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Challenges of Dengue in Hematological Disease Patients: Descriptive Analysis From the DANGO Registry During the 2023–2024 Outbreak in Argentina

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ABSTRACT

Background: Dengue virus (DENV) infection is an increasing public health concern in immunocompromised patients, including those with hematological disease (HD). Clinical overlap between DENV and HD-related complications often leads to underdiagnosis, and data on DENV outcomes in HD patients were limited during the 2023–2024 outbreak in Argentina.

Methods: We conducted a retrospective, multicenter analysis of HD patients with laboratory-confirmed or highly probable DENV infection reported to the Argentine DANGO registry between November 2023 and May 2024. Seven centers participated. Patients aged ≥16 years were included, and demographic, clinical, laboratory, treatment, and outcome data were analyzed descriptively.

Results: Thirty-three HD patients with DENV were included. Median age was 54 years (IQR 33–63), and 70% were male. Non-Hodgkin lymphoma (30%) and acute myeloid leukemia (21%) were the most common HD. Most patients (82%) were receiving active chemotherapy, and 24% had undergone hematopoietic stem cell transplantation (HSCT). Hospitalization was required in 64% of cases. Thrombocytopenia occurred in 90%, leukopenia in 67%, and hematocrit <30% in 52%. DENV with warning signs was observed in 64% of patients. Two cases of transfusion-associated DENV were documented via PCR-positive platelet donor samples. Overall mortality was 6% (2/33), with both deaths directly attributable to DENV-related complications.

Abbreviations: AA, aplastic anemia; AKI, acute kidney injury; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CDC, Centers for Disease Control and Prevention; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DANGO, Dengue en Argentina registry; DENV, dengue virus; HCT, hematopoietic cell transplantation; HD, hematological disease; HL, Hodgkin lymphoma; HLA, human leukocyte antigen; HM, hematological malignancy; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; Ig, immunoglobulin; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; MDS, Myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NS1, non-structural Protein 1 (dengue virus antigen); OMS, Organización Mundial de la Salud (World Health Organization); OPS, Organización Panamericana de la Salud (Pan American Health Organization); PCR, polymerase chain reaction; RNA, ribonucleic acid; SADI, Sociedad Argentina de Infectología (Argentinian Infectious Diseases Society); SAH, Sociedad Argentina de Hematología (Argentinian Hematology Society); SE, Semana Epidemiológica (Epidemiological week); SFTSV, severe fever with thrombocytopenia syndrome virus; SPSS, Statistical Package for the Social Sciences; WHO, World Health Organization.

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Conclusions: DENV infection in patients with HD is associated with frequent complications, high hospitalization rates, and substantial morbidity and non-negligible mortality. Symptom overlap with HD-related conditions complicates diagnosis. Increased clinical awareness, standardized diagnostic approaches, and strengthened transfusion safety measures are essential in endemic areas, especially during outbreaks.

1 | Introduction

Arbovirus infections, including dengue, pose a significant threat to both the general population and immunocompromised hosts, such as patients with hematological disease (HD) [1]. Dengue virus (DENV), a single-stranded ribonucleic acid (RNA) virus with four serotypes (dengue serotypes DENV-1 to DENV-4), is primarily transmitted by the *Aedes aegypti* mosquito, and to a lesser extent by *Aedes albopictus* [2]. However, transmission via blood transfusion, solid organ transplantation, and hematopoietic stem cell transplantation (HSCT) has also been reported [3, 4].

Despite the potential severity, evidence evaluating the behavior of DENV infection in patients with HD remains scarce. Symptoms such as fever, leukopenia, and thrombocytopenia are common in patients with HD and HSCT recipients, frequently leading to DENV infection being overlooked in this population, even in endemic areas. In published reports, dengue infection in patients with hematological malignancies and HSCT recipients has been more commonly recognized beyond the initial aplastic phase, often after neutrophil recovery and hospital discharge, although early post-transplant cases, including transfusion-transmitted infections, have also been described [4, 5].

The dengue outbreak in Argentina during 2023 and 2024 has been unprecedented, with over 544 778 cases recorded between the epidemiological weeks 31/2023 and 28/2024, making it the largest outbreak in the country's history [6]. The surge in cases has been attributed to warmer and more humid weather conditions, which have facilitated the breeding of the *A. aegypti* mosquito, the primary vector for dengue [7]. The outbreak has led to significant public health challenges, including a shortage of insect repellent and medical supplies, straining healthcare resources [8]. This situation underscores the importance of effective vector control measures and public awareness to mitigate the impact of arbovirus infections.

Regional data from the Americas have begun to elucidate the clinical relevance of DENV infection in patients with HD. In Brazil, de Souza Pereira et al. described prolonged dengue viremia and atypical clinical courses, highlighting the potential for persistent infection and significant diagnostic challenges in immunocompromised hosts. In addition, nosocomial DENV transmission involving HSCT recipients has been reported in Argentina during epidemic periods, emphasizing the susceptibility of transplant populations within highly specialized care settings [9]. Collectively, these regional experiences underscore that DENV should be regarded as an emerging and clinically relevant complication in HD and HSCT patients living in, or exposed to, dengue-endemic regions, particularly during outbreaks [10–12].

This study aims to describe the clinical and laboratory profiles, as well as the progression of DENV infection in patients with HD or HSCT.

