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Comparative study between COVID-19 Outcomes for Patients on Chronic Immunosuppressive Drugs, Patients on Active chemotherapy and Non- Immunosuppressed Patients: A Single-Center Egyptian Experience

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ABSTRACT

Background: Patients with hematological disorders especially those who underwent bone marrow transplantation are known for having some degree of immune system derangement and cytokine signaling instability as well as patients who were diagnosed with active malignancy and needed chemotherapy.

Objective: The study aimed to compare the outcome between patients infected with COVID 19 who use immune suppression (either acute or chronic immune suppression) to fight COVID infection and how our different bodies and immune systems can handle it versus the normal population.

Patients and Methods: This study was a cross-sectional study in December 2020 conducted on 96 subjects who caught COVID-19 infection, the subjects were categorized into three groups: **Group 1**: consists of 32 patients who underwent BMT (patients on chronic immunosuppressive drugs), **Group 2:** consists of 32 patients with hematological diseases (patients on chemotherapy or acute immunosuppressive drugs), and **Group 3:** control group (non- immunosuppressed patients) consists of 32 patients with patients had symptomatic COVID-19 infections requiring hospital admission.

Results: We found improved overall survival in group 1 with 4 out of the total 32 patients succumbed to their deaths, 2 of the 4 patients were in the peri-engraftment period with the statistically significant improved OS when compared to patients in group 2 with a P-value of 0.038.

Conclusion: Acute immune suppression is done by chemotherapy worsen the outcome of COVID-19 infection, while chronic immunosuppression had the best outcome in COVID-19 patients even better than the normal population due to loss of immune cell signaling and absent cytokines storm that might occur.

Keywords: HSCT, COVID-19, Hematological malignancies

INTRODUCTION

Hematopoietic stem cell transplantation had a rapid increase over the last decades. It is an established therapy for many hematological disorders. HSCT had many possible serious complications. One of those complications is prolonged immunosuppression, Coronavirus disease 2019 (COVID-19) is caused by the novel SARS-CoV-2 virus and has been declared a pandemic on the 9th of March by the WHO [(1)]. Severe COVID-19 infection characterized by acute respiratory distress syndrome (ARDS), secondary bacterial pneumonia, thrombotic complications, myocarditis, and gastrointestinal involvement is more prevalent in those with comorbidities such as hypertension, diabetes, and old age [(2)].

Patients with cancer have at least a two-times higher risk of COVID-19- associated intensive care unit admission, invasive ventilation, and death compared with the general population. Hematopoietic stem-cell transplantation (HSCT) recipients might be an especially vulnerable group due to nascent immune systems or organ impairment from treatment-related toxicities, specifically concerning infection-related and respiratory complications. To date, data on outcomes of HSCT recipients with COVID-19 are limited to small case series and single-center experiences. Better characterization of HSCT patients infected with SARS-CoV-2 is needed. Here we describe the clinical characteristics, treatment patterns, and factors associated with outcomes of HSCT recipients who developed COVID-19 [(3)].

Aim of the work was to determine the prevalence and outcomes in a population who had HSCT and was infected by COVID 19 versus normal population and patients who had hematological disorders (mainly malignancies) and correlate mortality rate among each group with other clinical and laboratory parameters.

PATIENTS AND METHODS

This study was a cross-sectional study in December 2020 conducted on 96 subjects who caught COVID-19 infection in Ain Shams University Hospitals Hematology and bone marrow transplant unit and inpatient COVID-19 unit; the subjects were categorized as follows:

Group 1: consists of 32 patients who underwent BMT (patients on chronic immunosuppressive drugs).

Group 2: consists of 32 patients with hematological diseases (patients on chemotherapy or acute immunosuppressive drugs).

Group 3: control group (non- immunosuppressed patients) consists of 32 patients with patients who had symptomatic COVID-19 infections requiring hospital admission with no antecedent hematological disorders.

Methods:

COVID-19 19 infection was confirmed by a positive real-time PCR assay of a specimen collected from a nasopharyngeal swab, After diagnosis; all included patients received the protocol of therapy

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according to their stage of severity, the severity of COVID-19 was defined as mild (no oxygen supplementation), moderate (supplemental oxygen needed), or severe (mechanical ventilation required). Duration of disease was defined as the time from diagnosis to infection resolution or death.

Ethical approval:

We reviewed medical records to collect data from COVID 19 cases in the Faculty of Medicine, Ain Shams University, all data recorded were following the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individuals who participated in the study. The study was approved by the Ethics Board of Ain Shams University.

All patients were subjected to:

1. Full history taking.
2. Clinical examination.
3. Laboratory or radiological workup

Radiological workup:

1. Chest X-ray.
2. Computed tomography scan (CT Scan) of the chest HRCT.

Laboratory workup:

- CBC, kidney function, liver function (AST, ALT, ALK phosphatase, γ GT, albumin, bilirubin total and direct) coagulation factors by measuring (PT, PTT, INR), Serum ferritin level and Pregnancy test for females in the childbearing period.
- PCR of COVID – 19.

Statistical analysis

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) to calculate the difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P-value < 0.05 was considered significant.

RESULTS

This study was conducted on 3 groups and each group consist of about 32 patients matched as regard age and sex.

Group 1: consisted of 32 patients who underwent BMT, 13 of them received allogeneic graft (34.4%) and the other 19 patients received autograft (65.6 %) and were 40.6% females & males were 59.4% with mean age 37.5 and range from 18–63.

