



COVID-19 infection in children with blood cancer: A 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 COVID-19 in children with blood cancer and analyse the demographic parameters, clinical characteristics and treatment outcomes in children with blood cancer with COVID-19 illness.

Methods We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and searched ProQuest, Medline, Embase, PubMed, CINAHL, Wiley online library, Scopus and Nature 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 children with blood cancer 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 severe acute respiratory syndrome coronavirus 2 (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 (MV) (n = 111, 8.6%), suffered acute respiratory distress syndrome (ARDS) (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 78.6% of all included cases (COVID-19 severity: asymptomatic = 238, mild = 601, or moderate = 171). Treatment for COVID-19 was not necessary in a small number of children with blood cancer (n = 94, 7.3%). Fatality in children with blood cancer with COVID-19 was reported in any of the included blood cancer categories for leukaemias (n = 99/1141, 8.7%), non-Hodgkin's lymphomas (n = 7/59, 11.9%), Hodgkin's lymphomas (n = 2/36, 5.5%), myelodysplastic syndrome (n = 1/7, 14.3%) or myeloid neoplasm (n = 1/1, 100%). Fatality rate in children with blood cancer 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 children with blood cancer 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 infected with SARS-CoV-2 may experience higher rates of ICU admission and mortality in comparison with the healthy pediatric populations. Mortality in children with blood cancer and infected with SARS-CoV-2 was highest in cases belonging to male gender and Hispanic ethnicity. However, 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.

Keywords Children · COVID-19 · Blood · Cancer · Haematological · Paediatric · SARS-CoV-2 · Systematic Review

Extended author information available on the last page of the article

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

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]. Previous studies shown majority of pediatric patients with cancer and COVID-19 had blood cancer type of malignancy [5–7]. For example, a global cohort of children with cancer and COVID-19 from 131 institutions in 45 countries shown most cases of SARS-CoV-2 infection occurred in children with a diagnosis of blood cancer (1003/1500, 66.9%) [7]. 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 [8, 9], immunosuppressive cancer treatments and/or comorbidities [4, 10, 11]. 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).

Despite an increasing number of studies regarding COVID-19 in children with cancer [12–14], 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 [15–17]. 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, 10, 11, 18–20], more recent data indicate that paediatric cases with blood cancer may not be at greater risk than others [21–25]. These publications suggest that COVID-19 in paediatric patients with blood cancer is generally asymptomatic [26–30], mild [3, 31–35] or moderate [17, 36–39] in children

receiving anticancer therapy. However, some severe COVID-19 cases have been described, mostly in highly immunocompromised children with severe haematologic malignancies [19, 20, 40–43]. 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) [13, 44–46] or focused on a particular common subtype of blood cancer [47–51].

Therefore, in this systematic review, we will review the available published literature reporting the incidence of COVID-19 in children with blood cancer and analyse the demographic parameters, clinical characteristics and treatment outcomes in children with blood cancer with COVID-19 illness.

Methods

Design

This systematic review was conducted based on the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [52]. Published articles from 1 December 2019 to 30 April 2023, with English language restriction, 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 [53, 54] (see Supplementary Table 1 for search keywords used). 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

We included observational studies that reported real-world development of COVID-19 in children with blood cancer. We excluded 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; non-human studies, or studies available in other languages other than English.

Data extraction

The screening of the papers was performed independently by six reviewers 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 third reviewer was involved.

A standardised data collection form was used to collate information and facilitate study quality assessment and data analysis (see Tables 1, 2, 3, 4, 5, 6, 7, 8 for data extracted and collected).

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 [55]; and [2] NOS to evaluate cohort studies [56]. Quality assessment was conducted by six co-authors who separately evaluated the possibility of bias using these two tools.

Table 1 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and age, gender and blood cancer status (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a	Age	Males ^a	Blood cancer status ^a		
				Active	Remission	Relapsed/ Refractory
Leukaemia	1141 (88.5)	Median 96 months (48–156 months)	185 (16.2)	258 (22.6)	256 (22.4)	60 (5.2)
Lymphoblastic leukaemia, unclassified	579 (50.7)	Median 101.5 months (60–145.5 months)	70 (12.1)	84 (14.5)	140 (24.2)	30 (5.2)
Unspecified leukaemia	202 (17.7)	Median 134.5 months (105–178.2 months)	9 (4.4)	70 (34.6)	34 (16.8)	5 (2.5)
Lymphoblastic leukaemia, B-cell	185 (16.2)	Median 90 months (46.5–168 months)	55 (29.7)	57 (30.8)	42 (22.7)	6 (3.2)
Myeloid leukaemia, unclassified	150 (13.1)	Median 102 months (36–180 months)	36 (24)	37 (24.7)	35 (23.3)	18 (12)
Lymphoblastic leukaemia, T-cell	23 (2)	Median 108 months (84–171.5 months)	14 (60.9)	8 (34.8)	5 (21.7)	1 (4.3)
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	12 months and 18 months	1 (50)	2 (100)	0	0
Non-Hodgkin's lymphoma	59 (4.6)	Median 180 months (132–192 months)	17 (28.8)	16 (27.1)	14 (23.7)	2 (3.4)
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	Median 164 months (118.5–193.5 months)	6 (17.6)	6 (17.6)	6 (17.6)	0
Burkitt's lymphoma	11 (18.6)	Median 186 months (177–196.5 months)	5 (45.4)	3 (27.3)	5 (45.4)	0
T-cell lymphoma	5 (8.5)	72 months & 216 months	2 (40)	3 (60)	0	1 (20)
B-cell lymphoma	4 (6.8)	62 months & 204 months	2 (50)	1 (25)	2 (50)	0
Lymphoblastic lymphoma	3 (5.1)	132 months & 180 months	1 (33.3)	2 (66.7)	1 (33.3)	0
ALCL, positive NPM-ALK transcript	2 (3.4)	144 months	1 (50)	1 (50)	0	1 (50)
Unspecified lymphoma	38 (2.9)	NR	0	22 (57.9)	9 (23.7)	0
Hodgkin's lymphoma	36 (2.8)	Median 192 months (168–204 months)	9 (25)	8 (22.2)	9 (25)	2 (5.5)
Langerhans cell histiocytosis	7 (0.5)	10 months & 21 months	3 (42.8)	1 (14.3)	0	0
Myelodysplastic syndrome	7 (0.5)	Median 156 months (143–174 months)	3 (42.8)	1 (14.3)	1 (14.3)	0
Myeloid neoplasm	1 (0.1)	NR	NR	1 (100)	0	0
Total	1289 (100)	Median 108 months (57–178.5 months)	217 (16.8)	307 (23.8)	289 (22.4)	64 (5)

Abbreviations: ALCL, anaplastic large cell lymphoma; COVID-19, coronavirus disease 2019; NR, not reported

