Blood cancer in children infected with COVID-19: A comprehensive systematic review

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Abstract

Background: Blood cancer is the most common type of cancer and the leading cause of death by disease past infancy among children. Children with blood cancer are vulnerable population to viral infections such as coronavirus disease 2019 (COVID-19).

Objectives: To estimate the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in blood cancer children and analyse the demographic parameters, clinical characteristics and treatment outcomes in blood cancer children with COVID-19 illness.

Methods: For this systematic review, we searched ProQuest, Medline, Embase, PubMed, CINAHL, Wiley online library, Scopus and Nature through the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline for studies on the development of COVID-19 in children with blood cancer, published from December 1, 2019 to April 30, 2023, with English language restriction.

Results: Of the 3077 papers that were identified, 155 articles were included in the systematic review (83 case report, 54 cohort and 18 case-series studies). Studies involving 1289 blood cancer children with confirmed COVID-19 were analysed. Leukaemias (1141 cases) were the most frequent types of blood cancer observed in children who developed COVID-19, followed by non-Hodgkin's lymphomas (59 cases), Hodgkin's lymphomas (36 cases), Langerhans cell histiocytosis (7 cases), myelodysplastic syndrome (7 cases) and myeloid neoplasm (1 case). Among all 1289 blood cancer paediatric cases who transmitted SARS-CoV-2, some children were documented to be admitted to the intensive care unit (ICU) (n = 175, 13.6%), intubated and placed on mechanical ventilation (n = 111, 8.6%), suffered acute respiratory distress syndrome (n = 144, 11.2%) or died (n = 111, 8.6%). Overall, COVID-19 in children with different types of blood cancer resulted in no or low severity of disease in more than 78.6% of all included cases (COVID-19 severity: asymptomatic = 239, mild = 603, or moderate = 171). Treatment for COVID-19 was not necessary in a high number of blood cancer children (n = 94, 7.3%). Fatality in blood cancer children with COVID-19 was reported in any of the included blood cancer categories for leukaemias (n = 99, 8.7%), non-Hodgkin's lymphomas (n = 7, 11.9%), Hodgkin's lymphomas (n = 2, 5.5%), myelodysplastic syndrome (n = 1, 14.3%) or myeloid neoplasm (n = 1, 100%). Fatality rate in blood cancer children infected with SARS-CoV-2 was the highest in patients with Hispanic ethnicity (n = 44/111, 39.6%) and COVID-19–related fatality was highest in male patients (76.5% of deceased patients). Most studies reported to alter the intensity and regimen of anticancer treatment in blood cancer children during course of SARS-CoV-2 infection, however, many studies have reported to successfully treat COVID-19 without any changes to the anticancer treatment.

Conclusion: Globally, leukaemias were the most prevalent and myeloid neoplasms were the least prevalent blood cancer types in children who developed SARS-CoV-2 infection. Children with blood cancer tend to have milder COVID-19 symptoms and are less likely to be hospitalized and have better prognosis when compared to adults. Continuation of anticancer treatment in individual paediatric blood cancer patients with COVID-19 seems to be possible.

Background

Blood cancer is the most common type of cancer and the leading cause of death by disease past infancy among children (1, 2). Children with blood cancer are vulnerable population to viral infections and the emerging coronavirus disease 2019 (COVID-19) is not an exception (3, 4). Children with blood cancer undergoing cancer-directed therapy were assumed to be at higher risk for severe COVID-19 possibly due to their immunocompromised status (5, 6), immunosuppressive cancer treatments and/or comorbidities (4, 7, 8). Affected children with blood cancer and infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) usually have several immune dysfunctions of the innate and adaptive immune system and functionally impaired cellular and humoral immunity (such as reduced neutrophils, eosinophils and basophils; low serum immunoglobulin G levels and/or malfunctioning type I and type III interferons signalling) (see Figure 1).

Despite an increasing number of studies regarding COVID-19 in children with cancer (9-11), it remained unclear, which cancer patients were at high risk for a severe clinical course and data in children with blood cancer are still limited (12-14). While some early studies in older cancer patients with blood cancer suggested that the risk of severe COVID-19 is higher in this population (4, 7, 8, 15-17), more recent data indicate that paediatric cases with blood cancer may not be at greater risk than others (18-22). These publications suggest that COVID-19 in paediatric patients with blood cancer is generally asymptomatic (23-27), mild (3, 28-32) or moderate (14, 33-36) in children receiving anticancer therapy. However, some severe cases have been described, mostly in highly immunocompromised children and/or with severe cancer conditions (16, 17, 37-40). Most reports have been limited to cases or small sample populations and many of these studies report different results regarding the association of cancer type and therapy with clinical treatment outcomes in oncologic children infected with SARS-CoV-2. To strengthen body of evidence, several systematic reviews have reported on the association between COVID-19 and blood cancer; however, these studies aggregated findings on different types of cancer and included mixed populations of adults and children (with most data for adults and very few paediatric patients) (10, 41-43) or focused on a particular common subtype of blood cancer (44-48).

Therefore, in this systematic review, we will comprehensively review the available published literatures reporting the COVID-19 outcomes and underlying diseases in children with blood cancer. We aim to provide evidence-based guidance in the management of these vulnerable patients from diagnosis to treatment and follow-up.

Methods

Design

This systematic review was performed with reference to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statemen (49). Published articles from 1 December 2019 to 30 April 2023, were selected for review from eight electronic databases (PubMed,

CINAHL, Embase, Scopus, ProQuest, Wiley online library, Medline, and Nature). Search terms were based on the 2022 updated Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms as described by the 5th edition of the World Health Organization (50, 51). Articles discussing and reporting the development of COVID-19 in children with blood cancer were selected based on the title and abstract.

Inclusion-exclusion criteria

Readily accessible peer-reviewed full articles, observational cohort studies, clinical trials, case reports, case series, and not peer-reviewed preprints that focused on development of COVID-19 in blood cancer patients were included. Exclusion criteria were editorials, commentaries, reviews and meta-analyses; studies that reported blood cancer in children with negative SARS-CoV-2 polymerase chain reaction tests or reported blood cancer in adult COVID-19 patients; in vitro, in silico, or in vivo studies; or non-human studies.

Data extraction

The screening of the papers was performed independently by six reviewers (Saad Alhumaid, Khalid Al Noaim, Anwar A Almuslim, Jamela A. Turkistani, Zainab Sabri Alqurini, and Abdullah Mohammed Alshakhs) by screening the titles with abstracts using the selection criteria. Disagreements in the study selection after the full-text screening were discussed; if agreement could not be reached, a seventh reviewer was involved. We categorized articles as case report, case-series, case-control or cohort studies. The following data were extracted from the selected studies: authors; publication year; study location; study design and setting; age; proportion of male patients; patient ethnicity; comorbidities; blood cancer type, status and symptoms; blood cancer treatment at SARS-CoV-2 infection; laboratory findings; history of SARS-CoV-2 vaccination (brand and dose); COVID-19 severity; if patient experienced multisystem inflammatory syndrome in children (MIS-C); if patient was admitted to the intensive care unit (ICU), placed on mechanical ventilation and/or suffered acute respiratory distress syndrome (ARDS); assessment of study risk of bias; and final treatment outcome (survived or died); and they are noted in Table 1.

Quality assessment

Two tools were used appropriately to assess the quality of the studies included in this review: (1) Modified Newcastle–Ottawa Scale (NOS) to evaluate case report and case-series studies (scoring criteria: 5 criteria fulfilled = good, 4 criteria fulfilled = moderate, and 3 criteria fulfilled = low) (52); and (2) NOS to evaluate cohort studies (scoring criteria: >7 scores = high quality, 5–7 scores = moderate quality, and <5 scores = low quality) (53). Quality assessment was conducted by six co-authors (Wafa Alabdulmohsen, Zakaria Ali Alsharidah, Munther Saleh Alkhamees, Laith Abbas AlAithan, Abdulaziz Ahmed Almurayhil, and Yousuf Ahmed Almurayhil) who separately evaluated the possibility of bias using these two tools.

Data analysis

We examined primarily the proportion of confirmed SARS-CoV-2 infection in children with blood cancer. This proportion was further classified based on the 2022 updated Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms (i.e., identified blood cancer cases were categorized into family, type (disease/tumour), and subtype), as compiled by the editorial board that included *standing members* of the World Health Organization (50, 51). Clinical Spectrum of SARS-CoV-2 Infection from the National Institutes of Health was applied to define severity of COVID-19 (asymptomatic, mild, moderate, severe and critical) (54). MIS-C was defined according to the current United States Centers for Disease Control and Prevention case definition in an individual aged <21 years (55). Cancer status was defined as per the American Cancer Society (active, remission and relapsed/refractory) (56).

