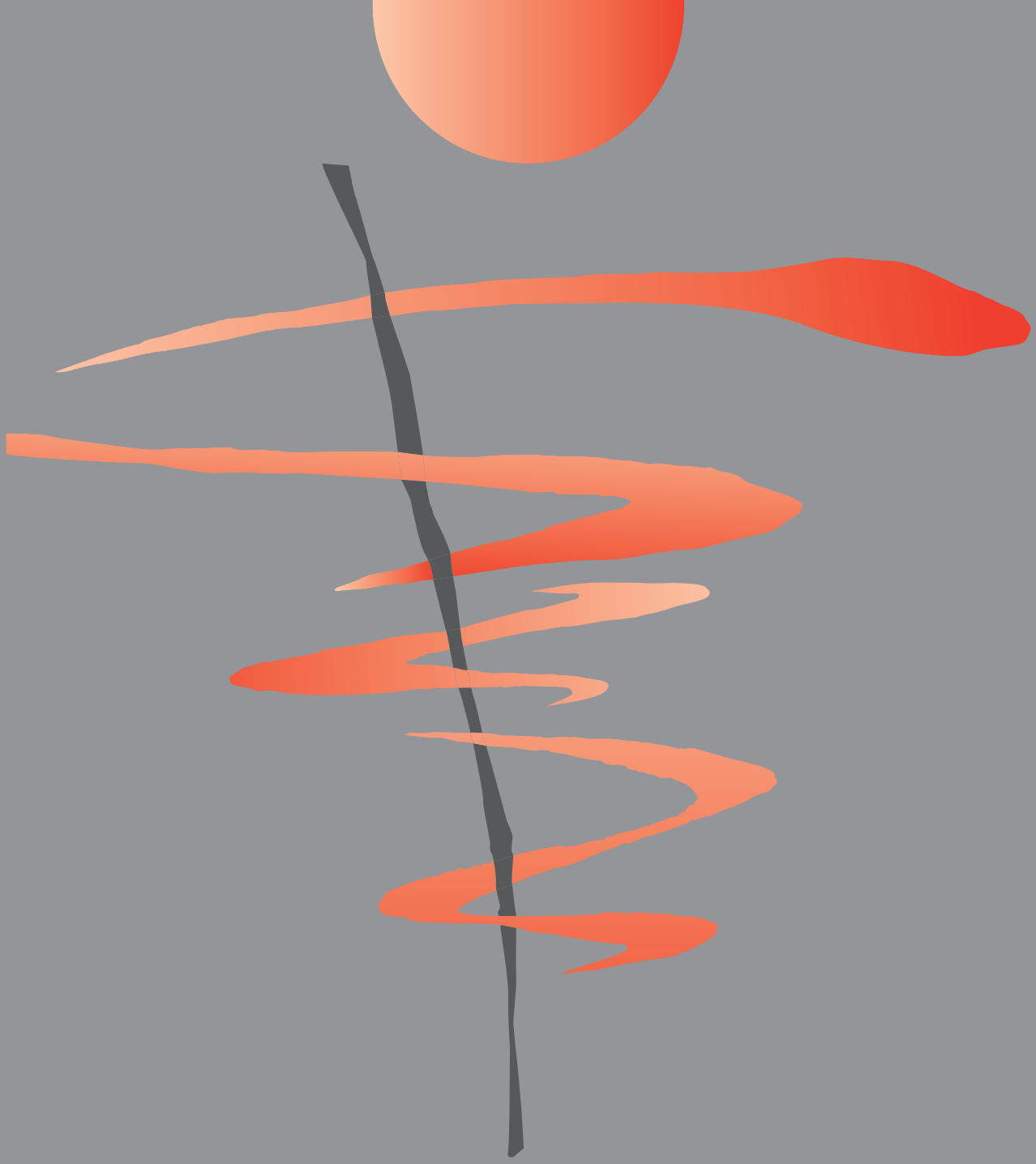

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- Perspectives
- Data articles

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EDITORIAL

Effective manuscript revision responses: Best practices for turning feedback into publication success

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Scientific publishing functions as a complex ecosystem where journal editors, reviewers, and authors play interdependent and often challenging roles [1]. Editors act as gatekeepers, relying heavily on reviewers' dedicated and honest assessment to make informed decisions, while balancing diverse factors including manuscript quality, journal scope, and ethical considerations. This reliance on reviewers' feedback is a well-established norm in academic publishing. Reviewers are highly valued, as they volunteer their time and expertise without material compensation and their feedback is crucial to uphold academic rigor [2]. Many publishers, however, offer reviewers limited free access to journal contents [3, 4] and sometimes provide discounted article processing charges [4, 5] if their own manuscript is accepted within a specific timeframe after completing a review. Authors, especially new authors navigating this triad for the first of few times, may find the process daunting.

Securing reviewers is highly challenging; obtaining high-quality comments is even rarer. Variations among reviewers are common. Authors' responses to these comments require skill, especially for beginners or young authors. Many become upset when faced with dozens of comments from reviewers and editors. Thus, successful navigation of this dynamic requires strategy, patience, professionalism, and an understanding that the peer review process is a collaborative dialogue rather than an adversarial game. Here are some points to consider when authors receive comments from reviewers via the editor:

Stay calm and process feedback carefully

Take time to read the comments and don't plan anything immediately. Read multiple times for thorough understanding. Be appreciative that someone has made time to review your work so that you have received comments. Many submissions are rejected outright without reaching the review stage, known as a "Desk rejection". If the rejection happens after going through the peer review phase, the comments you received will be helpful for improving the manuscript for further submission elsewhere.

Don't rush the response

Make sure to be polite and convey appreciation of the reviewers' efforts, even if you disagree. If you agree with a comment, simply affirm it. Never leave a comment unaddressed.

Organise responses systematically

List all comments under each reviewer. Discuss with your co-authors to draft the best responses. Prepare a point-by-point reply, preferably using a table. Always include page and line numbers; referencing line numbers given continuously is sufficient. Some journals prefer a Q&A format without a table; this applies to Bangabandhu Sheikh Mujib Medical University Journal too.

Disagree respectfully and with evidence

Be concise, insightful, and polite when expressing disagreement. Provide a clear, well-reasoned explanation supported by evidence or references. Avoid emotional or dismissive language. Remember, reviewers are helping improve your draft and assisting the editor's decision-making. Clarify any misunderstandings and revise language as needed to avoid misinterpretation.

Seek assistance for unclear comments

If some points are unclear or you don't understand them, acknowledge this. Clarification might be

Key messages

Scientific journal editors rely on reviewers' assessments to make decisions. Reviewers volunteer their time and expertise to uphold scientific rigour. Authors' responses to comments require skill. Authors should write a professional and polite response addressing each point raised by the reviewers and editor, using a point-by-point format to incorporate their suggestions in track-change mode, or politely explain why a change wasn't made.

provided in the next review if the editor deems the issue significant; minor points may be disregarded.

Strengthen manuscript incorporating additional changes

Feel free to add points from your side to make the revised manuscript more comprehensive and informative after addressing the reviewers' comments.

Make changes visible

Highlight the changes for easy identification and review. Follow the journal's instruction regarding highlighting the changes. You may use track-changes mode for this purpose. You can submit both a tracked changes file and a clean version. After accepting the changes, review the document again to correct any remaining formatting, paragraph structure, punctuation, and other issues.

Update visuals and materials, where necessary

This is also the stage to replace any poor-quality images or graphs with high-resolution versions, while maintaining the same number and size. Inform the editor of any such replacements.

Review your responses thoroughly

Review and revise your point-by-point response carefully. Have it checked by co-authors before submitting alongside the cover letter and the revised manuscript.

