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A Significant Role of Soluble Programmed Death Ligand (sPDL-1) in a Progressive Infection Among Patients with Omicron SARS-CoV-2

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Abstract

Immune checkpoint inhibitors (ICIs) are thought to be critical in developing COVID-19. Even if Omicron had a lower risk of hospitalization and mortality than other variants, some progress has been observed. Programmed cell death-1 (PD-1) is an essential ICI target because it suppresses immune cell activity and serves as a fatigue signal for immune cells. To determine the function of soluble Program Death-Ligand1 (sPD-L1) in SARS-CoV-2 (Omicron variant) infection progression and its relation with biomarkers. A case-control study (43 COVID-19 patients and 30 healthy controls) was tested for the Omicron variant infection by real-time PCR, and the biomarker and sPD-L1 were measured with an ELISA kit. Median sPD-L1 levels in infected individuals were significantly higher than in healthy controls (1079 pg/mL vs. 618.8 pg/mL; p <0.0001). According to the two-tailed Fisher exact test, 93.3 % of mild-moderate individuals had an sPDL-1 level below the median of 1079 pg/ml, indicating minimal production. In contrast, significantly high levels were found in 76.9 % of severe-critical patients. sPD-L1 levels were strongly associated with viral load (Ct value) (p < 0.0001) and increased with older age (p = 0.024) along with CRP and Ferritin levels, serving as predictive indicators for infection progression. sPD-L1 may play a role in developing infection, together with the SARS-CoV-2 Omicron variants, high viral load (low Ct value), the aged group, and severe infection, and with clinical symptoms. Additional research is needed to decrease sPD-L1-based interferon production.

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1. Introduction

The fast global spread of SARS-CoV-2 caused various levels of anxiety, culminating in a catastrophic and fatal outbreak. SARS-CoV-2 is responsible for the COVID-19 pandemic [1]. Despite mitigating measures, such as vaccination, new variants emerged during the pandemic, including Omicron (B.1.1.529), a further modified strain with a short incubation period; it was called VOC by the WHO [2]. The emergence of the Omicron variant raises significant questions about how such boundless and intense mutational changes must occur quickly since the initial variant, Wuhan-Hu-1, was first identified in December 2019 [3]. Any viral strain from a patient sample has a genetic code, as various ways its genetic code is defined by specific biomolecular perturbations or factors (mutations, recombination, duplication, insertion, and deletion) into the genomic sequences that can affect properties such as virus transmission rate, pathogenicity, duration, and evasion of host responses [4,5]. Alterations in programmed death ligand (PD-L1) expression levels could significantly impact the capacity of SARS-CoV-2 to escape the immune response. The increasingly rapid emergence rate of SARS-CoV-2 variants has highlighted gaps in the existing immunotherapeutic approaches. The effect of the new variant on the programmed death ligand-1 (PD-L1) pathway and its implications for patient care are mainly discussed here. The PD-L1 pathway mediates cancer progression and plays a critical role in immunomodulation, acting as a part of the immune evasion strategies of cancerous cells [6-8]. Likewise, catastrophic clinical outcomes in COVID-19 patients have been linked to high PD-L1 pathway activation, potentially providing promising drug targets for the treatment of symptoms of the

disease [9]. However, the expanded emergence rate of variants, particularly the Omicron variant, can increase PD-L1 expression levels, disrupting a balance between antiviral and regulatory immune responses. Because of this, more adaptive and innovative strategies are urgently needed to treat patients. It investigates how immunotherapies can be modified in response to changes in PD-L1 expression levels using a mathematical model particular to PD-L1. COVID-19 patients have a dysregulated PD-1/PD-L1 axis, affecting dendritic and monocyte cells, leading to decreased T cell response and stimulatory capability [10]. Elevated PD-L1 expression in platelets impacts CD4+ T cell IFN-γ production. Soluble PD-L1 (sPD-L1) is found in membrane PD-L1-positive cells and has a detrimental influence on cancer prognosis, with higher levels increasing death probability and lower levels improving prognosis [11]. The current study aimed to detect the role of progressive infection among Omicron variants of SARS-CoV-2 and identify sPD-L1 as an inflammatory biomarker in progressive infection among variants of SARS-CoV-2.

