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ORIGINAL ARTICLE

The Prevalence of Coagulation Factor Deficiency Among Pediatric Populations in Medina City, Saudi Arabia

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SUMMARY

Background: **Coagulation factor deficiencies, a subset of inherited bleeding disorders, are characterized by impaired clotting due to insufficient or dysfunctional coagulation factors. This study aims to explore the prevalence of coagulation factor deficiencies in pediatric patients at the Maternity and Children Hospital in Medina, Saudi Arabia, between 2019 and 2023, and to assess their impact on platelet counts and coagulation profile parameters.**
Methods: **A retrospective analysis was conducted involving 221 pediatric patients diagnosed with coagulation factor deficiencies. Clinical and laboratory data, including platelet count, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and coagulation factor levels, were extracted from patient clinical metadata. A control group of 50 healthy children were included for comparison.**
Results: **Retrospective analysis revealed that the most common deficiencies were factor VIII (hemophilia A, 15.38%) and factor IX (hemophilia B, 14.47%), among both males and females (50.22% males and 49.78% females). Prothrombin time, INR, and APTT were significantly prolonged across all coagulation deficiencies ($p < 0.0001$). The findings also highlighted the importance of monitoring platelet and coagulation parameters in children with unexplained bleeding symptoms.**
Conclusions: **The high prevalence of coagulation factor deficiencies in Medina, Saudi Arabia, underscores the need for early diagnosis, genetic counseling, and specialized care. This study emphasizes the importance of a comprehensive approach to managing bleeding disorders, including close monitoring of coagulation profiles and platelet counts.**
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KEYWORDS

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INTRODUCTION

Inherited bleeding disorders comprise a diverse group of hemostatic abnormalities characterized by bleeding disorders in joints, muscles, or mucocutaneous tissues [1]. The severity of these disorders ranges from mild to severe [2]. They arise due to defects in the blood vessel wall, connective tissue, platelets, or coagulation proteins. Platelet-related disorders may result from abnor-

malities in platelet count or function, including disorder defects in adhesion, activation, or aggregation [3]. Similarly, coagulation protein deficiencies disrupt the clotting cascade, leading to impaired hemostasis and an increased risk of bleeding complications [4,5]. Coagulation factor deficiencies represent a specific subset of bleeding disorders caused by insufficient levels or dysfunction of specific clotting factors, such as factor VIII, factor IX, and factor XI which are responsible for hemophilia A, B, and C, respectively [6]. Other deficiencies, including those of factor VII, factor V, factor II (prothrombin), also contribute to bleeding tendencies [7]. Each specific deficiency presents with distinct clinical manifestations, ranging from easy bruising and mucosal bleeding (e.g., nosebleeds, gum bleeding) to joint hemorrhages and prolonged bleeding following minor trauma or invasive procedures [8,9]. The severity of bleeding episodes varies depending on the degree of deficiency, ranging from mild to life-threatening [10].

To date, the primary treatment for coagulation factor deficiencies has focused on factor replacement therapy using recombinant or plasma-derived concentrates. Secondary treatments include prothrombin complex concentrates, cryoprecipitate, or desmopressin [11,12].

Several studies have documented hereditary bleeding disorders in the Saudi population [13]. However, most research has primarily focused on hemophilia A and B, von Willebrand disease, and platelet disorders with limited data on coagulation factor deficiencies [14]. Additionally, population screening, may overestimate disease prevalence if based on a limited set of symptoms [15]. Implementing more stringent diagnostic criteria could improve accuracy and reduce false-positive cases [16]. A significant gap in the literature is the lack of studies investigating coagulation factor deficiencies in children. This study aims to address this gap by assessing the prevalence of coagulation factor deficiencies in children in Medina, Saudi Arabia, and their impact on platelet and coagulation profile parameters.

MATERIALS AND METHODS

Study design and inclusion and exclusion criteria

This retrospective study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the King Khalid University Committee of Research Ethics (approval number ECM#2024-3137). For this study, being retrospective in nature, informed consent was waived by the Institutional Review Board.

Data were extracted in January 2024 from the CLOUD-CARE hospital information system at the Maternity and Children Hospital, King Salman bin Abdulaziz Medical City, Medina, Saudi Arabia. The study included pediatric patients aged 2 months to 14 years diagnosed with a deficiency of a single coagulation factor between January 1, 2019, and December 31, 2023.

Patients were referred for coagulation testing based on clinical indications such as spontaneous bleeding, easy bruising, or prolonged bleeding after trauma. Initial screening tests included prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) were performed. Those with abnormal screening results underwent specific coagulation factor assays for factors I, II, V, VII, VIII, IX, X, XI, XII, and XIII, using automated analyzers (Sysmex CS-5100). Only patients with a confirmed deficiency restricted to a single coagulation factor, with all other factors within normal reference ranges, were included.