Group 2: consisted of 32 patients with hematological diseases and was (50.0%) females and (50.0%) males with mean age 40 and range from 18–62. Underlying malignancy as shown in figure (1)

Group3: control group consisted of 32 patients with patients diagnosed symptomatic COVID-19 with no antecedent hematological disorders was (50.0%) females and (50.0%) males with a mean age of 44 and a range of 23-70 and at some point, of their management need ICU admission.

There was no statistically significant difference between groups according to demographic data with **a p-value of 0.686.**

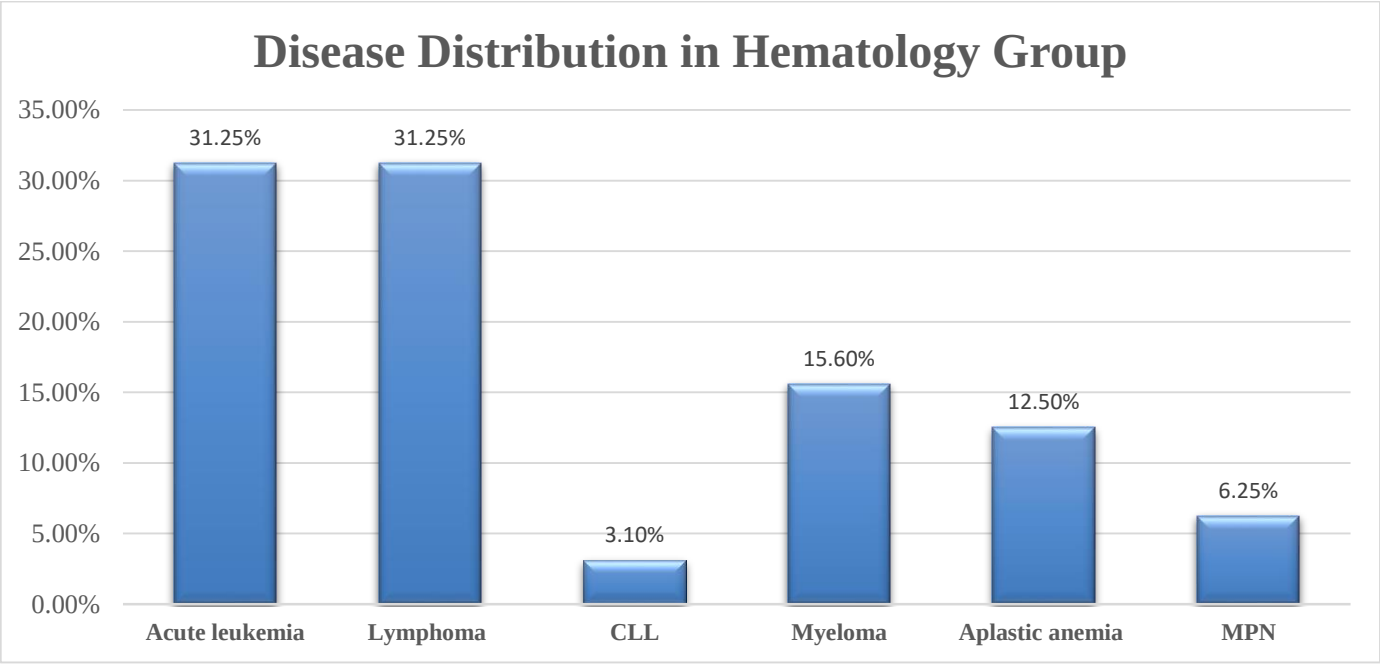

Figure (1): Hematological disorders distribution among the group (2).

Patients' baseline laboratory data are shown in table (1), and table (2) shows a Comparison between groups according to comorbidity, symptoms, and immunosuppression.

Table (1): Comparison between groups according to laboratory parameters

CBC parameters	Group 1 (Post HSCT) (n=32)	Group 2 (Hematological disorders) (n=32)	Group 3 (Control Group) (n=32)	Test value	p-value
WBCs (mcL) Mean± SD	4.5±1.1	8.0±1.9	11.5±2.6	H=23.353	<0.001**
Neutrophils (Mean± SD)	3.0±0.61	1.85±0.3	8.4±1.2	H=28.758	<0.001**
Lymphocytes (µL) Mean± SD	0.85±0.19	0.75±0.12	1.0±0.2	H=5.061	0.080
Monocytes (Mean± SD)	0.40±0.09	0.35±0.079	0.50±0.11	H=2.995	0.224
Hemoglobin (g/dL)					
Mean± SD	10.00±1.86	8.38±2.18	10.99±1.77	F=12.599	<0.001**
Platelets (mcL)					
Median (IQR)	205.5(142.5-250)	47.5(30-149)	333(257.5-400)	H=58.472	<0.001**
ESR (mm/hr)					
Mean± SD	42.75±4.59	65.52±3.41	72.81±3.52	F=8.886	<0.001**
CRP (mg/L)					
Median (IQR)	17(6-19.8)	21(7.5-98)	18(12-91.575)	H=4.231	0.121
Serum Ferritin (mcg/dL)					
Mean± SD	658.09±86.33	960.44±70.60	686.84±70.57	F=2.259	0.110
D dimer (ng/mL)					
Mean± SD	0.59±0.09	0.87±0.2	0.88±0.2	F=4.325	0.016*
Serum Creatinine					
Occurrence of Acute kidney injury	5 (15.6%)	14 (43.8%)	7 (21.9%)	x^2=7.068	0.029*
Normal kidney functions	27 (84.4%)	18 (56.3%)	25 (78.1%)		

This table shows a statistically significant difference between groups according to WBCs, Neutrophil, HGB, Platelets, ESR, D -dimer, and Creatinine.