2. Materials and Methods

2.1. Study population

This study included 73 individuals. These participants comprised 43 patients who had previously been diagnosed in cooperation with the Iraqi Ministry of Health/National Central Health Laboratory. Patients were distributed, 30 falling into the mild-moderate category and 13 falling into the severe-critical category. The University of Baghdad Academic and Ethical Committee (CSEC/1124/0097) approved this study on November 8, 2024. To ensure a balanced representation, the patients and healthy controls were divided into sex (male and female) and age groups (22–35, 36–50). Patients from Iraq in Baghdad Teaching Hospital between August 2024 and December 2024 were characterized as positive in the rRT-PCR (reverse transcriptase real-time PCR) test. Healthy controls did not have COVID-19 antibodies (IgM and IgG), and rRT-PCR results were negative. Remarkably, every participant took part in providing the consent forms, guaranteeing that they were all aware and completely included in the study. With a medium oxygen saturation (SpO2) of 90% in room air, Persons suffering from hypoxia or pneumonia-related signs do not exhibit any severe symptoms. Still, moderate symptoms of COVID-19 include everything from fever and cough to dyspnea and even respiratory distress. It is worth mentioning that the sounds of moderately severe pneumonia could also be associated with several other severe symptoms. There are two groups of patients, severe and moderate WHO Interim Guidance recognized Criteria: 1- moderate (patient infected with pneumonia and without severe pneumonia) 2- severe (pulse oxygen saturation (SpO2) ≤ 93% or the rate of respiration ≥ 30 breaths/min, severe respiratory distress) (WHO, 2020).

2.2. Sample Collection

Data collection for this study involved various steps. Firstly, demographic information and medical history. In the second place, the nasal swabs and blood samples were taken from the study groups to diagnose SARS-CoV-2 with variants and to measure sPD-L1 along with other biomarkers, ensuring detailed information about each participant's sPD-L1 levels for scientific excellence. Seventy-three nasal swabs and five milliliters of blood were extracted from patients (43), as well as healthy controls (HC) (30). An EDTA-blood tube (2 ml) completes the blood count and d-dimer. Serum was collected by evenly dividing blood (3 ml) into gel tubes for ferritin and LDH, and freezing the remaining serum and swabs at 70 °C until the sPD-L1 testing and rRT-PCR (reverse transcriptase real-time PCR) test.

2.3. Laboratory tests for SARS-CoV-2 and Omicron Variants

The viral delivery medium was immediately filled with the swabs. Viral RNA Mini kit-A QIA amp (Qiagen Germany) is used for viral RNA extraction. SARS-CoV-2 was detected according to the manufacturer's instructions using rRT-PCR (DIAGNOVITAL SARS-COV-2 real-time PCR kit). Omicron variant detected using TaqPath (CE-IVD RT-PCR Kit, Thermo Fisher, Germany). If a patient had a cycle threshold of 36 or below in TaqPath, the COVID-19 PCR test and the ORF1ab or nucleocapsid gene targets returned positive. However, the S gene was not found, so the infection was classified as SGTF (s gene target failure assay) [12].

2.4. Biomarker Detection

Three sodium citrate tubes, gel, and EDTA separated the blood samples. Following a 20-minute centrifugation at 3500 rpm of the first segment of the blood samples (sodium citrate tubes), an automated protein analyzer was used to perform plasma d-dimer analysis. Plain tubes and EDTA tubes were filled with five milliliters of venous blood (2 and 3 mL, respectively). After allowing the plain tube to clot, the serum was collected by centrifuging it for 15 minutes at 4 °C. CRP was detected in the serum by electro-

chemiluminescence immunoassay system (Roche Cobas Integra 400 plus, Switzerland). Whereas the total white blood cells (neutrophils and lymphocytes) were counted by an automated hematology analyzer (ABX Micros ES 60, Horiba, USA) in EDTA blood. The serum needed to measure ferritin and lactate dehydrogenase (LDH) was extracted from the gel tube holding the second portion of the blood samples by spinning it for ten minutes at 6000 rpm. The Roche Cobas Integra 400 plus electro-chemiluminescence immunoassay was used to measure the serum levels of LDH. Ferritin was also evaluated using a miniVIDAS analyzer (ELFA) from BioMerieux, following the manufacturer's instructions.

2.4.1. Immunoassay of sPDL-1

An enzyme-linked immunosorbent test (ELISA) kit from SunLong Biotech, China (Catalogue Number: SL2269Hu) is used to assess the levels sPDL-1. Serum levels were measured following the manufacturer's directive. The test ranges from 35 to 2000 pg/mL, with a 26 pg/mL sensitivity.

