RESEARCH ARTICLE

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Clinical Characteristics and Outcome of COVID-19 in Turkish Hematological Malignancy Patients

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Abstract

Patients with solid malignancies are more vulnerable to SARS-CoV-2 infection than healthy population. The outcome of SARS-CoV-2 infection in highly immunosupressed populations, such as in patients with hematological malignancies is a point of interest.We aimed to analyze the symptoms, complications, intensive care unit (ICU) admission and mortality rates of patients with hematological malignancies infected with SARS-CoV-2 in Turkey. In this multicenter study, we included 340 adult and pediatric patients diagnosed as COVID-19 from March to November. Forty four (12.9%) patients were asymptomatic at diagnosis. In symptomatic patients, fever, cough and dyspnea were observed in 62.6%, 48.8 % and 41.8% of the patients, respectively. Sixty nine (20%) patients had mild SARS-Cov-2 disease, whereas moderate, severe and critical diseases were reported in 101 (29%), 71 (20%) and 55 (16%) patients, respectively. Two hundered fifty one (73.8%) patients were hospitalized for SARS-Cov2. Mortality related to SARS-CoV-2 infection was 26.5% in all cohort; 4.4% in those patients with mild disease, 12.4% in moderate disease and 83% in severe and critical disease. Active hematological disease, lower life expectancy related with primary hematological disease, neutropenia at diagnosis of SARS- CoV-2, ICU admission and first-line therapy used for COVID 19 treatment were found to be related to higher mortality rates. Treatments with hydroxychloroquine alone or in combination with azitromycin were associated with a higher rate of mortality in comparison with favipiravir use.In conclusion, patients with hematological malignancy infected with SARS-CoV-2 have an increased risk of severe disease and mortality.

Keywords: COVID-19,SARSCOV2 infection

Introduction

Millions of people have been infected with severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) worldwide. Comorbidities like diabetes mellitus, hypertension, chronic renal failure as well as older age have been identified as risk factors for severity of COVID-19(1-4). Cancer patients also are found to be more vulnerable to SARS-CoV-2 infection than healthy population in studies which mostly included solid malignancies (5-7).

The increased risk of respiratory tract viral infections in hematological malignancy and hematopoietic stem cell transplantation(HSCT) patients have been previously reported (8,9). Either the underlying diagnosis or the treatments may influence the humoral and cellular immune function negatively, and result in poor outcome. The clinical characteristics and risk factors that may be predictive for severity or mortality of COVID-19 in hematological malignancy patients needs to be addressed.

In this registry data, we aimed to analyze the symptoms, complications, ICU admission and mortality rates of SARS CoV-2 infection in patients with underlying hematological malignancies, as well as clarifying the risk factors associated with mortality of COVID 19, in Turkey. Additionally, the influence of national treatment protocols for SARS-CoV-2 infection on the outcome were analyzed.

Methods

On behalf of Turkish Society of Hematology, Infectious Complications and Supportive Care Working Party, we retrospectively collected data from 25 centers in Turkey from March to November 2020. The study was approved by both the Turkish Ministry of Health and the Ethical Committee of Istanbul University- Cerrahpaşa School of Medicine(22-Sep-2020/80350) and also locally by the participating centers.

Patients were included in the study according to the following criteria ; a)if they had SARS-CoV-2 PCR positivity via nasal swabs b) if they had negative PCR results but symptoms related with SARS-CoV-2 with highly suggestive thoracal computerized tomography (CT) findings. Patients who were followed up as both outpatient and inpatient for COVID were eligible for the study Forms for data collection were e-mailed to participating centers.

Diagnosis and status of primary disease, treatment schedules for hematological malignancies, time from the last treatment, life expectancy related to the hematological disease have been recorded. Data regarding symptoms related to SARS-CoV-2 infection, hospitalization and oxygen requirement, severity, complications organ involvement, laboratory parameters on admission and treatments given for COVID 19 have also been investigated. Co-morbidities were defined as diabetes mellitus, hypertension, chronic renal failure, chronic obstructive pulmonary disease, cardiovascular disease or pre-existing solid malignancy diagnosis were also recorded.

