Impact of COVID 19 Infection on Advanced Non-Small Cell Lung Cancer Patients and Correlation with PDL1 Expression

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COVID-19; PDL1: Non-Small Cell Lung Cancer.

ABSTRACT:
Background: COVID-19, a respiratory tract infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, in late 2019. Elevated IL-10 levels in COVID-19 patients may indicate the role of the PD-1/PD-L1 axis in the development of acute viral infections and monocyte rearrangement. **Aim of work:** To assess the correlation between COVID 19 infection in advanced NSCLC patients and PDL1 expression with its impact on clinical outcome. **Methods:** A prospective cohort study was conducted in Medical Oncology departments, National Cancer Institute (NCI) during the period from (April 2021- to October 2023). Patients were recruited over 6 months, and they were being followed up for 24 months. Demographic and clinical features of the patients were collected in addition to the histopathological results, the radiological studies, different lines of treatment received and the response to it. Re-evaluation with CT scans every 3 months to detect tumor response to chemotherapy according to RECIST criteria 1.1. Nasopharyngeal & nasal swab specimens were collected for Nucleic acid amplification testing (NAAT), with a reverse-transcription polymerase chain reaction (RT-PCR) assay, to detect SARS-CoV-2 RNA. Detection of PDL1 expression by immunohistochemistry was done. **Results:** 19.2% of our patients had a negative PDL1 expression and 80.8% had a positive PDL1 expression. **Conclusion:** COVID 19 infection in advanced NSCLC patients can be correlated with PDL1 expression.

Introduction:

Lung cancer is the most commonly diagnosed cancer worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. It is divided further into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma histologies. Because of the importance of stage in guiding the therapeutic decision-making process, all patients with NSCLC must be staged adequately ***(Moyer, 2017).***

Programmed death ligand 1 (PD-L1), also known as CD274, is considered an immune checkpoint facilitating anti-tumor suppression of the immune pathway. PD-L1 can be expressed on the surface of various cells. The main inducer of PD-L1 expression in vivo is interferon gamma (IFN-γ), which is released by CD8+ T-cells. The expression of PD-L1 is observed on the surface of macrophages, antigen-presenting cells, B and T lymphocytes, epithelial, muscle and endothelial cells, whereas PD-1 receptor is expressed predominantly by activated cytotoxic T cells. PD-L1 ligand binds to PD-1 receptor on activated T cells and this connection results in suppression of the immune system ***(Villalobos et al., 2018).*** The connection of PD-1 with PD-L1 prevents an autoimmune response in peripheral tissues during inflammation. The ligand–receptor complex elicits two reactions which inhibit the immune response. The first effect is inhibition of interleukin 2 (IL-2) synthesis. Another additional

effect of PD-L1 engagement is related to the inhibition of the T cell receptor, known as a "stop signal". This pathway can alter the duration of T cell contact with target cells and antigen-presenting cells ***(Liang et al., 2017).***

The latest method of immunotherapy uses monoclonal antibodies directed against the immune-checkpoint molecules such as receptor programmed cell death 1 (PD-1) or its ligand (PD-L1). Their roles in the first- or second-line treatment of advanced stages of NSCLC are well established, but the association between PD-L1 expression and clinicopathological features is still unclear ***(Lin et al., 2017).*** COVID-19, a respiratory tract infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, in late 2019. Elevated IL-10 levels in COVID-19 patients may indicate the role of the PD-1/PD-L1 axis in the development of acute viral infections and monocyte rearrangement. Neutrophils of the patients with COVID-19 are not able to regulate the expression of PD-L1 on the surface of immune cells compared to a healthy individual, so the level of PD-L1's expression in these patients is low. Patients with more severe states had greater expressions of PD-L1 on both monocytes and DCs ***(Aghbash et al., 2021).***

Aim of work:

To assess the correlation between COVID 19 infection in advanced NSCLC patients and PDL1 expression with its impact on clinical outcome.