Patients were excluded if they were aged 15 years or older, had deficiencies involving multiple coagulation factors, or had missing or insufficient clinical or laboratory data for analysis.

A control group of 50 healthy, age and gender matched children who visited the hospital for routine check-ups was included for comparison. All individuals in the control group had normal blood coagulation profiles and no history of bleeding disorders, infections, or chronic illnesses. Blood samples were collected under the same standardized conditions as for the patient group. The mean values for the control group were platelet count: $335.54 \pm 63.97 \times 10^9$/L, PT: 11.46 ± 0.68 seconds, and APTT: 28.93 ± 3.62 seconds.

All blood samples from patients and controls were analyzed using the Sysmex CS-5100 for coagulation profiles and the Sysmex XN-1000 for platelet count.

Statistical analysis

Data analysis was performed using GraphPad Prism (9.5.1) and Microsoft Excel 19. Descriptive statistics, including, percentage, mean, and standard deviation (SD), were calculated. Independent sample *t*-tests were conducted to compare groups, with statistical significance set at $p < 0.05$.

RESULTS

Between 2019 and 2023, a total of 221 pediatric patients at the Maternity and Children Hospital in Medina were diagnosed with one or more coagulation factor deficiencies. The cohort comprised of 111 males (50.2%) and 110 females (49.8%), with ages ranging from 2 months to 14 years.

Distribution of coagulation factor deficiencies

Table 1 shows the distribution of coagulation factor deficiencies among the study population. The most prevalent deficiency was factor VIII, associated with hemophilia A, which affected 34 patients (15.4%), including 23 males (10.4%) and 11 females (5.0%). This was followed by factor IX deficiency (hemophilia B), affecting 32 patients (14.5%), with 21 males (9.5%) and 11 females (5.0%). Factor X deficiency was identified in 25 patients (11.3%), comprising 12 males (5.4%) and 13 females (5.9%). Other notable deficiencies included factor II deficiency in 24 patients (10.8%), factor I (fibrin-

Table 1. Demographic and Clinical Characteristics of Pediatric Patients (≤ 14 Years) with Coagulation factor abnormalities.

	Age in years (mean ± SD) 5 ± 4.13					
Gender	total (n = 221, 100%)		male (n = 111, 50.2%)		female (n = 110, 49.8%)	
Factor	N	%	N	%	N	%
F-I	23	10.4%	8	3.6%	15	6.8%
F-II	24	10.8%	11	5.0%	13	5.9%
F-V	20	9.0%	9	4.1%	11	5.0%
F-VII	20	9.0%	10	4.5%	10	4.5%
F-VIII	34	15.4%	23	10.4%	11	5.0%
F-IX	32	14.5%	21	9.5%	11	5.0%
F-X	25	11.3%	12	5.4%	13	5.9%
F-XI	7	3.2%	4	1.8%	3	1.4%
F-XII	17	7.7%	8	3.6%	9	4.1%
F-XIII	19	8.6%	5	2.3%	14	6.3%

Table 2. The coagulation profiles of the patient group.

Factor	PT			APTT		
	second	results *	p-value *	second	results *	p-value *
F-I	16.4 ± 4.54	prolonged	p < 0.0001	49.4 ± 16.41	prolonged	p < 0.0001
F-II	21.1 ± 16.36	prolonged	p < 0.0001	56.1 ± 37.13	prolonged	p < 0.0001
F-V	21.2 ± 15.13	prolonged	p < 0.0001	56.9 ± 39.45	prolonged	p < 0.0001
F-VII	24.3 ± 26.02	prolonged	p < 0.0001	54.5 ± 33.35	prolonged	p < 0.0001
F-VIII	13.7 ± 2.22	prolonged	p < 0.0001	59.2 ± 25.59	prolonged	p < 0.0001
F-IX	18.9 ± 13.84	prolonged	p < 0.0001	61.1 ± 36.13	prolonged	p < 0.0001
F-X	20.9 ± 14.53	prolonged	p < 0.0001	53.0 ± 22.35	prolonged	p < 0.0001
F-XI	14.9 ± 2.72	prolonged	p < 0.0001	41.2 ± 10.15	prolonged	p = 0.0004
F-XII	14.6 ± 1.4	prolonged	p < 0.0001	57.5 ± 35.78	prolonged	p < 0.0001
F-XIII	18.8 ± 12.79	prolonged	p < 0.0001	45.5 ± 35.05	prolonged	p < 0.0001

Data are expressed as mean ± SD. Statistical analysis was performed using the Mann-Whitney U test, with $p < 0.05$ considered statistically significant, * Compared to control group.

ogen) deficiency in 23 patients (10.4%), and deficiencies of factor V and factor VII, each affecting 20 patients (9.1%). Factor XIII deficiency occurred in 19 patients (8.6%), and factor XII deficiency in 17 patients (7.7%). The least common was factor XI deficiency, affecting 7 patients (3.2%).

