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Soluble PD-L2 and LAG-3 serum concentrations may be associated with COVID-19 activity and recovery

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Abstract

Introduction: *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces strong innate immune responses and sustained inflammation, which may promote immune exhaustion via PD-1-PD-L1/PD-L2 and LAG-3-MHC pathways. The longitudinal dynamics and prognostic significance of soluble immune checkpoint molecules in moderate to severe COVID-19 remain unclear. Therefore, we assessed whether markers of immune exhaustion are associated with disease severity and recovery.*

Material and methods: *We analyzed 51 hospitalized patients (36 males and 15 females) with moderate to severe COVID-19 on day 1 of hospitalization, day 8, and on days 40-50. Laboratory tests, including complete blood count (CBC), C-reactive protein, fibrinogen, D-dimers, and ferritin concentration in sera, were routinely performed in the hospital diagnostic unit using applicable diagnostic automated methods. Soluble exhaustion markers, including sPD-L1, sPD-L2, and sLAG-3, were assessed by ELISA.*

Results: *sPD-L2 and sLAG-3 levels were elevated at the time of admission. sPD-L2 and sLAG-3 levels decreased in the course of the disease. LAG-3 concentrations had decreased by day 8 and remained lower on days 40-50. PD-L2 levels decreased only in the recovery phase. Decreases of sPD-L2 and sLAG-3 were associated with clinical improvement and declining inflammatory parameters.*

Conclusions: *High serum levels of sPD-L2 and sLAG-3 characterize the early phase of COVID-19, may be associated with active infection with SARS-CoV-2, and may reflect disease activity. Declining levels of markers of immune exhaustion have potential prognostic value for recovery from COVID-19.*

Key words: *COVID-19, SARS-CoV-2, immune exhaustion, sPD-L1, sPD-L2, sLAG-3.*

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Introduction

Moderate and severe SARS-CoV-2 infection is characterized by robust activation of innate and adaptive immune responses associated with inflammatory cytokine production, including tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8, IL-1β, monocyte chemoattractant protein-1 (MCP-1), IP-10. The uncontrolled release of inflammatory cytokines may lead to the immune dysregulation called the cytokine storm [1].

In order to overcome excessive immune activation that would lead to lethal exploitation of the host, the immune system may limit inflammatory processes through mechanisms based on co-inhibitory molecule interactions, including programmed cell death protein 1 (PD-1), lymphocyte activation gene 3 (LAG-3), programmed death-ligand 1 (PD-L1; also known as CD274 or B7-H1), and programmed death-ligand 2 (PD-L2; also known as CD273 or B7-DC) [2]. PD-1 and LAG-3 are expressed on T cells, B cells, natural killer (NK) cells, monocytes and dendritic cells (DCs) [3]. PD-L1 is broadly expressed on T, mesenchymal, and endothelial cells, while PD-L2 may be found on DCs, macrophages, mast cells, and B cells [3]. PD-L1, PD-L2, and LAG-3 have been detected in soluble forms in human serum.

PD-1 and LAG-3 ligation by their ligands may lead to the condition called cell exhaustion, resulting in subsequent apoptosis of adaptive and innate immune cells. Thus, the mechanism based on the interaction between checkpoint molecules expressed on immune cells may counterbalance the activatory effect of co-stimulatory receptors during an

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acute phase of infection and inflammation and eventually lead to immune homeostasis. They were also shown to be involved in pulmonary fibrosis. Moreover, providing the check and balance properties of the immune response is crucial for the development of immune tolerance and, consequently, the prevention of autoimmunity [4].

Abnormal immune responses, such as lymphopenia, cytokine storm, and T cell exhaustion, are observed during SARS-CoV-2 infection [5]. Moreover, $CD4^+$ and $CD8^+$ T cells exhibit overexpression of the co-inhibitory molecules PD-1, PD-L1, CTLA-4, and TIM-3 in severe COVID-19 patients [6]. Additionally, PD-L1 is overexpressed in the pulmonary tissue of subjects who died from COVID-19, and mainly in subjects with a high viral load [7].

The importance of soluble co-inhibitory molecules for COVID-19 activity, severity, and recovery remains unclear. Establishing relevant markers of disease severity and prognosis of recovery is imperative. Therefore, this study aimed to assess whether soluble markers of immune exhaustion, including sPD-L1, sPD-L2, and sLAG-3, present in sera are associated COVID-19 activity and severity, and whether they correlate with clinical recovery.

