Comorbidities and mortality rate in COVID-19 patients with hematological malignancies: A systematic review and meta-analysis

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Abstract
Introduction: The global pandemic of coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It seems that there is an association between blood cancer and an increased risk of severe COVID-19. This study aimed to review the literature reporting the COVID-19 outcomes in patients with hematological malignancies.

Material and methods: In this systematic review and meta-analysis, Pubmed, Embase, and Web of Science databases were searched using the following keywords: COVID-19, SARS-CoV-2, blood cancer, myeloma, lymphoma, and leukemia. All the published articles in English from January 1, 2019, until March 10, 2021 were collected and evaluated.

Results: In total, 53 studies with 2395 patients were included based on inclusion criteria. Most of these studies took place in Spain (14.81%), followed by the USA (11.11%), China (9.26%), and the UK (9.26%). More than half of COVID-19 patients with hematological malignancy were male (56.73%). Oxygen therapy played an important role in COVID-19 treatment. Moreover, anticoagulant therapies such as enoxaparin and heparin were two great assists for these patients. Fever (74.24%), cough (67.64%), and fatigue (53.19%) were the most reported clinical manifestations. In addition, hypertension and dyslipidemia were the most common comorbidities. The mortality rate due to COVID-19 in patients with hematological malignancies was 21.34%.

Conclusion: This study demonstrated that hematologic cancer patients were more susceptible to a severe COVID-19 than patients without blood cancer. Thus, the management of COVID-19 in these patients requires much more attention, and their screening should be performed regularly.

KEYWORDS
COVID-19, leukemia, lymphoma, myeloma, review
1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the current global pandemic of coronavirus disease 2019 (COVID-19). Although most patients with COVID-19 have mild symptoms, some have more severe manifestations. Recent findings have suggested an association between cancer and an increased risk of developing severe symptoms of COVID-19. Dai et al. reported that about 39% of the COVID-19 patients with cancer had severe events such as intensive care unit admission, the need for mechanical ventilation, and even death. They showed that only 8% of the COVID-19 patients without cancer had those severe symptoms. In addition, hematologic cancer patients with COVID-19 had a high frequency of severe events like a higher mortality rate and a more severe COVID-19 course. The immune system dysfunction is one of the main reasons that confirm patients with hematological malignancies are more vulnerable. Moreover, anti-cancer therapies such as chemotherapy, radiotherapy, and immunosuppressive drugs worsen the condition of these patients. There are a limited number of studies on the prevalence of comorbidities and mortality rate in COVID-19 patients with hematological malignancies. Therefore, in this systematic review and meta-analysis, we will comprehensively review the available published literatures reporting the COVID-19 outcomes and underlying diseases in patients with hematological malignancies from around the world.

2 | MATERIALS AND METHODS

This study was performed following the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statements.9

2.1 | Search strategy

The Pubmed/Medline, Embase, and Web of Science databases, from January 1, 2019, until March 10, 2021, were searched to collect the potentially relevant articles reporting COVID-19 disease in patients with hematological malignancies. The search was limited solely to publications in English.

The following keywords or Medical Subject Headings (MESH) terms were used in text, title, or abstract with the help of Boolean operators (“and,” “or”): “COVID-19,” “severe acute respiratory syndrome coronavirus 2,” “SARS-CoV-2,” “nCoV disease,” “2019-nCoV,” “coronavirus disease 2019,” “bone marrow cancer,” “blood cancer,” “myeloma,” “lymphoma,” “Waldenstrom macroglobulinemia,” “leukemia,” “hematological malignancy,” “myelodysplastic syndrome,” and “myeloproliferative disorder.”

2.2 | Study selection

All the articles reporting COVID-19 positive patients with at least one type of hematological malignancies were included. In other words, patients with blood cancer infected with the SARS-CoV-2 were enrolled in the study. The allogeneic stem cell transplantation patients were included as well. According to World Health Organization (WHO) guidelines, COVID-19 cases are defined as patients whose reverse transcription-polymerase chain reaction (RT-PCR) is positive. Duplicate publications, narrative reviews, meta-analyses, systematic reviews, editorials, correspondences, guidelines, articles published in languages other than English, and publications without enough data or available only in abstract form were also excluded. The included studies were screened in two stages for eligibility. First, title/abstract screening was done, and then, the full text of those that had the inclusion criteria was retrieved. It is worth noting that although we reviewed case-report articles to evaluate some variables, only research articles and case series were included for meta-analysis.

2.3 | Data extraction

The extracted data included the first author’s name, country of the study, published time, type of study, number of patients, median age, gender, hematological malignancy type, blood cancer therapy, the median duration of blood cancer, COVID-19 diagnosis method, COVID-19 therapy, clinical manifestations, laboratory findings, comorbidities, and outcome. Two authors independently applied the inclusion criteria to the potentially relevant article, and discrepancies between the authors were resolved by consensus discussion.

2.4 | Quality assessment

The quality assessment of the studies was carried out through the critical appraisal checklist provided by the Joanna Briggs Institute (JBI).10

2.5 | Meta-analysis

Data were analyzed using STATA software, version 17.0. The fixed-effects model and random-effects model were used to compute pooled estimates of the relative risk. The heterogeneity was quantified by the Cochran Q statistic and I² statistical methods. The p-value < .05 was considered statistically significant.11

3 | RESULTS

3.1 | Characteristics of included studies

Initially, a total of 1169 articles were collected from databases. After removing the duplicates, 704 studies remained. In the screening phase, 548 of them were excluded through the title and abstract
evaluation. Out of these studies, 53 met the inclusion pellucid criteria based on the full-text screening. At the final stage, 15 eligible articles were included in the meta-analysis (Figure 1). Characteristics of the selected articles are summarized in Table 1. Most of the studies took place in Spain (8/53, 14.81%), followed by the United States (6/53, 11.11%), China (5/53, 9.26%), and the United Kingdom (5/53, 9.26%).

3.2 | Demographic, clinical and laboratory findings

The demographic information, clinical features, and laboratory findings in COVID-19 patients with hematological malignancies are shown in Tables 2 and 3. The results of laboratory data showed that ALT, AST, CRP, and LDH tests have increased in COVID-19 patients with hematological malignancies. However, hemoglobin level, platelet count, lymphocyte count, and RBC decreased in these patients. The majority of patients were male (56.73%). Fever (74.24%), cough (67.64%), and fatigue (53.19%) were the most common clinical manifestations among the included patients.

3.3 | Treatments for COVID-19 and hematological malignancies

The treatment options for COVID-19 patients with hematological malignancies are summarized in Tables 2 and 3. Hydroxychloroquine (69.3%), oxygen therapy (65.3%), and anticoagulant therapies (64.0%) such as enoxaparin and heparin were the most administered treatments options for COVID-19. On the contrary, proteasome inhibitors (30.71%) and chemotherapy (23.46%) were the most used therapeutics to cure different types of blood cancer among patients with hematological malignancies.

