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Impact of COVID-19 on Hematologic Disorders: Clinical Insights and Challenges

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ABSTRACT

Introduction: Early studies indicated that patients with cancer had substantially elevated risks of undesirable coronavirus disease-2019 (COVID-19) outcomes, especially higher mortality rates. There are several reports that not all hematological malignancies have a fatality risk. We aim to contribute to the literature by evaluating patients diagnosed with COVID-19 during the pandemic in the field of hematology.

Methods: This single-center, retrospective, cohort study included adult patients (aged ≥18 years) with COVID-19 who had a World Health Organization-defined hematological malignancy or non-neoplastic hematologic disorder and were admitted to İstanbul University, İstanbul Faculty of Medicine between March 2020 and May 2023. The primary outcome was mortality. We also evaluated the outcomes according to the type of hematologic disorder, age, disease status at the time of COVID-19 diagnosis, severity of COVID-19, comorbidities, and vaccination status. Treatment modalities were also collected. Statistical analysis was performed using StataMP 17.

Results: We enrolled 285 patients. The median age was 57 years, and male predominance (55%). Fifty-one (17.89%) patients died. Patients aged ≥65 years were at increased risk of death ($p<0.001$). The mortality rate was significantly higher in patients with lymphoid malignancy, especially those with chronic lymphocytic leukemia (CLL) ($p<0.001$). In the multivariate analysis, the need for anakinra administration, intubation, and COVID-19 progression increased the risk of death.

Conclusion: Hematologic patients are susceptible to COVID-19. Elderly individuals with active hematological disease are particularly at risk. Patients with CLL should be closely monitored. The need for anakinra, intubation, and COVID-19 progression increased the risk of death.

Keywords: Chronic lymphocytic leukemia, hematological malignancy, SARS-CoV-2

Introduction

Numerous challenges were encountered during the first coronavirus disease-2019 (COVID-19) wave in various populations. Physicians play active roles not only as key healthcare providers but also as sources of information and commentators on digital platforms. These shared experiences, documented and published by colleagues, significantly contributed to the development of treatment guidelines.

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was officially identified in March 2020 when the World Health Organization (WHO) declared a pandemic. Among the elderly, patients with malignant disorders were considered the population at the greatest risk of poor COVID-19 outcomes (1). Indeed, studies conducted during early pandemic experiences indicated that cancer had a substantially undesirable impact on COVID-19 outcomes, including higher mortality rates. Lung cancer and hematologic malignancies have the highest probability of serious COVID-19 complications (2,3). Because patients with hematological disorders have very different immune conditions that exhibit heightened vulnerability, more preventative measures and management programs were established during this period. As the pandemic progressively spreads to other countries, consecutive papers have declared that not all hematological malignancies bear the same risk, with varying numbers of patients (4-7).

This study aimed to investigate the impact of COVID-19 on patients with hematological disorders by documenting our single-center experience with a homogenous management approach and providing insights into patient outcomes and management strategies.

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Methods

Clinical and laboratory data, including treatment details and patient outcomes, were obtained from accessing institutional electronic medical records. The data of 285 adult patients diagnosed with COVID-19 between March 2020 and May 2023 from İstanbul University, İstanbul Faculty of Medicine were retrospectively analyzed.

No funding was used in this study, which received approval from the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (approval number: 08, date: 02.04.2021).

Only symptomatic patients were screened. All patients were screened by lung computed tomography (CT) scans and microbiologically by real-time polymerase chain reaction (RT-PCR) testing of nasal and oropharyngeal swab specimens. COVID-19 diagnosis was based mainly on lung imaging. Patients with negative RT-PCR results but diagnosed with COVID-19 based on typical clinical, laboratory, and thoracic CT imaging were also included in the study. According to the WHO's recommendations, COVID-19 illness severity was categorized as mild, moderate, and severe.

Patients: Patients were stratified according to their malignant or benign disorders, progressing to macrophage activating syndrome, experiencing thromboembolic events, necessitating intensive care unit admission, or succumbing to COVID-19.

Treatment strategies: The treatment protocol was based on the National Health Authority protocol, which included the early periods of hydroxychloroquine, azithromycin, and intravenous immunoglobulin (IVIG). Hydroxychloroquine was administered to patients with mild to moderate symptoms who also had comorbidities, while azithromycin was used in the same group if there was suspicion of bacterial superinfection. IVIG was administered to immunosuppressed patients, those with severe inflammatory responses/cytokine storms, or critically ill patients who were unresponsive to other treatments. For some patients, immune plasma was used, which is not routine.

The use of hydroxychloroquine and azithromycin was discontinued following their removal from the treatment guidelines. In a short time, the antiviral agent favipiravir was replaced by molnupiravir. For patients with cytokine storm, steroids were used as the frontline treatment. For steroid-refractory cases, anti-cytokines, such as tocilizumab or anakinra, were used, which were chosen by availability.