Disclose conflicts of interest

Have all co-authors review the revised manuscript and the point-by-point response. Always disclose any relevant conflicts of interest transparently to the editors.

Adhere to the authorship criteria

Once submitted, the author list and authorship order should not be changed without informing the editor. Every journal has an official procedure for these types of changes. Seek the editor's advice on the process if such changes are necessary.

Meet deadlines or request extensions early

Be prompt; adhere to the deadline given by the editor. If you need an extension, ask for it early, as the editor will consider your request. Take the deadline seriously.

Be prepared for multiple revision rounds

Keep in mind that editorial decisions may be influenced by journal priorities or scope; prepare mentally for iterative revision rounds and factor this into workflows. Approach the process as a dialogue, not a competition.

Handling conflicting reviews

When reviewers make opposing recommendations, explain your choice and back it up with data or literature; describe any compromise solutions you implemented. If the conflict is fundamental, politely ask the editor for guidance.

Requests for new experiments or analyses

If reviewers request additional experiments that are not feasible within the revision timeline, explain constraints concisely (e.g. time, cost, IRB, etc.). Offer alternative analyses or propose the work as future research, clarifying why the current data suffice for the manuscript's conclusions.

Appeals and editorial queries

Formal appeals should be used only for procedural errors or demonstrable factual mistakes. Follow the journal's policy for appeals; present facts calmly and professionally.

In conclusion, effectively handling journal reviewers and editors requires politeness and professionalism. Address every point systematically within the given timeline. Finally, manage communication with the production team diligently, as this is the last chance to check for production errors or your own mistakes. Remember, no major changes are permitted once the proof is finalised.

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RESEARCH ARTICLE

Clinical and biochemical profile of wasp sting patients in a tertiary care hospital

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Abstract

Background: Wasp stings and the resulting allergic reactions are common reasons for visiting the emergency department. Stings can be fatal due to multi-system involvement. In our country, the impact of massive wasp stings has been significantly underestimated and has not been systematically investigated. This study aimed to identify the clinical presentations and biochemical profiles of patients experiencing wasp stings in our context.

Methods: This case-series study was conducted at the Department of Medicine in Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh. The research involved species identification, based on photographic evidence, in conjunction with the patient's history and informed consent. The study documented the socio-demographic history, details of the wasp bite, and related complications.

Results: Among the 30 patients studied, there were 22 males, and 8 females, mean (standard deviation) 36.5 (13.1) years. The average number of stings was 57.6 (114.7) (2 to 500 bites), and hospital arrival time ranged from 15 minutes to 8 days. All the patients experienced local pain, swelling, myalgia and rhabdomyolysis. Systemic complications, such as acute kidney injury, were observed in 20% of cases, with half of these requiring hemodialysis. Biochemically, elevated creatine phosphokinase, hyponatremia, and hyperkalemia were frequent. Most of the stings were attributed to Vespa affinis (21; 70%) and Vespa tropica (7; 23%).

Conclusion: Rhabdomyolysis was a universal finding in wasp sting cases. Delayed arrival to the hospital significantly increases systemic complications, with acute kidney injury emerging as the most common severe outcome. Early medical intervention is necessary to minimise these risks.

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Declaration
This article encompasses FCPS thesis of Dr Parash Ullah

Key messages

Wasp stings are a relatively common but often underreported injury caused by arthropods, with Vespa affinis and Vespa tropica being identified as the most common offenders. Early detection and swift treatment can help minimise complications. To understand the burden of this issue, countrywide species-specific epidemiological studies are required.

Introduction

The interface between humans and animals contributes significantly to morbidity and mortality in humans. This interaction has intensified due to both natural and human-induced changes in population dynamics, ecological factors, and behavior [1]. Wasps, which belong to the vespid subgroup within the order Hymenoptera, typically sting when provoked, with incidents most frequently occurring in late summer and early autumn [2]. There are are over 6,000 wasp species worldwide, and wasp stings are common. In the U.S., they account for 27.4% to 29.7% of animal-related injuries, with a yearly mortality rate of 0.14 to 0.74 per million people [3, 4]. Insects that sting to protect their colonies are part of the order Hymenoptera. The medically significant groups within this order include Apoidea (bees), Vespoidea (wasps, hornets, and yellow jackets), and Formicidae (ants). These insects deliver venom to their targets through stings.

Bees possess a barbed stinger, which they leave behind after stinging, ultimately leading to their demise. In contrast, Wasps, hornets, and yellowjackets are capable of stinging multiple times [5, 6]. Stinging incidents involving honeybees and wasps are infrequent, with most deaths or serious cases resulting from fewer than 10 stings, often due to anaphylactic shock. However, mass stinging can be life-threatening due to the toxic effects of large amounts of venom being injected [5]. Wasp venom is a complex mixture of proteins capable of impacting various tissues [7]. Stings from wasps and bees can cause reactions ranging from mild symptoms like swelling and redness to severe complications such as anaphylactic shock, rhabdomyolysis, acute kidney injury, heart attack, acute liver failure, and encephalitis [8, 9, 10, 11]. Undetected anaphylactic reactions to Hymenoptera stings are a major cause of sudden and unexpected deaths in young individuals, regardless of whether they have a history of atopic conditions [12]. Fatalities from honeybee or wasp stings are rare and usually result from Type I anaphylaxis linked to a single sting. Anaphylactic symptoms typically occur within 10 minutes and do not correlate with the amount or number of stings[13].

Wasp stings are common in our country but often go unreported. This study aims to examine the clinical and biochemical characteristics of sting victims and will also address the lack of taxonomic research on local wasp species, providing a foundation for future studies.

Methods

This case-series study was conducted in the Department of Medicine at Sylhet MAG Osmani Medical College Hospital, Sylhet, between April 2014 and March 2015. The study population consisted of all patients admitted to the Department of Medicine who met the inclusion criteria. The inclusion criteria were a recent history of wasp bite (the offending agent will be confirmed by showing photographs or by bringing live or dead species) and an age of 13 years and above, irrespective of gender. Patients poisoned by any other animals or arthropods except wasp (Excluded by history and photograph of wasp), and patients with mutism, stupor, and non-communicable conditions were excluded from the study. The wasp is locally known as "Bolla" or "Bola". Some individuals have provided dead specimens of the Bolla. A total of 30 cases were enrolled within the anticipated timeframe. Consecutive sampling was employed as the sampling technique, and all available participants who met the criteria were included until the desired sample size was reached. Data were collected using a semi-structured questionnaire.

Data collection procedure

Initially, informed written consent was obtained from the patients. A brief history of the wasp sting was then collected from the patient or their attendant. Once the offending wasp was identified in accordance with the inclusion criteria, a thorough clinical examination was performed, and necessary investigations were conducted. The investigation plan was based on the findings from the clinical examination, including both local and systemic assessments. If there was any uncertainty regarding species identification, the expertise of a zoologist was sought.

Statistical analysis

Data was processed manually using SPSS (Version 16.0. Quantitative data were presented as means with standard deviations. Qualitative data were reported in terms of frequency and percentage, with comparisons conducted using Fisher's exact test.

Results

A total of 30 patients' data were analysed. The mean (standard deviation (SD)) age of the respondents was 36.5 (13.1), and the age range was 13–70 years. The majority of affected individuals were male. Patients were primarily managed with symptomatic care, focusing on those who developed acute kidney injury (AKI). Out of six AKI cases, one required dialysis after sustaining 180–200 bite marks, with initial creatinine levels at 3.2 mg/dL, peaking at 7.2 mg/dL, and creatine phosphokinase (CPK) levels reaching 800 U/L. A total of 20 dialysis cycles were administered to normalise kidney function. The other cases were treated supportively, utilising forced diuresis with furosemide, along with intravenous saline, sodium bicarbonate, hydrocortisone, antihistamines, and antibiotics. The offender species was Vespa affinis.

