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Research Article

Contribution of kynurenine/tryptophan ratio to early prediction of COVID-19 severity in the emergency department

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Abstract

Objectives: Kynurenine is the breakdown product of tryptophan. The tryptophan metabolic pathway increases in COVID-19 infection. This study was designed to reveal the relationship between tryptophan and kynurenine levels and disease severity. Our study also aimed to explore the relationship between tryptophan-kynurenine levels and patient survival, need for mechanical ventilation, and length of hospital stay.

Methods: All 82 COVID-19 patients were grouped as severe and mild cases. Serum tryptophan and kynurenine levels were measured by the ELISA method. Receiver operating characteristic curves were generated to plot the KYN/TRP ratio and other variables. Multivariate logistic regression analyses were used to assess the strength of associations between risk factors and patient status. Categorical variables were compared.

Results: The kynurenine/tryptophan level was significantly higher ($p<0.001$), and the tryptophan level was significantly lower ($p=0.008$) in the severe group. With a cutoff point of 14.2, the kynurenine/tryptophan ratio had 56.1% sensitivity and 80.49% specificity in predicting COVID-19 severity. In the multivariate logistic regression analysis using age, troponin, platelet count, ferritin, and kynurenine/tryptophan levels, with a cut-off value of 0.34, the sensitivity and specificity were 92.6% and 87.8%, respectively. There was no significant difference in tryptophan and kynurenine levels in terms of patient survival, need for mechanical ventilation, and length of hospital stay.

Conclusion: The kynurenine/tryptophan ratio is valuable in evaluating clinical outcomes of COVID-19 patients, especially when used in conjunction with age, troponin, platelet count, and ferritin. It is useful in predicting the clinical course at the time of admission to the emergency department. To our knowledge, the kynurenine/tryptophan ratio, together with age, troponin, platelet count, and ferritin parameters, is the best model with the highest AUC that can be used to show early prediction of clinical outcomes in COVID-19.

Keywords: COVID-19, disease severity, indoleamine 2, 3 dioxygenase, kynurenine, tryptophan

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The COVID-19 virus has caused a global pandemic [1]. Proinflammatory cytokines cause pulmonary fibrinolysis and damage alveolar epithelial and endothelial cells. As a result, oxygen (O_2) and carbon dioxide (CO_2) exchange is prevented, and hypoxia occurs. Cytokine storms, hypoxia, and fibrosis are associated with a poor clinical course and increased mortality [2–4]. Controlling immune reactions is the most vital and challenging management process for COVID-19 patients [5].

Approximately 95% of tryptophan (TRP), an essential amino acid, is converted to kynurenine (KYN) and its metabolites in the liver and kidney. Two rate-limiting enzymes that metabolize TRP are tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase 1/2 (IDO1/2) [6, 7]. Under physiological conditions, TDO, which is expressed mainly in the liver, is regulated by hormones such as cortisol, insulin, glucagon, and epinephrine, while IDO1 is expressed in monocytes and dendritic

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cells and is expressed as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [8–10]. The recently identified IDO2 gene, which has 45% homology with IDO1, is expressed in the brain, liver, kidney, and epididymis. However, the metabolic activity of IDO2 is thought to be much lower than that of IDO1 [11]. In this study, the term 'IDO' refers to IDO1 unless stated otherwise. Local TRP depletion (via the stress-responsive kinase GCN2 pathway) and an increase in kynurenine metabolites (via the aryl hydrocarbon receptor (AhR)) inhibit the proliferation of T cells, convert naïve CD4+ T cells into Treg cells, and direct dendritic cells (DCs) and macrophages towards an immunosuppressive phenotype [12, 13]. By IDO activation, APCs produce inhibitory cytokines such as IL-10 and transforming growth factor β (TGFβ) rather than inflammatory cytokines such as IL-12. Therefore, IDO activation can change the nature of APCs and change the entire local environment from immunogenic to tolerogenic [14, 15].