Methods:

A prospective cohort study was conducted in Medical Oncology departments, National Cancer Institute (NCI) during the period from (April 2021- to October 2023). Recruitment of patients was over 6 months, and they were being followed up for 24 months. All patients with advanced non-small cell lung cancer stage 3&4, with COVID 19 infection confirmed by positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) and with performance status (ECOG 0-2) were included. Patients with performance status (ECOG 3-4) or with non-small cell lung cancer stage 1&2 were excluded. Demographic and clinical features of the patients including age, sex, residency, smoking history, performance status and comorbidities were collected in addition to the histopathological results, the radiological studies, different lines of treatment received and the response to it. All patients with COVID 19 infection received the treatment protocol which was approved by the Egyptian Ministry of Health. Any active treatment (chemotherapy or radiotherapy) was being held for patients with COVID 19 infection until their nasopharyngeal swabs became negative for SARS-CoV-2 RNA by RT-PCR. Re-evaluation with CT scans every 3 months to detect tumor response to chemotherapy according to RECIST criteria 1.1. Nasopharyngeal & nasal swab specimens were collected for Nucleic acid amplification testing (NAAT), with a reverse-transcription polymerase chain reaction (RT-PCR) assay, to detect SARS-CoV-2 RNA. Detection of PDL1 expression by immunohistochemistry was done.

Statistics/data analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 27. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t-test while with non-parametric distribution were done by using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: Non-significant (NS), P-value < 0.05: Significant (S) while P-value < 0.01: Highly significant (HS).

Results:

Table (1) shows that the patients were categorized according to PDL1 expression to 25 patients (19.2%) and 105 patients (80.8%) positive. Also, they were categorized according to positive PDL1 percentage to 36 patients (34.3%) < 1%, 40 patients (38.1%) 1-49% and 29 patients (27.6%) > 50%. Table (2) shows that Covid infection occurred in 56 patients (43.1%). The most common presenting symptom was fever in 55 patients (98.2%) followed by cough in 48 patients (85.7%) and smell loss in 40 patients (71.4%) while the least percentage was found in headache in 15 patients (26.8%). The patients were categorized according to CT CORAD to 1 patient (1.8%) with grade 2, 15 patients (26.8%) with grade 3, 28 patients (50.0%) with grade 4 and 12 patients (21.4%) with grade 5. 12 patients (21.4%) were admitted to ICU, of them 11 patients (19.6%) were mechanically ventilated, ARDS observed in 8 patients (14.3%), pulmonary embolism in 5 patients (8.9%), septic shock in only one patient (1.8%) and acute MI in 3 patients (5.4%). Table (3) shows that the percentage of patients with performance status 2 was significantly higher in infected group [48 (85.7%)] than non-infected group [42 (56.8%)] with p-value <0.001 and the percentage of smokers also was significantly higher in infected group [52 (92.9%)] than non-infected group [57 (77%)] with p-value = 0.015. There was no statistically significant difference between infected and non-infected patients regarding pathological subtype with p-value = 0.191. Also, no statistically significant difference between both groups regarding percentage of symptoms except statistically significant increase in the percentage of patients with bone mets in infected group [40 (71.4%)] than non-infected group [40 (54.1%)] with p-value = 0.044. Table (4) shows that there was statistically significant increase in the percentage of patients with sore throat in patients with negative PDL-1 [11 (73.3%)] than patients with positive PDL-1 [9 (22.0%)] with p-value <0.001 while the percentage of patients with dyspnea was significantly higher in patients with positive PDL-1 [33 (80.5%)] than patients with negative PDL-1 [6 (40.0%)] with p-value = 0.004. Table (4) also shows that there was statistically significant increase in the percentage of patients with CT CORAD score 4 and 5 in positive PDL-1 patients [24 (58.5%) and 12 (29.3%); respectively] than negative PDL-1 patients [4 (26.7%) and 0 (0.0%); respectively] with p-value <0.001. The percentage of hospitalized patients also was significantly higher in patients with positive PDL-1 [36 (87.8%)] than patients with negative PDL-1 [6 (40.0%)] with p-value <0.001 while the mean duration of hospitalization was significantly higher in negative PDL-1 group [33 ± 0] than patients with positive PDL-1 [30.95 ± 5.99] with p-value = 0.001. The percentage of patients with ICU admission and mechanical ventilation was significantly higher in positive PDL-1 group [12 (29.3%) and 11 (26.8%); respectively] than negative PDL-1 group [0 (0.0%) and 0 (0.0%); respectively] with p-value = 0.018 and 0.025.