2 | Methods

A retrospective, multicenter registry was set across seven Argentine institutions—six in Misiones and one in Buenos Aires province—documenting dengue cases in HD patients between November 2023 and May 2024 as part of the DANGO registry (Dengue en Argentina). The DANGO registry is a multicenter Argentine registry created to collect and analyze data on patients diagnosed with dengue during the 2023–2024 outbreak in Argentina. It includes patients with clinically suspected and serologically confirmed dengue (through AgNS1, IgM, and/or PCR for DENV). The primary objective of the registry is to gain a deeper understanding of the clinical characteristics, complications, outcomes, and treatment responses of this infection across diverse populations. By pooling data from different study populations, including patients with HD for a sub-analysis, DANGO aims to enhance diagnostic strategies, treatment protocols, and public health interventions for dengue. Linking clinical data with patient outcomes, it contributes to global efforts to reduce the burden of dengue. This online registry, accessible at www.clinicalsurveys.net (TIVIAN GmbH, Cologne, Germany), was created during the 2023–2024 dengue outbreak. Ethical approval was granted by the "Dr Ramón Madariaga" Acute Care Teaching Hospital of Posadas, Misiones (Argentina) (ID: 05062024), and local ethics committee approval was obtained from each participating institution as required.

To be included in the study, patients needed to have a confirmed dengue diagnosis, an existing HD at the time of DENV diagnosis, and be at least 16 years old. Prior hospital admission was not required. Data collected included patient details such as age, sex, and medical history before the dengue episode, along with information about their HD, such as any prior HSCT, clinical stage, and recent treatments. Symptoms during the dengue episode were recorded, as well as intensive care unit (ICU) admissions and laboratory results such as hematocrit, white blood cells, platelets, and liver and kidney function. Serological tests for DENV infection, including non-structural Protein 1 (NS1) antigen detection, polymerase chain reaction (PCR), and immunoglobulin (Ig) M and IgG assays, were performed using commercially available diagnostic kits. The diagnostic tools employed in this study included the Panbio Dengue Early NS1 antigen ELISA (Abbott, Sydney, NSW, Australia), the Panbio Dengue IgM and IgG Capture ELISA (Abbott, Sydney, NSW, Australia), and the Viasure Dengue Virus Real-Time PCR Detection Kit

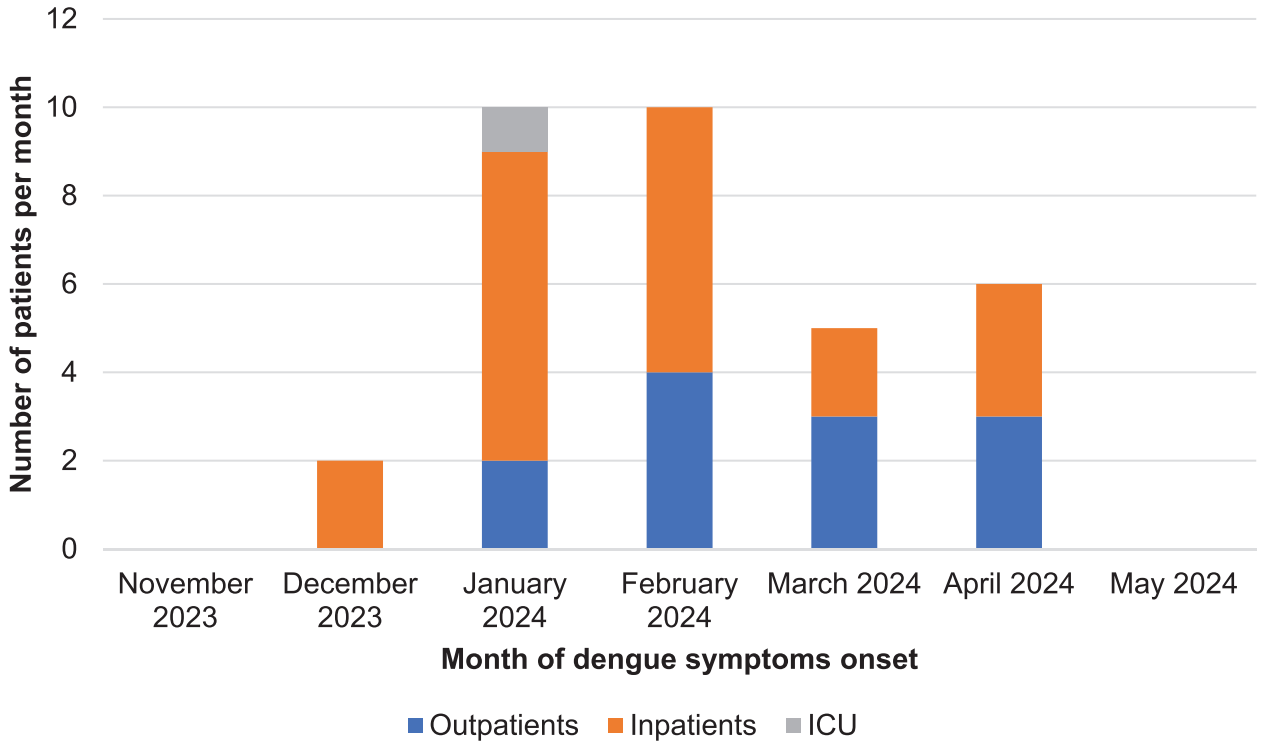

FIGURE 1 | Patient distribution by symptom onset month. ICU, intensive care unit. The viral peak occurred between January and February 2024, both in our sample and in the general population [6]. Outpatients are defined as individuals who did not require hospital admission during their dengue episode. Inpatients refer to those who were hospitalized, while ICU patients are those admitted to intensive care units.

