Red cell distribution width, a predictive factor in immunocompromised patients with COVID-19: A comparison retrospective study between cancer and kidney transplant patients

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Abstract

We aimed to review the records of cancer and kidney transplant patients of out of 1135 COVID-19 patients, who were referred to our hospital (Valiasr) in Zanjan, from March 16th, 2020, to June 11th, 2020. This was single-center, historical cohort study. Patients were divided into different subgroups and compared of disease outcomes. The only predictor of death was lactate dehydrogenase (LDH). The rate of red cell distribution width (RDW) in patients with active cancer was higher than kidney transplant patients and was statistically significant. There was no statistically significant difference in mortality between active and non-active cancer groups. Female sex and low SpO2 has increased the chances of ICU admission. Patients with active cancer generally have severe and more complicated disease and RDW can be a predictable option.

Key Words: COVID-19; kidney transplantation, cancer, immunocompromised patient.

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The pandemic of COVID-19 has a huge effect on public health and is still a major cause of death in Iran.[1] During the COVID-19 pandemic, cancer patients are an especially vulnerable group. Because of their underlying condition and treatment complication, they are often immunosuppressed.[2] Many individuals assume that cancer patients who receive systemic anticancer drugs are at a higher risk of developing the disease than patients who do not receive anticancer treatment.[3] There is few information on the risk of developing COVID-19 in hematological cancer patients. Many people with hematological cancer take anti-cancer drugs that suppress bone marrow function, putting them at risk of acquiring infections in the community and hospitals.[4] The epidemiology, clinical characteristics, and outcomes of COVID-19 among solid organ transplant (SOT) recipients are undefined. Few early descriptive case reports and case series of SOT recipients with COVID-19 suggest poor outcomes; but, difference is unclear between in the SOT and non-transplant population.[5] Due to chronic immunosuppression and coexisting conditions, kidney transplant recipients are particularly vulnerable to COVID-19.[6] Patients with COVID-19 have hematological abnormality, such as a lower lymphocyte and platelet count but a normal white blood cell (WBC).[7] Red cell distribution width (RDW) conveys the degree of anisocytosis between red blood cells. Anisocytosis is a mechanism that is highly dependent on inflammation. Many of the proinflammatory cytokines like TNF-α and interleukin-1 decrease erythropoietin synthesis during cytokine storm.[8] In addition, hypoxia causes erythropoietic disturbance in COVID-19. Super infections are prevalent in COVID-19, thus increasing sepsis. RDW plays a considerable alarm in sepsis.[8] In particular, several previous studies have shown that increased RDW is correlated with mortality in non-specific acute respiratory distress syndrome (ARDS) patients.[9] Adding RDW at diagnosis of ARDS increased discrimination in the model using 4 clinical factors to estimate ICU mortality.[10] Since the beginning of the pandemic, there have been grave concerns over the risk of developing severe COVID-19 for individuals with immunodeficiency's or those taking immunosuppressive therapies. Two main immunosuppressant diseases are cancer and SOT. There are conflicting data about increased risk of COVID-19 in patients with a history of immunosuppressant.[11,12] Type and duration of immunosuppressant are important in evaluation of