Material and methods

Patients

We analyzed 51 hospitalized patients, 36 males and 15 females, with moderate to severe COVID-19, who were admitted to COVID-19 Medical Centers in Wrocław, Poland, between 2020 and 2021. On the first day of admission, SARS-CoV2 infection was confirmed by reverse transcription-polymerase chain reaction (RT-PCR). Disease severity was established based on the National Institute of Health COVID-19 treatment guidelines. COVID-19 patients were categorized as moderate ($n = 16$) if they showed evidence of lower respiratory disease (pneumonia) or imaging and who had an oxygen saturation (SpO_2) ≥ 94% on room air at sea level. Patients were categorized as severe ($n = 35$) if they met any of the following criteria: SpO_2 ≤ 94% on room air at sea level, a ratio of arterial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, a respiratory rate ≥ 30 breaths/min, or lung infiltrates > 50%. The average hospitalization time was 10.8 ±3.8 (SD) days. One patient died. Healthy patients without COVID-19 and any other concomitant diseases were included in the study as healthy controls ($n = 29$).

Patients were assessed on the first (V1) and eighth day of hospitalization (V2), and then on days 40-50 (V3). Samples were collected from COVID-19 patients at hospital admission, briefly stored at –20°C, and then kept at –80°C until analysis.

The study protocol received approval from the Institutional Review Board and the local Ethics Committees (No. 497/2020, RNN/204/19KE). Written informed consent was obtained from all participants.

Laboratory tests

Laboratory tests, including complete blood count (CBC) and C-reactive protein (immunochemical method), fibrinogen (coagulometric method), D-dimers (immunoenzymatic method), and ferritin (immunochemical method) concentrations in sera, were routinely performed in the hospital diagnostic unit using applicable diagnostic automated methods. SARS-CoV-2 infection was confirmed in the hospital diagnostic unit using the appropriate diagnostic method based on real-time PCR according to current WHO guidelines.

Computed tomography scans

Chest computed tomography (CT) was performed with a 128-slice multidetector CT scanner, using automatic exposure control to reduce and optimize the radiation dose. Patients were examined with a dedicated a non-contrast chest scanning protocol, in the supine position and in the craniocaudal direction. CT scans were made with full inspiration and breath-holding. Before the examination, patients were instructed on how to properly perform the maneuver. All CT scans were performed and analyzed by a radiologist on the first day of hospitalization. Multiplanar reconstructions were used to obtain spatial images. The presence and distribution of ground-glass opacities, lung consolidations, reticular and streak opacities, vascular dilatations, nodules, and others were analyzed. The results are presented descriptively along with the percentage of lung involvement.

Cytokine assessment

Soluble exhaustion markers and interferon β (IFN-β) concentrations in sera of patients included in the study were measured using enzyme-linked immunosorbent assays (ELISA) following the manufacturer's instructions. Levels of soluble proteins were evaluated using the human PD-L1/B7-H1, PD-L2/B7-DC, LAG-3, and IFN-β DuoSet ELISA kits (R&D Systems, DY156, DY1224, DY2319B, and DY814 respectively). Briefly, 96-well plates were coated with capture antibodies diluted in PBS and incubated overnight at 4°C. After washing, plates were blocked to avoid unspecific binding. Standards (50 µl) together with serum sample and controls were added to the wells and incubated for 2 h at room temperature. After washing the plate, 50 µl/well of biotinylated detection antibody was added and incubated for 1 h at room temperature. Subsequently, streptavidin-HRP A solution was added, and the mixture was incubated for 20 min. Finally, following multiple washes, the wells were incubated with 50 µl/well of substrate solution and were stopped after 20 min with 2N H_2SO_4. The readout was made by reading the absorbance at 450 nm and 570 nm with a Multiskan GO microplate

reader (Thermo Scientific). The amount of protein of interest in the sample was estimated using a standard curve.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 10.1.2 (GraphPad Software, San Diego, California). All values are presented as mean ± standard error of the mean (SEM). Samples were tested for normal gaussian distribution using a Shapiro-Wilk normality test. Since not all data were normally distributed, comparisons between groups of patients were analyzed using the Mann-Whitney test. The Kruskal-Wallis test followed by Dunn's multiple comparisons post hoc test was used for non-normally distributed data, while one-way ANOVA with multiple comparison was used for normally distributed data. P values < 0.05 were considered statistically significant ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$).

