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Prevalence and Severity of Anaemia in Persons with Haemophilia and Von Willebrand Disease at Charlotte Maxeke Johannesburg Academic Hospital



A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of requirements for the degree of Master of Medicine (Haematology)

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DECLARATION

I, Refilwe Monaheng, declare that this Research Report is my own, unaided work. It is being submitted for the degree of Master of Medicine (Haematology) at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree of examination at any other university.

_____ (Signature)

21/10/2024, Johannesburg, South Africa.

CERTIFICATE OF SUBMISSION

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

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Entitled: **Prevalence of Anaemia in Persons with Haemophilia and Von Willebrand Disease at Charlotte Maxeke Johannesburg Academic Hospital.**

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1. Schapkaitz E, Rhemtula H, Monaheng R, Louw M, Gerber A, Masebe M, Sithole J. Warfarin Anticoagulation and Fetal Central Nervous System Abnormalities: a Case Report. Clin Lab. 2021 Jun 1;67(6). doi: 10.7754/Clin.Lab.2020.201013. PMID: 34107617.

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1

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The names of the examiners should be confidential during the examination process and may only be revealed to the candidate with the acquiescence of the examiner once the final version of the thesis has been submitted to the Faculty and the process has been completed.

ACKNOWLEDGEMENTS

Thank you my supervisor, Prof JN Mahlangu for his patience, support and guidance.

Thank you to Sr Bertha and Mr K Modisenyane for their assistance with data collection and Dr B Ter Morshuizen for helping/advising with data analysis.

Finally, to my husband, thank you for your unwavering support and encouragement.

PUBLICATIONS FROM THIS STUDY

This research is presented as a submissable article for publication in the monthly, peer–reviewed, internationally indexed, general medical journal, SAMJ (South African medical journal)

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Abbreviations

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

FBC: Full Blood Count

HB: Haemoglobin

HRQoL: Health-related quality of life

IBD: Inherited bleeding disorders

IDA: Iron deficiency anaemia

IQR: Interquartile range

vWD: Von Willebrand disease

WHO: World Health Organization

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Abstract

Background: Haemophilia and von Willebrand Disease (vWD) are inherited bleeding diathesis characterized by spontaneous or traumatic bleeding resulting in varying degrees of anaemia. Early diagnosis, treatment and prevention of anaemia are crucial to improving physical and mental health and enhancing health-related quality of life. The global prevalence of anaemia and associated risk factors are well established, however, there is paucity of data on those with inherited bleeding disorders (IBD). The objective of this study was to describe the prevalence and severity of anaemia in haemophilia and vWD in a quaternary care facility.

Methods: This study was approved by the institutional ethics and facility authorities. Adult patients with haemophilia or vWD of any subtype were identified through the hospital record reviews. After excluding those who did not fulfil the inclusion criteria, data from the selected patients was anonymised, captured, collated and analysed. Quantitative data was summarised with standard statistical tools and qualitative data was described. The IBD cohort demographics, anaemia severity and prevalence data was compared to those of the controls.

Results: Of the 1 100 IBD patients screened, 77 met the eligibility criteria. This comprised of 68 (88,3%) haemophilia patients and 9 (11.7%) patients with VWD. The majority of IBD patients were males, accounting for 90.9% (n=70), while females comprised 9.1% (n=7). Of the 886 screened controls, 77 age and sex-matched were selected for comparison. This comprised 85.7% (n=66) male patients and 14.3% (n=11) female patients. The prevalence of anaemia in the IBD cohort was 38,96% (n=30); of which 96.7% (n=29) were male and only a single female. The majority (40%, n=12) of the anaemic IBD patients had a borderline anaemia compared to the control population which displayed a predominance of life-threatening anaemia (31,2%, n=24). Mild anaemia (HB <11g/dL) was noted in 37% of the anaemic IBD study cohort vs 13% in the control population. The prevalence of moderate anaemia was 3% in the IBD cohort vs 28,6% in controls. Life-threatening anaemia, was seen in 13% of the anaemic IBD cohort vs 31,2% in the control population. 43% of the anaemic patients had a documented iron deficiency anaemia while 6.5% control patients had an iron deficiency.

Conclusion: This study indicates the burden of anaemia in the IBD population. Thus health professionals must be proactive in screening and treating their anaemia. Further research is required to explore additional contributing factors. Optimization of therapeutic strategies tailored to the unique needs of these patients is vital.

Introduction

The global prevalence of anaemia remains high, with a third of the world population, in excess of 2.5 billion people, having this diagnosis(1). Since its presence is rarely isolated and often indicates an underlying inherited or acquired disorder (2), further investigation is usually required. The most common cause of anaemia worldwide is iron deficiency, affecting over 1.2 billion individuals globally (3). Beyond the well-recognized populations susceptible to anaemia, such as infants, children under the age of 2, pregnant and breastfeeding individuals, and the elderly (4), there is a tendency to overlook those with inherited bleeding disorders. There is, therefore, a paucity of data on the prevalence of anaemia in this specific group.

