyi hafif-orta pnömoni grubunda daha yüksekti.*

Sonuç: *Hafif-orta şiddette COVID-19 pnömonisi olan hastaların serumunda istatistiksel olarak anlamlı fark tespit edilmese de daha yüksek İDO-1 seviyeleri gözlenmiştir. Bu sonuçlar histopatolojik düzeyde hafif-orta şiddette COVID-19 pnömonisi olan hastalarda yüksek İDO-1 seviyeleri bildiren diğer çalışmaların bulgularıyla tutarlıdır.*

Anahtar Kelimeler: *COVID-19; İDO-1; İDO-1-kynurenine-ahr yolağı*

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease-2019 (COVID-19), is a member of the coronavirus family. SARS-CoV-2 infection manifests across a broad clinical spectrum, from asymptomatic cases to severe respiratory failure[1]. It is known that immune activation plays an important role in the severity of COVID-19 disease[2]. Several inflammatory processes occur during the disease[3]. Studies show that the tryptophan-kynurenine pathway (TKP) is one of the key immune pathways influencing the clinical course of the disease[4].

Indolamine-2,3-dioxygenase (IDO) is an intracellular cytosolic enzyme that regulates the rate-limiting step in the conversion of tryptophan, the essential amino acid, to kynurenes in TKP. It is induced by proinflammatory cytokines, particularly IFN gamma. Infection-induced inflammation triggers tryptophan catabolism in several bacterial, protozoan and viral infections. Studies have shown that IDO plays a role in the pathogenesis of some viral infections such as influenza, HIV, hepatitis B and C[5,6].

Although IDO-1 and IDO-2 are isoforms of each other, they have different expression patterns and roles. Both are involved in autoimmune functions. While IDO-1 causes anti-autoimmune effects by suppressing T cells, IDO-2 causes pro-inflammatory activity on B cells[7]. IDO-1 is induced by interferons, whereas IDO-2 is not stimulated by interferons, but is stimulated by the aryl hydrocarbon receptor (AhR). IDO-1 has been implicated in the pathogenesis of autoimmunity[8].

The aim of this study was to measure IDO-1 activity in COVID-19 patients and to evaluate the effect of IDO-1 activity and acute phase reactants on disease severity.

MATERIALS and METHODS

Study Design and Data Collection

This study was designed as a prospective cross-sectional analysis. As the majority of studies on IDO-1 levels were conducted with the objective of determining IDO-1 at the histopathological level, it was not possible to calculate the sample size, given the absence of similar studies on the determination of IDO-1 levels in serum. Hospitalized patients who were found positive for COVID-19 PCR at the infectious diseases clinic of our hospital between 15 March 2020 and 5 April 2020 were included. The patients were divided into two groups based on WHO's COVID-19 clinical classification: mild to moderate and severe to critical disease[9]. The data were retrieved from the hospital medical records and electronic system.

Inclusion Criteria

Patients aged 18 years and older with positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests from nasopharyngeal swabs within the specified period were enrolled in the study.

Exclusion Criteria

Patients were excluded from the study if they had a history of immunosuppressive drug use.

Determination of Indoleamine 2,3 Dioxygenase-1 (IDO-1) Enzyme Activity Levels

The IDO-1 level was measured from the blood samples obtained from the patients on the first day of hospitalization. The hIDO ELISA kit for IDO (Shanghai YL Biotech Co., Ltd., YLA 1644HU) was used in the hospital's research laboratory, Department of Immunology. Measurements were performed on a Sunrise TECAN plate reader and analyzed using the Magellan™ software.

Laboratory Parameters

C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer and leukocyte counts measured on the first day of hospitalization were recorded.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS; IBM; Chicago, IL) version 27 software package.

The distribution of continuous data was represented by the median and interquartile range (IQR), while categorical data were described using numbers and percentages. Frequency tables and descriptive statistics were used to interpret the results. Non-parametric methods were used for measures that did not follow a normal distribution. Among the non-parametric methods, the "Mann-Whitney U" test (Z-table value) was used to compare the measurements of two independent groups. Pearson χ^2 cross-tabulations were used to determine the relationships between two qualitative variables. A binary logistic regression with a backward LR model was used to identify factors influencing critical and serious risk status. Statistical significance was set at $p< 0.05$.