Results

Analysis of serum inflammatory markers in moderate and severe COVID-19 patients

Clinical characteristics, comorbidities, and treatment of patients with moderate and severe COVID-19 are presented in Table 1. Serum concentrations of inflammatory markers, including C-reactive protein (CRP), fibrinogen, D-dimers, and ferritin, as well as eosinophil and lymphocyte counts, and changes observed in CT scans, are described in Table 2. At the time of admission, levels of CRP, fibrinogen, and D-dimers were elevated in both groups, and they significantly decreased in the recovery phase (days 40-50). Interestingly, concentrations of CRP, fibrinogen, and ferritin were significantly higher in the severe as compared to moderate COVID-19 patients. We also observed lower eosinophil and lymphocyte counts in the peripheral blood in the severe group as compared to moderate patients; however, these differences were not statistically significant. They increased in the recovery phase. Lung changes assessed in CT scans covered significantly larger areas in severe as compared to moderate COVID-19 patients (Table 2).

Concentrations of sPD-L2 in patients with moderate and severe COVID-19

In patients with moderate COVID-19 at admission, the serum level of sPD-L2 was 6092 ±358 pg/ml (Fig. 1A). By day 8, it had decreased to 5500 ±557 pg/ml. At V3, it reached 4053 ±148 pg/ml and it was significantly lower as compared to the admission value ($p < 0.01$). Similarly, in patients with severe COVID-19, sPD-L2 serum concentration reached 6075 ±354 pg/ml at V1, at V2 it was 5826 ±376 pg/ml, whereas at V3 it decreased to 3945 ±333 pg/ml, and it was significantly lower as compared to the admission value ($p < 0.0001$). There were no statistically significant differences in sPD-L2 serum concentrations between patients with moderate and severe COVID-19 at any of analyzed time points. In the healthy control group, level of sPD-L2 was 2946 ±171 pg/ml, which was significantly lower as compared to both moderate and severe COVID-19 patients.

Concentrations of sLAG-3 in patients with moderate and severe COVID-19

In patients with moderate COVID-19 at admission, the serum level of sLAG-3 was 4517 ±1209 pg/ml (Fig. 1B).

Table 1. Clinical characteristics, comorbidities, and treatment of COVID-19 patients. Statistical significance of differences between groups of patients was determined using the Fisher's exact test. P values of < 0.05 were considered statistically significant

Parameter	Moderate COVID-19 (n = 16)	Severe COVID-19 (n = 35)	p
Treatment, *n*			
Remdesivir	8	15	1.000
Systemic GCs	11	25	0.532
Tocilizumab	0	2	0.546
Comorbidities, *n*			
Hypertension	8	11	0.365
Diabetes	0	6	0.161
Hypothyroidism	2	4	1.000
Asthma	3	3	0.387
Allergic rhinitis	2	3	1.000
Food allergy	1	0	0.333
Ischemic heart disease	2	2	0.592
Gout	2	3	1.000
Psoriasis	1	2	1.000
Arrhythmia	2	1	0.254
Prostate hyperplasia	2	1	0.254
Varicose disease	1	1	1.000
Nephrolithiasis	1	1	1.000
Reflux disease	1	1	1.000
Heart failure	1	0	0.333
Sleep apnea	1	0	0.333
Chronic sinusitis	1	0	0.333
COPD	0	1	1.000
Chronic kidney disease	0	1	1.000
Adrenal adenoma	0	1	1.000
Osteoporosis	0	1	1.000

COPD – chronic obstructive pulmonary disease, GCs – glucocorticoids

Table 2. Baseline clinical characteristics of patients with moderate ($n = 16$) and severe ($n = 35$) COVID-19. Results are presented as mean ±SEM. Statistical significance of differences between groups of patients was determined using the Mann-Whitney test or Kruskal-Wallis test followed by Dunn's multiple comparisons post hoc test. *P* values of < 0.05 were considered statistically significant ($p < 0.05$, $p < 0.01$, $p < 0.001$)