Inherited bleeding disorders encompass a spectrum of conditions affecting coagulation clotting factors, platelets, or vessel wall abnormalities. They have varying clinical manifestations that depend largely on the underlying cause (5). The most common IBD are vWD and haemophilia. Patients living with haemophilia, particularly those with a severe bleeding phenotype, frequently present with persistent joint and muscle bleeds. This chronic bleeding thus poses an increased risk of developing anaemia, which may also include iron deficiency. Studies demonstrating this are, however, limited. As in patients with haemophilia, patients living with vWD face chronic bleeding commonly due to heavy menstrual bleeding in females and thus also carrying an increased risk of iron deficiency anaemia. Our knowledge of anaemia, particularly iron deficiency anaemia, in patients with vWD, is better compared to haemophilia.

The sequelae and complications of anaemia in people with IBD are many and include musculoskeletal, neurological and other organ dysfunctions. Quality of life is negatively affected by both anaemia and IBD. It is, therefore, crucial to recognise the risk factors of anaemia and to prevent the development of anaemia through adequate management. The goal is to limit the effect of impaired health-related quality of life (HRQoL) in individuals with bleeding disorders.(6).

In light of the paucity of available literature on this issue, this paper aims to explore the prevalence of anaemia in persons with haemophilia and vWD at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), with the hope of improving the current available data and overall awareness.

Objectives

In this study, we evaluated the prevalence and severity of anaemia in patients with haemophilia and vWD at a quaternary- public healthcare centre/ hospital in Johannesburg, South Africa. We further characterised the anaemia into various aetiological causes including iron deficiency

Methods and Design

Study design and population

This is a single-centre retrospective case-control study performed at CMJAH, a quaternary healthcare facility in Johannesburg, South Africa. Data was collected from January 2016 to December 2019. This was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (ref. no. M210818) and the CMJAH CEO and research committee (ref. no. GP_202107_045).

Data collection and file reviews were conducted on all the adult outpatients who are followed up at CMJAH, during the years 2016 to 2019. Data was recorded on a data collection sheet prior to being analysed.

Study setting
CMJAH is a quaternary hospital in Parktown, Johannesburg South Africa. It serves patients from across the Gauteng province and neighbouring provinces the bulk of which are from low to middle income class, offering both inpatient and outpatient's services ranging from tertiary to highly specialised. The haemophilia care centre cares for 1 100 patients both paediatric and adult who are seen and reviewed by the paediatric and adult departments respectively. It is additionally staffed with a multidisciplinary team including specialised nursing staff skilled in the care of Haemophilia and other rare chronic bleeding disorders.

Study population
Of the 1 100 patients attending the haemophilia care centre at Area 295 at CMJAH, 77 patients were eligible for record assessment using the eligibility criteria.

Inclusion criteria
The study included patients aged 18 and older with documented IBD confirmation. Specifically, it encompassed individuals with haemophilia showing a factor level below 50% and those with vWD exhibiting antigen and/or activity levels below the normal range, with a laboratory threshold of 50% set for both. Compliance with treatment was additionally required, relating particularly to haemophilia patients on prophylactic factor regimens. This was assessed using their bleeding charts which record the total factor given at each follow up/clinic visit (can predict how long a prescription should last). Lastly, the presence of comprehensive clinical records was required. Control patients included adult patients who were admitted to the haematology ward and documented to have an anaemia with a formal record of a full blood count (FBC).

Exclusion criteria
Patients without documented/traceable diagnostic records, paediatric patients (<18 years) and non-compliance were excluded from the study. Patients with established causes of bleeding other than an inherited bleeding disorder were also excluded from being reviewed. For the control patients, those with no FBC record were not reviewed. Haemophilia patients admitted to the ward were also excluded from the control population.

Statistical analysis
Quantitative data was summarised into tables and figures and presented graphically. Summary statistics was described using means, medians with interquartile ranges (IQRs) and counts with percentages. Statistical analysis was performed using excel. A p-value of < 0.05 was considered statistically significant.

Results

Patient demographics
Of all the reviewed files, 77 adult patients were eligible for assessment.

The majority of the study patients were expectedly male, accounting for 90.9% (n=70) while female patients comprised 9.1% (n=7), one of which was identified as a haemophilia carrier. The ages ranged from 20 years old to 72 years old with a median age of 40 (IQR:17) [Table 1].

