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Temporal Changes in SARS-CoV-2 Infection Pattern in Patients Admitted with Hematological Diseases—A Single Center Experience from North India

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Abstract: Previous studies have shown the vulnerability of hematological patients with the Coronavirus disease of 2019 (COVID-19). We aimed to compare the outcomes and risk factors for poor survival in patients with hematological conditions hospitalized with COVID-19 infection. Single centre, retrospective, cohort study included all patients with a hematological condition admitted to Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India between 1 April 2020 and 31 May 2021. Of a total of 154 patients, 81 were in the pre-delta group and 73 were in the delta group out of which 21 (25.97%) in the pre-delta group and 24 (33.88%) patients in the delta group died. Haematological characteristics—age > 60 years, progressive hematological cancer, more than two lines of anti-cancer therapy, and active chemo-immunotherapy or targeted therapy were associated with higher mortality in the delta group. COVID-19 characteristics associated with higher mortality during the delta wave were severity of COVID infection, higher oxygen requirements, and COVID plasma therapy There were no deaths in individuals (n = 15) within the delta group who received COVID-19 vaccination. This study adds to the evidence that patients with hematological diseases are a particularly vulnerable group and the delta variant of the virus is associated with higher mortality. We could identify patient characteristics and features related to COVID-19 infection and underlying hematological conditions that were associated with poor outcomes in the delta sub-group. Vaccination was found to be an effective strategy for overcoming mortality and morbidity in these patients.

Keywords: delta-covid; hematological malignancy; pre-delta covid; vaccination

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1. Introduction

The novel coronavirus (SARS-CoV2) 2019 placed an unparalleled burden on the healthcare system globally [1]. Although widespread vaccination has helped in curbing deaths, vaccine hesitancy, poor vaccine coverage, and poor healthcare facilities in low/middle-income countries, poor antibody responses and upcoming variants have blunted its benefits.

Patients with hematological conditions (benign & malignant) are recognized to be particularly vulnerable to Coronavirus disease of 2019 (COVID-19) infection [2]. Underlying immune dysfunction, use of chemotherapy, monoclonal antibodies, immunomodulatory drugs, and frequent hospital visits for anti-cancer therapy/blood transfusion put patients at greater risk of contracting the infection and severe COVID-19 disease [3]. The wave of COVID-19 cases that were seen in India in 2021 was due to the delta variant of the virus as reported by the World Health Organization (WHO) [4]. Here we present a comparative analysis of the original SARS-CoV2 and delta variant of SARS-CoV2 in patients with hematological diseases.

2. Materials and Methods

After obtaining institutional ethics approval, we retrospectively studied the case records of patients with hematological diseases (benign & malignant) with SARS-CoV2 infection. Patients admitted (including those in Intensive Care Unit) between 1 April 2020 to 31 December 2020 were included in the pre-delta group and from 1 January to 31 May 2021 in the delta group. This cut-off was conservatively chosen as very few cases (n = 2) presented to us between January and March 2021.

Quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) of nasal and/or oropharyngeal swabs was used to diagnose SARS-CoV-2 infection. Repeat evaluation was carried out following institutional protocols. Patients with COVID-19 infection who were hospitalized (ICUs; n = 58) irrespective of severity were included. The severity of COVID-19 at admission was graded according to severity criteria described in the National Institutes of Health (NIH) guidelines [5].

Benign hematological conditions were diagnosed as per the Modified Camitta et al. criteria for aplastic anemia [6], thalassemia international federation guidelines [7] and immune thrombocytopenia as per American Society of Hematology guidelines 2019 [8]. Diagnosis of hematological malignancy was based on the most recent WHO classification of hematopoietic tumors [9]. Patients with lymphoma or multiple myeloma were considered to have the progressive disease if their lymph nodes were larger on CT or PET/CT scans, or if their plasma protein levels increased by 25%. European Leukemia Net (ELN) recommendations were used for the response assessment in acute leukemia, primary myelofibrosis and chronic myeloid leukemia whereas International Myeloma Working Group (IMWG) and Response Evaluation Criteria in Lymphoma (RECIL) were used for response assessment in myeloma and lymphoma respectively [10–13].

In our study, we defined active therapy as treatment delivered during admission for COVID-19 or within the past three months.