Patients who had autologous stem cell transplantation and were in the first 100 days after transplantation were grouped as "auto-HSCT". All patients who had allogeneic hematopoietic stem cell transplantation has been accepted as "allo-HSCT" patients irrespective of their primary diagnosis and status of the disease.

The severity of SARS-CoV-2 infection was classified according to WHO definitions as (11): Mild disease; symptomatic patients without findings of pneumonia or hypoxia. Moderate disease; patients with signs of pneumonia, like cough, fever, dyspnea without signs of severe pneumonia or SpO2 >90% on room air. Severe disease; patients with symptoms of pneumonia and respiratory rate > 30/min; severe respiratory distress; or SpO2 <90% on room air. Critical disease; patients with acute respiratory distress syndrome (ARDS), sepsis and septic shock.

The COVID 19 treatment of patients were determined according to guidelines released by Turkish Ministry of Health. Due to the antiviral potency of hydroxychloroquine(HCQ), it has been introduced as the initial treatment schedule alone or in combination with azithromycin and favipiravir as salvage treatment. In the follow up of the pandemic, favipiravir has been moved to first line in treatment consistent with the next version of guidelines.

The primary objective of the study was to identify the clinical outcomes and complications of COVID-19 in patients with hematological malignancies and to determine the rates of hospitalization, ICU admission, overall 45 day mortality rates. Secondary objective was to find additional risk factors for mortality specifically defined for this group of immunosupressed patients.

Descriptive statistics were performed as median in continuous and percentage in categorical variables. Cox-regression model has been used for univariate analysis. Parameters which could achieve p<0.20 was added into multivariate Cox-regression model and significant factors were detected with stepwise method.

Results

Patient characteristics of 335 adult and 5 pediatric patients were summarized in Table 1.Median age was 59 years (7-93). COVID 19 was more frequent in males (M:F ratio=1,3). The most common underlying hematological diagnosis was multiple myeloma(MM) (25%), followed by acute myeloid leukemia(AML) (20%) and non-Hodgkin lymphoma(NHL)(18%). Heamatological disease status of the patients were shown in Table 1. Twenty eight percent of the patients had active disease. Twenty eight of these patients were newly diagnosed but treatment could not be started as a consequence of SARS Cov2 infection. The treatment schedules for hematological malignancies were also summarized in Table 1. Treatment protocols for primary disease have been changed before the diagnosis of COVID 19 in 21% of the patients.

Nasopharyngeal swab PCR positivity for SARS-CoV-2 was observed in 264 out of 340(77%) patients. Forty four (12.9%) patients were asymptomatic at diagnosis. In symptomatic patients, fever, cough and dyspnea were observed in 62.6%, 48.8 % and 41.8% respectively. In allo-HSCT group, 13% of the patients were asymptomatic. Fever was present in 55%, cough in 50%, dyspnea in 28%, myalgia and malaise in 34% and 31% of the patients respectively. In auto HSCT group, 9 patients (64%) had fever, 5 (35%) patients had cough and malaise, 4 (28%) patients had dyspnea, whereas one patient (7%) was asymptomatic.

Median febrile days were 3 (1-20). Sixty nine (20,2%) patients had mild disease, whereas moderate, severe and critical disease was reported in 101(29,7%), 71(20,8%) and 55(16,1%) patients, respectively. ARDS was reported in 11 patients, sepsis and septic shock were observed in 31 and 13 patients. Two out of five pediatric patients were asymptomatic, two had severe and one had critical disease Severity of COVID 19 was not found to be related with age, comorbidities, primary disease status, malignancy treatments, HSCT and the type of COVID 19 treatment.

In Allo-HSCT group, mild, moderate, severe and critical COVID 19 was observed in 18%, 44%, 13% and 10% respectively. Patients with graft versus host disease (GVHD) had more severe and critical disease in comparison with those without GVHD(p=0.03) In patients who have been diagnosed as COVID 19 in the posttransplantation 30 day of auto HSCT; mild disease was observed in 4 out of 14 patients, moderate, severe and critical disease was observed in 3, 4 and 2 patients, respectively.

Laboratory variables of the patients were summarized in Table1. Neutropenia and lymphopenia at diagnosis was observed in 23% and 57% repectively.