Table 1: Demographic data of study cohort and control population

	Study population	Control population
Number of patients	77	77
Age	20-72	18-87
Range	41,1	42,4
Mean	40 (17)	37 (24)
Median (IQR)		
Sex, n (%)		
Male	70 (90,9)	67 (87,0)
Female	7 (9,1)	10 (13.0)

Disease distribution

Haemophilia patients accounted for the majority of the study population, comprising 88.3% (n=68) while patients living with von Willebrand disease accounted for 11.7% (n=9) of all patients. Of the haemophilia patients, Haemophilia A was more prevalent with 56 patients (72.7%). There were 11 (14.3%) patients that had haemophilia B and a single patient was identified as a haemophilia carrier (1.3%). More than half of all the haemophilia patients were noted to have severe disease, that is, a factor level of <1%. These patients made up 55.9% (n=38) of all haemophilia patients. Patients with moderate disease accounted for 22% (n=15) while patients with mild disease comprised 13.2% (n=9) of all haemophilia patients. Disease severity/diagnostic factor levels of four haemophilia patients (7.4%) could not be determined. Regarding presence of inhibitors, 11(16.2%) patients were identified to have inhibitors, all of which were patients with haemophilia A. Only a single patient with inhibitors had moderate disease while the remaining patients, accounting for 90.9%, all had severe disease.

Patients with vWD accounted for 11, 7% (n=9) of all study patients, the majority of which were female (n=6) and an expected minority of male patients (n=3).
The most common type of vWD noted was Type 1 with 4 patients (44.4%). Both Type 2 and Type 3 had 2 patients each, accounting for 22.2%. A single patient was undocumented. [Table 2]

Table 2: Disease distribution of study cohort (n=77)

		Anaemia prevalence
Haemophilia, n (%)	68 (88,3)	29 (42,6)
Type		
Haemophilia A	56 (82,4)	24 (42,9)
Haemophilia B	11 (16,2)	5 (45,5)

Haemophilia Carrier	1 (1,5)	
Severity		
Mild	9 (13,2)	4 (44,4)
Moderate	15 (23,5)	5 (33,3)
Severe	38 (55,9)	15 (39,5)
Unknown/undocumented	5 (7,4)	
Sex		
Male	67 (98,5)	29 (43,3)
Female	1 (1,5)	0
von Willebrand disease, n (%)	9 (11,7)	1 (11,1)
Type		
Type 1	4 (44,4)	1 (25)
Type 2	2 (22,2)	
Type 3	2 (22,2)	
Unknown/undocumented	1 (11,1)	
Sex		
Male	3 (33,3)	
Female	6 (66,7)	

Prevalence of anaemia

Of the total 77 enrolled patients, 38.96% (n=30) patients were noted to have an anaemia as per the WHO classification, that is, a haemoglobin less than 12g/dL. Of these, the majority of patients had a Grade 0/ borderline anaemia (40%, n=12), followed by 36.7% (n=11) patients with a Grade 1/mild anaemia. A single patient had grade 2/moderate anaemia while 6.7% (n=2) patients had grade 3/severe anaemia. 13% (n=4) had a grade 4/life-threatening anaemia. A large proportion of the anaemic cohort was accounted for by patients haemophilia (96.7%, n=29) while only a singly patient one had vWD.

When comparing to the control patients, it was noted that the majority of patients admitted into the haematology ward with anaemia had a life-threatening/grade 4 anaemia (31,2%; n=24), followed by a grade 2/moderate anaemia (28,6%; n=22). Patients with a grade 3/severe anaemia accounted for 22,1% (n=17) and 12.9% (n=10) had a grade 1/mild anaemia. In contrast to the study patients, a minority had borderline/grade 0 anaemia accounting for 5.2% (n=4). [Figure 1]

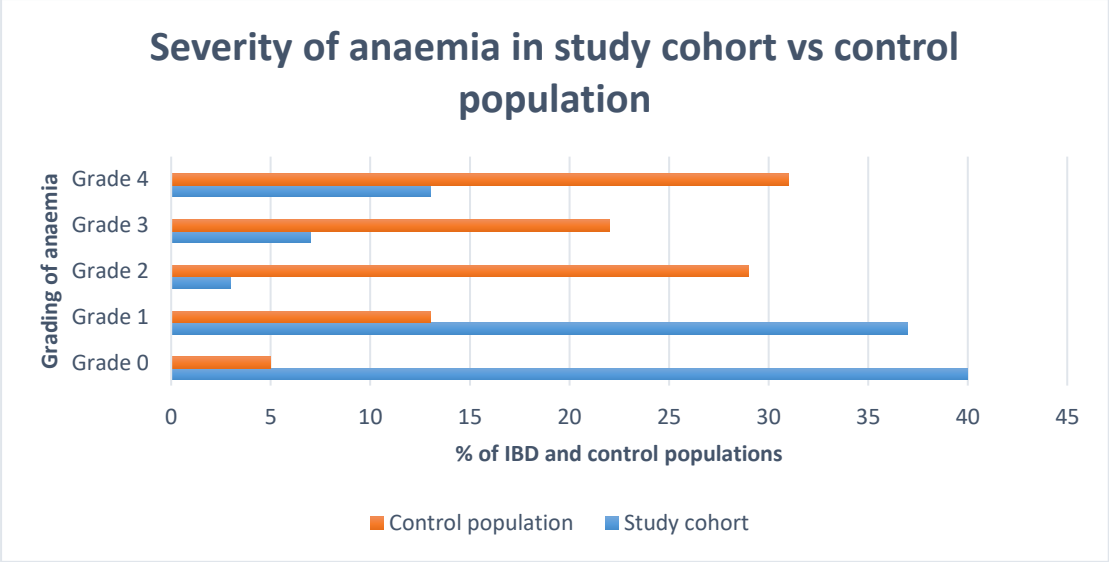


Figure 1

Just under half of the patients with anaemia were noted to have an iron deficiency, accounting to 43,4% (n=13). Of additional note, there were a population of patients who were assessed and found to have an iron deficiency but did no manifest with an anaemia. These patients accounted for 5,2% (n=4) of the whole study cohort. These patients thus had a non-anaemic iron deficiency.