The KYN/TRP ratio, which reflects IDO activity, is reportedly higher in COVID-19 patients than in controls [16, 17]. Paradoxically, in COVID-19, a cytokine storm occurs despite IDO activation [3]. There are some hypotheses on this topic. Firstly, the TRP metabolic pathway can occur in response to inflammation and represents an attempt to limit excessive immune reactivity. However, if it is not enough, a cytokine storm begins [16]. Secondly, immune tolerance resulting from the activation of the TRP metabolic pathway weakens the immune response to the virus and delays its clearance, thus leading to the development of acute respiratory distress syndrome (ARDS) and multiple organ failure [18].

The IDO enzyme is probably induced by increased levels of IFN-γ, IL-1, IL-6, TNF-α, and ROS in COVID-19 patients [19]. KYN, which increases with IDO activation, stimulates AhR and may cause "systemic aryl hydrocarbon receptor activation syndrome," which is associated with hyperinflammation, hypercoagulation, and multiple organ damage [20]. For this reason, it has been hypothesized that the TRP metabolic pathway may worsen the clinical course of COVID-19 and possibly reduce the patient's recovery potential [21].

Determining the severity of the disease before the onset of the cytokine storm in COVID-19 and starting appropriate treatment accordingly is life-saving. There is a need for parameters that shed more light on clinicians working under intense conditions. The results of our study will provide further information on the use of KYN and TRP levels at the time of admission to emergency departments and will help better predict the severity of COVID-19.

Materials and Methods

Participant acquisition and sample collection

The study included 82 patients aged >18 years who presented to the hospital emergency department between 01.01.2022 and 01.08.2022 and had a positive SARS-CoV-2 PCR test. The exclusion criteria included cancer, inflammatory diseases, rheumatological diseases, and allergic diseases that could affect IDO enzyme activity. Patients were grouped into severe and mild cases according to the criteria established by the Ministry of Health [22]. By evaluating the following criteria, patients with at least one criterion were included in the severe group. Patients who did not meet these criteria were considered mildly ill.

- Shortness of breath,
- Respiratory rate ≥28/minute,
- Oxygen saturation <93% or PAO_2 <60 mmHg despite oxygen support of 5 liters/minute or more
- PAO_2/FIO_2 <300,
- More than 50% involvement with clinical worsening on chest X-ray or tomography,
- Hypotension (systolic blood pressure <90 mmHg, >40 mmHg decrease from normal systolic blood pressure, mean arterial pressure <65 mmHg) or vasopressor requirement,
- Skin perfusion disorders, lactate >4 mmol/L, sequential organ failure assessment score (≥2 unit increase in SOFA score),
- Troponin elevation or arrhythmia.

Patients were followed for 4 months to determine their survival. Follow-up lasted 4 months, as surviving patients fully recovered during this time. All participants gave informed consent to participate in this study, which was approved by the local ethics committee. Yellow cap gel blood tubes (SARSTED) were used to collect blood samples during admission to the emergency department. Samples were allowed to clot for 20–30 min. Samples were centrifuged at 4000xg for 10 minutes. Serum obtained from blood samples was divided into two equal parts and placed in Eppendorf tubes. Samples were stored at -80°C until the day of analysis. Samples were kept at room temperature until completely thawed before analysis. All laboratory records, radiological imaging, and clinical examination findings were recorded.

Sample analysis

Serum KYN levels were measured using a Human Kynurenine ELISA Kit (Sunred Biological Technology, China). Different standard concentrations were obtained by diluting the lyophilized standard included in the kit. Following the kit procedure, the absorbance of the examined samples was measured at 450 nm with an EBLX-800 microplate reader (BioTek Instruments, Inc., USA). Concentrations corresponding to sample absorbance were calculated by the formula obtained from the standard curve plot (sensitivity: 13.672 nmol/mL, assay range: 15 nmol/mL →4000 nmol/mL, intra-assay CV<10%). Serum TRP levels were measured using a Human Tryptophan ELISA Kit (Cloud Clone USCN, USA). Different standard concentrations were obtained by diluting the lyophilized standard included in the kit. Following the kit procedure, the absorbance of the examined samples was measured at 450 nm with an EBLX-800 microplate reader (BioTek Instruments, Inc., USA). Concentrations corresponding to sample absorbance were calculated by the formula obtained from the standard curve (sensitivity: 0.55 µg/mL, detection range: 1.23–100 µg/mL, intra-assay: CV<10%).