^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

Table 2 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and ethnicity (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a	Ethnicity								
		Hispanic ^a	White (Caucasian) ^a	Arab ^a	Indian ^a	Persian ^a	Asian ^a	Jew ^a	Pakistani ^a	Black ^{a,b}
Leukaemia	1141 (88.5)	310 (27.2)	292 (25.6)	160 (14)	134 (11.7)	28 (2.4)	16 (1.4)	10 (0.9)	6 (0.5)	3 (0.3)
Lymphoblastic leukaemia, unclassified	579 (50.7)	113 (19.5)	128 (22.1)	102 (17.6)	91 (15.7)	21 (3.6)	8 (1.4)	10 (1.7)	3 (0.5)	0
Unspecified leukaemia	202 (17.7)	56 (27.7)	82 (40.6)	0	0	0	2 (1)	0	0	0
Lymphoblastic leukaemia, B-cell	185 (16.2)	93 (50.3)	52 (28.1)	11 (5.9)	20 (10.8)	2 (1.1)	4 (2.2)	0	1 (0.5)	2 (1.1)
Myeloid leukaemia, unclassified	150 (13.1)	39 (26)	23 (15.3)	44 (29.3)	17 (11.3)	5 (3.3)	2 (1.3)	0	2 (1.3)	1 (0.7)
Lymphoblastic leukaemia, T-cell	23 (2)	9 (39.1)	6 (26.1)	2 (8.7)	6 (26.1)	0	0	0	0	0
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	0	1 (50)	1 (50)	0	0	0	0	0	0
Non-Hodgkin's lymphoma	59 (4.6)	21 (35.6)	20 (33.9)	3 (5.1)	9 (15.2)	2 (3.4)	0	2 (3.4)	0	0
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	15 (44.1)	13 (38.2)	1 (2.9)	4 (11.8)	1 (2.9)	0	0	0	0
Burkitt's lymphoma	11 (18.6)	3 (27.3)	2 (18.2)	1 (9.1)	0	1 (9.1)	0	2 (18.2)	0	0
T-cell lymphoma	5 (8.5)	0	1 (20)	0	4 (80)	0	0	0	0	0
B-cell lymphoma	4 (6.8)	1 (25)	2 (50)	0	1 (25)	0	0	0	0	0
Lymphoblastic lymphoma	3 (5.1)	1 (33.3)	1 (33.3)	1 (33.3)	0	0	0	0	0	0
ALCL, positive NPM-ALK transcript	2 (3.4)	1 (50)	1 (50)	0	0	0	0	0	0	0
Unspecified lymphoma	38 (2.9)	8 (21)	1 (2.6)	4 (10.5)	4 (10.5)	0	0	0	0	0
Hodgkin's lymphoma	36 (2.8)	4 (11.1)	12 (33.3)	4 (11.1)	9 (25)	2 (5.5)	0	1 (2.8)	2 (5.5)	0
Langerhans cell histiocytosis	7 (0.5)	0	1 (14.3)	0	4 (57.1)	0	1 (14.3)	1 (14.3)	0	0
Myelodysplastic syndrome	7 (0.5)	2 (28.6)	5 (71.4)	0	0	0	0	0	0	0
Myeloid neoplasm	1 (0.1)	1 (100)	0	0	0	0	0	0	0	0
Total	1289 (100)	346 (26.8)	331 (25.7)	171 (13.3)	160 (12.4)	32 (2.5)	17 (1.3)	14 (1.1)	8 (0.6)	3 (0.2)

Abbreviations: ALCL, anaplastic large cell lymphoma; COVID-19, coronavirus disease 2019

^aData are presented as number (%). Data were calculated based on patients for whom the information were available^bPatients with black ethnicity include African-American, Black African, African and Afro-Caribbean patients

Percentages do not total 100% owing to missing data

Table 3 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and medical comorbidities (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a Medical comorbidities											
	ACIs ^a	HSCT ^a	GvHD ^a	ICS ^a	CVD ^a	Obesity ^a	HTN ^a	Asthma ^a	Rhinitis ^a	DS ^a	DM ^a	IEIs ^a CVST ^a
Leukaemia	1141 (88.5)	33 (2.9)	15 (1.3)	15 (1.3)	4 (0.3)	5 (0.4)	4 (0.3)	3 (0.3)	3 (0.3)	2 (0.2)	1 (0.1)	1 (0.1)
Lymphoblastic leukaemia, unclassified	579 (50.7)	9 (1.5)	2 (0.3)	7 (1.2)	1 (0.2)	4 (0.7)	0	3 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.2)
Unspecified leukaemia	202 (17.7)	3 (1.5)	2 (1)	0	0	0	0	0	0	0	0	0
Lymphoblastic leukaemia, B-cell	185 (16.2)	9 (4.9)	2 (1.1)	4 (2.2)	1 (0.5)	0	2 (1.1)	0	0	1 (0.5)	0	0
Myeloid leukaemia, unclassified	150 (13.1)	12 (8)	8 (5.3)	4 (1.3)	1 (0.7)	1 (0.7)	2 (1.3)	0	1 (0.7)	1 (0.7)	0	0
Lymphoblastic leukaemia, T-cell	23 (2)	0	0	0	0	0	0	0	1 (4.3)	0	0	0
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	0	1 (50)	0	1 (50)	0	0	0	0	0	0	0
Non-Hodgkin's lymphoma	59 (4.6)	0	0	0	3 (5.1)	0	0	0	0	0	0	0
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	0	0	0	0	0	0	0	0	0	0	0
Burkitt's lymphoma	11 (18.6)	0	0	0	3 (27.3)	0	0	0	0	0	0	0
T-cell lymphoma	5 (8.5)	0	0	0	0	0	0	0	0	0	0	0
B-cell lymphoma	4 (6.8)	0	0	0	0	0	0	0	0	0	0	0
Lymphoblastic lymphoma	3 (5.1)	0	0	0	0	0	0	0	0	0	0	0
ALCL, positive NPM-ALK transcript	2 (3.4)	1 (50)	0	0	0	0	0	0	0	0	0	0
Unspecified lymphoma	38 (2.9)	0	0	0	0	0	0	0	0	0	0	0
Hodgkin's lymphoma	36 (2.8)	5 (13.9)	0	1 (2.8)	4 (11.1)	1 (2.8)	0	0	0	0	0	1 (2.8)
Langerhans cell histiocytosis	7 (0.5)	0	0	0	0	0	0	0	0	0	0	0
Myelodysplastic syndrome	7 (0.5)	4 (57.1)	1 (14.3)	0	1 (14.3)	2 (28.6)	0	0	0	0	1 (14.3)	0
Myeloid neoplasm	1 (0.1)	0	0	0	1 (100)	0	0	0	0	0	0	0
Total	1289 (100)	42 (3.2)	16 (1.2)	16 (1.2)	13 (1)	8 (0.6)	4 (0.3)	3 (0.2)	3 (0.2)	2 (0.1)	2 (0.1)	1 (0.1)

Abbreviations: ACIs, active concurrent infections; ALCL, anaplastic large cell lymphoma; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; CVST, cerebral venous sinus thrombosis; DM, diabetes mellitus; DS, Down syndrome; GvHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; ICS, immunocompromised status; IEIs, inborn errors of immunity

^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

Table 4 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and symptoms from blood cancer (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a	Symptoms from blood cancer													
		FN ^a	Sepsis ^a	BMS ^a	MOF ^a	LAP ^a	RF ^a	Lethargy ^a	AP ^a	Sm ^a	Hm ^a	Diarrhoea ^a	Paleness ^a	Vomiting ^a	Skin rash ^a
Leukaemia	1141 (88.5)	29 (2.5)	23 (2)	21 (1.8)	18 (1.6)	14 (1.2)	14 (1.2)	13 (1.1)	12 (1)	8 (0.7)	9 (0.8)	9 (0.8)	8 (0.7)	8 (0.7)	8 (0.7)
Lymphoblastic leukaemia, unclassified	579 (50.7)	6 (1)	9 (1.5)	5 (0.9)	7 (1.2)	2 (0.3)	9 (1.5)	2 (0.3)	2 (0.3)	1 (0.2)	2 (0.3)	1 (0.2)	2 (0.3)	0	1 (0.2)
Unspecified leukaemia	202 (17.7)	0	0	1 (0.5)	0	0	0	0	3 (1.5)	0	0	2 (1)	0	0	0
Lymphoblastic leukaemia, B-cell	185 (16.2)	12 (6.5)	3 (1.6)	11 (5.9)	6 (3.2)	10 (5.4)	5 (2.7)	10 (5.4)	6 (3.2)	7 (3.8)	7 (3.8)	3 (1.6)	6 (3.2)	6 (3.2)	5 (2.7)
Myeloid leukaemia, unclassified	150 (13.1)	9 (6)	10 (6.7)	4 (2.7)	4 (2.7)	0	0	1 (0.7)	1 (0.7)	0	0	3 (2)	0	2 (1.3)	2 (1.3)
Lymphoblastic leukaemia, T-cell	23 (2)	2 (8.7)	1 (4.3)	0	1 (4.3)	1 (4.3)	0	0	0	0	0	0	0	0	0
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	0	0	0	0	1 (4.3)	0	0	0	0	0	0	0	0	0
Non-Hodgkin's lymphoma	59 (4.6)	0	2 (3.4)	0	1 (1.7)	2 (3.4)	1 (1.7)	0	1 (1.7)	1 (1.7)	0	0	0	0	0
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	0	0	0	0	0	0	0	0	1 (2.9)	0	0	0	0	0
Burkitt's lymphoma	11 (18.6)	0	1 (9.1)	0	1 (9.1)	1 (9.1)	1 (9.1)	0	0	0	0	0	0	0	0
T-cell lymphoma	5 (8.5)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B-cell lymphoma	4 (6.8)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymphoblastic lymphoma	3 (5.1)	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0
ALCL, positive NPM-ALK transcript	2 (3.4)	0	1 (50)	0	0	1 (50)	0	0	0	0	0	0	0	0	0
Unspecified lymphoma	38 (2.9)	0	0	0	0	0	0	0	1 (2.6)	0	0	1 (2.6)	0	0	0
Hodgkin's lymphoma	36 (2.8)	0	0	0	1 (2.8)	1 (2.8)	2 (5.5)	1 (2.8)	0	1 (2.8)	0	0	0	0	0
Langerhans cell histiocytosis	7 (0.5)	0	0	0	0	1 (14.3)	0	0	0	1 (14.3)	1 (14.3)	0	1 (14.3)	0	0
Myelodysplastic syndrome	7 (0.5)	1 (14.3)	1 (14.3)	0	0	0	0	0	0	1 (14.3)	0	0	0	0	0
Myeloid neoplasm	1 (0.1)	0	1 (100)	0	1 (100)	0	1 (100)	0	0	0	0	0	0	0	0
Total	1289 (100)	30 (2.3)	27 (2.1)	21 (1.6)	21 (1.6)	18 (1.4)	18 (1.4)	14 (1.1)	14 (1.1)	12 (0.9)	10 (0.8)	10 (0.8)	9 (0.7)	8 (0.6)	8 (0.6)