Descriptive statistics were used to describe the data. For continuous variables, mean and standard deviation were used to summarize the data; and for categorical variables, frequencies and percentages were reported. Microsoft Excel 2019 (Microsoft Corp., Redmond, USA) was used for all statistical analyses.

Results

Study characteristics and quality

A total of 3077 publications were identified (Figure 2). After exclusion of duplicates and articles that did not fulfil the study inclusion criteria, one hundred and fifty-five articles were included in the qualitative synthesis of this systematic review (3, 4, 7, 8, 12-40, 57-178). The reports of one thousand two hundred and eighty-nine cases identified from these articles are presented by groups based on the 2022 updated Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms as described by the 5th edition of the World Health Organization (50, 51). The detailed characteristics of the included studies are shown in Table 1. There were 83 case report (3, 4, 17, 22, 25, 28-30, 33, 34, 36, 57, 58, 61, 63-66, 68, 71-73, 76, 77, 79-84, 86-90, 94, 95, 97-102, 105, 106, 109, 111, 112, 114, 115, 117, 118, 120-122, 124-127, 132-142, 145, 147-149, 152, 154, 156-158, 160, 164-166), 54 cohort (7, 8, 12-16, 18, 20, 21, 24, 26, 31, 32, 35, 37-40, 59, 62, 67, 69, 70, 74, 75, 91-93, 96, 103, 104, 107, 108, 113, 116, 123, 129-131, 144, 150, 155, 159, 161, 167-172, 174-176), and 18 case-series (19, 23, 27, 60, 78, 85, 110, 119, 128, 143, 146, 151, 153, 162, 163, 173, 177, 178) studies. These studies were conducted in United States (n = 27), India (n = 17), China (n = 10), Turkey (n = 9), Italy (n = 9), Iran (n = 8), Mexico (n = 8), United Kingdom (n = 6), Spain (n = 6), Poland (n = 5), Brazil (n = 5), France (n = 4), Peru (n = 3), Switzerland (n = 3), Greece (n = 3), Pakistan (n = 2), Saudi Arabia (n = 2), Russia (n = 2), Austria (n = 2), Germany (n = 2), Jordan (n = 2), Algeria (n = 1), The Netherlands (n = 1), Kuwait (n = 1), Egypt (n = 3), Oman (n = 1), Romania (n = 1), Colombia (n = 1), Israel (n = 1), Taiwan (n = 1), Canada (n = 1), Indonesia (n = 1), Argentina (n = 1), Tunisia (n = 1), Palestine (n = 1), Japan (n = 1) and Sweden (n = 1). Only two studies were made within multi-countries (n = 2) (35, 144). The majority of the studies were single centre (3, 4, 7, 8, 14-18, 21-34, 36, 37, 57-66, 68, 70-90, 92-107, 109-128, 130-143, 145-160, 162-166, 169-175, 178) and only 19 studies were multi-centre (12, 13, 19, 20, 35, 38-40, 67, 69, 91, 108, 129, 144, 161, 167, 168, 176, 177). Almost all

studies included in this review were retrospective in design except few studies were prospective (n = 5) (7, 24, 67, 92, 159) and one study utilized both retrospective and prospective designs (129). All children diagnosed with blood cancer who had concurrent COVID-19 among all included studies in our systematic review were not vaccinated against SARS-CoV-2 (3, 4, 7, 8, 12-40, 57-178). Ninety-four studies were deemed to have high methodological quality, 3 moderate methodological quality, and 4 low methodological quality. Among the 54 included cohort studies, 38 cohort studies were found to be moderate-quality studies (i.e., NOS scores between 5 and 7) and 16 study demonstrated a relatively high quality (i.e., NOS scores > 7); Table 1.

Leukaemia

Leukaemia was the first most-common blood cancer in children who experienced COVID-19 (n = 1141, 88.5%) (3, 4, 7, 8, 12-15, 17-21, 23-40, 58-64, 66-82, 84-86, 89-100, 102-104, 106-129, 131-137, 139-143, 146-151, 153-163, 167-178) (see Table 1). Among them, 579 have unclassified lymphoblastic leukaemia (50.7% of all leukaemias) (3, 4, 8, 12, 13, 15, 19-21, 23, 24, 26, 29-32, 39, 40, 61, 67, 70-72, 74, 75, 81, 82, 84, 86, 92, 104, 108, 113, 116, 123, 127, 132, 150, 153, 155, 161, 162, 167-174, 177, 178), 202 have unspecified leukaemia (17.7%) (14, 18, 20, 35, 93, 96, 103, 107, 134, 147, 159, 167, 176), 185 have B-cell lymphoblastic leukaemia (16.2%) (7, 13, 27, 28, 33, 34, 36-38, 58-60, 62, 63, 66, 68, 73, 78-80, 85, 89, 90, 94, 95, 97-100, 102, 109, 112, 115, 119-122, 124, 125, 128, 129, 131, 133, 135-137, 139, 140, 142, 143, 146, 151, 154, 156, 158, 163, 175), 150 have unclassified myeloid leukaemia (13.1%) (13, 15, 17, 19-21, 23, 25, 31, 32, 37-40, 59, 64, 67, 69, 77, 78, 91, 92, 94, 104, 106, 108, 110, 111, 113, 114, 116, 117, 123, 128, 129, 141, 148-150, 153, 160, 171-175), 23 have T-cell lymphoblastic leukaemia (2%) (37, 38, 59, 76, 78, 118, 119, 126, 128, 157, 175), and 2 have biphenotypic leukaemia (a mixture of both types of lymphoblastic and myeloid leukaemias) (0.2%) (23, 99). Most of those patients had acute leukaemic conditions (n = 892, 78.2%) (3, 4, 7, 8, 13-15, 17, 19-21, 23-34, 36-40, 58-64, 66-82, 84-86, 89, 90, 92-95, 97-100, 102, 104, 106, 108-129, 131-133, 135-137, 139-143, 146-151, 153-158, 160-163, 167-175, 177, 178) and only few cases had chronic leukaemia (n = 5, 0.4%) (91, 92, 129). Reported blood cancer status for the leukaemia in children infected with SARS-CoV-2 were active (n = 258/574, 44.9%) (8, 12-15, 17, 19-21, 23, 24, 29, 31, 32, 34, 35, 37, 40, 58-60, 64, 66, 73, 74, 76, 78, 79, 81, 82, 85, 86, 90, 92, 93, 95, 97-100, 102, 103, 108-112, 114, 115, 118, 120-122, 124, 127-129, 134, 136, 140, 142, 143, 146, 148-151, 154, 156, 158-160, 167, 169, 170, 172, 174, 175, 177), remission (n = 256/574, 44.6%) (3, 4, 8, 14, 15, 21, 23-28, 30, 33, 35-37, 40, 59-62, 67-72, 74, 78, 84, 89, 91, 92, 94, 107, 126, 128, 132, 135, 137, 139, 141, 150, 155, 157, 163, 167-177), or relapsed/refractory (n = 60/574, 10.4%) (7, 13, 14, 29, 37, 63, 67, 74, 77, 80, 92, 106, 117, 125, 131, 133, 147, 150, 169, 171, 173, 174, 176, 178), however, blood cancer status in these leukaemia cases was not reported in a high percentage of patients (n = 567/1141, 49.7%) (18, 20, 21, 38, 39, 92, 96, 104, 108, 113, 116, 119, 123, 129, 153, 161, 162, 167, 174). The median interquartile range (IQR) age of this group was 96 months [48 to 156], with an increased male predominance in leukaemia patients diagnosed with COVID-19 in most of the studies (198/304 = 65.1%) (4, 7, 13-15, 17, 23, 31, 33, 34, 36, 37, 40, 59-63, 70, 72, 73, 76-78, 82, 89-92, 99, 100, 102, 109-112, 115, 118-122, 124-128, 133, 136, 137, 140, 142, 143, 146-151, 153-157, 159, 160, 163, 167, 168, 170, 177), and majority of the patients belonged to Hispanic (310/896 = 34.6%) (13, 14, 17, 18, 24, 28, 38, 39, 60, 74, 75, 77, 81, 84, 93, 104, 111, 116, 149, 154, 160, 175), White