(Certest BIOTEC, Saragossa, Spain). Given the retrospective nature of the study, diagnostic testing was performed according to clinical availability and timing of presentation; therefore, not all patients underwent all diagnostic assays, and tests were not systematically performed in parallel. Dengue cases were classified according to World Health Organization (WHO) criteria as dengue without warning signs, dengue with warning signs, or severe dengue [13]. Clinical management followed national recommendations issued by the Argentine Ministry of Health and the Pan American Health Organization during the outbreak period, in accordance with standard clinical practice [14]. Dengue-attributable mortality was defined as death occurring during the acute dengue episode, in which dengue infection was considered the primary or a major contributing cause based on clinical assessment and review of medical records.

Beyond clinical and laboratory aspects, the study also collected information on the therapeutic management of dengue in each patient, the occurrence of complications during hospitalization or the episode, and final mortality, specifying whether it was associated with the DENV episode when applicable.

To ensure data consistency and completeness, all patient records underwent a validation process. Efforts were made to minimize missing data by contacting researchers to resolve outstanding queries. This validation process was crucial for maintaining the reliability and integrity of the data collected from the DANGO registry. No a priori sample size calculation was performed due to the exploratory nature of the study. Data from the participating institutions were summarized using frequencies and percentages for categorical variables, and medians, interquartile ranges (IQRs), and absolute ranges for continuous variables. Regression models were not formulated due to the limited number of cases. Statistical analyses were conducted using SPSS version 25.0 (SPSS, IBM Corp., Chicago, IL, United States).

3 | Results

This study analyzed 33 dengue patients diagnosed at five of the seven participating hospitals in Argentina between December 2023 and April 2024 (Figure 1). The median age of patients at the onset of symptoms was 54 years (IQR 33–63), with a range from 16 to 79 years. Survivors ($n = 31$, 93.9%) had a median age of 46 years (IQR 31–63, range 16–79), while those who died ($n = 2$, 6.0%) had a median age of 63 years (IQR 63-64, range 63–64). Most patients were male (23/33, 70%) (Table 1).

The most common comorbidities were hypertension in six patients (18%) and renal insufficiency in three patients (9%). In addition, seven patients (21%) had a previous episode of dengue confirmed (positive IgG and symptoms suggestive of DENV). Among hematological malignancies, non-Hodgkin lymphoma was the most frequent, affecting 10 patients (30%). Other conditions included acute myeloid leukemia in seven patients (21%) and multiple myeloma in three patients (9%). Regarding the baseline status of the hematological malignancies, 10 patients (30%) were stable, 13 patients (39%) were in remission, and six patients (18%) had a recent diagnosis. At the time of dengue diagnosis, most patients (27/33, or 82%) were undergoing chemotherapy. Specifically, 22 patients (67%) were treated with antineoplastic, while nine patients (27%) received either corti-

TABLE 1 | Underlying characteristics of 33 patients with baseline hematological malignancy and dengue.

	Total		Alive		Dead	
	n	**%**	***n***	**%**	***n***	**%**
Age at symptom onset, years Median (IQR) [range]	54 (33–63) [16–79]		46 (31–63) [16–79]		63.5 (63–64) [63–64]	
Age at first hospitalization, years Median (IQR) [range]	46 (33–64) [16–79]		45 (31–66) [16–79]		64 (63–64) [63–64]	
Sex						
Male	23	70	21	68	2	100
Female	10	30	10	32	0	0
Previous dengue episode history	7	21	7	23	0	0
Comorbidities[a]						
Hypertension	6	18	6	19	0	0
Renal failure	3	9	2	7	1	50
Diabetes mellitus	2	6	2	7	0	0
HD						
NHL	10	30	10	32	0	0
AML	7	21	7	23	0	0
CLL	3	9	3	10	0	0
CML	3	9	3	10	0	0
MM	3	9	1	3	2	100
ALL	2	6	2	7	0	0
HL	2	6	2	7	0	0
MDS	2	6	2	7	0	0
AA	1	3	1	3	0	0
Days from HD diagnosis to dengue symptom onset Median (IQR) [range]	478 (199–822) [0–4125]		510 (141–824) [0–4125]		207 (199–215) [199–215]	
Days from HD diagnosis to first dengue-related hospitalization Median (IQR) [range]	452 (28–625) [0–4125]		466 (21–721) [0–4125]		210 (202–218) [202–218]	
Status						
Onset	6	18	6	19	0	0
Complete remission	9	27	8	26	1	50
Partial remission	4	12	4	13	0	0
Refractory/resistant	3	9	3	10	0	0
Unknown	1	3	1	3	0	0
Stable malignancy	10	30	9	29	1	50
HD treatment						
Chemotherapy	27	82	25	81	2	100
Antineoplastic drugs	22	67	20	65	2	100
Immunosuppressive drugs	4	12	4	13	0	0
Corticosteroids	9	27	8	26	1	50
Monoclonal antibodies	9	27	9	29	0	0
Small molecules	5	15	4	13	1	50
Allogeneic HSCT	6	18	6	19	0	0
Days from transplant to dengue symptom onset Median (IQR) [range]	287.5 (137–477) [82–812]		287.5 (137–477) [82–812]		(–) [–]	

(Continues)

TABLE 1 | (Continued)

