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Efficacy of human interleukin-11 analogs for treating dengue fever-associated thrombocytopenia: a prospective cohort

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Abstract

Aim Dengue fever (DF), carried by Aedes mosquitoes, affects millions worldwide. Platelet-inducing human IL-11 analogues may be effective in treating DF-associated thrombocytopenia.

Methodology A prospective study was done at Dr. Ziauddin Hospital, a tertiary care hospital in Karachi, Pakistan, from September 2023 to April 30, 2024.

Results This study recruited 300 DF patients characterized by thrombocytopenia (platelet count < 30,000), including 159 in the treatment and 141 in the control group. The median age of patients was 34 ± 11.05 years, with 187 males (62.3%) and 113 females (37.7%). The treatment group had a higher proportion of fever (80%, $p < 0.0001$) and headache (96%, $p = 0.012$) compared to the control group; however, no significant changes were observed in other clinical parameters between the two groups. Following treatment for 5 days, platelet counts of the treatment group increased significantly in response to IL-11 treatment compared to the control group at all time intervals (day 0, day 1, day 2, day 3, day 4, and day 5). Following treatment, males consistently exhibited higher platelet counts than females (all $p < 0.05$). In addition, patients admitted on day 3 of their course of illness showed a significantly slow response to the treatment compared to those admitted on day 5. Although young individuals exhibited a significant increase in platelet count, the age showed no significant intergroup differences.

Conclusions IL-11 analogs have promising potential for treating DF-associated thrombocytopenia. Additional investigation is necessary to refine administration protocols and examine the wider therapeutic ramifications of IL-11 in managing DF.

Keywords Dengue fever, Interleukin-11, Thrombocytopenia, Platelet counts

Introduction

Dengue is a viral infection spread worldwide, primarily disseminated through insect vectors. It has been designated as an endemic disease [1]. There are four serotypes of dengue viruses (DV), all of which belong to the Flaviviridae family [2]. About 50–20 million people throughout the globe are infected with DF every year. Tropical countries are more susceptible to the illness since there are 3.6 billion people who are in danger of catching it every year, which eventually results in 20,000 deaths [3].

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Many factors significantly contribute to DF infection, encompassing socioeconomics, settlement, the contemporary dynamics of climate change and globalization, travel, and commerce [4].

Dengue fever encompasses a diverse array of clinical presentations, some of which are potentially fatal [5]. Symptoms typically manifest between 4 and 10 days following an infected mosquito bite [6]. Acute onset of fever (typically 40 °C or 104°F), severe headache, retroorbital pain (pain behind the eyes), muscle and joint pain (arthralgia and myalgia), fatigue, and generalized weakness are among the symptoms. Additional symptoms that may be present include nausea, vomiting, rash, and mild manifestations of bleeding, such as ecchymosis (bruising), petechiae (small red or purple spots on the skin), or gum bleeding. Typically, symptoms persist for 2–7 days, after which patients begin to recover [7]. Effective pharmacological interventions for dengue fever-associated thrombocytopenia continue to be scarce, notwithstanding developments in supportive care. Human interleukin-11 (IL-11) analogs have garnered attention as prospective therapeutic agents because they can induce platelet production and megakaryopoiesis [8].

Clinically, it has been reported that IL-11 is associated with disease etiology and clinical symptoms. IL-11m plays a vital role in several physiological processes, including circulation, hematopoiesis (the creation of blood cells), tissue healing, and interleukin-11 (IL-11). [9]. The underlying mechanism of IL-11 and dengue fever has not been fully elucidated due to its multifactorial and complex nature and complex [10]. When the body is exposed to a viral infection, it stimulates a cascade of reactions in the immune system against the dengue virus. Various immune cells, including dendritic cells and macrophages, are involved in the inflammation process in response to IL-2 production [11]. Therefore, multiple studies have reported increased IL-11 levels in patients with DF [12]. In addition, IL-11 differentiates precursor cells in the bone marrow into platelets and other blood cells. In severe cases of DF, thrombocytopenia, a common complication of dengue fever characterized by reduced platelet counts, has been reported. Therefore, it is hypothesized that the hematopoietic effect of IL-11 in patients with DF with reduced platelet production and regulation can provide insight into understanding the role of IL-11 in DF infection [13]. The possible mechanisms through which IL-11 is involved are the increase in antibodies neutralizing antibodies in the peripheral circulation and the direct inhibition of bone marrow function [14]. Despite the reduced platelet counts observed during the thrombocytopenic phase of the disease (third to eighth days), there was no discernible increase in the concentrations of positive humoral regulators of megakaryopoiesis [15]. It is hypothesized that dengue viruses may cause temporary disruptions in the regulation of platelet synthesis by the humoral immune system. This may be facilitated by lymphoid tissue injury [16].