(Caucasian) (292/896 = 32.6%) (3, 8, 12, 13, 19, 25, 26, 28, 31, 32, 34, 62-64, 67-69, 73, 76, 78-80, 82, 85, 86, 89-91, 94-97, 99, 100, 102, 103, 109, 110, 112, 114, 115, 118-122, 125, 128, 129, 133-137, 141, 147, 150, 151, 153, 156, 161, 167, 176, 177), Arab (160/896 = 17.8%) (23, 29, 58, 59, 92, 123, 126, 140, 150, 171, 173, 178) and Indian (134/896 = 14.9%) (21, 27, 30, 37, 66, 117, 124, 127, 139, 142, 143, 157, 169, 172, 174) ethnicity. Many of these leukaemic children infected with SARS-CoV-2 were found to have active concurrent infections (n = 96) [including unspecified pathogens (n = 35) (19 bacteria (14, 37, 108, 151, 171-173), 12 fungi (66, 108, 172, 173), and 4 other unknown pathogens) (113); *Rhinovirus* (n = 6) (28, 76, 133, 153, 160); *Pseudomonas* (n = 6) (17, 19, 21, 31, 33, 128); *Aspergillus* (n = 4) (61, 71, 110, 171); Dengue virus (n = 4) (169); *Influenza A* virus (n = 4) (72, 133, 146, 168); *Enterovirus* (n = 3) (28, 76, 133); *Clostridium difficile* (n = 3) (19, 86, 136); *Parainfluenza 1&4* virus (n = 2) *(153); Epstein–Barr virus* (n = 2) (17, 88, 102); *Staphylococcus aureus* (n = 2) (99, 158); *Human adenovirus* (n = 2) (19, 133); bacilli (n = 2) (66, 133); *Pneumocystis jirovecii* (n = 2) (112, 139); *Escherichia coli* (n = 2) (7, 86); streptococci (n = 2) (102, 122); *Influenza B* virus (n = 1) (153); *Cytomegalovirus* (n = 1) (61); *Scopulariopsis* species (n = 1) (71); *Human metapneumovirus* (n = 1) (95); respiratory syncytial virus (n = 1) (95); *Absidia corybifera* (n = 1) (171); *Acinetobacter junii* (n = 1) (128); *Salmonella* (n = 1) (132); toxoplasmosis (n = 1) (129); *Rothia mucilaginosa* (n = 1) (136); hepatitis C virus (n = 1) (142); *Klebsiella pneumonia* (n = 1) (154); *Parvovirus B19* (n = 1) (169); BK virus (n = 1) (161) and *Coronavirus NL63* (n = 1) (153)]. Few of those leukaemia children presented with a previous known history of hematopoietic stem cell transplantation (n = 32) [allogeneic (n = 31) (13, 19, 23, 62, 64, 74, 77, 78, 84, 106, 114, 119, 128, 129, 133, 147, 153, 160, 176, 178) and autologous (n = 1) (27)], graft versus host disease (n = 15) (13, 19, 64, 99, 114, 128, 129, 136, 153, 160, 176), immunocompromised status (n = 15) (80, 99, 104, 111, 117, 125, 127, 132, 135, 172), obesity (n = 5) (17, 104), hypertension (n = 4) (13, 19, 66), asthma (n = 3) (104), rhinitis (n = 3) (3, 76, 114), dilated cardiomyopathy (n = 3) (66, 114, 150) and Down syndrome (n = 2) (13, 63), however, a significant number of leukaemic cases who experienced COVID-19 presented with no previous medical history (n = 86, 7.5%) (4, 23, 25, 27, 29, 30, 34, 36, 58, 62, 68, 73, 79, 81, 82, 84, 85, 97, 98, 100, 104, 109, 112, 115, 118-121, 124, 126, 128, 134, 137, 140, 141, 148, 150, 151, 154-159, 163). Most common clinical symptoms from leukaemia were febrile neutropenia (n = 29) (21, 25, 31, 58, 59, 61, 66, 76, 84, 97, 111, 122, 136, 139, 148, 149, 173, 175), sepsis (n = 23) (17, 21, 37, 59, 99, 110, 114, 132, 150, 154, 172, 173), bone marrow suppression (n = 21) (3, 25, 28, 59, 60, 81, 82, 86, 90, 95, 112, 114, 122, 125, 133, 134, 149, 151, 169), multiorgan failure (n = 18) (17, 37, 59, 99, 146, 150, 154) (172, 173, 175), lymphadenopathy (n = 17) (7 cervical, 3 inguinal, 3 multiple, 2 mediastinal, 1 mandibular and 1 hilar) (58, 66, 72, 73, 81, 99, 102, 109, 118, 127, 140, 142, 143), respiratory failure (n = 14) (15, 104, 112, 150, 175), lethargy (n = 13) (3, 28, 58, 85, 94, 95, 102, 125, 132, 133, 142, 149), abdominal pain (n = 12) (14, 58, 81, 89, 111, 120, 132, 151, 156), hepatomegaly (n = 9) (58, 81, 102, 109, 127, 140, 142, 143, 156), diarrhoea (n = 9) (14, 111, 117, 120, 132, 136, 139, 149), splenomegaly (n = 8) (58, 81, 94, 98, 109, 120, 142, 143), vomiting (n = 8) (58, 89, 99, 111, 139, 149, 151), paleness (n = 8) (3, 33, 81, 85, 98, 121, 140, 142), skin rash (n = 8) (58, 61, 102, 109, 111, 136, 140, 149), tumor lysis syndrome (n = 7) (37, 118, 121, 143, 169), septic shock (n = 7) (58, 81, 136, 146, 175), acute kidney injury (n = 6) (99, 108, 149), decreased appetite (n = 5) (28, 61, 120), petechiae (n = 5) (30, 115, 134, 142, 149), hypotension (n = 5) (81, 121, 128, 136, 156), headache (n = 5) (104, 125, 126, 149), encephalopathy (n = 5) (104), thromboembolism (n = 5) (33, 108), weight loss (n = 4) (61, 109,

133, 149), isolated CNS relapse (n = 4) (59, 99, 154), seizures (n = 4) (13, 98, 104, 108), hemophagocytic lymphohistiocytosis (n = 4) (66, 119, 121, 133), fever (n = 4) (28, 132, 158), coagulopathy (n = 3) (61, 89, 99), ascites (n = 3) (59, 89, 140), bruising (n = 3) (85, 109, 149), cardiopulmonary arrest (n = 3) (17, 61, 84) and intracranial haemorrhage (n = 3) (8, 104). As expected, most prescribed therapies in these leukaemic cases infected with SARS-CoV-2 were antibiotics (n = 230) (3, 4, 13-15, 23, 28, 29, 31, 33, 34, 36-39, 58, 59, 61, 63, 66-68, 71, 72, 76, 79, 80, 84, 86, 89, 95, 97, 99, 102, 106, 108-112, 114, 117, 121-123, 128, 133, 136, 139-142, 146, 148-150, 153, 156, 158, 160, 163, 167, 169-173, 176-178), steroids (n = 147) (4, 7, 8, 14, 19, 21, 28, 30, 33, 34, 37-40, 59, 61, 64, 66, 68, 71-73, 79-82, 84, 89, 97-99, 103, 104, 106, 109-111, 115, 117-119, 121, 123, 127, 128, 132, 134, 136, 139, 140, 143, 146, 148, 150, 156, 160, 163, 167, 169, 171-173, 178), oxygen supplementation (n = 131) (13, 14, 17, 37, 40, 71, 72, 76, 80-82, 86, 89, 92, 98, 108, 110-112, 116-118, 120, 122, 123, 125, 128, 129, 136, 139, 142, 146, 149-151, 160, 163, 167, 169, 172, 175, 176), chemotherapy (n = 106) (12, 13, 17, 20, 23, 25, 31, 37, 38, 40, 58, 63, 64, 67, 73, 76-78, 80, 81, 84, 90, 99, 110, 115, 117, 118, 128, 150, 156, 157), hydroxychloroquine (n = 63) (13, 15, 17, 31, 32, 35, 38, 63, 67, 78, 80, 82, 100, 108, 109, 112, 119, 122, 141, 150, 153, 157, 160, 167, 173, 176, 178), intravenous immunoglobulin (n = 40) (7, 8, 28, 30, 31, 37, 38, 59, 66, 72, 80, 81, 89, 99, 106, 110, 111, 114, 123, 125, 133, 136, 139, 146, 156, 169, 175), antivirals (n = 46) (3, 4, 15, 27, 38, 61, 72, 95, 114, 133, 139, 146, 149, 156, 167, 173, 176), packed red blood cells (n = 29) (28, 30, 72, 77, 81, 86, 89, 109, 122, 136, 141, 142, 148-150, 156), anticoagulants (n = 25) (31, 33, 38, 63, 84, 98, 103, 104, 117, 125, 148, 150), remdesivir (n = 33) (17, 37, 61, 71, 78-80, 82, 86, 98, 103, 108, 115, 119, 125, 132, 133, 136, 148, 151, 171), antifungals (n = 43) (58, 61, 66, 71, 72, 86, 95, 106, 110-112, 114, 122, 133, 136, 139-141, 148, 149, 156, 163, 171-173), tocilizumab (n = 27) (19, 63, 64, 92, 99, 104, 108, 112, 119, 122, 125, 171), granulocyte colony-stimulating factor (n = 23) (77, 97, 126, 137, 150, 156), intravenous inotropes (n = 19) (7, 8, 37, 59, 66, 81, 82, 104, 121, 156, 175), intravenous fluids (n = 14) (34, 36, 61, 109, 118, 121, 128, 136, 140, 143, 149, 156), convalescent plasma (n = 10) (64, 79, 99, 100, 103, 111, 125, 139, 156), fresh frozen plasma (n = 9) (64, 140, 150), antiparasitic (n = 9) (39, 77), vincristine (n = 8) (40, 58, 73, 115, 118, 128, 129, 156), favipiravir (n = 8) (69, 150, 158), lopinavir/ritonavir (n = 7) (35, 67, 109, 112, 141, 163), and allogeneic hematopoietic stem cell transplantation (n = 7) (25, 67, 95, 99, 111), nevertheless, treatment for COVID-19 was not necessary in a high number of leukaemic children (n = 74, 6.5%) (19, 26, 39, 40, 59, 78, 85, 120, 123, 124, 135, 143, 151, 153, 154, 170, 175, 177). Children who suffered leukaemia and experienced COVID-19 were more likely to have high C-reactive protein (n = 111) (3, 4, 13, 14, 28, 29, 31, 33, 37, 40, 58, 63, 66, 70, 73, 76, 79-82, 84, 86, 89, 95, 98-100, 102, 106, 107, 109-112, 117, 119, 120, 122, 125, 129, 132, 133, 136, 139, 141, 142, 146, 149, 150, 154, 156, 158, 163, 166, 173), neutropenia (n = 130) (3, 13, 14, 19, 28, 31, 36, 37, 58, 59, 61, 66-68, 71, 72, 76, 79, 80, 82, 84, 94, 97, 98, 102, 111, 112, 114, 122, 124, 126, 129, 131, 134-137, 139, 142, 146, 148-151, 156-158, 167, 168, 172, 173, 175, 177), lymphopenia (n = 96) (3, 4, 13, 23, 28, 29, 31, 59, 61, 67, 68, 72, 78-80, 84, 89, 90, 97, 100, 106, 107, 111, 112, 114, 119, 124, 128, 129, 139, 146, 150, 151, 154, 157, 168, 172, 173, 175, 176), high D-dimer (n = 86) (14, 28, 33, 37, 40, 58, 66, 73, 78, 80, 84, 89, 106, 107, 110, 112, 117, 119, 125, 136, 139, 150, 175), thrombocytopenia (n = 83) (3, 7, 8, 13, 17, 28, 30, 33, 40, 58, 59, 61, 66, 72, 73, 81, 84-86, 89, 94, 98, 99, 102, 106, 109-112, 114, 115, 117, 120, 121, 132, 134, 140-143, 148-150, 154, 156, 158, 166-168, 172, 173), elevated ferritin (n = 68) (7, 13, 14, 28, 31, 40, 58, 66, 73, 76, 84, 89, 99, 100, 110-112, 117, 119-122, 125, 129, 133, 135, 136, 139, 141, 142, 149, 150, 154, 163,