	Total		Alive		Dead	
	n	**%**	***n***	**%**	***n***	**%**
Days from transplant to first dengue-related hospitalization Median (IQR) [range]	288 (141–294) [141–294]		288 (141–294) [141–294]		(–) [–]	
Autologous HSCT	2	6	2	7	0	0
No treatment	4	12	4	13	0	0
Months from last HD therapy to first dengue diagnosis						
Last month, before dengue	11	33	10	32	1	50
Last 3 months before dengue	8	24	7	23	1	50
> 3 months before dengue	7	21	7	23	0	0
Use of corticosteroids > 10 mg/day prednisone or similar	7	21	5	16	2	100

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HD, hematological disease; HL, Hodgkin lymphoma; HSCT, hematopoietic stem-cell transplantation; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

[a]Comorbidity numbers are superadditive.

costeroids or monoclonal antibodies. The median time between the diagnosis of the HD and the onset of dengue symptoms was 478 days (IQR 199–822, range 0–4125). Three patients (9%) were co-diagnosed with both dengue and hematologic malignancies. In patients receiving immunosuppressive treatment, this was suspended during the dengue episode. Eight patients (24%) received HSCT, including six allogeneic HSCT (18%), with a median of 288 days (IQR 137–477, range 82–812) from allogeneic HSCT to dengue symptoms. Two patients (6%) acquired dengue during the early post-autologous HSCT period. In the first case, a patient with non-Hodgkin lymphoma developed febrile neutropenia on Day +17 post-HSCT, presenting negative blood cultures and a positive NS1 antigen test. In the second case, a patient with Hodgkin lymphoma did not recover white blood cells and platelets by Day +19 post-HSCT and tested positive for the NS1 antigen. In both instances, dengue infection was considered most consistent with transfusion-related transmission, based on the detection of DENV RNA by PCR in stored platelet donor samples obtained prior to the onset of the recipients' clinical manifestations. The six patients who underwent related allogeneic bone marrow transplantation were 100% HLA-matched; they were not receiving immunosuppressive treatment at the time of the dengue episode. No episodes of graft-versus-host disease were reported. PCR testing of donor blood samples from the platelet units transfused to both patients—retrieved from the Blood and Tissue Bank serum repository confirmed DENV viremia. Notably, one donor reported fever 48 h post-donation, while the other remained asymptomatic.

Hospitalization was required for 21 patients (64%), with a median stay of 7 days (IQR 5–29, range 1–72). The median time between symptom onset and laboratory confirmation of dengue infection was 1 day, with a range of 0–6 days (IQR 0–2 days). In the two fatal cases, the interval between symptom onset and diagnosis was 3 days. Laboratory abnormalities included hematocrit less than 30% in 17 patients (52%), leukopenia in 22 patients (67%), and thrombocytopenia in 30 patients (90%) (with counts <20 000/mm^3 in 13 patients, 39%). Dengue diagnostic testing yielded heterogeneous results according to the assay performed. Among the 29 NS1 antigen tests conducted, 25 patients (86%) had a positive result. DENV IgM serology was performed in seven patients, of whom five (71%) tested positive. PCR testing for DENV was performed in seven patients, with four (57%) yielding positive results. Seven patients had more than one positive diagnostic marker (Table 2 and Table S1).

Fever above 38°C was reported by 29 patients (88%), 25 patients (76%) experienced asthenia, and 22 patients (67%) had adynemia. Other common symptoms included myalgias in 12 patients (36%) and arthralgia or headache in 11 patients (33%) each. Complications were minimal in 19 patients (58%), though 10 patients (30%) had diarrhea, and six patients (18%) developed renal insufficiency. Dengue with warning signs was observed in 21 patients (64%), with the most frequent signs being abdominal pain in 10 patients (30%), persistent vomiting (defined as more than twice a day or every 1.5 h over several hours) in four patients (12%), and mucosal bleeding in three patients (9%). In addition, seven patients (21%) required platelet transfusions, and two patients (6%) needed red blood cell transfusions for the treatment of dengue symptoms (Table 2).

The mortality rate was 6% (n = 2/33), with both deaths linked to dengue-related complications. The deceased patients, who had underlying stable or in-remission multiple myeloma, were admitted to hospital; one required intensive care. They presented with severe thrombocytopenia, leukopenia, renal failure, and a hematocrit level of less than 30% (Tables 2 and 3). In the two fatal cases, death occurred 2 and 12 days after dengue diagnosis.

4 | Discussion

Our findings indicate that DENV infection in patients with HD is associated with distinct clinical features and disease progression compared with the general population, largely related to immunosuppression and treatment-associated hematological

TABLE 2 | Dengue episode characteristics of 33 patients with baseline hematological malignancy and dengue.