Parameter	Moderate COVID-19			p		Severe COVID-19			p			p	
Age (years)	54.1					52.6						ns	
Gender	Female	Male				Female	Male						
	6	10				10	25						
% lungs CT	31					60						< 0.001	
	V1	V2	V3	V2/V1	V3/V2	V3/V1	V1	V2	V3	V2/V1	V3/V2	V3/V1	mV1/sV1	mV2/sV2	mV3/sV3
CRP (mg/l)	53.5 ±19.1	10.8 ±2.5	1.6 ±0.4	ns	< 0.05	< 0.001	117.9 ±14.6	16.2 ±8.6	4.3 ±1.2	< 0.001	< 0.001	< 0.05	< 0.01	ns	ns
Fibrinogen (g/l)	5.0 ±0.4	4.2 ±0.3	2.9 ±0.2	ns	< 0.05	< 0.001	6.0 ±0.3	4.6 ±0.3	3.0 ±0.1	< 0.05	< 0.001	< 0.001	< 0.05	ns	ns
D-dimer (µg/l)	765 ±91	660 ±119	264 ±66	ns	< 0.001	< 0.001	1762 ±156	1124 ±200	371 ±38	ns	< 0.001	< 0.001	ns	ns	ns
Ferritin (µg/l)	716 ±233	748 ±274	122 ±27	ns	< 0.01	< 0.01	1280 ±193	887 ±132	227 ±60	ns	< 0.001	< 0.001	< 0.01	ns	ns
Eosinophil (count/µl)	12 ±4.9	84 ±22	223 ±48	< 0.05	ns	< 0.001	62.7 ±12	68 ±10	155 ±21	< 0.001	< 0.01	< 0.001	ns	ns	ns
Lymphocyte (count/µl)	1117 ±135	1991 ±160	1994 ±177	< 0.001	ns	< 0.01	1092 ±77	1889 ±119	2028 ±75	< 0.001	ns	< 0.001	ns	ns	ns

By day 8, it had significantly decreased to 2843 ±263 pg/ml ($p < 0.001$). At V3, it reached 1940 ±221 pg/ml, and it was significantly lower as compared to the admission value ($p < 0.0001$). Similarly, in patients with severe COVID-19, sLAG-3 serum concentration was 4303 ±314 pg/ml at V1, at V2 it significantly decreased to 3055 ±316 pg/ml ($p < 0.01$), then it further decreased to 2495 ±259 pg/ml at V3, and it was significantly lower as compared to the admission value ($p < 0.001$). There were no statistically significant differences in sLAG-3 serum concentrations between patients with moderate and severe COVID-19 at any of analyzed time points. In the healthy control group, the level of sPD-L2 was 332 ±52 pg/ml, and it was significantly lower as compared to both moderate and severe COVID-19 patients.

Concentrations of sPD-L1 in patients with moderate and severe COVID-19

In patients with moderate COVID-19 at admission, the serum level of sPD-L1 was 203 ±67 pg/ml (Fig. 1C). On day 8, it was 214 ±59 pg/ml, and at V3 it reached 215 ±78 pg/ml. Similarly, in patients with severe COVID-19, at V1 sPD-L1 was 227 ±39 pg/ml, at V2 it was 278 ±60 pg/ml, whereas at V3 it decreased to 246 ±50 pg/ml. There were no statistically significant differences in sPD-L1 serum concentrations between patients with moderate and severe COVID-19 at any of analyzed time points. In the healthy control group, the level of sPD-L2 was 27.3 ±14.1 pg/ml, and it was significantly lower as compared to both moderate and severe COVID-19 patients.

Analysis of associations between exhaustion markers and concentrations of clinical parameters in patients with moderate and severe COVID-19

We observed a negative correlation between white blood cell (WBC) counts and sPD-L2 ($R = –0.26$, $p < 0.05$) and sLAG-3 ($R = –0.32$, $p < 0.01$) (Table 3). Neutrophil counts negatively correlated with sPD-L2 ($R = –0.31$, $p < 0.05$) and sLAG-3 ($R = –0.38$, $p < 0.01$). We also found a negative association between Ney/Lymph ratio and sPD-L2 ($R = –0.29$, $p < 0.05$) and sLAG-3 ($R = –0.29$, $p < 0.05$). In contrast, sPD-L2 and sPD-L1 positively correlated with IFN-β ($R = 0.29$, $p < 0.05$; $R = 0.3$, $p < 0.01$, respectively). Finally, we observed a positive association between sPD-L2 and sLAG-3 ($R = 0.42$, $p < 0.001$).