All patients (30; 100%) experienced localised pain, swelling, and muscle pain, with all showing signs of rhabdomyolysis. Six patients (20%) developed acute kidney injury (AKI). Additional symptoms included vomiting (6; 20%), oliguria (6; 20%), hepatitis (4; 13.3%), and dyselectrolytaemia (4; 13.3%). Rare cases included hemolysis (2; 6.7%), myocarditis (1, 3.3%), pulmonary oedema (1; 3.3%), and sepsis (1; 3.3%) (Figure 1).

Table 1 outlines a study of 30 patients, categorised by bite count (fewer than 50 bites, n=21; more than or equal to 50 bites, n=9) and time to hospital presentation (within 1 hour, n=10; after 1 hour, n=20). All patients experienced rhabdomyolysis, but complications such as AKI, hemolysis, myocarditis, pulmonary oedema, septicemia, and hyponatremia were exclusive to those with over 50 bites, with AKI affecting 6 out of 9 in that group. Hepatitis was equally observed in both groups (n=2 each). Delayed hospital arrival (more than 1 hour) correlated with

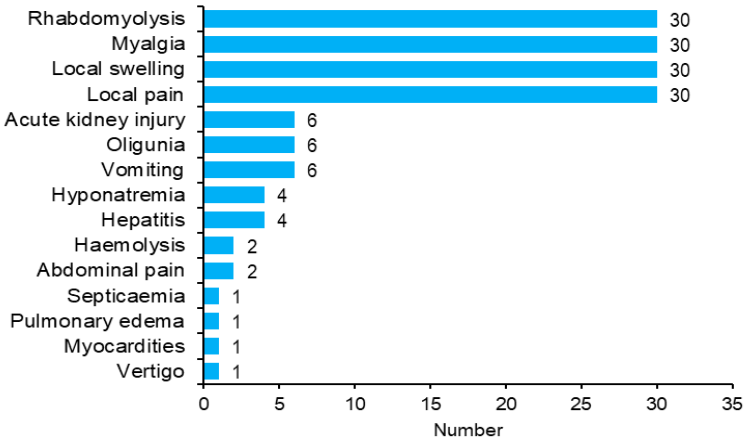

Figure 1 Systemic involvement of patients with wasp bite (n=30)

increased systemic complications, including AKI (n=5), hemolysis (n=2), myocarditis (n=1), pulmonary oedema (n=1), septicemia (n=1), and hyponatremia (n=4), with a significant association noted (P=0.04). Table 2 summarises the results of various biochemical parameters. The mean (SD) SGPT level was 42.6 U/L (39.2 U/L), showing considerable variation among the individuals. The serum creatinine level had a mean (SD) of 1.8 mg/dL (2.0 mg/dl). CPK levels were significantly elevated, with a mean (SD) value of 1495.5 U/L (2676.2 U/L). Hyponatremia was common, with a mean (SD) value of 122.4 mmol/L (6.2 mmol/L). Serum potassium showed a mean (SD) value of 6.0 mmol/L (0.1 mmol/L). The study also identified the specific species of wasps responsible for the stings. Most cases involved 'Vespa affinis' (21; 70%), followed by 'Vespa tropica' (7; 2%), 'Vespa mandarina' (1; 3.3%) and 'Vespa velutina' (1; 3.3%) were rarely reported.

Discussion

In this study, two-thirds of the patients fell within the 20 to 40 year age group. The findings are consistent with another study by Paudel *et al.* where the mean age was 35.5 years. Pérez Pimiento *et al.* [14] reported a mean age of 40.2 years, which differs slightly from our findings [15]. Males were affected significantly more than females, and the findings are quite similar to those of other studies [14, 15, 16]. This increased incidence in males is attributed to their greater outdoor activity compared to females.

Table 1 Relation of systemic involvement (n=30) with the number of bite and time to hospital arrival

Characteristics	Number of bites		Lag period between bite to hospitalisation	
	<50 (n=21)	≥50 (n=9)	≤1 hour (n=10)	>1 hour (n=20)
Rhabdomyolysis	21	9	10	20
Acute kidney injury	0	6	1	5
Haemolysis	0	2	0	2
Myocarditis	0	1	0	1
Hepatitis	2	2	1	3
Pulmonary edema	0	1	0	1
Septicaemia	0	1	0	1
Dyselectrolytaemia (Hyponatremia)	0	4	0	4
P	0.01		0.04	

Interestingly, most of the symptoms were more common in males, except for vertigo, hemolysis, and myocarditis. The cause of this gender difference remains unclear. Witharana *et al.* observed that all patients (100%) experienced local pain, but there was a notable difference in the occurrence of local swelling between studies. In our study, local swelling was present in 100% of cases, compared to 86.7% in their study [16]. In this study, all patients developed myalgia and rhabdomyolysis, which were more prevalent compared to the cases reported from Nepal, where these conditions affected 73% of patients [14].

A fifth of the patients developed renal injury, including oliguria and Acute kidney injury. This result is consistent with the findings of Xie *et al.* in China, where they studied 1091 cases over 8 years from 2004 to 2011 [17]. In a study conducted in India, more than 85% of patients experienced severe AKI and required dialysis [18]. However, in this particular study, only six patients developed AKI, and just 1 of them needed dialysis. The incidence of liver injury, hemolysis, and pulmonary oedema was also lower compared to the Chinese study. The variation could be due to differences in wasp species, venom composition, and health-seeking behaviours of people in different geographies [17].

Table 2 Biochemical parameters of patients with wasp bite (n=30)

Parameter	Mean (SD)[a]	Reference ranges
Serum glutamic pyruvic transaminase	42.6 (39.2)	(7.0–56.0) U/L
Serum creatinine	1.7 (2.0)	(0.6–1.2) mg/dL
Creatine phosphokinase	1495.5 (2676.2)	(20.0–200.0) U/L
Sodium	122.4 (6.2)	(135.0–145.0) mmol/L
Potassium	6.0 (0.1)	(3.5–5.1) mmol/L

[a]SD indicates standard deviation

In this study, the occurrence of abnormal biochemical parameters was consistent with the findings of Xie *et al.* [17]. A notable difference in CPK levels was observed in our study, with significantly higher rates (100% versus 52%) amongst the patients who developed AKI. However, elevated CPK or rhabdomyolysis alone may not cause AKI, as other factors, such as wasp venom toxins and acute tubular necrosis, also contribute to renal impairment [19, 20]. Systemic manifestations were more commonly observed in patients with more than 50 stings, which aligns with the results reported by Paudel B *et al.* [14]. Other complications, such as haemolysis, myocarditis, hyponatremia, pulmonary edema, and septicemia, were consistent with Thiruventhiran *et al.* and Xuan *et al.* studies [10, 13]. Most clinical features and systemic manifestations were seen in patients who arrived at the healthcare centre after one hour. Those treated within the first hour had minimal symptoms. The lag period between sting and initiation of treatment directly correlates with patient outcomes, as was seen in a Nepalese same [14].

The commonest species were Vespa affinis and Vespa tropica. Since this is the first systematic study on species-specific envenomation in this area, no previous data were available for comparison of the findings. Although a case report by Ullah *et al.* from

this region found the Vespa affinis species to be the commonest offender [19, 20]. Patients with multiple stings should be hospitalised for hydration and urine alkalization to prevent AKI, as there is no antivenom available, and treatment is mainly supportive. This study is the first in Bangladesh to systematically examine wasp sting cases, providing valuable clinical, biochemical, and species-specific insights. It highlights the correlation between delayed treatment initiation and severe complications like AKI and offers practical recommendations for early management. A major limitation of the study was its small sample size and absence of a control group of other insect bites. Patients often provided species-specific information after viewing the album, which may lead to incorrect identification. Moreover, the study was limited to hospitalised patients.

