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Research Article

Evaluation of Clinical, Laboratory and Treatment Findings of Oncology Patients Diagnosed with COVID-19 Infection

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Abstract

Objectives: The knowledge of the possible differences in the clinical course of COVID-19 infection in cancer patients receiving treatment has not been sufficient to conclude. In this study, we retrospectively evaluated lymphocyte counts, LDH levels, neutrophil/lymphocyte ratios (NLR), platelet lymphocyte ratios (PLR), CRP albumin ratios (CRP/Alb), LDH/albumin ratios in COVID-19 infected cancer patients actively treated in our clinic.

Methods: Cancer patients who were currently under treatment in Department of Medical Oncology, Faculty of Medicine, Pamukkale University during the period between September 2020 and April 2021 were included in the study. During the period, 1363 stage 3-4 patients were received parenteral treatment and 60 patients were diagnosed with COVID-19 infection.

Results: The median age of the patients was 60 years (range 19-82 years). Stage of cancer (p=0.028), lymphopenia (p<0.001), elevated LDH (p=0.002), elevated NLR (p<0.001); and elevated LDH/Alb ratios (p<0.001) were identified as the factors affecting mortality.

Conclusion: In patients actively under treatment for cancer, clinical course of COVID-19 infection was found to be affected by the stage of the cancer, neutrophil lymphocyte ratios and by LDH/albumin ratios. We think that neutrophil lymphocyte ratios and LDH/albumin ratios are the important prognostic markers in the course of COVID-19 infection in cancer patients.

Keywords: Cancer; COVID-19, NLR, LDH/Alb

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COVID-19 since erupted in Wuhan city, China at the end of December 2019, has been exercising great influence all over the world and in Turkey as well. Cancer patients under treatment constitute a risk group for the infection. The management of specific side effects related to targeted treatment agents and immunotherapies have become a vital issue in this period. As COVİD-19 infecition is a novel clinical picture the avaible data on the possible effects caused by the virus on the clinical course in cancer patients is limited.[1] Cancer patients due to their systemic immunosuppressive state caused by both the cancer itself and the treatment are more prone to develop infections than other patients.[2] Given the necessity to continue cancer treatment and the possibility of high mortality due to COVID-19 in immunocompromised hosts managing treatment for cancer has become more difficult during the

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pandemic.[3] Patients receiving cytotoxic chemotherapy are under a high risk of being infected and of developing complications mainly due to the impairment in their protective barriers because of their compromised immune mechanisms which is essential in developing myeloproliferative cells and in immune response and of proliferative cells like intestinal mucosa.[4] In case of developing COVID-19 infection cancer patients on chemotherapy may develop more profound lymphopenia which in turn may worsen the clinical course of COVID-19.[5] Chemotherapeutic and immunotherapeutic combinations may also lead to profound lymphopenia.[6] During COVID-19 pandemic cancer patients currently on chemotherapy should be monitored closely. Cancer patients with symptoms and signs related to lower respiratory tract like cough, dyspnea, and hypoxia SARS-CoV-2 PCR testing should be considered preferential.

In this study, we aimed to analyze retrospectively, the effects of lymphocyte counts and LDH levels, neutrophile lymphocyte ratios (NLR), platelet lymphocyte ratios (PLR), CRP albumin ratios (CRP/Alb), LDH/albumin ratios; and of the current treatments on the clinical course of coronavirus infection in cancer patients infected with coronavirus while they were on active treatment in our oncology clinic.

Methods

Cancer patients who were on active treatment in Department of Medical Oncology, Faculty of Medicine, Pamukkale University during the period between September 2020 and April 2021 included in the study. During the period, 1363 stage 3-4 patients were received parenteral treatment and 60 were diagnosed with COVID-19 infection. Prognostic information related to age, sex, stage of the disease, received treatment, and survival was retrieved from patients' files and hospital's data processing system. The patients with complaints, such as difficulty in breathing or shortness of breath, fever, cough, sore throat, diarrhea, olfactory and gustatory dysfunction, were exposed to PCR amplification in case of possible infection. The enrolled patients were examined by ED clinicians, and their PCR samples were collected. Those with dyspnea, respiratory rate >28/min, SaO_2<93% at room air, PaO_2/FiO_2<300 and/or>50% increase in lung infiltration within 24 to 48h were hospitalized in the departments of Chest Diseases and Infectious Diseases, both of which are sub-disciplines under Internal Medicine. On the other hand, the patients were hospitalized to the intensive care unit in the case of severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, septic shock, arrhythmia, cardiogenic shock, acute renal failure or multi-organ failure.