2.5. Statistical Analysis

To ascertain the function of the gathered data, a comprehensive statistical analysis was conducted on sPD-L1 in COVID-19 infection with the Omicron variant. Descriptive statistics were utilized to summarize the participants' demographic characteristics and clinical variables. Spearman's rank correlation coefficient was checked to examine the association between the sPD-L1 levels and the severity of SARS-COV-2 infections. A statistical analysis, a Two-sided Fisher's exact test was used to assess numbers and percentages representing categorical variables. The Kolmogorov test is used for normality with continuous data. Variables were not normally distributed using the median and interquartile range (IQR) and compared using the Mann-Whitney U and Kruskal-Wallis tests. the odds ratio (OR) was determined with a 95% confidence interval (CI) using Logistic regression analysis. A statistically significant result was a probability (p) value ≤0.05. IBM SPSS Statistics 27.0 (Armonk, NY: IBM Corp.) and GraphPad Prism version 10.0 (San Diego, California, USA) were the statistical programs utilized for the analysis. The sample size power was determined using the compromise analysis method and G*Power software version 3.1.9.2.

3. Results and Discussion

3.1. Blood parameters and chronic disease

In moderate cases, mean platelet and WBC counts were higher than in severe ones (241.7 vs. 144; 6.48 vs. 3.49, respectively, $p < 0.001$). Severe cases had a significantly higher mean neutrophil count (2.4 vs. 1.5; $p < 0.001$). Severe patients had significantly higher levels of Ferritin and CRP than moderate instances (981 vs. 360; 29 vs. 9.7, respectively; $p < 0.001$). Severe cases had significantly higher mean D-dimer and LDH levels than mild instances (995 vs. 322; 289 vs. 200, respectively; $p < 0.001$). Severe cases had significantly higher rates of hypertension and diabetes compared to mild cases (29 vs. 24; 27 vs. 24; $p < 0.001$). Severe cases had significantly higher rates of hypertension and diabetes than mild cases (11 vs. 5; 7 vs. 4; $p < 0.001$), as shown in Table 1.

Table 1: Baseline blood parameters and chronic disease in COVID-19 patients.

Parameter	COVID-19 patients; N = 43		Reference	*p–value*
	Mild-moderate; N = 30	Severe; N = 13	range†	
Platelets (× 109/L)	241.7 (191.3 – 275.5)	144 (111 – 160)	135 – 317	< 0.001
WBC (× 109/L)	6.48 ± 1.4	3.49 ± 0.84	3.4 - 9.6	
Neutrophil / lymphocyte ratio	1.5 (1.2 – 1.6)	2.4 (2.2 – 2.9)	1.8 – 2	
CRP (mg/L)	9.7 (5 – 16.2)	29 (27.3 – 61.1)	8 – 10	
Ferritin (ng/ml)	360 (260 – 521)	981 (780 – 1297)	20 – 250	
D. dimer (mg/L)	322 (230 – 507)	995 (810 – 2106)	≤ 500	
LDH (IU/L)	200 (165 – 215)	289 (265 – 395)	105 – 333	
Diabetes	4 (13.3)	7 (53.9)	----	
Hypertension	5 (16.7)	11 (84.6)	----	

The results are disposed of as median with interquartile range (IQR) (continuous variables), mean ± standard deviation, number, and percentage (categorical variables as present). There is a comparison between means and Student t-test, Medians, and Mann-Whitney *U* test. The bold line of the *p*-value is referred to as significant. CRP (C-reactive protein), LDH (L dehydrogenase), WBC (White blood cell count), SD (Standard deviation), †: Data source from https://www.mayoclinic.org.

3.2. Age and Sex

As shown in Table 2, the patients were divided into ages 22–35 and 36–50 years. According to the statistical study, age is a significant risk factor, which revealed substantial (p <0.001) variations in age groups among COVID-19 patients. There was a significant sex difference in the patients (p =0.023), with males having more infections than females.

Table 2: Distribution of COVID-19 patients and healthy controls according to age and sex.

