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Beyond the Bleed: Clinical Spectrum, Emergency Management, and Outcomes of Persons with Haemophilia C (Factor XI Deficiency) Presenting to a Tertiary Care Emergency Department in India - A Ten- Year Retrospective Case Series

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Abstract

Background.

To characterise the clinical spectrum, emergency management, and outcomes of persons with Haemophilia C (Factor XI [FXI] deficiency) presenting to a tertiary care emergency department (ED) in India over ten years.

Methods.

Single-centre retrospective case series at Kasturba Medical College and Hospital, Manipal (January 2014-January 2024), reported in accordance with the STROBE statement. Persons with confirmed Haemophilia C were identified from among all persons with haemophilia recorded by the Medical Records Department. All ED encounters -haemorrhagic and non-haemorrhagic - were included. Analysis was descriptive; given the small, clustered sample, no inferential statistics were performed.

Results.

Haemophilia C was confirmed in 8 of 153 persons with haemophilia (5.2%) identified over the period; five (four female, one male; age 19–51 years) met inclusion and generated 17 ED encounters-four haemorrhagic and 13 non-haemorrhagic-with one patient contributing nine. All four haemorrhagic encounters were mucosal and of serious severity; none were life-threatening. Fresh frozen plasma (FFP, 10–15 mL/kg) with oral tranexamic acid was used in the two encounters with active bleeding; the other two had no active bleeding on evaluation. The most clinically salient finding was non-haemorrhagic: in five encounters the FXI deficiency was the rate-limiting factor for a planned intervention-two deliveries, two neurosurgical admissions, and one pre-hysterectomy assessment-each deferred for haematological input. The remaining eight non-haemorrhagic encounters were incidental intercurrent illnesses in which the deficiency played no role. All 17 encounters ended in survival, with no intensive care admission or death.

Conclusions.

In this ED case series, Haemophilia C presented less often as acute bleeding than as a coagulopathy that constrained a planned intervention. With FXI concentrate unavailable in India, bleeding was managed with FFP and tranexamic acid within guideline parameters. These hypothesis-generating observations suggest Haemophilia C warrants recognition not only in bleeding presentations but whenever it complicates a planned procedure; prospective multicentre data are needed to confirm the pattern.

INTRODUCTION

Background

Haemophilia C-the clinical term for congenital Factor XI (FXI) deficiency-was first described by Rosenthal and colleagues in 1953 as a new haemophilia-like disease, distinct from Haemophilia A and B in one fundamental respect: it follows autosomal rather than X-linked recessive inheritance.[1] Because the F11 gene sits on chromosome 4, both sexes are affected equally-and females, who are largely spared by the X-linked haemophilia's, make up a substantial share of those with clinical FXI deficiency.[2]

FXI deficiency gives rise to three genotypic groups. Homozygotes and compound heterozygotes develop severe deficiency (FXI activity < 20 IU/dL); simple heterozygotes develop partial deficiency (20–70 IU/dL), yet even here clinically significant bleeding can occur, particularly at sites of high local fibrinolytic activity.[2,3] More than 190 pathogenic F11 variants have been described. Severe deficiency affects roughly 1 per million in the general population, though South Asian prevalence is likely underestimated because the diagnosis is so often missed.[2]

What makes Haemophilia C diagnostically elusive is its poor phenotypic correlation: FXI activity does not reliably predict bleeding severity, even within families sharing an identical genotype.[2,3] FXI protects fibrin clots from premature fibrinolysis at sites where local fibrinolytic activity is highest-the oral mucosa, nasopharynx, genitourinary tract, and endometrium.[2,5] It is at these mucosal sites that the condition most often declares itself: through epistaxis, oral and gingival bleeding, haematuria, menorrhagia, and obstetric haemorrhage. Spontaneous joint bleeding is rare. The APTT, though usually prolonged in severe deficiency, may be normal or only mildly raised in partial deficiency- making routine coagulation screening an unreliable safety net.[2]

