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Clinical characteristics and mortality of patients with hematologic malignancies and COVID-19: a systematic review

J.S. KIM[1], K.H. LEE[2], G.E. KIM[3], S. KIM[3], J.W. YANG[1], H. LI[4], S.H. HONG[3,5], R.A. GHAYDA[5,6], A. KRONBICHLER[7], A. KOYANAGI[8,9], L. JACOB[8,10], J.I. SHIN[2], L. SMITH[11]

[1]Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[2]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[3]Yonsei University College of Medicine, Seoul, Republic of Korea
[4]University of Florida College of Medicine, Gainesville, FL, USA
[5]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[6]Division of Urology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[7]Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria
[8]Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, 08830 Barcelona, Spain
[9]ICREA, Pg. Lluis Companys 23, Barcelona, Spain
[10]Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
[11]The Cambridge Centre for Sport and Exercise Science, Anglia Ruskin University, Cambridge, UK

Abstract. – OBJECTIVE: Hematologic cancer patients with Coronavirus Disease 2019 (COVID-19) tend to have a more serious disease course than observed in the general population. Herein, we comprehensively reviewed existing literature and analyzed clinical characteristics and mortality of patients with hematologic malignancies and COVID-19.

MATERIALS AND METHODS: Through searching PubMed until June 03, 2020, we identified 16 relevant case studies (33 cases) from a total of 45 studies that have reported on patients with COVID-19 and hematologic malignancies. We investigated the clinical and laboratory characteristics including type of hematologic malignancies, initial symptoms, laboratory findings, and clinical outcomes. Then, we compared those characteristics and outcomes of patients with hematologic malignancies and COVID-19 to the general population infected with COVID-19.

RESULTS: The median age was 66-year-old. Chronic lymphocytic leukemia was the most common type of hematologic malignancy (39.4%). Fever was the most common symptom (75.9%). Most patients had normal leukocyte counts (55.6%), lymphocytosis (45.4%), and normal platelet counts (68.8%). In comparison to patients with COVID-19 without underlying hematologic malignancies, dyspnea was more prevalent (45.0 *vs.* 24.9%, p=0.025). Leukocytosis (38.9 *vs.* 9.8%, p=0.001), lymphocytosis (45.4 vs. 8.2%, p=0.001), and thrombocytopenia (31.3 vs. 11.4%, p=0.036) were significantly more prevalent and lymphopenia (18.2 *vs.* 57.4%, p=0.012) less prevalent in patients with hematologic malignancies. There were no clinical and laboratory characteristics predicting mortality in patients with hematologic malignancies. Mortality was much higher in patients with hematologic malignancies compared to those without this condition (40.0 vs. 3.6%, p<0.001).

CONCLUSIONS: Co-occurrence of hematologic malignancies and COVID-19 is rare. However, due to the high mortality rate from COVID-19 in this vulnerable population, further investigation on tailored treatment and management is required.

Key Words:
Coronavirus, Hematologic neoplasms, Mortality.

Introduction

The novel coronavirus known as severe acute respiratory syndrome coronavirus 2

Corresponding Authors: Keum Hwa Lee, MD; e-mail: AZSAGM@yuhs.ac
Jae Il Shin, MD, Ph.D; e-mail: shinji@yuhs.ac

(SARS-CoV-2), causing coronavirus disease-19 (COVID-19), has been rapidly spreading throughout the world since the first local outbreak in December 2019. While many people with COVID-19 are asymptomatic or only have cold symptoms, such as fever and cough, some have severe clinical manifestations such as dyspnea, respiratory failure, and multiple organ failure, leading to death[1]. Several studies[2,3] have suggested that this vulnerability to severe COVID-19 is associated with problems with genetic or type-1 interferons responses. Nevertheless, many studies have still reported that older patients generally have poor prognosis in the clinical course of COVID-19[4].