The combined naso-oropharyngeal swabs were collected from the patients and analyzed with reverse-transcription polymerase chain reaction (RT-PCR) in Central Laboratory of our hospital. Neutrophil, lymphocyte and absolute platelet counts along with CRP, albumin, LDH levels were collected retrospectively from Hospital Data Processing System. While the analysis of the parameters of hemogram were examined by using the electrical impedance and optical density method with Mindray CAL 8000 (Shanghai, China) device, analysis of the levels of CRP, albumin, and LDH were conducted by the method of electrochemiluminescence with Cobas 702 analyzer (Roche Diagnostics, Manheim, Germany). CRP, Albumin, LDH values are given in mg/L, g/L, U/L, respectively, and cell counts are given in 10^3/microliter. Cut-off points for NLR, PLR, CRP/Albumin, LDH/albumin are established by ROC analysis. Cut-off points for NLR, PLR, CRP/Alb, and for LDH/albumin are accepted as 4.21, 0.19, 5.76, and 73.1, respectively. Lymphocyte counts over 800 and LDH over 214 U/L are accepted high.

Statistical Analysis

SPSS v.23 software packages were used. Descriptive statistics are given in means and percentages. Factors affecting mortality were calculated by using Kaplan-Meier method. For the statistical significance value, Log rank was adopted and accepted as $p<0.05$. Multivariate analysis were conducted by using the method of Cox analysis.

Results

In the present study, we included 60 patients selected among 1363 cancer patients who were on active parenteral treatment in Department of Medical Oncology, Faculty of Medicine, Pamukkale University during the period between September 2020 and April 2021. The median age was 60 years (range 19-82 years). Of the patients 37 (61.7%) were below and 23 (38.3%) were above the age of 65. Twenty-four (40%) patients were at stage 3 and 36 (60%) patients were at stage 4.

Among the patients having coronavirus infection 15 (25%) were diagnosed with non-small cell lung carcinoma, 10 (16.7%) with colorectal carcinoma, and the remaining with various types of tumors. Forty-two (70%) patients were currently treated with cytotoxic combination therapy, 12 (20%) with targeted therapy and immunotherapy, and 6 (10%) with cytotoxic monotherapy. There were 2 (3.3%) neutropenic patients. NLR ratios in 21 (35%) patients, PLR ratios in 39 (60%) patients, CRP/Alb ratios in 52 (86.7%) patients, and LDH/Alb ratios in 24 (40%) were above the cut-off values. Twenty-five (41.7%) patients were hospitalized. Twenty (33.3%) were required intensive care. Twenty (33.3%) patients failed to respond to treatment and died (Table 1).

Table 1. Patients' Characteristics

	n	%
Age		
Median 60 (19-82 years interval)		
≤65	37	61.7
>65	23	38.3
Tumor Type		
NSCLC	15	25.0
Colorectal	10	16.7
Gynecological	8	13.3
Breast	7	11.7
Pancreatic and hepatobiliary	6	10.0
SCLC	4	6.7
Stomach	2	3.3
Sarcoma	2	3.3
Prostatic	2	3.3
Melanoma	2	3.3
Skin basal cell	1	1.7
Kidney	1	1.7
Stage		
3	24	40
4	36	60
Treatment Groups		
Cytotoxic combination	42	70
Targeted and immunotherapy	12	20
Cytotoxic monotherapy	6	10
Neutropenia		
Neutropenic	2	3.3
Non-neutropenic	58	96.7
Lymphocyte		
Low	17	28.3
High	43	71.7
LDH		
Low	20	33.3
High	40	66.7
NLR		
Low	39	65
High	21	35
PLR		
Low	39	60
High	24	40
CRP/Alb		
Low	8	13.3
High	52	86.7
LDH/Alb		
Low	36	60
High	24	40
Hospitalization		
Yes	25	41.7
No	35	58.3
Required intensive care		
Yes	20	33.3
No	40	66.7
Mortality		
Survived	40	66.7
Exitus	20	33.3

*NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; NLR: Neutrophil/Lymphocyte ratio; PLR: Thrombocyte/Lymphocyte ratio; CRP/Alb: CRP/albumin; LDH/Alb: LDH/albumin.

Stage of the disease (p=0.028), lymphopenia (p<0.001), elevated LDH (p=0.002), elevated NLR (p<0.001), and elevated LDH/Alb ratios were identified as the factors affecting mortality (Table 2). In multivariate analysis, stage of the disease and NLR and LDH/Alb ratios were also identified as the factors affecting mortality (Table 3).