3.4 | Comorbidities and mortality rate

Figure 2 shows a forest plot for the mortality rate in COVID-19 patients with hematological malignancies. Based on a random-effects model, the pooled estimate of death and discharge percent were 21.34% (95% CI: 11.24 to 33.11) and 77.60% (95% CI: 65.60 to 87.96), respectively. It means that more than three-quarters of cases

FIGURE 1 Flow diagram detailing review process and study selection
## Characteristics of the included studies

| First author          | Country       | Publish time | Type of study | No. of patients with blood cancer & COVID-19 | Median age | Male/ female | Type of blood cancer | Treatment of blood cancer                                                                 |
|-----------------------|---------------|--------------|---------------|---------------------------------------------|------------|--------------|----------------------|------------------------------------------------------------------------------------------|
| Santana               | Brazil        | Feb 2021     | Case report   | 1                                           | 47         | F            | Grade 3A follicular lymphoma | rituximab, cyclophosphamide, vincristine, and PRED                                         |
| Ali                   | Qatar         | Oct 2020     | Case report   | 1                                           | 49         | M            | CLL                  | None                                                                                     |
| Nesr                  | UK            | Sep 2020     | Case report   | 1                                           | 80         | F            | CLL                  | NR                                                                                       |
| Molina-Cerrillo       | Spain         | Jan 2021     | Case report   | 1                                           | 72         | M            | CLL                  | IBR                                                                                      |
| Largeaud              | France        | Nov 2020     | Case report   | 1                                           | 83         | M            | CLL                  | NR                                                                                       |
| Bolaman               | Turkey        | Feb 2021     | Case report   | 1                                           | NR         | F            | DLBCL                | Chemotherapy                                                                             |
| Pasin                 | Africa        | Jul 2020     | Case report   | 1                                           | 20         | M            | Refractory NK/T-cell lymphoma | rituximab, pembrolizumab, l-asparaginase                                                     |
| Ibrahim               | Saudi Arabia  | Sep 2020     | Case report   | 1                                           | 57         | M            | CML                  | Imatinib                                                                                 |
| Chaidos               | UK            | May 2020     | Case series   | 2                                           | 62.5       | M 2          | MM 2                 | lenalidomide 1, bortezomib 1, panobinostat 1                                               |
| O’Kelly               | Ireland       | May 2020     | Case report   | 1                                           | 22         | F            | HL                   | ABVD, BEACOPP, ICE, brentuximab vedotin, IFRT, pembrolizumab                               |
| Day                   | UK            | May 2020     | Case series   | 3                                           | 35.6       | M 3          | AML 2, ALL 1         | daunorubicin 2, cytarabine 2, gemtuzumab, ozogamicin 2, blinatumomab 1                   |
| Median duration of Blood cancer | SARS-CoV-2 diagnosis method | COVID-19 treatment and ancillary medications | Clinical manifestations | Laboratory findings | Other comorbidities | Outcomes |
|---|---|---|---|---|---|---|
| NR | RT-PCR, CT scans | mPDRL, oxygen support | Dyspnea, hypoxemia | Increased: D-dimer, CRP | None | Discharged |
| NR | RT-PCR, CT scans | OTV, AZ, HCO, IV CRO, amoxicillin/clavulanate | Fever, mild dyspnea, body aches | Increased: WBC, ANC, lymphocyte, monocyte, ferritin, CRP Decreased: Albumin | None | Discharged |
| NR | RT-PCR, CT scans | IV DOX, oxygen support | Fever, cough, dyspnea | Increased: Lymphocyte, reticulocyte, LDH, bilirubin, CRP Decreased: Hb | Congestive cardiac failure, atrial fibrillation, AIHA | Discharged |
| 4y | RT-PCR, CT scans | Oxygen support, HCQ, LPV/r | Cough, sore throat, fever | Increased: D-dimer, CRP, LDH, lymphocyte, ferritin, IL-6, IL-8 Decreased: Hb | Hypertension, dyslipidemia | Discharged |
| NR | RT-PCR, CT scans | Paracetamol, amoxicillin, clavulanic acid, corticosteroid therapy, anticoagulant therapy, oxygen support | Fever, cough, dyspnea, rectal bleeding | Increased: CRP Decrease: Hb, WBC, ANC, lymphocyte, PLT | None | Discharged |
| NR | RT-PCR, CT scans | HCQ, AZ, favipiravir, oxygen support | Cough, dyspnea, orthopnea | Increased: Fibrinogen, D-dimer, LDH Decreased: Hb, WBC, lymphocyte | None | Death |
| NR | RT-PCR, CT scans | RBC transfusions, mPDRL, Oxygen support, IV levofoxacin, supportive therapy, steroid therapy | Fatigue, fever, cough, dyspnea | Increased: WBC, CRP, LDH, indirect bilirubin Decreased: Hb, PLT | EBV, AIHA | Discharged |
| 10y | RT-PCR, CT scans | Paracetamol and antitussive- HCQ, AZ, CRO, enoxaparin, oxygen support, mPDRL, LPV/r, ribavirin, IFN | Cough, fever, nausea | Increased: WBC, ANC, lymphocyte, D-dimer, ferritin, LDH | None | Discharged |
| NR | RT-PCR, CT scans | Tocilizumab 2, oxygen support 1 | Fever 2, cough 1, hypoxia 2 | Increased: CRP 2, ferritin 2, D-dimer 2 | None | Discharged 2 |
| 4y | RT-PCR, CT scans | TZP, DOX, LPV/r, antibiotics, HCQ, AZ, oxygen support, corticosteroids | Cough, fever, sore throat, chills, rigors | Increased: CRP, LDH Decreased: Lymphocyte, PLT | None | Discharged |
| less than 1 y | RT-PCR, CT scans | antibiotics 3, anakinra 3, IVIg 2, oxygen support 3 | Cough 2, rhinorrhea 1, sore throat 1, diarrhea 2, fever 3, rash 2, dyspnea 1 | Increased: Ferritin 3, triglycerides 3, CRP 1 Decreased: PLT 3, RBC 2, WBC 2, lymphocyte 1 | None | Discharged 3 |