Management depends heavily on geography. In select European centres, two plasma-derived FXI concentrates-BPL Factor XI and Hemoleven-allow targeted, volume-efficient replacement.[6,7] Both are effective but carry real risks: thrombosis in up to 10% of treatment episodes, and inhibitor development in around 30% of patients homozygous for the null Glu135Stop allele.[8,9] Neither concentrate is licensed in the United States, India, or most of the low- and middle-income world,[10] and a 2025 survey of Indian treatment centres confirmed that FXI concentrate remains entirely unavailable in the country.[11] Management there rests on fresh frozen plasma-typically 10–20 mL/kg -and tranexamic acid, which is especially effective at mucosal bleeding sites.[12,13]

Importance

Haemophilia has been aptly described as a high-risk, low-prevalence emergency -rare enough that hands-on familiarity is difficult to develop, yet serious enough that any delay in recognition or treatment risks preventable harm.[13] In India, where many persons with haemophilia remain undiagnosed or without

specialist access, the emergency department is often the first -and sometimes only -point of contact with the health system.[14,15] For Haemophilia C specifically, the literature from emergency settings is silent. Western series have characterised FXI deficiency in obstetric and surgical contexts,[4,5] but no Indian study has described how it presents in the ED, how it is managed without FXI concentrate, or what follows. That gap has a particular texture: because the condition is autosomal, those who arrive are not the patients most emergency physicians associate with haemophilia - they are women with obstetric or mucosal bleeding, and adults whose intercurrent illness carries a haemostatic dimension.

Goals of This Investigation

This study set out to document the clinical spectrum of Haemophilia C presenting to a tertiary care emergency department in India over ten years - haemorrhagic and non-haemorrhagic encounters alike - and the haemostatic management employed in the absence of FXI concentrate. What follows is, to our knowledge, the first Indian ED-based characterisation of Haemophilia C.

METHODS

Study Design and Setting

This was a single-centre retrospective case series, reported in accordance with the STROBE statement for observational studies.[16] Because it describes a single group without a concurrent comparison cohort, it is a descriptive rather than comparative case series. It was conducted at the Department of Emergency Medicine, Kasturba Medical College and Hospital (KMCH), Manipal, Karnataka - a 2032-bed academic tertiary referral centre affiliated with the Manipal Academy of Higher Education (MAHE), serving as the regional hub for a large catchment across coastal and inland Karnataka. The study period spanned January 1, 2014 to January 31, 2024.

Selection of Participants

Patients were identified from Medical Records Department (MRD) data for all haemophilia-related encounters during the study period. The Haemophilia Society of Manipal does not maintain a Haemophilia C registry, so all cases were identified from MRD records alone. Of 180 persons with haemophilia initially identified, 27 were excluded (22 with untraceable records, 3 elective visits, 2 misclassified diagnoses), leaving 153 persons across 565 encounters. Of these 153, eight (5.2%) had confirmed Haemophilia C; after three further exclusions, five patients contributing 17 encounters (four haemorrhagic, 13 non-haemorrhagic) formed the study cohort.

Because ascertainment relied on haemophilia-coded MRD records, persons with mild or undiagnosed FXI deficiency - in whom the APTT may be normal - would not have been captured; the series therefore describes already-diagnosed Haemophilia C reaching the ED rather than the condition’s full population spectrum (addressed further under Limitations).

Haemophilia C was confirmed in all five patients by a mixing study demonstrating correction of a prolonged APTT with normal plasma, performed by a consultant haematologist at KMCH - the standard method where an in-house FXI activity assay is unavailable.[2] Quantitative FXI activity was available in three patients from external or prior haematology assessments. Patients with acquired FXI deficiency were excluded. Each ED encounter was treated as the unit of analysis; because encounters clustered within patients - one patient contributed nine of the 17 - they are not statistically independent, and no encounter-level inference was attempted.

Data Collection and Measurements

Data were extracted using a structured proforma and entered into the Ninox relational database (Ninox Software GmbH, Berlin, © 2023). Each patient received a coded identifier (PWH-C-01 to PWH-C-05) and each encounter a separate encounter ID. All 17 encounter records were independently re-verified by a co-investigator against the original case notes; the judgement of whether Haemophilia C influenced management was made independently by two investigators, with any discrepancy resolved by consensus, and none remained unresolved.