Endothelial cells lining blood vessels maintain vascular integrity and regulate immune responses. In severe dengue infection, endothelial dysfunction is a key pathological feature leading to plasma leakage, bleeding, and organ dysfunction [17]. IL-11 has been implicated in endothelial cell activation and dysfunction in various inflammatory conditions. In dengue fever, IL-11 may contribute to endothelial dysfunction, vascular leakage, and the development of severe clinical manifestations such as plasma leakage syndrome observed in DHF/DSS [18]. Limited studies have investigated the use of IL-11 in treating dengue fever. Therefore, the present study aims to determine the potential use of IL-11 in the therapeutic management of dengue fever.

Methods

Study design

This prospective cohort study was conducted at Dr. Ziauddin University Hospital between September 2023 and April 30, 2024. This study included DF patients presenting in the outpatient clinical or emergency department of the hospital and were admitted. The use of a non-probability sequential sampling approach determined the sample size. The number of individuals recruited came to a total of 300. The participants were provided with an explanation of the study objectives in their native language, and they were required to provide written and signed informed consent. If the patient could not provide a signature, the immediate relative's signature was obtained in their place. The hospital study received approval from the Ethical Review Board.

Study subjects

The study included patients aged between 18 and 65 years, including both genders, diagnosed with dengue fever. The infection was confirmed through ELISA or positive NS-1 antigen. ELISA was performed to measure the quantitative and qualitative dengue virus IgG and IgM antibodies in the serum samples. Patients with confirmed dengue fever and baseline platelet count of less than 30,000 were included in the study. Pregnant women and patients with comorbid conditions, including hypertension, diabetes, and cardiovascular disease, were excluded.

Sample collection and processing

From each patient, 5mL of the venous blood was collected in a purple cap EDTA tube and a gel and clot activator tube. The blood samples were processed to perform

ELISA and complete blood profiling. Hemoglobin, red blood cells (RBCs), RBC indices, hematocrit, total leukocyte count, differential leukocyte count, platelets, lymphocytes, and ESR (Eosin sedimentation rate) are all components of the complete blood profile analysis. Hematological parameters that were assessed included the following: AST (Aspartate Aminotransferase), ALT (Alanine Transaminase), ALP (Alkaline Phosphatase), direct bilirubin, total protein, albumin, urea, and creatinine.

Clinical data of patient characterization

The basic demographic characteristics of each patient, including age, gender, and clinical symptoms, were recorded. The clinical symptoms included fever, headache, muscle and joint pain, pain behind the eyes, fatigue, nausea, vomiting, abdominal pain, skin rash, and mild bleeding. Patients were categorized into two groups. The treatment group ($n=159$) included patients who received human interleukin-11 analog in their treatment regimen. The control group ($n=141$) included the patients who received no human interleukin-11 analogs but were treated with the normal regimen. rhIL-11 analog was administered subcutaneously in a single dose of 1.5 mg for five consecutive days. Following the administration of human interleukin-11 analogs to test platelet counts, patients were monitored for a period of up to 120 h, and their blood profiles were determined at days 0, 1, 2, 3, 4, and 5, following the administration of the IL-11 analog. In addition, treatment of dengue fever with low platelet counts was mainly supportive, focusing on careful monitoring, maintaining fluid balance, and preventing complications. Platelet transfusions was reserved for severe cases with active bleeding; however, it was not administered in any patient.

Data analysis

The mean and standard deviation (mean and SD) were used to present quantitative data, while qualitative data were given as frequency or percentages (%). Continuous data from both groups was compared using the Mann–Whitney *t* test. We used the Chi-square test, often known as the $\chi 2$ test, to compare categorical data. First, a one-way analysis of variance (ANOVA) was carried out for multiple comparisons, and then Tukey's test was carried out. Statistical significance was determined for all experiments if the p value < 0.05. All analyses were conducted using Excel, GraphPad Prism, version 8.0), and MedCal online version (https://www.medcalc.org/calc/).