Only 6,5% (n=5) of the control patients had a documented iron deficiency.

Discussion

This retrospective case-control study provides insight into the prevalence of anaemia in 77 persons living with haemophilia or vWD who attend the CMJAH haemophilia comprehensive care centre compared to a control group admitted to the haematology ward. In addition, our study demonstrates the disease distribution of these said coagulation disorders in our centre, a quaternary public healthcare facility. With the paucity of available data proving the prevalence of anaemia in persons living with haemophilia or vWD, this study aims to narrow that gap.

Consistent with existing literature (7), our study found a male predominance among patients with haemophilia, with Haemophilia A being the most prevalent subtype. Severe forms of haemophilia, characterized by factor levels below 1%, were observed in a substantial proportion of patients (55.9%), correlating with a higher likelihood of developing inhibitors. This subset of patients is at heightened risk for spontaneous bleeding episodes and subsequent complications, emphasizing the critical need for regular monitoring and comprehensive management strategies. Moderate and mild forms of haemophilia accounted for 22% (n=15) and 13.2% (n= 9) of the cohort, respectively, highlighting the spectrum of disease severity observed in clinical practice (8) (9). These patients are known to generally present with milder bleeding phenotypes, triggered by major surgery or trauma.

vWD is the most common bleeding disorder (11). Patients who have been diagnosed with vWD often do not seek medical care because their symptoms are usually mild.

They typically only present to healthcare facilities after undergoing surgical procedures, post trauma or when experiencing severe and unusual mucocutaneous bleeding. vWD affected a smaller proportion of our study population (11.7%). This bleeding disorder, characterized by deficiency or dysfunction of von Willebrand factor (VWF), exhibited a notable gender disparity with most affected individuals being female (66.7%) , in keeping with the available literature (10).

Among the patients with vWD, Type 1 was the most prevalent subtype (44.4%, n=4), characterized by a quantitative deficiency in VWF and consistent with what is demonstrated in the literature (12). Types 2 and 3 vWD, though less common, represented significant subsets of the vWD cohort, each comprising 22.2% (n=2) of the patients with documented subtype classification.

Anaemia, defined by the World Health Organization (WHO) as a haemoglobin level below 12g/dL in females and <13g/dL in males, was identified in 38.96% of the study cohort. Patients with anaemia were predominantly male persons with haemophilia. This was expected as the majority of the IBD cohort was composed of haemophilia patients known to primarily affect male persons. Life-threatening (Grade 4) and moderate (Grade 2) anaemia categories were more prevalent in the control group compared to the study cohort which demonstrated milder grades of anaemia, that is, grade 0/borderline anaemia (n=12) followed by 36.6% (n=11) with grade 1/mild anaemia. This finding underscores the significant burden of anaemia in our study patients who represent persons with bleeding disorders. This is likely attributed to chronic bleeding episodes and co-morbidities associated with chronic bleeding, that is, an anaemia of inflammation. Moreover, it is important to note that this distinction may also reflect the differences in the underlying pathophysiology of anaemia and their treatment strategies.

Literature highlights an increased prevalence of anaemia particularly in women and children, highlighting them as a population at risk and being impacted to a greater degree than men (13). Our study emphasizes men, primarily those with haemophilia, as an additional population at risk of developing anaemia.

Iron deficiency was identified in a significant proportion of anaemic patients with haemophilia and vWD compared to the control group (43.4% vs 6.5%), emphasizing the high prevalence of anaemia in persons with haemophilia and vWD as well as highlighting the role of chronic blood loss as a primary contributing factor of anaemia. Interestingly, a subset of patients exhibited iron deficiency without anaemia (5.2%), suggesting a crucial need for ongoing monitoring and detection for anaemia in these vulnerable patients allowing for early intervention.

Limitations and Future Directions

Several limitations should be acknowledged, including the retrospective nature of data collection and potential selection bias inherent in single-centre studies. The limited number of patients in our study cohort is an additional limitation. However, this highlights the scarcity of these disorders. Future research could benefit from prospective cohort designs and inclusion of a broader demographic and clinical

variables to elucidate multifactorial contributors to anaemia in patients with inherited bleeding disorders.

An additional limitation to consider includes a selection bias of the control group, selected from the years 2018 and 2019, opposed to including 2016 and 2017 as with the study cohort population. Comparison to available literature, although scarce, helped alleviate this bias.