Table 1. Demographic data and laboratory findings of patients infected with COVID-19 upon admission to the hospital

Parameters	Mild (n=41)	Severe (n=41)	p
Gender (male), n (%)	16 (39)	27 (66)	0.013
Age (years)	56 (40–65)	67 (56–82)	<0.001
Oxygen saturation	96 (94–97)	89 (86–91)	<0.001
Glucose (mmol/L)	6.82 (5.62–8.41)	8.15 (7.00–13.48)	<0.001
Urea (mmol/L)	5.16 (4.16–5.99)	8.15 (5.16–14.15)	<0.001
Creatinine (µmol/L)	77.8 (62.8–94.6)	89.3 (81.4–121.1)	0.002
AST* (U/L)	26 (20–40)	36 (29–47)	0.020
ALT† (U/L)	24 (18–34)	26 (18–33)	0.714
CRP‡ (mg/L)	37.6 (13.9–87.2)	114.78 (66.97–175.7)	<0.001
Ferritin (µg/L)	233 (108–650)	625 (234–1105)	0.006
Procalcitonin (µg/L)	0.07 (0.05–0.11)	0.17 (0.12–0.43)	<0.001
Laktate (mmol/L)	1.51 (1.23–2.03)	2.09 (1.57–3.25)	<0.001
PaO_2/FiO_2 (mmHg)	377.9 (310.2–402.1)	300.2 (280.8–315.6)	<0.001
Hemoglobin (g/L)	13.2 (12.2–14.2)	13.6 (11.6–14.9)	0.752
Hematocrit (%)	38.2 (36–42.5)	40.6 (35.4–45.4)	0.207
Platelet ($\times10^9$/L)	206 (155–268)	195 (166–262)	0.802
WBC§ ($\times10^9$/L)	7.15 (5.21–9.74)	7.24 (5.76–11.29)	0.481
Lymphocyte (%)	20 (14.1–26.6)	11.5 (8.7–20)	<0.001
NLR‖	3.62 (2.49–5.51)	7.04 (3.7–10.06)	<0.001
D-dimer (mg/L)	420 (260–889.45)	710 (520–1830)	0.004
aPTT¶ (sec)	30 (27.6–31.6)	30.6 (27.7–32.7)	0.484
INR**	0.99 (0.93–1.08)	1.1 (1–1.21)	0.002
Troponin (ng/L)	0.007 (0.004–0.015)	0.014 (0.009–0.064)	<0.001
Kynurenine (nmol/mL)	268 (151–507)	272 (187–1014)	0.068
Tyrptophan (ug/mL)	23.2 (7.9–48.5)	18.6 (7.4–36.7)	0.008
Kynurenine/Tyrptophan	11.1 (4.7–28.1)	15.0 (6.0–53.5)	<0.001
Exitus, n	3	23	<0.001
Need of mechanic ventilation, n	0	9	<0.001

Descriptive statistics are presented as medians (IQR) or frequencies with percentages. *: Aspartate aminotransferase; †: Alanine aminotransferase; ‡: C reactive protein; §: White Blood Cell; ‖: Neutrophil-to-lymphocyte ratio; ¶: Activated Partial Thromboplastin Time; **: International Normalized Ratio. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; PaO_2: Arterial partial pressure of oxygen; FiO_2: Fraction of inspired oxygen; WBC: White blood cell; NLR: Neutrophil-lymphocyte ratio; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; n: Number.

Statistical analysis

The Shapiro–Wilk test was used to determine whether the data were normally distributed. The results are presented as the mean±standard deviation, median (minimum-maximum), or frequency and percentage. Normally distributed data were compared with independent sample t-tests or one-way ANOVA. The Kruskal–Wallis and Mann–Whitney U tests were used for nonnormally distributed data. The Bonferroni correction was used as a multiple comparison test. Categorical variables were compared between groups using Pearson's chi-square and Fisher's exact tests. $p<0.05$ was considered to indicate statistical significance. All the statistical analyses were performed with IBM SPSS ver. 23.0.