Treatment for COVID was either with hydroxychloroquine (HCQ) or favipiravir alone or in combination with other treatments (Table1). Favipiravir alone was given to 41.4% of the entire cohort, in combination with HCQ to 14.7% and in combination with HCQ and azithromycin to 12.4% of the patients.Ten percent of the patients recieved HCQ alone and in combination with azithromycin in 12.4%.

Thirty six patients(12.3%) received convalescent plasma and the rest of the anticytokine treatment were summarized in Table1.

Two hundred fifty one (73.8%) patients were hospitalized; 86 (25%) of these patients were admitted directly to ICU. Median hospitalization days in ward and ICU were 11 (1-49), 2 (1-63), respectively.

Thrombotic events were observed in 7 (2%) patients; 3 of them had thrombotic attack under prophylactic dose low molecular weight heparin. One out of three patients had a previous pulmonary embolism history.

PCR negativity could be achieved in median 11 days (1-60). Patients who have received rituximab for primary disease within one year before COVID 19, showed a significantly prolonged viral shedding (median 14 days (3-60) vs 11 days (1-59) p=0.023).

Mortality was 26.5% in all cohort and 4.4% in mild disease, 12.4% in moderate disease and 83% in severe and critical patients. Nine out of thirty eight(23.7%) patients in Allo-HSCT and 3(21%) out of fourteen patients in auto-HSCT group died. No difference in mortality was observed in patients according to the timing of HSCT or graft versus host disease.

Table 1. Patient characteristics, clinical outcome and treatment of hematological malignancy patients infected with SARS Cov2.	
	N:340
Age median (min-max)	59 (7-93)
M/F	194/144
Diagnosis	AML:69 (%20.3) NHL:64 (%18.8) MM:85 (%25) ALL:30 (%8.8) MDS:27 (%7.9) Hodgkin:18 (%5.3) CLL:18 (%5.3) CMPD: 10 (%2.9) CML : 8 (% 2.4) CMML: 4 (%1.2) HCL: 7 (%2.1)
Comorbidity	144 (%42.4)
Smoking status Active smoker/ex smoker/nonsmoker/NA	8 (%2.4)/84 (%24.7)/175(%51.5)/73 (%21,5)
Contact Yes/no/NA	103/175/62
Disease status	New diagnosis: 65(19.1%) CR: 135(39.7%) PR: 13 (3.8%) Active disease: 98 (28.8%) Untreated: 20 (5.9%) NA:9 (2.6%)
Treatment Untreated Induction/consolidation/salvage/immunotherapy/maintenance AutoHSCT/Allo HSCT Steroid/Rituximab/IvIG/GCSF	 48 134/19/68/13/14 14/38 100/57/42/55
Clinic Asymptomatic Symptomatic	 44 (%12.9) 297 (%87,1)
Symptoms Fever Cough Dyspnea Myalgia Diarrhea Malaise Sore throat Headache Nausea Anosmi	 213 (%62.6) 166 (%62.6) 142 (%41.8) 64 (%18.8) 19 (%5.6) 75 (%22.1) 12 (%3.5) 9 (%2.6) 9 (%2.6) 8 (%2,4)
Days with fever Median(min-max)	 3 (1-20)
Extrapulmonary disease Myocarditis Liver Renal Skin Neurological	 6 2 2 1 2

Table 1 .Continued	
	N:340
COVID severity Asymptomatic/Mild/Pneumonia/Severe penumonia/ARDS/Sepsis/Septic shock Asymptomatic/Mild/Moderate/Severe/Critical	44/69/101/71/11/31/13 44/69/101/71/55 (12.9%)/(20,2%)/(29,7%)/(20,8%)/(16,1%)
Thrombosis	7 (%2)
Hospitalization **Ward/ICU**	251 (73.8%) 165 (48.5%)/86(25.3%)
Hospitalization days Median(min-max) **ICU days** Median(min-max)	 11(1-49) 2 (1-63)
Laboratory variables Hb Wbc Lymphocte Neutrophile Plt Ferritin	 10,1(6,0-15,3) 4300(30-343000) 780(0-326200) 2500(0-67480) 1250000(5000-654000) 1461(17-40000)
Antiviral treatment Hydroxychloroquine(HCQ) Favipiravir HCQ +favipiravir HCQ+Azitromycin HCQ+Azitromycin+Favipiravir NA	 35 (10%) 140 (41.2%) 50(14.7%) 42 (12.4%) 42 (12.4%) 31(9.1%)
Anticytokine treatment Convalescent plasma Steroid Tocilizumab İvig Anakinra Ruxolitinib	 36 (12.3%) 27(7%) 24(7%) 21(6%) 5(1%) 1(2%)
Anticoagulan teratment Prophylactic dose Treatment dose	 198 (58.2%) 26 (%7,6)

