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Determinants of clinical course and mortality in COVID-19 patients with hematological disorders: real life data from a single center

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ABSTRACT

Objectives: Patients with hematological disorders are often immunosuppressive due to underlying diseases, immunosuppressive therapies or cytotoxic chemotherapeutics. In the case of coronavirus disease 2019 (COVID-19), they are at high risk of poor prognosis. Therefore, the present study aimed to evaluate the determinants of clinical course and mortality in COVID-19 patients with hematological disorders.

Methods: Sixty-two hospitalized patients older than 18 years with documented COVID-19 and hematological disorders were included in the study. The clinical and laboratory data of the patients were recorded. Age, gender, overall follow-up time, duration of hospitalization, neutropenia, D-dimer levels, disease status, presence of underlying diseases, prior autologous and allogeneic stem cell transplant, immunosuppressive drug use, chemotherapy within 28 days, pneumonia, secondary bacterial infection, intubation, survival and mortality of the patients were evaluated.

Results: Twenty-eight (45.2%) of 62 patients died due to COVID-19 and its complications. It was observed that presence of pneumonia, secondary bacterial infection, intubation, neutropenia developed after the diagnosis of COVID-19, and elevated D-dimer levels were associated with significant mortality. A D-dimer level of > 1.2 µg/dL was found to be associated with 5.02 fold increase in the risk of death, with 60.7% sensitivity and 76.5% specificity. Presence of rheumatologic diseases also affected survival negatively.

Conclusions: D-dimer levels have high predictive value for mortality. Considering the identified risk factors, it can be concluded that broad spectrum antibiotics can be administered earlier for prevention of high mortality rates in COVID-19 patients with underlying hematological disorders. These observations can give confidence to clinicians that delivery of effective anticancer regimens should continue during this difficult pandemic.

Keywords: COVID-19, hematological disorders, mortality

Novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS Cov-2) disease (coronavirus disease 2019, COVID-19) has been the most important global health problem since the end of

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2019 [1]. According to the current World Health Organization (WHO) data, approximately 150 million people have been infected with the virus to date, and more than 3 million have died due to COVID-19 and/or its complications [2]. Characteristics of COVID-19 symptoms in hematological patients share similarities with the general population with fever, dry cough, fatigue and diarrhea being the most common initial signs/symptoms of infection [3]. Some special patient groups such as diabetics, older patients and especially immunosuppressive patients have poor outcome [4]. Patients with hematological disorders are often immunosuppressive due to underlying diseases, immunosuppressive therapies or cytotoxic chemotherapeutics [5]. Therefore, assessment and determination of the best therapeutic needs of the immunosuppressed patient with COVID-19 is critical. However, there are few published data on the consequences of COVID-19 in hematological patients so far [5-9]. Based on available information, patients with hematological malignancies and bone marrow transplants are at high risk of poor prognosis in case of COVID-19 [10]. Furthermore, patients with hematological malignancies have worse outcomes than patients with solid tumors [11]. During COVID-19 outbreak, it is of extreme importance to understand that cancer patients should be considered as a special population due to their higher risk of acquiring secondary infections and faster decline rate. Therefore patients with hematological disorders, both benign and malignant need special attention during this crisis time [12]. Mortality reports have shown a higher mortality rate in cancer patients with COVID-19 compared to the general population [13]. COVID-19 is a respiratory infection with a significant impact on the hematopoietic system and hemostasis leading to several cardiovascular complications. A better understanding of COVID-19 in particular hematological disorders will help to choose appropriate treatment strategies in the future [14]. COVID-19 infection is associated with a coagulopathy characterized by an increase in procoagulant factors such as fibrinogen, together with a strong increase of D-dimers that have been associated with a higher mortality [15, 16]. Accordingly, the present study aimed to evaluate the determinants of clinical course and mortality in COVID-19 patients with hematological disorders.

METHODS

Patients

Patients with documented COVID-19 and hematological disorders older than 18 years were included in the study. Diagnostic analysis, survival data, predictors of death and laboratory results of those patients were evaluated. Only hospitalized patients were accepted. The endpoint of the study was hospital discharge with clinical recovery or death. The clinical and laboratory data of the patients were recorded. D-dimer levels were recorded at the time of admission. Written informed consent was obtained from all patients. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and reviewed and approved by the Ethics Committee of Memorial Hospitals Group after obtaining permission of the Turkish Ministry of Health Ethics Committee.