Conclusion

This study emphasises that stings from Vespa affinis and Vespa tropica can cause serious complications like rhabdomyolysis and AKI, particularly when treatment is delayed. The link between treatment timing and outcome severity underscores the importance of prompt medical care and improved protocols for managing wasp envenomation. Quick treatment is essential to save lives and reduce hospital stays. To prevent complications, avoid nephrotoxic analgesics. Additionally, tracking specific wasp species is important for a better understanding of biodiversity.

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Author contributions

Conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: FRC. *Drafting the work or reviewing it critically for important intellectual content:* PU, HK, FRC. *Final approval of the version to be published: PU,* HK, FRC, MMJA, MSB. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* FRC, PU.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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RESEARCH ARTICLE

Patterns of thyroid disorders among patients attending an endocrine clinic in Dhaka city

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Abstract

Background: Data on the presentation patterns of thyroid disorders are almost lacking in Bangladesh. We present here the data of an Endocrine Outpatient Clinic based in Dhaka city.

Methods: We reviewed data from the electronic health records of an Endocrine Outpatient Clinic in Dhaka, Bangladesh, over a two-year period. Thyroid function status was interpreted according to the reference range of the corresponding laboratory and classified according to the International Classification of Diseases 11th Revision (ICD-11).

Results: Among 3140 patients, 1015 (32.3%) had thyroid disorders. The age of patients with thyroid disorders ranged from 1 to 84 years, with a median age of 36.0 years (interquartile range: 28.0–48.0 years), and 802 (79.0%) were female. Hypothyroidism [overt hypothyroidism, n=568 (56.0%) and subclinical hypothyroidism, n=281 (27.7%)] was the most common thyroid disorder, followed by thyrotoxicosis (106; 10.4%). Graves' disease (n=68; 6.7%) was the most common cause of thyrotoxicosis, followed by toxic multinodular goitre (n=12; 1.2%). Structural abnormalities with euthyroid status were present in 42 (4.1%) patients. Those with overt hypothyroidism had a higher age (38.0 vs. 34.0 years; P <0.001). Diabetes and hypertension were co-existent. Participants with nodular goitre had a higher mean age (47.1 versus 37.9 years; P =0.14).

Conclusion: Thyroid disorders account for one-third of patients who attended an Endocrine Outpatient Clinic, with the predominance of overt hypothyroidism, followed by subclinical hypothyroidism, and thyrotoxicosis.

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Key messages

One-third of patients who attended the Endocrine Clinic in Dhaka city have thyroid disorders. There is a female predominance (79.0%) of among patients with thyroid disorders. The most common pattern is overt hypothyroidism (56.0%), followed by subclinical hypothyroidism (27.7%), Graves' disease (6.7%), and structural abnormalities with euthyroid (4.1%) status.

Introduction

Nearly 200 million people worldwide are estimated to have thyroid disorders [1]. These issues are most often caused by iodine deficiency in areas where iodine is lacking, and by autoimmune thyroid conditions where iodine intake is sufficient. Surprisingly, one-third of the global population still lives in iodine-deficient regions [2]. In areas with enough iodine, hypothyroidism affects about 1% to 2% of people, while hyperthyroidism is seen in 0.2% to 1.3%. Moreover, the percentage of palpable thyroid nodules in the general population is 4% to 7% [3]. In Bangladesh, although the exact numbers are unknown, it's estimated that approximately 20% of the population may have some form of thyroid disorders but half of them are unaware of their condition [4]. Asymptomatic and mild cases are often neglected and out of medical attention. However, patients visiting specialised endocrine clinics usually have severe and complex problems, providing important insights into the challenges of diagnosing and managing these disorders. This study aimed to understand the range of thyroid disorders seen at on Endocrine clinic.

Methods

Study population

We have a specialised endocrinology outpatient clinic at Uttara, Dhaka, Bangladesh. The clinic keeps clinical and demographic details of the patients' electronic health records. We included all consecutive patients with any thyroid disorder who visited the clinic between 30 August 2022 and 15 December 2024. Of these, 1,015 patients (male and female) were identified as having thyroid disorders of any age. Among them, 217 (21.3%) patients with type 2 diabetes were reported elsewhere [5].

Classifications and diagnosis of thyroid disorders

The diagnosis of thyroid disorders was made either based on previous medical records or a recent investigation of thyroid function based on clinical presentations of the patients. Disorders of the thyroid gland were classified according to the ICD-11 for Mortality and Morbidity Statistics [6]. Estimation of TSH and FT4 was carried out using an indirect chemiluminescence method for newly diagnosed cases. For non-pregnant adults, a TSH range 0.35–5.5 µIU/mL, FT4: 0.78–2.19 ng/dL, and FT3: 2.30–4.20 pg/mL were considered normal. Thyroid ultrasonogram findings were used to define structural thyroid disease in suspected cases. In hyperthyroid patients, TSH

Table 1 The type of thyroid disorders among patients attending an endocrine outpatient department according to International Classification of Diseases, 11th revision, ICD -11 (n=1015)

ICD-11	Number (%)
5A00 Hypothyroidism (n=858)	
5A00.0 Congenital hypothyroidism	
5A00.01 Permanent congenital hypothyroidism without goitre	4 (0.4)
5A00.2 Acquired hypothyroidism (n=849)	
5A00.2Y Other specified acquired hypothyroidism (Primary acquired hypothyroidism)	568 (56.0)
5A00.2Z Acquired hypothyroidism, unspecified (Subclinical hypothyroidism)	281 (27.7)
5A61.40 Acquired central hypothyroidism	5 (0.5)
5A01 Nontoxic goitre (n=36)	
5A01.0 Nontoxic diffuse goitre	14 (1.4)
5A01.1 Nontoxic single thyroid nodule	11 (1.1)
5A01.2 Nontoxic multinodular goitre	11 (1.1)
5A02 Thyrotoxicosis (n=106)	
5A02.0 Thyrotoxicosis with diffuse goitre (Graves' disease)	68 (6.7)
5A02.1 Thyrotoxicosis with toxic single thyroid nodule	2 (0.2)
5A02.2 Thyrotoxicosis with toxic multinodular goitre	12 (1.2)
5A02.Y Other specified thyrotoxicosis (n=8)	
Subclinical thyrotoxicosis	4 (0.4)
Gestational thyrotoxicosis (JB44.5)	4 (0.4)
5A02.Z Thyrotoxicosis, unspecified (Thyrotoxicosis under evaluation)	16 (1.6)
5A03 Thyroiditis (n=8)	
5A03.1 Subacute thyroiditis	8 (0.8)
JB44 Certain specified complications of the puerperium (n=1)	
JB44.5 Postpartum thyroiditis	1 (0.1)
DA05 Cysts of oral or facial-neck region (n=1)	
DA05.Y Other specified cysts of oral or facial-neck region (Thyroglossal duct cyst)	1 (0.1)
2D10 Malignant neoplasms of thyroid gland (n=5)	
2D10.0 Follicular carcinoma of the thyroid gland	1 (0.1)
2D10.1 Papillary carcinoma of the thyroid gland	4 (0.4)
Total	1015

Table 2 Number (%) of overt primary and subclinical hypothyroidism (n=849)