Abbreviations: ALCL, anaplastic large cell lymphoma; AP, abdominal pain; BMS, bone marrow suppression; COVID-19, coronavirus disease 2019; FN, febrile neutropenia; Hm, hepatomegaly; LAP, lymphadenopathy; MOF, multiorgan failure; RF, respiratory failure; Sm, splenomegaly

^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

Table 5 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and laboratory findings (n = 155 studies), 2020–2023

Type of blood cancer	Num-ber of patients ^a	Most laboratory findings													
		Neutrope-nia ^a	High CRP ^a	Lympho-penia ^d	High D-dimer ^a	Throm-bocyte-penia ^a	Elevated ferritin ^a	Low WBCs ^a	Low Hb ^a	Anaemia ^a	High ESR ^a	High IL-6 ^a	High LDH ^a	High procalcitonin ^a	Pancytopenia ^a
Leukae-mia	1141 (88.5)	130 (11.4)	110 (9.6)	96 (8.4)	86 (7.5)	82 (7.2)	67 (5.9)	55 (4.8)	51 (4.5)	41 (3.6)	35 (3.1)	36 (3.1)	25 (2.2)	19 (1.7)	17 (1.5)
Lympho-blastic leukaemia, unclassified	579 (50.7)	36 (6.2)	30 (5.2)	47 (8.1)	23 (4)	31 (5.3)	14 (2.4)	16 (2.8)	11 (1.9)	21 (3.6)	14 (2.4)	4 (0.7)	8 (1.4)	4 (0.7)	3 (0.5)
Unspeci-fied leukaemia	202 (17.7)	7 (3.5)	8 (4)	2 (1)	6 (3)	1 (0.5)	6 (3)	0	0	1 (0.5)	0	0	1 (0.5)	0	0
Lympho-blastic leukaemia, B-cell	185 (16.2)	53 (28.6)	49 (26.5)	29 (15.7)	37 (20)	30 (16.2)	30 (16.2)	28 (15.1)	29 (15.7)	15 (8.1)	15 (8.1)	23 (12.4)	12 (6.5)	9 (4.9)	10 (5.4)
Myeloid leukaemia, unclassified	150 (13.1)	26 (17.3)	18 (12)	15 (10)	12 (8)	19 (12.7)	14 (9.3)	9 (6)	10 (6.7)	4 (2.7)	5 (3.3)	3 (2)	4 (2.7)	5 (3.3)	3 (2)
Lympho-blastic leukaemia, T-cell	23 (2)	8 (34.8)	4 (17.4)	3 (13)	8 (34.8)	0	2 (8.7)	1 (4.3)	0	0	1 (4.3)	6 (26.1)	0	1 (4.3)	0
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	0	1 (50)	0	0	1 (50)	1 (50)	1 (50)	1 (50)	0	0	0	0	0	1 (50)

Table 5 (continued)

Type of blood cancer	Num-ber of patients ^a	Most laboratory findings													
		Neutrope-nia ^a	High CRP ^a	Lympho-penia ^a	High D-dimer ^a	Throm-bocyte-penia ^a	Elevated ferritin ^a	Low WBCs ^a	Low Hb ^a	Anaemia ^a	High ESR ^a	High IL-6 ^a	High LDH ^a	High procalcitonin ^a	Pancytopenia ^a
Non-Hodg-kin's lymphoma	59 (4.6)	2 (3.4)	4 (6.8)	5 (8.5)	5 (4.5)	2 (3.4)	3 (5.1)	2 (3.4)	1 (1.7)	1 (1.7)	1 (1.7)	0	0	0	
Non-Hodg-kin's lymphomas (unclassified)	34 (57.6)	1 (2.9)	3 (8.8)	3 (8.8)	4 (11.8)	2 (5.9)	1 (2.9)	1 (2.9)	0	0	1 (2.9)	0	0	0	
Burkitt's lymphoma	11 (18.6)	0	1 (9.1)	0	1 (9.1)	0	1 (9.1)	0	0	0	0	0	0	0	
T-cell lymphoma	5 (8.5)	0	0	0	0	0	0	0	0	0	0	0	0	0	
B-cell lymphoma	4 (6.8)	0	0	0	0	0	0	0	0	0	0	0	0	0	
Lympho-blastic lymphoma	3 (5.1)	0	0	1 (33.3)	0	0	0	0	0	0	0	0	0	0	
ALCL, positive NPM-ALK trans-script	2 (3.4)	1 (50)	0	1 (50)	0	0	1 (50)	1 (50)	1 (50)	0	0	0	0	0	
Unspecified lymphoma	38 (2.9)	2 (5.3)	1 (2.6)	1 (2.6)	1 (2.6)	2 (5.3)	1 (2.6)	0	0	0	0	0	0	0	
Hodg-kin's lymphoma	36 (2.8)	3 (8.3)	3 (8.3)	5 (13.9)	1 (2.8)	5 (13.9)	0	3 (8.3)	4 (11.1)	1 (2.8)	2 (5.5)	0	1 (2.8)	1 (2.8)	2 (5.5)

Table 5 (continued)

Type of blood cancer	Num-ber of patients ^a	Most laboratory findings													
		Neutrope-nia ^a	High CRP ^a	Lympho-penia ^a	High D-dimer ^a	Throm-bocyte-penia ^a	Elevated ferritin ^a	Low WBCs ^a	Low Hb ^a	Anaemia ^a	High ESR ^a	High IL-6 ^a	High LDH ^a	High procalcitonin ^a	Pancytopenia ^a
Langerhans cell histiocytosis	7 (0.5)	1 (14.3)	1 (14.3)	0	0	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)	0	0	0	0	0	0
Myelodysplastic syndrome	7 (0.5)	1 (14.3)	2 (28.6)	0	1 (14.3)	1 (14.3)	1 (14.3)	0	1 (14.3)	0	0	0	0	0	0
Myeloid neoplasm	1 (0.1)	0	0	0	1 (100)	0	0	0	0	1 (100)	0	1 (100)	0	0	0
Total	1289 (100)	139 (10.8)	121 (9.4)	107 (8.3)	95 (7.4)	93 (7.2)	72 (5.6)	61 (4.7)	58 (4.5)	44 (3.4)	38 (2.9)	37 (2.9)	26 (2)	20 (1.5)	19 (1.5)