Results

Demographic characteristics of patients

The demographic and clinical characteristics of the 300 cases of DF included in this study are summarized in Table 1. The patients were divided into two groups: the Control group ($n=141$), which did not receive IL-11, and the Treatment group ($n=159$), which received an IL-11 analog. Patients averaged 34 ± 11.05 years in age; 187 were male (62.3%) and 113 were female (37.7%). The median age of the patients in the treatment group was considerably higher (35 years ± 11.81 years) in comparison to the control group (30.14 years; $p<0.0001$). The proportion of male patients was significantly higher ($p<0.001$) than female cases (Fig. 1). Clinical information from the patients revealed that a significant proportion of them presented with the following symptoms: fatigue ($n=286$; 95.3%), fever ($n=236$; 78.6%), joint pain

Table 1 Demographic and clinical variables of study cases (n = 300)

Variable	All cases $n=300$		Control group $n=141$ (47%)		Treatment group $n=159$ (53%)		p value
	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	
Age (median ± SD)	34 ± 11.77		30 ± 9.14		35 ± 11.81		< 0.0001
Fever	236(78.6)	64(21.4)	99(70.2)	42(29.8)	137(86)	22(14)	< 0.0001
Skin rash	76(25.3)	224(74.7)	40(28.3)	101(71.7)	36(22.6)	123(77.4)	0.254
Fatigue	286(95.3)	14(4.6)	137(97)	4(3)	149(93.7)	10(6.3)	0.157
Nausea	244(81.3)	56(18.6)	114(80)	27(20)	130(81.7)	29(18.3)	0.841
Vomiting	233(77.6)	67(22.4)	112(79.4)	29(20.6)	121(76)	38(24)	0.489
Muscle pain	145(48.3)	155(51.7)	68(48.2)	73(51.8)	77(48.4)	82(51.6)	0.972
Joint pain	263(87.6)	37(12.4)	127(90)	14(10)	136(85.5)	23(14.5)	0.233
Pain in eyes	184(61.3)	116(38.7)	88(62.4)	53(37.7)	96(60)	63(40)	0.718
Abdominal pain	294(98)	6(2)	131(93)	10(7)	153(96)	6(4)	0.362
Headache	278(92.6)	22(7.4)	125(88.6)	16((11.4)	153(96)	6(40)	0.012

SD Standard deviation

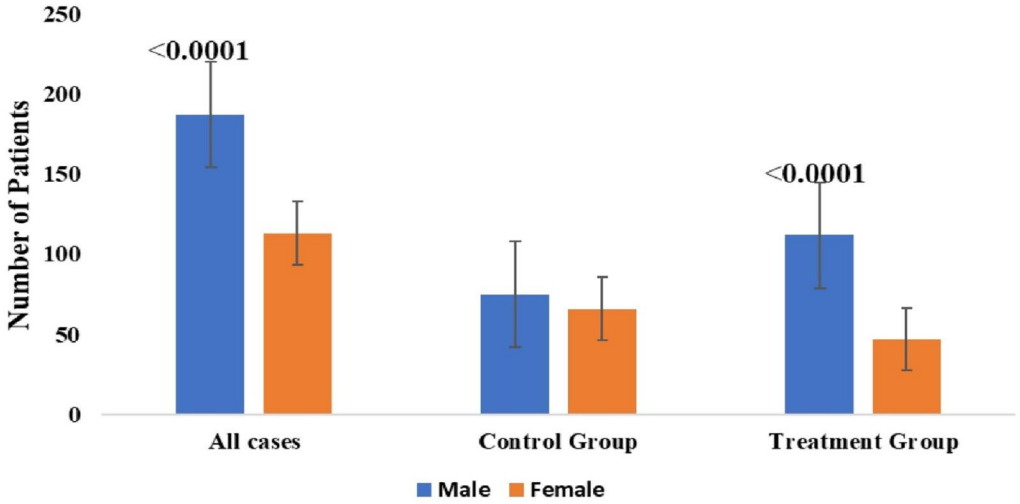

Fig. 1 Gender distribution among DF cases, including the control and the treatment group

(*n* = 263; 87.6%), abdominal pain (*n* = 294; 98%), and headache (*n* = 78; 92.6%). However, the incidence of skin lesions, muscle pain, or ocular irritation among patients was less frequent. Moreover, in comparison to the control group, a significantly higher proportion of patients in the treatment group reported fever ($p < 0.0001$) and headache ($p = 0.012$). At the same time, other symptoms were not statistically significant between the two groups.