Ethics Approval

Our study was approved by the ethics committee of the hospital, ensuring compliance with ethical standards and guidelines (decision number E1-23-45-28). The study was conducted according to the principles of the declaration of Helsinki.

RESULTS

A total of 82 patients were hospitalized with COVID-19 disease during the study period. Of the patients, 40 were female (48.8%) and 42 were male (51.2%), with a median age of 46 years (min= 18-max= 90) (Table 1,2).

There were 63 patients in the mild and moderate COVID-19 infection group, of which 30 (47.6%) were women and 33 (52.4%) were men. There were 19 patients in the severe and critical COVID-19 infection group, of which 10 (52.6%) were women and 9 (47.4%) were men. There was no statistically significant difference in gender between the two groups (p= 0.702) (Table 1).

The mean age was 66.21 ± 11.18 in the critical/severe COVID-19 infection group and 39.41 ± 17.14 in the mild/moderate COVID-19 infection group. There was a statistically significant difference between the two groups, and the mean age was higher in the critical/severe COVID-19 infection group (Table 2).

Table 1. Examination of clinical status and gender

	Severe + Critical Pneumonia (n= 19)		Mild + Moderate Pneumonia (n= 63)		
Variable	n	%	n	%	**p***
Gender					
Female	10	52.6	30	47.6	χ^2= 0.147
Male	9	47.4	33	52.4	p= 0.702

*Pearson-χ^2 crosstabs were used.

Table 2. Comparison of age and laboratory findings according to clinical status

	Severe + Critical Pneumonia (n= 19)	Mild + Moderate Pneumonia (n= 63)	
Variable	**Median (min-max)**	**Median (min-max)**	**p***
Age (year)	67.0 (46.0-83.0)	34.0 (12.0-90.0)	Z= -5.151 **p< 0.001**
IDO-1 (U/L)	11.3 (6.4-36.3)	12.2 (1.4-68.4)	Z= -0.245 p= 0.806
CRP (mg/L)	0.10 (0.0-267.0)	0.01 (0.0-47.0)	Z= -2.066 **p= 0.039**
PCT (ng/mL)	0.13 (0.0-0.67)	0.03 (0.0-1.02)	Z= -1.745 p= 0.081
Ferritin (µg/L)	121.0 (25.0-1363.0)	61.0 (20.0-526.0)	Z= -2.645 **p= 0.008**
D-dimer (µg/L)	1.33 (0.4-35.2)	0.38 (0.1-35.2)	Z= -4.886 **p< 0.001**
Leukocyte (cell/µL)	5600.0 (2950.0-19210.0)	5350.0 (1280.0-16180.0)	Z= -1.116 p= 0.265

*Mann-Whitney U test (Z-table value) statistics were used.

The median CRP values on the first day of hospitalization were 0.10 (0.0-267.0) mg/L in the critical/severe COVID-19 infection group and 0.01 (0.0-47.0) mg/L in the mild/moderate COVID-19 infection group. There was a statistically significant difference between the two groups and the median CRP value was higher in the critical/severe COVID-19 infection group. (Table 2).

The median ferritin values on the first day of hospitalization were 121.0 (25.0-1363.0) µg/L in the critical/severe COVID-19 infection group and 61.0 (20.0-526.0) µg/L in the mild/moderate COVID-19 infection group. There was a statistically significant difference between the two groups, and the median ferritin value was higher in the critical/severe COVID-19 infection group (Table 2).

The median D-dimer values on the first day of hospitalization were 1.33 (0.4-35.2) µg/L in the critical/severe COVID-19 infection group and 0.38 (0.1-35.2) µg/L in the mild/moderate COVID-19 infection group. There was a statistically significant difference between the two groups, and the median D-dimer value was higher in the critical/severe COVID-19 infection group (Table 2).

There was no statistically significant difference between the two groups in mean procalcitonin and leukocyte levels on the first day of hospitalization (p= 0.081 and p= 0.265 respectively) (Table 2).