Table (2): Comparison between groups according to comorbidity, symptoms, and immunosuppression.

	Group 1 (Post HSCT) (n=32)	Group 2 (Hematological disorders) (n=32)	Group 3 (Control Group) (n=32)	X^2	p-value
Comorbidity					
DM	5 (15.6%)	6 (18.8%)	18 (56.3%)	15.514	<0.001**
HTN	6 (18.8%)	8 (25.0%)	3 (9.4%)	2.716	0.257
BA	2 (6.3%)	0 (0.0%)	0 (0.0%)	4.085	0.130
CKD	4 (12.5%)	5 (15.6%)	7 (21.9%)	1.050	0.592
PRGNANCY	0 (0.0%)	0 (0.0%)	1 (3.1%)	2.021	0.364
Symptoms					
Asymptomatic	14 (43.8%)	7 (21.9%)	0 (0.0%)	17.920	<0.001**
Dyspnea	9 (28.1%)	16 (50.0%)	17 (53.1%)	4.825	0.090
Fever	5 (15.6%)	8 (25.0%)	6 (18.8%)	0.919	0.632
Diarrhea	4 (12.5%)	1 (3.1%)	9 (28.1%)	8.195	0.017*
Immunosuppression	10 (31.3%)	17 (53.1%)	3 (9.4%)	14.255	<0.001**
Complication					
Bacterial infection association	4 (12.5%)	14 (43.8%)	7 (21.9%)	8.545	0.014*
No Complications	22 (68.8%)	11 (34.4%)	11 (34.4%)	10.154	0.006*
ARDS	4 (12.5%)	12 (37.5%)	5 (15.6%)	6.949	0.031*
AKI	5 (15.6%)	5 (15.6%)	9 (28.1%)	2.100	0.350
Thrombotic	2 (6.3%)	5 (15.6%)	12 (37.5%)	10.368	0.006*
Mucor mycosis	0 (0.0%)	1 (3.1%)	1 (3.1%)	1.021	0.600

Using: x^2: Chi-square test; p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

This table shows a statistically significant difference between groups according to DM, Symptoms of presentation and use of immunosuppression, and complications.

The most significant pre-infection comorbidity was DM with a **p-value <0.001** as shown in table (2). It was of note that associated chest infections based on sputum cultures were positive as a superinfection in patients with COVID-19 and as shown in table (2) as 44% of patients in group 2 had the highest rate than others and made statistically significant P-value when compared to patients in group 1 **(P-value 0.014).**

Thrombotic events were higher in the control group (who need ICU admission at some point of their management) than in patients with active hematological illness and the least group was group 1 with only 2 patients who had thrombotic events with a **p-value of 0.006.**

Also, 2 patients had mucormycosis one in the control group and the other patients had active acute leukemia with a non-significant p-value**.**

We found a huge statistically difference between three groups in CBC parameters (WBCs, neutrophils, RBCs, and Platelets) with **a p-value <0.001**, all the patients in the three groups had lymphopenia so it was statistically un significant when we compare them **p-value 0.080.**

CRP, serum ferritin was a statistically insignificant difference between groups as they both are elevated in all groups as an acute phase reactants.

ESR was found statistically significant between the three groups it was lower in the BMT group with a mean of 42 and higher in the control group with a mean of 72.8 with a **p-value <0.001.**

D-dimer and serum creatinine had statistically difference between the three groups as only 15.6% of the patients in the HSCT group had AKI while hematology group almost 44% had AKI while control group 22% had kidney injury, D-dimer difference came from the level between BMT group with the mean of 0.5 and most of the patients did not need to receive anticoagulation while two other groups D-dimer mean level was 0.88 and most of the patients need prophylactic/therapeutic anticoagulation.