Table 2. Factors affecting mortality

	Mean and 95% CI of Survival Time	p
Age		
≤65	141 (114-167)	0.351
>65	107 (75-139)	
Stage		
3	144 (121-167)	0.028
4	113 (83-142)	
Treatment Groups		
Cytotoxic monotherapy	105 (32-177)	0.268
Cytotoxic combination therapy	111 (89-133)	
Targeted and immunotherapy	146 (112-155)	
Neutrophile counts		
Neutropenic	77 (1-159)	0.624
Non-neutropenic	135 (123-157)	
Lymphocyte counts		
Low	60 (27-93)	<0.001
High	158 (136-179)	
LDH		
Low	162 (146-177)	0.002
High	110 (82-137)	
NLR		
Low	163 (142-184)	<0.001
High	60 (35-85)	
PLR		
Low	120 (97-143)	0.802
High	132 (97-167)	
CRP/Alb		
Low	168 (130-205)	0.167
High	112 (91-132)	
LDH/Alb		
Low	189 (179-199)	<0.001
High	54 (28-79)	

NLR: Neutrophile/Lymphocyte ratio; PLR: Thrombocyte/Lymphocyte ratio; CRP/Alb: CRP/albumin; LDH/Alb: LDH/albumin.

Table 3. Multivariate analysis of factors affecting mortality

	Hazard ratio	95%CI	p
Stage	0.251	0.079-0.800	0.019
NLR	0.185	0.066-0.518	0.001
LDH/Albumin	0.025	0.003-0189	<0.001

* p values were calculated by Cox multivariate analysis.

Discussion

COVID-19 infection has a great impact all over the world, and so in Turkey. Especially the patients currently under treatment for cancer constitute a high-risk group. COVID-19 infections more frequently occur in patients with lung cancer and with hematological malignancies than with other malignancies.[7,8] In our study, among 1363 patients receiving parenteral treatment in Oncology Department, Faculty of Medicine, Pamukkale University, we identified 60 (4%) patients with coronavirus infection. The corresponding ratio in the literature is within the range of 1-4 percent.[9] More studies in the literature have reported COVID-19 infection incidence among cancer patients approximately 1 percent which is slightly higher than the corresponding value in the general population.[10,11]

In our study, we established that the course of COVID-19 infection was not affected by patients' age, whether they are under 65 or older. In the literature, patients showing a severe clinical course were tend to be older than the patients showing a mild clinical course were (69 vs 64 years; $p<0.01$). [12] Lymphopenia, on the other hand, has a significant effect on the clinical course of COVID-19 infection. Likewise, in our study, we established shorter survival among patients with lower lymphocyte counts than the patients with higher counts. In the study by Zhou et al., it was reported that lymphopenia, neutrophilia, elevated D-dimer and LDH levels frequently observed among cancer patients may increase the risk of developing severe COVID-19 infections.[13] In our study, we still found a statistically significant shorter survival for patients with elevated levels of LDH and LDH/alb ratios ($p=0.002$; $p<0.001$).

In case of developing COVID-19 infection, cancer patients receiving chemotherapies, which are known to be associated with a high risk of lymphopenia, may show a more profound lymphopenia which in turn increases the severity of the course of COVID-19 infection. Similarly cyclin dependent kinase inhibitors should also be used with caution due to their myelosuppressive potential.[14] Cyclophosphamide, methotrexate, fludarabine, and taxanes are the most myelosuppressive agents, which induce lymphopenia.[15] Chemotherapy and immunotherapy combinations also may lead to profound lymphopenia.[6] Since targeted therapies are expected to cause bone marrow suppression to a lesser degree than chemotherapies, targeted therapies seemed to be a safer choice for COVID-19 and its related complications. However, targeted agents that may cause lymphopenia such as the mammalian target of rapamycin (mTOR) inhibitors and tyrosine kinase inhibitors (TKI) targeting vascular endothelial growth factor receptor (VEGFR) should not be overlooked.[16] Therefore we classified the treatments our patients were given into three groups: cytotoxic combination treatments; cytotoxic monotherapy, and targeted and immunotherapy groups. We found treatment groups have no effect in the course of COVID-19 infection in our patients.

In our study, patients with elevated NLR ratios were found to have a statistically significant shorter survival ($p<0.001$). NLR was reported to have an effect on the course of COVID-19 infection in a prospective study. Patients with elevated NLR ratios indicated poorer prognosis.[17] Although the patients receiving immune checkpoint inhibitors have a lower risk of developing severe COVID-19 infection than those receiving cytotoxic chemotherapy, these patients in theory known to have a risk of cytokine release syndrome that may increase the severity of COVID-19 infection.[18, 19, 20] Robilotti et al. analyzed 423 cancer patients on active treatment. While the patients receiving cytotoxic treatment did not show any difference with respect to the severity of the disease and the need for hospitalization, patients treated with immunotherapy, had more severe course of infection and presented nearly three times higher hospitalization rates (HR 2.84, 95% CI, 1.24-6.72). It can be said that the majority of patients on immunotherapy diagnosed with lung carcinoma contribute to the increase in hospitalization rates.[21] In different studies immunotherapy has been reported not to increase the severity of COVID-19 infection. [22] In the study by Zhang et al., mortality rate was 29% in 28 cancer patients developing COVID-19 infection. It was also reported that 22-25% of these patients were with lung cancer, 14-16% with gastrointestinal cancer, and 11% with breast cancer. Laboratory tests on the cases revealed hypoproteinemia (89%), lymphopenia (82%), elevated CRP (82%), and anemia (75%).[23] Current reports showed no compounding effect for different oncological treatments on COVID-19 mortality.[24-26]