Laboratory Assay

D-dimer was determined on Cobas C501 automatic biochemistry analyzer (Roche Diagnostics, Tokyo, Japan) via immunoturbidimetric assay. The laboratory reference range was 0-0.5 µg/mL. The D-dimer result was expressed in µg/mL FEU (Fibrinogen Equivalent Unit). All measurements were performed within 2 hours after blood sampling. Confirmed COVID-19 infection was defined as a positive result on a SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab specimen.

Statistical Analysis

Data analyses were performed using the IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) software. Normality of the univariate data was assessed using the Shapiro-Wilk and Shapiro-Francia tests, while Levene's test was used to assess the homogeneity of variances. For the comparison of two independent groups of quantitative data, independent samples t-test was used together with Bootstrap results, and Mann-Whitney U test. For the comparison between categorical variables, Pearsons chi-square and Fisher's exact tests were used with the Monte Carlo Simulation technique. Odds ratio was used to demonstrate the relative risk of death in patients with a risk factor compared to those without. Receiver Operating Curve (ROC) analysis was used to

show the relationship between sensitivity and specificity for every possible cut-off value calculated according to the variables of the groups and the actual classification. Kaplan-Meier (product limit method) - Log-Rank (Mantel-Cox) analysis was used to examine the effects of the factors on mortality and lifespan. Quantitative variables are expressed as mean (standard deviation) and median (25th Percentile [Q1]/75th percentile [Q3]) in the tables, while categorical variables are shown as number (percentage, %). Variables were analyzed at a 95% confidence level and a p value of less than 0.05 was considered significant.

RESULTS

Sixty-two hospitalized patients with documented COVID-19 and hematological disorders older than 18 years were enrolled in the study. Nineteen patients had acute myeloid leukemia (AML) and 17 patients had non-Hodgkin's lymphoma (NHL) with a mortality rate of 57.9% and 29.4%, respectively. Of 62 patients, 28 (45.2%) died due to COVID-19 and its complications (Table 1). Patients had an average age of 60.9 years and the average duration of hospitalization was 14 days. When clinical and demographic data were evaluated, it was found that age, gender, overall follow-up time, duration of hospitalization, presence of neutropenia at the diagnosis of COVID-19, underlying diseases and disease status were not associated with mortality; however, the presence of pneumonia, secondary bacterial infection, intubation, neutropenia developed after the diagnosis of COVID-19, and D-dimer levels were associated with a statistically significant mortality ($p < 0.05$) (Fig. 1). A D-dimer level over 1.2 µg/dL is the percentile 75 value of the alive group; therefore it is accepted as a cut off value in this patient group to predict the risk of death. A D-dimer level greater than 1.2 µg/dL was found to be associated with a 5.02 fold increase in the risk of death with 60.7% sensitivity and 76.5% specificity (Table 2). Similarly presence of pneumonia, secondary bacterial infection, intubation, neutropenia after the diagnosis of COVID-19, a D-dimer levels > 1.2 µg/dL had a negative effect on the survival of the patients. Presence of rheumatologic diseases also affected survival negatively ($p < 0.05$) (Table 3).

DISCUSSION

The relationship between COVID-19 and pre-existing diseases is poorly described and based on small retrospective studies [17]. The current pandemic coronavirus, SARS-CoV-2, is known to cause severe infection in patients with comorbidities, particularly cancer or immunosuppression [18]. Patients suffering from cancer are vulnerable to the effects of COVID-19, and they have been postulated to be at increased risk of mortality [19]. In addition, male sex, older age, hypertension, diabetes, and obesity have been shown to be associated with higher COVID-19 mortality [20]. In general population, data from different countries suggest a case-fatality of 2.3% in patients with COVID-19, with more than 50% of the fatalities occurring in patients 50 years of age or older [21]. In our

Table 1. Mortality rates of the study patients according to the type of hematological disorder