	Total		Alive		Dead	
	n	**%**	***n***	**%**	***n***	**%**
Hospitalization	21	64	19	61	2	100
Days of dengue-related hospitalization Median (IQR) [range]	7 (5–29) [1–72]		9 (5–31) [3–72]		3 (1–5) [1–5]	
Signs and symptoms at dengue onset[a]						
Asymptomatic	1	3	1	3	0	0
Fever> 38°C	29	88	27	87	2	100
Asthenia	25	76	24	77	1	50
Adynemia	22	67	21	68	1	50
Myalgias	12	36	10	32	2	100
Arthralgia	11	33	9	29	2	100
Headache	11	33	9	29	2	100
Diarrhea	8	24	7	23	1	50
Abdominal pain	6	18	5	16	1	50
Retro-orbital pain	5	15	4	13	1	50
Petechiae	4	12	4	13	0	0
Nausea	3	9	2	7	1	50
Vomiting	3	9	3	10	0	0
Epistaxis	2	6	2	7	0	0
Gingival bleeding	2	6	2	7	0	0
Encephalitis	1	3	1	3	0	0
Tachypnea	1	3	0	0	1	50
Confusional syndrome	1	3	0	0	1	50
Warning signs at dengue onset[a]						
No warning signs	14	42	14	45	0	0
Abdominal pain	10	30	9	29	1	50
Vomiting	4	12	3	10	1	50
Mucosal bleeding	3	9	3	10	0	0
Drowsiness or irritability	2	6	0	0	2	100
Elevated hematocrit with low platelets	2	6	2	7	0	0
Laboratory values at dengue onset						
Hematocrit						
Hematocrit ≤30	17	52	15	48	2	100
Hematocrit >30	15	46	15	48	0	0
Unknown	1	3	1	3	0	0
Leukocytes						
Leukopenia						
<4000 cells/mm^3	22	67	20	65	2	100
Normal 4000–10 000 cells/mm^3	8	24	8	26	0	0
Leukocytosis >10 000 cells/mm^3	0	0	0	0	0	0
Unknown	3	9	3	10	0	0

(Continues)

TABLE 2 | (Continued)

	Total		Alive		Dead	
	n	**%**	***n***	**%**	***n***	**%**
Platelets						
Mild thrombocytopenia 150 000–100 001 cells/mm^3	10	30	10	32	0	0
Moderate thrombocytopenia 100 000–50 001 cells/mm^3	3	9	3	10	0	0
Severe thrombocytopenia 50 000–20 000 cells/mm^3	4	12	3	10	1	50
Very severe thrombocytopenia < 20 000 cells/mm^3	13	39	12	39	1	50
Unknown	3	9	1	3	0	0
Liver values						
ALT or AST <200 IU	25	76	24	77	1	50
ALT or AST ≥200 IU	1	3	1	3	0	0
Unknown	7	21	6	19	1	50
Renal values						
Insufficiency Cr ≥ 2 mg/dL	4	12	2	7	2	100
Sufficiency Cr < 2 mg/dL	21	64	21	68	0	0
Unknown	8	24	8	26	0	0
Dengue serology						
NS1 Ag +	25	76	23	74	2	100
Dengue PCR +	4	12	4	13	0	0
Dengue IgM +	5	15	5	16	0	0
Dengue IgG +	4	12	4	13	0	0
Dengue treatment[a]						
Antibiotics	11	33	9	29	2	100
G-CSF	6	18	4	12.9	2	100
Immunoglobulin	2	6	2	7	0	0
Hydration	32	97	30	97	2	100
Paracetamol	27	82	25	81	2	100
Red blood cell transfusion	2	6	0	0	2	100
Platelet transfusion	7	21	6	19	1	50
Complications at any time of dengue[a]						
No complications	19	58	19	61	0	0
Diarrhea	10	30	9	29	1	50
Renal failure	6	18	4	13	2	100
ARDS	1	3	0	0	1	50
Dengue classification						
Dengue without warning signs	12	36	12	39	0	0
Dengue with warning signs	21	64	19	61	2	100
Severe dengue	2	6	0	0	2	100
Overall mortality	2	6	0	0	2	100
Associated with dengue	2	6	0	0	2	100

Abbreviations:°C, degrees Celsius; Ag, antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; G-CSF, granulocyte-colony stimulating factor; Ig, immunoglobulin; IU, international units; mm^3, cubic millimeters; NS1, non-structural Protein 1; PCR, polymerase chain reaction.
[a]Signs and symptoms at onset, warning signs at dengue onset, dengue treatment, and complications at any time of dengue numbers are superadditive.

TABLE 3 | Clinical characteristics of deceasing hematological patients with dengue.

	Case 1	Case 2
Sex	Male	Male
Age in years at dengue diagnosis	65	63
Baseline status	No vaccination Renal insufficiency Multiple myeloma (stable disease, 1st line: last month, bortezomib + cyclophosphamide) Prolonged corticosteroid use	No vaccination Multiple myeloma (complete remission, 1st line: last 3 months, bortezomib + dexamethasone + thalidomide) Prolonged corticosteroid use
Hospital stay	1 day in ICU	5 days
Signs and symptoms at onset	Arthralgia Confusional syndrome Dyspnea Headache Hypotension Fever >38°C Myalgia Somnolence Tachypnea	Abdominal pain Adynmia Arthralgia Asthenia Diarrhea Headache Fever >38°C Myalgia Nausea Somnolence Vomiting
Hematocrit	≤30%	≤30%
Leukopenia	<4000 cells/mm^3	<4000 cells/mm^3
Platelets	Severe thrombocytopenia (20 000–50 000/mm^3)	Very severe thrombocytopenia (<20 000/mm^3)
Liver enzymes	ALT/AST <200 IU	Unknown
Renal function	Creatinine ≥2 mg/dL	Creatinine ≥2 mg/dL
NS1 antigen	Positive	Positive
Dengue serotype	Unknown	Unknown
Complications	Renal failure ARDS	Acute abdomen Diarrhea Renal failure
WHO dengue classification	Dengue with warning signs and comorbidity	Dengue with warning signs and comorbidity
Treatment	G-CSF Hydration Paracetamol Piperacillin–tazobactam Platelet transfusion RBC transfusion Vancomycin	G-CSF Hydration Paracetamol RBC transfusion
Outcome	Death, dengue-associated	Death, dengue-associated