Conclusion

We established that the modality of treatment oncology patients actively treated with had no effect on the course of COVID-19 infection. We believe neutrophil/lymphocyte and LDH/albumin ratios are significant prognostic markers and patients showing high values for these particular markers should be monitored closely.

Disclosures

Ethics Committee Approval: The study was approved by Pamukkale University Faculty of Medicine Ethics Committee in compliance with Helsinki Declaration (Approval number: 60116787-020/56182, approval date: 25.05.2021).

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Conflict of Interest: None declared.

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References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507–13.
2. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARSCoV-2 infection: A nationwide analysis in China. Lancet Oncol 2020;21:335–7.
3. Lewis MA. Between scylla and charybdis - oncologic decision making in the time of Covid-19. N Engl J Med 2020;382:2285–7.
4. Zimmer AJ, Freifeld AG. Optimal management neutropenic fever in patients with cancer. J Oncol Pract 2019;15:19–24.
5. Patel R, Park J, Shah A, Saif MW. COVID-19 and cancer patients. Cancer Med J 2020;3:40–8.
6. Novello S, Camps C, Grossi F, Mazieres J, Abrey L, Vernejoux JM, et al. Phase II study of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases. J Thorac Oncol 2011;6:1260–6.
7. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: A multicenter study during the COVID-19 outbreak. Cancer Discov 2020;10:783–91.
8. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: A systematic review and meta-analysis of 3377 patients. Blood 2020;136:2881–92.
9. Berghoff AS, Gansterer M, Bathke AC, Trutschnig W, Hungerländer P, Berger JM, et al. SARS-CoV-2 testing in patients with cancer treated at a tertiary care hospital during the COVID-19 pandemic. J Clin Oncol 2020;38:3547–54.
10. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol 2020;6:1108–10.
11. Bertuzzi AF, Marrari A, Gennaro N, Cariboni U, Ciccarelli M, Giordano L, et al. Low incidence of SARS-CoV-2 in patients with solid tumours on active treatment: An observational study at a tertiary cancer centre in Lombardy, Italy. Cancers (Basel) 2020;12:2352.
12. Zhang HY, Wang LW, Chen YY, Shen X, Wang Q, Yan Y, et al. A multicentre study of 2019 novel coronavirus disease 2019 outcomes of cancer patients in Wuhan, China. MedRxiv 2020;21:20037127.
13. 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;395:1054–62.
14. Patel R, Park J, Shah A, Saif MW. COVID-19 and cancer patients. Cancer Med J 2020;3:40–8.
15. Ménétrier-Caux C, Ray-Coquard I, Blay JY, Caux C. Lymphopenia in cancer patients and its effects on response to immunotherapy: An opportunity for combination with Cytokines? J Immunother Cancer 2019;7:85.
16. Ray-Coquard I, Favier L, Weber B, Roemer-Becuwe C, Bougnoux P, Fabbro M, et al. Everolimus as second-or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. Br J Cancer 2013;108:1771–7.
17. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage. MedRxiv 2020;18:206.
18. Rassy EE, Assi T, Rizkallah J, Kattan J. Diffuse edema suggestive of cytokine release syndrome in a metastatic lung carcinoma patient treated with pembrolizumab. Immunotherapy 2017;9:309–11.
19. Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Immunotherapy 2020;12:269–73.
20. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
21. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020;26:1218–23.
22. Rogiers A, Pires da Silva I, Tentori C, Tondini CA, Grimes JM, Trager MH, et al. Clinical impact of COVID-19 on patients with cancer treated with immune checkpoint inhibition. J Immunother Cancer 2021;9:001931.
23. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020;31:894–901.
24. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): A cohort study. Lancet 2020;395:1907–18.
25. Albiges L, Foulon S, Bayle A, Gachot B, Pommeret F, Willekens C, et al. Determinants of the outcomes of patients with cancer infected with SARS-CoV-2: Results from the Gustave Roussy cohort. Nat Cancer 2020;1:965–75.
26. Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: A prospective cohort study. Lancet 2020;395:1919–26.