Complications and outcomes of DF patients

The data for the complications and outcomes of the DF patients are summarized in Table 2. The data showed that bleeding (7.5% vs. 14.1%), shock (2.5% vs. 8.5%), organ failure (0.6% vs. 2.8%), death (1.2% vs. 16.3%), and recovery (88% vs. 59.5%) were significantly less frequent in the treatment group compared to the control group (all $p < 0.05$).

Biochemical characteristics of patients

The *t* test was used to compare the norms of several hematological and biochemical parameters in the treatment and control groups. The results showed significant differences among the cohorts about several parameters (Table 3). The data showed that treatment group participants had significantly higher mean values of Hb concentration (mean = 13.08 g/dl, SD = 2.20) than the control group (mean = 12.39 g/dl, SD = 2.34, $p = 0.004$), WBC count (mean = 4597 cells/cubic mm, SD = 3262) than the control group (mean = 5782 cells/cubic mm, SD = 2790, $p < 0.001$), neutrophil count (mean = 8.65, SD = 0.88) than the control group (mean = 7.98, SD = 1.49, $p < 0.001$), hematocrit percentage (mean = 39.48%, SD = 5.98) than the control group (mean = 37.48%, SD = 7.20, $p = 0.006$), INR (mean = 1.05, SD = 0.79) than the control group (mean = 0.78, SD = 0.25, $p = 0.004$), and total bilirubin concentration (mean = 0.89 mg/dL, SD = 1.29) than the control group (mean = 0.47 mg/dL, SD = 0.21, $p < 0.001$). However, no significant differences were observed in the concentrations of alanine transaminase (ALT), lymphocyte count, monocyte count, platelets count, prothrombin time (PT), and creatinine between the treatment group and the control group (all $P > 0.05$).

Table 2 Complications and outcome of DF patients (*n* = 300)

	All cases *n* = 300 (%)	Control group *n* = 141 (%)	Treatment group *n* = 159 (%)	*p* value
Hemorrhage	32(10.6)	20(14.1)	12(7.5)	0.004
Shock	14 (4.6)	10(8.5)	4(2.5)	0.001
Organ Failure	5(1.6)	4(2.8)	1(0.6)	< 0.0001
Death	25(8.3)	23(16.3)	2(1.2)	0.135
Recovered	224(74.6)	84(59.5)	140(88%)	0.116

Table 3 Biochemical and hematological characteristics of patients (n = 300)

	All cases (*n* = 300) Mean ± SD	Control group (*n* = 141) Mean ± SD	Treatment group (*n* = 159) Mean ± SD	*p* value
Hemoglobin g/dL	12.75 ± 2.29	12.39 ± 2.34	13.08 ± 2.20	0.004
WBC/mm^3	5154 ± 3101	5782 ± 2790	4597 ± 3262	0.001
Neutrophils	8.33 ± 1.26	7.98 ± 1.49	8.65 ± 0.88	< 0.0001
Lymphocytes	1.28 ± 0.45	1.31 ± 0.48	1.26 ± 0.42	0.135
Monocytes	0.39 ± 0.23	0.41 ± 0.22	0.37 ± 0.23	0.116
Hematocrit %	38.52 ± 6.65	37.48 ± 7.20	39.48 ± 5.98	0.006
Platelets/mcL	25933 ± 12403	24893 ± 17112	26855 ± 5463	0.0859
APTT/Sec	28.24 ± 5.85	28.97 ± 6.71	27.38 ± 4.52	0.344
PT/Sec	12.56 ± 4.44	12.25 ± 6.14	12.82 ± 2.29	0.204
INR	0.94 ± 0.63	0.78 ± 0.25	1.05 ± 0.79	0.004
ALT U/L	48.79 ± 34.81	49.22 ± 39.45	48.39 ± 29.94	0.429
Total bilirubin	0.68 ± 0.96	0.47 ± 0.21	0.89 ± 1.29	< 0.001
Creatinine	1.55 ± 1.72	1.69 ± 2.23	1.43 ± 1.16	0.149