Discussion

Robust activation of innate and adaptive immune responses is observed in moderate and severe SARS-CoV-2 infection. Acute and chronic inflammation may lead to immune exhaustion, mediated by interactions among

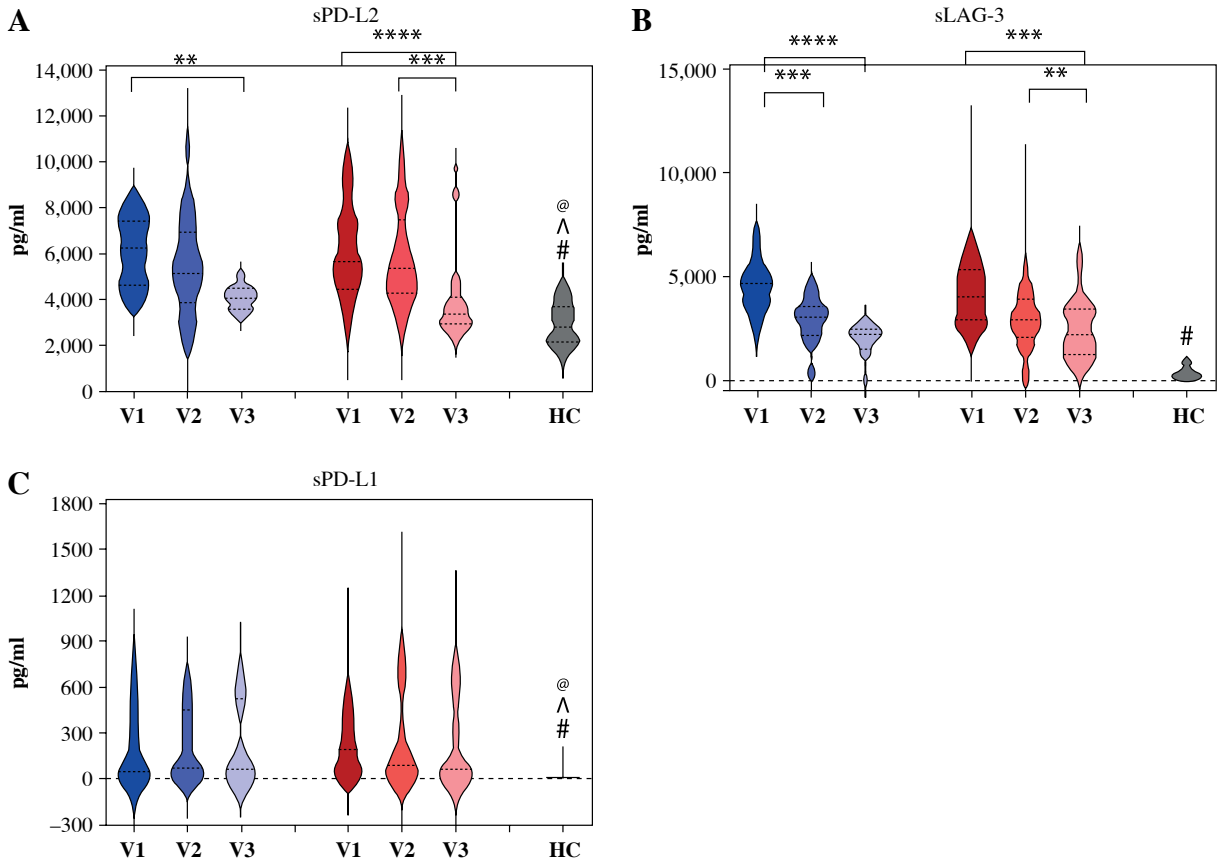

Fig. 1. A) sPD-L2 (programmed death ligand 2), **B**) sLAG-3 (lymphocyte-activation gene 3), and **C**) sPD-L1 (programmed death ligand 1). Serum concentrations in moderate (n = 16, blue violin plots) and severe (n = 35, red violin plots) COVID-19 patients at V1 (hospital admission), V2 (day 8), and V3 (days 40-50). Healthy controls (n = 29, grey violin plots). Statistical significance of differences between groups of patients was determined using the Mann-Whitney test. The Kruskal-Wallis test followed by Dunn's multiple comparisons post hoc test was used for non-normally distributed data, while one-way ANOVA with multiple comparison was used for normally distributed data. P values < 0.05 were considered statistically significant (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$). **A**) $^{\#}p < 0.0001$ as compared to moderate V1, V2 and severe V1, V2, ^$p < 0.001$ as compared to moderate V3, $^{@}p < 0.05$ as compared to severe V3; **B**) $^{\#}p < 0.0001$ as compared to moderate V1, V2, V3, and severe V1, V2, V3; **C**) ^$p < 0.001$ as compared to moderate V2 and severe V1, V2, $^{@}p < 0.05$ as compared to moderate V1 and severe V3, $^{\#}$???