166, 173, 175, 176), low white blood cells (n = 55) (3, 4, 13, 17, 28, 29, 31, 33, 36, 58, 66, 67, 72, 73, 78, 79, 81, 84-86, 98, 99, 102, 111, 112, 114, 121, 124, 129, 132, 140-143, 148, 149, 151, 154-156, 158), low haemoglobin (n = 53) (3, 4, 17, 28, 33, 36, 40, 58, 59, 63, 66, 72, 73, 79, 81, 84, 86, 89, 98, 99, 102, 109, 111, 112, 114, 115, 117, 120, 121, 132, 136, 139-141, 143, 146, 148, 149, 154-156, 158, 166), anaemia (n = 41) (28, 36, 59, 79, 85, 89, 94, 102, 109, 115, 121, 134, 150, 156, 158, 168), high interleukin-6 level (n = 36) (3, 13, 37, 61, 72, 79, 80, 84, 89, 112, 117, 119, 121, 122, 125, 141, 146, 154, 163), high erythrocyte sedimentation rate (n = 35) (28, 33, 37, 58, 73, 98, 132, 136, 150, 154), high lactate dehydrogenase (n = 25) (7, 33, 40, 79, 80, 84, 89, 102, 107, 110, 112, 120, 121, 132, 139, 141, 146, 158, 167), high procalcitonin (n = 19) (31, 63, 72, 76, 86, 95, 106, 110-112, 117, 136, 139, 142, 146, 156, 163), pancytopenia (n = 18) (3, 17, 28, 58, 73, 81, 85, 86, 99, 102, 111, 112, 140, 148, 154, 158), leukopenia (n = 13) (3, 28, 36, 68, 89, 95, 100, 102, 112, 139, 146, 157), elevated liver enzymes (n = 13) (4, 7, 13, 34, 61, 66, 68, 76, 80, 115, 125, 142, 146, 156, 166), leucocytosis (n = 10) (13, 17, 37, 81, 85, 94, 109, 134, 149, 169), high fibrinogen (n = 11) (28, 30, 33, 66, 73, 84, 111, 125, 175), high bilirubin (n = 8) (34, 61, 66, 99, 121, 142, 156, 166), high prothrombin time (n = 7) (34, 58, 61, 63, 89, 109, 111), high partial thromboplastin time (n = 7) (7, 34, 58, 61, 89, 99, 109), high troponin I (n = 7) (31, 81, 99, 156), high uric acid (n = 6) (79, 109, 120, 121, 134, 158) and lymphocytosis (n = 6) (7, 36, 40, 128). COVID-19 in leukaemic children infected with SARS-CoV-2 was asymptomatic (221/1041 = 21.2%) (12, 13, 19-21, 23-27, 31, 39, 59, 67-70, 78, 96, 99, 108, 116, 123, 124, 126, 128, 129, 135, 154, 155, 157, 160, 167, 170, 172, 174-176), mild (n = 524/1041= 50.3%) (3, 4, 8, 12-15, 17-21, 23, 24, 28-32, 35, 37-40, 59, 60, 67, 70, 71, 73-78, 84-86, 90-92, 94-97, 100, 102, 104, 106, 108-110, 113, 114, 116, 118, 119, 123, 127-129, 131, 132, 134, 137, 140, 141, 143, 150, 151, 153, 154, 159, 167, 169, 170, 172, 174-177), moderate (n = 152/1041= 14.6%) (14, 18, 33-40, 59, 60, 62, 63, 67, 74, 75, 78, 92, 104, 108, 116, 120, 123, 129, 133, 150, 153, 158, 163, 167, 169, 171, 173, 177), severe (101/1041= 9.7%) (13, 20, 21, 28, 38-40, 64, 66, 72, 74, 75, 78-80, 82, 84, 89, 92, 98, 103, 104, 107, 108, 111, 113, 115, 117, 119, 121-123, 125, 129, 139, 142, 148-151, 153, 156, 167-169, 171-175, 178) or critical (n = 43/1041= 4.1%) (7, 20, 21, 35, 37-39, 58, 59, 61, 81, 92, 99, 112, 136, 146, 150, 167, 169, 171-173, 175). Most leukaemic paediatric cases did not get multisystem inflammatory syndrome in children (MIS-C) (651/736, 88.4%) (3, 4, 8, 12-15, 17, 19, 23-38, 40, 59, 60, 62-64, 67-71, 73-79, 84-86, 90-92, 94-97, 99, 100, 102-104, 106, 109, 110, 114-116, 118-120, 123, 124, 126-128, 131-135, 137, 140, 141, 143, 150, 151, 153-155, 157-160, 163, 167, 169, 170, 173-177), however, few leukaemic children were reported to experience MIS-C (85/736, 11.5%) (7, 13, 28, 35, 37, 38, 40, 58, 59, 61, 66, 72, 74, 80-82, 84, 89, 92, 98, 99, 104, 107, 111, 112, 117, 121, 122, 125, 136, 139, 142, 146, 148-151, 153, 156, 167, 169, 173, 175, 176). Leukaemic children who tested positive for SARS-CoV-2 were admitted to the intensive care units (n = 155, 13.6%) (7, 8, 13, 18, 20, 21, 35, 37-40, 59, 61, 62, 66, 72, 74, 75, 80-82, 84, 92, 98, 99, 103, 104, 107, 108, 110-113, 115, 116, 119, 121, 123, 129, 139, 142, 146, 148, 150, 153, 154, 160, 167-169, 171-173, 175, 176, 178), intubated and placed on mechanical ventilation (n = 103, 9%) (7, 8, 13, 18, 20, 35, 37-40, 59, 61, 66, 74, 75, 81, 82, 84, 92, 98, 103, 104, 107, 108, 110, 112, 113, 116, 121, 129, 146, 148, 150, 153, 154, 168, 169, 171-173, 175, 176, 178) and suffered acute respiratory distress syndrome (n = 133, 11.6%) (7, 13, 18, 20, 35, 37-40, 59, 61, 64, 66, 72, 74, 75, 80-82, 84, 89, 92, 98, 99, 103, 104, 107, 108, 110-113, 119, 121, 125, 129, 139, 146, 148, 150, 153, 154, 168, 171-173, 175, 176, 178). Paediatric leukaemic cases with concurrent COVID-19 had a documented mortality of 99 (8.7%) (7, 8, 15, 17-21, 35, 37-40, 59-61, 74, 77, 84, 92, 93, 99, 104,