Diagnosis	n (%)	Alive	Dead	Mortality (%)
Acute myeloid leukemia	19 (27.4)	8	11	57.9
Non-Hodgkin's lymphoma	17 (27.4)	12	5	29.4
Multiple myeloma	8 (12.9)	6	2	25.0
Chronic lymphocytic leukemia	4 (6.5)	2	2	50.0
Chronic myeloid leukemia	3 (4.8)	2	1	33.3
Myelodisplastic syndrome	3 (4.8)	2	1	33.3
Hodgkin's lymphoma	3 (4.8)	1	2	66.6
Idiopathic thrombocytopenic purpura	2 (3.2)	0	2	100.0
Chronic myelomonocytic leukemia	2 (3.2)	1	1	50.0
Myelofibrosis	1 (1.6)	0	1	100

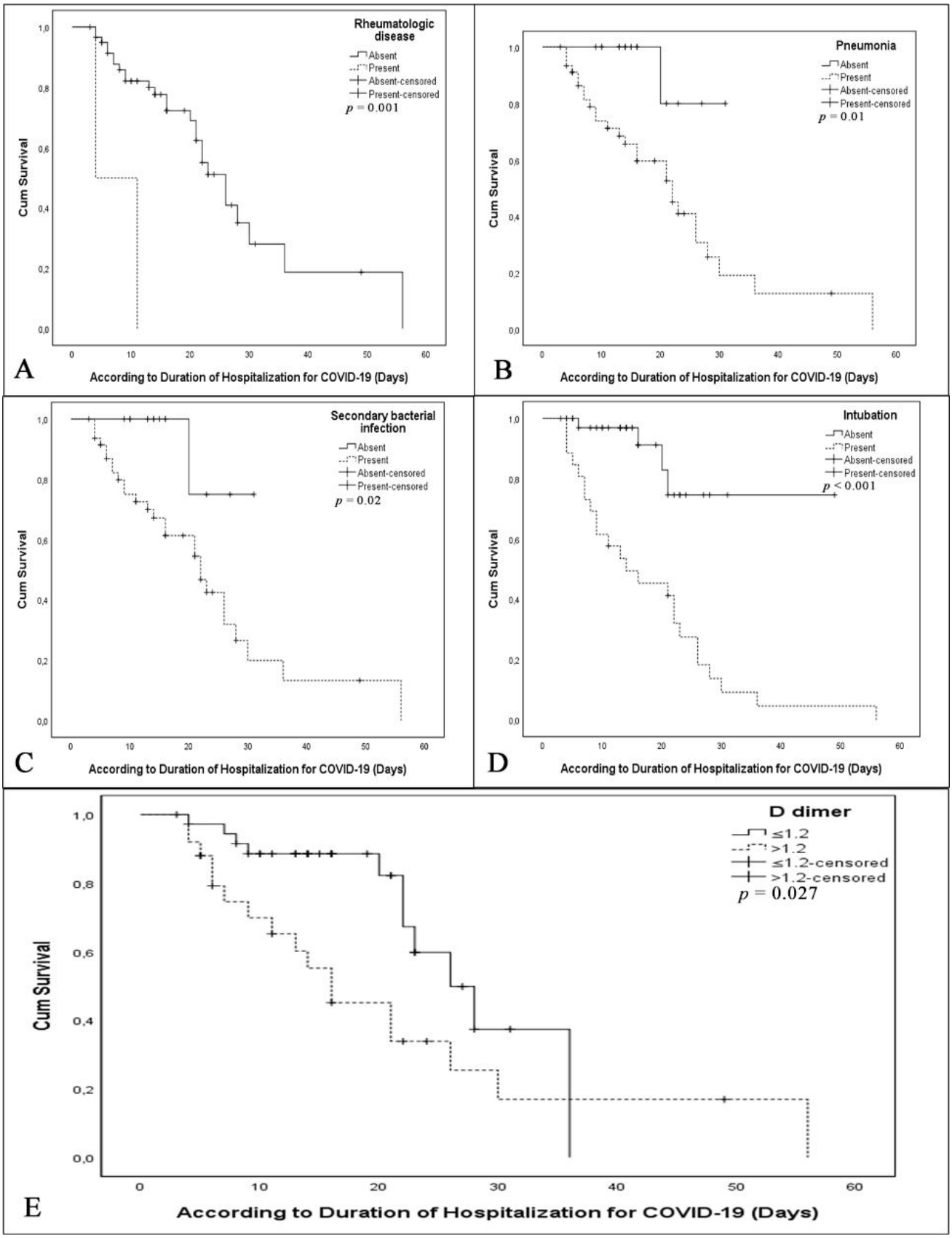

Fig. 1. Significant predictors of mortality. (A) Rheumatologic disease, (B) Pneumonia, (C) Secondary bacterial infection, (D) Intubation and (E) D-Dimer level.