Table 3. Relationship between sPD-L1 (programmed death ligand 1), sPD-L2 (programmed death ligand 2), sLAG-3 (lymphocyte-activation gene 3) and WBC (white blood cells), Neu (neutrophil) counts, Neu/Lymph ratio (neutrophil/lymphocyte) and IFN-β serum concentrations in COVID-19 patients (Spearman's correlation, R; $p < 0.05$, $p < 0.01$)

Parameter	sPD-L2		sLAG-3		sPD-L1	
	R	***p***	***R***	***p***	***R***	***p***
WBC/μl	–0.26	< 0.05	–0.32	< 0.01		
Neu (μl)	–0.31	< 0.05	–0.38	< 0.01		
Neu/Lymph	–0.29	< 0.05	–0.29	< 0.05		
IFN-β	0.29	< 0.05			0.31	< 0.01
PD-L2			0.42	< 0.001		

co-inhibitory molecules such as PD-1-PD-L1/PD-L2 and LAG-3-MHC [3]. Recent studies indicate that SARS-CoV-2 infection can trigger abnormal immune responses, such as lymphopenia, cytokine storm, and T cell exhaustion [5]. $CD4^+$ and $CD8^+$ T cells exhibit overexpression of the co-inhibitory molecules PD-1, PD-L1, CTLA-4 and TIM-3 in severe COVID-19 patients [6]. Moreover, PD-L1 is upregulated in the pulmonary tissue of subjects who died from COVID-19, particularly in subjects with a high viral load [7]. These findings highlight the need to identify relevant markers of COVID-19 activity, severity, and recovery prognosis. In this study, we analyzed concentrations of immune soluble exhaustion markers, including sPD-L1, sPD-L2, and sLAG-3 and their association with the activity and severity of COVID-19.

We included 51 hospitalized patients with moderate to severe COVID-19, admitted to Medical COVID-19 Centers in Wrocław, Poland, between 2020 and 2021. Patients were assessed on the first day of hospitalization (V1), 8 days later (V2), and subsequently on days 40-50 (V3, recovery phase). In the severe COVID-19 group, clinical parameters, including lung changes in CT scans, CRP, fibrinogen, and ferritin concentrations, were significantly elevated at V1 as compared to the moderate group. Low eosinophil and lymphocyte counts observed in both severe and moderate patients at the very early stage of infection are consistent with results of other studies. Thus, they may potentially serve as early biomarkers of COVID-19. Additionally, eosinopenia is a risk factor for severe outcomes of COVID-19, including death.

As regards exhaustion markers, sPD-L2 and sLAG-3 levels were elevated in COVID-19 patients at the time of hospital admission. Secondly, sPD-L2 and LAG-3 levels decreased in the course of the disease. Interestingly, sLAG-3 concentrations had already decreased by day 8 and remained lower on days 40-50, while sPD-L2 levels decreased only in the recovery phase (days 40-50). sPD-L1 serum levels did not change at any time point. Third, there were no differences between moderate and severe COVID-19 patients in sPD-L2, LAG-3, or PD-L1 concentrations. Decreases of sPD-L2 and sLAG-3 levels were associated with clinical features of recovery such as symptoms and inflammatory parameter serum concentrations. These findings suggest that the decreases in levels of sPD-L2 and sLAG-3 observed in the course of COVID-19 may reflect recovery from the disease.

Although *ex vivo* data on the associations between COVID-19 and exhaustion markers are limited, increased expression of membrane-bound and soluble co-inhibitory molecules, including PD-1, has been reported in several viral infections, including SARS-CoV-2. Interestingly, these markers were suggested to be associated with COVID-19 severity and death [2, 3, 8]. Moreover, increased sPD-L2 and an altered CD4/CD8 ratio after 12 months of COVID-19 are associated with the persistence of lung lesions, suggesting that they may contribute to post-COVID-19 lung damage [9]. Potentially, sPD-L1 and sPD-L2 may bind to their receptors including PD-1 on many immune cells such as T, B, NK cells, and monocytes in an "unspecific" manner, thus leading to their inactivation, exhaustion, and death. Similarly, sLAG-3, which binds to MHCII, might limit antigen presentation by APCs. This raises the possibility that increased soluble co-inhibitory molecule production in COVID-19 may counterbalance robust immune activation, thus avoiding excessive immune exploitation, and facilitating recovery. Indeed, selective absence of PD-L1 on hematopoietic cells results in lethal immunopathology [10].