All patients received aspirin for a short period with a dipyridamole combination, which was changed to enoxaparin in hospitalized patients. The enoxaparin dose was increased to the therapeutic dose in patients with D-dimer levels >1000 U/mL or documented thromboembolic events.

Statistical Analysis

Continuous variables are presented as medians, and the number of categorical variables is given. The differences between groups were analyzed with X^2 test. Risk factors were evaluated using univariate and multivariate logistic regression models. The primary endpoint was the survival rate of the cohort. We evaluated the outcomes according to hematologic malignancies, age, disease status at the time of COVID-19 diagnosis, administration of monoclonal antibody, COVID-19 severity, comorbidities, and vaccination status. We also evaluated the effects of COVID-19 treatment type, thrombosis occurrence, and oxygenation status on the survival rate. Statistical analysis was performed using StataMP 17.

Results

The data collection encompassed the 3 years of the pandemic with changing management algorithms and intervening vaccination. The latter was not obligatory, and the type of vaccine was chosen according to the patient's preference.

A total of 285 patients' data were evaluated. The median age was 57 years (range: 18-87) with a male predominance (55%). The rate of COVID-19 PCR-positivity was 96%.

The majority of patients (89%) had malignant hematological disease (Figure 1). The most common hematologic disease was multiple myeloma with a ratio of 24% among malignant disorders and immune thrombocytopenic purpura with a ratio of 40% among benign disorders (Table 1). Two patients had prior solid organ transplantation, 62 had blood or bone marrow transplantation, and 43.5% had allogeneic transplantation. In 5.6% of patients, COVID-19 led to a new diagnosis of a hematologic disease.

The comorbid disorders are presented in Figure 2. The most common comorbid association was hypertension, with a frequency of 32%; diabetes mellitus and cardiovascular disorders were the followers, with a frequency of 23% and 19%, respectively.

The severity of COVID-19 was available in 133 patients. Most patients experienced mild COVID-19 severity (59.5%). Severe COVID-19 was infrequent (10.4%) and fatal at 61% ($p<0.001$). The intensive care unit (ICU) was necessary for 38 patients (13.3%), 25 of whom (8.8%) were intubated, and 28 (73.7%) died of COVID-19 ($p<0.001$).

The overall mortality rate was 17.89%. Patients aged 65 years or older were at increased risk of death ($p<0.001$). Among the disorders, patients with lymphoid malignancies had a significantly higher mortality rate compared with those with myeloid malignancies ($p=0.009$).

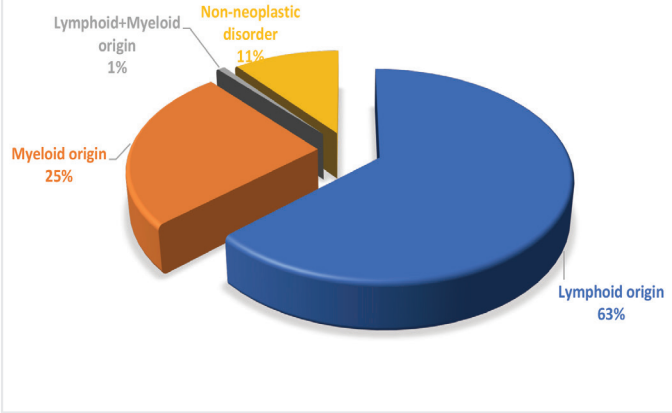

Figure 1. Distribution of hematologic disease among patients with COVID-19

COVID-19: Coronavirus disease-2019

Chronic lymphocytic leukemis (CLL) patient's had the poorest outcomes. Indeed, 11 of the 23 CLL patients died (p<0.001). The variables determined in the multivariate analysis are presented in Table 2 with the hazard ratios, p-values, and confidence intervals.