Parameters analyzed for relationship with mortality in univariate analysis with Cox regression has been shown in Table 2. Age, co-morbidity, status of primary hematological disease, neutropenia and lymphopenia at diagnosis of SARS-CoV-2 infection, severity of COVID 19, hospitalization, admission to ICU, entubation, the type of COVID 19 treatment convalescent plasma treatment and decreased life expectancy related to primary hematological disease were found to be associated with higher mortality rates. Also, patients with PCR positivity had a higher mortality rate in comparison with patients who had only CT findings but negative PCR results(Table 2).

In multivariate Cox-regression analysis by stepwise approach all the significant parameters related with mortality in univariate analysis were included into multivariate analysis. Hematological disease status, decreased life expectancy related to primary hematological disease, neutropenia, ICU admission and the type of COVID 19 treatment were found to be associated with higher mortality (Table 3). Patients treated with HCQ alone had 4.9 fold, HCQ plus favipiravir 2.,044 fold and HCQ plus azithromycin had 2.14 fold mortality risk in comparison with patients treated with favipiravir alone.

Discussion

Herein, we report the outcomes of 340 hematological malignancy patients who contracted SARS-CoV-2 infection from March to November 2020 in Turkey. Patients with hematological malignancies are a high risk population for SARS-Cov2 infection as a result of immunosupression which comes out with the disease and the treatment also. In our study, severe/critical disease defined according to WHO classificiation,

Table 2. Univariate analysis for mortality of the patients by cox regression model (p<0.20 =statistically signifacnt).

	n	p	HR	95% CI for HR	
				Lower	Upper
Gender					
Female			1		
Male	195	,448	1,180	,769	1,810
Age					
<60	170		1		
≥60	167	**,094**	1,432	,941	2,180
Diagnosis					
Acute leukemia	99	,459			
Lymphoma	106	,376	1,270	,748	2,156
Myeloproliferative	22	,251	1,599	,718	3,561
Myelom	84	,548	,827	,444	1,539
MDS	27	,486	1,329	,597	2,959
Hem disease status					
Newly diagnosed	47	**,000**			
CR	136	**,001**	,354	,187	,672
PR	21	,963	1,020	,440	2,365
Active disease	104	,928	1,027	,582	1,812
Untreated	21	**,038**	,212	,049	,918
NA	9	**,167**	,241	,032	1,812
Comorbidity					
No	194		1		
Yes	144	**,016**	1,672	1,102	2,537
Smoke					
No smoker	174	,992			
Ex-smoker	83	,975	1,008	,616	1,648
Active smoker	8	,903	,916	,222	3,773
Hematological treatment					
İnduction	134	,232			
Consolidation	21	,248	,546	,196	1,525
Salvage	69	,514	1,182	,714	1,957
İmmunotherapy	13	,313	,481	,116	1,992
Maintenance	15	,183	,381	,092	1,575
Allo-HSCT	32	,103	,462	,182	1,168
Auto HSCT	6	,459	,473	,065	3,436
Untreated	48	,201	,636	,318	1,272
Hem. treat-COVID					
Untreated	17	,205			
During treatment	152	,979	,988	,392	2,488
<1 month	48	,790	1,145	,423	3,105
<3 month	24	,917	,941	,299	2,965
3-6 month	16	,500	1,484	,471	4,677
6-12 month	15	,122	,183	,021	1,570
≥12 month	19	,183	,328	,064	1,691
≥2 month	20	,144	,294	,057	1,518