Age group	Patients (N = 43)		Healthy controls (N = 30)	
	N	%	N	%
22-35	15	34.9	23	76.7
36-50	28	65.1	7	23.3
Statistical analysis	Pearson X2 = 12.361; D.F. = 1; $p < 0.001$			
Sex				
Male	26	60.5	10	33.3
Female	17	39.5	20	66.7
Statistical analysis	Pearson X2 = 5.204; D.F. = 1; $p = 0.023$			

According to the two-tailed Fisher exact test (Table 3), 93.3 % of mild-moderate individuals had an sPDL-1 level below the median of 1079 pg/ml, indicating minimal production. In contrast, significantly high levels were found in 76.9 % of severe-critical patients.

Table 3: Distribution of COVID-19 patients (mild-moderate and severe) and controls stratified according to the median level of sPDL-1

Group	sPD-L1 level, pg/ml		OR	95% CI	p-value
	High (>median)	Low (≤median)			
Control	7	23	Reference		
Mild-moderate	2	28	0.23	0.05 – 1.21	0.145
Severe-critical	10	3	10.95	2.46 – 48.73	0.002

OR: Odds ratio; CI: Confidence interval; p: the probability of a two-tailed Fisher exact test (to compare categorical variables).

3.3. Soluble programmed death-ligand 1

The median sPD-L1 level in patients was significantly higher than in healthy controls (1079 pg/mL vs. 618.8 pg/mL; p<0.0001), as seen in Figure 1. Most patients were identified as high producers of sPDL-1, which differed significantly from HC and was a significant indicator for progressive infection.

Patients with severe COVID-19 had lower platelet counts. Proplatelet formation and abnormal megakaryocyte distribution (e.g., in the heart, lung, kidney, and microvasculature tissue) were seen in these individuals. Viral antigen-antibody complexes or host inflammatory reactions can stimulate platelets; the reticuloendothelial system can more readily remove excited platelets from circulation. Through some receptors, platelets can directly communicate with the virus [13]. Platelet-released products can kill viral infections or enhance virus persistence, depending on the kind of infection. Viral interactions with megakaryocytes limit platelet production. WBC counts were also reduced in individuals with severe COVID-19 because SARS-CoV-2 infected and lysed these cells. Apoptosis may be triggered by a cytokine storm, including elevated levels of TNFα and interleukins [14]. Table 1 shows that the neutrophil-to-lymphocyte ratio (NLR) increased due to poor clinical outcomes and increasing illness severity. CRP, a nonspecific protein generated by hepatocytes during inflammation and infection, was elevated in 68% of severe cases. Patients with SpO2 < 90% had higher CRP levels than those with SpO2 > 90%. Moreover, COVID-19 patients have higher CRP, IL-10, and IL-6 levels, which correlate with lower SpO_2 [15]. Ferritin was linked to severe instances in this study because ferritin is the key to immune system dysregulation, particularly hyperferritinemia, and plays an important role in cytokine storm by inhibiting the immune system and pro-inflammatory effects. Hyperferritinemia is caused by cytokines and

macrophages producing active ferritin, which increases IL-10 (immune suppression) and IL-1β (proinflammatory cytokines). Extra ferritin induces fibrosis or tissue damage, resulting in the generation of reactive oxygen species. As a result, ferritin may have a role in determining the severity of COVID-19 [16].

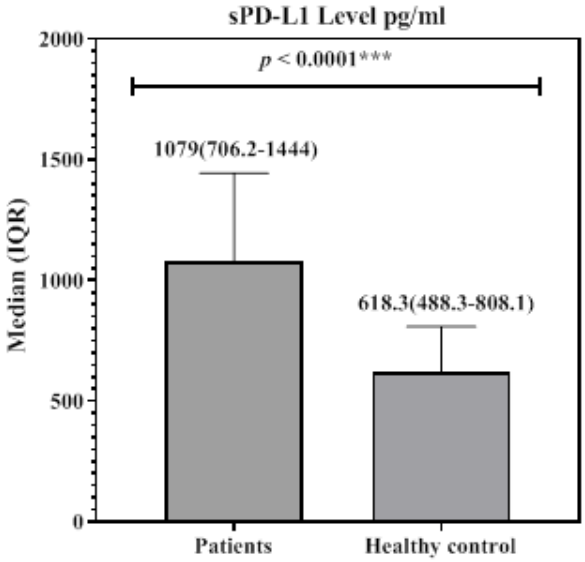

Figure 1: Soluble programmed death-ligand one median in COVID-19 patients and Healthy Controls. *p:* the probability of the Mann-Whitney U test (to compare continuous variables).