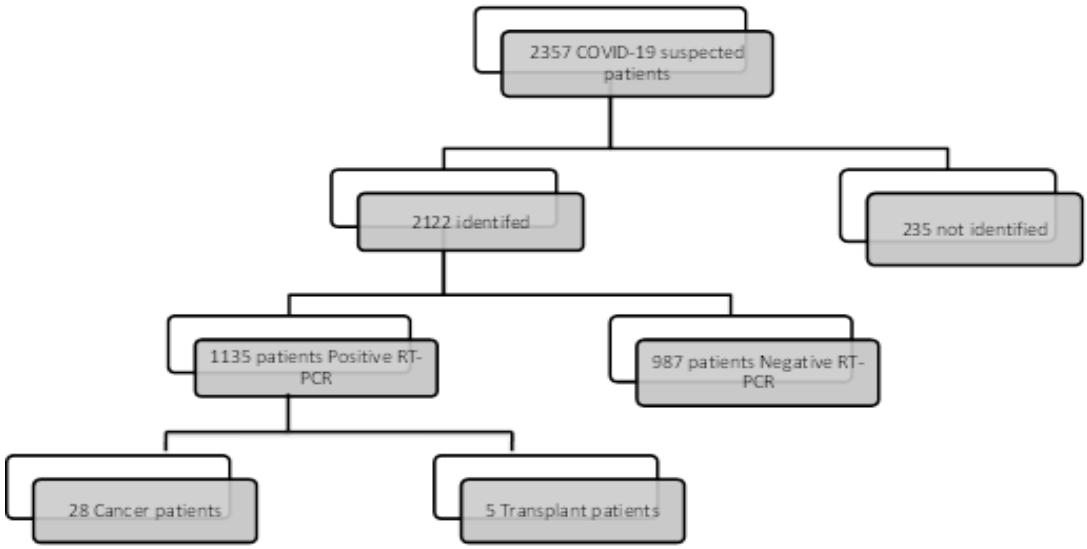

Fig 1. *Statistics of patients suspected to COVID-19: Cancer and kidney transplant patients with positive COVID-19 RT-PCR were included.*

susceptibility to infection. Therefore, we aimed to review the records of cancer and kidney transplant patients of out of 1135 COVID-19 patients, who were referred to our hospital (Valiasr) in Zanjan, Iran.

Materials and Methods

Study design

This was a single-center, historical cohort study. We reviewed the records of cancer and kidney transplant patients with COVID-19 were referred to our hospital (Valiasr) in Zanjan, from March 16th, 2020, to June 11th, 2020 (Figure 1). The most prevalence between SOT patients that referred to our system was kidney transplant. Cancer (solid tumor and hematologic malignancy) and kidney transplant patients with positive COVID-19 RT-PCR (reverse-transcriptase polymerase chain reaction) were included.

This study was approved by the institutional ethics review boards of our university (approval number IR.ZUMS.REC.1399.265 date: Oct 15th, 2020). The Research Ethics Committee waived the requirement informed consent before the study started because of the urgent need to collect epidemiological and clinical data. We analyzed all the data anonymously.

Diagnostic methods

The method of diagnosis is RT-PCR assay test using throat swab specimens collected from upper respiratory tracts. All patient aged was more than 18. Patients with a radiological or clinical diagnosis of COVID-19, without a positive RT-PCR test were not included in this analysis.

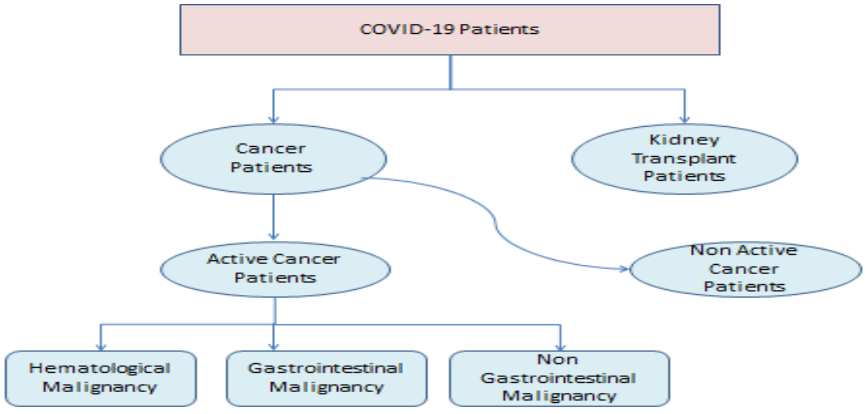

Fig 2. *Division algorithm of patients with COVID-19, including two groups 1: Patients with cancer, 2: Patients with renal transplant. Patients with cancer were studied in two groups: active cancer and inactive cancer. Cancers were studied in 3 groups: blood malignancy, gastrointestinal cancer and non-gastrointestinal cancers.*

Table 1. *Description of patients on admission.*

	Variables	Cancer patient's N (%)	Graft patients N (%)
Sex	Male	16(57.1)	**4(80)**
	Female	12(42.9)	**1(20)**
Age		M ± SD	**M ± SD**
		62.54±14.78	**48.60±15.14**
Severity	severe	11(39.3)	**2(40)**
	Non-severe	17(60.7)	**3(60)**
Comorbidity	DM	3(10.7)	**1(20)**
	HTN	6(21.4)	**4(80)**
Cancer activity	Active	22(78.5)	
	Non-active	6(21.4)	
Type of cancer	Hematologic	5(17.9)	**N/A**
	GI	8(28.6)	
	Non-GI	15(53.6)	
Total		28(100)	**5(100)**