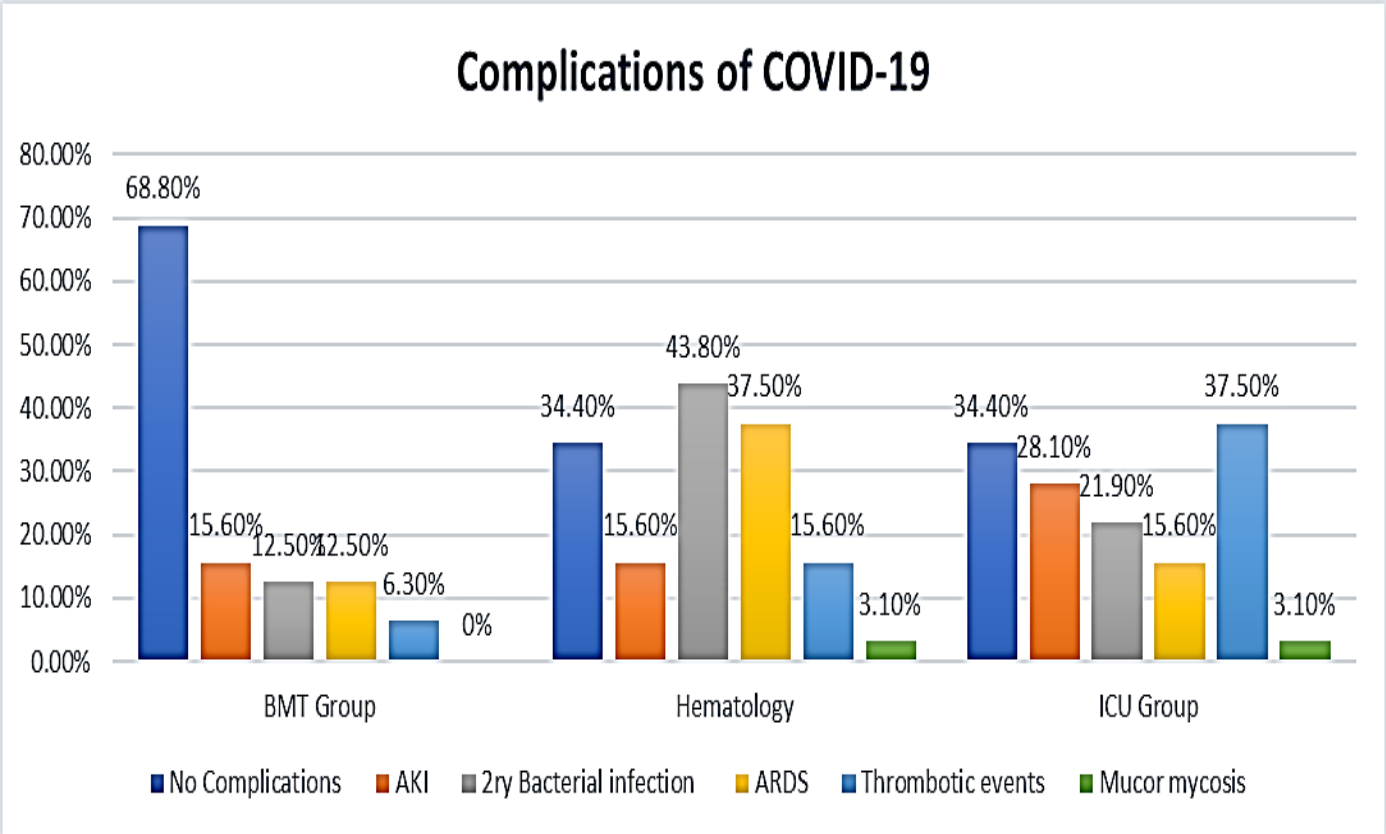

Figure (2): Showing the percentage of complications in different groups

When we assessed complications of COVID-19 infection, we found that almost 69% of patients in group 1 passed their infection smoothly with no significant complications reported while in group 2 most reported complication was superimposed bacterial infection reported in 43.8% and ARDS documented in 37.5%, on the other hand in the control group most reported complication was thrombotic insults mainly in CNS in 37.5% and AKI reported in 28.1% (Figure 3). We follow up the patients for 3 months and record mortality, the highest mortality was in Group 2 as 16/32 patients (50%) unfortunately died; as well as there was 11/32 patients (34.4%) mortality in the control group and the least mortality was in BMT group as we lost 4/32 patients (12.5%). There was a statistically significant difference among the 3 survival curves (p-value = 0.006) (Figures 4 & 5).

Table (3): Comparison between groups according to overall survival.

Survival	Group 1 (n=32)	Group 2 (n=32)	Group 3 (n=32)	X^2	p-value
Improved	28 (87.5%)	16 (50.0%)	21 (65.6%)	10.386	0.006*
Died	4 (12.5%)	16 (50.0%)	11 (34.4%)		

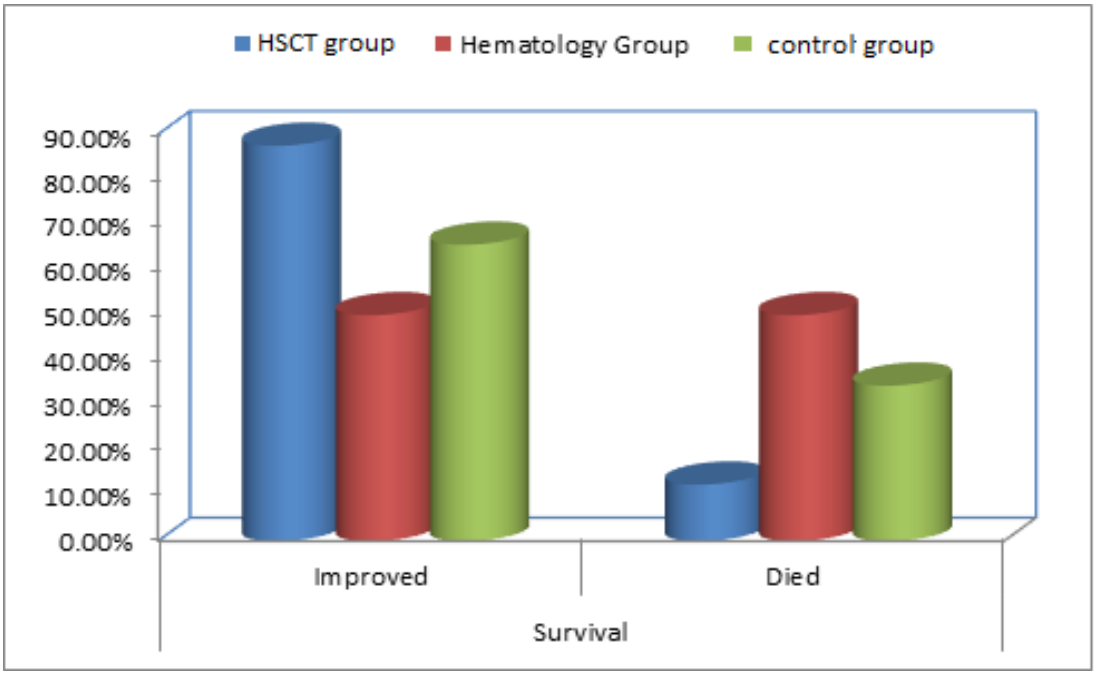

Figure (3): Bar chart between groups according to survival.