(Continues)
| First author       | Country  | Publish time | Type of study | No. of patients with blood cancer & COVID-19 | Median age | Male/female | Type of blood cancer                  | Treatment of blood cancer                                                                 |
|-------------------|----------|--------------|---------------|---------------------------------------------|------------|-------------|---------------------------------------|------------------------------------------------------------------------------------------|
| Bellmann-Weiler   | Austria  | Jun 2020     | Case series   | 3                                           | 65         | M 3         | AML 1, follicular lymphoma 1, hairy cell leukemia 1 | Bendamustine 1, rituximab                                                               |
|                    |          |              |               |                                             |            |             |                                       |                                                                                         |
| Susek             | Sweden   | Aug 2020     | Original article | 9                                         | 70.4       | M 6 F 3     | MM 8, smoldering MM 1                  | daratumumab 6, DEX 8, venetoclax 1, carfilzomib 1, bortezomib 1, lenalidomide 3        |
| Ye                | China    | Jul 2020     | Case report   | 1                                           | 72         | F           | CLL                                   | vincristine, daunorubicin, mPDRL                                                        |
| Phillips          | US       | Sep 2020     | Case report   | 1                                           | 18         | M           | ALL                                   |                                                                                         |
| Zamani            | Iran     | Jan 2021     | Case report   | 1                                           | 35         | F           | AML                                   | Chemotherapy                                                                             |
| Krengli           | Italy    | Dec 2020     | Case report   | 1                                           | 62         | F           | MM                                    | Bortezomib-thalidomide-DEX, cyclophosphamide, melphalan, radiotherapy, carfilzomib +DEX |
| Kohla             | Qatar    | Dec 2020     | Case report   | 1                                           | 58         | M           | Hairy Cell Leukemia                   | NR                                                                                       |
| Engelhardt        | Germany  | 2020 Jul     | Cohort        | 21                                          | 59         | M 17 F 4    | MM                                    | daratumumab-combination 5, elotuzumab-combination 1, VCD/KRd 2/1, lenalidomide 3, none 9 |
| Rusconi           | Italy    | July 2020    | Case report   | 1                                           | 62         | M           | classical HL                          | ABVD                                                                                     |
| Denis             | France   | Jul 2020     | Case report   | 1                                           | 72         | F           | Mantle cell lymphoma                  | R-CHOP                                                                                  |
| Moore             | US       | Oct 2020     | Case report   | 1                                           | 63         | F           | non-HL                                | obinutuzumab                                                                             |
| Vardanyan         | UK       | Jul 2020     | Case report   | 1                                           | 61         | F           | CLL                                   | NR                                                                                       |
| Abdalhadi         | Qatar    | May 2020     | Case report   | 1                                           | 65         | M           | CML                                   | Dasatinib                                                                                |
| Median duration of Blood cancer | SARS-CoV-2 diagnosis method | COVID-19 treatment and ancillary medications | Clinical manifestations | Laboratory findings | Other comorbidities | Outcomes |
|--------------------------------|-----------------------------|---------------------------------------------|------------------------|-------------------|-------------------|----------|
| 8y                             | RT-PCR, CT scans            | Oxygen support 3, physiotherapy 1, HCQ 1, AZ 1, favipiravir 2, antibiotics 1 | Fever 2, dyspnea 2, cough 3, asthenia 2, anorexia 1, diarrhea 1 | Increased: CRP, IL-6 Decreased: WBC 3, lymphocyte 3, Hb, PLT | diabetes 1, hypertension 2, obesity 3, coronary heart disease 1 | Discharged 3 |
| NR                             | RT-PCR                     | Oxygen support 4 | Fever 9, cough 8, dyspnea 3, diarrhea 3, arthralgia 3, ageusia 3 | Increased: CRP 5 Decreased: Hb 9, WBC 3, ANC 2, lymphocyte | Diabetes 4, hypertension 3, obesity 2 | Discharged 5 Died 4 |
| NR                             | RT-PCR, CT scans           | LPV/r, IFN, IVig, ARB | Fever, cough | Increased: Lymphocyte, D-dimer | NR | Discharged |
| NR                             | RT-PCR                     | Oxygen support, corticosteroids, vasopressor | Fever, cough | Increased: WBC, LDH Decreased: Hb, PLT, hyperuricemia | AIHA | Discharge |
| less than 1 y                  | RT-PCR, CT scans           | NR | Dyspnea, malaise, cough | NR | AMN | Death |
| 2y                             | RT-PCR, CT scans           | HCQ, darunavir-cobicistat, oxygen support | Cough, fever, dysphagia | Increased: CRP Decreased: Hb | hypercholesterolemia, osteoporosis | Death |
| 0y                             | RT-PCR, CT scans           | HCQ, AZ, tocilizumab, mPDRL, IVig, vasopressors, antibiotics, oxygen support | Fever, fatigue, cough, dyspnea | Increase: Creatinine, ALT, AST, LDH, IL-6, D-dimer, ferritin Decrease: WBC, ANC, Hb, PLT | None | NR |
| NR                             | RT-PCR.                    | Antibiotics 17, AZ 4, HCQ 7, RDV 1, Tocilizumab 1, Anakinra 1, oxygen support 3 | Cough 17, fever 16, myalgia 4, GI symptoms 2 | NR | None 4, cardiac/ hypertension 11, renal impairment 3, obesity 1, PNP 4, diabetes 4, hypothyreosis 4 | Discharged 21 |
| 2 y                            | RT-PCR, CT scans           | Levofloxacin, oxygen support, HCQ, LPV/r, enoxaparin, tocilizumab, CRO | Fever | Increased: Creatinine, fibrinogen, D-dimer, CRP, LDH, ferritin Decreased: WBC, ANC, Hb, PLT | Hypertension, melanoma, papillary renal cell cancer | Discharged |
| NR                             | RT-PCR, CT scans           | Kaletra, CRO | Confusion | NR | NR | NR |
| NR                             | RT-PCR                     | Plasma | Fever, myalgia, cough | Increased: CRP, LDH Decreased: WBC, lymphocyte | NR | Discharged |
| NR                             | RT-PCR, CT scans           | Oxygen support, amoxicillin-clavulanic acid, TZP, clarithromycin, tocilizumab | Fever, dyspnea, cough, fatigue | Increased: D-dimer, ferritin Decreased: Hb, WBC, lymphocyte | NR | NR |
| 4 y                            | RT-PCR, CT scans           | HCQ, AZ, OTV, TZP, oxygen support, LPV/r, tocilizumab, mPDRL | Fever, cough, chest pain | Increased: D-dimer, CRP, LDH Decreased: ANC, Hb, PLT | NR | Discharged |

(Continues)
| First author | Country | Publish time | Type of study | No. of patients with blood cancer & COVID-19 | Median age | Male/female | Type of blood cancer | Treatment of blood cancer |
|--------------|---------|--------------|---------------|---------------------------------------------|------------|-------------|---------------------|--------------------------|
| Giammarco | Italy | Dec 2020 | Case report | 1 | 50 | M | AML | all-trans PRED |
| Li | China | Dec 2020 | Case report | 1 | 61 | M | MM | bortezomib, DEX |
| Marcia | Italy | Jul 2020 | Case report | 1 | 3 | M | ALL | PRED, vincristine-daunorubicin |
| Kamit | Turkey | Nov 2020 | Case report | 1 | 9 | F | ALL | intrathecal-IV methotrexate, vincristine, cyclophosphamide, cytosine arabinoside, L-asparaginase, DEX |
| Otsuka | Japan | Nov 2020 | Case report | 1 | 56 | M | Mantle lymphoma | rituximab/cyclophosphamide/vincristine sulfate/doxorubicin, hydrochloride/DEX/methotrexate/cytarabine, bendamustine/rituximab |
| Bellesso | Brazil | Mar 2021 | Case report | 1 | 76 | F | MM | Bortezomib, DEX, radiotherapy, daratumumab |
| Glenthøj | Denmark | Sep 2020 | Cohort | 66 | 66.7 | M 40 F 26 | MM 11, CLL 31, AML 8 | rituximab 14, daratumumab 4, purine analogues 7, ibrutinib 3, non-cancer immunosuppressive treatment 5 |
| Wang | US | July 2020 | Cohort | 58 | 67 | M 30 F 28 | MM 54, smoldering MM 4 | daratumumab 28, immunomodulatory drugs 32, proteasome inhibitor 22, venetoclax 5, corticosteroids 30 |
| First author | Country | Publish time | Type of study | No. of patients with blood cancer | Median duration of Blood cancer | SARS-CoV-2 diagnosis method | Clinical manifestations | Laboratory findings | Other comorbidities | Outcomes |
|--------------|---------|--------------|---------------|---------------------------------|-------------------------------|-----------------------------|------------------------|---------------------|-------------------|---------|
| Giammarco    | Italy   | Dec 2020     | Case report 1 | 1                               | NR                           | RT-PCR, CT scans            | Fever, ostealgia        | Increased: LDH, creatine kinase, D-dimer | None              | Death              |
| Li           | China   | Dec 2020     | Case report 1 | 61                              | 0 y                          | RT-PCR, CT scans, CT scans  | Fever, cough, chest pain, dyspnea | Increased: CRP, D-dimer Decreased: Hb, lymphocyte | NR                | Discharged          |
| Marcia       | Italy   | Jul 2020     | Case report 1 | 3                               | NR                           | RT-PCR, CT scans            | Fever, epistaxis, weight loss, bruises, hepatosplenomegaly | Increased: WBC Decreased: Hb, PLT | NR                | Discharged          |
| Kamit        | Turkey  | Nov 2020     | Case report 1 | 9                               | 0.5 y                        | RT-PCR, CT scans, CT scans  | Fever, cough             | Decrease: WBC, lymphocyte, ANC | Angelman syndrome | Death              |
| Otsuka       | Japan   | Nov 2020     | Case report 1 | 56                              | 2 y                          | RT-PCR, CT scans            | Fever                   | Increased: AST, ALT, Decreased: WBC, lymphocyte, Hb, PLT | NR                | Death              |
| Bellesso     | Brazil  | Mar 2021     | Case report 1 | 76                              | 1.5 y                        | RT-PCR                      | Fever                   | Decrease: lymphocyte | Angelman syndrome | Death              |
| Glenthøj     | Denmark | Sep 2020     | Cohort 66     | 66.7                            | NR                           | RT-PCR, CT scans            | Fever, Cough, Dyspnea, Headache | Decreased: lymphocyte, ESRD, Hypertension, glucose intolerance | Obesity 8, smokers 3, heart disease 3, lung disease 9, diabetes 9, renal disease 7, liver disease 1 | Discharged 50 | Death 16           |
| Wang         | US      | July 2020    | Cohort 58     | 67                              | 2 y (29.8 months)            | RT-PCR                      | Fever, Cough, Dyspnea, Headache | Decreased: lymphocyte, ESRD, Hypertension, glucose intolerance | Obesity 8, smokers 3, heart disease 3, lung disease 9, diabetes 9, renal disease 7, liver disease 1 | Discharged 44 | Death 14           |