Guan et al[5] have revealed that COVID-19 patients with comorbidities have also poor clinical outcomes. Patients with hypertension, diabetes mellitus, and chronic obstructive pulmonary disease had a higher risk of exacerbation, and those with cardiovascular disease and cerebrovascular disease had more severe COVID-19 (i.e., admission to the intensive care unit requiring mechanical ventilation, or death[6]).

Cancer is rare but a clinically important comorbidity among COVID-19 patients as those with cancer are more vulnerable to infection due to their systemic immunosuppressive state caused by malignancy itself or anticancer treatments[7]. Liang et al[8] have emphasized that cancer patients with COVID-19 have a higher risk of severe events and higher mortality than individuals without cancer. However, to our knowledge, previous meta-analyses on cancer and COVID-19 mainly focused on solid tumors, not hematologic malignancies. Only few studies[9,10] have been reported on patients with hematologic malignancies and these have been limited by a small number of cases. Due to the immunodeficiency state of patients with hematologic malignancies such as leukemia, lymphoma, and multiple myeloma[11], more research is needed to evaluate the clinical relationship between hematologic malignancies and COVID-19. To the best of our knowledge, there have been no comprehensive analyses of clinical characteristics and mortality in hematologic cancer patients with COVID-19. In this study, we aim to analyze the clinical and laboratory characteristics comprehensively, and mortality from existing case reports of hematologic malignancies with COVID-19, and to show the differences between patients with COVID-19 without hematologic malignancies for the first time.

Materials and Methods

Search Strategy

We searched PubMed for case reports and series of COVID-19 patients with concomitant hematologic malignancies, including leukemia, lymphoma, and multiple myeloma, published until June 03, 2020. The search terms were as follows: ("COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "novel coronavirus 2019") AND ("leukemia" OR "lymphoma" OR "multiple myeloma"). Two of the authors (GEK and SK) screened the titles, abstracts, and full texts of the articles.

We included the following studies: (1) patients with laboratory or clinically confirmed COVID-19; (2) described concomitant hematologic malignancy in infected patients. The exclusion criteria were as follows: (1) studies not related to COVID-19 infection and hematologic malignancies; (2) review articles, protocols, guidelines, consensus, and comments; (3) full text of the article is inaccessible. Two reviewers (GEK and SK) separately executed the initial search, which yielded 45 articles published until June 03, 2020. This systematic review is reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[12]. We excluded 29 articles after reviewing the abstracts and full texts according to the exclusion criteria stated above: 3 were irrelevant, 10 were review articles, 13 were recommendations, and 2 were inaccessible. Finally, 16 articles that met the inclusion criteria for this systematic review were identified (a total of 33 cases). The detailed process of article selection is presented in Figure 1.

Data Extraction

From the 16 articles, two reviewers (GEK and SK) separately screened the titles, abstracts, and full texts to determine if they met the inclusion criteria. Then, two reviewers (GEK and SK) extracted the data independently and organized the information as follows: 1) study characteristics (journal title, author names, year of publication), 2) population characteristics (patient age and sex, concomitant hematologic malignancies), 3) variables of interest (initial symptoms, laboratory findings, and clinical outcomes).

Data Analysis

The data extracted from the articles are presented in **Supplementary Table I**. We or-