The median sPDL-1 revealed no significant difference in the sex group, while the age group ($p = 0.024$) and Ct-value ($p < 0.0001$) were significant among Omicron patients, as shown in Figure 2.

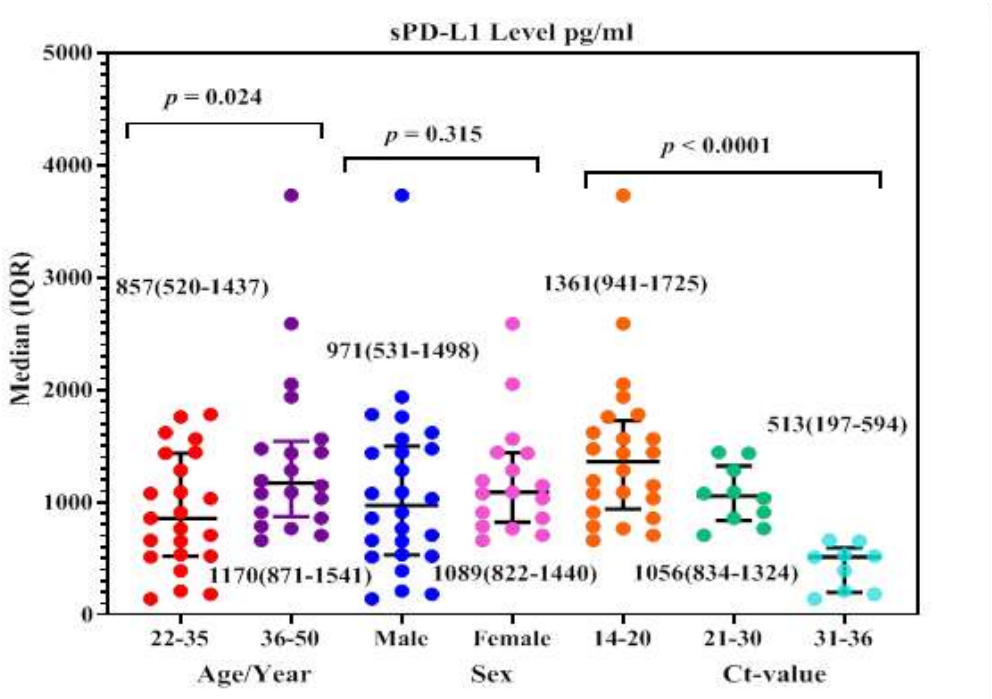

Figure 2: Concentration of sPD-L1 stratified by age group/year (22-35 and 36-50 years) and sex (male and female) in COVID-19 patients. p: the probability for continuous variables tested with the Mann-Whitney U test and the Kruskal-Wallis test.

D-dimers rise in severe instances; they are used to predict and diagnose thrombus recurrence and intravascular coagulation. The value of D-dimers in COVID-19 patients was associated with death and severe disease progression. Several postmortem liver biopsy investigations identified modest lobular, portal inflammatory, and microvesicular steatosis [17]. Further investigation revealed arterial walls with fibrous thickening, luminal ectasia, and thrombosis, indicating that COVID-19 liver failure includes coagulation, dysfunction, and endothelial lesions. As a result, elevated D-dimer levels can cause liver damage [18]. LDH levels are connected with severe COVID-19 instances. LDH is an enzyme produced in all cells in the body that is responsible for energy. The LDH was used to assess tissue damage caused by interstitial lung and liver disorders. Increased LDH levels are thought to be a sign of cell/tissue damage, which might indicate lung injury, such as SARS pneumonia [19]. A study found that COVID-19 negatively impacted hypertension and type 2 diabetes mellitus (T2DM), triggering NLRP3 inflammasome activity and increased caspase-1, monocytes, IL-18, and IL-1ß levels. NLRP3 also contributes to atherosclerosis and endothelial inflammation in diabetes [20].