(Continues)
| First author                  | Country      | Publish time | Type of study          | No. of patients with blood cancer & COVID-19 | Median age | Male/ Female | Type of blood cancer | Treatment of blood cancer |
|------------------------------|--------------|--------------|------------------------|---------------------------------------------|------------|-------------|---------------------|----------------------------|
| Sánchez-Jara                 | Mexico       | Mar 2021     | Original article       | 15                                          | 7.5        | M 8 F 7     | ALL 12, AML 3       | Chemotherapy               |
| Garcia-Suarez                | Spain        | Oct 2020     | Observational study    | 697                                         | 72         | NR          | non-HL 187, MM 136, CLL 109, HL 32, ALL 13, myelodysplastic syndrome 78, AML 61, CML 16, Ph-negative myeloproliferative neoplasms 63 | Chemotherapy 169, molecular targeted therapies 81, immunomodulatory drugs 45, monoclonal antibodies 44, Hypomethylating agents 33, none 286 |
| Martinez-Lopez               | Spain        | Oct 2020     | Case series            | 167                                         | 71         | M 95 F 72  | MM 167             | Proteasome inhibitor 138, immunomodulatory drug 119, monoclonal antibody 38 |
| Regalado-Artamendi           | Spain        | Feb 2021     | Original article       | 177                                         | 70         | M 99 F 78  | HL 19, follicular lymphoma 62, DLBCL 39, other aggressive lymphomas 27, other indolent lymphomas 30 | CD20-chemotherapy 58, CD20-bendamustine 20, Chemotherapy 33, Molecular targets 3, Immunotherapy 38 |
| Yigenoglu                    | Turkey       | Aug 2020     | Cohort                 | 740                                         | 56         | M 397 F 343| HL 27, CLL 54, MM 77, ALL 18, myeloproliferative neoplasm 116, CML 30, non-HL 223, Myelodysplastic syndrome 146, AML 40, hairy cell leukemia 9 | NR                          |
| Piñana                       | Spain        | Aug 2020     | Observational study    | 367                                         | 64         | M 225 F 142| Non-HL 91, AML 67, ALL 25, Myelodysplastic syndrome 22, chronic myeloproliferative disease 29, CLL 4 | NR                          |
| de la Cruz-Benito            | Spain        | August 2020  | Cohort                 | 1                                           | 52         | F           | DLBCL               | R-CHOP                      |
| Median duration of Blood cancer | SARS-CoV-2 diagnosis method | COVID-19 treatment and ancillary medications | Clinical manifestations | Laboratory findings | Other comorbidities | Outcomes |
|--------------------------------|-----------------------------|---------------------------------------------|------------------------|-------------------|-------------------|----------|
| NR                             | RT-PCR, CT scans           | Oxygen therapy 13                           | Fever 13, rhinorrhea 2, cough 9, headache 4, respiratory distress 8, seizures 1, irritability 4, sore throat 2, diarrhea 2, drowsiness 2 | Increased: CRP 13 Decreased: ANC 13, RBC 13, WBC 13, lymphocyte 14, PLT 13 | NR | Discharged 8 Death 7 |
| NR                             | RT-PCR                     | HCQ 558, AZ 276, antiretrovirals 337, IFN 50, corticosteroid 318, tocilizumab 132 | NR | NR | Hypertension 277, cardiac disease 138, diabetes 121, renal disease 77, pulmonary disease 90 | Discharged 467 Death 230 |
| >18 m 112, <18 m 55            | RT-PCR                     | HCQ 148, AZ 91, antiretrovirals 103, steroids 83, Anti-interleukin-6 receptor antibody therapy 22, heparin 109, oxygen support 128 | Fever 134, cough 115, dyspnea 87, myalgia 45, diarrhea 36, chest pain 25, rhinorrhea 15, anosmia 14, sore throat 7 | NR | None 41, cardiac disease 35, pulmonary disease 23, diabetes 28, renal disease 32, hypertension 67 | Discharged 111 Death 56 |
| NR                             | RT-PCR                     | LPV/r 89, HCQ 156, IFN 13, AZ 79, RDV 9, plasma 7, tocilizumab 51, anakinra 11, mPDL 65, DEX 20, oxygen support 125 | Fever 30, fever 259, rhinorrhea 54, pharyngitis 27, fatigue 196, myalgia 73, cough 244, diarrhea 81, vomiting 37 | Increased: CRP 200, D-dimer 172, ferritin 119 Decreased: ANC 48, lymphocyte 140 | Smoking 33, hypertension 142, cardiomyopathy 65, dyslipidemia 94, diabetes 86 | Discharged 262 Death 105 |
| NR                             | RT-PCR                     | Favipiravir 189, OTV 309, LPV/r 35, HCQ 508 | NR | NR | Hypertension 379, diabetes 198, cardiovascular disease 156, respiratory disease 175 | Discharged 701 Death 39 |
| NR                             | RT-PCR                     | AZ 156, HCQ 147, LPV/r 163, RDV 8, corticosteroid 10, tocilizumab 50, anakinra 18, baricitinib 7 | None 30, fever 259, rhinorrhea 54, pharyngitis 27, fatigue 196, myalgia 73, cough 244, diarrhea 81, vomiting 37 | Smoking 33, hypertension 142, cardiomyopathy 65, dyslipidemia 94, diabetes 86 | Discharged 701 Death 39 |