Initial diagnosis and those on observation were included together. Patients in complete remission (CR) were classified separately. Those who had relapsed/refractory disease, progressive disease, stable disease, or partial response were clubbed together as patients, not in remission and had significant disease burden for analysis of hematological characteristics.

2.1. Outcomes

The primary outcome was day 30 mortality among patients with hematological conditions and COVID-19. Evaluation of potential predictive parameters of mortality was undertaken for the pre-delta and the delta COVID-19 group, including hematological malignancy characteristics (disease type, disease status, and therapy status); COVID-19 severity; oxygen requirement-low (FiO_2 < 40%) or high (FiO_2 > 40%); and COVID-19 infection characteristics (antiviral prophylaxis, vaccination status {ChAdOx1 adenovirus/Inactivated vaccine}, therapy received).

2.2. Statistical Analysis

Descriptive statistics (including median, mean, and range) were used to describe the measures of central tendency. Categorical and continuous variables were analyzed using Pearson's chi-square (χ) or Fisher's exact independent *t*-test to determine the potential factors for severe COVID-19 infection and day 30 mortality post-COVID-19 infection. The overall survival curve was plotted using the Kaplan–Meier method and univariate analysis was done using the log-rank method. A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the statistical software STATA 16.

3. Results

3.1. Patient Demographics

Among the 154 patients who fulfilled the inclusion criteria, 81 were in the pre-delta group and 73 were in the delta group. The median age in the pre-delta and delta groups was similar (52 years, range 15 to 71 years vs. 53 years, range 9 to 78 years; p = 0.91).

There were 62 (76.5%) males in the pre-delta group against 44 (60.2%) males in the delta group. On average 51 (33%) patients had comorbidities and n = 26 (16.8%) had more than one comorbidity. There were 21 (25.93%) pre-morbid smokers in the pre-delta group and 37 (50.68%) in the delta group (p value = 0.003). The following characteristics were compared between the two groups. Table 1.

Table 1. Baseline characteristics of pre-delta and delta groups.

Characteristics	PRE-DELTA N (%)	DELTA N (%)	Total (p Value)
Total Patients (N%)	81 (52.60%)	73 (47.40)	154
Final Outcome (Alive)	60 (74.07%)	49 (67.12%)	109 (0.344)
Median Age (Q1, Q3)	52 (35, 65)	53 (36, 62)	(0.9150)
Male	62 (76.54%)	44 (60.27%)	106 (0.030)
Female	19 (23.46%)	29 (39.73%)	
Severity at Diagnosis			
• Mild	40 (49.38%)	32 (43.84%)	<0.001
• Moderate	1 (1.23%)	23 (31.51%)	
• Severe	40 (49.38%)	18 (24.66%)	
Smoking Status			
• Yes	3 (3.70%)	0 (0%)	0.003
• No	21 (25.93%)	37 (50.68%)	
• Unknown	57 (70.37%)	36 (49.32%)	
Delay in Admission			
• ≥72 h	77 (95.06%)	56 (76.71%)	0.001
• <72 h	4 (4.94%)	17 (23.29%)	
Active Treat			
• Yes	62 (76.54%)	49 (67.12%)	0.193
• No	19 (23.46%)	24 (32.88%)	
Vaccination			
• Received	0 (0%)	15 (20.55%)	<0.001
• None	81 (100%)	58 (79.45%)	
Number of doses Received			
• No Dose	81 (100%)	58 (79.45%)	<0.001
• 1 Dose	-	11 (15.07%)	
• 2 Doses	-	4 (5.48%)	
Comorbidity			
• None	47 (58.02%)	50 (68.49%)	0.179
• At least 1	34 (41.98%)	23 (31.51%)	
Valacyclovir Prophylaxis (Yes)	2 (2.47%)	11 (15.28%)	0.005
Malignancy Status			
• Initial Diagnosis + Observation	37 (45.68%)	35 (47.95%)	0.189
• In Remission	19 (23.46%)	24 (32.88%)	
• Not in Remission (Relapsed/Refractory + Progressive/Stable Disease + PR)	25 (30.86%)	14 (19.18%)	
Types of Therapy at the time of COVID-19 diagnosis			
• Observation	10 (12.35%)	5 (6.85%)	0.276
• Chemotherapy	27 (33.33%)	35 (47.95%)	
• Chemo-Immunotherapy	24 (29.63%)	18 (24.66%)	
• Others	20 (24.69%)	15 (20.55%)	