For haemorrhagic encounters, variables included triage category, bleeding site, severity (minor, serious, or life-threatening per WFH 2020 Guidelines[17]), precipitating trigger, documented laboratory values, FFP and tranexamic acid use, imaging, disposition, and length of stay. For non-haemorrhagic encounters, we recorded diagnosis, organ-system group, whether Haemophilia C delayed care or influenced clinical decision-making, and disposition (Table 1).

Table 1
Operational definitions of key variables

Variable	Definition
Bleeding severity — Minor	Superficial bleeding of the Skin or soft tissue
Bleeding severity — Serious	Bleeding in joint space, deep muscle compartment, mucosal membranes
Bleeding severity — Life-threatening	Intracranial, retroperitoneal, or major GI haemorrhage with haemodynamic compromise, or airway-threatening bleed
Mechanism — Spontaneous	No identifiable precipitant documented
Haemostatic management	FFP and/or tranexamic acid; FXI concentrate not available in India
HC delayed care	FXI deficiency made the planned intervention high-risk, requiring haematological input before proceeding

Analysis and Ethics

The analysis was entirely descriptive. Continuous variables are reported as median and IQR or mean and SD as appropriate; categorical variables as counts and proportions. Given the small, clustered sample, no inferential statistics, hypothesis tests, or sample-size/power calculations were performed or would be valid; the findings are descriptive and hypothesis-generating. Where documentation was incomplete, proportions reflect the encounters with available data, with denominators stated. Institutional Ethics Committee approval was obtained from KMCH, MAHE, Manipal (June 19, 2024). Written MRD access permission was granted by the Medical Superintendent. Records were de-identified before analysis, and the Committee granted a consent waiver for the retrospective review.

RESULTS

Cohort

Eight of the 153 persons with haemophilia identified over the study period (5.2%) had confirmed Haemophilia C. Two were excluded because their records could not be traced and one for unresolvable data-classification issues, leaving five patients — four female and one male -who together generated 17 emergency encounters; one patient (PWH-C-01) accounted for nine of these. Ages at presentation ranged from 19 to 51 years, with no paediatric encounters. Haemophilia C was a pre-existing diagnosis in one patient (PWH-C-01, diagnosed 2011); in the other four it was confirmed during the study period by mixing study. Quantitative FXI activity was documented in three patients – 0.9%, 2%, and 0.9% - all within the severe-deficiency range; it was not assessed in the remaining two, as KMCH does not perform an in-house FXI assay. Inhibitor status was not checked in any patient. One patient (PWH-C-01) had a personal bleeding history of intermenstrual bleeding; the other four had none. Patient characteristics are shown in Table 2.

Table 2
Patient-level characteristics (n = 5)

PWH Code	Sex	Age (years)	FXI activity	Diagnosis method	Personal bleeding history	Encounters (H / NH)
PWH-C-01	Female	19–28	0.9%*	Pre-existing (2011); FXI level from prior haematology visit	Yes — intermenstrual bleeding	9 (2H / 7NH)
PWH-C-02	Female	24–29	Not assessed	Mixing study at first ED presentation — diagnosis made at that visit	No	2 (0H / 2NH)
PWH-C-03	Male	47–51	2%*	Mixing study + FXI level at prior haematology visit	No	3 (1H / 2NH)
PWH-C-04	Female	39	Not assessed	Mixing study at KMCH	No	1 (0H / 1NH)
PWH-C-05	Female	42–43	0.9%	Mixing study + FXI level confirmed at this encounter	No	2 (1H / 1NH)

*H: haemorrhagic; NH: non-haemorrhagic. FXI activity expressed as percentage of normal. *Value from a prior haematology visit. Patient names and hospital numbers replaced by coded identifiers throughout.*