GI: Gastrointestinal; Non GI: Non Gastrointestinal; HTN: Hypertension; DM: Diabetes Mellitus; N: Number; SD: standard deviation

Patients with non-invasive cancers including non-melanomatous skin cancer, in-situ carcinoma, or precursor hematological neoplasms were excluded from this analysis. Patients with room air oxygen saturation (SpO2) < 90% were considered as severe COVID-19, and ≥90% were considered moderate COVID-19.[13] Clinical data of each patient were collected, which included age, gender, and known comorbidities (diabetes mellitus (DM), hypertension (HTN)). Other underlying diseases were not included in the study due to their lower prevalence. Cancer stage was not chosen for the multivariable analysis as this variable was only collected in solid tumors. Patients with cancer were studied in two

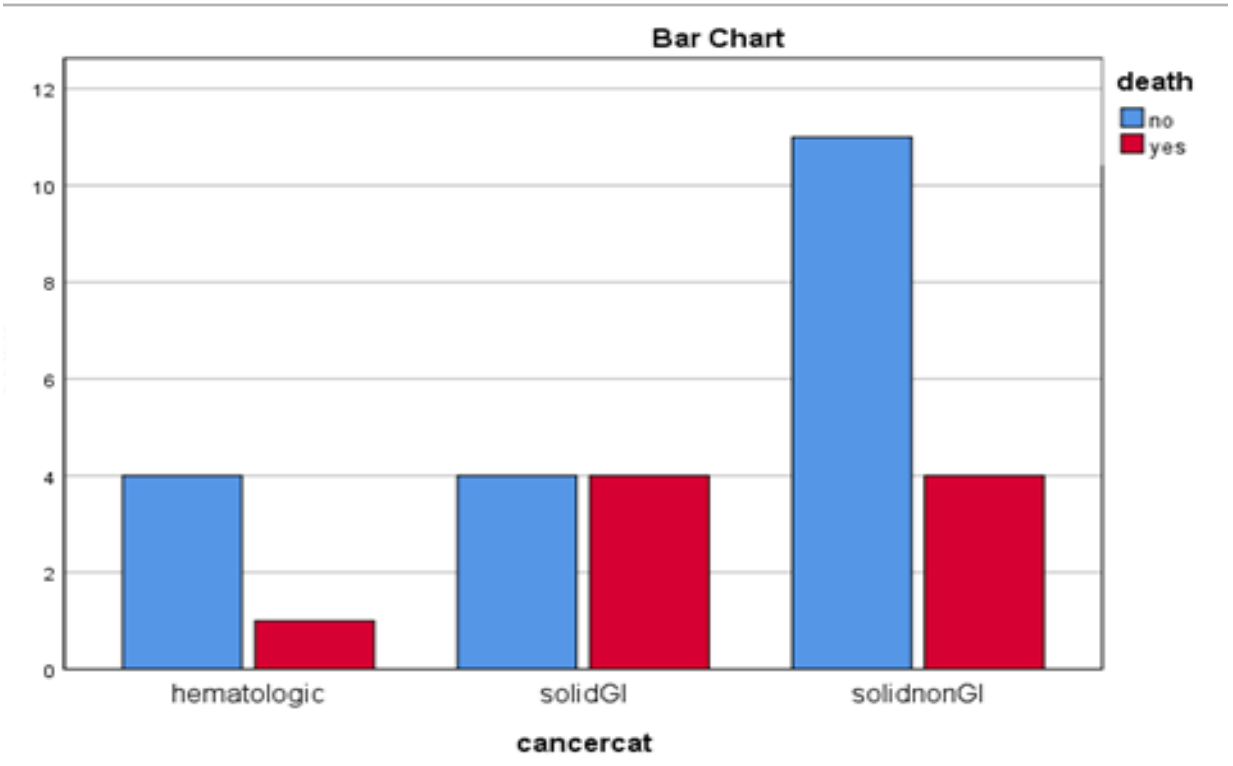

Fig 3. Comparison of cancer type with mortality. GI: Gastrointestinal, Non GI: Non Gastrointestinal