(Continues)
| First author   | Country | Publish time | Type of study | No. of patients with blood cancer & COVID-19 | Median age | Male/ female | Type of blood cancer | Treatment of blood cancer |
|---------------|---------|--------------|---------------|---------------------------------------------|------------|-------------|---------------------|--------------------------|
| Başçi         | Turkey  | July 2020    | Original article | 16                                          | 51         | M 6 F 10    | CML 16              | Imatinib 9, Nilotinib 3, Dasatinib 4 |
| Naseri        | Iran    | Oct 2020     | Case report    | 1                                           | 42         | F           | AML                 | Idarubicin, cytarabine    |
| Song          | China   | Dec 2019     | Case report    | 1                                           | 78         | F           | CLL                 | None                      |
| Li            | China   | May 2020     | Case report    | 1                                           | 26         | M           | B-cell lymphoma    | DA-EPOCH-R                |
| Baldacini     | France  | May 2020     | Case report    | 1                                           | 62         | F           | AML                 | NR                       |
| Farmer        | UK      | Jun 2020     | Case report    | 1                                           | 36         | M           | AML                 | Arsenic trioxide          |
| Puyo          | Spain   | Jan 2020     | Case report    | 1                                           | 20 months  | M           | ALL                 | Chemotherapy              |
| Malek         | US      | Jul 2020     | Case report    | 1                                           | 41         | F           | CLL                 | NR                       |
| Schied        | US      | Sep 2020     | Case report    | 1                                           | 6          | F           | B-lymphoblastic lymphoma | Chemotherapy              |
| Pandrowala    | US      | Mar 2021     | Case report    | 1                                           | 5          | F           | AML                 | Daunorubicin, cytarabine, fludarabine, idarubicin, ventoclyx, 5-azacytidine |
| Rathore       | India   | Jun 2020     | Case report    | 1                                           | 10         | M           | ALL                 | Chemotherapy              |
| Zhang         | China   | Apr 2020     | Case report    | 1                                           | 60         | M           | MM                  | Bortezomib, thalidomide, DEX |
| Ghandili      | Germany | Dec 2020     | Case series    | 12                                          | 60         | M 9 F 3     | AML 8, ALL 3, lymphoblastic lymphoma | NR                       |
| Kos           | Germany | Sep 2020     | Case report    | 1                                           | 72         | M           | Marginal zone lymphoma | Bendamustine, rituximab   |
| Nunez Torron  | Spain   | Jun 2020     | Cohort         | 4                                           | 54.5       | M 3 F 1     | AML 4               | Chemotherapy              |
| Median duration of Blood cancer | SARS-CoV-2 diagnosis method | COVID-19 treatment and ancillary medications | Clinical manifestations | Laboratory findings | Other comorbidities | Outcomes |
|---------------------------------|-----------------------------|---------------------------------------------|------------------------|--------------------|------------------|----------|
| NR                              | RT-PCR                      | Favipiravir 4, OTV 9, LPV/r 1, HCQ 13        | NR                     | NR                 | None 5, COPD 4, diabetes 3, hypertension 7, CAD 5, chronic renal disease 2, CVD 1 | NR       |
| new                             | RT-PCR, CT scans            | Oxygen support, linezolid, meropenem, LPV/r, IFN | Fever, dyspnea, myalgia | Increased: CRP, ferritin, LDH, D-dimer Decreased: WBC, Hb, PLT, ANC, lymphocyte | Diabetes | Death    |
| 5 y                             | RT-PCR, CT scans            | OTV, cefoperazone, sulbactam, linezolid, mPDR, oxygen support | Fatigue, malaise, hyporexia | Increased: WBC, lymphocyte, CRP Decreased: Hb | Hypertension, cardiovascular disease, COPD | Death    |
| NR                              | RT-PCR, CT scans            | Meropenem, linezolid, AZ, ganciclovir, OTV, ARB | Fever                  | Decreased: ANC, lymphocyte | None | Discharged |
| less than 1 y                   | RT-PCR, CT scans            | NR                                           | Asthenia, dyspnea, epistaxis | Increased: WBC, CRP, D-dimer Decreased: Hb, PLT, ANC | NR | Death    |
| less than 1 y                   | RT-PCR                      | NR                                           | Fever, cough, sweats    | Increased: D-dimer, ferritin, creatinine, LDH, CRP Decreased: WBC, Hb, ANC, lymphocyte, PLT | NR | NR       |
| 2 months                        | RT-PCR                      | TZP, amikacin, oxygen support, HCQ, AZ, VAN, tocolizumab | Fever                  | Decreased: ANC | NR | Discharged |
| NR                              | RT-PCR, CT scans            | Cefepime, linezolid, DOX, mPDR, oxygen support | Fever, nausea, vomiting, diarrhea, cough, dyspnea, myalgia | Increased: WBC, Lymphocyte, ALT, AST, CRP, D-dimer, LDH, ferritin | Obesity | Discharged |
| NR                              | RT-PCR                      | Supportive care                              | None                    | Increased: Ferritin | NR | Discharged |
| NR                              | RT-PCR                      | Oxygen support, mPDR, meropenem, amikacin    | Fever                  | Increased: WBC, CRP Decreased: Hb, ANC, PLT | NR | Discharged |
| 3 months                        | RT-PCR                      | DEX                                          | Cough                  | NR                 | NR | Discharged |
| 5 y                             | RT-PCR, CT scans            | Moxifloxacin, ARB, oxygen support            | Chest tightness, dyspnea | Increased: CRP Decreased: Lymphocyte | None | Discharged |
| NR                              | RT-PCR                      | Oxygen support 5, LPV/r 1, pentaglobin 2, plasma 1, tocolizumab 1, None 5 | None 4 | Decreased: ANC 12, lymphocyte 12 | Hypothyroidism 1, Asthma 1, allergic rhinitis 1, smoker 1 | Discharged 10 Death 2 |
| NR                              | RT-PCR                      | Ampicillin, sulbactam, meropenem, clarithromycin, IVig | Fever, cough           | Increased: CRP, LDH Decreased: Hb | None | Discharged |
| new                             | RT-PCR, CT scans            | HCQ 4, LPV/r 3, AZ 1, corticosteroids 3, tocolizumab 2, oxygen support 4 | Fever 4, cough 1, asthenia 1 | Increased: WBC 1 Decreased: Hb 1, PLT 1 | None 4 | Discharged 1 Death 3 |
### TABLE 2
Summary of the findings in COVID-19 patients with hematological malignancies

|                          | n/n (%)                        | No. of studies that mentioned |
|--------------------------|--------------------------------|------------------------------|
| **Gender**               |                                |                              |
| Male                     | 962/1698 (56.65%)              | 53                           |
| Female                   | 736/1698 (43.35%)              |                              |
| **Treatment of blood cancer** |                              |                              |
| Proteasome inhibitor     | 160/521 (30.71%)               | 5                            |
| Chemotherapy             | 209/891 (23.46%)               | 11                           |
| Immunotherapy            | 239/1175 (20.34%)              | 7                            |
| Monoclonal antibodies    | 140/1051 (13.32%)              | 6                            |
| Daratumumab             | 44/442 (9.95%)                 | 7                            |
| Molecular targeted therapy |                              |                              |
| Corticosteroids          | 47/371 (12.66%)                | 13                           |
| Rituximab                | 19/370 (5.14%)                 | 10                           |
| Bendamustine             | 23/478 (4.81%)                 | 7                            |
| Hypomethylating agents   | 33/707 (4.67%)                 | 3                            |
| Imatinib                 | 10/313 (3.19%)                 | 5                            |
| Lenalidomide             | 7/319 (2.19%)                  | 5                            |
| Purine analogues         | 7/362 (1.93%)                  | 4                            |
| Bortezomib               | 6/311 (1.92%)                  | 9                            |
| Ventoclax                | 7/364 (1.91%)                  | 6                            |
| Vincristine              | 5/301 (1.66%)                  | 6                            |
| Cytarabine               | 5/302 (1.65%)                  | 7                            |
| Daunorubicin             | 5/302 (1.65%)                  | 7                            |
| Dasatinib                | 5/313 (1.60%)                  | 2                            |
| Cyclophosphamide         | 4/301 (1.33%)                  | 8                            |
| Nilutinib                | 3/312 (0.96%)                  | 4                            |
| Ibrutinib                | 3/362 (0.82%)                  | 4                            |
| ABVD                     | 2/298 (0.67%)                  | 5                            |
| Idarubicin               | 2/298 (0.34%)                  | 5                            |
| L-asparaginase           | 2/298 (0.67%)                  | 5                            |
| Methotrexate             | 2/298 (0.67%)                  | 5                            |
| Pembriluzumab            | 2/298 (0.67%)                  | 5                            |
| Radiotherapy             | 2/298 (0.67%)                  | 5                            |
| R-CHOP                   | 2/298 (0.67%)                  | 5                            |
| Thalidomide              | 2/298 (0.67%)                  | 5                            |
| Gemtuzumab ozogamicin    | 2/299 (0.66%)                  | 4                            |
| Carfilzomib              | 2/306 (0.65%)                  | 5                            |
| VCD                      | 2/308 (0.64%)                  | 4                            |
| 5-Azacytide              | 1/297 (0.34%)                  | 4                            |
| Arsenic trioxide         | 1/297 (0.34%)                  | 4                            |
| BEACOPP                  | 1/297 (0.34%)                  | 4                            |
| Brentuximab              | 1/297 (0.34%)                  | 4                            |