Receiver operating characteristic (ROC) curves were generated to plot the KYN/TRP ratio and other variables. The sensitivity, specificity, positive likelihood ratio (+LR), and negative (-) LR were also determined for the optimal cutoff value. The performance of the KYN/TRP ratio and other variables in predicting patient status was determined using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) being the primary interest. Multivariate logistic regression analyses were used to assess the strength of associations between risk factors and patient status, and curves were generated to determine optimal cutoff values. MedCalc Statistical Software version 20.015 was used for ROC analysis.

Results

In the severe group, the KYN/TRP ratio reflecting IDO activity was significantly higher than that in the mild group ($p<0.001$), while the TRP level was significantly lower in the severe group ($p=0.008$). The KYN level was higher in severely ill patients than in healthy patients ($p>0.05$) (Table 1).

There was no significant difference between genders in KYN/TRP, TRP, or KYN levels. After the patients were grouped as se-

Table 2. Diagnostic test results for the prediction of severe COVID-19

	AUC	Cutoff	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Likelihood ratio	Negative Likelihood ratio
Age	0.736	52	87.80 (73.8–95.9)	48.78 (32.9–64.9)	1.71	0.25
Kynurenine	0.617	225.07	90.24 (76.9–97.3)	34.15 (20.1–50.6)	1.37	0.29
Tyrptophan	0.67	18.1	48.8 (32.9–64.9)	80.5 (65.1–91.2)	2.50	0.64
Kynurenine/Tyrptophan	0.71	14.2	56.1 (39.7–71.5)	80.5 (65.1–91.2)	2.88	0.55
Ferritin	0.675	226.8	80.49 (65.1–91.2)	48.78 (32.9–64.9)	1.57	0.40
Platelet	0.516	102	12.20 (4.1–26.2)	100.00 (91.4–100.0)	–	0.88
Troponin	0.747	0.026	41.46 (26.3–57.9)	97.56 (87.1–99.9)	17.00	0.60
Kynurenine/Tyrptophan, Ferritin, Platelet, Troponin, Age	0.94	0.39	92.6 (80.1–98.5)	87.8 (73.8–95.9)	7.60	0.08

AUC:Area under the curve; CI: Confidence interval.

vere or mild, it was observed that KYN levels were significantly higher in men (299 (151–404) nmol/mL) than in women (227 (168–507) nmol/mL) only in mild patients (p=0.010).

There was no correlation between the laboratory parameters in Table 1 and TRP-KYN levels. After patients were grouped into severe and mild groups, correlations were observed between KYN/TRP levels and Hb (p=0.009), Hct (p=0.003), INR (p=0.031), and aPTT (p=0.002) levels only in mild patients.

Only 9 patients died during treatment. There were no significant differences in TRP, KYN, or KYN/TRP levels between deceased and surviving patients. In addition, no significant differences were detected in TRP or KYN levels in terms of mechanical ventilation need or hospital stay duration.

ROC analysis was performed to determine the effect of TRP, KYN, and KYN/TRP levels on disease severity (Table 2).

According to the univariate logistic regression analysis, the AUC of TRP was 0.67, its sensitivity was 48.8%, its specificity was 80.5%, the AUC of KYN/TRP was 0.71, its sensitivity was 56.1%, and its specificity was 80.5%. Multiple logistic regression analysis was performed with various variations using the patients' demographic data and laboratory parameters. The combination of age, troponin level, platelet count, ferritin level, and KYN/TRP ratio had the highest AUC. According to the multivariate logistic regression analysis, the AUC was 0.94, the sensitivity was 92.6%, and the specificity was 87.8% in determining disease severity (Fig. 1).