Conclusion

In conclusion, our findings emphasize the high prevalence of anaemia among patients with haemophilia and vWD, particularly among those with severe disease. Early detection and management of anaemia, including iron deficiency, are critical to improving this populations clinical outcomes and quality of life. Further research is warranted to explore additional contributing factors and optimize therapeutic strategies tailored to the unique needs of patients with inherited bleeding disorders.

Competing interests: None

Author contributions. Prof JM conceived the study topic, supervised the study conduct and data collection, analysed the data, wrote the article and approved the final version. Dr RM wrote the study protocol, collected data, analysed the data, wrote the article and approved the final version.

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APPENDICES

APPENDIX 1: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr R Monaheng

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210818

NAME: (Principal Investigator)	Dr R Monaheng
DEPARTMENT:	School of Pathology Department of Molecular Medicine and Haematology Medical School University
PROJECT TITLE:	*Prevalence and severity of anaemia in persons with Haemophilia and Von Willebrand disease at Charlotte Maxeke Johannesburg Academic Hospital*
DATE CONSIDERED:	2021/08/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor J Mahlangu
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/10/11

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Philip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in August and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

APPENDIX II: TURN-IT-IN REPORT

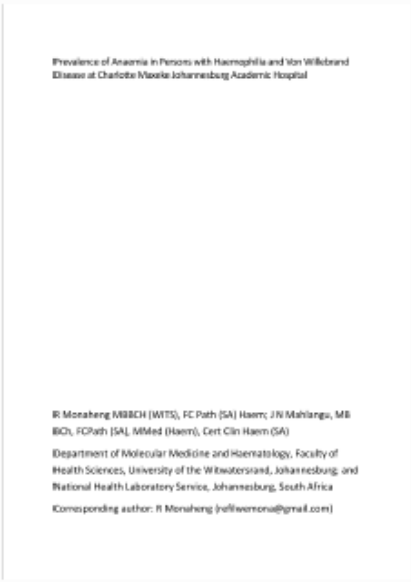
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APPENDIX III: RESEARCH PROTOCOL

University of the Witwatersrand

Faculty of Health Sciences

Department of Molecular Medicine and Haematology

Prevalence and Severity of Anaemia in Persons with Haemophilia and Von Willebrand Disease at Charlotte Maxeke Johannesburg Academic Hospital



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Abbreviations

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

FII: Factor II

FV: Factor V

FVII: Factor VII

FVIII: Factor VIII

FIX: Factor IX

FX: Factor X

FXI: Factor XI

FXIII: Factor XIII

HA: Haemophilia A

HB: Haemoglobin

IBD: Inherited bleeding disorders

IDA: Iron deficiency anaemia

RBD: Rare bleeding disorders

VKCFD: Vitamin K-dependent coagulation factors deficiency

vWD: Von Willebrand disease

WHO: World Health Organization

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Background

1.1 Inherited bleeding disorders (IBDs)

Inherited bleeding disorders (IBDs) are diverse in pathophysiology and include a spectrum of conditions which affect the blood vessel wall, coagulation clotting factors or platelets, each one with varying degree of symptomatic clinical presentations (1). Globally and in South Africa, Von Willebrand Disease (vWD) and Haemophilia (A and B) represent 95-97% of all the IBDs(2). The remaining 3% are rare bleeding disorders (RBDs) which include deficiency of fibrinogen, factor II (FII), factor V(FV), factor X(FX), factor XI(FXI), factor XIII(FXIII) or combined FV + FVIII and inherited vitamin K-dependent coagulation factors deficiency (VKCFD).

1.1.1 Haemophilia

Haemophilia is an X-linked recessive bleeding disorder that predominantly affects males with females being asymptomatic carriers. It is caused by a deficiency of coagulation factors VIII or IX, termed Haemophilia A and B, respectively. Haemophilia A is more common, affecting 1 in 5 000 live male births while haemophilia B affects 1 in 25 000 live male births(3). Severity is classified according to the level of clotting factor activity with severe haemophilia demonstrating an activity level less than 1%, moderate haemophilia between 1 and 5% and mild haemophilia from 6 to 40% (4). Although bleeding can occur anywhere, patients with haemophilia commonly present with bleeding into their joints, termed haemarthrosis. Other bleeding sites include muscles, skin, and mucous membrane bleeding.

Patients with severe haemophilia characteristically present with spontaneous haemarthroses. Such bleeding results in iron deposition into the affected joints. This iron, however, is not physiological available for haemoglobin use (5). Compensative use of this iron is thus not possible in patients who have frequent bleeds that are unrelated to the joint, that is, gastrointestinal bleeds or occult bleeding into the urinary tract. Since patients with haemophilia are at risk of bleeding, particularly those with severe phenotypes or those who develop inhibitors, one would assume that they are at an increased risk of developing anaemia, particularly secondary to iron deficiency.