Table 3. Logistic regression model based on severe + critical pneumonia status

Variable	β	SE	Wald	df	p	OR	95% Confidence Interval (OR)	
							Lower	Upper
Age (year)	0.112	0.032	12.491	1	**<0.001**	1.119	1.051	1.191
Ferritin (µg/L)	0.004	0.002	4.820	1	**0.028**	1.004	1.001	1.008
Constant	-8.295	2.096	15.667	1	**0.000**	0.000		

CCR= 85.1%, $\chi^2(8)$= 3.672; p= 0.885.
β: Regression coefficient, SE: Standard error, df: Degress of freedom, OR: Odds ratio.

On the first day of hospitalization, the mean IDO-1 values were 14.95 ± 8.24 U/L in the critical/severe COVID-19 infection group and 17.82 ± 14.72 U/L in the mild/moderate COVID-19 infection group. The mean IDO value was higher in the group with mild/moderate COVID-19 infection, but there was no statistically significant difference between the two groups (p= 0.806) (Table 2).

As a result of the backward: LR logistic regression analysis performed to determine the factors influencing critical/severe risk status using all parameters that were significant in the univariate analysis, the optimal model is shown in Table 3. Age was found to be an important parameter influencing critical/severe COVID-19 infection (p< 0.05). For every one-year increase in age, the risk of critical/severe COVID-19 infection increased by 11.9% (OR= 1.119). Ferritin level was found to be an important parameter influencing the status of critical/severe COVID-19 infection (p< 0.05). For every one unit increase in ferritin, the risk of critical/severe COVID-19 infection increased by 0.4% (OR= 1.004).

DISCUSSION

For the past three years, COVID-19 has been a global pandemic that continues to affect quality of life. Novel therapeutic strategies are also being informed by our growing understanding of the immune response to SARS-CoV-2 infection[10].

In our study, the average age of patients with severe COVID-19 pneumonia was statistically significantly higher. The number of naive T cells decreases with age and the disease becomes more difficult to control. Therefore, it may be more fatal, especially in patients aged 65 years and older[11].

The clinical course of the disease varies greatly, ranging from asymptomatic to lethal, depending on the immune response generated against the SARS-CoV-2 virus[12]. A cytokine storm is brought on by a substantial rise in pro-inflammatory cytokines and biomarkers during the systemic hyperinflammatory phase of COVID-19. The following substances are elevated during this process: D-dimer, ferritin, PCT, CRP, IL-2, IL-6, IL-7, and tumor necrosis factor-alpha (TNF-alpha)[13]. Studies have shown that elevated CRP, D-dimer, and ferritin levels have a prognostic value for mortality and are correlated with the severity of COVID-19 disease[14]. CRP, ferritin, and D-dimer levels were shown to be statistically significantly higher in severe critical COVID-19 pneumonia compared to mild to moderate COVID-19 pneumonia in our study, which is consistent with the literature. In COVID-19 patients, serum CRP> 30 ng/mL, D-dimer≥ 400 ng/mL, and ferritin≥ 200 ng/mL may indicate a fatal outcome[15].

One nuclear receptor implicated in inflammatory processes is the aryl hydrocarbon receptor (AhR)[16]. Systemic AhR Activation Syndrome, which can cause various organ damage and death and include thrombosis, fibrosis, and inflammation, is the consequence of AhR activation by SARS-CoV-2 viruses[17]. Furthermore, AhRs enhance their own activity via the positive feedback loop IDO1-AhR-IDO1[18].

IDO-1 is a rate-limiting enzyme that converts tryptophan to kynurenine. AhR is activated by the endogenous ligand kynurenine[19]. IDO-1 activation starves T lymphocytes of tryptophan, which is converted to kynurenine, therefore suppressing T cell activation[20]. Numerous

viral infections can cause an increase in the transcription of the IDO-1 gene[21]. INF-γ can also induce this effect[20]. In the lung tissue of COVID-19 patients with early-stage and moderate pneumonia, IDO-1 is more prevalent than IDO-2 in cases that are severe or fatal[22]. IDO-2 expression was widely found in the cytoplasm of type 1 and type 2 pneumocytes, endothelial cells, and the lung interstitium in a study involving cadavers of patients who died from COVID-19 infection[23]. In our study, IDO-1 levels were measured in the serum of patients from both groups. Although the mean IDO-1 level was higher in mild to moderate COVID-19 pneumonia, the difference was not statistically significant. The study faced challenges, including a limited sample size and the inability to concurrently examine IDO-2 levels. Nevertheless, the findings were consistent with other studies that reported higher IDO-1 levels in mild to moderate COVID-19 pneumonia at the histopathological level.