Table 1. The proportions of hematological disorders

Neoplastic hematologic diagnosis	n	Benign hematologic diagnosis	n
	254		31
Multiple myeloma	56	Immune thrombocytopenic purpura	12
Diffuse large B-cell lymphoma	24	Thrombotic thrombocytopenic purpura	5
Hodgkin lymphoma	24	Aplastic anemia	4
Chronic lymphocytic leukemia	23	Thalassemia major	4
Acute myeloid leukemia	21	PNH	3
Chronic myeloid leukemia	15	Autoimmune hemolytic anemia	2
Myelodysplastic syndrome	11	PNH + aplastic anemia	1
Follicular lymphoma	8	Immune neutropenia	1
B-cell ALL	6	Aceruloplasminemia	1
Primary myelofibrosis	6	Protein S deficiency + factor V Leiden deficiency	1
Essential thrombocythemia	6		
Low-grade NHL	5		
Mantle cell lymphoma	5		
T-cell NHL	5		
Polycythemia vera	4		
Primary central nervous system lymphoma	4		
Waldenstrom macroglobulinemia	3		
Secondary myelofibrosis	3		
T-cell ALL	3		
Hairy cell leukemia	3		
Chronic myelomonocytic leukemia	2		
Plasma cell leukemia	2		
Monoclonal gammopathy unknown significance	2		
Cutaneous B-cell lymphoma	2		
Granulocytic sarcoma	1		
Mycosis fungoides	1		
Systemic mastocytosis + marginal zone lymphoma	1		
Al amyloidosis	1		
Burkitt lymphoma	1		
Chronic myeloproliferative neoplasia	1		
Erdheim Chester disease	1		
Langerhans cell histiocytosis	1		

PNH: Paroxysmal nocturnal hemoglobinuria, ALL: Acute lymphoblastic leukemia, NHL: Non-Hodgkin lymphoma

Among thromboembolic events and coagulopathy, 10 of the 20 patients developed arterial thrombosis, 9 of the 21 patients developed venous thrombosis, 8 of the 17 patients had thrombotic microangiopathic anemia, and 9 of the 18 patients experienced disseminated intravascular coagulation died (p<0.001 for each).

Among the cytokine storm-developed patients, 20 of 81 patients died during steroid (p<0.001) and 12 of the 25 patients died during anakinra use (p=0.059).

Discussion

Since 2019, when SARS-CoV-2 originated in Wuhan, China, waves of death have occurred in nearly all countries. The initial defense strategy was to recognize the disease, implement strict protective measures, and provide appropriate treatment. Subsequently, vaccine discovery and vaccination policies were the next steps. In every stage of progress, a group of people were found to be more prone to the disease and to experience more severe forms than those initially identified. Patients with hematologic malignancies were one such group. Hematologists from various countries, through either single-center or multicenter studies,

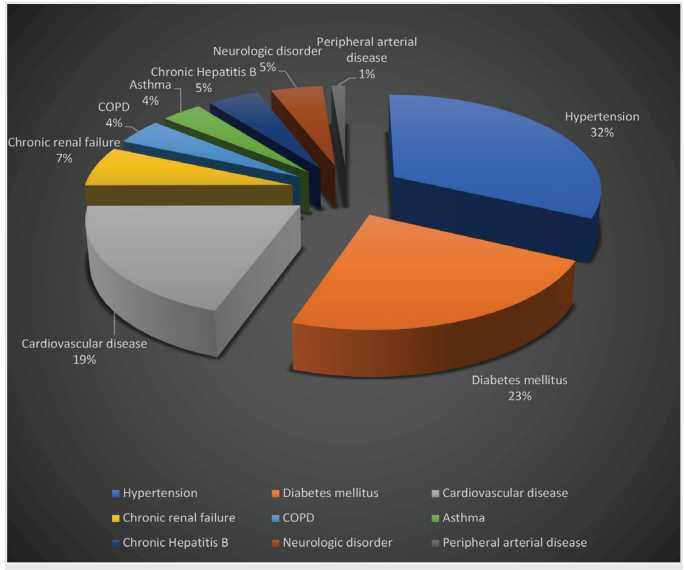

Figure 2. The associated comorbid conditions
COPD: Chronic obstructive pulmonary disease

Table 2. Hazard ratios with age, lymphoid malignancy, CLL diagnosis, disease status, severity of COVID-19, and vaccination status

Variable	HR	p	95% CI
Age ≥65	2.579937	<0.001	1.972285-6.498022
Lymphoid malignancy	2.0122485	0.051	0.9970529-4.062067
CLL diagnosis	3.533434	0.001	1.730691-7.213973
Active disease	1.782202	0.087	0.9189597-3.456348
COVID-19 severity	5.159932	<0.001	2.564944-10.38031
Unvaccinated	6.154189	<0.001	2.975884-12.72699

CLL: Chronic lymphocytic leukemia, COVID-19: Coronavirus disease-2019, HR: Hazard ratio, CI: Confidence interval

have published their experiences to define common management protocols and guidelines (8-16).

Our study primarily aimed to delineate the fatality rate among patients with various hematologic disorders by utilizing a highly homogenous team of healthcare workers and physicians. Our analysis revealed an overall mortality rate of 17.89%, which was lower than that of previously reported early experiences. However, a cohort study in Wuhan, China, covering the first month of 2020, reported a case fatality rate of 62% (17). This investigation included hospitalized patients diagnosed with hematologic malignancies who subsequently contracted COVID-19. The high fatality rate may be attributable to early experiences and the inclusion of already hospitalized patients.