Table 2. Comparison of alive and dead patients in terms of clinical and demographic data

	Total	Alive	Dead	*p* value	OR (95% CI) or AUC (SE)
	(n = 62)	(n = 34)	(n = 28)		
Age, years, mean (SD)	60.9 (14.6)	58.0 (15.3)	64.3 (13.1)	0.106	-
Age, n (%)					
< 65	33 (53.2)	21 (61.8)	12 (42.9)	0.201	-
≥ 65	29 (46.8)	13 (38.2)	16 (57.1)		
Sex					
Female	28 (45.2)	13 (38.2)	15 (53.6)	0.306	-
Male	34 (54.8)	21 (61.8)	13 (46.4)		
Overall follow-up time, median (Q1/Q3)	478 (159/1477)	697 (148 / 1513)	404 (160/888.5)	0.563	
Duration of hospitalization for COVID-19, days, median (Q1/Q3)	14 (9/22)	14 (10/21)	15 (7/22.5)	0.959	-
Neutropenia at COVID-19 diagnosis, n (%)					
Absent	45 (72.6)	28 (82.4)	17 (60.7)	0.086	-
Present	17 (27.4)	6 (17.6)	11 (39.3)		
Neutropenia after COVID-19 diagnosis, n (%)					
Absent	36 (58.1)	25 (73.5)	11 (39.3)	**0.010**	**4.3 (1.5-12.6)** OR
Present	26 (41.9)	9 (26.5)	17 (60.7)		
Disease status, n (%)					
Active	34 (54.8)	17 (50.0)	17 (60.7)	0.450	-
Remission	28 (45.2)	17 (50.0)	11 (39.3)		
Diabetes, n (%)					
Absent	50 (80.6)	29 (85.3)	21 (75.0)	0.349	-
Present	12 (19.4)	5 (14.7)	7 (25.0)		
Hypertension, n (%)					
Absent	35 (56.5)	21 (61.8)	14 (50.0)	0.443	-
Present	27 (43.5)	13 (38.2)	14 (50.0)		
Coronary disease, n (%)					
Absent	48 (77.4)	29 (85.3)	19 (67.9)	0.132	-
Present	14 (22.6)	5 (14.7)	9 (32.1)		
Rheumatologic disease, n (%)					
Absent	60 (96.8)	34 (100.0)	26 (92.9)	0.200	-
Present	2 (3.2)	0 (0.0)	2 (7.1)		
Chronic obstrucive lung disease/asthma, n (%)					
Absent	59 (95.2)	34 (100.0)	25 (89.3)	0.087	-
Present	3 (4.8)	0 (0.0)	3 (10.7)		
Prior autologus stem cell transplant, n (%)					

Table 2 contunied. Comparison of alive and dead patients in terms of clinical and demographic data

	Total	Alive	Dead	*p* value	OR (95% CI) or AUC (SE)
	(n = 62)	(n = 34)	(n = 28)		
Absent	53 (85.5)	28 (82.4)	25 (89.3)	0.494	-
Present	9 (14.5)	6 (17.6)	3 (10.7)		
Prior allogeneic stem cell transplant, n (%)					
Absent	54 (87.1)	30 (88.2)	24 (85.7)	0.999	-
Present	8 (12.9)	4 (11.8)	4 (14.3)		
Immunosuppressive drug use, n (%)					
Absent	51 (82.3)	31 (91.2)	20 (71.4)	0.092	-
Present	11 (17.7)	3 (8.8)	8 (28.6)		
Chemotherapy within 28 days, n (%)					
Absent	29 (46.8)	14 (41.2)	15 (53.6)	0.444	-
Present	33 (53.2)	20 (58.8)	13 (46.4)		
Pneumonia, n (%)					
Absent	17 (27.4)	16 (47.1)	1 (3.6)	**< 0.001**	**24 (2.9-197.3) OR**
Present	45 (72.6)	18 (52.9)	27 (96.4)		
Secondary bacterial infection, n (%)					
Absent	15 (24.2)	14 (41.2)	1 (3.6)	**0.001**	**18.9 (2.3-155.8) OR**
Present	47 (75.8)	20 (58.8)	27 (96.4)		
Intubation					
Absent	36 (58.1)	32 (94.1)	4 (14.3)	**< 0.001**	**96 (16.2-568.1) OR**
Present	26 (41.9)	2 (5.9)	24 (85.7)		
D-dimer, median (Q1/Q3), µg/dL	1.03 (0.37 / 2.22)	0.765 (0.28 / 1.2)	1.49 (0.765 / 2.925)	**0.001**	
D-dimer, n (%)					
≤ 1.2	37 (59.7)	**26 (76.5) sp**	11 (39.3)	**0.002 rc**	**0.709 (0.067) AUC (SE) 5.02 (1.7-15.04) OR**
> 1.2	25 (40.3)	8 (23.5)	**17 (60.7) ss**		