Characteristics	Total (n=849)	Overt primary hypothyroidism (n=568)	Subclinical hypo-thyroidism (n=281)	*P*
Age, years				
<18 years	54 (6.4)	26 (4.6)	28 (10.0)	0.002
≥18 years	795 (93.6)	542 (95.4)	253 (90.0)	
Sex				
Female	684 (80.6)	465 (81.9)	219 (77.9)	0.17
Male	165 (19.4)	103 (18.1)	62 (22.1)	
Co-morbidities				
Diabetes mellitus	229 (27.0)	173 (30.5)	56 (19.9)	0.001
Hypertension	348 (41.0)	258 (45.4)	90 (32.0)	<0.001

receptor antibody (TRAb), thyroid scan, and radioactive iodine uptake were used as appropriate to differentiate Graves' disease from other causes of thyrotoxicosis. We used the following criteria to diagnose different types of thyroid disorders in non-pregnant adults:

a) Subclinical hypothyroidism (SCH): FT4= 0.78–2.19 ng/dL and TSH=5.5 to <20.0 µIU/mL
b) Overt primary hypothyroidism: FT4 <0.78 ng/dL and TSH ≥20.0 µIU/mL
c) Secondary hypothyroidism: FT4 <0.78 ng/dL and TSH= undetectable to <20.0 µIU/mL
d) Subclinical thyrotoxicosis: FT4 = 0.78–2.19 ng/dL and TSH <0.35 µIU/mL
e) Primary thyrotoxicosis: FT4 >2.19 ng/dL and TSH <0.35 µIU/mL
f) Solitary thyroid nodule and multinodular goitre – diagnosed based on ultrasonogram and thyroid scan findings
g) Thyroid malignancy- diagnosed by histopathology. In case of Pregnancy, children, and adolescents, specific laboratory values were used in this group of patients.

Statistical analysis

Data were analysed using SPSS software (version 25.0). Continuous variables were expressed as the mean ± standard deviation (SD), or median with interquartile range (IQR), depending on their distribution. Categorical variables were presented as numbers and percentages.

Results

We present the data of 1015 (32.3%) patients who had a functional or structural thyroid disorders. Table 1 shows the spectrum of thyroid disorders according to ICD-11. The predominant disorders were acquired hypothyroidism (83.7%), thyrotoxicosis with diffuse goitre (6.7%), and different types of nontoxic goitres (3.6%). Four patients had congenital hypothyroidism without goitre. Among 36 patients with nontoxic goitre, 14 had diffuse goitre, and the frequency of single and multinodular goitre was 11 for both. Sixteen patients presented with thyrotoxicosis; however, they were lost to follow-up. Eight patients had a diagnosis of subacute thyroiditis. Among five patients with malignant neoplasms, four had papillary carcinoma and one had follicular carcinoma of the thyroid. Uncommon disorders included subclinical thyrotoxicosis (n=4), gestational thyrotoxicosis (n=4), postpartum thyroiditis (n=1), and thyroglossal duct cyst (n=1), etc. The predominant etiologies of hypothyroidism were primary acquired hypothyroidism (n=568) and subclinical hypothyroidism (n=281).

Table 3 Number (%) of goitre types (n=82)

Characteristics	All goitres (n=82)	Diffuse goitres (n=68)	Nodular goitres (n=14)	*P*
Age, years				
<18 years	2 (2.4)	2 (2.9)	0 (–)	0.99
≥18 years	80 (97.6)	66 (97.1)	14 (100.0)	
Sex				
Female	61 (74.4)	51 (75.0)	10 (71.4)	0.75
Male	21 (25.6)	17 (25.0)	4 (28.6)	
Co-morbidities				
Diabetes mellitus	21 (25.6)	14 (20.6)	7 (50.0)	0.04
Hypertension	30 (36.6)	26 (38.2)	4 (28.6)	0.49

The median age of the subjects were 36 years (interquartile range, 28.0–48.0) Those with overt primary hypothyroidism had higher age (*P* =0.002) as well as higher frequencies of diabetes (*P* =0.001) and hypertension (*P* <0.001) (Table 2) . The predominant causes of thyrotoxicosis were thyrotoxicosis with diffuse and nodular goitre (single or multiple). Participants with nodular goitre had a higher mean age and frequency of DM (*P* <0.04) than those with diffuse goitre with thyrotoxicosis (Table 3).

Discussion

There is hardly any published database on thyroid disorders in Bangladesh. The dataset we present here is one of the few available. We believe that publication of other datasets would provide a broader evidence base for future use in generating hypotheses for further research.

The most common thyroid disorder in the study population was acquired hypothyroidism, followed by thyrotoxicosis with diffuse goitre and various nontoxic goitre. These findings align with the global data, where acquired hypothyroidism remains the leading thyroid disorder. In general, hypothyroidism affects up to 5% of the general population, and over 99% of affected people suffer from acquired hypothyroidism. Iodine deficiency is the top cause of thyroid disorders worldwide. Yet, where iodine is sufficient, Hashimoto's thyroiditis (an autoimmune disease) is the most common cause of thyroid failure [7]. Primary acquired hypothyroidism (56%) was the most common thyroid issue in this analysis, with subclinical hypothyroidism (27.7%) also being a major contributor, highlighting the importance of detecting these often symptomless cases due to potential long-term risks. Missing data on several variables limits our effort to generate hypotheses, e.g., thyroid autoantibodies and iodine levels [8].

The data from Kerala, India, provides a contrasting picture, the most common type of thyroid disorder there is non-toxic multinodular goitre (48.5%), followed by hypothyroidism (18.1%) [9]. Development of nodular thyroid enlargement is multi-factorial; goitrogens, iodine deficiency, malnutrition, and genetic factors might contribute, and these factors

probably differ from patient to patient and have geographical variation [10]. In our data, there was a relatively lower prevalence of thyrotoxicosis, including Graves' disease (diffuse goitre) and toxic multinodular goitre. The prevalence of goitre and iodine deficiency in Bangladesh has been considerably reduced over the last two decades due to the "Universal Salt Iodization Programme" and autoimmunity is currently the leading cause of thyroid disorders [4]. There is a paucity of patients with sub-acute thyroiditis, gestational thyrotoxicosis, and postpartum thyroiditis, all of which were relatively rare. Data from other outpatient endocrinology settings indicate that thyroid malignancies are relatively common [11].

Children predominantly presented with subclinical hypothyroidism. Hypothyroidism in children and adolescents has deleterious effects on physical growth, mental development, and school performance, which may lead to more investigations among this age group, which possibly could have contributed to more cases of undiagnosed subclinical hypothyroidism [12, 13]. Overt primary hypothyroid patients were found to be more likely to have diabetes and hypertension compared to subclinical hypothyroidism [14, 15]. Thyrotoxicosis patients with nodular goitre were predominantly older than thyrotoxicosis with diffuse goitre, which was a typical picture we are familiar with.

Limitation

The data are generated from a single outpatient clinic, which limits their generalisability. We couldn't classify hypothyroidism types due to a lack of autoantibody and urinary iodine data. There are some missing values to confirm the diagnosis.

Conclusion

Our findings are valuable as the first large-scale report on thyroid disorders in Bangladesh, providing a foundation for future research. The one-third patients who seek services at the endocrine clinic have thyroid disorders. There is a predominance of overt hypothyroidism, following by subclinical hypothyroidism and thyrotoxicosis.