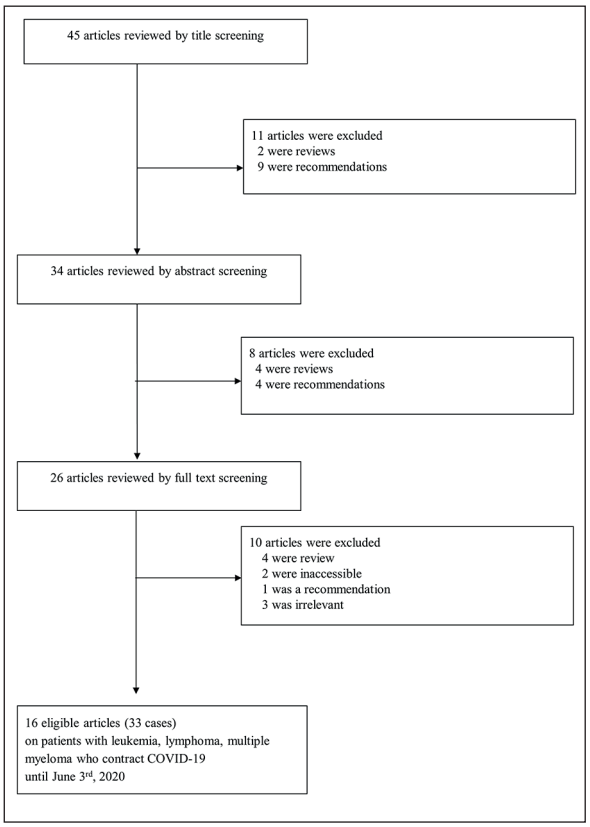

Figure 1. Flow chart of literature search.

ganized the information, including the patient age and sex, concomitant hematologic malignancies, initial symptoms, laboratory findings, and clinical outcomes. Then, we compared the clinical characteristics and mortality of patients with hematologic malignancies and the general population infected with COVID-19[13]. We used the χ^2 test or Fisher's exact test as a statistical method, Graphpad InStat 3 was used for statistical analyses.

Results

Baseline Characteristics of Patients with Hematologic Malignancies and COVID-19

In our study, 16 eligible articles were retrieved by the literature search, from which 33 cases of hematologic malignancies and COVID-19 were collected. The median age was 66 years. Eighteen male patients (54.5%) and 15 females (45.5%) were included (Table I). Chronic lymphocytic leukemia (CLL) was the most common type of hematologic malignancy (39.4%), followed by multiple myeloma (MM) (33.3%). Others were acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin lymphoma, and Hodgkin lymphoma, all disease entities with fewer than 4 patients (Table I).

Initial Symptoms and Laboratory Features of Patients with Hematologic Malignancies and COVID-19

The most common symptoms were fever (75.9%), similar to that in patients without hematologic malignancies (83.3%). Next, cough was common (65.5%), followed by dyspnea (45.0%) and sore throat (14.0%) (Table II). In laboratory tests, a large proportion of patients had normal white blood cell counts (55.6%) and lymphocytosis (45.4%). Normal platelet counts were present in 68.8%. Nevertheless, most patients showed elevated levels of C-reactive protein (86.4%) (Table III).

Table I. Baseline characteristics of patients with hematologic malignancies and COVID-19.

Age (years)	No. patients (%) (N = 33)
< 10	1 (3.0)
10-29	2 (6.1)
30-49	3 (9.1)
50-59	4 (12.1)
60-69	8 (24.2)
70-79	10 (30.3)
> 80	5 (15.2)
Median (min, max)	66 (4, 88)
Sex	
Male	18 (54.5)
Female	15 (45.5)
Types	
CLL	13 (39.4)
MM	11 (33.3)
NHL	3 (9.1)
ALL	2 (6.1)
AML	2 (6.1)
CML	1 (3.0)
HL	1 (3.0)

CLL: chronic lymphocytic leukemia, MM: multiple myeloma, NHL: non-Hodgkin lymphoma, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, HL: Hodgkin lymphoma.

Table II. Initial symptoms and comparisons between recovery and death groups in patients with hematologic malignancies and COVID-19.

	Symptoms (N = 29) No. (%)	Recovery (N = 15) No. (%)	Death (N = 11) No. (%)	*p*-value
Fever	22 (75.9)	12 (80.0)	9 (81.8)	1.000
Cough	19 (65.5)	11 (73.3)	5 (45.5)	0.228
Dyspnea	13 (45.0)	5 (33.3)	7 (63.6)	0.232
Sore throat	4 (14.0)	3 (20.0)	1 (9.1)	0.613
Others*	13 (45.0)	–	–	–

*chest tightness (n=1), fatigue (n=8), epistaxis (n=1), chills (n=1), abdominal pain (n=1), vomiting (n=1), nausea (n=1), diarrhea (n=1), body aches (n=1), coryzal symptoms (n=1), ageusia (n=1), anosmia (n=1).