Studies investigating iron deficiency anaemia in patients with haemophilia and vWD are limited. One of these studies is that published by Lottenberg and colleagues which, questioned whether recurrent occult blood loss into urine or stool may predispose haemophilia patients to developing chronic iron deficiency (6). The study enrolled seven men

diagnosed with haemophilia and analyzed iron in their blood, bone marrow, urine, and stool samples. Although no excessive loss of blood occurred during the study period, assessment of marrow samples demonstrated decreased iron stores. In a different analysis of 39 treatment-naïve patients with Haemophilia A in Nigeria, iron deficiency was present in 48% of the study subjects. In this study, it was noted that patients with severe haemophilia had a higher frequency of anaemia compared to those with mild or moderate phenotypes (5).

1.1.2 Von Willebrand disease

Von Willebrand Disease (vWD) is the most common inherited bleeding disorder affecting both males and females with a frequency of 1 per 100 individuals in the general population. It is caused by a deficiency and/or qualitative disorder of Von Willebrand factor (vWF) (7). VWF is a large multimeric adhesive plasma glycoprotein that plays an essential role in both primary and secondary haemostasis. An additional function of vWF is to serve as a carrier protein for coagulation FVIII. This protects FVIII from proteolytic degradation and thus extending its half-life in plasma (8). The clinical presentation of vWD, based on the severity of presenting symptoms, is much more variable compared to other bleeding disorders thus leaving a significant number of the population undiagnosed (9, 10). It is classified into three main categories; namely Type 1, 2 and 3. Type 1 and 3 are quantitative abnormalities of VWF while Type 2 is a qualitative abnormality that is further subclassified into subtypes 2A, 2B, 2M, 2N. Review of the literature indicate that there are currently no studies reporting on the frequency of anaemia in patients with vWD.

Table 1. Classification of von Willebrand Disease (adopted from Sadler et al)

Type	Classification
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defects
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight VWF multimers
2B	Increased affinity for platelet glycoprotein 1b
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of high-molecular- weight VWF multimers
2N	Markedly decreased binding affinity to FVIII
3	Virtually complete deficiency of VWF

1.1.3 Rare bleeding disorders

Rare bleeding disorders (RBDs) cover approximately 3%–5% of all inherited bleeding disorders. They are characterized by a significant variability of bleeding manifestations that range from mild to severe even in patients with the same genotype and biochemical phenotype (2). These disorders are usually transmitted as autosomal recessive conditions, but some cases of FXI deficiency, hypofibrinogenemia and dysfibrinogenemia can be inherited in an autosomal dominant manner (11). Bleeding manifestations are heterogeneous with mucosal bleeding and bleeding at the time of invasive procedure being the most common manifestations. Women with RBDs may present with menorrhagia, spontaneous miscarriage, and bleeding at delivery. Gastrointestinal bleeding, haematomas and haemarthroses are more common in patients with FX deficiency. Significant symptoms such as umbilical cord bleeding and cerebral hemorrhages, are seen more frequently in patients with severe deficiencies of fibrinogen, FVII or FXIII (11, 12).

1.2 Anaemia

Anaemia, according to the World Health Organization (WHO), is a medical condition in which the number of red blood cells and their oxygen-carrying capacity is insufficient to meet physiologic needs (13). Its identification is universally demonstrated by a lower-than-normal haemoglobin (HB) value for age and gender. Normal HB ranges are different for different laboratories and are defined according to the population used in their establishment. According the WHO, the defining HB levels for anaemia are an Hb <13 and Hb<12 g/dL in men and women, respectively (14). The ideal haemoglobin level needed to meet physiological needs varies in individuals depending on age, sex, pregnancy status, smoking habits, and altitude.

1.2.1 Anaemia global epidemiology

Anaemia is one of the most common encountered medical conditions worldwide, affecting approximately one third of the world population with more than two billion people with anaemia globally (13). It affects predominantly young children and women, particularly those of reproductive age and those who are pregnant. Globally, 43% of young children aged between 6 to 60 months are anaemic while 25% of children aged 5–15 years are anaemic (15). In these populations specifically, anaemia is associated with increased morbidity and

mortality. Anaemia in children is additionally associated with impaired cognitive and behavioral development and if left untreated in pregnancy, anaemia is associated with poor birth outcomes (16). It is therefore of particular interest to identify and treat anaemia in children with inherited bleeding disorders.

1.2.2 Pathophysiology/aetiology of anaemia

Anaemia develops when there is an established imbalance between erythrocyte production and loss. Its pathophysiology hence depends on the underlying cause which may be due to either decreased or ineffective erythropoiesis (seen in bone marrow aplasia, nutritional deficiencies, and genetic HB abnormalities) or increased erythrocyte loss due to haemolysis, bleeding, or splenic sequestration.

The critical role of HB to carry oxygen to the tissues explains the most common clinical symptoms of anemia, which include fatigue, shortness of breath, bounding pulses or palpitations, and conjunctival and palmar pallor. The severity of symptoms depends largely on the degree of anaemia as well as rate of HB decline. An example of this would be two patients who present to the emergency department with a HB of 5g/dL each, one from acute blood loss and the other from an iron deficiency anaemia secondary to menorrhagia. The patient with the acute and rapid decline in HB would have severe manifestation of anaemia compared to the patient with the chronic and insidious onset. Also, to consider are symptoms present during early childhood, which should highlight the possibility of inherited forms of anaemia such as thalassaemia (17).