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Author contributions

Concept and design of the study: MRH, RS, SAM, MSM, MFA. *Acquisition, analysis, and interpretation of data:* MRH, RS, SAM, MSM. *Manuscript drafting and revising it critically:* MRH, MSM, MFA. *Approval of the final version of the manuscript:* MRH, RS, SAM, MSM, MFA. *Guarantor accuracy and integrity of the work:* MRH

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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Association of *p53* codon 72 polymorphisms with expression status of hormone receptors like ER, PR, and HER-2 in invasive ductal breast carcinoma in Bangladeshi women

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Abstract

Background: There is a lack of data on prevalent genetic factors among female breast cancer patients from Bangladesh. *p53*, a suppressor gene, is crucial in breast cancer's aetiology. This study aimed to investigate the association between *p53* codon 72 polymorphisms and invasive ductal breast carcinoma (IDC) in Bangladeshi women.

Methods: This study included 203 formalin-fixed paraffin-embedded specimens of histologically confirmed IDC, with immunohistochemical analyses for ER, PR, and HER-2 status from November 2021 to October 2022. The specimens were collected from one laboratory in each of the Dhaka and Chattogram cities. *p53* codon 72 genotypes were detected using PCR-RFLP.

Results: Most patients (77%) were aged 41–60 years. All cases were IDC, with grade II (79.3%) and stage II being most prevalent (82%). ER-positive tumours were observed in 65.5% of patients, while 69% tumours were PR-negative and HER-2-negative. The GC (Arg/Pro) genotype was predominant (58.6%), followed by CC and GG (20.7% each). Statistically significant associations were found between the GC genotype and size less than 5 cm (P<0.01), axillary lymph node metastasis (P<0.01), and PR-negative tumours (P=0.02). Patients with GC+GG genotypes had higher odds of axillary lymph node metastasis (age, tumour grade and tumour stage adjusted odds ratio 21.8; 95% confidence interval 7.0–67.9), PR-negative tumours (aOR 0.2; 95% CI 0.1–0.6) and HER-2 negative tumours (aOR 0.3; 95% CI 0.1–0.9).

Conclusion: Our study suggests that the Arginine allele at *p53* codon 72, in either homozygous or heterozygous form, is associated with more aggressive IDC features in Bangladeshi women, including axillary lymph node metastasis and hormone receptor negative tumours.

Key messages

The study suggests that the presence of the Arginine allele in heterozygous (GC) or homozygous (GG) forms at codon 72 of the *p53* gene is associated with an increased risk of axillary lymph node metastasis, as well as PR-negative and HER-2-negative tumours, in female patients with invasive ductal breast carcinoma in Bangladesh. No significant link was found between this polymorphism and the ER status of the tumour.

Introduction

The Breast cancer, characterised by the malignant proliferation of epithelial cells within the ducts or lobules of the breast, is the most common malignancy in women, accounting for roughly one-third of all cancers in women worldwide [1]. Several risk factors have been identified, including some reproductive factors (age at menarche, menopause, first pregnancy, breastfeeding, and parity) and non-reproductive factors (menopausal hormone therapy, family history of cancer, body mass index, alcohol intake, and others) that are linked with breast cancer risk [2]. Besides these, women are adopting new lifestyles and undergoing significant demographic transitions. The higher incidence rates of breast cancer may also be due to genetic risk factors, which are still less studied.

Breast cancer is linked to various types of somatic genetic alterations, including mutations in oncogenes and suppressor genes [3]. The TP53 (*p53* gene, chromosome 17p13) protein function is altered in all cancers, including breast carcinomas, in approximately 20–40% of cases, depending on size and stage of disease [4]. The human tumour suppressor gene *p53* encodes a transcription factor that plays a central role in maintaining cellular integrity by inhibiting cell growth and stimulating apoptosis in response to DNA damage [5]. A common single-nucleotide polymorphism (SNP) occurs at the second position of codon 72 in exon 4 (rs1042522: CCC to CGC, Arg72Pro polymorphism), leading to an amino acid substitution of Proline (Pro) with Arginine (Arg) in the Pro-rich region of TP53 protein [6]. The distribution of the Pro and Arg alleles across three genotypic forms—CC (Pro/Pro), GG (Arg/Arg), and GC (Arg/Pro)—largely depends on the ethnic composition of the population studied [7]. The association of *p53* polymorphism at codon 72 and breast cancer development has been studied, but results have been controversial and not conclusive. Several studies have reported a significant association between the *p53* codon 72 polymorphism and breast cancer risk [7, 8, 9]. whereas others have identified no such association [10, 11]. In some studies, the Pro-allele has been associated with increased breast cancer risk [12, 13]. Other studies found the homozygous Arg-allele (GG genotype) associated with breast cancer predisposition [14, 15, 16]. Yet other studies, including most of the newer and larger studies and meta-analyses, did not detect any association of the Arg72Pro polymorphism with breast cancer risk [17, 18]. These discrepancies are attributed to the failure to determine the mutational status of *p53* in the study populations and/or the observed latitudinal differences in allele frequency [19].

The study of genetic influences in breast cancer is complex. Careful case selection is important, taking into account ethnic homogeneity, disease phenotype, and exposure to environmental risk factors. Targeted breast cancer management strategies may require not only molecular profiling but also knowledge of an individual's genetic susceptibility to develop metastatic disease. There is still a great deal more that needs to be discovered and understood before this type of genetic knowledge will find a valid place in the clinical care of individuals and families with breast cancer. However, such genetic study data regarding the association of *p53* codon 72 gene polymorphism with (a) invasive ductal breast carcinoma (IDC), and (b) hormone receptor expression status, i.e. estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) of the IDC patients, are inadequate in Bangladesh. As *p53* mutations are potential prognostic and predictive markers, as well as targets for therapy [20, 21]. this study aimed to investigate the association of *p53* codon 72 polymorphisms with IDC in adult females and to assess the effect of this polymorphism on the ER, PR and HER-2 expression status of the tumour.

Methods

Breast tissue specimens

This study is based on formalin-fixed paraffin-embedded (FFPE) specimen blocks randomly selected from two institutions with similar competency in Bangladesh: the Department of Pathology at Bangladesh Medical University, Dhaka, and the Care Investigation Histopathology and Cytopathology Laboratory in Chattogram, from November 2021 to October 2022. A simple random sampling of specimens was conducted using the sampling frame maintained by the laboratories' registry.

We short-listed 374 registered IDC cases from the histopathology registries. The inclusion criteria were: (i) Bangladeshi adult females diagnosed with unilateral IDC for the first time; (ii) availability of data on expression status for three hormone receptors important for IDC diagnosis and treatment, i.e. ER, PR and HER-2; (iii) availability of other clinical and pathological data, *e.g.* patients' age, tumor size, axillary lymph node metastasis, number of lymph node involved; (iv) the patients did not receive any extensive treatment for IDC prior to surgical removal of the tumour. The exclusion criteria were: (i) IDC cases other than adult females; (ii) recurrence or patients had other cancers as primary disease; (iii) core FFPE block is not available for research; (iv) FFPE blocks not in good condition for taking microtome sections for DNA isolation, histopathology imaging for the study, and immunohistochemical analysis, (v) necesssary clinical and pathological data of the cases are not available. Finally, a total of 203 cases were selected for the study.

FFPE tissue blocks, along with relevant clinical and pathological data of the 203 cases, were collected from the mentioned institutions for the analyses of this study. Here, the presence of hormone receptor expression of ER, PR and HER-2 was recorded as positive, and the absence of such expression was recorded as negative for corresponding hormone receptors. Polymorphism detection of *p53* codon 72 and data analyses were done at the Functional Genomics and Proteomics Laboratory of the Department of Genetic Engineering and Biotechnology, University of Chittagong.