Table 1. *Cont.*

Characteristics	PRE-DELTA N (%)	DELTA N (%)	Total (*p* Value)
Transplant			
• No Transplant	73 (90.12%)	62 (84.93%)	0.078
• Allogeneic Transplant	2 (2.47%)	8 (10.96%)	
• Autologous Transplant	6 (7.41%)	3 (4.11%)	
Therapy Received for COVID	54 (66.67%)	49 (67.12%)	0.952
• Steroids	46 (56.79%)	60 (82.19%)	
• Remdesivir	2 (2.47%)	5 (6.85%)	0.001
• Favipiravir	46 (56.79%)	34 (46.58%)	0.193
• Anticoagulant	19 (23.46%)	35 (47.95%)	0.205
• COPLA (COVID Plasma)	6 (7.41%)	4 (5.48%)	0.001
• Azithromycin	6 (7.41%)	4 (5.48%)	0.749
Oxygen Support			
• Not Received	43 (53.09%)	37 (50.68%)	
• Nasal prongs (FiO_2 < 40%)	20 (24.69%)	12 (16.44%)	0.244
• HFNC or NIV or InVent (FiO_2 > 40%)	18 (22.22%)	24 (32.88%)	
Prior no. of lines of therapy			
• ≤2	64 (79.01%)	55 (75.34%)	0.508
• >2	17 (20.99%)	18 (24.66%)	
Diagnosis			
• Benign	0	8 (10.96%)	
• Lymphoid	37 (46.68%)	36 (49.32%)	
• Multiple Myeloma	20 (24.69%)	14 (19.18%)	0.009
• Myeloid Neoplasm	24 (29.63%)	15 (20.55%)	

3.2. COVID-19 Characteristics

Forty (49.38%) patients had mild, one (1.23%) moderate, and 40 (49.38%) had severe COVID-19 infection at the time of admission in the pre-delta group as compared to 32 (43.84%) had mild, 23 (31.51%) moderate and 18 (24.66%) had severe COVID infections at admission in the delta group (p value < 0.001). There was a significant delay in the admission of patients in the pre-delta group compared to the delta group (p value < 0.001). The oxygen requirement in the pre-delta group and the delta group was not statistically significant (p value = 0.24). Steroids, Remdesivir and COVID plasma therapy was received by 54 (66.67%), 46 (56.79%), and 19 (23.46%) in the pre-delta group and 49 (67.12%) (p value = 0.952), 60 (82.19%) (p value = 0.001), 35 (47.95%) (p value = 0.001) in the delta group respectively.

The pre-delta group had a significantly higher number of patients with severe COVID-19 when compared to the delta group which had a higher number of moderate COVID-19 patients (p value < 0.001). A significantly higher percentage of patients received Remdesivir (p value = 0.001), and COVID plasma (p value = 0.001) in the delta group. A higher oxygen requirement (p value = 0.244) was also observed in the delta group although this was not found to be statistically significant. A significant number (33.3%) of patients in the delta group progressed from mild to moderate/severe disease whereas only (23.07%) progressed to moderate/severe disease in the pre-delta group.

3.3. Hematological Disease Characteristics

Lymphoid malignancy (including Diffuse Large B-Cell Lymphoma (DLBCL) (n = 26), Follicular Lymphoma (FL) (n = 2), Chronic Lymphocytic Leukemia (CLL) (n = 10), Acute Lymphocytic Leukemia (ALL) (n = 19), Plasma Cell Neoplasm (PCN) or Multiple Myeloma (MM) (n = 33), amyloidosis (n = 1) and myeloid malignancy (Acute Myeloid Leukemia

(AML) (n = 24), Myelodysplastic Syndrome (MDS) (n = 5), Chronic Myeloid Leukemia [CML] (n = 9) were seen in 37 (46.68%), 20 (24.69%), 24 (29.63%) in the pre-delta group and 36 (49.32%), 14 (19.18%), 15 (20.55%) in the delta group respectively (p value = 0.009). Six (7.41%), and two (2.47%) patients underwent an autologous and allogeneic transplant in the pre-delta group and three (4.11%), and eight (10.96%) in the delta group respectively (p value = 0.07).