COVID-19 treatment & ancillary medications

|                          | n/n (%)                        | No. of studies that mentioned |
|--------------------------|--------------------------------|------------------------------|
| Cytosine arabinose       | 1/297 (0.34%)                  | 4                            |
| DA-EPOCH                 | 1/297 (0.34%)                  | 4                            |
| Doxorubicin              | 1/297 (0.34%)                  | 4                            |
| Hydrochloride            | 1/297 (0.34%)                  | 4                            |
| Fludarabine              | 1/297 (0.34%)                  | 4                            |
| ICE                      | 1/297 (0.34%)                  | 4                            |
| IFRT                     | 1/297 (0.34%)                  | 4                            |
| Melphalan                | 1/297 (0.34%)                  | 4                            |
| mPDRL                    | 1/297 (0.34%)                  | 4                            |
| Obinutuzumab             | 1/297 (0.34%)                  | 4                            |
| Panobinostat             | 1/297 (0.34%)                  | 4                            |
| Vedotin                  | 1/297 (0.34%)                  | 4                            |
| Blinatumomab             | 1/299 (0.33%)                  | 4                            |
| Elotuzumab               | 1/308 (0.32%)                  | 4                            |
| KRd                      | 1/308 (0.32%)                  | 4                            |

|                          | n/n (%)                        | No. of studies that mentioned |
|--------------------------|--------------------------------|------------------------------|
| Hydroxychloroquine (HCQ)| 1571/2267 (69.30%)             | 23                           |
| Oxygen support           | 365/559 (65.30%)               | 36                           |
| Anticoagulant therapy    | 112/175 (64%)                  | 5                            |
| Meropenem                | 8/13 (61.54%)                  | 9                            |
| IV immunoglobulin (IVIg)| 8/14 (57.14%)                  | 8                            |
| Antiretrovirals          | 440/869 (50.63%)               | 2                            |
| Ceftriaxone (CRO)        | 5/10 (50%)                     | 6                            |
| Piperacillin/ tazobactam (TZP) | 5/10 (50%) | 6                            |
| Antibiotics              | 44/94 (46.81%)                 | 8                            |
| Arbidol (ARB)            | 4/9 (44.44%)                   | 5                            |
| Linezolid                | 4/9 (44.44%)                   | 5                            |
| Vancomycin (VAN)         | 4/9 (44.44%)                   | 5                            |
| Corticosteroid therapy   | 429/1009 (42.52%)              | 10                           |
| Oseltamivir (OTV)        | 323/766 (42.17%)               | 8                            |
| Azithromycin (AZ)        | 633/1502 (42.14%)              | 16                           |
| Methylprednisolone (mPDRL) | 73/190 (38.42%) | 11                           |
| Amoxicillin/ clavulanate | 3/8 (37.50%)                   | 4                            |
| Doxycycline (DOX)        | 3/8 (37.50%)                   | 4                            |
| Ganciclovir              | 3/8 (37.50%)                   | 4                            |
| Vasoactive drugs (including vasopressor) | 3/8 (37.50%) | 4                            |
| Supportive therapy       | 3/10 (30%)                     | 4                            |
| Amikacin                 | 2/7 (28.57%)                   | 3                            |
| Drug                                      | No. of studies that mentioned | n/n (%)      |
|-------------------------------------------|------------------------------|--------------|
| Cefepime                                  | 2/7 (28.57%)               | 3            |
| Clarithromycin                            | 2/7 (28.57%)               | 3            |
| Levofloxacin                              | 2/7 (28.57%)               | 3            |
| Moxifloxacin                              | 2/7 (28.57%)               | 3            |
| Paracetamol                               | 2/7 (28.57%)               | 3            |
| Sulbactam                                  | 2/7 (28.57%)               | 3            |
| Teicoplanin                               | 2/7 (28.57%)               | 3            |
| Favipiravir                                | 198/830 (23.85%)           | 7            |
| Lopinavir/ritonavir (LPV/r)               | 300/1324 (22.66%)          | 14           |
| Tocilizumab                               | 245/1286 (19.05%)          | 13           |
| Ampicillin                                | 1/6 (16.67%)               | 2            |
| Cefoperazone                              | 1/6 (16.67%)               | 2            |
| Ceftazidime                               | 1/6 (16.67%)               | 2            |
| Ciclosporide                              | 1/6 (16.67%)               | 2            |
| Darunavir-cobicistat                      | 1/6 (16.67%)               | 2            |
| Kaletra                                   | 1/6 (16.67%)               | 2            |
| Pentaglobin                               | 2/12 (16.67%)              | 1            |
| RBC transfusion                           | 1/6 (16.67%)               | 2            |
| Ribavirin                                 | 1/6 (16.67%)               | 2            |
| Trimethoprim-sulfamethoxazole             | 1/6 (16.67%)               | 2            |
| Anti-IL-6                                 | 26/240 (10.83%)            | 3            |
| Selinexor                                 | 5/63 (7.93%)               | 2            |
| Interferon (IFN)                          | 67/883 (7.59%)             | 6            |
| Anakinra                                  | 33/573 (5.76%)             | 5            |
| Plasma                                    | 11/249 (4.42%)             | 5            |
| Anti-IL-2                                 | 2/63 (3.17%)               | 2            |
| Remdesivir (RDV)                          | 19/628 (3.03%)             | 4            |
| Baricitinib                               | 7/372 (1.88%)              | 2            |
| Anti TNF                                  | 1/63 (1.59%)               | 2            |

**Clinical manifestations**

- Fever: 562/757 (74.24%) 38
- Cough: 508/751 (67.64%) 30
- Fatigue: 200/376 (53.19%) 7
- Dyspnea: 155/366 (42.34%) 23
- Myalgia: 131/639 (20.50%) 7
- Respiratory distress: 9/51 (17.65%) 5
- Diarrhea: 48/309 (15.53%) 10
- Chest pain or tightness: 28/215 (13.02%) 7
- Headache: 15/116 (12.93%) 5
- Rhinorrhea: 72/567 (12.70%) 6
- Vomiting: 38/373 (10.19%) 4
- Asthenia: 4/43 (9.30%) 6

**Laboratory findings**

- ALT: 3/3 (100%) 3
- ANC: 2/2 (100%) 2
- AST: 3/3 (100%) 3
- Bilirubin: 2/2 (100%) 1
- Creatinine kinase: 1/1 (100%) 1
- Creatinine: 2/2 (100%) 2
- Fibrinogen: 2/2 (100%) 2
- IL-6: 3/3 (100%) 2
- IL-8: 1/1 (100%) 1
- LDH: 16/16 (100%) 16
- Lymphocyte: 7/7 (100%) 7
- Monocyte: 1/1 (100%) 1
- Reticulocyte: 1/1 (100%) 1
- Triglycerides: 3/3 (100%) 1
TABLE 2 ( Continued)

|                | n/n (%) | No. of studies that mentioned |
|----------------|---------|------------------------------|
| WBC            | 10/13 (76.92%) | 10 |
| CRP            | 242/417 (58.03%) | 26 |
| D-dimer        | 189/384 (49.22%) | 17 |
| Ferritin       | 134/382 (35.08%) | 13 |
| Decreased      |         |                              |
| Albumin        | 1/1 (100%)   | 1   |
| Uric acid      | 1/1 (100%)   | 1   |
| Hb             | 29/32 (90.62%) | 21  |
| PLT            | 31/36 (86.11%) | 17  |
| RBC            | 15/18 (83.33%) | 2   |
| WBC            | 50/97 (51.55%) | 14  |
| Lymphocyte     | 218/538 (40.52%) | 20  |
| ANC            | 105/538 (19.52%) | 17  |