Comparisons of Clinical Characteristics According to Clinical Outcome of Patients with Hematologic Malignancies and COVID-19

Out of a total of 30 cases, excluding 3 cases that did not report clinical outcomes, 12 deaths were observed which corresponds to a fatality rate of 40%, while the other 18 patients recovered from COVID-19. The recovery rate was 60% (18 out of a total of 30 patients). In comparison with clinical characteristics according to clinical outcomes, there were no significant differences between recovery and death groups (Table II and III).

Comparisons of Clinical Characteristics between COVID-19 Patients with and without Hematologic Malignancies

The median age of patients from the case studies reporting hematologic malignancies and COVID-19 was 66 years (min 4, max 88), and thus, older than that of patients without hema-

Table III. Laboratory findings and comparisons between recovery and death groups in patients with hematologic malignancies and COVID-19.

	Laboratory findings No. (%)	Recovery No. (%)	Death No. (%)	*p*-value
WBC count	**N = 18**	**N = 9**	**N = 8**	
Leukocytosis (> 15 000/μL)	7 (38.9)	2 (22.2)	5 (62.5)	0.153
Leukopenia (< 4 000/μL)	1 (5.5)	0 (0.0)	1 (12.5)	0.470
Abnormal (> 15 000 or < 4 000/μL)	8 (44.4)	2 (22.2)	6 (75)	0.056
Normal (4 000-15 000/μL)	10 (55.6)	7 (77.8)	2 (25)	0.056
Lymphocyte count	**N = 11**	**N = 4**	**N=6**	
Lymphocytosis (> 4 800/μL)	5 (45.4)	1 (25)	4 (66.6)	0.523
Lymphopenia (< 1 000/μL)	2 (18.2)	1 (25)	1 (16.7)	1.000
Abnormal (> 4 800 or <1 000/μL)	7 (63.6)	2 (50)	5 (83.3)	0.500
Normal (1 000-4 800/μL)	4 (36.4)	2 (50)	1 (16.7)	0.500
Platelet count	**N = 16**	**N = 8**	**N = 7**	
Thrombocytopenia (< 150 000/μL)	5 (31.2)	2 (25)	2 (28.6)	1.000
Normal (150 000-450 000/μL)	11 (68.8)	6 (75)	5 (71.4)	1.000
CRP	**N = 22**	**N = 13**	**N = 7**	
Elevated (> 8 mg/L)	19 (86.4)	11 (84.6)	6 (85.7)	1.000
Normal (< 8 mg/L)	3 (13.6)	2 (15.4)	1 (14.3)	1.000

WBC: white blood cell, CRP: C-reactive protein.

tologic malignancies (median 41, min 39, max 72). The proportion of initial symptoms were comparable, but dyspnea was significantly more frequently reported in patients with hematologic malignancies (45.0 *vs.* 24.9%, p=0.025) (Table IV). Among laboratory tests, leukocytosis (38.9 *vs.* 9.8%, p=0.001), lymphocytosis (45.4 *vs.* 8.2%, p=0.001), and thrombocytopenia (31.3 *vs.* 11.4%, p=0.036) were more frequent in patients with hematologic malignancies, while lymphopenia (18.2 *vs.* 57.4%, p=0.012) was significantly less frequent (Table IV). Among clinical outcomes, the mortality rate of patients with hematologic malignancies contracting COVID-19 was significantly higher (40.0 *vs.* 3.6%, p<0.001) (Table IV).

Discussion

Older age and comorbid diseases such as diabetes, chronic pulmonary disease, and cardiovascular disease are important risk factors for poor outcomes of COVID-19[6,14,15]. Malignancies are also considered a risk factor for severe COVID-19[5], but the true impact appears to be hidden due to low prevalence. According to epidemiologic studies of COVID-19, the prevalence of malignancy was estimated to be about 1~2%[16-18], with the most common malignancy being lung cancer[8]. In the COVID-19 pandemic, cancer patients have several important issues. The first issue is the immunosuppressive state of cancer patients. Cancer patients have a significantly lower level of immunity due to the malignancy itself or chemotherapy[11]. They are vulnerable to infection and have a worse COVID-19 disease course and a higher mortality rate. The second issue is that cancer patients are often missing the scheduled treatment approaches due to the risk of COVID-19[18]. They often cannot receive proper treatments because of limited medical resources focused on the COVID-19 pandemic, and deliberately delay the treatment plan due to increased risk of COVID-19 by chemotherapy[19]. Ultimately, cancer patients comprise a very small proportion of COVID-19 cases, but in reality, they are at high risk, so special attention is required.