108, 110, 113, 116, 147, 150, 153, 161, 171-173, 175, 176, 178), while 1034 (90.6%) of the leukaemic children recovered (3, 4, 8, 12-15, 18-21, 23-40, 58-60, 62-64, 66-82, 84-86, 89-100, 102-104, 106-109, 111-129, 131-137, 139-143, 146, 148-151, 153-163, 167-177). Mortality was COVID-19-related in a considerable number of paediatric leukaemic cases (41/99, 41.4%) (7, 21, 35, 39, 40, 61, 74, 84, 92, 93, 99, 104, 113, 150, 153, 161, 171, 173, 175, 176), however, COVID-19 was not attributable to death in many of the reported leukaemic children (36/99, 36.4%) (8, 15, 17, 19-21, 37, 39, 40, 59, 60, 77, 92, 104, 108, 110, 116, 154, 171, 173, 175) and few studies failed to report if COVID-19 was a leading or an underlying cause of death in those leukaemic children (22/, 22.2%) (18, 38, 93, 147, 172, 178) (see Table 2).

Lymphoma

Lymphoma was the second most-common blood cancer in children who experienced COVID-19 (n = 133, 10.3%) (12-22, 31, 35, 38-40, 57, 59, 67, 78, 87, 88, 92, 93, 96, 101, 105, 108, 123, 128-130, 144, 145, 150, 152, 164, 165, 169-175, 177, 178) (see Table 1). Among them, 59 have non-Hodgkin's lymphoma (44.4% of all lymphomas) (12, 15, 16, 18, 20-22, 32, 38, 39, 57, 59, 67, 78, 87, 101, 105, 129, 130, 144, 150, 165, 169-171, 174, 175, 177), 38 have unspecified lymphoma (28.6%) (14, 35, 92, 93, 96, 108, 172, 173, 178), and 36 have Hodgkin's lymphoma (27.1%) (13, 15, 17, 19-21, 38, 40, 67, 88, 123, 128, 145, 150, 152, 164, 169-171, 174, 177). Reported blood cancer status for the lymphoma in children infected with SARS-CoV-2 were active (n = 46/82, 56.1%) (12-15, 17, 19, 22, 31, 35, 59, 78, 87, 88, 93, 101, 105, 130, 145, 164, 165, 169, 170), remission (n = 32/82, 39%) (16, 35, 40, 57, 128, 144, 150, 170-173, 175, 177), or relapsed/refractory (n = 4/82, 4.9%) (67, 152, 169), however, blood cancer status in these lymphoma cases was not reported in a high percentage of patients (n = 48/133, 36.1%) (18, 20, 21, 38, 39, 67, 92, 96, 108, 123, 129, 174, 178). The median interquartile range (IQR) age of this group was 180 months [141 to 199.5], with an increased male predominance in lymphoma patients diagnosed with COVID-19 in most of the studies (26/30 = 86.7%) (13, 15-17, 21, 22, 31, 40, 57, 78, 87, 88, 101, 105, 130, 144, 145, 150, 165, 170, 177), and majority of the patients belonged to White (Caucasian) (33/99 = 33.3%) (12, 13, 16, 17, 19, 22, 31, 67, 78, 87, 101, 128-130, 144, 145, 150, 152, 164, 177), Hispanic (33/99 = 33.3%) (14, 18, 38, 39, 93, 105, 175), Indian (22/99 = 22.2%) (21, 165, 169, 172, 174) and Arab (11/99 = 11%) (57, 59, 92, 123, 171, 173, 178) ethnicity. Some of these lymphomatous children infected with SARS-CoV-2 were found to have active concurrent infections (n = 9) [including unspecified fungi (n = 3) (171), *Epstein–Barr virus* (n = 2) (17, 88); *Human immunodeficiency virus* (n = 1) (101); *Pseudomonas aeruginosa* (n = 1) (17); cocci (n = 1) (105) and unspecified bacteria (n = 1) (152)]. Few of those lymphoma children presented with a previous known history of cardiovascular diseases (n = 7) [including superior vena cava syndrome (n = 2) (57, 170), mild mitral regurgitation (n = 1) (88), tricuspid regurgitation (n = 1) (88), pulmonary insufficiency (n = 1) (88), coronary artery ectasia (n = 1) (88) and main bronchus stenosis (n = 1) (170)], hematopoietic stem cell transplantation (n = 5) [autologous (n = 3) (152, 171) and allogeneic (n = 2) (15, 19)], immunocompromised status (n = 1) (88), inborn error of immunity (CD27 deficiency) (n = 1) (88), obesity (n = 1) (145), inherited cancer genes (n = 1) (57), secondary and central nervous system syphilis (n = 1) (101), dermatomyoscitis and myopathy (n = 1) (165) and contractures and deformity (n = 1) (165), however, a significant number of lymphomatous cases who experienced COVID-19 presented with no previous medical history (n = 13, 9.8%) (13, 14, 16, 22, 59, 105, 128, 130, 150, 164). Most common clinical

symptoms from lymphoma were masses (n = 8) (2 mediastinal, 1 transverse colon, 1 nasopharyngeal, 1 adrenal, 1 groin, 1 iliopsoas and 1 parotid glands) (22, 57, 88, 105, 170), lymphadenopathy (n = 6) (2 cervical, 1 neck, 1 supraclavicular, 1 groin and 1 auricular) (57, 88, 105), bleeding (n = 3) (1 gastrointestinal, 1 central nervous system and 1 gingival) (101, 105, 145), respiratory failure (n = 3) (16, 152, 164), sepsis (n = 2) (16, 105), splenomegaly (n = 2) (22, 88), swollen neck (n = 2) (57, 164), abdominal pain (n = 2) (14, 87), multiorgan failure (n = 2) (16, 17) and acute renal failure due to methotrexate intoxication (n = 1) (105). As expected, most prescribed therapies in these lymphomatous cases infected with SARS-CoV-2 were antibiotics (n = 30) (14, 15, 22, 38, 39, 59, 67, 78, 87, 105, 110, 123, 150, 152, 169, 172, 173, 177, 178), chemotherapy (n = 15) (12, 13, 15, 17, 38, 40, 57, 78, 87, 105), steroids (n = 15) (16, 21, 22, 38-40, 59, 87, 123, 130, 150, 152, 171), antivirals (n = 10) (15, 38, 87, 145, 152, 173), oxygen supplementation (n = 11) (14, 17, 40, 59, 67, 78, 145, 150, 152, 169, 175), hydroxychloroquine (n = 8) (17, 67, 78, 108, 145, 150, 173), remdesivir (n = 6) (17, 40, 101, 108, 145, 152), intravenous fluids (n = 5) (15, 22, 145), fresh frozen plasma (n = 4) (22, 145, 150), anticoagulants (n = 4) (16, 59, 145, 175), intravenous inotropes (n = 4) (16, 59, 152, 175), tocilizumab (n = 4) (16, 78, 152, 171), radiotherapy (n = 3) (12, 101, 130), intravenous immunoglobulin (n = 3) (16, 59, 105) and lopinavir/ritonavir (n = 2) (67, 78), nevertheless, treatment for COVID-19 was not necessary in a high number of lymphomatous children (n = 17, 12.8%) (19, 31, 39, 40, 123, 128, 164, 170, 175, 177). Children who suffered lymphoma and experienced COVID-19 were more likely to have lymphopenia (n = 11) (13, 59, 67, 78, 128, 150, 152, 173), thrombocytopenia (n = 9) (17, 40, 88, 145, 150, 172, 173), high C-reactive protein (n = 8) (14, 16, 22, 88, 150, 152), high D-dimer (n = 7) (14, 16, 22, 78, 150), neutropenia (n = 7) (14, 67, 171, 173), low haemoglobin (n = 5) (17, 40, 105, 145), low white blood cells (n = 5) (17, 67, 78, 145), elevated ferritin (n = 4) (14, 16, 105, 150) and high erythrocyte sedimentation rate (n = 3) (88, 150). COVID-19 in lymphomatous children infected with SARS-CoV-2 was asymptomatic (16/115 = %) (12, 21, 31, 39, 88, 123, 129, 172, 178), mild (68/115 = 59.1%) (12-15, 17-22, 35, 38-40, 57, 67, 78, 92, 96, 101, 123, 128-130, 144, 150, 169, 170, 172-175, 177), moderate (19/115 = 16.5%) (16, 21, 35, 38, 39, 67, 87, 92, 108, 150, 169, 171, 174), severe (9/115 = 7.8%) (40, 59, 108, 129, 145, 164, 165, 170, 175) or critical (3/115 = 2.6%) (105, 152, 169). Most lymphomatous paediatric cases did not get MIS-C (78/84, 92.8%) (12-15, 17-19, 22, 31, 35, 38, 40, 57, 67, 78, 87, 88, 92, 96, 101, 123, 128, 130, 144, 150, 164, 169, 170, 173-175, 177), however, few lymphomatous children were reported to experience MIS-C (6/84, 7.1%) (16, 59, 105, 145, 152, 165). Lymphomatous children who tested positive for SARS-CoV-2 were admitted to the intensive care units (n = 16, 12%) (16, 35, 39, 40, 59, 129, 145, 150, 152, 164, 165, 170, 175), intubated and placed on mechanical ventilation (n = 5, 3.7%) (16, 39, 40, 152, 170) and suffered acute respiratory distress syndrome (n = 7, 5.3%) (16, 40, 59, 145, 152, 165, 170). Paediatric lymphomatous cases with concurrent COVID-19 had a documented mortality of 10 (7.5%) (15-17, 38-40, 93, 170), while 119 (89.5%) of the lymphomatous children recovered (12-15, 18-22, 31, 35, 38-40, 57, 59, 67, 78, 87, 88, 93, 96, 101, 105, 108, 123, 128-130, 144, 145, 150, 152, 164, 165, 169-175, 177, 178). COVID-19 was not attributable to death in many of the reported lymphomatous children (7/10, 70%) (15-17, 39, 40, 170) and few studies failed to report if COVID-19 was a leading or an underlying cause of death in those lymphomatous children (3/10, 30%) (38, 93) (see Table 2).