Table 1: PDL-1 expression among the studied patients

	Total no.= 130
PDL1 expression	
Positive	105 (80.8%)
Negative	25 (19.2%)
Positive PDL1 percent	
<1 %	36 (34.3%)
1-49%	40 (38.1%)
>50%	29 (27.6%)

Table 2: COVID infection details among the studied patients

	Total no.= 130
COVID infection	
Yes	56 (43.1%)
No	74 (56.9%)
Fever	55 (98.2%)
Cough	48 (85.7%)
Sore throat	20 (35.7%)
Headache	15 (26.8%)
Body ache	37 (66.1%)
Dyspnea	39 (69.6%)
Smell loss	40 (71.4%)
Days of positive SWAB	
Mean ± SD	24.04 ± 6.07
Range	14 – 35
CT CORAD	
2	1 (1.8%)
3	15 (26.8%)
4	28 (50.0%)
5	12 (21.4%)
Hospitalization	42 (75%)
Duration of hospitalization (days)	
Mean ± SD	31.05 ± 5.86
Range	21 – 46
ICU admission	12 (21.4%)
Mechanical vent	11 (19.6%)
ARDS	8 (14.3%)
Pulmonary embolism	5 (8.9%)
Septic shock	1 (1.8%)
Acute MI	3 (5.4%)

Table 3: Comparison between infected and not infected cases regarding pathological subtypes, symptoms, performance status and smoking among the studied patients

	COVID		**Test value**	**P-value**	**Sig.**
	Infected	**Not infected**			
	No.= 56	**No.= 74**			
Path subtype					
Non squamous	45 (80.4%)	52 (70.3%)	1.712*	0.191	NS
Squamous	11 (19.6%)	22 (29.7%)			
Cough	53 (94.6%)	73 (98.6%)	1.715*	0.190	NS
Dyspnea	46 (82.1%)	51 (68.9%)	2.943*	0.086	NS
Chest pain	29 (51.8%)	35 (47.3%)	0.257*	0.612	NS
Hemoptyosis	11 (19.6%)	20 (27%)	0.957*	0.328	NS
Lung mets	36 (64.3%)	52 (70.3%)	0.522*	0.470	NS
Liver mets	33 (58.9%)	35 (47.3%)	1.729*	0.189	NS
Bone mets	40 (71.4%)	40 (54.1%)	4.066*	0.044	S
Brain mets	9 (16.1%)	11 (14.9%)	0.036*	0.850	NS
Adrenal mets	10 (17.9%)	17 (23%)	0.507*	0.476	NS
Performance stat					
1	8 (14.3%)	32 (43.2%)	12.548*	0.000	HS
2	48 (85.7%)	42 (56.8%)			
Smoking	52 (92.9%)	57 (77%)	5.898*	0.015	S

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test

Table 4: Relation of PDL-1 with symptoms, days of positive SWAB, CT CORAD, hospitalization data and post COVID complications of cases with COVID infection

	Positive PDL-1	**Negative PDL-1**	**Test value**	**P-value**	**Sig.**
	No. = 41	**No. = 15**			
Fever	40 (97.6%)	15 (100.0%)	0.373*	0.542	NS
Cough	35 (85.4%)	13 (86.7%)	0.015*	0.902	NS
Sore throat	9 (22.0%)	11 (73.3%)	12.629*	0.000	HS
Headache	9 (22.0%)	6 (40.0%)	1.824*	0.177	NS
Body ache	30 (73.2%)	7 (46.7%)	3.441*	0.064	NS
Dyspnea	33 (80.5%)	6 (40.0%)	8.515*	0.004	HS
Smell loss	31 (75.6%)	9 (60.0%)	1.311*	0.252	NS
Days of positive SWAB Mean ± SD Range	 23.77 ± 6.03 14 – 35	 31 ± 0 31 – 31	 -0.322•	 0.745	 NS
CT CORAD 2 3 4 5	 1 (2.4%) 4 (9.8%) 24 (58.5%) 12 (29.3%)	 0 (0.0%) 11 (73.3%) 4 (26.7%) 0 (0.0%)	 23.559*	 0.000	 HS
Duration of hospitalization (days) Mean ± SD Range	 33.5 ± 5.99 21 – 46	 23 ± 0 14– 33	 -5.376•	 0.001	 HS
ICU admission	12 (29.3%)	0 (0.0%)	5.588*	0.018	S
Mechanical vent	11 (26.8%)	0 (0.0%)	5.008*	0.025	S
ARDS	8 (19.5%)	0 (0.0%)	3.415*	0.065	NS
Pulmonary embolism	5 (12.2%)	0 (0.0%)	2.009*	0.156	NS
Septic shock	1 (2.4%)	0 (0.0%)	0.373*	0.542	NS
Acute MI	3 (7.3%)	0 (0.0%)	1.160*	0.282	NS