Through an IDO1-dependent mechanism, SARS-CoV-2 activates AhR, enabling it to exacerbate infection and cause inflammation. Furthermore, SARS-CoV-2 bypasses the IDO1-kynurenine AhR route and activates AhR through an IDO1-independent mechanism[24]. Because kynurenines decrease inflammation, the host immunosuppressive effects of SARS-CoV-2 infection are prevented by this mechanism. The host immune response's self-limiting regulation systems could fail as a result of the intensity of AhR activation by several pathways of action, potentially triggering a cytokine storm[25]. This could be the reason for the cytokine storm associated with COVID-19 infection.

The anti-autoimmune effect of IDO-1, due to T-cell suppression, may have contributed to mild to moderate COVID-19 pneumonia. It may be possible to develop treatment plans for COVID-19 infection that raise IDO-1 levels. Like many other infections, COVID-19 pneumonia has been shown to be affected by the IDO1-kynurenine-AhR pathway. Clarifying this mechanism might result in new approaches to treating COVID-19[25].

CONCLUSION

Despite its continued global significance, the full impact of COVID-19 infection on the immune system is still not entirely understood. The group with severe pneumonia in our research was older and exhibited considerably higher levels of CRP, ferritin, and D-dimer. IDO-1 were detected in the serum of patients in both groups. The group with mild to moderate pneumonia had a higher mean IDO-1 level, although the difference was not statistically significant. These results are consistent with other studies that reported higher IDO-1 levels in mild to moderate COVID-19 pneumonia at the histopathological level.

ETHICS COMMITTEE APPROVAL

This study was approved by the Ankara City Hospital No 1 Clinical Research Ethics Committee (Decision no: E1/4528/2023, Date: 27.12.2023).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: ESÇ, AKK, RG

Analysis/Interpretation: BÇD, AKK

Data Collection or Processing: ESÇ, AKK

Writing: ESÇ, BÇD, ST

Review and Correction: BÇD, RG, ST

Final Approval: RG, ST

REFERENCES

1. *Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5*
2. *Primorac D, Vrdoljak K, Brlek P, Pavelić E, Molnar V, Matišić V, et al. Adaptive immune responses and immunity to SARS-CoV-2. Front Immun 2022;13:848582. https://doi.org/10.3389/fimmu.2022.848582*
3. *Gusev E, Sarapultsev A, Solomatina L, Chereshnev V. SARS-CoV-2-specific immune response and the pathogenesis of COVID-19. Int J Mol Sci 2022;23:1716. https://doi.org/10.3390/ijms23031716*