Abbreviations: ALCL, anaplastic large cell lymphoma; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; IL-6, interleukin-6; LDH, lactate dehydrogenase; WBCs, white blood cells

^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

Table 6 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and COVID-19 severity or if children experienced MIS-C (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a	COVID-19 severity					If children experienced MIS-C	
		Asymptomatic ^a	Mild ^a	Moderate ^a	Severe ^a	Critical ^a	Yes ^a	No ^a
Leukaemia	1141 (88.5)	220 (19.3)	522 (45.7)	152 (13.3)	101 (8.8)	43 (3.8)	85 (7.4)	703 (61.6)
Lymphoblastic leukaemia, unclassified	579 (50.7)	133 (23)	237 (41)	66 (11.4)	48 (8.3)	17 (2.9)	25 (4.3)	314 (54.2)
Unspecified leukaemia	202 (17.7)	49 (24.2)	114 (56.4)	11 (1.9)	3 (1.5)	2 (1)	11 (5.4)	142 (70.3)
Lymphoblastic leukaemia, B-cell	185 (16.2)	17 (9.2)	93 (50.3)	39 (21.1)	23 (12.4)	11 (5.9)	28 (15.1)	139 (75.1)
Myeloid leukaemia, unclassified	150 (13.1)	17 (11.3)	65 (43.3)	33 (22)	24 (16)	11 (7.3)	18 (12)	86 (57.3)
Lymphoblastic leukaemia, T-cell	23 (2)	3 (13)	13 (56.5)	3 (13)	3 (13)	1 (4.3)	2 (8.7)	21 (91.3)
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	1 (50)	0	0	0	1 (50)	1 (50)	1 (50)
Non-Hodgkin's lymphoma	59 (4.6)	6 (10.2)	26 (44.1)	9 (15.2)	5 (8.5)	2 (3.4)	4 (6.8)	31 (52.5)
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	4 (11.8)	13 (38.2)	4 (11.8)	2 (5.9)	0	1 (2.9)	13 (38.2)
Burkitt's lymphoma	11 (18.6)	1 (9.1)	8 (72.7)	1 (9.1)	1 (9.1)	0	1 (9.1)	8 (72.7)
T-cell lymphoma	5 (8.5)	0	2 (40)	2 (40)	0	1 (20)	0	4 (80)
B-cell lymphoma	4 (6.8)	1 (25)	3 (75)	0	0	0	0	3 (75)
Lymphoblastic lymphoma	3 (5.1)	0	0	1 (33.3)	2 (66.7)	0	1 (33.3)	2 (66.7)
ALCL, positive NPM-ALK transcript	2 (3.4)	0	0	1 (50)	0	1 (50)	1 (50)	1 (50)
Unspecified lymphoma	38 (2.9)	3 (7.9)	21 (55.3)	6 (15.8)	1 (2.6)	0	0	23 (60.5)
Hodgkin's lymphoma	36 (2.8)	7 (19.4)	21 (58.3)	4 (11.1)	3 (8.3)	1 (2.8)	2 (5.5)	24 (66.7)
Langerhans cell histiocytosis	7 (0.5)	2 (28.6)	5 (71.4)	0	0	0	1 (14.3)	4 (57.1)
Myelodysplastic syndrome	7 (0.5)	0	5 (71.4)	0	1 (14.3)	1 (14.3)	2 (28.6)	5 (71.4)
Myeloid neoplasm	1 (0.1)	0	1 (100)	0	0	0	0	1 (100)
Total	1289 (100)	238 (18.5)	601 (46.6)	171 (13.3)	111 (8.6)	47 (3.6)	94 (7.3)	791 (61.4)

Abbreviations: ALCL, anaplastic large cell lymphoma; COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children

^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

Data analysis

We examined primarily the proportion of confirmed COVID-19 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 [53, 54]. 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) [57]. Multisystem inflammatory syndrome in children (MIS-C) was defined according to the current United States Centers for Disease Control and Prevention case definition in an individual aged < 21 years [58]. Cancer status was defined

as per the American Cancer Society (active, remission and relapsed/refractory) [59].

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were used to summarise the data.

Results

Study characteristics and quality

A total of 3077 publications were identified (Fig. 1). 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, 6, 10, 11, 15–43, 60–180]. The reports of one thousand two hundred and eighty-nine cases identified

Table 7 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer and most used therapies (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a	Most used therapies													
		ABs ^a	Steroids ^a	O ₂ suppl. ^a	CTX ^a	HCO ^a	Antivirals ^a	IVIg ^a	RDV ^a	ACTs ^a	TOZ ^a	Packed RBCs ^a	CP ^a	FPV ^a	LPV/RTV ^a
Leukaemia	1141 (88.5)	228 (20)	145 (12.7)	131 (11.5)	106 (9.3)	63 (5.5)	46 (4)	40 (3.5)	33 (2.9)	30 (2.6)	27 (2.4)	29 (2.5)	10 (0.9)	8 (0.7)	7 (0.6)
Lymphoblastic leukaemia, unclassified	579 (50.7)	122 (21.1)	68 (11.7)	71 (12.3)	17 (2.9)	25 (4.3)	13 (2.2)	12 (2.1)	11 (1.9)	14 (2.4)	10 (1.7)	16 (2.8)	0	5 (0.9)	1 (0.2)
Unspecified leukaemia	202 (17.7)	8 (4)	5 (2.5)	7 (3.5)	0	3 (1.5)	2 (1)	0	1 (0.5)	1 (0.5)	0	0	1 (0.5)	0	1 (0.5)
Lymphoblastic leukaemia, B-cell	185 (16.2)	51 (27.6)	42 (22.7)	28 (15.1)	55 (29.7)	14 (7.6)	17 (9.2)	19 (10.3)	9 (4.9)	7 (3.8)	5 (2.7)	8 (4.3)	7 (3.8)	1 (0.5)	3 (1.6)
Myeloid leukaemia, unclassified	150 (13.1)	37 (24.7)	25 (16.7)	22 (14.7)	22 (14.7)	17 (11.3)	12 (8)	7 (4.7)	9 (6)	8 (5.3)	11 (7.3)	5 (3.3)	2 (1.3)	2 (1.3)	2 (1.3)
Lymphoblastic leukaemia, T-cell	23 (2)	8 (34.8)	5 (21.7)	3 (13)	11 (47.8)	4 (17.4)	2 (8.7)	1 (4.3)	3 (13)	0	1 (4.3)	0	0	0	0
Biphenotypic leukaemia (lympho-blastic & myeloid)	2 (0.2)	2 (100)	0	0	1 (50)	0	0	1 (50)	0	0	1 (50)	0	0	0	0
Non-Hodgkin's lymphoma	59 (4.6)	17 (28.8)	11 (18.6)	6 (10.2)	10 (16.9)	3 (5.1)	5 (8.5)	3 (5.1)	1 (1.7)	3 (5.1)	3 (5.1)	0	1 (1.7)	1 (1.7)	2 (3.4)
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	9 (26.5)	7 (20.6)	2 (5.9)	6 (17.6)	2 (5.9)	3 (8.8)	0	0	0	2 (6.2)	0	0	1 (2.9)	1 (2.9)
Burkitt's lymphoma	11 (18.6)	1 (9.1)	1 (9.1)	0	2 (18.2)	0	1 (9.1)	1 (9.1)	0	1 (9.1)	1 (9.1)	0	0	0	0
T-cell lymphoma	5 (8.5)	3 (60)	1 (20)	1 (20)	0	0	0	0	0	0	0	0	0	0	0
B-cell lymphoma	4 (6.8)	0	0	0	0	0	0	0	1 (25)	0	0	0	0	0	0
Lymphoblastic lymphoma	3 (5.1)	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	0	1 (33.3)	1 (33.3)	0	2 (66.7)	0	0	1 (33.3)	0	0
ALL, positive NPM-ALK transcript	2 (3.4)	2 (100)	0	1 (50)	1 (50)	1 (50)	0	1 (50)	0	0	0	0	0	0	1 (50)
Unspecified lymphoma	38 (2.9)	7 (18.4)	0	1 (2.6)	0	3 (7.9)	1 (2.6)	0	1 (2.6)	0	0	0	0	0	0