3.4. Outcomes

Twenty-one (25.97%) patients in the pre-delta group and 24 (33.88%) patients in the delta group died by day 30. On univariate analysis aged >60 years (p value = 0.033), those who received >two lines of anti-cancer treatment (p value = 0.009), those with severe COVID-19 illness (p value < 0.001), malignancy status at the time of COVID illness (p value = 0.006), and patients who were on chemotherapy (p value = 0.044) were significantly associated with mortality in the delta group when compared to the pre-delta group. Also, patients who received steroids (p value = 0.004), Covid plasma therapy (p value = 0.022), anticoagulation (p value = 0.035) and higher oxygen support for COVID-19 treatment (p value < 0.001) were associated with higher mortality in the delta group (Table 2).

On multivariate analysis, the following COVID-19 characteristics had a higher risk of death at day 30 in the delta group but not in the pre-delta group: higher oxygen requirement, the severity of COVID-19 illness and COVID plasma therapy. Characteristics of the underlying hematological condition associated with a higher risk of death in the delta group were patients who received (>2 lines) multiple lines of therapy and those who received chemo-immunotherapy and/or targeted therapy (Table 3).

Table 2. Predictors of survival from Univariate analysis for the Delta cohort.

Covariate	Univariate Analysis				
	Dead	**Alive**	**Hazard Ratio**	**95% CI**	***p* Value**
Sex (Male)	32 (30.19%)	74 (69.81%)	1.00		
Female	13 (27.08%)	35 (72.92%)	1.218	(0.633, 2.343)	0.554
Age < 60 years	35 (26.52%)	97 (73.48%)	1.00		
Age ≥ 60 years	10 (45.45%)	12 (54.55%)	1.902	(1.054, 3.4332)	0.033
Prior no. of lines of therapy	29 (24.37%)	90 (75.63%)	1.00		
• ≤2 • >2	16 (45.71)	19 (54.29%)	2.265	(1.224, 4.192)	0.009
Smoking Status (No)	17 (29.31%)	41 (70.69%)	1.00		
(Yes)	1 (33.33%)	2 (66.67%)	1.546	(0.194, 12.306)	0.680
(Unknown)	27 (29.03%)	66 (70.97%)	1.081	(0.578, 2.024)	0.578
Vaccination • Received	0	15 (100%)	1.00		
• No	45 (32.37%)	94 (67.63%)	2.53×10^{15}	(0, inf)	
Delay in Admission • ≤72 h	35 (26.32%)	98 (73.68%)	1.00		
• >72 h	10 (47.62%)	11 (52.38%)	1.485	(0.709, 3.109)	0.293
Active Treatment (No)	11 (25.58%)	32 (74.42%)	1.00		
• Yes	34 (30.63%)	77 (69.37%)	1.165	(0.588, 2.308)	0.661