Discussion

Lower TRP and higher KYN levels have been reported in COVID-19 patients compared to healthy individuals [17, 23]. A meta-analysis of 1269 individuals, consisting of 794 COVID-19 patients and 475 controls, revealed a significant increase in the KYN/TRP ratio (p<0.0001) and KYN level, and a significant decrease in the TRP level [17]. In a study including 239 healthy individuals and 89 COVID-19 patients, it was observed that the KYN/TRP ratio in patients was 3.7 times higher than in healthy controls. The AUC for KYN/TRP levels at the time of COVID-19 diagnosis was 0.97 (95% CI=0.9463–0.9937, p<0.0001). Plasma TRP concentrations of the patients at admission were higher than the last sample before death (30.1±10.0 vs. 25.5±9.4 µmol/L), KYN (p=0.013) and KYN/TRP levels (p=0.080) lower [23]. McPadden et al. [24] reported that TRP levels in the cerebrospinal fluid of patients with and without COVID-19 were 19.4±16.4 and 24.8±18.9 µmol/L, respectively. In a meta-analysis study including 773 patients, KYN/TRP levels were found to be significantly higher in seriously ill patients (p<0.001) [17]. Similarly, we detected significantly lower TRP levels (p=0.008), higher KYN levels, and higher KYN/TRP ratios reflecting IDO activity (p=0.001) in severe patients compared to mild patients. Our results support the hypothesis that the TRP metabolic pathway is a potential marker of COVID-19 severity and can be targeted by therapeutic intervention.

Studies show that COVID-19 progresses worse in men than in women. Lionetto et al. [16] reported that KYN levels were higher in male patients than in female patients (p=0.004), but there was no gender-related difference in TRP levels. McPadden et al. [24] found higher hospitalization (OR 1.68, 95% CI=1.45–1.90) and in-hospital mortality (OR 1.87, 95% CI=1.33–2.63) rates in male patients. In our study, no significant difference was detected in TRP or KYN levels between genders in the severe group, while in the mild group, KYN