OR = Odds Ratio; CI = Confidence interval, rc Roc (Receiver Operating Curve) Analysis (Honley&Mc Nell - Youden index J), AUC = Area under the ROC curve; SE = Standard Error.

ss Sensitivity; sp Specificity; SD = standard deviation, Q1, 25th percentile; Q3, 75th percentile; Q1/Q3, 25th percentile / 75th percentile.

study, the mortality rate of COVID-19 in hematological disorders was 45.2% showing a range of 25% to 100% according to the type of the hematological disorder. This shows that mortality rates and clinical course of COVID-19 in specific underlying diseases and conditions can be very different compared to general population. The highest mortality rates were observed in ITP, AML and NHL with 100%, 57.9% and 29.4% of the patients respectively. The findings of our study support the data published in the literature on the expected high mortality of COVID-19 in cancer patients.

Our study is important for showing the results of 62 patients with co-occurrence of COVID-19 and hematological disorders in a single center, while individual health-care centers and physicians only see a

Table 3. Survival estimates in dead and alive patients in terms of clinical and demographic data

	Dead	Alive	According to Duration of Hospitalization for COVID-19 (Days)		
			Estimate Survival	Estimate Proportion Surviving at	*p*
	n (%)	n (%)	Mean ± SE	7 / 14 / 28 days (SE)	
Overall	28 (45.2)	34 (54.8)	26.7 (3.17)	86.4 (4.5) / 90.0 (3.9) / 79.1 (5.4)	
Age					
< 65	12 (36.4)	21 (63.6)	26 (3.72)	93.4 (4.5) / 72.4 (9.1) / 44.7 (14.2)	0.779
≥ 65	16 (55.2)	13 (44.8)	26.8 (4.52)	78.9 (7.7) / 75.3 (8.1) / 22.9 (12.4)	
Gender					
Female	15 (53.6)	13 (46.4)	25.4 (4.89)	82.0 (7.3) / 85.7 (6.6) / 74.1 (8.5)	0.466
Male	13 (38.2)	21 (61.8)	26.9 (3.45)	90.0 (5.5) / 93.3 (4.6) / 83.1 (6.9)	
Neutropenia at COVID-19 Diagnosis					
Absent	17 (37.8)	28 (62.2)	27 (3.12)	88.4 (4.9) / 93.2 (3.8) / 80.9 (6.1)	0.229
Present	11 (64.7)	6 (35.3)	22.4 (5.04)	80.4 (10.2) / 80.4 (10.2) / 73.7 (11.3)	
Neutropenia after COVID-19 diagnosis					
Absent	11 (30.6)	25 (69.4)	32.8 (3.87)	85.7(5.9) / 91.6 (4.7) / 79.6 (6.9)	0.210
Present	17 (65.4)	9 (34.6)	23 (3.18)	87.5 (6.8) / 87.5 (6.8) / 78.7 (8.5)	
Disease status					
Active	17 (50.0)	17 (50.0)	27.6 (4.41)	84.4 (6.4) / 87.7 (5.8) / 81.2 (6.9)	0.991
Remission	11 (39.3)	17 (60.7)	23.7 (2.69)	88.9 (6.1) / 92.7 (5.0) / 76.5 (8.4)	
Diabetes					
Absent	21 (42.0)	29 (58.0)	29 (3.95)	89.5 (4.5) / 91.7 (4.0) / 80.4 (5.9)	0.481
Present	7 (58.3)	5 (41.7)	21.8 (3.9)	74.1 (12.9) / 83.3 (10.8) / 74.1 (12.9)	
Hypertension					
Absent	14 (40.0)	21 (60.0)	29.4 (5.12)	88.0 (5.6) / 91.2 (4.9) / 81.2 (6.9)	0.624
Present	14 (51.9)	13 (48.1)	22.7 (2.44)	84.3 (7.2) / 88.3 (6.4) / 76.2 (8.5)	
Coronary disease					
Absent	19 (39.6)	29 (60.4)	29 (4.41)	91.2 (4.2) / 93.5 (3.6) / 81.7 (5.9)	0.414
Present	9 (64.3)	5 (35.7)	21.3 (3.53)	70.1 (12.6) / 77.9 (11.3) / 70.1(12.6)	
Rheumatologic disease					
Absent	26 (43.3)	34(56.7)	27.4 (3.25)	87.7 (4.4) / 91.3 (3.7) / 82.1 (5.1)	**0.001**
Present	2 (100.0)	0(0.0)	7.5 (3.5)	50.0 (35.4) / 50.0 (35.4) / 0.0 (0.0)	
Chronic obstrucive lung disease/asthma					
Absent	25 (42.4)	34 (57.6)	27.9 (3.41)	89.4 (4.1) / 91.2 (3.7) / 81.7 (5.3)	0.065
Present	3 (100.0)	0 (0.0)	13 (6.51)	33.3 (27.2) / 66.7 (27.2) / 33.3 (27.2)	
Prior autologous stem cell transplant					
Absent	25 (47.2)	28(52.8)	27 (3.32)	88.1 (4.6) / 92.2 (3.8) / 79.6 (5.8)	0.784
Present	3 (33.3)	6 (66.7)	18.7 (3.24)	76.2 (14.8) / 76.2 (14.8) / 76.2 (14.8)	