Table 2. *Cont.*

Covariate	Univariate Analysis				
	Dead	**Alive**	**Hazard Ratio**	**95% CI**	***p* Value**
Severity (Mild)	8 (11.11%)	64 (88.89%)	1.00		
• Moderate	8 (33.33%)	16 (66.67%)	2.505	(0.913, 6.873)	0.075
• Severe	29 (50%)	29 (50%)		(2.094, 15.368)	<0.001
Comorbidity • None	26 (26.80%)	71 (73.20%)	1.00		
• At least 1	19 (33.33%)	38 (66.67%)	1.455	(0.803, 2.639)	0.216
Valacyclovir Prophylaxis	41 (29.29%)	99 (70.71)	1.00		
• No • Yes	3 (23.08%)	10 (76.92%)	0.712	(0.216, 2.345)	0.577
Malignancy Status • Initial Diagnosis + Observation	18 (25%)	54 (75%)	1.00		
• In Remission	8 (18.60%)	35 (81.40%)	0.654	(0.284, 1.507)	0.319
• Relapsed/Refractory + Progressive/Stable Disease + PR	19 (48.72%)	20 (51.28%)	2.504	(1.297, 4.832)	0.006
Therapy Received for COVID					
Steroids (No)	7 (13.73%)	44 (86.27%)	1.00		
• (Yes)	38 (36.89%)	65 (63.11%)	3.227	(1.437, 7.239)	0.004
Remdesivir (No)	12 (25%)	36 (75%)	1.00		
• (Yes)	22 (31.13%)	73 (68.87%)	1.347	(0.672, 2.702)	0.400
Favipiravir (No)	42 (28.57%)	105 (71.43%)	1.00		
• (Yes)	3 (42.86%)	4 (57.14%)	1.535	(0.472, 4.988)	0.476
Anticoagulant (No)	16 (21.62%)	58 (78.38%)	1.00		
• (Yes)	29 (36.25%)	51 (63.75%)	1.939	(1.048, 3.587)	0.035
Covariate	Univariate Analysis				
	Dead	Alive	Hazard Ratio	95% CI	*p* value
COPLA (COVID Plasma) (No)	22 (22%)	78 (78%)	1.00		
• Yes	23 (42.59%)	31 (57.41%)	2.037	(1.109, 3.742)	0.022
Azithromycin (No)	39 (27.08%)	105 (72.92%)	1.00		
• Yes	6 (60%)	4 (40%)	2.472	(1.029, 5.940)	0.043
Types of Therapy at the time of COVID-19 diagnosis					
• Observation	6 (40%)	9 (60%)	1.00		
• Chemotherapy	16 (25.81%)	46 (74.19%)	0.375	(0.143, 0.976)	0.044
• Chemo-immunotherapy	13 (30.95%)	29 (69.05%)	0.521	(0.196, 1.383)	0.191
• Others	10 (28.57%)	25 (70.78%)	0.516	(0.186, 1.428)	0.203

Table 2. *Cont.*

Covariate	Univariate Analysis				
	Dead	**Alive**	**Hazard Ratio**	**95% CI**	***p* Value**
Transplant					
• No Transplant	42 (31.11%)	93 (68.89%)	1.00		
• Allogeneic Transplant	2 (20%)	8 (80%)	0.525	(0.125, 2.205)	0.380
• Autologous Transplant	1 (11.11%)	8 (88.89%)	0.335	(0.0461, 2.444)	0.281
Oxygen Support					
• Not Received	7 (8.75%)	73 (91.25%)	1		
• FiO_2 < 40%	6 (18.75%)	26 (81.25%)	2.310	(0.774, 6.896)	0.133
• FiO_2 ≥40%	32 (76.19%)	10 (23.81%)	14.760	(6.447, 33.797)	<0.001
Diagnosis					
• Benign	1 (12.50%)	7 (87.50%)	1		
• Lymphoid	21 (28.77%)	52 (71.23%)	2.801	(0.370, 21.196)	0.318
• Multiple Myeloma	8 (23.53%)	26 (76.47%)	2.474	(0.301, 20.295)	0.399
• Myeloid Neoplasm	15 (38.46%)	24 (61.54%)	4.344	(0.561, 33.613)	0.159

Table 3. Predictors of survival from Multivariate Cox regression Model.

Covariate	Multivariate Analysis			
	N	**Hazard Ratio**	**95% CI**	***p* Value**
Sex (Female)	48	1		
Male	106	1.023	(0.523, 2.003)	0.945
Age < 60 years	132	1		
Age ≥ 60 years	22	1.839	(0.987, 3.429)	0.055
Prior no. of lines of therapy	119	1		
• ≤2				
• >2	35	2.085	(1.106, 3.933)	0.023
Comorbidity				
• No	97	1		
• Yes	57	1.204	(0.650, 2.227)	0.554
Severity of COVID				
• Mild	72	1		
• Moderate	24	0.342	(0.023, 4.987)	0.433
• Severe	58	0.438	(0.034, 5.607)	0.526
Malignancy status				
• Initial Diagnosis + Observation	72	1		
• In Remission	43	0.759	(0.279, 2.066)	0.590
• Relapsed/Refractory + Progressive/Stable Disease + Partial Response	39	2.718	(0.896, 8.237)	0.077

Table 3. *Cont.*

Covariate	Multivariate Analysis			
	N	**Hazard Ratio**	**95% CI**	***p* Value**
Steroids				
• No	51	1		
• Yes	103	0.733	(0.209, 2.563)	0.627
COPLA (COVID Plasma)				
• (Yes)	54	1		
• No	100	0.515	(0.274, 0.963)	0.039
Remdesivir				
• (Yes)	106	1		
• No	48	0.907	(0.448, 1.835)	0.786
Types of Therapy at the time of COVID-19 diagnosis				
• Observation	15	1		
• Chemotherapy	62	0.451	(0.131, 1.552)	0.207
• Chemo-immunotherapy	42	0.224	(0.059, 0.842)	0.027
• Others/targeted therapy	35	0.154	(0.040, 0.591)	0.006