Abbreviations: °C, Celsius degrees; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; G-CSF, granulocyte colony-stimulating factor; ICU, intensive care unit; NS1 Ag, non-structural Protein 1 antigen; RBC, red blood cells; WHO, World Health Organization.

abnormalities. Severe disease and hemorrhagic complications appear to be more frequent in this group. The DANGO study included 399 DENV cases, of which 33 (8.27%) occurred in patients with HD or HSCT. In this Argentine cohort, the median age at symptom onset was 54 years, all patients were unvaccinated, and survivors were younger than those who died. Most patients were male and receiving chemotherapy, predominantly for non-Hodgkin lymphoma. Dengue-related complications were common, with nearly two-thirds presenting warning signs and an overall mortality of 6%. Dengue transmission was linked to platelet transfusions in a subset of cases, and NS1 antigen testing showed a high diagnostic yield [15].

Dengue infection was diagnosed in both outpatients and hospitalized patients. While most cases were likely acquired through community exposure to mosquitoes, dengue was not exclusively

community-acquired. In two patients diagnosed during the early post-autologous HSCT period, the most plausible route of infection was transfusion-related. This hypothesis is strongly supported by the retrospective detection of DENV RNA by PCR in stored platelet donor samples obtained prior to the onset of the recipients' clinical manifestations. One patient developed febrile symptoms within 48 h after transfusion, whereas the second case did not present a typical febrile syndrome but showed persistent cytopenias and a positive NS1 antigen test, leading to the diagnosis of dengue infection.

These observations raise important questions regarding transfusion safety and the role of donor screening strategies during dengue outbreaks, especially in onco-hematological settings. Routine DENV screening of blood products merits careful consideration during epidemic periods, particularly in dengue-endemic regions where formal guidelines remain heterogeneous or absent [3, 16]. This is relevant given the feasibility of multimodal screening strategies, including NS1 antigen, IgM, and nucleic acid amplification testing, as asymptomatic donor viremia may reach 0.04%–0.3% during outbreaks [17, 18]. The potential clinical relevance of transfusion-transmitted dengue in vulnerable populations is highlighted by Cowan et al., who reported donor-derived dengue infection in 3 of 20 hematopoietic stem cell transplant recipients, all of whom developed severe disease with a mortality rate of 66.7%. These findings underscore the risks associated with non-universal screening strategies and the need for greater policy alignment across dengue-endemic regions [19].

In endemic settings, clinical management strategies should prioritize the systematic inclusion of dengue in the diagnostic work-up of patients presenting with fever and thrombocytopenia. In high-risk populations, such as onco-hematological patients, the evaluation of cost-effective donor screening approaches during epidemic periods may represent an important complementary strategy to reduce preventable morbidity and mortality [20–22].

Comorbidities such as hypertension and renal insufficiency were observed, which is consistent with other studies linking these conditions to severe dengue [23, 24]. Regarding the association between arterial hypertension and the risk of severe dengue, several studies have shown that hypertensive adults have up to 1.6 times higher odds of progressing to severe dengue [25]. In parallel, a meta-analysis evaluating predictors of acute kidney injury (AKI) in patients with dengue reported an odds ratio of 2.22 (95% CI: 1.02–3.42) for AKI in severe dengue cases [26]. Also, different case series reported instances where adult cancer patients undergoing chemotherapy and HSCT developed severe thrombocytopenia and required platelet transfusions during illness [5, 27]. A previous history of dengue infection was reported in 21% of patients; however, serotype-specific data and neutralizing antibody assays were unavailable, precluding confirmation of reinfection or assessment of its impact on disease severity [28]. The study found non-Hodgkin lymphoma to be the most frequent hematologic malignancy (30%), followed by acute myeloid leukemia (21%). The distribution of HD in our sample aligns with the general prevalence in the Argentine population, where non-Hodgkin lymphoma, acute myeloid leukemia, and other HD, such as acute lymphoblastic leukemia and multiple myeloma, are common [29–31]. The high incidence of these malignancies among dengue HD patients might be due to their severe immunosuppression, which results from both the malignancy itself and its aggressive treatments [32]. The median interval of 478 days between HD diagnosis and dengue onset also notes the prolonged risk of infections in patients with sustained immunosuppression. While no specific humoral factors have been identified as associated with DENV infection in patients with these malignancies, some studies suggest that the relatively mild course of dengue in this population may be attributed to factors such as the use of corticosteroids, other immunosuppressive treatments, or the nature of the underlying disease itself. These factors could potentially modulate the immune response, reducing the likelihood of a severe presentation [20, 33]. Further studies are needed to explore the interactions between these factors and dengue outcomes.

In our study, diagnostic discordance was observed in a subset of patients who underwent more than one diagnostic assay for DENV infection. Specifically, three patients tested with both NS1 antigen detection and PCR showed discordant results. These discrepancies may be explained by several factors, including the timing of sample collection in relation to the course of infection, differences in the biological targets detected by each assay, and host-related factors affecting viral kinetics in immunocompromised patients.

Such findings highlight the limitations of relying on a single diagnostic marker for dengue in patients with hematological malignancies and underscore that the use of complementary diagnostic assays may improve diagnostic yield in this population. In this context, the high rate of NS1 antigen positivity observed in our series supports its clinical utility, particularly early in the course of infection, when antibody responses may be delayed or absent. Nevertheless, given the retrospective design and the lack of systematic parallel testing, these observations should be interpreted with caution. Further studies with larger cohorts and standardized diagnostic approaches are needed to better define the optimal diagnostic strategy for dengue in immunocompromised hosts.