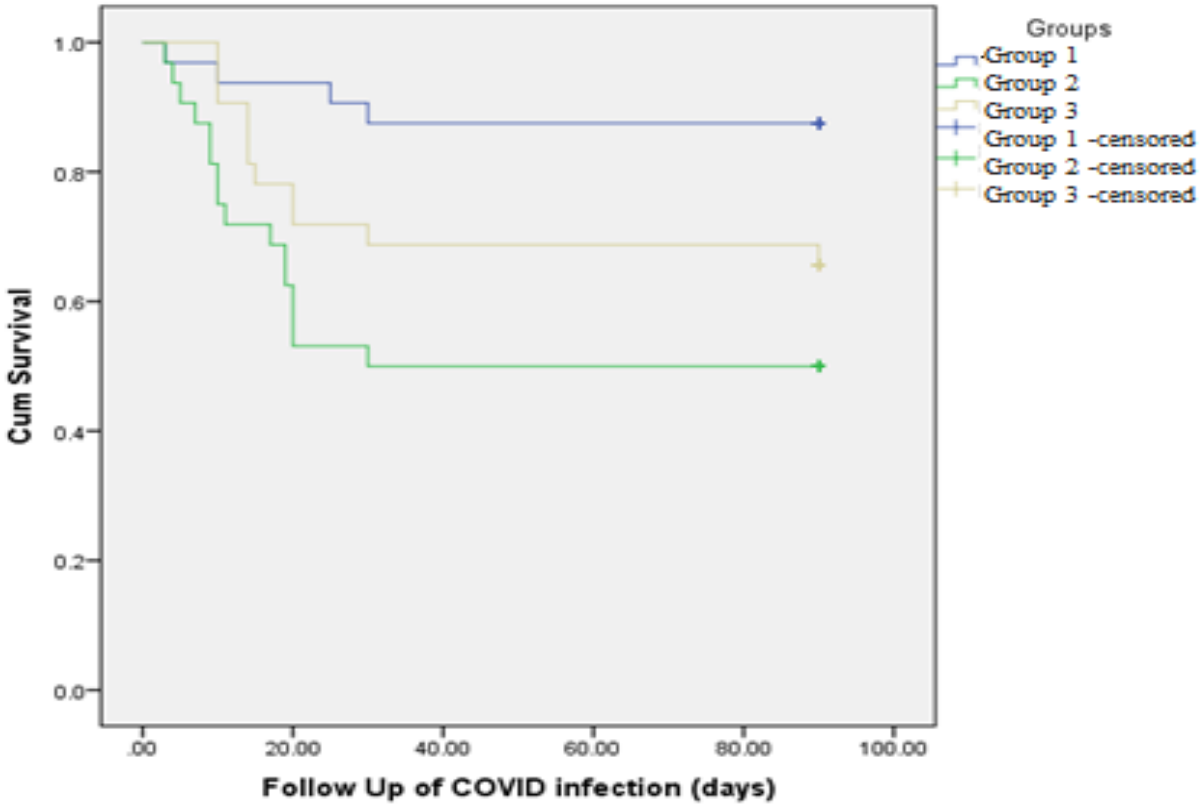

Figure (4): Kaplan-Meier survival curves in Group 1, Group 2, and Control Group. There was a statistically significant difference among the 3 survival curves (Log-rank chi-squared = 10.386, df = 2, p-value = 0.006), there were 31 patients (32.3%) by No. of events at overall, there were 4/32 patients (12.5%) out of them were group 1; while, there were 16/32 patients (50%) out of them were in Group 2; as well as, there were 11/32 patients (34.4%) out of them were the control group.