4. *Blasco H, Bessy C, Plantier L, Lefevre A, Piver E, Bernard L, et al. The specific metabolome profiling of patients infected by SARS-COV-2 supports the key role of tryptophan-nicotinamide pathway and cytosine metabolism. Sci Rep 2020;10:16824. https://doi.org/10.1038/s41598-020-73966-5*
5. *Schmidt SV, Schultze JL. New insights into IDO biology in bacterial and viral infections. Front Immun 2014;5:384. https://doi.org/10.3389/fimmu.2014.00384*
6. *Huengsberg M, Winer JB, Gompels M, Round R, Ross J, Shahmanesh M. Serum kynurenine-to-tryptophan ratio increases with progressive disease in HIV-infected patients. Clin Chem 1998;44:858-62. https://doi.org/10.1093/clinchem/44.4.858*
7. *Merlo LM, DuHadaway JB, Montgomery JD, Peng WD, Murray PJ, Prendergast GC, et al. Differential roles of IDO1 and IDO2 in T and B cell inflammatory immune responses. Front Immun 2020;11:1861. https://doi.org/10.3389/fimmu.2020.01861*
8. *Grunewald ME, Shaban MG, Mackin SR, Fehr AR, Perlman S. Murine coronavirus infection activates the aryl hydrocarbon receptor in an indoleamine 2, 3-dioxygenase-independent manner, contributing to cytokine modulation and proviral TCDD-inducible-PARP expression. J Virol 2020;94:10. https://doi.org/10.1128/JVI.01743-19*
9. *World Health Organization (WHO). Clinical management of COVID-19: Living guideline, 2022.*
10. *Li Q, Wang Y, Sun Q, Knopf J, Herrmann M, Lin L, et al. Immune response in COVID-19: What is next? Cell Death Different 2022;29:1107-22. https://doi.org/10.1038/s41418-022-01015-x*
11. *Moderbacher CR, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell 2020;183:996-1012.e19. https://doi.org/10.1016/j.cell.2020.09.038*
12. *Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA 2020;324:782-93. https://doi.org/10.1001/jama.2020.12839*
13. *Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis 2020;14:1753466620937175. https://doi.org/10.1177/1753466620937175*
14. *Topcu H, Arik YE. The importance of D-dimer, ferritin, CRP and lymphocyte values in determining mortality in COVID-19 disease in Turkey. Clin Lab 2022;68:2274-80. https://doi.org/10.7754/Clin.Lab.2021.210720*
15. *Yousaf MN, Sarwar S, Tarique S, Ahmed M, Tahir H. Mortality in patients of COVID-19 infection: Biochemical markers and its cut-off values for predicting outcome. J Coll Physicians Surg Pak 2022;32:37-41. https://doi.org/10.29271/jcpsp.2022.01.37*
16. *Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008;453:106-9. https://doi.org/10.1038/nature06881*
17. *Turski WA, Wnorowski A, Turski GN, Turski CA, Turski L. AhR and IDO1 in pathogenesis of Covid-19 and the "Systemic AhR Activation Syndrome:" A translational review and therapeutic perspectives. Restor Neurol Neurosci 2020;38:343-54. https://doi.org/10.3233/RNN-201042*
18. *Jaronen M, Quintana FJ. Immunological relevance of the coevolution of IDO1 and AHR. Front Immun 2014;5:521. https://doi.org/10.3389/fimmu.2014.00521*
19. *Larigot L, Juricek L, Dairou J, Coumoul X. AhR signaling pathways and regulatory functions. Biochimie Open 2018;7:1-9. https://doi.org/10.1016/j.biopen.2018.05.001*
20. *Neavin DR, Liu D, Ray B, Weinshilboum RM. The role of the aryl hydrocarbon receptor (AHR) in immune and inflammatory diseases. Int J Mol Sci 2018;19:3851. https://doi.org/10.3390/ijms19123851*
21. *Benavente FM, Soto JA, Pizarro-Ortega MS, Bohmwald K, González PA, Bueno SM, et al. Contribution of IDO to human respiratory syncytial virus infection. J Leukocyte Biol 2019;106:933-42. https://doi.org/10.1002/JLB.4RU0219-051RR*
22. *Chilosi M, Doglioni C, Ravaglia C, Martignoni G, Salvagno GL, Pizzolo G, et al. Unbalanced IDO1/IDO2 endothelial expression and skewed keynurenine pathway in the pathogenesis of COVID-19 and post-COVID-19 pneumonia. Biomedicines 2022;10:1332. https://doi.org/10.3390/biomedicines10061332*
23. *Guo L, Schurink B, Roos E, Nossent EJ, Duitman JW, Vlaar AP, et al. Indoleamine 2, 3-dioxygenase (IDO)-1 and IDO-2 activity and severe course of COVID-19. J Pathol 2022;256:256-61. https://doi.org/10.1002/path.5842*
24. *Thomas T, Stefanoni D, Reisz JA, Nemkov T, Bertolone L, Francis RO, et al. COVID-19 infection alters kynurenine and fatty acid metabolism, correlating with IL-6 levels and renal status. JCI Insight 2020;5. https://doi.org/10.1172/jci.insight.140327*
25. *Belladonna ML, Orabona C. Potential benefits of tryptophan metabolism to the efficacy of tocilizumab in COVID-19. Front Pharmacol 2020;11:959. https://doi.org/10.3389/fphar.2020.00959*

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