Table 7 (continued)

Type of blood cancer	Number of patients ^a	Most used therapies													
		ABs ^a	Steroids ^a	O ₂ suppl. ^a	CTx ^a	HCQ ^a	Antivirals ^a	IVIg ^a	RDV ^a	ACTs ^a	TOZ ^a	Packed RBCs ^a	CP ^a	FPV ^a	LPV/RTV ^a
Hodgkin's lymphoma	36 (2.8)	6 (16.7)	4 (11.1)	4 (11.1)	5 (13.9)	2 (5.5)	4 (11.1)	0	4 (11.1)	1 (2.8)	1 (2.8)	0	0	0	0
Langerhans cell histiocytosis	7 (0.5)	2 (28.6)	0	0	0	1 (14.3)	0	1 (14.3)	0	0	0	1 (14.3)	0	0	0
Myelodysplastic syndrome	7 (0.5)	2 (28.6)	2 (28.6)	2 (28.6)	0	2 (28.6)	1 (14.3)	0	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)	0	1 (14.3)	0
Myeloid neoplasm	1 (0.1)	1 (100)	1 (100)	1 (100)	0	0	0	1 (100)	1 (100)	1 (100)	0	0	0	0	0
Total	1289 (100)	263 (20.4)	163 (12.6)	145 (11.2)	121 (9.4)	74 (5.7)	57 (4.4)	45 (3.5)	41 (3.2)	36 (2.8)	32 (2.5)	31 (2.4)	11 (0.8)	10 (0.8)	9 (0.7)

Abbreviations: ABs, antibiotics; ACTs, anticoagulants; ALCL, anaplastic large cell lymphoma; COVID-19, coronavirus disease 2019; CP, convalescent plasma; CTx, chemotherapy; FPV, favipiravir; HCO, hydroxychloroquine; IVIG, intravenous immunoglobulin; LPV/RTV, lopinavir-ritonavir; O₂ suppl., oxygen supplementation; RBCs, red blood cells; RDV, remdesivir; TOZ, tocilizumab
^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

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 [53, 54]. There were 83 case report, 54 cohort, and 18 case-series 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) [38, 146]. The majority of the studies were single centre and only 19 studies were multi-centre. Almost all studies included in this review were retrospective in design except few studies were prospective (n = 5) [10, 27, 70, 95, 161] and one study utilized both retrospective and prospective designs [131]. 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. 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).

Leukaemia

Leukaemia was the first most-common blood cancer in children who experienced COVID-19 (n = 1141, 88.5%) [3, 4, 6, 10, 11, 15–18, 20–24, 26–43, 61–67, 69–85, 87–89, 92–103, 105–107, 109–131, 133–139, 141–145, 148–153, 155–165, 169–180]. Among them, 579 have unclassified lymphoblastic leukaemia (50.7% of all leukaemias), 202 have unspecified leukaemia (17.7%), 185 have B-cell lymphoblastic leukaemia (16.2%), 150 have unclassified myeloid leukaemia (13.1%), 23 have T-cell lymphoblastic leukaemia (2%), and 2 have biphenotypic leukaemia (a mixture of both types of lymphoblastic and myeloid leukaemias) (0.2%). Most of those patients had acute leukaemic conditions (n = 892, 78.2%) and only few cases had chronic leukaemia (n = 5, 0.4%). 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 (185/304 = 60.8%). Reported blood cancer status for the leukaemia in children infected with SARS-CoV-2 were active (n = 258/574,

Table 8 Pediatric patients with blood cancer affected by COVID-19, stratified by type of blood cancer, ICU admission, use of MV, or if children suffered ARDS and final treatment outcome (n = 155 studies), 2020–2023

Type of blood cancer	Number of patients ^a	ICU admission rate ^a	Use of MV ^a	Suffered ARDS ^a	Case fatality rate ^a
Leukaemia	1141 (88.5)	155 (13.6)	103 (9)	133 (11.6)	99 (8.7)
Lymphoblastic leukaemia, unclassified	579 (50.7)	69 (11.9)	46 (7.9)	59 (10.2)	41 (7.1)
Unspecified leukaemia	202 (17.7)	16 (7.9)	11 (5.4)	14 (6.9)	11 (5.4)
Lymphoblastic leukaemia, B-cell	185 (16.2)	31 (16.7)	20 (10.8)	29 (15.7)	15 (8.1)
Myeloid leukaemia, unclassified	150 (13.1)	36 (24)	24 (16)	28 (18.7)	30 (20)
Lymphoblastic leukaemia, T-cell	23 (2)	3 (13)	2 (8.7)	3 (13)	2 (8.7)
Biphenotypic leukaemia (lymphoblastic & myeloid)	2 (0.2)	0	0	0	0
Non-Hodgkin's lymphoma	59 (4.6)	9 (15.2)	3 (5.1)	4 (6.8)	7 (11.9)
Non-Hodgkin's lymphomas (unclassified)	34 (57.6)	5 (14.7)	1 (2.9)	1 (2.9)	4 (11.8)
Burkitt's lymphoma	11 (18.6)	2 (18.2)	2 (18.2)	2 (18.2)	3 (27.3)
T-cell lymphoma	5 (8.5)	0	0	0	0
B-cell lymphoma	4 (6.8)	0	0	0	0
Lymphoblastic lymphoma	3 (5.1)	2 (66.7)	0	1 (33.3)	0
ALCL, positive NPM-ALK transcript	2 (3.4)	0	0	0	0
Unspecified lymphoma	38 (2.9)	3 (7.9)	0	0	1 (2.6)
Hodgkin's lymphoma	36 (2.8)	4 (11.1)	2 (5.5)	3 (8.3)	2 (5.5)
Langerhans cell histiocytosis	7 (0.5)	0	0	0	0
Myelodysplastic syndrome	7 (0.5)	3 (42.8)	2 (28.6)	3 (42.8)	1 (14.3)
Myeloid neoplasm	1 (0.1)	1 (100)	1 (100)	1 (100)	1 (100)
Total	1289 (100)	175 (13.6)	111 (8.6)	144 (11.2)	111 (8.6)

Abbreviations: ALCL, anaplastic large cell lymphoma; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MV, mechanical ventilation

^aData are presented as number (%). Data were calculated based on patients for whom the information were available