Table 2. *Patients' laboratory tests and the type of cancer.*

	Patient with Cancer type	WBC	Hb	PLT	RDW	LDH	Lymph count
1	Breast Cancer	2900	12.3	89000	13.2	403	41.6
2	Lung Cancer	15200	8.9	215000	15.3	612	6.4
3	Esophageal Cancer	3200	10.1	404000	13.4	259	9.9
4	Oral SCC	4200	12.3	252000	14.1	570	18.2
5	Hypopharyngeal Cancer	19400	7.3	276000	17.5		3.5
6	Gastric Cancer	10300	11.6	204000	16.2	587	17.1
7	CLL	116000	11.5	44000	15.2	786	0
8	Metastatic Lung Cancer	5300	10.5	256000	17.4	539	37.6
9	Prostate cancer	4300	13.4	126000	13.6	405	18.7
10	Glioblastoma multiforme						
11	Prostate Cancer	5000	16.6	171000	13.5	514	23.9
12	Breast Cancer	7500	12	191000	12.4	419	10.7
13	Thyroid Cancer	4800	13.8	160000	13.1	316	16.8
14	Gastric Cancer	7.9	9.7	317	14.9	316	25.3
15	CLL	79.6	8.8	31	15.3	887	87.8
16	Ovarian Cancer	15.6	12.2	473	15.8	298	22.3
17	Non Hodgkin Lymphoma + Prostate	2.5	8.3	30	21.6	548	11.8
18	Multiple Myeloma	0.6	7	65	15.1	194	
19	RCC	4	10.4	114	15.1	659	21.3
20	Laryngeal Carcinoma					254	
21	Chollangiocarcinoma	0.8	11.2	167	15.1	1338	
22	Hodgkin Lymphoma	6.5	12.5	90	13.5	197	10.1
23	Anal Cancer	3.2	13.6	70	14.2	408	13.4
24	Astrocytoma	3.7	13.2	149	15.3	753	35.6
25	Lung Cancer	9	10.3	211	17.8	351	14.7
26	Breast Cancer	7.9	12.1	279	13.3	416	21.8
27	Esophageal Cancer	0.3	10.1	33	16.8	445	
28	Gastric Cancer	2.6	10.3	172	13.2	461	37.2

Graft patient	Sex	Age	Underlying disease		SPO2	WBC	Hb	PLT	RDW	LDH
Patient 1	Male	41		HTN	93	6100	16.2	133000	12.1	319
Patient 2	Female	27		HTN	89	6500	8.4	234000	12.8	769
Patient 3	Male	50	DM	HTN	82	7000	13.2	177	13.5	1145
Patient 4	Female	61		HTN	93	4800	9.8	130	12.4	477
Patient 5	Male	64			97	11300	11.8	166	14.4	209

SCC: Squamous Cell Carcinoma; CLL: Chronic Lymphocytic Leukemia; GBM: Glioblastoma Multiform; RCC: Renal Cell Carcinoma; WBC: White Blood Cell; Hb: Hemoglobin; PLT: Platelets; RDW: Red Distribution Width; LDH: Lactate Dehydrogenase; SPO_2: Oxygen Saturation; HTN: Hypertension; DM: Diabetes Mellitus

groups: active cancer (for which anticancer treatment (chemotherapy) had been administered in the past 6 months; or hematological cancer that is not in complete remission) and inactive cancer. Also cancer patients were studied in 3 groups: blood malignancy, gastrointestinal cancer and non-gastrointestinal cancers (Figure 2).

Table 3. *Cancer and Graft patients*

		Cancer patients			Graft patients		
		ICU admission N (%)	Days of hospitalization (Med ±IQR)	Mortality N (%)	ICU admission N (%)	Days of hospitalization (Med ±IQR)	Mortality N (%)
Sex	Male	4(25)	7±5	5(31.3)	1(25)	8±11	1(25)
	Female	5(41)	5.5±5	4(33.3%)	0	4	0
Severity	Severe	4(36.4%)	6±6	4(36.4%)	1(50)	18	1(50)
	Non severe	5(29.4%)	7±7	5(29.4%)	0	5.5±4.5	0
Cancer activity	Active	7(31.8%)	6±5	8(36.4%)	N/A	N/A	N/A
	Non active	2(33.3%)	7±13	1(16.7%)	N/A	N/A	N/A
Total		9(32)	6.50±6	9(32.1)	1(20)	7±10	1(20)

IQR: Inter Quartile Range, N: Number, Med: Medium

Indicators measurements and analysis

The main outcome was patient survival during hospitalization. Measurements included RDW (elevated RDW defined as greater than 14.5%), Lymphocyte count (ALC < 1,000 cells/mm3 was defined as lymphopenia) and Platelet (PLT < 150,000 platelets/mm3 was defined as thrombocytopenia) at first day admission in hospital. Secondary outcomes were: a composite of severe illness (death, severe illness, admission to an intensive care unit (ICU), or a combination of these). Statistical analysis carried out using SPSS version 22. Significance level considered 0.05.