Viral isolation was not conducted in this study due to the requirement for specialized laboratory facilities, the time-intensive nature of the procedure, and the high associated costs. However, data from the National Epidemiological Bulletin No. 735, issued by the Ministry of Health of the Argentine Republic, reports that during the 2023–2024 dengue season, a total of 583 297 confirmed dengue cases and 419 fatalities were recorded since SE 31/2023. In terms of serotype distribution, DENV-2 was the most prevalent, accounting for 65.6% of cases, with Genotype II-Cosmopolitan, lineage F 1.2, while DENV-1, genotype V, lineages D1 and E, represented 32.2%. Notably, cases of DENV-3 and DENV-4 were predominantly associated with travel history [6]. In the cases presented, other viral infections, such as severe fever with thrombocytopenia syndrome virus (SFTSV), were not considered as potential causes of fever and thrombocytopenia, given that the diagnosis of DENV was already confirmed. This decision was made in the context of one of the largest dengue outbreaks in the past decade, which provided a strong epidemiological basis for prioritizing DENV as the primary cause. Future studies may consider the simultaneous evaluation of other viral pathogens, particularly in regions with concurrent outbreaks.

Empirical antibiotic therapy was commonly initiated because of febrile neutropenia or clinical instability, reflecting standard practice in patients with hematological malignancies. Overall, 11 of 33 patients (33%) received antibiotic therapy during their DENV episode, and antibiotics were discontinued in several cases once DENV infection was confirmed and bacterial infection excluded.

The lack of significant liver enzyme elevation in our sample, commonly seen in severe dengue, may be attributed to other influencing factors. Specifically, the patients' underlying conditions, such as hepatic infiltration due to leukemia, or the medications they were receiving, could have affected the enzyme levels. These factors may have masked the typical increase in liver enzymes associated with severe dengue, providing a potential explanation for the absence of such elevations in this cohort [34–36]. A more detailed review of the patients' medical histories and treatment regimens could offer further insight into these findings.

The clinical features observed—fever, asthenia, and thrombocytopenia—match those reported in other studies of dengue among immunocompromised patients [37]. Complications such as diarrhea and renal insufficiency were noted in almost half of patients, consistent with the higher complication rates seen in dengue patients with underlying conditions [20, 21]. A retrospective study from India analyzed 28 oncology patients with dengue, nine of whom had hematological malignancies. Among these, 66.6% developed dengue hemorrhagic fever, compared to 21% of patients with solid tumors. In addition, 35.7% experienced severe thrombocytopenia (<20 000 platelets/mm^3), and 46.4% required platelet transfusions [5]. In patients with hematological malignancies and those who have undergone hematopoietic stem cell transplantation, prolonged viremia has also been reported, potentially complicating diagnosis and increasing the risk of severe outcomes. In our own series, only one case of prolonged viremia was documented—in a 58-year-old woman with acute lymphoblastic leukemia, who remained PCR-positive for DENV until Day 23 after infection onset [17]. Finally, dengue diagnosis in these patients is further complicated by symptom overlap with chemotherapy side effects, such as fever and thrombocytopenia, which can delay timely diagnosis and treatment [5].

The 6% mortality rate observed in this study exceeds the global case fatality rate for dengue, which is estimated at 0.5%–1% [38, 39]. Increased mortality and morbidity among elderly patients with dengue have been attributed to multiple factors, including delayed diagnosis, limited physiological reserve, and a higher burden of comorbidities such as diabetes and hypertension. Age-related changes, particularly immunosenescence and impaired vascular integrity, further contribute to increased rates of hospitalization and death. In this context, Jeng et al. reported a crude mortality rate of 18% among patients aged ≥ 65 years with DENV infection, compared with 2.7% in younger individuals, and identified older age as an independent predictor of mortality [40]. Diagnostic delay, however, does not appear to account for the observed mortality in our cohort. The median interval between symptom onset and laboratory confirmation was 1 day (range 0–6 days), indicating early clinical suspicion in most cases. Despite this short diagnostic interval, mortality remained considerable, suggesting that factors beyond delayed recognition—such as the underlying HD, profound immunosuppression, and overlapping transplant-related complications—likely contributed to adverse outcomes.

Although our observed mortality rate remains lower than that reported in some series of patients with hematological malignancies, where mortality rates exceeding 10% and up to 40% have been described [10, 37, 41, 42], the limited number of cases in this population precludes definitive conclusions regarding statistical significance. Variations in healthcare access, clinical management, and cohort characteristics may partly explain these differences. Notably, fatal cases in our cohort were characterized by severe complications, including multi-organ failure and renal insufficiency, underscoring the substantial clinical impact of dengue in immunocompromised patients.

Attributing mortality exclusively to dengue infection in patients with hematological malignancies remains challenging, as the underlying disease and immunosuppressive therapies likely amplify susceptibility to severe outcomes. The clinical course is therefore best understood as the result of a multifactorial interplay between viral infection, host immune dysfunction, and comorbid conditions. Consistent with previous reports, adult patients receiving chemotherapy or undergoing HSCT frequently developed severe thrombocytopenia and required platelet transfusions during the acute illness [5, 27]. These findings highlight the need for careful clinical assessment to disentangle dengue-related complications from those attributable to the underlying hematological condition.