Table 3 contunied. Survival estimates in dead and alive patients in terms of clinical and demographic data

	Dead	Alive	According to Duration of Hospitalization for COVID-19 (Days)		
			Estimate Survival	Estimate Proportion Surviving at	*p*
	n (%)	n (%)	Mean ± SE	7 / 14 / 28 days (SE)	
Prior allogeneic stem cell transplant					
Absent	24 (44.4)	30 (55.6)	27.9 (3.65)	84.3(5.1)/88.4(4.5)/77.9(5.9)	0.867
Present	4 (50.0)	4 (50.0)	23.7 (5.36)	84.3(5.1)/88.4(4.5)/85.7(13.2)	
Immunosuppressive drug use					
Absent	20 (39.2)	31 (60.8)	29.8 (3.92)	85.5 (5.1) / 87.7(4.7) / 83.3 (5.4)	0.054
Present	8 (72.7)	3 (27.3)	17.8 (3.68)	90.9 (8.7) /87.7 (4.7) /60.6 (15.4)	
Chemotherapy within 28 days					
Absent	15 (51.7)	14 (48.3)	20.4 (2.18)	89.1 (5.9) / 96.6 (3.4) /77.1 (8.3)	0.107
Present	13 (39.4)	20 (60.6)	32.7 (5.01)	83.9 (6.6)/ 83.9 (6.6)/ 80.6 (7.1)	
Pneumonia					
Absent	1 (5.9)	16 (94.1)	28.8 (1.97)	100 (0) / 100 (0) / 100 (0)	**0.010**
Present	27 (60.0)	18 (40.0)	23.2 (2.99)	81.3 (6.0) / 86.3 (5.2) / 71.2 (7.0)	
Secondary bacterial infection					
Absent	1 (6.7)	14(93.3)	28.3 (2.38)	100 (0) / 100 (0) / 100 (0)	**0.020**
Present	27 (57.4)	20 (42.6)	23.7 (3.02)	82.2 (5.7) / 86.9 (5.0) / 72.6 (6.8)	
Intubation					
Absent	4 (11.1)	32 (88.9)	41.1 (3.57)	96.9 (3.1) /96.9 (3.1) / 96.9 (3.1)	**< 0.001**
Present	24 (92.3)	2 (7.7)	17.8 (2.6)	73.1 (8.7) /80.8 (7.7) / 57.7 (9.7)	
D-dimer					
≤ 1.2	11 (29.7)	26 (70.3)	26.6 (2.19)	94.4(3.9) / 97.2(2.7) / 88.6 (5.4)	**0.027**
> 1.2	17 (68.0)	8 (32.0)	21.9 (4.21)	74.5(9.0) / 79.2 (8.3) / 65.2 (10.0)	