Results

We retrospectively enrolled 28 cancer (2.4%) and 5 kidney transplant patients of the 1135 patients admitted to Valiasr hospital for treatment of COVID-19. Demographic, clinical feature and underlying diseases of the patients are shown in Table 1. The mean age was 62 for cancer and 48 for kidney transplant patients (Mann-Whitney sig=0.053). The sex distribution in patients was not significantly different between cancer and kidney transplant patients (Exact sig=0.625). The most types of cancer patients were Gastric (3 patients), lung (3 patients), Breast (3 patients). Gastrointestinal cancer was the most frequent type of cancer (28.6%). The patient

Table 4. *Main Laboratory Findings according to clinical situation*

		Cancer patients		Graft patients	
		PLT count<150.000 N (%)	RDW>14.5 % N (%)	PLT count<150.000 N (%)	**RDW>14.5% N (%)**
Sex	Male	11(68%)	11(68.8%)	3(75)	**0**
	Female	7(63.6%)	6(50%)	1(100)	**0**
	Exact sig	1.00	0.441	0.78	**N/A**
Severity	Severe	8(72.7%)	8(72.7%)	1(50)	**0**
	Non-severe	10(62.5%)	9(52.9%)	3(100)	**0**
	Exact sig	0.692	0.435	0.04	**N/A**
Cancer activity	Active	15(71.4%)	15(68.2%)		
	Non-active	3(50%)	2(33.3%)		
	Exact sig	0.305	0.174		

PLT: Platelets, RDW: Red Distribution Width, N: Number

Table 5. *Comparison of active cancer patients with kidney transplant patients*

	Active Cancer	Kidney Transplant	p-value
ICU admission	7(31.8%)	1(20%)	0.52
Mortality	8(36.4%)	1(20%)	0.44
RDW>14.5%	15(68.2%)	0	0.01

ICU: Intensive Care Unit; RDW: Red Distribution Width.

with Glioblastoma Multiform (GBM) died on the day of referral and no blood test was recorded for the patient, but the RT-PCR test came back positive later. The result of CBC taken in first day of case with laryngeal carcinoma was laboratory's missing, in which the results of the patient's tests were not entered in the system.

In comparison between cancers type, gastrointestinal had higher mortality, but there was no statistically significant difference (P-Value= 0.54) (Figure 3). Among cancer patients, 9 (32.1%) patients had at least one or more underlying diseases whereas 80% kidney transplant patients had chronic comorbidity (Exact sig=0.041). In the severe cancer group, 6 of the 9 patients with the underlying disease had severe COVID-19. The patients' laboratory tests and the type of cancer in Table 2 are shown. Twenty-two (78.5%) cancer patients had active and six (21.4%) had inactive disease. Eight patients (36.3%) of active cancer and one (16.6%) inactive cancer died. Mortality of active versus inactive cancer patients was higher, but the differences was not statistically significant (Exact sig=0.63). Comparing mortality rate of cancer (32%) and graft patients (20%), the difference was not significant (Exact sig=1.000). Frequency of ICU admission was not statistically different between graft (20%) and cancer patients (32%) (Exact sig=1.000), also duration of hospitalization was not different between groups of patients (Mann-Whitney p=0.88) (Table 3). Nine (32.1%) of cancer patients needed invasive mechanical ventilation. In this study, among age, sex, diabetes mellitus, hypertension and baseline laboratory values, the only predictor of mortality was LDH level. The prevalence of thrombocytopenia (PLT<150000) and RDW> 14.5% were higher in severe patients but the difference was not statistically significant (Table 4). With each unit increase in LDH, the patient's chance of death increased by 0.5%. Patients were assessed for risk of mortality using LDH. ROC analysis with AUC = 0.750 and sig = 0.038 revealed the cut-off values of 404 with a sensitivity of 0.87 and a specificity of 0.64. To predict the need for ICU based on clinical conditions and laboratory findings, two variables of sex and O_2 saturation were entered the Logistic regression model.