Haemorrhagic Encounters

Four of the 17 encounters were haemorrhagic, all classified as serious severity; none were life-threatening. Bleeding was exclusively mucosal - oral mucosa, anal canal, tongue, and vagina. Two encounters had no identifiable trigger, while two followed a clear provocation: chronic periodontitis in one and recent surgery in another. Three encounters were triaged yellow and one green; none were triaged red or blue. All four patients were haemodynamically stable on arrival. Fresh frozen plasma was given in two encounters - at 10 mL/kg and 15 mL/kg, both within the guideline range - each with oral tranexamic acid. The other two encounters had no active bleeding on evaluation and were discharged the same day without treatment. Laboratory documentation was sparse: a complete coagulation screen was available for only one encounter (APTT 46.9 s, PT 10.6 s, INR 0.98), and haemoglobin for two (13.0 and 9.2 g/dL). Imaging, performed in two encounters, showed incidental hepatosplenomegaly in one and post-operative uterine inflammatory changes in the other. Details are in Table 3.

Table 3
Haemorrhagic encounters — clinical details (n = 4, 3 patients)

PWH Code	Year	Age (y)	Bleeding site	Triage	Trigger	FFP (dose / units)	TXA (dose / route / freq)	Disposition / LOS
PWH-C-01	2016	21	Oral mucosa	Green	None	10 mL/kg (4 units)	500 mg oral BD	Ward; 5 days
PWH-C-01	2019	24	Anal canal	Yellow	None	Not given*	Not given	ED discharge; 0 days
PWH-C-03	2022	51	Tongue	Yellow	Chronic periodontitis	Not given*	Not given	ED discharge; 0 days
PWH-C-05	2023	43	Vagina	Yellow	Recent surgery	15 mL/kg (5 units)	500 mg oral TID	Ward; 5 days

*Severity per WFH Guidelines, 3rd edition [ref 17]. *No active bleeding on evaluation. BD: twice daily; TID: three times daily; LOS: length of stay. FXI concentrate not available in India; no encounter required packed red cell transfusion.*

Non-Haemorrhagic Encounters

The 13 non-haemorrhagic encounters spanned six organ-system groups: respiratory or ENT (4), obstetric (2), neurological (2), musculoskeletal (2), dermatological (2), and genitourinary (1). Nine ended in same-day discharge and four in ward admission.

The clinically important subset comprised five encounters in which the FXI deficiency itself became the rate-limiting factor for a planned intervention - delaying a planned delivery, neurosurgical resection, or hysterectomy until haematological input could be obtained (Table 4). Imaging in these five was confirmatory: a live fetus at both deliveries, a pituitary macroadenoma at both neurological admissions, and a fibroid uterus before the planned hysterectomy. The remaining eight encounters were incidental intercurrent illnesses - routine ED presentations in which the deficiency played no part (Table 5); we report them for completeness but do not regard them as part of the Haemophilia C-specific emergency burden.

Table 4
Non-haemorrhagic encounters in which Haemophilia C directly influenced management (n = 5)

PWH Code	Year	Age (y)	Diagnosis	How Haemophilia C influenced management	Disposition / LOS
PWH-C-02	2017	24	Induced vaginal delivery	Diagnosed via pre-delivery coagulation screen; delivery delayed for haematological input	Ward; 6 days
PWH-C-02	2022	29	Induced vaginal delivery	Prophylactic FFP given before delivery	Ward; 8 days
PWH-C-03	2018	47	Pituitary macroadenoma	Surgical resection deferred pending haemostatic assessment	ED discharge; 0 days
PWH-C-03	2019	48	Pituitary macroadenoma	Surgery again deferred; multidisciplinary planning	Ward; 4 days
PWH-C-05	2022	42	Uterine leiomyoma	Hysterectomy required pre-operative haematological clearance	Ward; 2 days

Table 5
Non-haemorrhagic encounters in which Haemophilia C was not clinically relevant (n = 8)

System group	n	Diagnoses	Disposition
Respiratory / ENT	4	Lower respiratory tract disease, URTI, sinusitis, deviated nasal septum	All ED discharge
Musculoskeletal	2	Musculoskeletal pain (×2)	All ED discharge
Dermatology	2	Furuncle, dermatitis	All ED discharge

Table 4 *lists the five encounters where FXI deficiency shaped management, one per row;* Table 5 *aggregates the eight encounters where it was not clinically relevant. LOS: length of stay; ENT: ear, nose, throat; URTI: upper respiratory tract infection.*

Outcomes

Every encounter ended in survival to discharge. There were no deaths, no intensive care admissions, and no patient left against medical advice. Ward stays ranged from two to eight days; the remaining encounters were managed and discharged the same day.