This study, while informative, has several limitations. The relatively small sample size of 33 patients may limit the generalizability of the findings, and a larger sample would provide more robust data for more definitive conclusions. The retrospective nature of the study, based on existing medical records, may introduce bias or incomplete information. Furthermore, diagnostic testing strategies varied across centers and over time due to differences in the availability of assays during the outbreak period. Baseline hematological values and serial measurements were not uniformly available, precluding analysis of time to onset and recovery of cytopenias. Dengue IgG testing was performed for diagnostic purposes only and was reported qualitatively; quantitative IgG levels were not systematically available, precluding assessment of baseline humoral immunity. In parallel, this study did not include a systematic assessment of plasma leakage in severe dengue cases with warning signs, nor were radiological or ultrasonographic evaluations performed to support its presence. Nonetheless, efforts to ensure data reliability, including validation and follow-up, were undertaken to strengthen the study's integrity. In addition, while dengue transmission through platelet transfusions was identified, data on blood product screening and management practices were not comprehensively detailed, affecting the evaluation of the effectiveness of current protocols. A lack of a standardized procedure for dengue testing across institutions further complicates comparisons and consistency of diagnosis. In addition, the absence of a control group of HD patients without dengue, or dengue without HD, limits the ability to directly compare clinical features and outcomes between these groups and identify specific characteristics that could aid in early recognition and management of dengue in this population. Finally, in hematological malignancy patients—

particularly those undergoing chemotherapy—symptoms such as fever, fatigue, leukopenia, and thrombocytopenia are common and may result from either the treatment itself or a dengue infection. This symptom overlap can lead to dengue being mistakenly attributed to treatment side effects, delaying accurate diagnosis. Studies have documented delays of 7–9 days in the diagnosis of dengue in cancer patients due to this clinical similarity [5, 27]. In contrast, the short diagnostic interval observed in our cohort suggests heightened clinical awareness during the outbreak period.

Future research should prioritize prospective, multicenter studies with larger cohorts to better delineate the clinical course, risk factors, and outcomes of dengue in patients with HD, particularly considering the challenges of early diagnosis in immunocompromised populations. Given that approximately 20% of cases may present without fever, it is crucial not to dismiss afebrile patients, especially those with unexplained thrombocytopenia or leukopenia. Developing and validating diagnostic algorithms tailored to this group, potentially incorporating advanced biomarkers or imaging modalities, is essential. The safety of blood product transfusion, especially platelet transfusions, in dengue-endemic areas requires urgent attention. Two cases in patients who received platelet transfusions during the early stages of HSCT highlighted the lack of a dengue screening protocol. Retrospective PCR testing of platelet donors identified two DENV-positive cases, with one patient developing symptoms 48 h after transfusion, while the other remained asymptomatic. Routine screening of blood products should be evaluated to prevent arbovirus transmission. In addition, integration of transfusion safety protocols and gathering mortality data from other center will provide valuable insights. These efforts will contribute to a comprehensive understanding of dengue, guide evidence-based guidelines, and improve patient outcomes.

In conclusion, this study highlights the significant impact of dengue on patients with hematologic malignancies, emphasizing the need for early detection and rigorous screening protocols, particularly during outbreaks. The findings stress the importance of timely diagnosis and management to mitigate severe complications and improve patient outcomes. Further research with larger, multicenter trials and prospective designs is needed to explore the interplay between dengue and hematologic malignancies more comprehensively and to refine screening and management strategies for this vulnerable population.

Author Contributions

G.A.M., O.A.C., and J.S.G. were in charge of study design, data analysis, data interpretation, manuscript writing, manuscript review and approval. G.A.M., C.N., P.A.V.A., V.I.M., L.M.C.K., M.C.T., M.D.C.M., H.I.B., C.P.L.F., M.F.T., M.F.H., K.B.D., and A.D.J. performed data collection, manuscript review and approval.

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Conflicts of Interest

Jon Salmanton-García has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead, Menarini, and Pfizer; and has participated on a Data Safety Monitoring Board or Advisory Board for Pfizer, outside of the submitted work. Pedro Andrés Villalba Apestegui reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, outside of the submitted work. Oliver A. Cornely has received grants or contracts from BMBF, Cidara, EU-DG RTD (101037867), F2 G, Gilead, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; consulting fees from Abbvie, AiCuris, Biocon, Cidara, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Moderna, Molecular Partners, MSG-ERC, Noxxon, Octapharm, Pfizer, PSI, Scynexis, Seres; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbott, Abbvie, Al-Jazeera Pharmaceuticals/Hikma, Gilead, Grupo Biotoscana/United Medical/Knight, MedScape, MedUpdate, Merck/MSD, Noscendo, Pfizer, Shionogi, streamedup!; Payment for expert testimony from Cidara; a German patent ("Geschlossene Inkubationssysteme mit verbessertem Atemwegszugang für Untersuchungsvorrichtungen," DE 10 2021 113 007.7), filed by the University of Cologne and listing Oliver A. Cornely as one of three inventors; Participation on a Data Safety Monitoring Board or Advisory Board from Boston Strategic Partners, Cidara, IQVIA, Janssen, MedPace, PSI, Pulmocide, Shionogi, The Prime Meridian Group; Stock or stock options from CoRe Consulting, EasyRadiology; and Other financial or non-financial interests from Wiley, outside of the submitted work. The other authors declare no conflicts of interest.

Data Availability Statement

The corresponding author can provide the data supporting the findings of this study upon a reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File 1: tid70201-sup-0001-tableS1.docx **Supporting File 2:** Visual Abstract