Female sex and SpO_2 <90% increased the chances of admission in ICU. None of the variables could estimate the number of days a patient will spend in the hospital based on clinical conditions and laboratory results at the time of patient admission using linear regression. Comparing active cancer and kidney transplant patients, interesting results were obtained that are shown in Table 5. Mortality and the need for hospitalization in ICU were higher in patients with active cancer, although the difference was not statistically significant (exact sig>0.05). RDW in patients with active cancer was higher than kidney transplant patients (exact sig=0.01).

Discussion

It was surprising for us that mortality and the need for ICU care were not significantly difference between active and inactive cancer patients. Liu study showed that the anti-tumor treatment did not lead to poorer prognosis in patients with solid tumors diagnosed with COVID-19.[14] Lee study showed that chemotherapy in the past 4 weeks had no significant effect on COVID-19 mortality.[15]

In our study, although the rate of mortality and admission in the ICU were higher in patients with active cancer, but there were not statistically significant.

Active hematologic malignancies with COVID-19 had a similar risk of death versus non active hematologic patients.[16] In Shoumariyeh study no significant difference was observed between solid tumor and hematological malignancy in overall survival.[17] Our study shows same result (between GI cancer, non-GI cancer and hematologic cancer) but mortality was higher in GI malignancy without statistical significance. In this study among the cancer patients, gastrointestinal was the most frequent type of cancer.

It is noteworthy that in the Ma study; the most common cancer was colorectal (29.7%), some studies indicated that lung cancer patients were the most common to be infected.[18,19] Elevated LDH have been observed in the blood of patients with COVID-19, and levels of this enzyme correlate with disease severity. The findings of this study also confirmed this point.[20] Men have a much greater risk of severe acute COVID-19 than women.[21] While in our study, woman had increased risk of admitted to the ICU.

COVID-19 is an immunosuppressant disease. An important question that has not yet been properly answered is: which patient with immunosuppression is more sensitive to COVID-19? Compared with active cancer and kidney transplant patients, interestingly high RDW was significant between the two groups, although the mortality rate was not statistically different, but it was higher in the active cancer group. In Sharma et al. study RDW in COVID-19 patients, was found to be higher than normal patients; however, it had no significant

association with disease severity.[22] In our study, the proportion of severe COVID-19 with active cancer was 31.8% which was also significantly higher than that of the Iranian general population with severe COVID-19 (11%).[23] It seems cancer patients were more likely to be immunosuppressed than kidney transplant patients included in our study and are more susceptible to COVID-19, but why there isn't statistical difference between mortality in active cancer and kidney transplant patients? One of the reasons is the presence of associated underlying disease (hypertension and diabetes) that more predispose patients to COVID-19 in most kidney transplant patients. However, we cannot ignore the limitations of our study, the most important of which is the small number of immunosuppressed patients in each group and don't enrolled other immunocompromised condition.

In conclusion, our data suggest that patients with active cancer generally have severe and more complicated disease. But in our study, there was no higher mortality among patients with active versus inactive cancer in COVID-19. Therefore, it seems logical not to deprive cancer patients who need chemotherapy as basic treatment. The severity of COVID-19 varies in different types of immunosuppressed patients. RDW can be a predictor in these patients, but for clearer results, studies with larger statistical populations should be evaluated.

List of acronyms

ALC - Lymphocyte count
ARDS - acute respiratory distress syndrome
CBC - complete blood count
CLL - Chronic Lymphocytic Leukemia
DM - diabetes mellitus
GBM - Glioblastoma Multiform
GI - Gastrointestinal;
Hb - Hemoglobin
HTN - hypertension
ICU - intensive care unit
LDH - lactate dehydrogenase
Non GI - Non Gastrointestinal
PLT - platelet
RCC- Renal Cell Carcinoma
RDW - red cell distribution width
ROC - receiver operating characteristic
RT-PCR - Reverse transcription polymerase chain reaction
SCC - Squamous Cell Carcinoma
SOT - solid organ transplant
SpO_2 - oxygen saturation
WBC - white blood cell

Contributions of Authors

Conceptualization: MM and KK; Methodology: MM, KK and MJ; Data Curation: MJ, SPS and SVAP; Analysis: NJ; Writing, MM and KK; Reviewing and Editing: MM, KK and NJ. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interests.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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