Hematologic malignancy has many clinical issues in the COVID-19 pandemic[10,20-22]. Unlike solid tumors, hematologic malignancy has more direct and negative effects on immunity as normal immune cells, which form the basic immune system, are replaced or inhibited by non-functional tumor cells[11]. The immune dysfunction increases susceptibility to COVID-19 and makes the clinical course serious in hematologic cancer patients[9]. In addition, the treatments of hematologic malignancies include a variety of potent immunosuppression, including hematopoietic stem cell transplantation. As a result, many hematologic cancer patients are forced to postpone timely treatment in the COVID-19 pandemic[21,23].

In our study, the most common hematologic malignancy was CLL, followed by MM. The two diseases accounted for more than two-thirds of hematologic malignancies. In contrast,

Table IV. Comparisons of clinical and laboratory features with the patients without hematologic malignancies

Initial symptoms	Patients with (N = 33) *vs.* without (N = 3600) hematologic malignancies (%)	*p*-value
Fever	75.9 *vs.* 83.3	0.412
Cough	65.5 *vs.* 60.3	0.704
Dyspnea	45.0 *vs.* 24.9	0.025*
Sore throat	14.0 *vs.* 12.3	0.810
Laboratory findings		
Leukocytosis	38.9 *vs.* 9.8	0.001*
Leukopenia	5.6 *vs.* 20.1	0.214
Lymphocytosis	45.4 *vs.* 8.2	0.001*
Lymphopenia	18.2 *vs.* 57.4	0.012*
Thrombocytopenia	31.3 *vs.* 11.4	0.036*
Elevated CRP	86.4 *vs.* 68.6	0.102
Mortality		
Death	40.0 *vs.* 3.6	< 0.001*

CRP: C-reactive protein, *p<0.05.

one recent retrospective study of 39 patients with hematologic malignancies and COVID-19 reported lymphoma as the most common tumor[24]. However, we believe that the study has a limitation as a single center retrospective study in which the conclusions are not general. According to the Haematological Malignancy Research Network, which is a United Kingdom population-based patient cohort, CLL, and MM in the general population also show a higher prevalence compared to other types[25]. Thus, the high prevalence of CLL and MM among patients with COVID-19 seems to be attributed to such a pattern of prevalence in the general population. In particular, it is noteworthy that lymphoma has a high prevalence in the general population, while a few cases with COVID-19 have been reported to date. Drawing conclusions on these preliminary reports is speculative, but we assume that the difference of negative effects on immunity according to the type of disease between leukemia and lymphoma may result in the difference of reported cases.