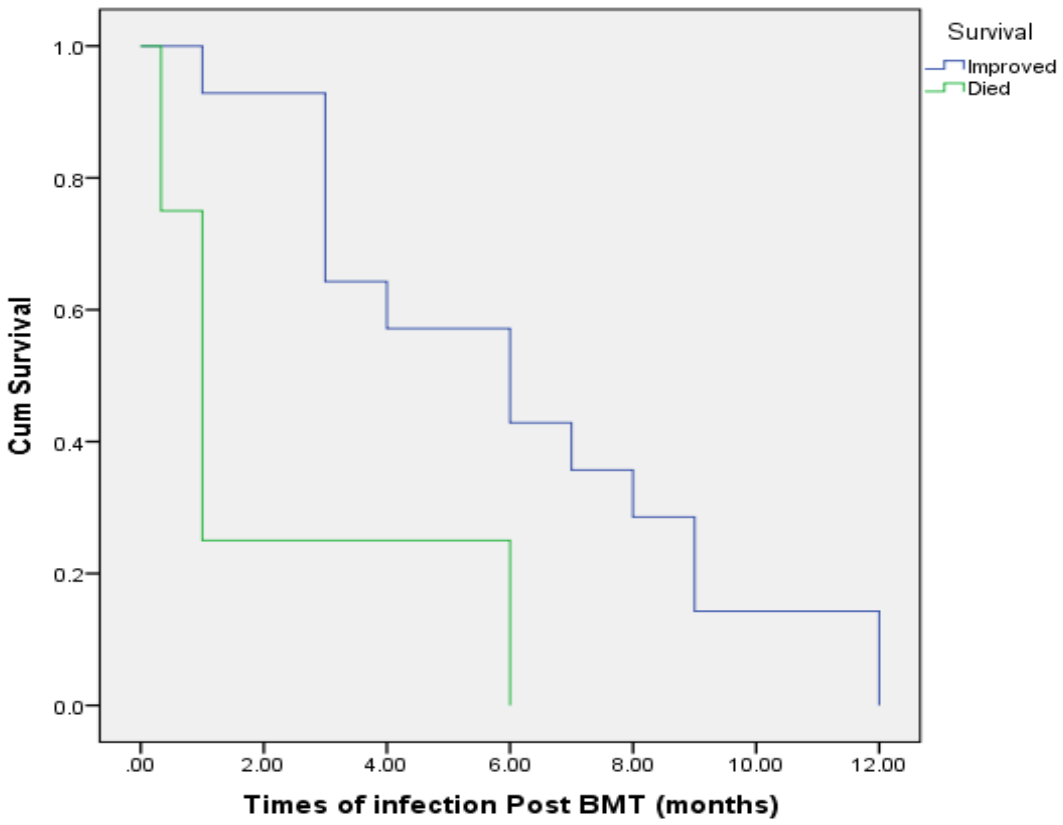

Figure (5): Kaplan-Meier survival curves between survived patients and patients who succumbed to their death in Group 1 regarding times of infection post HSCT "months". There was a statistically significant difference among the 2 survival curves (Log-rank chi-squared = 8.344, df = 1, p-value = 0.004), there were 32 patients (100%) by No. of event COVID infection at overall, there were 4/32 patients (12.5%) out of them were Dead; while there were 28/32 patients (87.5%) out of them were survival.

DISCUSSION

COVID -19 pandemic was a gamechanger for medical practice especially for fragile populations and immunocompromised patients, currently, there are no treatment options yet, but vaccine development will help to decrease the rate and severity of infection. COVID -19 behavior cannot be predicted when the infection is caught, it ranges from asymptomatic to severe illness [(4)].

People taking immunosuppressive drugs to prevent organ transplant rejection or to treat inflammatory or autoimmune diseases do not fare worse than others on average when they are hospitalized with COVID-19, according to a study from researchers at the Johns Hopkins Bloomberg School of Public Health [(5)].

COVID-19 diagnosis was determined by the PCR for the virus in our center, and a diagnostic method was requested [(6)]. The severity of COVID-19 was defined as mild (no oxygen supplementation), moderate (supplemental oxygen needed), or severe (mechanical ventilation required) [(7)]. Duration of disease was defined as the time from diagnosis to infection resolution or death, and infection status at last follow-up was as reported by the infection control center [(8)]. Indeed, our high-risk population underwent closer monitoring than the rest of the population who, according to the national government provisions, was not subjected to an intensive diagnostic strategy, particularly in the presence of mild symptoms. At least 10% of our patients underwent a virologic exam during the study period [(9)].

There was no significant difference in the proportion of male and female patients which is almost 50% with same age group and the mean age was 37.5 years old in patients who had HSCT, in patients with hematological malignancy the mean age was almost 40 years while the control (the average population that caught infection) the mean age was 44 years old with no statistically significant difference between groups, which was consistent with the results of a study performed by **Wang *et al.*** [(10)].

In our study, the main risk of COVID-19 infection was diabetes and was found mainly in the control group total number of patients was 18 of 32 patients with a p-value <0.001 in comparison to patients who had a hematological illness or underwent HSCT.

The patient in hematology group divided into 31.25% acute leukemia, 31.25% lymphoma, 12.5 % aplastic anemia, 15.6% multiple myeloma, 3.1% CLL and 6.25% MPN.

In the BMT group, the patients were 34.4% had allogenic HSCT 65.6% had autologous HSCT, (Indeed our high-risk population underwent closer monitoring than the rest of the population who, according to the

national government provisions, was not subjected to an intensive diagnostic strategy, particularly in the presence of mild symptoms. At least 10% of our patients underwent a virologic exam during the study period).

In a similar study done by **Malard *et al.* [11],** the most common symptoms at diagnosis were fever (89%), cough (79%), and shortness of breath (79%). The majority (80%) of patients had a lymphoid malignancy, including 10 with MM (40%), and only (16%) had a myeloid malignancy (myelodysplastic syndrome). One patient had paroxysmal nocturnal hemoglobinuria, with a median follow-up since symptom onset of 29 days (range, 14–40), (52%) developed acute respiratory distress syndrome (ARDS), and 6 received mechanical ventilation. Kaplan–Meier estimate of overall survival at 1 month was 60%. It is hypothesized that like patients with solid malignancies, those with hematologic neoplasms are more susceptible to COVID-19 and develop severe forms. This study highlighted the following observations: patients with a hematologic malignancy harbored a higher risk of developing a severe form of COVID-19 with ARDS, requiring mechanical ventilation, compared to those in the general population without an underlying medical condition. This translated into very high mortality (estimated as 40% at 1 month).

We found in our study that the primary symptoms were mainly different between groups, unexpectedly BMT patients were asymptomatic mainly while patients with hematological disease had mainly fever and dyspnea at presentation which could be attributed to the active and acute immunosuppression state and as most of them were on IV chemotherapy and control group had acute dyspnea and fever (50 %and 25%) respectively, which agreed with the research results of **Zhao *et al.* [12],** they found COVID-19 symptoms included mainly fever, dyspnea, cough respectively and may have less common presentation as myalgia, fatigue, anorexia and rarely developed intestinal signs and symptoms (e.g., diarrhea).

In a cohort study done by **Sanyaolu *et al.* [13]** of 7337 patients with COVID-19 the most common comorbidities identified were hypertension (15.8%), cardiovascular and cerebrovascular conditions (11.7%), and diabetes (9.4%). The less common comorbidities were coexisting infection with HIV and hepatitis B (1.5%), malignancy (1.5%), respiratory illnesses (1.4%), renal disorders (0.8%), and immunodeficiencies (0.01%), and those with type 2 diabetes required increased interventions for their hospital stay versus those that were nondiabetic. Among other comorbidities, chronic obstructive pulmonary disease (COPD) has also been associated with poor disease progression.