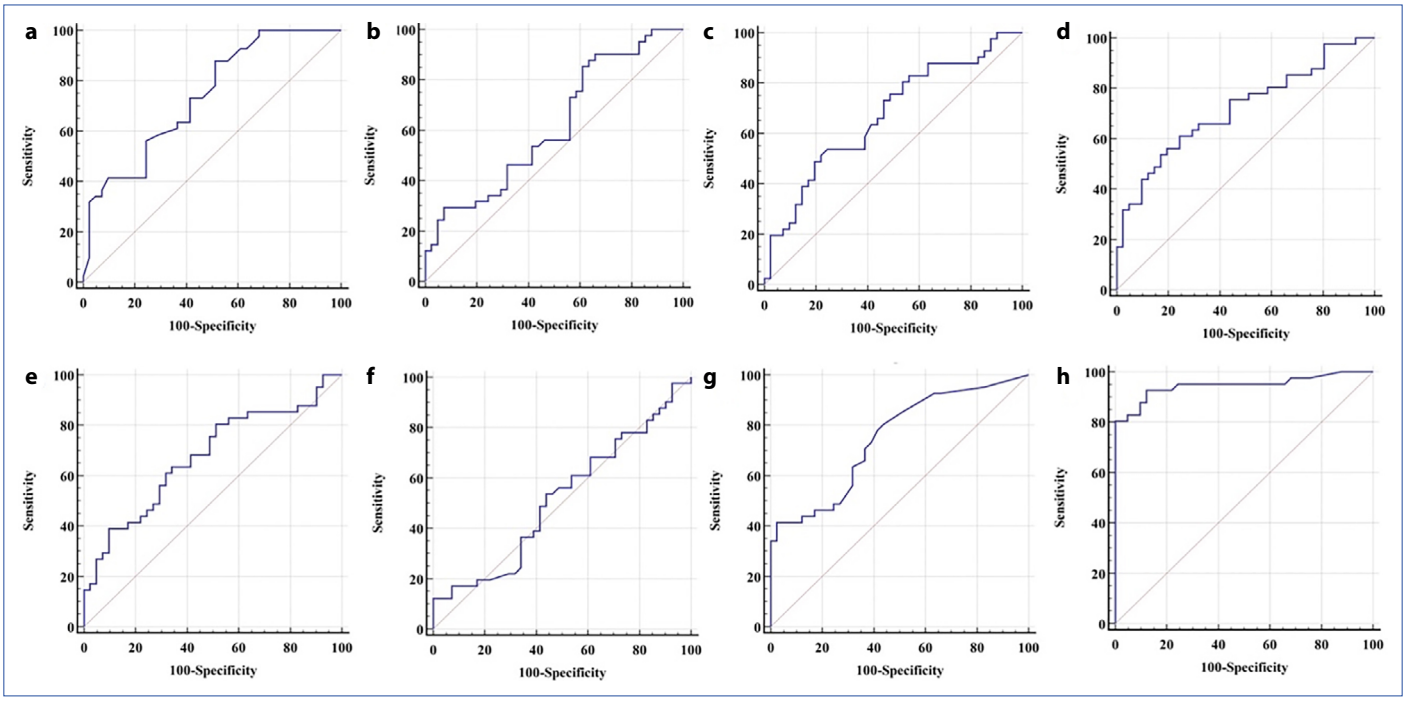

Figure 1. ROC analysis of univariate and multivariable logistic regression models for predicting severity of COVID-19. ROC analysis of parameters are shown in (a) age, (b) kynurenine, (c) tryptophan, (d) kynurenine/tryptophan, (e) ferritin, (f) platelet, (g) troponin, (h) kynurenine/tyrptophan, ferritin, platelet, troponin, age graphs.

ROC: Receiver operating characteristic.

levels were significantly higher in men (299 (151–404) nmol/mL) than in women (227 (168–507) nmol/mL) (p=0.010). This difference may be due to the rapid turnover rate of KYN in female patients.

ARDS is one of the causes of death in COVID-19 patients. Data obtained from a multicenter study showed that PaO_2/FiO_2, which reflects tissue oxygenation, was lower and lactate levels were higher in deceased patients [19]. Similarly, the PaO_2/FiO_2 ratio was significantly lower, and the lactate level was significantly higher in the severe group (p<0.001) in this study. However, we did not find a significant relationship between PaO_2/FiO_2 ratio, lactate level, mechanical ventilation need, and TRP-KYN levels.

In the study conducted by Michaelis et al. [25], no significant difference was found in the KYN/TRP ratio at the time of admission between deceased (n=24) and surviving (n=81) patients. However, after one week, a significant decrease in KYN levels was observed in the surviving group, while a significant increase in KYN levels was observed in the deceased group. Researchers stated that the decrease in KYN is associated with the improvement in the clinical course, while the increase in KYN may be a sign of worsening of the disease and poor outcomes. Similarly, in this study, there was no significant difference in TRP, KYN, or KYN/TRP levels at admission between deceased and surviving patients. However, since we did not measure TRP and KYN levels again in the following period, we could not reach such an interpretation. Additionally, there was no correlation between length of hospital stay and TRP, KYN, or KYN/TRP levels.

According to a meta-analysis, ferritin, D-dimer, procalcitonin, C-reactive protein, and troponin levels were associated with COVID-19 severity and mortality [26]. These parameters were significantly higher in the severe group but were not correlated with KYN or TRP levels in this study.

The TRP metabolic pathway likely contributes to the pathophysiology, severity, and progression of COVID-19 [17]. In this study, the KYN/TRP ratio had a sensitivity of 56.1% and specificity of 80.5% in predicting the severity of COVID-19, with an AUC of 0.71. Multivariate logistic regression analysis was performed with different parameter combinations to determine the role of these parameters in predicting disease severity. The highest AUC was reached by regression analysis of age, troponin level, platelet count, ferritin level, and KYN/TRP ratio. According to multivariate logistic regression analysis, sensitivity was 92.6%, specificity was 87.8%, and AUC was 0.94. Hu et al. [27] reported that the sensitivity and specificity of a model consisting of age, lymphocyte count, serum albumin level, and NLR in predicting severe COVID-19 were 90.5% and 84.2%, respectively. Liang et al. [28] reported the AUC as 0.77 in the COVID-19 Gram model they developed to predict critical diseases. According to the NEWS2 model developed by De Socio et al. [29], the AUC was 0.87. According to multivariate regression analysis in our study, AUC, sensitivity, and specificity were higher than other studies. When evaluated together with parameters such as age, troponin, and platelet count, ferritin, this result showed that the KYN/TRP ratio is more valuable than other prediction models in predicting disease severity in the early period.