Kaplan Meier Test- Log Rank (Mantel-Cox), SE = Standard Error

few patients with both diseases. Lee *et al*. [17] studied mortality patterns from COVID-19 in cancer patients (8% and 14% had lymphomas and hematological malignancies, respectively) and found no increased risk of death. On the other hand, He *et al*. [8] studied 13 patients with hematological cancers (acute myeloid leukemia, acute lymphoblastic leukemia, plasma cell myeloma, and myelodysplastic syndromes) who developed COVID-19, and found more severe disease and a higher case fatality rate than other hospitalized patients. The higher case fatality rates may be attributed to the therapy they were receiving or due to other comorbid conditions such as diabetes, which is common in this group of patients. There was no association between the type of cancer and risk of developing COVID-19 [8]. In another study on cancer patients (8.6% had hematological cancers-leukemia, myeloma, and lymphoma) with SARS-CoV-2 infection, those with hematological cancers had the highest severity and death rate (33%). This may be because patients with hematological cancers receive more immunosuppression than those with solid tumors [22]. In our study it was observed that the presence of prior autologous or allogeneic stem cell transplantation or

chemotherapy within 28 days had no effect on mortality in patients with hematological disorders with COVID-19 infection. Immunosuppressive drug use and neutropenia at diagnosis of COVID-19 infection increased mortality, although not significantly. In some studies in the literature, it was observed that COVID-19 mortality in patients with cancer was principally driven by advancing age and the presence of other non-cancer comorbidities. Chemotherapy or anticancer treatments did not necessarily increase the risk of mortality from COVID-19 [17, 19]. These observations can give confidence to oncologists and other clinicians that delivery of effective anticancer regimens should continue during this difficult time. Although male sex and older age are risk factors for increased mortality in general population [20], we observed in our study that age and gender did not affect the mortality and clinical course of COVID-19 in patients with hematological disorders. Duration of hospitalization also was not related to mortality in our patients. In order to obtain more definite results, larger group of patients are needed.

SARS-CoV-2 infection can cause several hematological abnormalities. Some cases of autoimmune cytopenias such as thrombocytopenia and hemolytic anemia have been described [23, 24]. Lymphopenia is the most common laboratory finding in patients with COVID-19. Neutrophilia predicts poor outcome and severe respiratory failure [25]. There are also cases of COVID-19 with severe neutropenia [26]. Other viral infections associated with the development of transient neutropenia are herpesvirus 6, parvovirus, EBV, adenovirus, influenza A, HIV, hepatitis C virus, and cytomegalovirus. These viruses can cause direct damage to bone marrow progenitors and trigger autoimmune destruction [27]. Neutropenia arising as a result of underlying hematologic disorders is far more significant. Such patients are at risk for infectious complications [28]. Although in our study the presence of neutropenia at the diagnosis of COVID-19 was not associated with mortality, neutropenia developed after the diagnosis of COVID-19 led to a statistically significant increase in the mortality rates. This can be due to the co-occurrence of hematological disorders and COVID-19, which is an important observation for predicting high mortality in these patients.