The imaging of pulmonary changes due to COVID-19, like most viral pneumonia, was pleomorphic with interstitial changes and patchy and ground glass shadows especially at peripheral lung zones **(11).** Sometimes, the imaging of pulmonary changes was often out of step with the patient's symptoms and nucleic acid test results. The expert group from our hospital called this phenomenon the "shadow syndrome discrepancy."

The most common and most important laboratory abnormalities in this study were leucopenia and lymphopenia at the time of COVID-19 diagnosis with a median count of 0.8 in patients who underwent BMT, 0.7 in patients with the hematological disease, and 1 in the control group and when we compared it between different groups we found a statistically significant difference between groups according to WBCs, Neutrophils Hb and Platelets (as it was highest in hematological patients, and control patients and within normal in BMT patients), in contrary to **Čerňan *et al.* [8],** who did not find any statistically significant difference of other CBC parameter while in **Wang *et al.* [10]** most patients had normal the leukocyte count and lymphocyte count was generally reduced.

CRP and serum ferritin used as acute phase reactants in our hospital as a marker of cytokines release of severe patients were significantly higher than those of mild patients, similar to our study another meta-analysis study done by **Elgohary *et al.* [14]** they found Several reports recently indicated that some of the inflammatory biomarkers can predict prognosis of COVID-19 as D-dimer levels correlate with COVID-19 severity (especially at levels >2.0 mg/mL) with measurement of serial measurements of serum procalcitonin, serum CRP and interleukin-6 levels correlate with disease severity and can predict outcomes in patients with COVID-19.

While **Wang *et al.* [10]** found D-dimer concentration was increased in 135 patients, especially in severe patients, and indicated the presence of a hypercoagulable state and secondary hyperfibrinolysis in vivo.

Patients were treated with glucocorticoids to reduce inflammatory injury in the lungs. However, due to the limitations of existing evidence, the use of glucocorticoids is still controversial. The latest clinical studies have suggested that glucocorticoids should not be used to treat lung injury or shock caused by COVID-19 without clinical trials [9].

The primary complications during hospitalization in our study included Fatal ARDS, AKI, thrombotic events (DVT, stroke, and thrombotic thrombocytopenic purpura), and shock, those complications were higher in hematology patients the control group and BMT patients had the lowest rate of complication among other.

In another study by **Pinato *et al.* [15]** done on large population 556 patients (62.5%) had evidence of active malignancy, and 479 (53.8%) were on systemic anticancer therapy, mostly with palliative intent (n = 276, 31.0%), whereas 403 patients (45.3%) were not on treatment. The most common presenting symptoms of SARS-CoV-2 infection were fever (63.9%), cough

(50.3%), and dyspnea (38.2%). SARS-CoV-2 was community-acquired in 708 patients (79.5%) and complicated a preexisting hospital admission in another (20.4%). Most patients (63.5%) developed at least 1 complication from COVID-19, the most common being acute respiratory failure (59.2%) followed by acute respiratory distress syndrome (22.5%). And (30.8%) had evidence of an uncomplicated illness which is close to our study findings in patients with the active hematological illness.

The primary outcome of our study analysis was overall survival 90 days after a COVID-19 diagnosis, We compare 2 immunocompromised groups to a normal population One of them is chronically immune-compromised with prolonged T Cell depletion and the other is acutely compromised through chemotherapy, We found the chronic immune-compromised patient had the best outcome in survival and illness symptoms even more normal population, the mortality rate was astonishingly the least in BMT group was 20% in comparison to Hematology Group (53.3%) and control group (33.3%).

BY other meaning on the contrary to what was expected it was found that patients BMT Group had the lowest mortality with only 4 patients out of 32 succumbed their deaths and two of them were in the peri-engraftment period one of them was relapsed BNHL undergoing autologous BMT and died in day +32 as a complication of AKI and TTP, the second one was 62 years old male patients undergoing autologous BMT for multiple myeloma and died of ARDS in day 14 (3rd day of engraftment). The highest mortality rate was among patients in group 2 in which 16 (50%) of them were acute leukemia and aplastic anemia and were receiving planned care of treatment and caught COVID-19 in nadir stage and 1 was BNHL died of ARDS. In the control group, the mortality caused mainly by ARDS and lung damage, and multiple comorbidities go along with **Passamonti *et al.*** [16], as he found an important issue is represented by the risk of developing more serious SARS CoV-2 infections with higher mortality than in nonhematologic populations and 3 out of 6 patients were in critical care and 2 of them died with persistent positive SARS-CoV-2, but both patients suffering from a very advanced hematologic disease with a long disease history and severe comorbidities.

Wang *et al.* [10] did a cohort study at 2 centers in Wuhan, China, hospitalized persons with hematologic cancers had a similar case rate of COVID-19(10%) compared to normal healthcare providers (7%), but they had more severe disease and a higher case fatality rate (62 vs. 0%), However, this study has important limitations including the heterogeneous patient population, hematologic diagnoses, and disease states, confounding covariates such as therapy of hematologic cancers, hospitalization, and interval to developing COVID-19; therefore, the independent role of the underlying malignancy in the evolution of the viral disease could not be documented.