Isolation of genomic DNA

Multiple sections (4-8 sections) each measuring 2-3 µm in thickness were taken from the selected FFPE

blocks using a semi-automatic microtome. These sections were used as starting material for DNA isolation. Isolation of genomic DNA from the sections was done according to the manufacturer's protocol of GeneJET FFPE DNA Purification Kit (Thermo Scientific, USA) [22]. After isolation, the DNA were preserved at -20°C for further analysis.

Polymerise chain reaction (PCR) for *p53* codon 72 region

Nested enrichment PCR and subsequent restriction enzyme digestion were done for the detection of *p53* c72 SNPs. The PCR primers used in this experiment were previously described [23, 24]. For the first round PCR, the primers (IDT, Singapore) F1: 5′-GCTCTTTTCACCCATCTACAG - 3′ and R1: 5′-TGAAGTCTCATGGAAGCCAGC - 3′ were used along with 100ng DNA from FFPE block. For the second round PCR, F2: 5′ - TCCCCCTTGCCGTCCCAA - 3′ and R2: 5′ - CGTGCAAGTCACAGACTT - 3′ primers (IDT, Singapore) were used along with 2µL of 10X diluted PCR product of first round PCR. In both first and second round PCR reactions, the reaction mixture contained 1X GoTaq® Flexi reaction buffer (Promega, USA), 2mM MgCl2 (Promega, USA) 0.1mM of each dNTPs (Sigma, USA), 1U GoTaq® Flexi DNA Polymerase (Promega, USA), and Nuclease free water (Invitrogen, USA) was used to make the reaction volume upto 25µL. The PCR thermal cycler (Qantarus, UK) profile included Initial denaturation at 95°C for 5 minutes, 35 (first round) and 30 (second round) cycles of denaturation at 95°C for 30 seconds, annealing at 58.5°C for 30 seconds, and elongation at 72°C for 1 minute.

Restriction fragment length polymorphism (RFLP) for *p53* codon 72 polymorphisms

RFLP for *p53* codon 72 polymorphism detection was done by digesting 10µL of second round PCR products by 2U of Bsh1236I restriction enzyme which contains the restriction site 5′-CGCG-3′ (BstUI, Thermo Scientific, USA) in 0.67X Buffer R (Thermo Scientific, USA) and nuclease free water (Invitrogen, USA) was used to make reaction volume upto 25µL. The temperature profile for restriction digestion consisted of incubation at 37°C for 4 hours and 30 minutes, followed by inactivation at 65°C for 20 minutes. All the restriction digestion reactions were carried out in a heating block (WiseCube, Daihan Scientific, Korea).

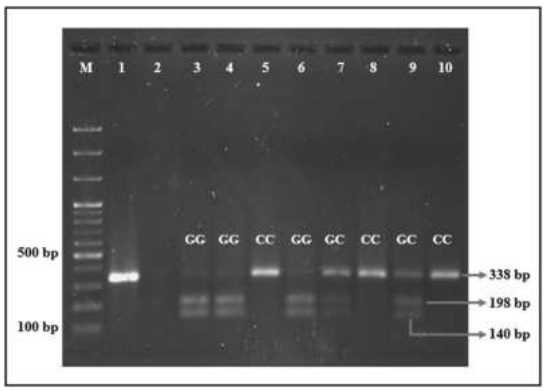

Figure 1 *p53* codon 72 polymorphism detection in invasive ductal breast carcinoma patients. Single-nucleotide polymorphism variants are marked in corresponding lanes. Band sizes are mentioned in base pairs (bp). Lane M: DNA size marker (100bp+ DNA marker). Lane 1: undigested *p53* codon 72 PCR product (338 bp). Lane 2: Blank. Lanes 3-10: BstUI digested *p53* codon 72 PCR products. Lanes 5, 8 and 10: presence of CC homozygous SNP variant caused the absence of BstUI recognition site and thus remained uncut (338 bp) Lane 3-4 and 6: presence of homozygous GG SNP variant caused complete digestion of PCR product into 198 bp and 140 bp fragments. Lanes 7 and 9: presence of heterozygous GC SNP variant caused incomplete digestion of PCR products and produced 338 bp, 198 bp and 140 bp bands.

Agarose gel electrophoresis and detection of *p53* codon 72 polymorphisms

2% w/v low electroendosmosis (Low EEO) agarose (Promega, USA) was completely dissolved in 1X TAE buffer (pH 7.9) by using a high-temperature quick-dissolve technique with a microwave oven. Five microliters of Safe Dye (AdBio Solutions, South Korea) were added while preparing the gel for visualisation of DNA bands in a UV Gel Documentation System (Vilber, France). In each agarose gel preparation, a thickness of 3-4 mm was maintained for clearer visualisation. Horizontal submarine electrophoresis was done in either Biometra Compact XS Electrophoresis Apparatus (Analytic Jena, Germany) or Hoefer HE 33 Mini Electrophoresis Unit (Thermo Fisher Scientific, USA) with the corresponding power supply kits. 1X TAE (pH 7.9) was used as running buffer during electrophoresis. 10 µL of PCR or PCR-RFLP products were loaded in the wells along with 2 µL 100 bp DNA size marker (Promega, USA) in the left-most well. Electrophoresis was carried out for the required durations with constant voltage (55V) control (Figure 1).

Statistical analyses

A Chi-squared test was performed to determine whether there was any significant deviation from the expected distribution of *p53* codon 72 genotypes among the IDC samples, considering variables such as tumour size, lymph node metastasis, and hormonal receptor expression status (ER, PR, and HER-2). To find the most influential *p53* codon 72 polymorphic variant upon pathological status and ER, PR, HER-2 expression status, by applying univariate and multivariate logistic regression, which are usually done in single-nucleotide polymorphism (SNP) association studies to calculate odds ratios and their 95% confidence intervals. In the univariate analysis, the SNP counts of CC homozygotes versus GC+GG genotypes (*i.e.* reflecting proline versus arginine alleles) were compared according to various parameters. Multivariate logistic regression analysis was conducted to adjust the results according to patients' age, tumour grade and tumour stages. $P<0.05$ was considered statistically significant. All data were analysed with SPSS Software v25.

Results

Pathological status of the cases

The age of the 203 patients spanned from 21 to 94 years. However, there were 99 patients from the 41–60 years age group (48.87%) (Table 1). All the samples were confirmed as invasive ductal carcinoma. Histopathological observation revealed that most patients (79.3%) had tumour grade II, and 82% were in

Table 1 Clinical and pathological details of the study patients (n=203)

Variables	Number (%)
Age (Years)	
21–40	63 (31.0)
41–60	99 (48.8)
61–94	41 (20.2)
Tumor grade	
Grade I	21 (10.3)
Grade II	161 (79.3)
Grade III	21 (10.3)
Tumor staging	
T1 (<2 cm)	8 (3.9)
T2 (2–5 cm)	167 (82.3)
T3 (>5 cm)	28 (13.8)
Axillary lymph node status	
Sinus histiocytosis	67 (33.0)
Metastatic ductal carcinoma	98 (48.3)
Follicular hyperplasia	38 (18.7)
Number of lymph node involved (n=98)	
N1 stage (1–3 lymph nodes involved)	63 (64.3)
N2 stage (4–9 lymph nodes involved)	28 (28.6)
N3 stage (>10 lymph node involved)	7 (7.1)
Estrogen expression	
Positive	133 (65.5)
Negative	70 (34.5)
Progesterone expression	
Positive	63 (31.0)
Negative	140 (69.0)
HER2 expression	
Positive	63 (31.0)
Negative	140 (69.0)
p53 codon 72 SNP	
CC genotype	42 (20.7)
GC genotype	119 (58.6)
GG genotype	42 (20.7)

tumour stage II. Forty-eight per cent had metastatic ductal carcinoma in their axillary lymph nodes, and 64.3% were in N1 stage (1-3 lymph nodes involved).