1.2.3 Classification of anaemia

Classification of anaemia may therefore be based on the underlying causative mechanism e.g., iron deficiency anaemia or haemolytic anaemia. Anaemia may also be classified according to red cell morphology and characteristics such as size, shape and chromia e.g., microcytic hypochromic anaemia, normocytic normochromic anaemia, or a macrocytic anaemia (17).

Iron deficiency

With anaemia affecting about a third of the world's population, half of these cases are secondary to iron deficiency which affects approximately 15% of the world's population (17, 18).

To evaluate an individual's iron status, the laboratory parameter used is ferritin. Ferritin is the most specific biochemical test that correlates with relative total body iron stores. Since ferritin is an acute phase reactant, in the absence of an infection or inflammatory state, a low level reflects diminished iron stores. According to the WHO, the accepted cut-off level for serum ferritin below which iron stores are depleted, is <15ug/L, however, further studies suggest that increasing the cut off to 30µg/L increases the sensitivity to 92% while maintaining a specificity of 98% (19). The gold standard for assessment of iron stores is, however, on bone marrow with the use of a Perls stain (20).

Causes of iron deficiency anaemia can be broadly classified into inadequate intake (seen in malabsorption), excessive loss which is commonly seen in chronic bleeding and haemolysis; and increased demand seen in childhood and pregnancy. Blood loss is a major cause of iron deficiency anaemia and should be considered in all cases of iron deficiency anaemia. Chronic blood loss from menstruation or hookworm infection has the greatest impact worldwide (19). As stated, individuals at the greatest risk of developing iron deficiency anaemia are children under 5 (due to increased requirements), young menstruating women and women in the second/third trimester of pregnancy and postpartum. Another population of patients affected includes vegetarians, more specifically vegans, and regular blood donors. A group of patients, not commonly mentioned in studies or reviews, are those with defective hemostasis. This includes patients with hereditary bleeding disorders such as Von Willebrand disease, haemophilia and other coagulation factor deficiencies such as deficiency of factors V and VII. Since this group of patients are prone to chronic bleeding episodes, it follows that they are, or should be at risk of developing anaemia, more so, an iron deficiency anaemia. Very few studies have assessed the risk and prevalence of iron deficiency anaemia in patients with IBDs.

1.3 Anaemia in patients with inherited bleeding disorders

There is an obvious paucity of studies that investigate the prevalence of anaemia in patients with IBDs. Iron deficiency in particular has several adverse effects on wound healing, immunity, and mental development of patients, all of which may affect their well-being (5).

This is just one illustration that demonstrates how the clinical implications of iron deficiency extends beyond anaemia in affected patients.

1.4 Research Question

What is the frequency and severity of anaemia in persons with haemophilia and von Willebrand disease?

1.5 Study Aims

To retrospectively assess the full blood counts (FBC) and iron studies of patients with haemophilia and vWD attending the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Haemophilia Clinic outpatient department to evaluate the presence and severity of anaemia in patients with inherited bleeding disorders.

1. Methods

2.1 Study design

A single center retrospective case control study

2.2 Study setting

The study will be conducted at Charlotte Maxeke Johannesburg Academic hospital, a quaternary care public hospital.

2.3 Study population

All patients that follow up at the CMJAH adult haemophilia outpatient's department with a documented inherited bleeding disorder.

2.3.1 Inclusion criteria

- Patients older than 18 years of age followed up at the CMJAH haemophilia clinic
- Documented laboratory confirmation of a bleeding disorder
  - Factor levels at diagnosis in haemophilia patients less than 50%
  - vWD screen or antigen and activity levels at diagnosis in patients with VWF below the normal range (<50% for both)
- Patients that are compliant with treatment
  - Compliance relates particularly to haemophilia patients on prophylactic factor regimens. This will be assessed using their bleeding charts. A bleeding chart records the total factor given at each follow up/clinic visit and can assist in predicting how long a prescription should last, depending on the recorded number of bleeds a patient has.

- Complete clinical records
  - Diagnostic records
  - Bleeding charts and follow up clinical notes.
  - Admission notes with the following results:
    - HB and iron studies on admission
    - Factor and inhibitor levels in haemophilia patients
    - CRP or infective markers where relevant
    - Treatment received during admission period (transfusion; intravenous iron or oral iron).