Limitations

Several limitations should be taken into account when interpreting these results. Due to the retrospective design, only routinely measured parameters were available for statistical analysis. Since all studies showed that there was a significant increase in KYN/TRP levels in the patient group compared to the control group and there was no study showing the opposite effect, we did not include the control group in our study to increase the patient population. We also had no information about how long the patients had been symptomatic. Therefore, it may be possible that these patients are at slightly different stages of COVID-19 disease. Measuring TRP and KYN levels on different days could explain their effect on the course of the disease more meaningfully. Therefore, a larger, long-term follow-up cohort with repeated measurements is required.

Conclusion

The TRP metabolic pathway is activated in severe COVID-19 patients. To our knowledge, the KYN/TRP ratio, together with age, troponin, platelet count, and ferritin parameters, is the model with the best AUC for early prediction of clinical outcomes in COVID-19. Our study provided emergency physicians with more information and offered an alternative to better guide them early in predicting the severity of COVID-19.

Ethics Committee Approval: The study was approved by The University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital Health Application and Research Center Clinical Research Ethics Committee (No: 2933, Date: 25/08/2020).

Authorship Contributions: Concept – M.S.O., A.O., G.O.; Design – M.S.O., G.O., Z.M.Y.K.; Supervision – M.S.O.; Materials – A.O., E.A., M.S.O., Z.M.Y.K., E.S., G.O.; Data collection &/or processing – M.S.O., A.O., E.A.; Analysis and/or interpretation – M.S.O., G.O., E.S.; Literature search – M.S.O., Z.M.Y.K., E.S., E.A.; Writing – M.S.O.; Critical review – Z.M.Y.K., E.S., E.A., G.O., A.O.

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33. [CrossRef]
2. Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Med Virol 2020;92(9):1449–59.
3. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol 2020;20(6):363–74. [CrossRef]
4. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: Vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med 2020;46(6):1105–8.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395(10229):1054–62. [CrossRef]
6. Salter M, Pogson CI. The role of tryptophan 2,3-dioxygenase in the hormonal control of tryptophan metabolism in isolated rat liver cells. Effects of glucocorticoids and experimental diabetes. Biochem J 1985;229(2):499–504. [CrossRef]
7. Lee A, Kanuri N, Zhang Y, Sayuk GS, Li E, Ciorba MA. IDO1 and IDO2 non-synonymous gene variants: Correlation with crohn's disease risk and clinical phenotype. PLoS One 2014;9(12):e115848.
8. Isenović ER, Zakula Z, Koricanac G, Ribarac-Stepić N. Comparative analysis of tryptophan oxygenase activity and glucocorticoid receptor under the influence of insulin. Physiol Res 2008;57(1):101–7. [CrossRef]
9. Ball HJ, Sanchez-Perez A, Weiser S, Austin CJ, Astelbauer F, Miu J, et al. Characterization of an indoleamine 2,3-dioxygenase-like protein found in humans and mice. Gene 2007;396(1):203–13.
10. Curti A, Trabanelli S, Salvestrini V, Baccarani M, Lemoli RM. The role of indoleamine 2,3-dioxygenase in the induction of immune tolerance: Focus on hematology. Blood 2009;113(11):2394–401. [CrossRef]
11. Fukunaga M, Yamamoto Y, Kawasoe M, Arioka Y, Murakami Y, Hoshi M, et al. Studies on tissue and cellular distribution of indoleamine 2,3-dioxygenase 2: The absence of IDO1 upregulates IDO2 expression in the epididymis. J Histochem Cytochem 2012;60(11):854–60. [CrossRef]
12. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity 2005;22(5):633–42. [CrossRef]
13. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 2010;185(6):3190–8. [CrossRef]
14. Manlapat AK, Kahler DJ, Chandler PR, Munn DH, Mellor AL. Cell-autonomous control of interferon type I expression by indoleamine 2,3-dioxygenase in regulatory CD19+ dendritic cells. Eur J Immunol 2007;37(4):1064–71. [CrossRef]
15. Ravishankar B, Liu H, Shinde R, Chaudhary K, Xiao W, Bradley J, et al. The amino acid sensor GCN2 inhibits inflammatory responses to apoptotic cells promoting tolerance and suppressing systemic autoimmunity. Proc Natl Acad Sci U S A 2015;112(34):10774–9. [CrossRef]
16. Lionetto L, Ulivieri M, Capi M, De Bernardini D, Fazio F, Petrucca A, et al. Increased kynurenine-to-tryptophan ratio in the serum of patients infected with SARS-CoV2: An observational cohort study. Biochim Biophys Acta Mol Basis Dis 2021;1867(3):166042. [CrossRef]
17. Almulla AF, Supasitthumrong T, Tunvirachaisakul C, Algon AAA, Al-Hakeim HK, Maes M. The tryptophan catabolite or kynurenine pathway in COVID-19 and critical COVID-19: A systematic review and meta-analysis. BMC Infect Dis