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; AIHA, autoimmune hemolytic anemia; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANM, acute macular neuroretinopathy; ANC, absolute neutrophil count; ARB, arbidol; AST, aspartate aminotransferase; AZ, azithromycin; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone (oncovin); WBCHV, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (oncovin), and prednisone; CLL, Chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRO, cetirizoxane; CRP, C-reactive protein; CXR, chest X-ray; DLBCL, diffuse large B-cell lymphoma; DOX, doxycycline; EBV, Epstein-Barr virus; HB, hemoglobin; HCG, hydroxychloroquine; HBGL, high grade B-cell lymphoma; HL, Hodgkin lymphoma; IBR, ibrutinib; ICE, ifosfamide, carboplatin, etoposide; IFN, interferon; IRRT, involved field radiotherapy; IV, intravenous; Ig, immunoglobulin; LDH, lactate dehydrogenase; LPV, lopinavir; LPV/r, lopinavir/ritonavir; MM, multiple myeloma; mPDRL, methylprednisolone; NR, not reported; OTV, oseltamivir; PLT, platelet; PRED, prednisone; RTV, ritonavir; RDV, remdesivir; TZIP, piperacillin/tazobactam; VAN, vancomycin; VCD/KRD, bortezomib-cyclophosphamide-dexamethasone/carfilzomib-lenalidomide-dexamethasone.

3.5 Risk of bias assessment

The results of the critical appraisal (JBI checklist) of included studies are summarized in Table S1. Overall, 53 articles were identified having a low risk of bias (quality assessment score > 7).

4 DISCUSSION

Since the onset of the COVID-19 outbreak, several studies have reported the effects of COVID-19 on cancer patients. In this regard, there is growing evidence that patients with a history of cancer have a higher rate of COVID-19 mortality than individuals without cancer. In addition, it has been reported that patients with hematological cancers had the highest frequency of major adverse events.5,12

Yeo et al. indicated that the cancer was associated with a 2.84-fold increased risk of severe illness in COVID-19 patients and a 2.60-fold increased risk of death.13 The prevalence of cancer in COVID-19 patients is very low. In a recent study, the pooled prevalence of cancer in COVID-19 patients was 2%.14,15

Also, the results of the same studies from China and the United States of America reported that about 1–2% and 6% of COVID-19 patients had cancer, respectively.14,16

The prevalence of hematological malignancies among COVID-19 patients has not yet been well studied. In a related study conducted by Yigenoglu et al., it has been reported that 0.39% of the COVID-19 patients had hematological malignancy. The most common hematological malignancies were non-Hodgkin lymphoma (30.1%) followed by myelodysplastic syndromes (19.7%). They reported that about 5.27% of the patients have died.17

In the other study conducted by Mehta et al. in New York, the mortality rate in lymphoid neoplasms was higher than the myeloid malignancies (35% vs. 43%). Our results estimated that the mortality rate in COVID-19 patients with hematological malignancies was 21.34%. This discrepancy observed in the results of these studies can be due to different sizes of studies. Therefore, the results of studies conducted in all areas highlight the urgent need to pay special attention to patients with hematologic malignancy infected with COVID-19.

The progression of blood malignancies is usually accompanied by a weakening of the immune system, which is initiated by the disease and continues through the strategy of anti-tumor therapies such as chemotherapy and radiation therapy. Therefore, the suppressed immune system may lead to a greater vulnerability of cancer patients to COVID-19.

A previous study showed that anti-tumor therapy increased the risk of dangerous symptoms within 14 days of the diagnosis of COVID-19 and recommended that cancer patients with COVID-19 avoid treatments that suppress the immune system.19

On the hand, cytotoxic chemotherapies cause neutropenia and lymphocytopenia that aggravate the immunosuppressive status. This status leads to high infection rates and poor prognosis.20–22

There is currently no advice on the effectiveness of conventional and targeted treatment strategies in these patients.23

Hence, the risk-benefit ratio of these treatment strategies remains a challenge. In this regard, it has been demonstrated that radiation therapy has no higher risk of severe events related to the COVID-19 for these patients.5

For example, Krengli et al.24 reported that radiation therapy could be considered a treatment strategy in COVID-19 patients affected by myeloma. Recently, Liu et al.25 demonstrated that patients...
| TABLE 3 | The main findings in COVID-19 patients with hematological malignancies categorized based on the type of malignancy |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
| Patients | 2395 | 77 (4.19) | 200 (9.16) | 214 (13.60) | 64 (4.40) | 80 (4.95) | 614 (30.01) | 486 (27.55) | 246 (13.63) | 208 (11.53) |

**Treatment of blood cancer**

|                         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
|-------------------------|-----------|-----|-----|-----|-----|----|-----|----|-----|-----|
| **Chemotherapy**         | 209 (23.46) | 20 (76.92) | 28 (41.27) | 4 (21.5) | 2 (12.5) | 21 (41.17) | 83 (34.15) | 33 (24.26) | 2 (2.56) | 31 (49.21) |
| **Immunotherapy**        | 239 (20.34) | - | - | - | - | 7 (26.84) | 20 (13.69) | 19 (54.29) | - | - |
| **Monoclonal antibodies**| 140 (13.32) | - | - | 1 (0.54) | - | - | 25 (13.37) | 52 (17.17) | - | - |
| **Molecular targeted therapy** | 84 (9.50) | 3 (4.91) | 28 (34.15) | 14 (87.5) | - | 8 (3.32) | 12 (8.82) | - | 18 (28.57) |
| **Hypomethylating agent** | 33 (4.67) | - | 17 (27.87) | - | - | 1 (0.53) | - | 15 (19.23) | - | - |

**COVID-19 treatment**

|                         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
|-------------------------|-----------|-----|-----|-----|-----|----|-----|----|-----|-----|
| **Oxygen support**      | 365 (65.30) | 17 (73.92) | 27 (69.23) | 2 (100) | 5 (100) | 157 (57.72) | - | - | - | - |
| **HCQ**                 | 1571 (69.30) | 5 (41.67) | 3 (100) | 2 (100) | 1 (100) | 153 (69.30) | - | - | - | - |
| **Antibiotics**          | 44 (46.81) | 22 (22.22) | 1 (100) | - | 1 (100) | 2 (100) | 33 (13.37) | 1 (100) | 93 (41.33) | - | - |
| **Corticosteroids**      | 429 (42.52) | 3 (75) | 1 (100) | - | 1 (100) | 1 (100) | - | 93 (41.33) | - | - |
| **LPV/r**               | 300 (22.66) | 4 (33.33) | 2 (100) | 3 (16.67) | 2 (100) | - | - | - | - | - |