Notably, we observed a positive correlation between both sPD-L1, sPD-L2, and IFN-β serum levels, while production of sPD-L2 was associated with sLAG-3 (Table 2). This is consistent with the fact that PD-L1 and PD-L2 synthesis is dependent on type I IFNs [2].

On the other hand, high levels of sPD-L2 and sLAG-3 observed in COVID-19 patients may induce general exhaustion of immune cells, including T, B, NK cells, and DCs, *via* death receptor stimulation, cell inactivation, and cell death. Indeed, lymphopenia – as observed in our study – is a hallmark of COVID-19 [2]. T cell exhaustion, which impairs IL-2, TNF-α, IFN-γ, and granzyme B production, has been reported in respiratory acute viral infections [11]. As a result, cytotoxic and helper functions may become compromised, thus leading to a weakened immune response and, eventually, to prolonged or persistent infection [4]. Moreover, viruses need to overcome immune barriers to replicate in hostile environments. Induction of soluble inhibitory molecule release leading to immune exhaustion may represent part of SARS-CoV-2's strategy to subvert antiviral immunity [4]. Indeed, the decrease of sPD-L2 and sLAG-3 serum concentration was accompanied by an increased lymphocyte count and recovery in our study.

Conclusions

High serum levels of sPD-L2 and sLAG-3 in the acute phase of COVID-19 may be associated with active infection with SARS-CoV-2 and reflect disease activity. Declining levels of these immune exhaustion markers may have prognostic value as indicators of virus elimination and recovery from COVID-19.

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Disclosures

The study was approved by the Institutional Review Board and the local Ethics Committee (No. 497/2020).

The authors report no conflict of interest.

References

1. Chałubiński M, Gajewski A, Kowalski ML (2020): The relationship between human coronaviruses, asthma and allergy-An unresolved dilemma. Clin Exp Allergy 50: 1122-1126.
2. Kong Y, Wang Y, Wu X, et al. (2020): Storm of soluble immune checkpoints associated with disease severity of Covid-19. Signal Transduct Target Ther 5: 192.
3. Al-Mterin MA, Alsalman A, Elkord E (2022): Inhibitory immune checkpoint receptors and ligands as prognostic biomarkers in COVID-19 patients. Front Immunol 13: 870283.
4. Schönrich G, Raftery MJ (2019): The PD-1/PD-L1 axis and virus infections: A delicate balance. Front Cell Infect Microbiol 9: 207.
5. Mishra KP, Singh M, Saraswat D, et al. (2022): Dysfunctional state of T cells or exhaustion during chronic viral infections and COVID-19: A review. Viral Immunol 35: 284-290.
6. Bidar F, Hamada S, Gossez M, et al. (2022): RICO Study Group. Recombinant human interleukin-7 reverses T cell exhaustion ex vivo in critically ill COVID-19 patients. Ann Intensive Care 12: 21.
7. Ronchi A, Marino FZ, Carraturo E et al. (2022): pd-l1 overexpression in the lungs of subjects who died from covid-19: are we on the way to understanding the immune system exhaustion induced by SARS-CoV-2? Crit Rev Eukaryot Gene Expr 32: 9-20.
8. Raftery MJ, Abdelaziz MO, Hofmann J et al. (2018): Hantavirus-driven PD-L1/PD-L2 upregulation: An imperfect viral immune evasion mechanism. Front Immunol 9: 2560.
9. Buendia-Roldan I, Martínez-Espinosa K, Aguirre MJ, et al. (2024): Persistence of lung structural and functional alterations at one year post-COVID-19 is associated with increased serum PD-L2 levels and altered CD4/CD8 ratio. Immun Inflamm Dis 12: e1305.
10. Mueller SN, Vanguri VK, Ha SJ, et al. (2010): PD-L1 has distinct functions in hematopoietic and nonhematopoietic cells in regulating T cell responses during chronic infection in mice. J Clin Invest 120: 2508-2515.
11. Rodríguez-Guilarte L, Ramírez MA, Andrade CA, et al. (2023): LAG-3 Contribution to T cell downmodulation during acute respiratory viral infections. Viruses 15: 147.