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test

Discussion:

Lung cancers still the leading cause of cancer mortality worldwide. Despite the standard treatment for advanced NSCLC, the overall prognosis is very poor Attempts to use molecular markers and detection of genetic mutations to predict the chemotherapeutic response are rapidly evolving ***(Baka et al., 2025).*** The COVID-19 pandemic poses a challenge to health systems worldwide. Limiting healthcare availability may delay early diagnosis and worsen the treatment effects of various diseases, including oncological diseases. It is known that patients with lung cancer are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments. Moreover, they have compromised underlying pulmonary function ***(Schoot et al., 2020).*** In the era of personalized medicine, we conducted this study to assess the correlation between COVID 19 infection in advanced NSCLC patients and PDL1 expression with its impact on clinical outcome and to assess the different clinicopathological characteristics of advanced NSCLC patients with COVID 19 infection and its impact on clinical outcome.

In our study non-squamous histology was found in 75% of cases (65% adenocarcinoma and 10% large cell carcinoma), while the rest 25% of cases are squamous subtype, this goes with many series ***(Ceppi et al., 2006; Bonanno et al., 2013; Leng et al., 2012).***

Additionally, we found that PDL1 expression was positive in 80% of patients, similar results were reported by ***Velcheti et al. (2014).*** We also observed a significant correlation between

positive PDL1 expression and duration of hospitalization, ICU admission, complications post COVID-19 infection in patients with COVID-19 infection.

Conclusion and recommendations:

We concluded that COVID 19 infection in advanced NSCLC patients can be correlated with PDL1 expression. Further prospective studies with large number of patients are recommended to evaluate the best measures helping in prevention of COVID 19 infection. A step must be taken toward tailoring the chemotherapy for patients with advanced NSCLC who could develop COVID 19 infection.

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References:

- Aghbash PS, Eslami N, Shamekh A, Entezari-Maleki T, Baghi HB. SARS-CoV-2 infection: The role of PD-1/PD-L1 and CTLA-4 axis. Life Sciences. 2021;270:119124.
- Baka S, Iraklis G, Papadopoulou E. Novel vaccines against lung cancer. Current Opinion in Oncology. 2025;37(1):73-83.
- Bonanno L. Predictive models for customizing chemotherapy in advanced non-small cell lung cancer (NSCLC). Translational Lung Cancer Research. 2013;2(3):160.
- Ceppi P, Volante M, Saviozzi S, Rapa I, Novello S, Cambieri A, Lo Iacono M, Cappia S, Papotti M, Scagliotti GV. Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. Cancer. 2006;107(7):1589-96.
- Leng S, Do K, Yingling CM, Picchi MA, Wolf HJ, Kennedy TC, Feser WJ, Baron AE, Franklin WA, Brock MV, Herman JG. Defining a gene promoter methylation signature in sputum for lung cancer risk assessment. Clinical Cancer Research. 2012;18(12):3387-95.
- Liang J, Bi N, Wu S, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol 2017; 28:777.
- Lin G, Fan X, Zhu W, Huang C, Zhuang W, Xu H. Prognostic significance of PD-L1 expression and tumor infiltrating lymphocyte in surgically resectable non-small cell lung cancer Patient characteristics. Oncotarget. 2017; 8:83986–83994.
- Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 160 (5):330-8.
- Schoot TS, Kerckhoffs AP, Hilbrands LB, Van Marum RJ. Immunosuppressive drugs and COVID-19: a review. Frontiers in pharmacology. 2020;11:1333.
- Velcheti V. Programmed death-1/programmed death-1 ligand axis as a therapeutic target in oncology: Current insights. Journal of Receptor, Ligand and Channel Research. 2014 Dec 23:1-7.
- Villalobos P, Mino B, Rodriguez-Canales J. Comparison of Different Antibody Clones for Immunohistochemistry Detection of Programmed Cell Death Ligand 1 (PD-L1) on Non-Small Cell Lung Carcinoma. Appl. Immunohistochem. Mol. Morphol. 2018; 26:83–93.