**Clinical manifestations**

|                         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
|-------------------------|-----------|-----|-----|-----|-----|----|-----|----|-----|-----|
| **Fever**               | 562 (74.24) | 20 (90.91) | 33 (82.5) | 2 (100) | 6 (84.71) | 78 (75.73) | - | - | - | - |
| **Cough**               | 508 (67.64) | 12 (5.89) | 32 (82.05) | 2 (100) | 5 (100) | 73 (70.87) | - | - | - | - |
| **Dyspnea**             | 155 (42.34) | 4 (36.36) | 19 (48.71) | - | 4 (80) | 33 (41.25) | - | - | - | - |
| **Diarrhea**            | 48 (15.53) | 3 (60) | 5 (15.15) | - | 3 (33.33) | - | - | - | - | - |
| **Respiratory distress**| 9 (17.65) | 1 (33.33) | - | - | - | 1 (100) | - | - | - | - |

**Laboratory findings – increase**

|                         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
|-------------------------|-----------|-----|-----|-----|-----|----|-----|----|-----|-----|
| **LDH**                 | 16 (100) | 2 (100) | 3 (100) | 2 (100) | 2 (100) | 4 (100) | - | - | - | - |
| **CRP**                 | 242 (58.03) | 4 (100) | 5 (100) | 1 (100) | 2 (100) | 5 (100) | 9 (69.23) | - | - | - |
| **D-dimer**             | 189 (49.22) | 3 (100) | 4 (100) | 2 (100) | 1 (100) | 2 (100) | 3 (100) | - | - | - |
| **Ferritin**            | 134 (35.08) | 4 (100) | 4 (100) | 1 (100) | 1 (100) | 1 (100) | 2 (100) | - | - | - |

**Laboratory findings – decrease**

|                         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
|-------------------------|-----------|-----|-----|-----|-----|----|-----|----|-----|-----|
| **Hb**                  | 29 (90.62) | 5 (62.5) | 5 (100) | 1 (100) | - | 5 (100) | 10 (100) | - | - | - |
| **PLT**                 | 31 (86.11) | 7 (70) | 2 (100) | 1 (100) | 3 (100) | - | - | - | - | - |
| **WBC**                 | 50 (51.55) | 3 (75) | 4 (100) | - | - | 4 (100) | 23 (34.33) | - | - | - |
| **Lymphocyte**          | 218 (40.52) | 2 (100) | 3 (100) | - | 2 (100) | 6 (100) | 14 (19.72) | - | - | - |

**Gender**

|                         | Total (%) | ALL | AML | CLL | CML | HL | NHL | MM | MDS | MPN |
|-------------------------|-----------|-----|-----|-----|-----|----|-----|----|-----|-----|
| **Male**                | 962 (56.65) | 20 (58.82) | 21 (65.62) | 24 (60) | 8 (44.44) | 13 (61.90) | 61 (53.98) | 158 (58.09) | 51 (65.38) | 43 (68.25) |
| **Female**              | 736 (43.35) | 14 (41.18) | 11 (34.38) | 16 | 10 (55.56) | 8 (38.01) | 52 (46.02) | 114 (41.91) | 27 (34.62) | 20 (31.75) |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, Chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRP, C-reactive protein; HCQ, hydroxychloroquine; HL, Hodgkin lymphoma; LDH, lactate dehydrogenase; LPV/r, lopinavir/ritonavir; MM, multiple myeloma; PLT, platelet.
with hematological malignancies were at a higher risk of death if they received chemotherapy 3 months before the COVID-19 diagnosis.

It is recommended that the cancer treatment strategies be postponed until the radiological and clinical symptoms of COVID-19 have been completely disappeared. These clinical symptoms were previously mostly treated by hydroxychloroquine. However, recently, WHO recommended healthcare systems cease the use of this drug.

The most common complications of COVID-19 are fever, dyspnea, cough, muscle ache, confusion, headache, pneumonia, acute respiratory distress, and acute respiratory failure. The findings of the present study show that the highest incidence of clinical manifestations in patients with hematologic malignancy infected with SARS-CoV-2 belonged to fever (74.24%), cough (67.64%), fatigue (53.19%), dyspnea (42.47%), myalgia (20.50%), and the respiratory distress (17.65%). These results are consistent with those of other studies and confirm that pulmonary symptoms are the main clinical manifestations of COVID-19 in more than half of the patients treated for the hematologic malignancies.

Our results demonstrated that the most common comorbidities in patients with COVID-19 and hematological malignancies were hypertension (44.61%) and dyslipidemia (32.13%). In addition, it revealed that the patients who died had more comorbidities. Also, it has been shown that the mortality rate of these patients is related to the disease status, the status of the immune system, and the level of inflammation.

The elevated levels of C-reactive proteins were observed in 58.03% of patients with hematologic malignancy infected with SARS-CoV-2. Also, other laboratory findings such as the increased d-dimer levels (49.22%), neutropenia (19.52%), and the increase in
Bilirubin levels were seen in these patients. It seems that laboratory findings on admission can help predict the severity of COVID-19 in patients with hematologic malignancy. Furthermore, it has been demonstrated that the monitoring of RNA load in plasma can be useful to anticipate the COVID-19 outcomes in these patients. Ghandili et al. reported that the increasing RNA titer is associated with the fatal outcomes in patients with acute myeloid leukemia infected SARS-CoV-2.

**Figure 3**: Pooled prevalence with 95% CI and heterogeneity indices of different comorbidity percent in patients with COVID-19 and malignancy. The diamond mark illustrates the pooled percent, and the length of the diamond indicates the 95% CI. N is the number of the study in the analysis.

**Figure 4**: Association among death rate and Median of age by means of meta-regression. The size of circles indicates the precision of each study. There is no significant association with respect to the death rate with Median of age.

| Subgroup               | Prevalence (95% CI)     |
|------------------------|-------------------------|
| Diabetes               | 19.72 (15.87, 23.57)    |
| Hypertension           | 44.61 (39.94, 49.28)    |
| Obesity                | 18.93 (3.66, 34.21)     |
| Cardiac disease        | 19.40 (15.64, 23.16)    |
| Renal disease          | 11.50 (4.38, 18.63)     |
| Pulmonary disease      | 15.76 (11.02, 20.50)    |
| Dyslipidemia           | 32.13 (8.69, 55.58)     |
| Liver disease          | 1.96 (0.05, 3.88)       |
| Hypothyroidism         | 23.79 (8.58, 39.00)     |

(Coef: 0.26; P=0.513)
There are several limitations to this study. First, as our search was restricted to articles published in English, we might have missed some relevant publications in other languages. Second, only case series and research articles were enrolled in the meta-analysis. Therefore, the existence of publication bias should be considered. Third, this study included patients whose RT-PCR tests were positive for SARS-CoV-2. However, it is confirmed that false-negative and false-positive RT-PCR may occur due to low amounts of SARS-CoV-2 concentrations and cross-reaction with something that’s not SARS-CoV-2, respectively. Forth, heterogeneity in the study population selection and the retrospective characteristics was observed in the studies. Although the random-effects model was assumed to reflect the similarity, there may still be differences of opinion. Fifth, all included studies have reported hospitalized patients. Due to these cases usually having a severe or moderate stage of disease, mild cases may be missed.

5 | CONCLUSIONS

In this study, we reviewed the literatures reporting the COVID-19 outcomes in patients with hematological malignancies. Our study reveals that about one-quarter of patients with COVID-19 and hematological malignancy have died during hospitalization. One of the most important reasons that confirm these patients are more vulnerable is their immune system dysfunction. Furthermore, anti-cancer therapies may worsen their conditions. Therefore, the management of COVID-19 in patients with hematological malignancies requires much more attention.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Adel Naimi, Ilya Yashmi, Reza Jebeleh, Mohammad Imani Mofrad, Shokib Azimian Abhar, Yasaman Janesra, and Mohsen Heidary contributed in revising and final approval of the version to be published. All authors agreed and confirmed the study for publication.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the results of this study is available within the article.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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