Myelodysplastic syndrome

Myelodysplastic syndrome was the third most-common blood cancer in children who experienced COVID-19 (n = 7, 0.7%) (38, 78, 83, 96, 119, 138, 153) (see Table 1). Reported blood cancer status for the myelodysplastic syndrome in children infected with SARS-CoV-2 were active (n = 1/7, 14.3%) (138) or remission (n = 1/7, 14.3%) (78), however, blood cancer status in these myelodysplastic syndrome cases was not reported in a high percentage of patients (n = 5/7, 71.4%) (38, 83, 96, 119, 153). The median interquartile range (IQR) age of this group was months 156 [143 to 174], with an increased male predominance in myelodysplastic syndrome patients diagnosed with COVID-19 in most of the studies (3/5 = 60%) , and majority of the patients belonged to White (Caucasian) (5/7 = 71.4%) (78, 96, 119, 138, 153) and Hispanic (2/7 = 28.6%) (38, 83) ethnicity. One of these myelodysplastic syndrome children infected with SARS-CoV-2 was found to have active concurrent infections (n = 2) [including *Cytomegalovirus* (n = 1) (138) and *Aspergillus terreus* (n = 1) (138)]. Some myelodysplastic syndrome children presented with a previous known history of allogeneic hematopoietic stem cell transplantation (n = 4) (96, 119, 138, 153), obesity (n = 2) (83, 96), diabetes mellitus (type 2) (n = 1) (96), left ventricular hypertrophy (n = 1) (96), obstructive sleep apnoea (n = 1) (96) and graft versus host disease (n = 1) (138). Two myelodysplastic syndrome children experienced the following clinical symptoms: pneumonitis (n = 1) (83), acute lung injury (n = 1) (83), macrophage activation-like syndrome (n = 1) (83), splenomegaly (n = 1) (83), hemophagocytic lymphohistiocytosis (n = 1) (83), acute renal failure (n = 1) (83), sepsis (n = 1) (83), febrile neutropenia (n = 1) (138), emphysema (n = 1) (138), pneumothorax (n = 1) (138), bronchiectasis (n = 1) (138), bronchiolitis obliterans syndrome (n = 1) (138), thoracic air leak syndrome (n = 1) (138), pulmonary aspergillosis (n = 1) (138), respiratory acidosis (n = 1) (138), and hypercapnia (n = 1) (138). As expected, most prescribed therapies in these myelodysplastic syndrome cases infected with SARS-CoV-2 were antibiotics (n = 3) (83, 138, 153), oxygen supplementation (n = 2) (83, 138), hydroxychloroquine (n = 2) (83, 153), steroids (n = 2) (83, 138), remdesivir (n = 1) (83), tocilizumab (n = 1) (83), favipiravir (n = 1) (138) and antivirals (n = 1) (138), nevertheless, treatment for COVID-19 was not necessary in two myelodysplastic syndrome children (n = 2, 28.6%) (78, 119). Children who suffered myelodysplastic syndrome and experienced COVID-19 were more likely to have high C-reactive protein (n = 2) (83, 119), high interleukin-2 and interleukin-6 levels (n = 2) (83, 119), elevated ferritin (n = 1) (83), high D-dimer (n = 1) (83), neutropenia (n = 1) (138), low haemoglobin (n = 1) (138) and thrombocytopenia (n = 1) (138). COVID-19 in myelodysplastic syndrome children infected with SARS-CoV-2 was mild (5/7 = 71.4%) (38, 78, 119, 138, 153), severe (1/7 = 14.3%) (96) or critical (1/7 = 14.3%) (83). Most myelodysplastic syndrome paediatric cases did not get MIS-C (5/7, 71.4%) (38, 78, 119, 138, 153), however, two myelodysplastic syndrome children were reported to experience MIS-C (2/7, 28.6%) (83, 96). Myelodysplastic syndrome children who tested positive for SARS-CoV-2 were admitted to the intensive care units (n = 3, 42.8%) (83, 96, 138), intubated and placed on mechanical ventilation (n = 2, 28.6%) (83, 138) and suffered acute respiratory distress syndrome (n = 3, 42.8%) (83, 96, 138). Paediatric myelodysplastic syndrome cases with concurrent COVID-19 had a documented mortality of 1 (14.3%) (138), while 6 (85.7%) of the myelodysplastic syndrome children recovered (38, 78, 83, 96, 119, 153).

COVID-19 was not attributable to death in any of the reported myelodysplastic syndrome children (38, 78, 83, 96, 119, 138, 153) (see Table 2).

Langerhans cell histiocytosis

Langerhans cell histiocytosis was the third most-common blood cancer in children who experienced COVID-19 (n = 7, 0.7%) (21, 67, 166, 168-170) (see Table 1). Reported blood cancer status for the Langerhans cell histiocytosis in children infected with SARS-CoV-2 was active (n = 1/7, 14.3%) (169), however, blood cancer status in these Langerhans cell histiocytosis cases was not reported in a high percentage of patients (n = 6/7, 85.7%) (21, 67, 166-168, 170). The median interquartile range (IQR) age of this group was months 15.5 [10 to 15.5], with an increased male predominance in Langerhans cell histiocytosis patients diagnosed with COVID-19 in most of the studies (3/4 = 75%) (21, 166), and majority of the patients belonged to Indian ethnicity (4/7 = 57.1%) (21, 166, 169). One Langerhans cell histiocytosis child experienced the following clinical symptoms: lymphadenopathy (cervical and occipital) (n = 1) (166), oedemas (different part of body) (n = 1) (166), hepatomegaly (n = 1) (166), splenomegaly (n = 1) (166), ascites (n = 1) (166), rash (n = 1) (166), lesions (n = 1) (166) and icterus (n = 1) (166). As expected, most prescribed therapies in these Langerhans cell histiocytosis cases infected with SARS-CoV-2 were antibiotics (n = 2) (67, 169) and hydroxychloroquine (n = 1) (67), nevertheless, treatment for COVID-19 was not necessary in one Langerhans cell histiocytosis child (n = 1, 14.3%) (170). Children who suffered Langerhans cell histiocytosis and experienced COVID-19 were more likely to have high C-reactive protein (n = 1) (166), elevated ferritin (n = 1) (166), neutropenia (n = 1) (67), low haemoglobin (n = 1) (166) and thrombocytopenia (n = 1) (166). COVID-19 in Langerhans cell histiocytosis children infected with SARS-CoV-2 was asymptomatic (2/7 = 28.6%) (67, 166) or mild (5/7 = 71.4%) (21, 168-170). Most Langerhans cell histiocytosis paediatric cases did not get MIS-C (3/7, 42.8%) (67, 168-170), however, one Langerhans cell histiocytosis child was reported to experience MIS-C (1/7, 14.3%) (166). None of the Langerhans cell histiocytosis children who tested positive for SARS-CoV-2 were admitted to the intensive care units, intubated and placed on mechanical ventilation or suffered acute respiratory distress syndrome (21, 67, 166, 168-170). All paediatric Langerhans cell histiocytosis cases with concurrent COVID-19 recovered (21, 67, 166, 168-170) (see Table 2).