Table 2. Continued

	n	p	HR	95% CI for HR	
				Lower	Upper
Steroid					
No	219				
Yes	100	,244	,745	,453	1,223
GCSF before COVID					
No	281				
Yes	55	,037	1,687	1,033	2,756
Rituximab before COVID					
No	281				
Yes	57	,357	1,275	,760	2,139
IVIG before COVID					
No	296				
Yes	42	,382	1,300	,722	2,343
COVID diagnosis method					
PCR	95	**,000**			
PCR+BT	169	**,000**	3,514	1,852	6,669
BT	74	**,196**	1,674	,767	3,653
COVİD severity					
asymptomatic	44	**,001**			
mild	69	**,122**	2,071	,822	5,219
moderate	101	,371	1,517	,609	3,778
severe	69	**,078**	2,283	,912	5,718
critically ill	55	**,001**	4,418	1,817	10,744
Lymphopenia					
No	126				
Yes	194	**,058**	1,563	,985	2,480
Neutropenia					
No	162				
Yes	78	**,000**	2,546	1,553	4,175
Hospitalization					
ICU admission	84	**,000**			
Outpatient	89	**,005**	5,479	1,668	17,996
Ward hospitalization	165	**,000**	30,986	9,684	99,149
Entubation					
No	260				
Yes	78	**,000**	21,883	13,360	35,844
COVID treatment					
HCQ	28	**,131**			
Favipiravir	130	,953	,976	,428	2,226
HCQ+Favipiravir	43	**,226**	1,724	,714	4,161
HCQ+Azitromycin	42	,910	,946	,360	2,488
HCQ+Azitromycin+Favipiravir	42	**,188**	1,799	,751	4,309
Prophylactic anticoagulant					
No	141				
Yes	197	,238	,778	,513	1,180

Table 2. Continued

	n	p	HR	95% CI for HR	
				Lower	Upper
Anticoagulant treatment					
No	215				
Yes	26	,477	1,291	,639	2,609
Life expectancy					
<3 Month	10	**,000**			
3-6 month	9	**,002**	,089	,019	,416
6-12 month	38	**,001**	,275	,124	,608
>12 month	208	**,000**	,075	,036	,158

Table 3. Multivariate analysis for mortality of the patients by cox regression model (p<0.20 =statistically significant).

	$\hat{\beta}$	SE ($\hat{\beta}$)	p	HR	95% CI for HR	
					Lower	Upper
COVID Treatment						
Favipiravir			,037			
HCQ	1,608	,537	**,003**	**4,992**	1,741	14,313
HCQ+Favipiravir	,715	,370	,053	2,044	,989	4,224
4=HCQ+Azitro	,744	,440	,091	2,104	,888	4,981
5=HCQ+Azitro+Favipiravir	,270	,356	,448	1,310	,652	2,630
ICU admission	1,116	,536	,038	3,051	1,066	8,731
Entubtation	2,484	,472	,000	11,987	4,756	30,210
Nutropenia	,670	,278	,016	1,954	1,132	3,372
Life expectancy						
≥ 12month			,021			
<6 month	,907	,409	,026	2,476	1,112	5,514
6-12 month	,755	,324	,020	2,127	1,127	4,015
Hematological disease status(active disease)	,880	,320	,006	2,410	1,287	4,512

has been observed in 36% of patients (11). Consistent with our results, another report from Turkey which included patients from Turkish Ministry of Health database showed more severe and critical disease in hematological malignancy patients with COVID 19 compared with patients without cancer(12). Pinana et al. (13), included patients grouped according to a different severity criteria (14) and observed severe disease in 55% of non-HSCT, 36% of autoHSCT and 43% of alloHSCT patients.

We could not find a relation between severity of COVID 19 and age, comorbidities, primary disease status, malignancy treatments, HSCT or treatment of COVID 19. But in allo-HSCT patients, GVHD was related with more severe-critical. Risk factors for severe disease were reported as hypertension, baseline lymphopenia, baseline CRP>20 mg/dl age, co-morbidities in different series(13,15,16).