Percentages do not total 100% owing to missing data

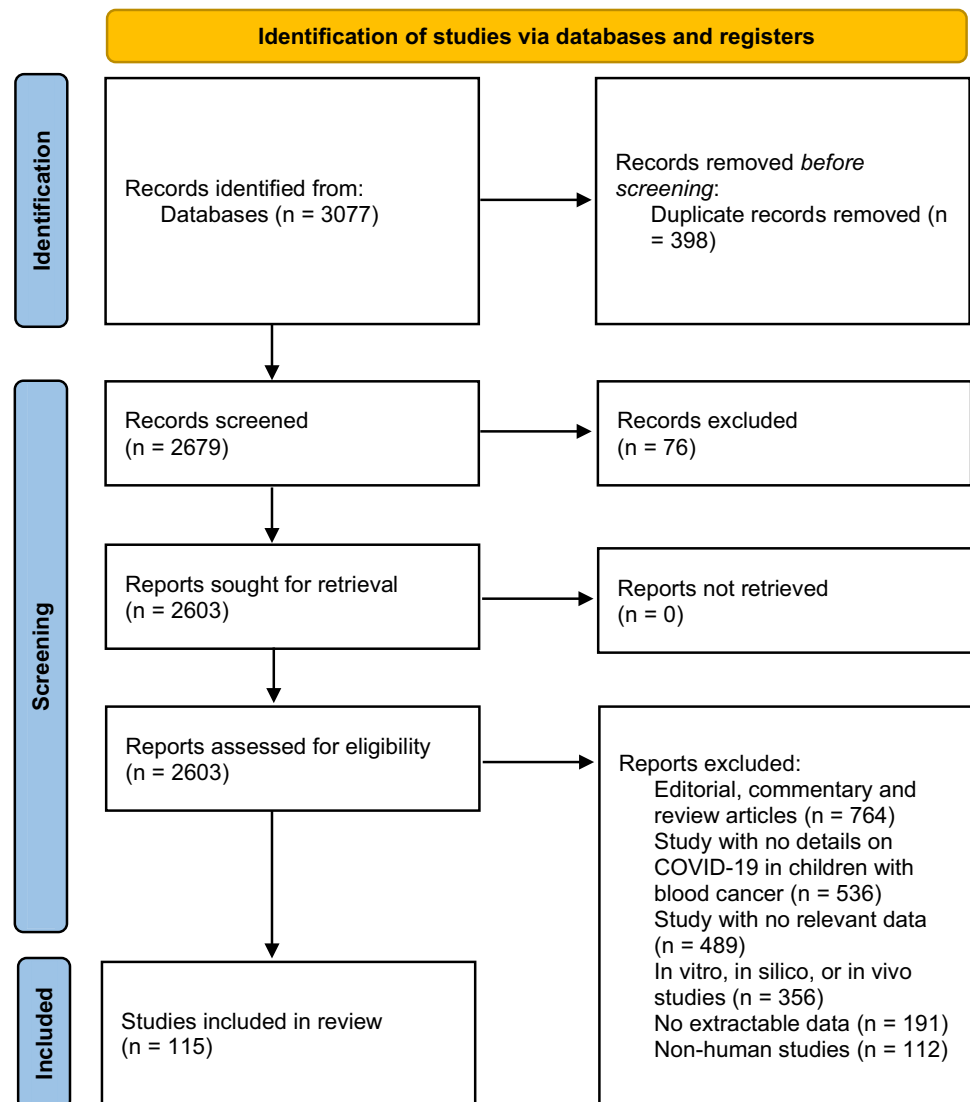
44.9%), remission (n = 256/574, 44.6%), or relapsed/refractory (n = 60/574, 10.4%), however, blood cancer status in these leukaemia cases was not reported in a high percentage of patients (n = 567/1141, 49.7%) (Table 1).

Majority of the patients belonged to Hispanic (310/1141 = 27.2%), White (Caucasian) (292/1141 = 25.6%), Arab (160/1141 = 14%) and Indian (134/1141 = 11.7%) ethnicity (Table 2). Some of these leukaemic children infected with SARS-CoV-2 were found to have active concurrent infections (n = 83) [including unspecified pathogens (n = 32) (18 bacteria, 10 fungi, and 4 other unknown pathogens); *Rhinovirus* (n = 6); *Pseudomonas* (n = 6); *Aspergillus* (n = 3); Dengue virus (n = 4); *Influenza A* virus (n = 4); *Enterovirus* (n = 3); *Clostridium difficile* (n = 3); *Parainfluenza 1&4* virus (n = 2); *Epstein–Barr virus* (n = 2); *Staphylococcus aureus* (n = 2); *Human adenovirus* (n = 2); bacilli (n = 2); *Pneumocystis jirovecii* (n = 2); *Escherichia coli* (n = 2); streptococci (n = 2); *Influenza B* virus (n = 1); *Cytomegalovirus* (n = 1); *Scopulariopsis* species (n = 1); *Human metapneumovirus* (n = 1); respiratory syncytial virus (n = 1); *Absidia corybifera* (n = 1); *Acinetobacter junii* (n = 1); *Salmonella* (n = 1); toxoplasmosis (n = 1); *Rothia mucilaginosa* (n = 1); hepatitis C virus (n = 1); *Klebsiella pneumonia* (n = 1); *Parvovirus*

B19 (n = 1); BK virus (n = 1) and *Coronavirus NL63* (n = 1)]. Few of those leukaemia children presented with a previous known history of hematopoietic stem cell transplantation (n = 33) [allogeneic (n = 32) and autologous (n = 1)], graft versus host disease (n = 15), immunocompromised status (n = 15), obesity (n = 5), hypertension (n = 4), cardiovascular disease (n = 4), asthma (n = 3), rhinitis (n = 3), Down syndrome (n = 2), diabetes (n = 1) and cerebral venous sinus thrombosis (n = 1), however, a significant number of leukaemic cases who experienced COVID-19 presented with no previous medical history (n = 86, 7.5%) (Table 3).

Most common clinical symptoms from leukaemia were febrile neutropenia (n = 29), sepsis (n = 23), bone marrow suppression (n = 21), multiorgan failure (n = 18), lymphadenopathy (n = 14) (cervical, inguinal, multiple, mediastinal, mandibular and hilar), respiratory failure (n = 14), lethargy (n = 13), abdominal pain (n = 12), hepatomegaly (n = 9), diarrhoea (n = 9), splenomegaly (n = 8), vomiting (n = 8), paleness (n = 8), skin rash (n = 8), tumor lysis syndrome (n = 7), septic shock (n = 7), acute kidney injury (n = 6), decreased appetite (n = 5), petechiae (n = 5), hypotension (n = 5), headache (n = 5), encephalopathy (n = 5), thromboembolism (n = 5), weight loss (n = 4), isolated CNS relapse

Fig. 1 Flow diagram of studies included in the systematic review



(n=4), seizures (n=4), hemophagocytic lymphohistiocytosis (n=4), fever (n=4), coagulopathy (n=3), ascites (n=3), bruising (n=3), cardiopulmonary arrest (n=3) and intracranial haemorrhage (n=3) (Table 4).

Children who suffered leukaemia and experienced COVID-19 were more likely to have neutropenia (n=130), high C-reactive protein (n=110), lymphopenia (n=96), high D-dimer (n=86), thrombocytopenia (n=82), elevated ferritin (n=67), low white blood cells (n=55), low haemoglobin (n=51), anaemia (n=41), high interleukin-6 level (n=36), high erythrocyte sedimentation rate (n=35), high lactate dehydrogenase (n=25), high procalcitonin (n=19), pancytopenia (n=17), leukopenia (n=13), elevated liver enzymes (n=13), leucocytosis (n=10), high fibrinogen (n=11), high bilirubin (n=8), high prothrombin time (n=7), high partial thromboplastin time (n=7), high troponin I (n=7), high uric acid (n=6) and lymphocytosis (n=6) (Table 5).

COVID-19 in leukaemic children infected with SARS-CoV-2 was asymptomatic (220/1141=19.3%), mild (522/1141=45.7%), moderate (152/1141=13.3%), severe (101/1141=8.8%) or critical (43/1141=3.8%). Most leukaemic paediatric cases did not experience multisystem inflammatory syndrome in children (MIS-C) (703/1141, 61.6%), however, few leukaemic children were reported to experience MIS-C (85/1141, 7.4%) (Table 6).

As expected, most used therapies in these leukaemic cases infected with SARS-CoV-2 were antibiotics (n=228), steroids (n=145), oxygen supplementation (n=131), chemotherapy (n=106), hydroxychloroquine (n=63), intravenous immunoglobulin (n=40), antivirals (n=46), packed red blood cells (n=29), anticoagulants (n=30), remdesivir (n=33), antifungals (n=43), tocilizumab (n=27), granulocyte colony-stimulating factor (n=23), intravenous inotropes (n=19), intravenous fluids (n=14), convalescent plasma (n=10), fresh frozen plasma (n=9), antiparasitic

(n = 9), vincristine (n = 8), favipiravir (n = 8), lopinavir/ritonavir (n = 7), and allogeneic hematopoietic stem cell transplantation (n = 7), nevertheless, treatment for COVID-19 was not necessary in a small number of leukaemic children (n = 74, 6.5%) (Table 7).