Myeloid neoplasm

Myeloid neoplasm was reported in a white child following SARS-CoV-2 infection, with development of hypereosinophilic syndrome, pleural fibrosis, respiratory failure, sepsis and multiorgan failure (65). Patient needed intensive care unit admission, mechanical ventilation, and suffered acute respiratory distress syndrome. This was a mild case of COVID-19 and patient never experienced MIS-C, however, patient died albeit many therapies were offered and final treatment outcome was not COVID-19-related (see Table 1).

Discussion

This systematic review included 1289 blood cancer children with laboratory-confirmed COVID-19 from 155 observational studies to provide an insight into the clinical course and treatment outcomes in paediatric cases with blood cancer who were infected with SARS-CoV-2. To the best of our knowledge, this is the first and largest systematic review to report exclusively on development of SARS-CoV-2 infection in children with blood cancer, in an effort to refine large amounts of data and effectively summarize and analyse evidence in unbiased fashion. Of all the blood cancer types, we found leukaemia was the most common blood cancer (n = 1141, 88.5%) and myeloid neoplasm was the least common blood cancer (n = 1, 0.1%) in children who experienced COVID-19, in line with findings of four previous systematic reviews which reported rate of SARS-CoV-2 infection in children with various types of cancer was highest in the leukaemic cases (10, 179-181). Our finding is also in parallel to the findings reported by Global Burden of Diseases, Injuries, and Risk Factors Study in 2017 that found global rate blood cancer was highest for leukaemias (n = 149,500, 35.9%) (1).

Lack of epidemiological studies to report clinical characteristics and treatment outcomes in children diagnosed with blood cancer and concurrent COVID-19 makes it plausible to compare our review findings with publications that involved adult patients. We report a lower pooled percentage of ICU admission in blood cancer children infected with SARS-CoV-2 compared to the rates reported in adults with blood cancer and COVID-19 in a recent systematic review made in United States (13.6% vs 18.9%) (182) and an older review published from Canada (13.6% vs 21%) (43). Moreover, pooled proportion of blood cancer children who suffered COVID-19 and needed mechanical ventilation was much lower than in blood cancer adults who had concurrent COVID-19 according to two systematic reviews (8.6% vs 15.3% or 17%) (43, 182). Pooled risk of death in our study (8.6%) was lower than the rates reported in blood cancer adults who were infected with SARS-CoV-2 in four reviews made in United States (41.4%) (182), Canada (34%) (43), United Kingdom (32%) (183) and Iran (21.3%) (41). However, we report >twofold higher fatality rate in blood cancer children with COVID-19 compared to the only out-of-date meta-analysis that addressed the mortality of children with blood cancer and COVID-19 which included lower number of studies and fewer paediatric cases (8.6% vs 4%) (43). Our current and comprehensive review included a total of 155 studies that contributed to the refinement of evidence on the clinical characteristics and final treatment outcomes in blood cancer children and concurrent COVID-19 (3, 4, 7, 8, 12-40, 57-178). Across the studies we included in our review, rates of ICU admission and use of mechanical ventilation in blood cancer children with COVID-19 differ due to different healthcare systems, medical practice and admission criteria as well as differences in predisposing factors such as age, comorbidities and testing availability in the patients served. Moreover, there was a large variation in acute respiratory distress syndrome and fatality rates in those blood cancer children infected with SARS-CoV-2, which could be explained by differences in child's baseline characteristics and severity of blood cancer illness and the result of a better clinical management of COVID-19.

Children with blood cancer tend to have milder COVID-19 symptoms and are less likely to be hospitalized and have better prognosis when compared to adults with blood cancer and COVID-19 (41, 43, 182, 183). Our review shown that out of 1289 reported blood cancer children infected with SARS-CoV-2, (n = 239, 18.5%) of patients were asymptomatic and the clinical course of COVID-19 was mild (n = 603, 46.8%) or

moderate (n = 171, 13.3%). Clinical course of COVID-19 in blood cancer children was severe (n = 111, 8.6%) or critical (n = 47, 3.6%), and 41 children (3.2%) eventually died related to COVID-19. Indeed, majority of blood cancer children who died from SARS-CoV-2 infection had relapsed/refractory and advanced blood cancer (7, 37, 74, 77, 92, 147, 150, 171, 173, 176, 178) or significant medical comorbidities in addition to the uncontrollable cancer (17, 19, 21, 65, 99, 104, 108, 110, 138, 150, 153, 170, 172). Lower COVID-19 severity in blood cancer children infected with SARS-CoV-2 compared to the adults can be explained by the following theories: a) Less expression of angiotensin-converting enzyme 2 distribution that may limit SARS-CoV-2 entry into child's body organs and subsequent inflammation, hypoxia, and tissue injury (184), b) Less risk to hyper inflammatory immune response in children (185), and/or c) Immature receptor system, immune-system-specific regulatory mechanisms, and possible cross-protection from other common pathogens in children (186).

In our review, male blood cancer paediatric patients with COVID-19 were predominant among all main blood cancer types and rate of mortality was higher in male children (26/34 = 76.5% deceased male patients). Our findings align with a prior systematic review that demonstrated most blood cancer children infected with COVID-19 were males (179). Male predominance in blood cancer adults infected with SARS-CoV-2 has also been observed previous systematic reviews (41, 181, 182), and severity of COVID-19 and prevalence of infectious diseases are generally higher in male children as described across multiple studies (187-189). We found development of COVID-19 in blood cancer children was highest in people of Hispanic and White (Caucasian) ethnicity (26.8% and 25.7%, respectively). In addition, fatality rate in blood cancer children infected with SARS-CoV-2 was the highest in patients with Hispanic ethnicity (n = 44/111, 39.6%). These findings are consistent with a previous systematic review that shown adult non-White (Caucasian) patients with blood cancer and infected with SARS-CoV-2 had a significantly higher risk of fatality compared with White patients (43). Whether differences in fatality rates among a specific ethnicity could be explained by factors such as inherent biologic risk of poor outcome, impact of comorbidities, impact of social determinants of health, vs clear bias in the provision of health care remains unknown. Perhaps just as importantly, representation of blood cancer in children with other ethnicities at risk to develop COVID-19 can be misleading as most studies we included in our review have been made in paediatric populations of a Hispanic background, therefore, there is less information about the development and health outcomes of SARS-CoV-2 infection in children with blood cancer in different ethnic groups.

Last but not least, it is worth mentioning that most studies included in our review have reported to alter the intensity and regimen of anticancer treatment in blood cancer children during course of SARS-CoV-2 infection, however, many studies have reported to successfully treat COVID-19 in blood cancer children by proceeding with no changes to the anticancer treatment (13, 23, 25, 31, 32, 38, 57, 58, 63, 64, 76, 78, 81, 87, 90, 105, 115, 117, 118, 128, 156, 157). Management of COVID-19 in children with blood cancer is limited and guidelines were largely based on adult data. In general, decision to start, continue or delay anticancer treatment and chemotherapy for blood cancer paediatric patients who had concurrent COVID-19 infection should be made on a case-by-case basis, depending on clinical symptoms and tumor biology (46). Continuation of anticancer treatment in individual paediatric blood cancer patients with SARS-CoV-2

infection seems to be possible, but more data is needed before robust recommendations can be made. Risk of blood cancer progress or relapse due to interruption of anticancer treatment has to be weighed against the risk of severe COVID-19 disease with potentially fatal outcome. Vaccinations against SARS-CoV-2 are now recommended in all patients older than 6 months who are undergoing chemotherapy and after a hematopoietic stem cell transplant in order to reduce the risk of anticancer treatment interruptions and complications that can occur from COVID-19 (190). COVID-19 vaccines were noted to be safe and effective in children, especially those who are immunocompromised (191).

Limitations

We acknowledge that our study was not without some limitations. First, all of the evidence discussed was based on case reports, many cohorts and few case-series, many of these studies were small and performed in single centres and are not necessarily generalizable to COVID-19 children with blood cancer. Second, the low number of cases in major blood cancer categories and subcategories could mean that the cases included in this review are not representative of those groups. Third, data included in this review is in the pre-COVID-19-vaccination and antiviral medications part of the pandemic, and therefore vaccinations and active treatments may impact on the observations made within our study. Last, important findings for COVID-19 outcomes in blood cancer paediatric cases may have been missed due to the exclusion of non-English articles.

Conclusion

Globally, leukaemias were the most prevalent and myeloid neoplasms were the least prevalent blood cancer types in children who developed SARS-CoV-2 infection. Children with blood cancer tend to have milder COVID-19 symptoms and are less likely to be hospitalized and have better prognosis when compared to adults. Continuation of anticancer treatment in individual paediatric blood cancer patients with COVID-19 seems to be possible. COVID-19 vaccines are now recommended to help prevent infection in this vulnerable immunocompromised population of paediatric cancer patients.