SD Standard deviation; *WBC* White blood cells; *APTT* Activated partial thromboplastin time; *PT* Prothrombin time; *ALT* Alanine aminotransferase; *INR* International normalised ratio

Effect of human interleukin-11 analogs on platelet counts of DF patients

After administering interleukin-11 analogs to the treatment group for 5 days, a comparison of mean platelet counts over time between the control and treatment groups was assessed using a *t* test (Table 4). At multiple time intervals, the results revealed significant differences in the average platelet counts between the two groups (Fig. 2). The treatment consistently exhibited higher mean platelet counts than the control group at subsequent time intervals (days 1, 2, 3, 4, and 5), as indicated by *t* test *p* values ranging from 0.043 to < 0.0001 (Fig. 2). The mean platelet counts in the treatment group increased exponentially in response to IL-11 treatment. However, in the control group, the platelet counts initially reduced and then increased on day 5. In addition, the patients who were admitted on day 3 of their illness showed a slower response to the treatment ($p < 0.001$) compared to those who were admitted on day 5 (Fig. 3). In addition, no adverse effect of the treatment were observed.

Effect of gender on response to human interleukin-11 analogs and platelet counts

Gender stratification of the data revealed significant differences in mean platelet counts between female and male patients at various timepoints (days 0, 1, 2, 3, 4, and 5) post-treatment, with corresponding *p* values of 0.023, 0.009, 0.005, 0.003, 0.005, and 0.018, respectively. At baseline (day 0) and subsequent timepoints (days 1, 2, 3, 4, and 5), male patients consistently exhibited a higher mean platelet count than female patients. These findings suggest that gender may influence platelet response to IL-11 treatment in dengue fever patients, with male patients showing a more robust increase in platelet counts over time than female patients (Fig. 4).

Table 4 Platelets count at different timepoints

	All cases (*n* = 300) Mean ± SD	Control group (*n* = 141) Mean ± SD		Treatment group (*n* = 159) Mean ± SD	*p* value
Day 0	25933 ± 12403	24893 ± 17112		26855 ± 5463	0.012
Day 1	28240 ± 12581	25854 ± 17323		30355 ± 5824	0.0431
Day 2	30800 ± 12798	27354 ± 17134		33855 ± 6007	0.0098
Day 3	33948 ± 13223	29054 ± 16733		38355 ± 6308	< 0.0001
Day 4	37339 ± 13935	30554 ± 14173		43355 ± 6585	< 0.0001
Day 5	41895 ± 15304		32354 ± 14740	50355 ± 7195	< 0.0001