Factors related to mortality in hematological malignancy patients is another debate. Mortality was 26% in our study and correlated with increasing COVID 19 severity. In a meta analysis of 34 adult and 5 pediatric studies which included predominantly hospitalized patients, risk of death was 34% and 4%, respectively (17). Although there were only five pediatric patients in our study, all were alive at the end of follow up. Pinana et al. showed an association between mortality and age, performance score, neutropenia, uncontrolled disease and CRP increase (13). In our study, hematological disease status, life expectancy related to the primary hematological disease, neutropenia, ICU admission and the type of COVID 19 treatment were risk factors for mortality in multivariate analysis. ICU admission highly reflected the disease severity and also mortality increased irrespective of age probably related to the primary hematological disease status.

Thirteen percent of our patients were asymptomatic at diagnosis which was lower than the general population. The most prominent symptoms at diagnosis were found as; fever, cough and dyspnea. In Italian data which included only adult patients,

fever was reported in 75%, dyspnea in 51%, cough in 45% and malaise in 39% of the patients (15). He et al. observed more fever, cough and dyspnea in hematology patients in comparison with health care professionals (18). Consistent with our findings, Pinana et al. failed to show a difference in symptoms of patients irrespectively from their HSCT status(13). Hospitalization was required in 73% of our patients and 25% have been admitted to ICU similar with other series(13,15). In Italy, within severe or critical COVID 19 patients those who were admitted to ICU were younger, and had lower co-morbidity index (15).

In our data, AML, NHL and MM were the most frequent hematological malignancies consistent with previous studies (16,17,19). Chronic myeloproliferative neoplasms(CMPN) were the least frequent patient population. In other Turkish study different from our data, besides non Hodgkin lymphoma, myelodysplastic syndrome and myeloproliferative diseases were common diagnosis(12).

There are controversial results about the impact of underlying hematological diagnosis on mortality of COVID-19. We suggest that not the diagnosis but the disease status before COVID 19 is a significant factor. In a population based registry data of 833 patients, besides age and comorbidities, diagnosis of AML was found to be related with highest mortality rate, whereas patients with Philadelphia(-) CMPN had the lowest risk (16). Passamonti et al., showed worse survival in uncontrolled disease and also AML, NHL or plasma cell dyscrasia patients (15). In a study which included only CLL patients, 79% were presented with severe COVID 19 findings. No difference was observed regarding the presence of three or more comorbidities or hypogammaglobulinemia (10). Predictors of adverse outcome in MM patients were revealed as age, having high-risk MM, renal disease, and suboptimal control of the disease (20,21).

Treatment schedules for various hematological malignancies have been suggested to be modified during pandemic in order to reduce immunosupression and admission of patients to hospital (22-24). In our cohort, the data revealed that hematological malignancy treatments were modified in 21% of our patients before COVID 19 diagnosis. There is controversial data about the impact of hematological malignancy treatment on COVID 19 outcomes. Vijhnethira et al. could not show the impact of recent hematological malignancy treatment on the risk of death irrespective of the type of therapy (17). In CLL, severity of COVID 19 increased in untreated patients and those who were treated within the last year, but administered Bruton kinase inhibitors exerted a protective effect against the virus (10). In myeloma patients, none of the anti-myeloma treatments including transplantation were found to be associated with outcome (25). We could not show a significant impact of either the type or the timing of last hematological malignancy treatment on mortality in our study.

In our study, treatment schedules designed by Turkish health authorities has been followed up. Favipiravir has been moved to first line in treatment as a consequence of studies which could not show benefit of HCQ(25-27). Patients treated with HCQ alone had 4,9 fold, HCQ plus favipiravir 2,0 fold and HCQ plus azitromycin had 2,1 fold mortality risk in comparison with patients treated with favipiravir alone. HCQ plus favipiravir group mostly included patients who received HCQ initially and favipiravir in further progress of pneumonia. In a multicenter randomized superiority trial, conventional therapy in combination with favipiravir or arbidol has been investigated, and favipiravir was found to be significantly superior to arbidol in 7 days clinical recovery date (28,29). The data on the impact of these drugs in immunosupressive patients are limited. The lowest mortality was observed in patients who received favipiravir alone in our study which may be a valuable data for further studies.

Conclusion

In conclusion, hematological malignancy patients infected with SARS Cov2 have an increased risk of mortality. Having active hematological malignancy, neutropenia, admission to ICU and lower life expectancy related to primary disease, increases mortality rates in these patients.

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