2.3.2 Exclusion criteria

- Patients without documented/traceable diagnostic records.
- Paediatric patients below 18 years of age
- Non-compliant patients
  - Non-adherence to factor replacement in haemophilia patients on prophylactic therapy
- Patients with established additional causes of bleeding other than the diagnosed bleeding disorder

2.3.3 Sampling Method

- This is a retrospective documentation and collation of all the haemoglobin levels, ferritin levels and treatment thereafter of anaemia of the patients with inherited bleeding disorders.
- Permission to use the data collected will be obtained from the CMJAH CEO.
- Patients with diagnosed inherited bleeding disorders (Haemophilia and Von Willebrand disease) presenting with an anaemia to the Haematology Department at CMJAH will be enrolled in the study.
- Permission to obtain additional blood results off the LIS will be attained from the NHLS gatekeeper.
- All data will be collected systematically using a data collection sheet

2.4 Control population

The control population will comprise patients admitted in the Haematology Department at CMJAH without inherited bleeding disorders.

2.5 Sample size

A total of 200 patients will be enrolled into the study, 100 patients with either haemophilia or vWD and 100 controls. The controls will be sex and age matched patients admitted to CMJAH with anaemia without IBDs.

2.6 Data collection

Approval will be required from:

1. The CEO of CMJAH for permission to access patient files from the haemophilia outpatient departments and hospital records in the event of an admission.
2. The NHLS, for access of captured patient results.

2.7 Data Analysis

Data will be summarized on Excel spreadsheets.

Quantitative data will be tabulated and presented graphically with summary statistics presented as means or medians. The severity of anaemia, frequency of anaemia, treatment of anaemia and treatment outcomes will be compared between the cases and controls. The Student T-test will be used to express the difference and a p-value of 0.05 will be taken as statistically significant

Qualitative data will be described and interpreted in the clinical context.

A statistician will be outsourced to aid with the analysis and interpretation of the collected data.

2.8 Ethical considerations

Study participants will be given study numbers and all data collected will be deidentified/anonymised. As this is a retrospective study, there are no participant ethical issues anticipated. This study will only commence once it has been approved by the Human Research Ethics Committee and all approvals are in place.

2.9 Study timelines

Patients with inherited bleeding disorders are all reviewed and managed on a long-term basis at the CMJAH Haemophilia Clinic. The clinic currently has >1100 patients that follow up on a regular basis. Information will be retrieved from the patient's files which are available at the clinic. Data will be analyzed from the January 2016 until December 2019. The estimated study period will be from May 2021 to January 2022.

	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb
Protocol write up										
Ethics application										
Submission to the Post graduate committee										
Data collection										
Data analysis										
Write up										
Submission										

2.10 Study funding

The data required for this study will be obtained from patient files and the NHLS laboratory information system. No funding will thus be required for the data collection and analysis of this study.

Funding may, however, be needed for presentation of the study findings at conferences and publication. This is estimated at R30 000 which will be provided by the supervisor or obtained from grant applications.

2.11 Study permissions

2.11.1 National Health Laboratory Services (NHLS)

For the acquisition of patient results captured over the years in the NHLS Laboratory Information System (LIS), permission will be obtained from the gatekeeper of the NHLS data.

2.11.2 CMJAH

Permission will be obtained from the CEO of CMJAH to access patient records.

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Appendix A

DATA COLLECTION SHEET								
HAEMOPHILIA PATIENT								
PATIENT DETAILS								
Study number								
Date of birth (age)								
DIAGNOSTIC RESULTS								
Year of diagnosis								
Haemophilia type								
Severity								
Factor level								
HB level								
Ferritin level								
TREATMENT								
Replacement therapy								
Dose								
PRESENTATION WITH ANAEMIA								
Date								
HB level								
Severity ● Mild (10 - 12g/dL) ● Moderate (8g - 10g/dL) ● Severe (6.5 - 8g/dL)								

• Life-threatening (<6.5g/dL)								
MCV								
MCH								
MCHC								
Haematocrit								
Iron studies • Ferritin • Transferrin • % Saturation								
CRP (if available)								
Bone marrow iron stores (if available)								

Appendix B

DATA COLLECTION SHEET								
VON WILLEBRANDS DISEASE								
PATIENT DETAILS								
Study number								
Date of birth (age)								
DIAGNOSTIC RESULTS								
Year of diagnosis								
Type of vWD								
vWF antigen								
vWF activity								
HB level								
Ferritin level								
TREATMENT								
PRESENTATION WITH ANAEMIA								
Date								
HB								
Severity ● Mild (10 - 12g/dL) ● Moderate (8g - 10g/dL) ● Severe (6.5 - 8g/dL)								

• Life-threatening (<6.5g/dL)								
MCV								
MCH								
MCHC								
Haematocrit								
Iron studies • Ferritin • Transferrin • % Saturation								
CRP (if available)								
Bone marrow stores (if available)								

APPENDIX IV: SAMJ SUBMISSION GUIDELINES

All submissions must meet the following requirements.

- Please ensure you have submitted a regular version of the manuscript i.e. full text with author details and an anonymised version (author details remove). Failure to do so will result in your manuscript being returned to you.
- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- The submission file is in Microsoft Word document file format.
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
- The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.
- Disclosure of whether any artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) has been used in the production of submitted work.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Please refer to these guidelines for further information on the format of a research article.

Guidelines to Research articles

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.