The statistical examination of platelet data indicated that patients with coagulation factor deficiencies often exhibit reductions in platelet count, even though the levels remain within the normal range when compared to the average of healthy individuals (Figure 1). The most pronounced decrease was observed in factor X deficient patients (mean = 205.0, n = 25) at $p < 0.0001$. The results indicate a relationship between factor deficiency and platelet reduction, with varying degrees depending on the specific factor involved.

The results of prothrombin time (PT) assays showed patients with a coagulation factor deficiency to be distinct from the control group (Table 2); specifically, PT was increased for all factor groups with a consistent degree of significance ($p < 0.0001$). For patients deficient in factor I, the mean prothrombin time was 16.4 seconds (n = 23); for factor II, 21.1 seconds (n = 24); factor V, 21.2 seconds (n = 20); factor VII, 24.3 seconds (n = 20); factor VIII, 13.7 seconds (n = 34); factor IX, 18.9 seconds (n = 32); factor X, 20.9 seconds (n = 25); factor XI, 14.9 seconds (n = 7); factor XII, 14.6 seconds (n = 17); and finally factor XIII with mean 18.8 seconds (n =

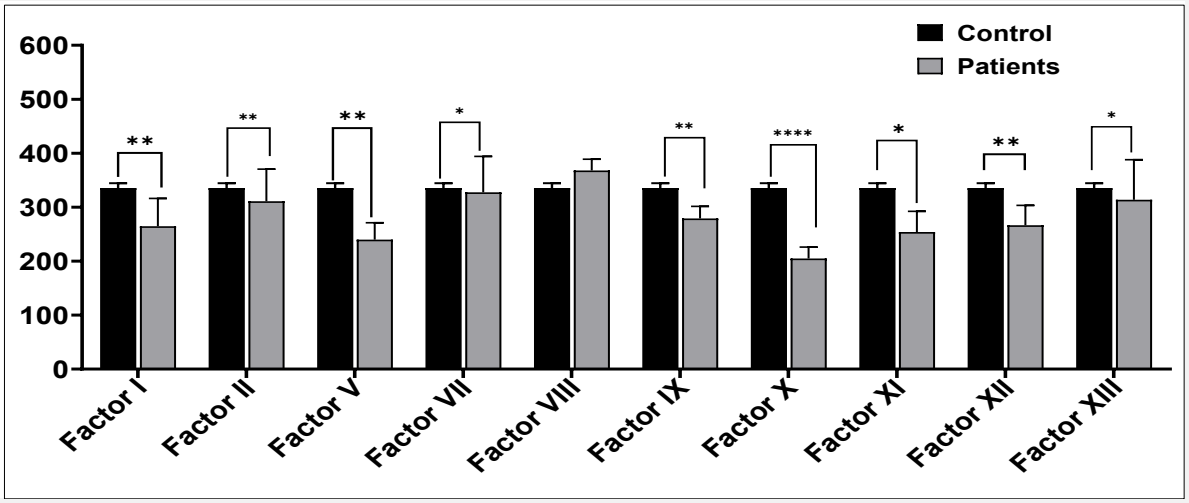

Figure 1. Comparison of platelet counts in coagulation factor deficient patients and controls.

Significance was determined using the non-parametric unpaired *t*-test. * p < 0.0469, ** p < 0.0068, **** p < 0.0001. Bars illustrate the mean ± SD.

19). These findings indicate a highly significant increase in PT across all factor deficiencies. INR values (data not shown) were consistent with the PT data to validate the prothrombin time findings.

As with PT, children with coagulation factor deficiency exhibited a consistently significant increase in APTT with p-value < 0.0001 (Table 2**)** except for factor XI deficiency, which achieved p = 0.0004. For patients deficient in factor I, the mean APTT was 49.4 seconds (n = 23); for factor II, 56.1 seconds (n = 24); factor V, 56.9 seconds (n = 20); factor VII, 54.5 seconds (n = 20); factor VIII, 59.2 seconds (n = 34); factor IX, 61.1 seconds (n = 32); factor X, 53.0 seconds (n = 25); factor XI, 41.2 seconds (n = 7); factor XII, 57.5 seconds (n = 17); and finally factor XIII with mean 45.5 seconds (n = 19). These results highlight a significant increase in APTT across all factor deficiencies, indicating a prolonged clotting time associated with these disorders.

DISCUSSION

Coagulation factor deficiencies represent a significant global health challenge, particularly in regions with a high prevalence of inherited genetic disorders, such as Saudi Arabia [17,18]. The Kingdom's unique genetic landscape, characterized by a high rate of consanguinity (marriage between close relatives) has contributed to an increased incidence of autosomal recessive conditions, including hemophilia and other coagulation disorders. This study, which analyzed 221 pediatric patients diagnosed with coagulation factor deficiencies at the Maternity and Children Hospital of Medina over a five-year period, provides valuable insights into the epidemiology and clinical implications of these disorders in the region.