Presence of underlying diseases such as diabetes, hypertension, coronary diseases and asthma had no effect on mortality in our study. Disease status either active disease or remission did not affect clinical course and mortality in our patients as well. In general population, it was observed that diabetes in patients with COVID-19 was associated with a two-fold increase in mortality as well as severity of COVID-19, as compared to non-diabetics [29]. It was also found that hypertension is associated with a 2.5 fold increased risk of both increased severity and mortality in COVID-19. In a meta-regression, it was observed that this effect is mainly attributed to those over the age of 60 [30]. Also underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with COVID-19 [31]. Studies show that asthma as a concomitant disease may not increase COVID-19 mortality [32]. Again, in some studies, the results show that there is no statistically significant relationship between asthma history and mortality, regardless of COVID-19 status (33). In the case of specific underlying diseases like hematological disorders in our study, the determinants of the clinical course of COVID-19 and mortality are affected by some different parameters like neutropenia developed after diagnosis of COVID-19 apart from the general risk factors. Additionally the presence of pneumonia, intubation, secondary bacterial infection, and a D-dimer level of >1.2 µg/dL were associated with a statistically significant mortality in our study. Studies suggested that older age and underlying comorbidities were associated with disease severity or death of COVID-19 pneumonia patients. Pneumonia itself is one of the most important factors leading to mortality [34]. COVID-19 pneumonia is a specific disease of which the main characteristic is the dissociation between the severity of hypoxemia and the maintenance of relatively good respiratory mechanics [35]. In our study, presence of pneumonia and intubation increased mortality precisely in COVID-19 patients with hematological disorders. Intubation is a risk factor for hospital-acquired infections and also indicates the severity of clinical manifestations. Therefore, its presence increased mortality and adversely affected the clinical course. Secondary bacterial infection was also related to mortality in our study. Although low rates of pulmonary bacterial coinfection was reported in some studies in patients with COVID-19, the low rate of coinfection described seems to be underestimated [36-38].

Infection induced coagulopathy and secondary hyper-fibrinolysis has been identified in severe cases of COVID-19. As well, higher D-dimer level on admission was related to a worse prognosis [16, 39]. Anticoagulant treatment may benefit severe COVID-19 patients, especially those without cardiovascular diseases [40]. D-dimer is commonly elevated in patients with COVID-19. D-dimer level correlates with disease severity and is a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19 [41]. Coagulopathy was reported, and D-dimer elevations were seen in 3.75-68.0% of the COVID-19 patients in previous studies [16]. In a previous study, it was found that D-dimer on admission greater than 2.0 ④g/mL could effectively predict mortality in patients with COVID-19, which indicates that D-dimer can be an early and helpful marker to improve management of COVID-19 patients [42]. In our study, D-dimer level greater than 1.2 µg/dL was found to be associated with 5.02 fold increase in the risk of death in COVID-19 patients with hematological disorders. In our study, results parallel to the literature were obtained. When estimated survival in terms of clinical and demographic data were analyzed on the basis of duration of hospitalization for COVID-19, it was observed that presence of pneumonia, secondary bacterial infection, intubation, neutropenia after the diagnosis of COVID-19 and a D-dimer level of > 1.2 had a negative effect on the estimated survival of the patients. Besides other risk factors identified, it was observed that presence of rheumatologic disease as an underlying condition also affected survival negatively in COVID-19 patients with hematological disorders. In a previous study, it was reported that rheumatic disease activity might be associated with mortality. Inflammation was closely related to severity of COVID-19 [43].

CONCLUSION

Although the clinical course and determinants of mortality in COVID-19 patients with hematological disorders are parallel to the literature to a certain extent, they have some distinctive features. In our study, mortality rate of COVID-19 in hematological disorders was 45.2% which is very high compared to general patients showing a range of 25 to 100 % according to diagnosis. This shows that mortality rate and clinical course of COVID-19 in specific underlying diseases and conditions can be very different compared to general population. Age, sex, disease status, duration of hospitalization, presence of hypertension, diabetes and coronary disease were not associated with mortality. Immunosuppressive drug use and neutropenia at diagnosis of COVID-19 infection somewhat increased mortality although not statistically significant. D-dimer level above 1.2 µg/mL has a high predictive value for mortality. In our study, it was observed that presence of prior autologous or allogeneic stem cell transplantation, chemotherapy within 28 days and immunosuppressive therapy had no effect on mortality in patients with hematological disorders with COVID-19 infection. These observations can give confidence to clinicians that delivery of effective anticancer regimens should continue during this difficult pandemic. The presence of pneumonia, secondary bacterial infection, intubation and neutropenia developed after the diagnosis of COVID-19 were associated with a statistically significant mortality.

Authors' Contribution

Study Conception: BD, RS; Study Design: BD, RS; Supervision: RS, LD; Funding: N/A; Materials: MYT; Data Collection and/or Processing: AA, GA, BÜ, MYA; Statistical Analysis and/or Data Interpretation: TT; Literature Review: BD; Manuscript Preparation: BD and Critical Review: BD, RS.

Conflict of interest

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