Many investigations discovered that the severity of the COVID-19 infection is highly associated with thrombo-cytopenia, with a more significant reduction in platelet counts in mortality cases [21]. Studies in China found a link between lymphopenia, the requirement for ICU care, and the development of acute respiratory distress syndrome (ARDS) [22]. The patients in the current study were separated into the age groups 22-35 and 36-50. The statistical study revealed substantial ($p = 0.001$) differences between the age groups of COVID-19 patients: the older the age, the greater the risk of severe-critical illness. At the same time, mild illness is less harmful in infants under a year. This finding is consistent with another study that found a causal link between aging and COVID-19 infection [23]. In terms of sex, patients showed that men had 26 (60.5%) instances and females 17 (39.5%), with a significant difference between groups ($p =0.023$) (Table 2). The male-to-female ratio of COVID-19 deaths is higher in countries like Iraq, the Netherlands, the Dominican Republic, the Philippines, and Denmark. The mortality rate is more significant in males than in females. A Chinese study found that 12.8% of men died while 7.3% of women died. Sex hormones, vitamin D, and obesity may contribute to sex differences. The X chromosome, densely packed with immune-related genes, has distinct effects on the immune system. Women generally have stronger adaptive and innate immune responses, faster pathogen clearance, and greater vaccine efficacy, which increases their susceptibility to autoimmune and inflammatory diseases. The study's findings might result from the sample being chosen for sex [24]. Previous local studies of COVID patients have shown that the infection rate is higher in males 65.2% than in females 34.8% [25]; other studies showed Infants sex males 67 (54.9%), females 55 (45.1%) [26], male 166 (70.94) female 68 (29.06) [27], male 172 (69%) female 75(30.4%) [28].

Serum sPD-L1 levels are generally low in healthy people but are more significant in severe instances, indicating weakened immunity and enhanced viral replication. This is comparable to HBV infection, where sPD-L1 levels rise during the acute phase, resulting in chronic infection with little immunity and insufficient resistance. The potential viral load indirectly raises sPD-L1 levels, aiding viral escape [29]. The study found significant diversity in soluble mediator sPDL-1 levels among individuals, with 76.9 % of severe cases producing high levels due to previous infections. Elevated sPD-L1 levels are linked to COVID-19 severity, indicating that they might be biomarkers for disease severity, prognosis, and vaccination response, allowing early intervention and treatment outcomes [30]. The findings of this study indicated that, while the level of sPDL-1 increases with older age and females in patients, it is statistically significant; nonetheless, this data suggests that higher sPD-L1 levels in the elderly may be caused by aging rather than age-related illnesses. However, we observed that age-related increases in sPD-L1 were associated with sex and chronic disease status. In contrast to healthy young girls and men, SARS-CoV-2 in males has a more significant likelihood of acquiring the disease as they age, with a higher increase in sPD-L1 levels, and the heightened severity is evident within the elderly male and female groups. This aligns with past research demonstrating that PD-L1/TC or PDL-1/TILS expression was independent of age, gender, clinical stage, histological grade, and drinking and smoking habits [31]. Moreover, the correlation between PD-L1 /TILS and PDL-1/TC expression and ages over 65 is explained by the elderly's weakened host immunity, which may be impacted by chronic illnesses, and the presence of persistent infections, which may trigger immunosuppressive signals, particularly PD-L1 [32]; The study of Admaski is in line with another study that found no correlation

between gender and the expression of PDL-1/TC or PDL-1/TILS [33]. However, the Hanna study discovered a link between females and PDL-1 expression [34]. Satgunaseelan found a connection between females and PDL1 expression; these investigations attributed their results to increased estrogen levels after menopause [35]. Li, however, discovered a link between smokers and PD-L1 expression in men [36].

4. Conclusions

sPD-L1 played a crucial role in the progression of infection alongside SARS-CoV-2 variants. Thus, future research is needed to suppress sPD-L1 expression because severe viral infections should consider immunological therapies that target PD-L1 (or IFN-like therapies that inhibit PD-L1 upregulation).

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References

[1] Santacroce, L.; Charitos, I.; Carretta, A.; De Nitto, DM.; and Lovero, R.; "The human coronaviruses (HCoVs) and the molecular mechanisms of SARS-CoV-2 infection". J. Mol Med. 99(1): 93-106, 2021.

[2] Sah, R.; Rais, M.; Mohanty, A.; chopra, H.; Chandran, D.; Emran, T.B.; and Dhama, K.; "Omicron (B.1.1.529) variant and its subvariants and lineages may lead to another COVID-19 wave in the world? -An overview of current evidence and counteracting strategies". Int. J. Surg. Open. 55:100625, 2023.

[3] Zafar, T.; "The emergence of severe acute respiratory syndrome-coronavirus 2 epidemic and pandemic". Adv.Biosens.Virus Detect. 1-18, 2022.