The Wilcoxon–Breslow–Gehan test showed a significant difference in the survival of patients, as measured by the outcome observed on day 30, between the delta and the pre-delta groups. (p value < 0.001). The Kaplan–Meir curves show that the survival of patients who were infected with the delta variant was worse when compared to the pre-delta group (Figure 1). The Kaplan–Meir curves also show shorter hospitalization lengths and faster deaths in the delta group compared to the pre-delta group. The median time to a final outcome in the pre-delta group was 162 days (IQR: 36266) compared to the 102 days (IQR: 32115) in the delta group.

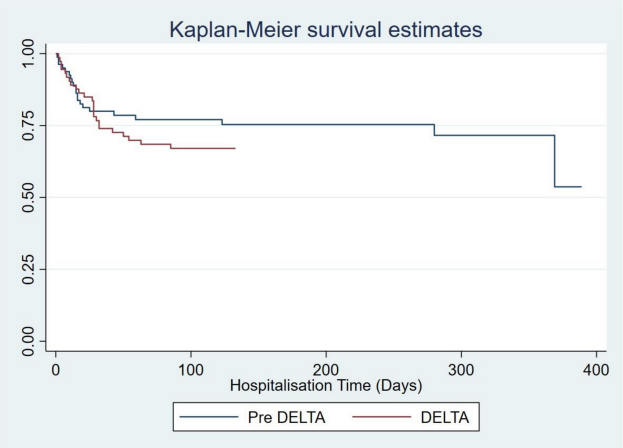

Figure 1. Kaplan–Meier curve depicting the survival of the pre-delta and delta cohort.

3.5. Dose and Duration of Steroids

In the pre-delta and delta groups, similar numbers of patients 54, (66.6%) vs. 49, (67.1%) received steroids. In the pre-delta group 44 patients received >6 mg (recommended dose) of steroids of which 13 (29.5%) died. Whereas, in the delta group 35 patients received higher doses of steroids of which 17 (48.5%) died.

3.6. Vaccination Cohort

There were 15 patients who were vaccinated; all belonged to the delta group. The median age of the vaccinated cohort was 57 years with nine males and five females. Nine (60%) of them had a mild infection and seven (46%) were on active treatment. There was no mortality in this group. Three (13%) were on observation, five (33%) on chemotherapy, three (20%) on chemo-immunotherapy and five (33%) on targeted therapy. Four (26%) had lymphoid malignancy, six (40%) had multiple myeloma and two (13%) had a myeloid neoplasm. Eight (53%) were in remission and there were no patients with progressive or relapsed disease.

4. Discussion

In this analysis of COVID-19 in hematological conditions, we focus specifically on comparing the outcomes and determinants of outcomes in patients during the pre-delta phase and the delta phase of the COVID-19 pandemic. We have also analyzed the impact of the dose and duration of steroids which is the backbone for the treatment of the cytokine storm during COVID-19; and the vaccination status of patients, noting that this was restricted to patients in the delta variant group as vaccines were not available in the pre-delta period.

The median age of the patients in our cohort was 52 years (range: 9 to 78 years) in the pre-delta group and 53 years (range: 9 to 71 years) in the delta group and our mortality rates for both groups were 25.92% and 32.87% respectively. The median age in our cohort is significantly lower when compared to the Italian cohort where it was 69 years [14] which may have had an impact on reported mortality rates. The higher age likely resulted in a higher mortality rate of 37% in their study compared to our pre-delta group (25.92%) [14]. The delta group in our cohort, being infected with a more virulent strain may have been the cause of much higher mortality (32.87%) despite having a similar median age as compared to the pre-delta group. Older age (>60 years) continued to be significantly associated with higher mortality in the delta group as seen from previous studies [15,16].