Leukaemic children who tested positive for SARS-CoV-2 were admitted to the intensive care unit (ICU) (n = 155, 13.6%), intubated and placed on mechanical ventilation (MV) (n = 103, 9%) and suffered acute respiratory distress syndrome (ARDS) (n = 133, 11.6%). Paediatric leukaemic cases with concurrent COVID-19 had a documented mortality of 99 (8.7%), while 1034 (90.6%) of the leukaemic children recovered. Mortality was COVID-19-related in a considerable number of paediatric leukaemic cases (41/99, 41.4%); however, COVID-19 was not attributable to death in many of the reported leukaemic children (36/99, 36.4%) and few studies failed to report if COVID-19 was a leading or an underlying cause of death in those leukaemic children (22/99, 22.2%) (Table 8).

Lymphoma

Lymphoma was the second most-common blood cancer in children who experienced COVID-19 (n = 133, 10.3%) [6, 15–25, 34, 38, 41–43, 60, 62, 70, 81, 90, 91, 95, 96, 99, 104, 108, 125, 130–132, 146, 147, 152, 154, 166, 167, 171–177, 179, 180]. Among them, 59 have non-Hodgkin's lymphoma (44.4% of all lymphomas), 38 have unspecified lymphoma (28.6%), and 36 have Hodgkin's lymphoma (27.1%). 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%). Reported blood cancer status for the lymphoma in children infected with SARS-CoV-2 were active (n = 46/82, 56.1%), remission (n = 32/82, 39%), or relapsed/refractory (n = 4/82, 4.9%), however, blood cancer status in these lymphoma cases was not reported in a high percentage of patients (n = 48/133, 36.1%) (Table 1). Majority of the patients belonged to White (Caucasian) (33/133 = 24.8%), Hispanic (33/133 = 24.8%), Indian (22/133 = 16.5%) and Arab (11/133 = 8.3%) ethnicity (Table 2).

Some of these lymphomatous children infected with SARS-CoV-2 were found to have active concurrent infections (n = 9) [including unspecified fungi (n = 3), *Epstein–Barr virus* (n = 2); *Human immunodeficiency virus* (n = 1); *Pseudomonas aeruginosa* (n = 1); cocci (n = 1) and unspecified bacteria (n = 1)]. Few of those lymphoma children presented with a previous known history of cardiovascular diseases (n = 7) [including superior vena cava syndrome (n = 2), mild mitral regurgitation (n = 1), tricuspid regurgitation (n = 1), pulmonary insufficiency (n = 1), coronary artery ectasia (n = 1) and main bronchus stenosis

(n = 1)], hematopoietic stem cell transplantation (n = 5) [autologous (n = 3) and allogeneic (n = 2)], immunocompromised status (n = 1), inborn error of immunity (CD27 deficiency) (n = 1), obesity (n = 1), inherited cancer genes (n = 1), secondary and central nervous system syphilis (n = 1), dermatomyositis and myopathy (n = 1) and contractures and deformity (n = 1), however, a significant number of lymphomatous cases who experienced COVID-19 presented with no previous medical history (n = 13, 9.8%) (Table 3).

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), lymphadenopathy (n = 3) (cervical, neck, supraclavicular, groin and auricular), bleeding (n = 3) (1 gastrointestinal, 1 central nervous system and 1 gingival), respiratory failure (n = 3), sepsis (n = 2), splenomegaly (n = 2), swollen neck (n = 2), abdominal pain (n = 2), multiorgan failure (n = 2) and acute renal failure due to methotrexate intoxication (n = 1) (Table 4). Children who suffered lymphoma and experienced COVID-19 were more likely to have lymphopenia (n = 11), thrombocytopenia (n = 9), high C-reactive protein (n = 8), high D-dimer (n = 7), neutropenia (n = 7), low haemoglobin (n = 5), low white blood cells (n = 5), elevated ferritin (n = 4) and high erythrocyte sedimentation rate (n = 3) (Table 5). COVID-19 in lymphomatous children infected with SARS-CoV-2 was asymptomatic (16/133 = 12%), mild (68/133 = 51.1%), moderate (19/133 = 14.3%), severe (9/133 = 6.8%) or critical (3/133 = 2.2%). Most lymphomatous paediatric cases did not experience MIS-C (78/133, 58.6%); however, few lymphomatous children were reported to experience MIS-C (6/133, 4.5%) (Table 6).

As expected, most used therapies in these lymphomatous cases infected with SARS-CoV-2 were antibiotics (n = 30), chemotherapy (n = 15), steroids (n = 15), oxygen supplementation (n = 11), antivirals (n = 10), hydroxychloroquine (n = 8), remdesivir (n = 6), intravenous fluids (n = 5), fresh frozen plasma (n = 4), anticoagulants (n = 4), intravenous inotropes (n = 4), tocilizumab (n = 4), radiotherapy (n = 3), intravenous immunoglobulin (n = 3) and lopinavir/ritonavir (n = 2), nevertheless, treatment for COVID-19 was not necessary in a small number of lymphomatous children (n = 17, 12.8%) (Table 7). Lymphomatous children who tested positive for SARS-CoV-2 were admitted to the ICU (n = 16, 12%), intubated and placed on MV (n = 5, 3.7%) and suffered ARDS (n = 7, 5.3%). Paediatric lymphomatous cases with concurrent COVID-19 had a documented mortality of 10 (7.5%), while 119 (89.5%) of the lymphomatous children recovered. COVID-19 was not attributable to death in many of the reported lymphomatous children (7/10, 70%) 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%) (Table 8).

Myelodysplastic syndrome

Myelodysplastic syndrome was the third most-common blood cancer in children who experienced COVID-19 ($n=7$, 0.7%) [41, 81, 86, 99, 121, 140, 155]. The median inter-quartile 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%). Reported blood cancer status for the myelodysplastic syndrome in children infected with SARS-CoV-2 were active ($n=1/7$, 14.3%) or remission ($n=1/7$, 14.3%), however, blood cancer status in these myelodysplastic syndrome cases was not reported in a high percentage of patients ($n=5/7$, 71.4%) (Table 1).

Majority of the patients belonged to White (Caucasian) (5/7 = 71.4%) and Hispanic (2/7 = 28.6%) ethnicity (Table 2). One of these myelodysplastic syndrome children infected with SARS-CoV-2 was found to have active concurrent infections ($n=2$) [including *Cytomegalovirus* ($n=1$) and *Aspergillus terreus* ($n=1$)]. Some myelodysplastic syndrome children presented with a previous known history of allogeneic hematopoietic stem cell transplantation ($n=4$), obesity ($n=2$), diabetes mellitus ($n=1$), left ventricular hypertrophy ($n=1$), obstructive sleep apnoea ($n=1$) and graft versus host disease ($n=1$) (Table 3).

Two myelodysplastic syndrome children experienced the following clinical symptoms: pneumonitis ($n=1$), acute lung injury ($n=1$), macrophage activation-like syndrome ($n=1$), splenomegaly ($n=1$), hemophagocytic lymphohistiocytosis ($n=1$), acute renal failure ($n=1$), sepsis ($n=1$), febrile neutropenia ($n=1$), emphysema ($n=1$), pneumothorax ($n=1$), bronchiectasis ($n=1$), bronchiolitis obliterans syndrome ($n=1$), thoracic air leak syndrome ($n=1$), pulmonary aspergillosis ($n=1$), respiratory acidosis ($n=1$), and hypercapnia ($n=1$) (Table 4).

Children who suffered myelodysplastic syndrome and experienced COVID-19 were more likely to have high C-reactive protein ($n=2$), elevated ferritin ($n=1$), high D-dimer ($n=1$), neutropenia ($n=1$), low haemoglobin ($n=1$) and thrombocytopenia ($n=1$) (Table 5). COVID-19 in myelodysplastic syndrome children infected with SARS-CoV-2 was mild (5/7 = 71.4%), severe (1/7 = 14.3%) or critical (1/7 = 14.3%). Most myelodysplastic syndrome paediatric cases did not experience MIS-C (5/7, 71.4%); however, two myelodysplastic syndrome children were reported to experience MIS-C (2/7, 28.6%) (Table 6).