2022;22(1):615.
18. Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: Immunosuppression by starvation? Immunol Today 1999;20(10):469–73. [CrossRef]
19. Gündoğan K, Akbudak İH, Hancı P, Halaçlı B, Temel Ş, Güllü Z, et al. Clinical outcomes and independent risk factors for 90-day mortality in critically ill patients with respiratory failure infected with SARS-CoV-2: A multicenter study in Turkish intensive care units. Balkan Med J 2021;38(5):296–303.
20. 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(4):343–54.
21. Robertson J, Gostner JM, Nilsson S, Andersson LM, Fuchs D, Gisslen M. Serum neopterin levels in relation to mild and severe COVID-19. BMC Infect Dis 2020;20(1):942. [CrossRef]
22. Türkiye Cumhuriyeti Sağlık Bakanlığı. Covid-19 erişkin hasta tedavisi. Available at: https://covid19.saglik.gov.tr/Eklenti/43095/0/covid-19rehberieriskinhastayonetimivetedavi-12042022pdf.pdf. Accessed Jul 1, 2024.
23. Guo L, Schurink B, Roos E, Nossent EJ, Duitman JW, Vlaar AP, et al; also on behalf of the Amsterdam UMC COVID-19 Biobank Study Group. Indoleamine 2,3-dioxygenase (IDO)-1 and IDO-2 activity and severe course of COVID-19. J Pathol 2022;256(3):256–61. [CrossRef]
24. McPadden J, Warner F, Young HP, Hurley NC, Pulk RA, Singh A, et al. Clinical characteristics and outcomes for 7,995 patients with SARS-CoV-2 infection. PLoS One 2021;16(3):e0243291.
25. Michaelis S, Zelzer S, Schnedl WJ, Baranyi A, Meinitzer A, Enko D. Assessment of tryptophan and kynurenine as prognostic markers in patients with SARS-CoV-2. Clin Chim Acta 2022;525:29–33.
26. 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. [CrossRef]
27. Hu H, Du H, Li J, Wang Y, Wu X, Wang C, et al. Early prediction and identification for severe patients during the pandemic of COVID-19: A severe COVID-19 risk model constructed by multivariate logistic regression analysis. J Glob Health 2020;10(2):020510. [CrossRef]
28. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al; China Medical Treatment Expert Group for COVID-19. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med 2020;180(8):1081–9. [CrossRef]
29. De Socio GV, Gidari A, Sicari F, Palumbo M, Francisci D. National Early Warning Score 2 (NEWS2) better predicts critical Coronavirus Disease 2019 (COVID-19) illness than COVID-GRAM, a multi-centre study. Infection 2021;49(5):1033–8. [CrossRef]