DISCUSSION

This study set out to describe what Haemophilia C looks like from inside an emergency department, and the most instructive answer is that it frequently presents as something other than a bleed. Alongside the expected mucosal haemorrhage, a distinct category emerged in which the coagulopathy itself - not any

active bleeding - determined what could safely happen next. This pattern is not captured by the existing FXI literature, because no published Haemophilia C study has examined the full ED encounter spectrum. The obstetric series of Chi et al., the perioperative cohort of Handa et al., and the paediatric study of Barg et al. are each built entirely around haemorrhagic or procedural endpoints.[4,19,3] The gap this reveals is clinical: physicians managing Haemophilia C in the ED must be ready not only for acute bleeding but for the distinct encounter in which the coagulopathy becomes the limiting factor for a planned intervention. We deliberately distinguish these encounters from the incidental intercurrent illnesses in the same cohort, which carried no haemostatic dimension and should not be mistaken for disease-specific burden.

That second category was well represented here. In five non-haemorrhagic encounters - two deliveries, two neurosurgical admissions, and one pre-hysterectomy assessment - the FXI deficiency delayed or reshaped care because the planned intervention carried haemostatic risk that needed expert input first, including anaesthetic implications specific to FXI deficiency.[5,18] Wheeler et al. frame multidisciplinary pre-procedural planning as central to FXI management, but that guidance is written for elective care.[5] These encounters suggest the same principle belongs in emergency medicine: when a person with Haemophilia C arrives for a reason unrelated to bleeding, the coagulopathy may still decide what can safely happen next.

The female predominance here (four of five) follows directly from the autosomal inheritance set out earlier, and echoes the predominantly female populations of the obstetric and perioperative series.[4,19] It carries a concrete implication: the presentations Haemophilia C generates — obstetric, gynaecological, and mucosal bleeding - are precisely those least likely to prompt a haemophilia diagnosis in a physician trained to associate the disease with male patients and joint bleeds. The haemorrhagic encounters reinforced this, being entirely mucosal and consistent with the fibrinolysis-site phenotype described by Duga and Salomon and Barg et al.[2,3] Two bled at sites of existing disruption - periodontitis and recent surgery - rather than spontaneously, and in one patient a mildly prolonged APTT accompanied an FXI activity of 0.9%, a reminder that an apparently reassuring coagulation screen should not dismiss the diagnosis in a compatible presentation.[2]

Both encounters treated with haemostatic agents received FFP within the recommended 10–20 mL/kg range,[12,17] with oral tranexamic acid at the bleeding site, and both recovered without complication. FXI concentrate, which offers more targeted replacement in European centres,[6,7] was unavailable throughout, consistent with the 2025 national survey,[11] yet FFP-based management produced acceptable outcomes - though the small numbers preclude any comparative claim.

The most instructive single thread was one patient's two deliveries. At the first, Haemophilia C surfaced incidentally on a routine pre-delivery coagulation screen; at the second, five years later, prophylactic FFP was given on the strength of that known diagnosis, and both deliveries passed without postpartum haemorrhage. Chi et al. found that 14 of 61 pregnancies in their series occurred before diagnosis, and

that personal bleeding history predicts obstetric bleeding more reliably than FXI level.[4] This patient had no bleeding history at either delivery, which may partly explain the uneventful course. Together these encounters make a quiet case for including a coagulation screen in antenatal assessment at Indian tertiary centres — not as a mandate, but as a low-cost chance to find FXI deficiency before the challenge of delivery rather than during it.