In a great study done by **Afshar *et al.*** [17] on a large multicentric population, they found mortality appears to be high, estimated at 34%, and age is strongly associated with mortality: among those >60 years, mortality is estimated at 47% among those <18 years, mortality is estimated at 4% and recent systemic anticancer therapy may not impact mortality and most patients with hematologic malignancy and COVID survive and this finding is near to our result as we have mortality rate about 50% in adults

In another smaller series, **Shah *et al.*** [18] reported a 30-day survival of 78% in 72 HCT patients and 5 CAR T-cell treated patients and he found overall favorable clinical outcomes for patients with COVID-19 without active malignancy and provide preliminary insights into the lymphocyte populations that are key for the antiviral response and immune reconstitution.

Wang *et al.* [10] did a cohort study at 2 centers in Wuhan, China, hospitalized persons with hematologic cancers had a similar case rate of COVID-19 (10%) compared to normal healthcare providers (7%), but they had more severe disease and a higher case fatality rate (62 vs. 0%), However, this study has important limitations including the heterogeneous patient population, hematologic diagnoses, and disease states, confounding covariates such as therapy of hematologic cancers, hospitalization, and interval to developing COVID-19; therefore, the independent role of the underlying malignancy in the evolution of the viral disease could not be documented.

Based on **Passamonti *et al.*** [16], and their institutional experience during the 2 months of the greatest spread of the epidemic in Italy, in which their organizational care strategies were modified because of the COVID-19 phenomenon while administration of the standard hematologic treatments was continued, they did not change the treatment strategies of the hematologic diseases and implementing infection control models in the overall patient management. We also did that in both the hematology and BMT unit. We did not change the treatment plan of chemotherapy but we modified it by doing PCR for COVID-19 before each cycle of chemotherapy with the extension of daycare working hours of chemotherapy infusion, isolation of donor and recipient of HSCT at least 28 days before starting conditioning protocols with serial PCR for COVID-19, we also did a closed circuit of medical team services as the nurses and physicians who were in both unit had a hospital stay of 14 days consecutive and other teams at home to rest and the new team should report any symptoms and do PCR for COVID-19 and work for another 28 days, etc.…

In contrast to **Varma *et al.*** [19], their study demonstrated that HSCT recipients are at an increased risk of mortality compared to the general population, we found that the incidence of mortality in HSCT recipients is less than the normal population. We can explain that by different age group as **Varma *et al.*** mean age in the

study were 59 and with different ethnic background, while the mean age was 37.5 and the same ethnicity.

To ascertain the true risk of mortality among all patients with hematologic malignancy and COVID-19 (including all outpatients), it will be important for studies to collect data on an unselected population of patients. The largest study included in this meta-analysis, by **Yigenoglu and colleagues[20] from Turkey**, likely has the best estimate for the true population mortality risk for patients with hematologic malignancy infected with COVID-19 (14%), as they used population-based data from a countrywide Ministry of Health database. This estimate remains higher than the risk of death for a control population in their study (7%), and the risk reported in a previous meta-analysis including noncancer inpatients and outpatients with COVID-19 (8%). The risk estimate of 14% reported b**y Yigenoglu** is also comparable to the estimated risk of death of 13% in patients with all cancers [20].

Following the outbreak of COVID-19, many hospitals, particularly in Europe, opened clinical areas where high-level care interventions such as noninvasive ventilation could be delivered to mitigate shortages of ICU beds. The establishment of such high-dependency areas outside of a traditional ICU setting made the risk of ICU admission difficult to quantify and introduced substantial heterogeneity in our analysis. A previous meta-analysis showed a risk of ICU admission of 38% among all patients with cancer, utilizing a modified definition of ICU admission to include these high dependency clinical areas.

Lee and his colleagues [21] Compared patients who received chemotherapy and who had not within 4 weeks of testing positive for COVID-19and they found no increased mortality when analyzed by univariate analysis (27% death rate with chemotherapy vs 29% death rate without recent chemotherapy). Therefore, they did a multivariate analysis with adjustment for age, gender, and comorbidities and found that deaths in patients with COVID-19 who have cancer who had received recent chemotherapy were still no more likely than in those who had not. This analysis had a borderline fit (Hosmer-Lemeshow p=0·048). They also did a forward regression model analysis (Hosmer-Lemeshow p=0·476) with similar findings (odds ratio 1·15 [95% CI 0·79–1·66]; p=0·467).

Similar to our study, The American Society for Transplant and Cellular Therapy, the European Society for Blood and Marrow Transplantation (EBMT), the Worldwide Network for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant.

Research (CIBMTR) continues to update guidelines for the treatment of COVID-19 in this population, their conclusion was including patients who had Allo, Auto, and CAR T therapy were able to recover from COVID-19 infection and mount an antibody response, with similar overall survival to the general hospitalized population.

Poor outcomes were more frequently seen in those with active relapsed disease and with risk factors akin to their noncancer counterparts, such as comorbidities and neutropenia.

Given the potential for prolonging survival and potential cure, it remains critical to safely continue treating patients with cellular therapies during the global pandemic and to determine successful interventions for those early after cellular therapy who remain immunocompromised.

Reduced CD4+ T cells in patients with COVID-19 have been confirmed by **Qin and colleagues [22],** revealing that an immunosuppression feature is pronounced in severe COVID-19 cases. A rapid and well-coordinated innate immune response is the first line of defense against viral infections. CD4+ T cells can enhance the ability of cytotoxic T cells to clear pathogens. However, persistent stimulation by the virus might induce T-cell exhaustion and facilitate host immune response disorders, causing excessive inflammation and even death.

CONCLUSION

Acute immune suppression is done by chemotherapy to worsen the outcome of COVID-19 infection, while chronic immunosuppression had the best outcome in COVID-19 patients even better than the normal population due to loss of immune cell signaling and absent cytokines storm due to chronic T-cell depletion that might occur.

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