The most observed deficiencies were those of factor VIII (15.4%) and factor IX (14.5%), both classically associated with hemophilia A and B, respectively. These X-linked disorders are typically more prevalent in males, as reflected in this cohort (factor VIII: 10.4% in males vs. 5.0% in females; factor IX: 9.5% in males vs. 5.0% in females). However, a notable proportion of affected females exhibited clinically significant deficiencies. In the absence of genetic testing, it remains uncertain whether these females are homozygous for the mutations possibly due to consanguinity or heterozygous carriers with skewed X-chromosome inactivation [19,20]. The severity of bleeding symptoms in female patients supports the plausibility of functionally significant deficiency, though molecular studies are necessary to determine the underlying mechanism.

In addition, autosomal recessive factor deficiencies such as those of factors I, II, V, X, and XIII were also prevalent and showed no major gender disparity. These findings are consistent with prior studies highlighting the increased frequency of rare autosomal recessive bleeding disorders in populations with high consanguinity rates [21,22]. Factor XIII deficiency, notably more frequent in females (6.3%) than males (2.3%), may suggest a local genetic founder effect or sample variability, meriting further genetic exploration.

This study revealed that patients with defects in factor X, factor V, and factor I exhibited reduced platelet counts relative to other coagulation deficiencies. This finding suggests a more complex pathophysiological relationship between primary and secondary hemostasis than previously understood.

While traditional paradigms consider platelet number and function to be largely independent of coagulation factor levels, recent evidence has challenged this assumption. Factor V, for instance, is not only present in plasma but also stored in platelet α-granules, from which it is released upon activation to enhance thrombin generation at the site of injury [23]. Similarly, fibrinogen plays a dual role in hemostasis by enabling platelet aggregation and serving as the substrate for fibrin clot formation. In cases of fibrinogen deficiency (afibrinogenemia or hypofibrinogenemia), defective clot stabilization may lead to a compensatory increase in platelet consumption or degradation, resulting in lower platelet counts [24]. The role of factor X, although less directly linked to platelet biology, is critical in thrombin generation, and its severe deficiency may indirectly affect platelet turnover or activation due to inadequate clot formation [25].

The study also found that PT, INR, and APTT were significantly prolonged in patients with coagulation factor deficiencies, a consistent finding across most factor deficiencies. These findings are expected, as these tests directly reflect clotting factor functionality. The statistically significant prolongation of PT and APTT across most deficiencies highlights the increased bleeding risk in affected children, reinforcing the need for early intervention and appropriate therapeutic strategies, such as factor replacement therapy [26].

Over the past decade, advancements in diagnostic tools and therapeutic options have significantly improved the management of hemophilia and other coagulation disorders in Saudi Arabi [27]. However, the high incidence of consanguinity necessitates enhanced genetic counseling and early screening programs, particularly in rural and underserved communities, where access to specialized care may be limited. The establishment of dedicated hemophilia treatment centers is crucial to providing comprehensive, multidisciplinary care, including regular monitoring of coagulation parameters, access to clotting factor concentrates and recombinant therapies, supportive treatments such as antifibrinolytic agents and patient and caregiver education on bleeding prevention and emergency management.

This study has some limitations. First, as a retrospective single-center study, the findings may not fully represent the broader pediatric population across Saudi Arabia. Second, missing genetic data and incomplete family history limited the ability to thoroughly evaluate inheritance patterns, particularly in cases suspected to follow autosomal recessive transmission. Additionally, longitudinal follow-up data on treatment outcomes and complications were not available, restricting the assessment of long-term prognosis and disease progression. Therefore, future studies should adopt multicenter, prospective designs to improve the generalizability of findings and allow for standardized data collection. Incorporating comprehensive genetic testing and long-term clinical follow-up will be essential to better understand the natural history, genotype-phenotype correlations, and therapeutic outcomes associated with coagulation factor deficiencies in the Saudi population.

CONCLUSION

In conclusion, this study highlights the high prevalence and clinical impact of coagulation factor deficiencies among children in Medina, Saudi Arabia. The findings underscore the importance of early identification and a comprehensive understanding of these disorders within the context of a population characterized by high rates of consanguinity. The near-equal gender distribution and predominance of autosomal recessive factor deficiencies reflect the unique genetic landscape of the region. The findings enhance our comprehension of the conditions and clinical traits associated with coagulation disorders in genetically diverse populations, establishing a foundation for future inquiries.

Informed Consent:
Informed consent was waived due to the retrospective nature of the study.

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Data Availability Statement:
The dataset used during this study is available.

Dedication of Interest:
No potential conflict of interest was reported by the author(s).

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