Limitations

Several limitations temper these findings. First, the design is descriptive and the sample very small - five patients and 17 encounters over a decade - so no inferential statistics, effect estimates, or power calculations are possible, and every finding is hypothesis-generating rather than confirmatory. Second, the encounters are not independent: one patient contributed nine of the 17, so aggregate encounter proportions are weighted toward a single individual and should be read as such. Third, ascertainment relied on haemophilia-coded MRD records; persons with mild or undiagnosed FXI deficiency, in whom the APTT may be normal, would not have been captured, so the series reflects already-diagnosed Haemophilia C presenting to the ED rather than the full population spectrum. Fourth, there was no concurrent comparison group of Haemophilia A or B encounters, so we cannot say how far the predominance of non-haemorrhagic and procedure-limiting encounters is specific to FXI deficiency as opposed to chronic-disease ED use in general. Fifth, the retrospective design meant data were created for clinical rather than research purposes: laboratory documentation was incomplete, quantitative FXI activity was available for only three of five patients, inhibitor status was assessed in none, and no genotyping or standardised bleeding-assessment score (e.g., ISTH-BAT) was available. Finally, as a single tertiary referral centre, KMCH tends to see more complex presentations, which limits generalisability to community settings.

Future Directions

Three directions follow. First, a comparative analysis of Haemophilia C against Haemophilia A and B encounters - feasible within datasets such as the 153-person haemophilia population screened here - would test whether the non-haemorrhagic and procedure-limiting predominance is specific to FXI deficiency. Second, prospective multicentre data from Indian tertiary centres would establish whether the pattern seen here is reproducible, and would support evaluating APTT-based coagulation screening within antenatal assessment, given the incidental obstetric diagnosis observed. Third, and most directly, emergency haemostasis protocols in this setting should address the non-haemorrhagic Haemophilia C encounter explicitly - when to seek haematological input, what cover an intervention requires, and how such encounters should be documented. This study offers, for the first time in the Indian emergency literature, a picture of what that encounter looks like.

CONCLUSIONS

In this ED case series, Haemophilia C presented less often as acute bleeding than as a coagulopathy that constrained a planned intervention. With FXI concentrate unavailable in India, bleeding was

managed with FFP and tranexamic acid within guideline parameters. These hypothesis-generating observations suggest that Haemophilia C warrants recognition not only in bleeding presentations but whenever it complicates a planned procedure, and that emergency haemostasis protocols should explicitly address the non-haemorrhagic Haemophilia C encounter. Prospective multicentre data are needed to confirm the pattern described here.

ABBREVIATIONS

APTT
activated partial thromboplastin time
ED
emergency department
FFP
fresh frozen plasma
FXI
Factor XI
IQR
interquartile range
ISTH-BAT
International Society on Thrombosis and Haemostasis Bleeding Assessment Tool
KMCH
Kasturba Medical College and Hospital
LOS
length of stay
MAHE
Manipal Academy of Higher Education
MRD
Medical Records Department
SD
standard deviation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TXA
tranexamic acid
WFH
World Federation of Haemophilia.

DECLARATIONS

Ethics approval and consent to participate

Institutional Ethics Committee approval was obtained from Kasturba Medical College and Hospital, Manipal Academy of Higher Education, Manipal (approval dated 19 June 2024; reference number: IEC2:274/2024). Written permission to access Medical Records Department data was granted by the Medical Superintendent. Records were de-identified before analysis, and the Ethics Committee granted a waiver of individual consent for this retrospective review.

Consent for publication

Not applicable. All patient data were de-identified and reported as coded aggregate findings; no individual images, videos, or identifiable details are included.

Competing interests

The authors declare that they have no competing interests

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Author Contribution

SK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft.JMB: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing.PP: Investigation, Methodology, Validation, Formal analysis, Writing – review & editing.MS : Conceptualization, Investigation, Formal analysis, Validation, Writing – review & editing.ASD: Investigation, Validation, Writing – review & editing.

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Availability of data and materials

The de-identified dataset(s) analysed during the current study are available from the corresponding author on reasonable request.

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