[4] Alkhatib, M.; "Update on SARS-CoV-2 Omicron Variant of Concern and Its Peculiar Mutational Profile". Microbiol. Spectr. 10(2): e0273221, 2022.

[5] Salah, H.A.; Aufi, I.M.; Fadhil, H.Y.; and Alhamdani, FG.; "Human Coronavirus Species and their correlation as co-infection detected by Fast Real-Time RT-PCR". Res. J. Pharm. Technol. 13(6): 2578-84, 2022.

[6] Doroshow, D.Y.; Bhalla, S.; Beasley, M.B.; Sholl, L.M.; Kerr M.K.; Gnjatic, S.; and Wistuba, I.I.; "PD-L1 as a biomarker of response to immune-checkpoint inhibitors". Nat. Rev. Clin. Oncol. 18(6): 345-362, 2021.

[7] Sabbatino, F.; Conti, V.; Franci, G.; Sellitto, C.; Manzo, V.; Pagliano, P.; and Bellis, E.De.; "PD-L1 Dysregulation in COVID-19 Patients". Front. Immunol. 12: 1-11, 2021.

[8] Chauhan, D.; Chakravarty, N.; Jeychandran, A.V.; Jayakarunakaran, A.; Sinha, S.; Mishra, R.; and Arumugaswani, V.; "In Silico Genome Analysis Reveals the Evolution and Potential Impact of SARS-CoV-2 Omicron Structural Changes on Host Immune Evasion and Antiviral Therapeutics". Viruses. 14(11):2461, 2022.

[9] Vivarelli, S.; Falzone, L.; Torino, F.; Scandurra, G.; Russo, G.; Bordonaro, R.; Pappalardo, F.; "Immune-checkpoint inhibitors from cancer to COVID-19: A promising avenue for the treatment of patients with COVID-19 (Review)". Int. J. Oncol. 14;58(2):145–157, 2022.

[10] Zhao, J. P.; Zhang, J.; Wang, Q.; Zhao, XI. X.; and Ji, M.; "Plasma levels of soluble programmed death ligand-1 may be associated with overall survival in nonsmall cell lung cancer patients receiving thoracic radiotherapy". Med. (Baltimore), 96(7): e6102, 2017.

[11] Dumolard, L.; Aspord, C.; Marche, PN.; and Jlikova, Z.M.; "Immune checkpoints on T and NK cells in the context of HBV infection: Landscape, pathophysiology and therapeutic exploitation". Front. Immunol. 28(14): 114811, 2023.

[12] Ghazzi, J.J.; Fadhil, H.Y.; and Aufi, I.M.; "Impact of SARS-COV-2 Variants on the Infection Severity among Iraqi Patients". Iraqi J. Sci. 64(7): 4163-4172, 2023.

[13] Zhang, S.; Liu, Y.; and Wang, X.; "SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19". J Hematol. Oncol.13(01):120, 2020.

[14] Farsalinos, K.; Barbouni, A.; and Niaura, R.; "Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: Could nicotine be a therapeutic option". Intern. Emerg. Med. 15 (5): 845–852, 2020.

[15] Ali, N.; "Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19". J. Med. Virol. 92, 2409–2411, 2020.