In patients with hematologic malignancies and COVID-19, the proportion of mild symptoms, such as fever, cough, and sore throat did not differ from the reported frequency in without hematologic malignancies. However, patients with hematologic malignancies had a larger proportion of dyspnea, suggesting that this patient group may have a more serious clinical course of COVID-19. Chen et al[26] demonstrated that various hematologic indices predict in-hospital death of a person with COVID-19. In this study, a specific range of the neutrophil-to-lymphocyte ratio, a decrease in platelet count, an increase in activated partial thromboplastin time, and D-dimer were associated with increased in-hospital death. In our study, hematologic cancer patients had high rates of leukocytosis and lymphocytosis, while a low rate of lymphopenia was observed. The findings, such as leukocytosis and lymphocytosis, are thought to reflect essential clinical features of abnormal proliferation of lymphoid and myeloid tumor cells in hematologic malignancies. Jin et al[10] emphasized that attention should be paid to the possibility that such laboratory features in hematologic malignancies may cause misdiagnosis by masking COVID-19, as continuous hematologic test abnormalities erase doubts about abnormal results caused by infection. Lymphopenia is a typical finding of COVID-19[1,4,13], and lymphopenia is related with a severe disease course and a potential predictor of poor prognosis[27,28]. However, absence of lymphopenia should not be considered as a sign of a mild disease form in patients with hematologic malignancies. Thrombocytopenia is usually accompanied by diffuse intravascular coagulation and represents a serious condition in systemic infection. Thus, the high proportion of thrombocytopenia in patients with hematologic malignancies is in line with a severe form of COVID-19. Taken together, the laboratory constellation might be misleading as patients with hematologic malignancies have typically leukocytosis and do not necessarily present with lymphopenia. We argue that monitoring the platelet count may be more informative about disease severity. This, however, needs to be observed in larger studies, which can be expected in the near future.

Our study indicated the very high mortality of the patients with hematologic malignancies compared to those without them, while there were no clinical and laboratory characteristics that were associated with clinical outcome. In this respect, a recent retrospective cohort study that involved a total of 536 patients with hematologic malignancies contracting COVID-19 from 66 hematology units, still showed the high standardized mortality ratio when compared with general population with COVID-19 as our study results. Moreover, the study demonstrated that older age, progressive disease, acute myeloid leukemia, non-Hodgkin lymphoma, plasma cell neoplasms, and severe COVID-19 predicted poor overall survival[29].

It is important to interpret findings from the present study in light of its limitations. First, the small number of patients with hematologic malignancies and COVID-19 limits the generalizability of our results. Nevertheless, we do not believe that the number of these subjects is small enough to reduce the credibility of the study. Other case studies except for a recent cohort study in Italy also included a small number of patients due to low incidence of hematologic malignancy. In addition, a recent large scale cohort study in Italy provided a valuable insight on risk factors for clinical outcome, while it could not show the details of clinical and laboratory characteristics as case studies including ours. Another limitation of our study is that the meta-analysis study of COVID-19, which served as a reference group, might include the patients with hematologic malignancies because some studies might not have reported pre-existing severe conditions such as hematologic malignancies. Nevertheless, in the meta-analysis study, the inclusion rate of malig-

nancy might be very low at 1%[13], and most are thought to be solid tumors, such as lung cancer[8]. Thus, it is unlikely that this limitation had a substantial impact on our presented results. Finally, despite our efforts, some case reports are continually being added, and our analysis may be limited in that respect. Nevertheless, our meta-analysis provides consistent and universal results for clinical characteristics by analyzing heterogeneous individual case studies in a comprehensive way. To the best of our knowledge, we performed for the first time a comparative analysis with the inclusion of a recent meta-analysis study reporting COVID-19 in the general population. Therefore, we believe that our study provides meaningful results for patients with hematologic malignancies.

Conclusions

The present study shows that patients with hematologic malignancies are at high risk of severe form of COVID-19, given the poor outcome of cases reported to date. It further implies that laboratory results, including typical leukocytosis, absence of lymphopenia, and a higher percentage of thrombocytopenia are different compared to patients without hematologic malignancies and should be interpreted with caution. Further studies are necessary to understand not only specific features of COVID-19 in patients with underlying hematologic malignancies but also to improve the survival rate of this heterogeneous group of patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

JSK, KHL, and JIS designed this study. GEK, SK, and KHL collected data. KHL and JSK did the analysis. GEK, SK, and JSK wrote the draft of the manuscript. JWY, HL, SHH, RAG, A. Kronbichler, A. Koyanagi, LJ and LS reviewed and edited the draft. JWY, HL, SHH, RAG, A. Kronbichler, A. Koyanagi, LJ and LS gave critical comments on the manuscript draft. All authors had full access to all the study data. All authors reviewed, wrote, and approved the final version. The corresponding author, KHL and JIS had ultimate responsibility for the decision to submit for publication.

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