As expected, most used therapies in these myelodysplastic syndrome cases infected with SARS-CoV-2 were antibiotics ($n=2$), oxygen supplementation ($n=2$), hydroxychloroquine ($n=2$), steroids ($n=2$), remdesivir ($n=1$), tocilizumab ($n=1$), favipiravir ($n=1$) and antivirals ($n=1$), nevertheless, treatment for COVID-19 was not necessary in two myelodysplastic syndrome children

($n=2$, 28.6%) (Table 7). Myelodysplastic syndrome children who tested positive for SARS-CoV-2 were admitted to the ICU ($n=3$, 42.8%), intubated and placed on MV ($n=2$, 28.6%) and suffered ARDS ($n=3$, 42.8%). Paediatric myelodysplastic syndrome cases with concurrent COVID-19 had a documented mortality of 1 (14.3%), while 6 (85.7%) of the myelodysplastic syndrome children recovered. COVID-19 was not attributable to death in any of the reported myelodysplastic syndrome children (Table 8).

Langerhans cell histiocytosis

Langerhans cell histiocytosis was the third most-common blood cancer in children who experienced COVID-19 ($n=7$, 0.7%) [24, 70, 168, 170–172]. Age was reported in two cases only (10 months and 21 months), and there was a male predominance in Langerhans cell histiocytosis patients diagnosed with COVID-19 (3/4 = 75%). Reported blood cancer status for the Langerhans cell histiocytosis in children infected with SARS-CoV-2 was active ($n=1/7$, 14.3%), however, blood cancer status in these Langerhans cell histiocytosis cases was not reported in a high percentage of patients ($n=6/7$, 85.7%) (Table 1).

Majority of the patients belonged to Indian ethnicity (4/7 = 57.1%) (Table 2). One Langerhans cell histiocytosis child experienced the following clinical symptoms: lymphadenopathy (cervical and occipital) ($n=1$), oedemas (different part of body) ($n=1$), hepatomegaly ($n=1$), splenomegaly ($n=1$), ascites ($n=1$), rash ($n=1$), lesions ($n=1$) and icterus ($n=1$) (Table 4). Children who suffered Langerhans cell histiocytosis and experienced COVID-19 were more likely to have high C-reactive protein ($n=1$), elevated ferritin ($n=1$), neutropenia ($n=1$), low haemoglobin ($n=1$) and thrombocytopenia ($n=1$) (Table 5). COVID-19 in Langerhans cell histiocytosis children infected with SARS-CoV-2 was asymptomatic (2/7 = 28.6%) or mild (5/7 = 71.4%). Most Langerhans cell histiocytosis paediatric cases did not experience MIS-C (4/7, 57.1%), however, one Langerhans cell histiocytosis child was reported to experience MIS-C (1/7, 14.3%) (Table 6).

As expected, most used therapies in these Langerhans cell histiocytosis cases infected with SARS-CoV-2 were antibiotics ($n=2$) and hydroxychloroquine ($n=1$), nevertheless, treatment for COVID-19 was not necessary in one Langerhans cell histiocytosis child ($n=1$, 14.3%) (Table 7). None of the Langerhans cell histiocytosis children who tested positive for SARS-CoV-2 were admitted to the ICU, intubated and placed on MV or suffered ARDS. All paediatric Langerhans cell histiocytosis cases with concurrent COVID-19 recovered (Table 8).

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 [68]. Patient needed ICU admission, MV, and suffered ARDS. 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.

Discussion

This systematic review included 1289 children with blood cancer 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. 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 [13, 181–183]. 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 children with blood cancer 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%) [184] and an older review published from Canada (13.6% vs 21%) [46]. Moreover, pooled proportion of children with blood cancer who suffered COVID-19 and needed MV 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%) [46, 184]. 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%) [184], Canada (34%) [46], United Kingdom (32%) [185] and Iran (21.3%) [44]. However, we report > twofold higher fatality rate in children with blood cancer and 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%) [46]. Our current review included a total of 155 studies that contributed to the refinement of evidence on the clinical characteristics and final treatment outcomes in children with blood cancer and concurrent COVID-19 [3, 4, 6, 10, 11, 15–43, 60–180]. Across the studies included in our review, rates of ICU admission and use of MV in children with blood cancer and 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 ARDS and fatality rates in those children with blood cancer 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 [44, 46, 184, 185]. Our review shown that out of 1289 reported children with blood cancer infected with SARS-CoV-2, ($n = 238$, 18.5%) of patients were asymptomatic and the clinical course of COVID-19 was mild ($n = 601$, 46.6%) or moderate ($n = 171$, 13.3%). Clinical course of COVID-19 in children with blood cancer 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 children with blood cancer who died from SARS-CoV-2 infection had relapsed/refractory and advanced blood cancer [10, 40, 77, 80, 95, 149, 152, 173, 175, 178, 180] or significant medical comorbidities in addition to the uncontrollable cancer [6, 20, 22, 24, 68, 102, 107, 112, 140, 152, 155, 172, 174]. It is important to mention that although most cases of COVID-19 in the pediatric population are mild or asymptomatic [186, 187], the overall rate of ICU admission and mortality rate we report in children with blood cancer who were infected with SARS-CoV-2 suggests that the risk of severe disease and mortality from SARS-CoV-2 is much higher in children with blood cancer compared to the general healthy children. For example, COVID-19-related ICU admission among healthy children was very low (141 per 20,458 (0.7%) children age ≤ 9 years and 216 per 49,245 (0.4%) children age 10 to 19 years) [188] and the pooled analysis from seven countries shown the COVID-19-related death rate among healthy children (age 0–19 years) was 0.17 per 100,000 population (0.48% of the estimated total mortality from all causes) [189]. Lower COVID-19 severity in children with blood cancer 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 [190], b) Less risk

to hyper inflammatory immune response in children [191], and/or c) Immature receptor system, immune-system-specific regulatory mechanisms, and possible cross-protection from other common pathogens in children [192].

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 children with blood cancer infected with COVID-19 were males [181]. Male predominance in blood cancer adults infected with SARS-CoV-2 has also been observed previous systematic reviews [44, 183, 184], and severity of COVID-19 and prevalence of infectious diseases are generally higher in male children as described across multiple studies [193–195]. We found development of COVID-19 in children with blood cancer was highest in people of Hispanic and White (Caucasian) ethnicity (26.8% and 25.7%, respectively). In addition, fatality rate in children with blood cancer 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 [46]. 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, or 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 children with blood cancer during course of SARS-CoV-2 infection, however, many studies have reported to successfully treat COVID-19 in children with blood cancer by proceeding with no changes to the anticancer treatment [16, 26, 28, 34, 35, 41, 60, 61, 66, 67, 79, 81, 84, 90, 93, 108, 117, 119, 120, 130, 158, 159]. 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 [49]. Continuation of anticancer treatment in individual paediatric blood cancer patients with SARS-CoV-2

infection seems to be possible, but more data are 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. All children diagnosed with blood cancer and COVID-19 among all included studies in our systematic review were not vaccinated against SARS-CoV-2 and that can be explained, in part, by the late authorization of COVID-19 vaccine for emergency use in children 5 through 11 years of age (approved on the 4th quarter of 2021) and in children under 5 years of age (approved on the 2nd quarter of 2022) by the US CDC and FDA [196, 197]. Furthermore, according to the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Roadmap for prioritizing the use of COVID-19 vaccines in the context of limited supply, children themselves were not directly prioritized as a population group for two reasons [198]. First, trials of COVID-19 vaccine candidates in children have not yet been initiated and thus data on safety and efficacy in this age group. Second, the low risk of severe COVID-19 and death in children does not make them a high priority for direct immunization [198]. However, 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 [199]. COVID-19 vaccines were noted to be safe and effective in children, especially those who are immunocompromised [200].

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 children with blood cancer and COVID-19. 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 are 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 infected with SARS-CoV-2 may experience higher rates of ICU admission and mortality in comparison with the healthy pediatric populations. Mortality in children with blood cancer and infected with SARS-CoV-2 was highest in cases belonging to male gender and Hispanic ethnicity. However, 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.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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