SD Standard deviation

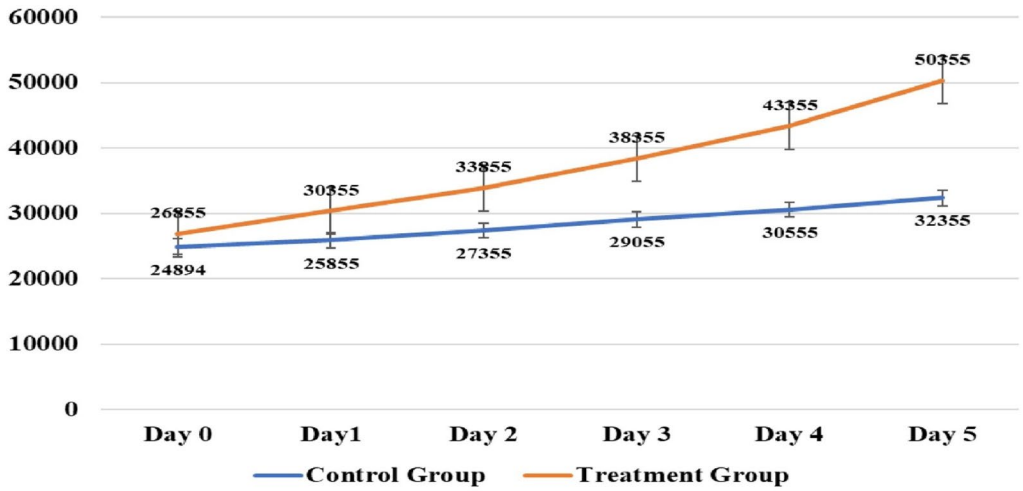

Fig. 2 Platelet counts in treatment and control groups at different timepoints

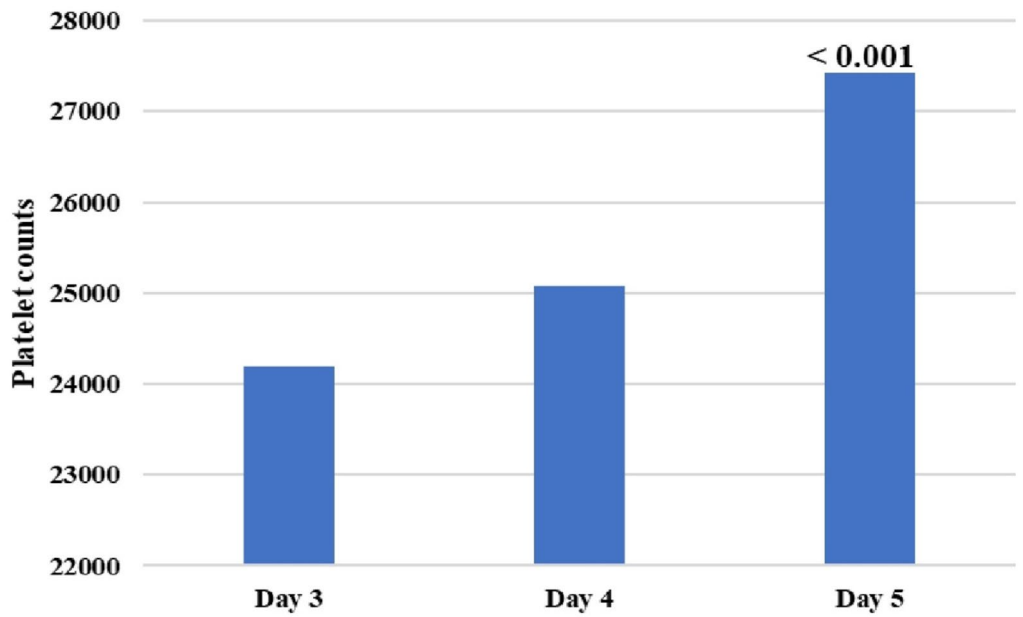

Fig. 3 Effect of duration of illness on platelets count in response to treatment

Effect of age on response to human interleukin-11 analogs and platelet counts:

One-way ANOVA was performed to determine the effect of age on the platelet counts over time in dengue fever patients receiving IL-11 treatment. The analysis revealed significant differences in mean platelet counts in each age group at various timepoints (days 0, 1, 2, 3, 4, and 5) post-treatment (all p value < 0.001). At baseline day 0, patients aged 18–35 had a mean platelet count of 23573, while patients in the other age groups had a mean platelet count of 30545 and 30700, respectively (Table 5). At subsequent timepoints, the platelet count increased rapidly in the patients of all age groups (Table 5; Fig. 5).

Discussion

This study aimed to evaluate the efficacy of human interleukin-11 (IL-11) analogs as a therapeutic intervention for dengue fever (DF). In addition, the impact of demographic factors (age and gender) on treatment outcomes was examined. A notable elevation in platelet counts was observed in the cohort that underwent IL-11 therapy at multiple time intervals (days 0, 1, 2, 3, 4, and 5) after