[16] Perricone, C.; "COVID-19 as part of the hyper ferritinemic syndromes: the role of iron depletion therapy". Immunol. Res. 68(4): 213–224, 2020.
[17] Abdul Hussein, T.A.; and Fadhil, H.Y.; "Impact of inflammatory markers, dread diseases and cycle threshold (Ct)Values in COVID-19 progression". Rev. Bionatura. 8(1):1-8,2023.
[18] Baroiu, L.; Dumitru, C.; and Iancu, A.; "COVID-19 impact on the liver". World. J. Clin. Med. Cases. 9(16):3814–3825, 2021.
[19] Kishaba, T.; Tamaki, H.; Shimaoka, Y.; Fukuyama, H.; and Yamashiro, S.; "Staging of acute exacerbation in patients with idiopathic pulmonary fibrosis". Lung. 192:141 9, 2014.
[20] Zhou, R.; Tardivel, A.; Thorens, B.; Choi, I.; and Tschopp, J.; "Thioredoxin-interacting protein links oxidative stress to inflammasome activation". Nat. Immunol. 11(2):136-140, 2010.
[21] Lippi, G.; Plebani, M.; and Henry, B.M.; "Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis". Clin. Chim. Acta. 506: 145-148, 2020.
[22] Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Yi.; Li.; Zhang, Li.; and Fan, G.; "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". Lancet. 395 (10223): 497-506, 2020.
[23] Chen, Y.; Wang, Q.; Shi, B.; Xu, P.; Hu, Z.; Bai, L.; and Zhang. X.; "Development of a sandwich ELISA for evaluating soluble PD-L1 (CD274) in human sera of different ages as well as supernatants of PD-L1+ cell lines". Cytokine. 56(2):231–238, 2011.
[24] Schurz, H.; Salie, M.; Tromp, G.; Hoal, E.G.; Kinnear, G.J.; and Möller, M.; "The X chromosome and sex-specific effects in infectious disease susceptibility". Hum. Genomics. 13(1):1-12, 2019.
[25] Al-Bayati, A.M.H.; Alwan, A.H.; and Fadhil, H.Y; "Potential Role of TLR3 and RIG-I Genes Expression in Surviving COVID-19 Patients with Different Severity of Infection". Iraqi J. Sci. 63(7):2873-2883, 2022.
[26] Abed Alhussien, T.A.; and Fadhil, H.Y.; "Exploring the Role of Caspase-3 and IL32 in SARS-CoV-2 Infection among Iraqi Patients". Iraqi J. Sci. 64 (8): 3837-3847, 2023.
[27] Ghazzi, J.J.; and Fadhil, H.Y.; "Relationship between Caspase-8 and SARS-CoV-2 Variants in a Sample of Iraqi Population". Egypt. J. Hosp. Med. Medicine. 89: 5392- 5399, 2022.
[28] Salah, K.T.; and Fadhil H.Y.; "Clinical Characteristics of the SARS-CoV-2 Alpha, Delta, Delta plus and Omicron Variants versus the Wild Type in Iraqi Patients". Iraqi J. Sci. 64 (9): 4329-4339, 2023.
[29] Li, J.; Zhang, Y.; and Luo, B.; "The programed death-1/programed death ligand-1 axis and its potential as a therapeutic target for virus-associated tumours". Rev. Med. Virol. 34(1) e2486, 2024.
[30] Chen, X.; Zhang, B.; Song, X.; Qian, T.; Zheng, X.; Zhang, Y.; and Wenxiong, X.U.; "Serum sPD-1 and sPD-L1 as HBeAg-negative CHB patients undergoing IFN-based therapy". Aliment. Pharmacol. Ther. 60(5): 593-603, 2024.
[31] Tan, N.; Luo, H.; Kang, Q.; Pan, J.; Cheng, R.; Hongli, X.I.; and Chen, H.; "High levels of soluble programmed death-1 are associated with virological response in chronic hepatitis B patients after antiviral treatment". Virus Res. 309 (6):198660, 2022.
[32] Adamski, L.J.; Starzyńska, A.; Adamska, P.; Kunc, M.; Burkiewicz, M.S.; Marvaso, G.; and Alterio, D.; "High PD-L1 Expression on Tumor Cells Indicates Worse Overall Survival in Advanced Oral Squamous Cell Carcinomas of the Tongue and the Floor of the Mouth but Not in Other Oral Compartments". Biomedicines. 9(9):1132, 2021.
[33] Hanna, G.J.; Woo, S-B.; Li, Y.Y.; Barletta, J.A.; Hammerman, P.S.; and Lorch, J.H.; "Tumor PD-L1 expression is associated with improved survival and lower recurrence risk in young women with oral cavity squamous cell carcinoma". Int. J. Oral Maxillofac Surg. 47(5):568-577, 2018.
[34] Satgunaseelan, L.; Gupta, R.; Madore, J.; Chia, N.; Lum, T.; Palme, C.E.; and Boyer, M.; "Programmed cell death-ligand 1 expression in oral squamous cell carcinoma is associated with an inflammatory phenotype". Pathology. 48(6):574-580, 2016.
[35] Li, W.; Syed, F.; Richard Y.u.; Yang, J.; Xia, Y.; Relich, R.F.; and Russell, P.M.; "Soluble immune checkpoints are dysregulated in COVID-19 and heavy alcohol users with HIV infection". Front. Immunol. 13: 833310, 2022.
[36] Cele, S.; Jackson, L.; Khoury, D.S.; Khan, K.; Gwete, T.M.; Tegally, H.; and San, J.E.; "SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection". medRxiv.12(8): 21267417, 2021.