Another study from the United Kingdom focused on hospitalized patients with hematologic malignancies who developed SARS-CoV-2 infection. The results revealed an overall preliminary case fatality rate of 51.5%, with most patients aged 70 years. An elevated fatality rate was observed during the early period of the pandemic, and the predominance of elderly patients, a significant risk factor for COVID-19, likely contributed to this outcome (18). The increased vulnerability of older adults to infection may stem from reduced immune function and vaccine effectiveness. Additionally, various other factors contribute to the increased risk of infections in this population, such as malnutrition, comorbidities, and weakened mucosal defenses, etc. (19).

It is well-established that various states of immune deficiency increase the risk of respiratory tract infection and poor outcomes. Patients with hematologic malignancies are particularly immunocompromised because of bone marrow infiltration and/or the type of treatment they receive, leading to conditions such as lymphopenia, neutropenia, or immune dysfunction. In the context of hematopoietic stem cell transplantation, treatments-particularly the use of corticosteroids or immunosuppressive medications-further exacerbate immune deficits. These factors contribute to the high-risk status of patients with CLL, who, as shown in our study, have significantly worse outcomes.

In our study, the primary endpoint was not hospitalization requirement, as this parameter may vary depending on the physician's initiatives and the social characteristics of the patients. However, ICU admission was a more descriptive and restrictive endpoint. We found that 13.3% of patients required ICU care, and 8.8% of these patients were intubated. A Turkish retrospective case-control study conducted during the early pandemic period reported an ICU admission rate of 22% among 156 immunocompromised patients, which was higher than in our cohort. We believe that this difference is primarily attributable to the timing of the two studies. Our study spanned the three years following the pandemic declaration, during which vaccines against SARS-CoV-2 were developed and widely administered, fundamentally changing game players (20). The difference in ICU admission rates between our study and earlier reports can be attributed to the widespread availability and administration of vaccines during our study period, which played a crucial role in reducing severe cases and mortality.

General studies involving patients with hematologic malignancies who developed COVID-19 have consistently found that mortality rates are often higher than those in otherwise healthy populations (21). In our study, the mortality rate of patients with hematologic malignancies who developed COVID-19 was 17.8%. Elderly individuals and those with lymphoid malignancies were identified as being at higher risk.

Patients with CLL exhibit intrinsic impairment of both humoral and cell-mediated immunity, which is associated with primary pathology. These conditions include hypogammaglobulinemia, disruption of T-cell subsets, and deficiencies in complement activity and neutrophil and monocyte function. Immune function is further compromised by therapy-induced immunosuppression (22). A multicenter study involving multiple countries reported high mortality rates in both watch-and-wait and treated CLL patients, with a case fatality rate of 33% among those admitted with COVID-19 (15). We also documented that outcomes for CLL patients were the worst, as 47.8% of the CLL patients succumbed to COVID-19.

A large-scale study involving 3,801 patients with hematologic malignancies reported a mortality rate of 31%. In contrast, this study found the highest mortality rate among patients with AML or myelodysplastic syndrome, reaching 40% (23). A research study assessing postvaccination risk factors has demonstrated that pre-existing medical conditions constitute a risk factor for a diminished cellular immune response following the administration of the third dose of the SARS-CoV-2 vaccine, and chemotherapy builds up a risky basis for impaired humoral immune response (24). However, in our cohort, the mortality rate was higher in patients with lymphoid malignancies.

Study Limitations

The limitations of our study include the relatively small sample size due to the single-center design, heterogeneity of the diseases, and partial data loss resulting from the retrospective design. Although we initially applied a consistent treatment approach at our center, the evolving nature of the pandemic has led to changes in treatment protocols worldwide. As a result, our patient care practices were also adapted based on the latest available literature.

Conclusion

In conclusion, although mortality was significantly higher in the unvaccinated group in our cohort, there is a clear need for documentation of vaccination efficacy. Clinically, several patients contracted SARS-CoV-2 during treatment, and viral clearance required time. However, the absence of COVID-19 severity resembling the initial phase of the pandemic may be an indirect indicator of the effectiveness of vaccines.

Ethics

Ethics Committee Approval: The ethics committee approved the study by the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (approval number: 08, date: 02.04.2021).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions: Surgical and Medical Practices - S.E., M.M., İ.Y.H., M.N.Y., M.N.; Concept - İ.Y.H., M.N.Y., M.N., S.K.B.; Design - M.Ö., S.K.B.; Data Collection or Processing - S.E., S.S.E., M.M., İ.Y.H., M.N.Y., M.N.; Analysis or Interpretation - S.E., M.Ö., S.K.B.; Literature Search - S.E., S.S.E., M.M., S.K.B.; Writing - S.E., S.K.B.

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