Abbreviations

ARDS, Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; HSCT, Hematopoietic stem cell transplantation; FN, Febrile neutropenia; GvHD, Graft versus host disease; MIS-C, Multisystem inflammatory syndrome in children; NOS: Newcastle-Ottawa scale; PRISMA: Preferred Reporting Items for systematic reviews and meta-Analyses; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TLS, Tumor lysis syndrome

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Authors’ contributions

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Competing interests

The authors declare that they have no competing interests.

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Tables

Tables 1 to 2 are available in the Supplementary Files section

Figures

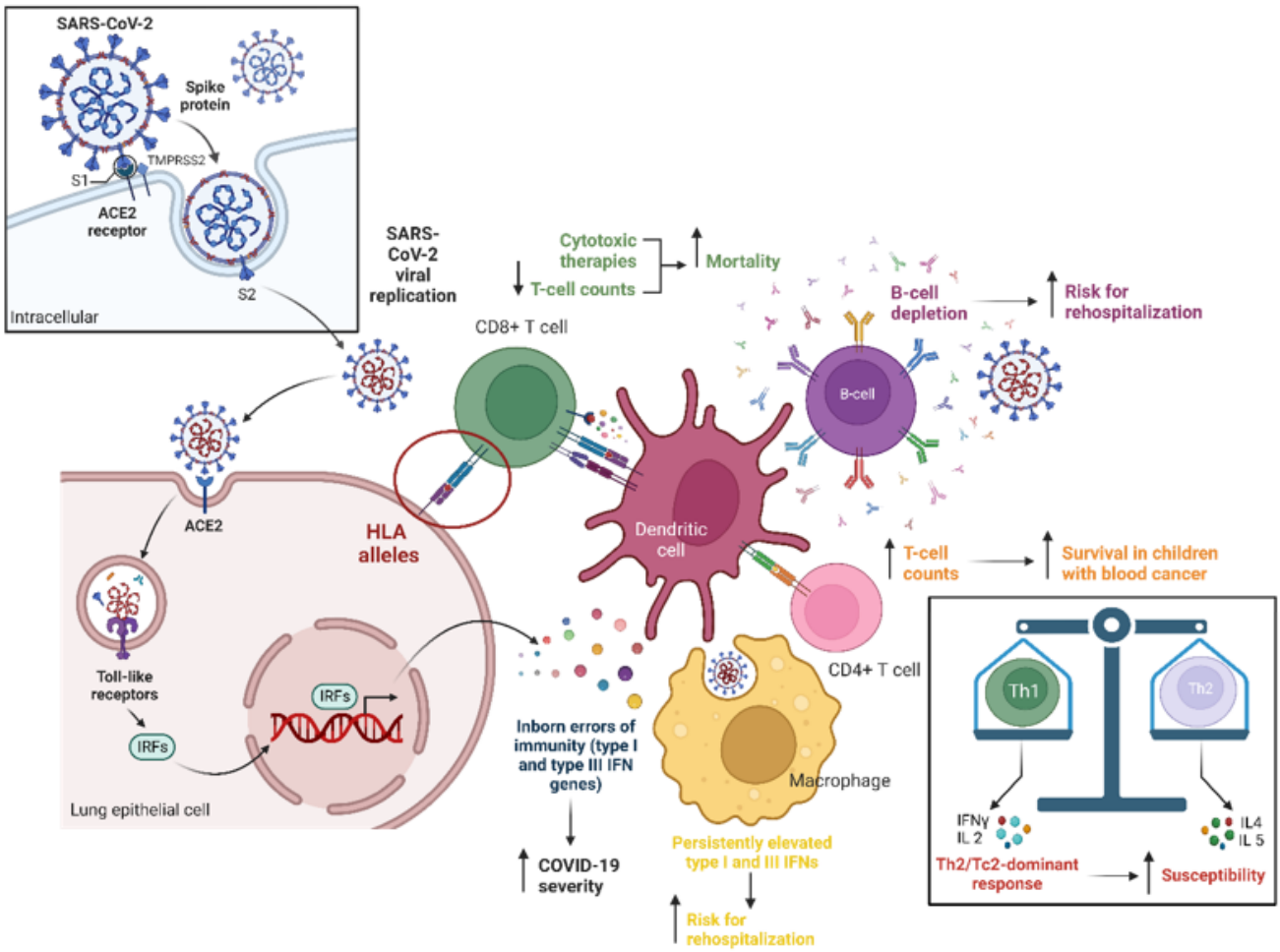

Figure 1

Suggested theories responsible for COVID-19 severity in children with blood cancer. Vulnerability to severe COVID-19 is possibly due to childhood immunocompromised status, immunosuppressive cancer treatments and/or medical comorbidities. Abbreviations: ACE2, angiotensin converting enzyme 2; COVID-19, coronavirus disease 2019; HLA, human leukocyte antigen; IFN, interferon; IFN-γ, interferon-gamma; IL2, interleukin-2; IL4, interleukin-4; IL5, interleukin-5; IRFs, interferon regulatory factors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th1, T-helper 1; Th2, T-helper 2; Tc2, type 2 cytokine secreting cells.

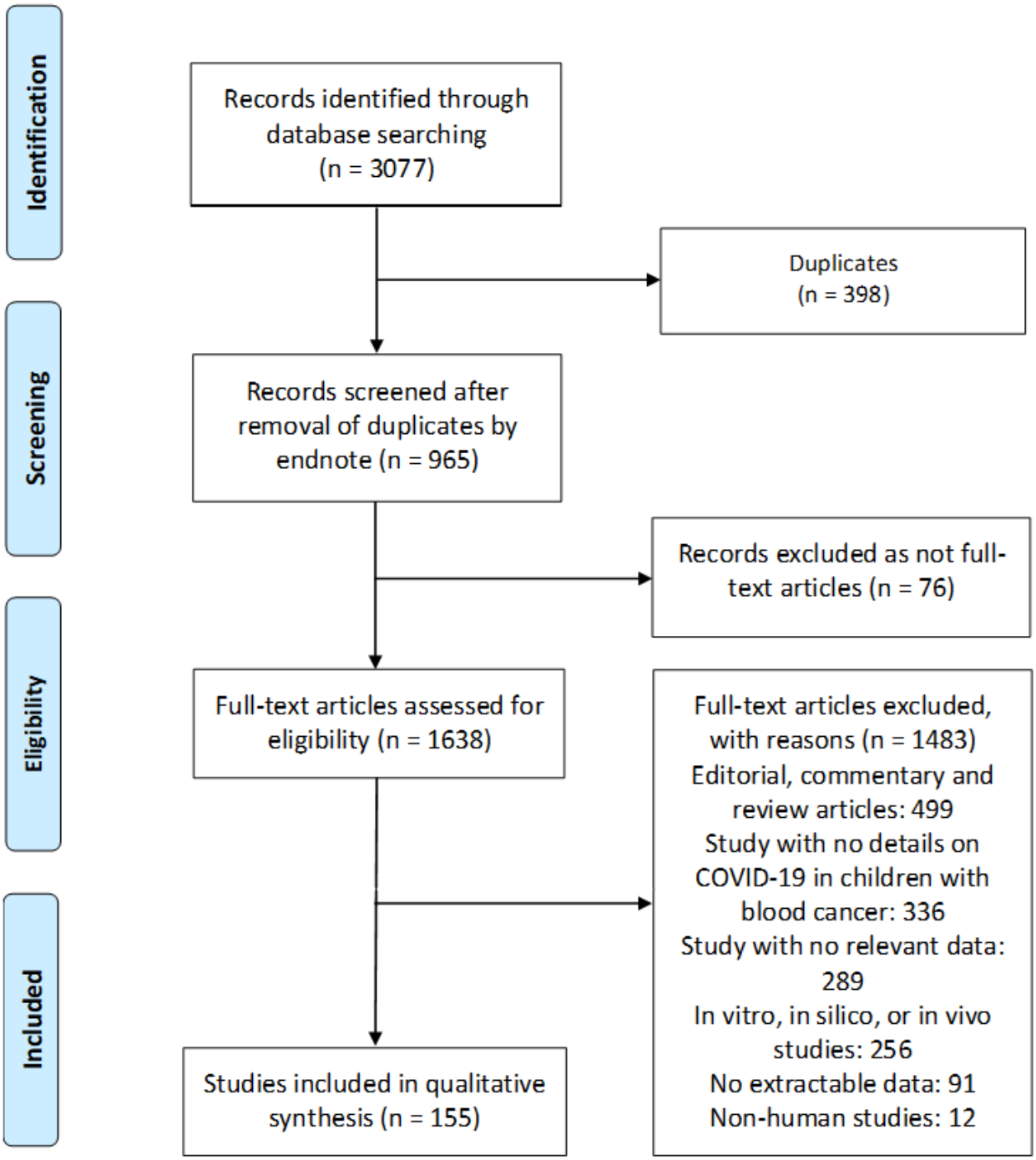

Figure 2

Flow diagram of studies included in the systematic review

Supplementary Files

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