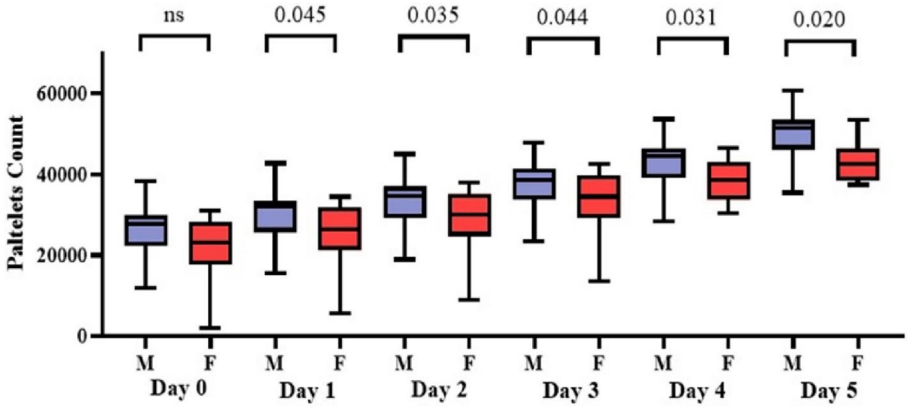

Fig. 4 Box and Whisker plot showing gender-based platelets count in response to treatment. M: male, F: female

Table 5 Effect of age on response to human interleukin-11 analogss and platelet counts

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	*p* value
18–35 Years	23573	30404	33904	38404	43404	50404	< 0.001
36–50 Years	30545	34045	37545	42045	47045	54045	< 0.001
> 50 Years	30700	34200	37700	42200	47200	54200	< 0.001

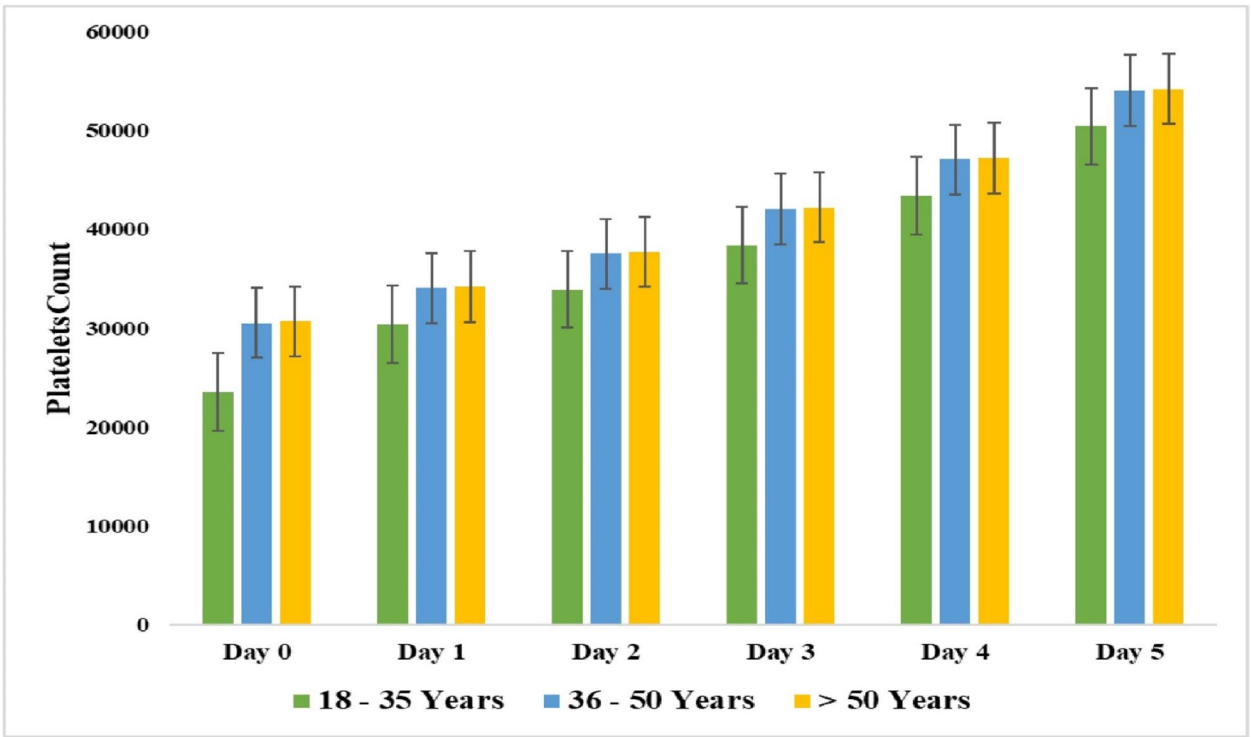

Fig. 5 Effect of age on response to human interleukin-11 analogs and platelet counts

the intervention compared to the control group. IL-11 is a hematopoietic growth factor that stimulates the production of platelets. Multiple mechanisms have been reported to contribute to developing thrombocytopenia in patients with DF, including platelet sequestration, reduced platelet production, and platelet differentiation [19].