The number and type of comorbidities were not a predictor of mortality in our cohort either in the pre-delta or the delta group. This is like the previous studies reported by Passamonti et al. [14]. Similarly, the American Society of Hematology (ASH) research collaborative on COVID-19 [17] who reported that morbidity and mortality were common in those who lived with comorbidities. They included patients in whom ICU care had been foregone in favor of palliation. Thus, it is likely that many patients who could have been saved with ICU care, received palliation, and this could have resulted in poor outcomes.

We found 49.38% of patients in the pre-delta and 24.66% in the delta phase had severe COVID-19 infection and of these groups, mortality was (37.5%) in the pre-delta and (77.77%) in the delta severe cases. This finding has been consistent across studies [14].

Those who received higher oxygen support (FiO_2 > 40%), corticosteroids, Remdesivir and plasma therapy had higher mortality in our delta cohort. Corticosteroid being associated with mortality is a surprising result contrary to the results of the RECOVERY trial where it was found to be protective in COVID-19 patients. [18] However, it must be noted that they did not include patients with hematological malignancy or those with the delta variant of COVID-19. Similarly, the use of corticosteroids and convalescent plasma therapy led to rapid clinical improvement in patients with lymphoma who received B cell-depleting therapies in a French study [16].

It is our observation that a higher percentage of patients died in the delta group who received higher than the recommended dose of steroids which led to an adverse outcome

in patients. However, the limited patient numbers and the retrospective nature of our study prevented us from drawing such conclusions and probably higher virulence of the delta variant is responsible for this observation. Plasma therapy and Remdesivir did not seem to be effective in the delta COVID-19 variant. When compared to the pre-delta group a higher number of patients with mild/moderate COVID-19 progressed to severe illness in the delta group which is consistent with the reported higher virulence of this variant. This likely is the reason for the higher number of patients requiring steroids, anticoagulation and COVID plasma therapy for treatment in the delta cohort, and for the associated higher mortality. In our cohort, the delta variant was able to affect outcomes irrespective of time since chemotherapy.

Patients with acute myeloid leukemia, non-Hodgkin lymphoma and plasma cell neoplasm had worse survival in the study by Passamonti et al. [14]. No such disease-specific predilection was observed with the delta variant in our cohort.

Progressive malignancy status or $\geq$2 prior lines of therapy was also associated with increased mortality in the delta COVID-19 cohort. Reasons for this association could be immunosuppression due to multiple lines of chemotherapy. Similar results were seen in patients with lymphoma who had the progressive disease in other studies [14,16].

Delta group patients who received in the past chemo-immunotherapy or other targeted therapies had higher mortality compared to the pre-delta group. It contrasts with previous reports where rituximab maintenance therapy was deemed as safe as described by Passamonti et al. [14]. Higher mortality was reported in patients on Bruton tyrosine kinase inhibitors and B cell-depleting therapies resulting in prolonged hospital stays and higher mortality [14,16].

Patients on targeted therapies seem to be particularly vulnerable to the delta variant of the COVID-19 virus. We postulate this is likely due to B cell depletion and T cell depletion secondary to targeted therapies as has been described previously [19–21]. It is possibly the blunted humoral and cytotoxic responses due to the targeted therapies that contributed to poor overall survival in these patients.

Our study showed the effectiveness of the COVID vaccine in preventing deaths in the 15 patients who received them during the delta variant outbreak. Forty-six per cent of patients who received the vaccine were on active therapy. We did not test antibody levels in our vaccinated cohort at presentation; however, our data demonstrate clinical protection against severe disease and death. It supports the recommendation that active therapy should not be a deterrent for offering the vaccine to patients with hematological malignancies.

Our study has some limitations which warrant caution. We included hospitalized patients only which is not a true representation of the impact of COVID-19 on all patients with hematological conditions. Also, there is a selection bias concerning testing as it was limited to patients with symptoms only and not through universal screening. We have not commented on the biochemical, thrombotic, and radiographic findings of these patients which would have further helped in describing these patients. The retrospective nature of our study carries inherent limitations.

To conclude, the delta variant is indeed more virulent and leads to higher mortality when compared to the pre-delta COVID-19 variant. Steroids, COVID plasma, anticoagulation and other therapies were ineffective in the treatment of the delta variant. Chemo-immunotherapy and targeted therapy is associated with higher mortality in patients infected with the delta variant. Despite limited numbers, vaccination seems to be an effective tool to prevent deaths in these patients due to COVID-19.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. Patient Permission to publish the data has been taken from the patient.

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