As a biomarker for the onset of the disease, its severity, and prognosis, increased levels of IL-11 have been reported in patients with DF [20]. IL-11 is involved in the stimulation, differentiation, and maturation of megakaryocytes in the bone marrow, activating platelet proliferation [21]. Clinicians can distinguish individuals vulnerable to developing severe problems by monitoring IL-11 levels along with other inflammatory indications and making personalized treatment decisions [22]. The use of IL-11 can boost platelet production, hence reducing the risk of hemorrhage problems associated with thrombocytopenia in patients with dengue fever [23].

Furthermore, targeting IL-11 or its downstream signaling pathways could potentially serve as a therapeutic approach to mitigate the vascular complications and inflammatory response that are hallmarks of severe dengue infection [24]. A comparative investigation revealed that blood cells, including platelets, white blood cells, neutrophils, lymphocytes, and large lymphocytes, exhibited stronger adhesion to dengue-infected endothelium cells than normal endothelium cells [25]. One possible hypothesis posits that the increased affinity between platelets and endothelial cells may contribute to thrombocytopenia in patients who experience acute heart failure. It has been demonstrated that regimens consisting of 50-μg per kilogram of recombinant IL-11 administered daily can decrease the necessity for platelet transfusions in patients undergoing conventional chemotherapy. The reduction in patients requiring platelet transfusions from 96% in the placebo group to 70% in the therapy group signifies a substantial and favorable transformation [26].

The ability of IL-11 analogs to ameliorate thrombocytopenia and enhance platelet counts in animal models of dengue virus infection has been established through preclinical investigations [27, 28]. Furthermore, initial clinical trials have shown positive results, as IL-11 analogs exhibited a favorable safety profile and significantly increased platelet counts among dengue fever patients [8]. However, large-scale randomized controlled trials are imperative for a more comprehensive understanding of the ideal administration protocols, effectiveness, and safety of IL-11 analogs in this particular context.

In this study, gender stratification has shown that male patients exhibited higher platelet counts than females, which aligns with previous studies [29, 30]. Multiple studies have reported the association of gender with platelet counts in patients with DF [31, 32]. The observed contradiction might be attributed to hormonal variations between males and females, as the authors hypothesize that androgens influence platelet inhibition.

In addition, throughout the treatment, a significant increase in platelet count was observed in all patient groups, which is consistent with previous studies [31, 33–37]. Age is an additional factor that influences platelet counts in dengue fever patients. Lee et al. [38] found that elderly DF patients had reduced platelet count. There has been a suggestion that aging-associated immune function changes and comorbidities may make thrombocytopenia worse in older people [38]. Furthermore, Lam et al. [39] looked at how gender and age affected the platelet counts of young dengue patients. The authors found that male pediatric patients with dengue fever who were 1 year of age or older had lower platelet counts. The authors hypothesize that the observed variances in platelet counts might have been caused by age-related alterations in the immunological response and hormonal and physiological differences between males and females [39].

Limitations

There are few limitations in this study. This was a single center study with small sample size. Additional studies with large sample size are required to investigate the advantages and disadvantages of IL-11 analogues and to determine the positive effects of IL11 analogs in managing severe thrombocytopenia in dengue infections.

Conclusion

This study's results indicate that treating DF-associated thrombocytopenia may benefit from using IL-11 analogs. Additional studies are required to fully comprehend the therapeutic efficacy of IL-11 analogs and maximize their practical applicability.

Author contributions

SK/IB: Conceptualization, writing original draft; JM: Writing Reviewing and editing; KA/M: Software, Data curation; SAA/ SHMZ: Resources, visualization; AW/FNUS: Methodology, validation; EAV: Formal analysis, project administration, supervision.

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Data availability

The data used in this study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The research was approved by the ethical review committee of Dr. Ziauddin University on September 10, 2023, following the completion of all tests in accordance with the Declaration of Helsinki. All participants in the study provided written informed permission.

Consent for publication
The ethical review committee of Dr. Ziauddin University provided written informed approval for publication.

Competing interests
The authors declare no competing interests.

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