ER, PR and HER-2 expression status

Immunohistochemical analysis revealed that most of the cases (65.5%) were positive for ER expression. Whereas most patients were negative for PR and HER-2 expression (Immunohistochemical features are shown in Figure 2).

p53 codon 72 genotype frequencies and their associations

The GC heterozygote variant was the most common among the study patients, accounting for 58.6%. Both CC and GG homozygous variants were found in equal numbers; that is, 20.7% of patients had the CC homozygote variant, and 20.7% had the GG homozygote variant. It was suggested that the GC genotype might be associated with the disease conditions in this study population.

A significant association was observed between the *p53* codon 72 polymorphic genotype and clinical parameters, including tumour size, axillary lymph node metastasis, and PR expression (Table 2). The Arg/Pro heterozygous allele (GC genotype) was significantly associated with tumours less than 5 cm in size ($P<0.01$), axillary lymph node metastasis ($P<0.005$). Furthermore, a statistically significant association was noted between the GC genotype and PR-negative tumours ($P=0.02$). No significant associations were observed between the *p53* codon 72 genotypes and ER or HER-2 status.

From logistic regression analyses (Table 3), it was found that patients carrying Arg/Pro+Arg/Arg alleles (GC+GG genotypes) were significantly more likely to be presented with axillary lymph node metastasis compared to homozygous Pro allele (CC genotype) carriers. The crude OR was 6.5 (95% CI 2.7–15.5), while the aOR increased markedly to 21.8 (95% CI 7.0 –67.9), indicating a strong probability. No significant association was found between the *p53* codon 72 polymorphism and the ER expression status. The OR was 0.9 (95% CI 0.5–1.9), and the aOR was 0.6 (95% CI 0.3–1.4). In contrast, PR-negative tumours were common among GC+GG genotype carriers. The OR was 0.4 (95% CI 0.2–0.7), and the aOR was 0.2 (95% CI 0.1–0.6), suggesting a strong probability of finding these genotypes in ER-negative tumours. There was no significant representation of any *p53* codon 72 genotype according to HER-2 expression status in univariate logistic regression (OR 0.9; 95% CI 0.4–1.2), whereas, adjusted multivariate logistic regression analysis revealed that the Arg/Pro+Arg/Arg alleles (GC+GG genotypes) were significantly more presented in HER-2-negative tumors (aOR 0.3; 95% CI 0.1–0.9).

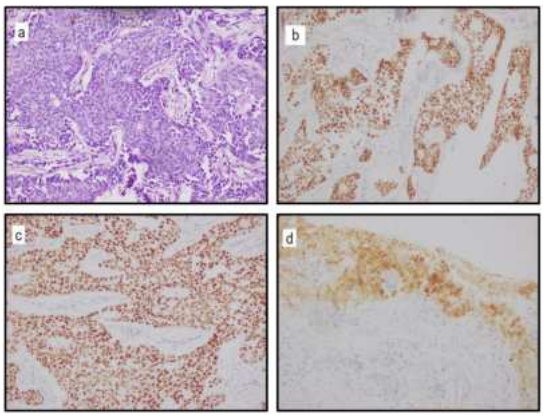

Figure 2 Immunohistochemical evaluation for ER, PR and HER2 expression after histological confirmation of invasive ductal breast carcinoma grade II. The patient was a 45-year-old female (case no.: 26). (a) Histological image of breast tissue sections of a showing features of invasive ductal carcinoma; (b), (c) and (d) are immunohistochemical images showing positive staining for ER, PR and HER2 expressions, respectively.

Discussion

This study investigated the association between *p53* codon 72 polymorphism and IDC in Bangladeshi adult women, with a focus on clinicopathological features and hormone receptor expression status. The *p53* codon 72 SNP results in either a proline or arginine residue in the TP53 protein, influencing its tumour suppressor functions and apoptotic capacity [25, 26]. Understanding this polymorphism's role could improve insights into breast cancer susceptibility, progression, and prognosis.

Table 2 Distribution of *p53* codon 72 CC homozygotes (Pro/Pro) versus GC heterozygotes (Arg/Pro) across variables

Variables	Pro/Pro (CC) (n=42)	Arg/Pro (GC) (n=119)	*P*
Tumor size (cm)			
<5	21	98	<0.001
≥5	21	21	
Axillary lymph node metastasis			
No metastasis	35	49	0.01
Metastatic ductal carcinoma	7	70	
Expression of estrogen receptor			
Negative	14	49	0.46
Positive	28	70	
Expression of progesterone receptor			
Negative	21	84	0.02
Positive	21	35	
Expression of human epidermal growth factor receptor 2			
Negative	28	91	0.23
Positive	14	28	

Our findings showed that Bangladeshi women aged 41–60 years exhibited the highest IDC prevalence. This observation aligns with data from the Polish population, which demonstrated a linear increase in breast cancer incidence among women aged 40–59, followed by a plateau in those aged 70 and above [27]. Similarly, studies conducted by Acharya *et al.* and Pathak *et al.* reported the 41–60-year age group as the most commonly affected by breast cancer [28, 29]. This trend may be associated with hormonal fluctuations during the peri- and postmenopausal periods, which are known to influence breast cancer risk [27].

Numerous studies have assessed the role of the Arg72Pro polymorphism in cancer risk, but findings have been inconsistent across populations [26]. In our study, the heterozygous Arg/Pro (GC genotype) was the most common, observed in 58.6% of patients. This contrasts with a recent study from Brazil involving 96 individuals, which reported a high prevalence of the Arginine allele (68%), whereas we found equal frequencies of the Arginine and Proline alleles [30]. Similar results were observed concerning the involvement of the heterozygous Arg/Pro (GC genotype) variant and an increased risk of breast cancer in the North Indian population [31]. Another study reported that Proline homozygosity (CC genotype) at *p53* codon 72 is associated with decreased breast cancer risk in Arabian women [32].

The current study's findings suggest that the presence of Arg allele (GC+GG genotypes) is significantly associated with an increased risk of axillary lymph node metastasis. Some studies have shown that the mechanism of breast carcinogenesis and its progression is associated with alterations in the expressions of ER, PR, and HER-2 [33]. Notably, a significant association was observed between the Arg-containing genotypes and PR-negative tumours, suggesting a possible link between the Arg allele and hormone-independent tumour biology. This result is consistent with findings from studies in Asian populations, where the Arg allele was more frequently associated with hormone receptor–negative tumours, which tend to be more aggressive and less responsive to endocrine therapy [33, 34].

In the case of HER-2 expression, the Arg/Pro+Arg/Arg alleles (GC+GG genotypes) were initially not associated in the univariate logistic regression analysis. However, after adjusting for patients' age, tumour grade and tumour stages, a significant association was found between GC+GG genotypes and HER-2-negative tumours. This observation is novel in our study as previous studies found no significant association [35, 36], and requires further investigation. No significant association was found between *p53* codon 72 polymorphism and ER status, which contrasts with some previous reports suggesting a genotype-specific interaction with ER expression [37]. This discrepancy may be due to population-specific genetic backgrounds, sample size, or environmental co-exposures such as heavy metals, which are particularly relevant in the Bangladeshi context. Thus, discrepancies between our findings and those of other studies may reflect population-specific genetic and environmental interactions.

Our findings suggest that patients who present a heterozygous genotype and/or Arginine allele at codon 72 of the *p53* gene may have a susceptibility towards breast cancer along with axillary lymph node metastasis. This could serve as a potential biomarker

Table 3 Likelihood of *p53* codon 72 polymorphic variants and axillary lymph node metastasis and hormone receptor expression status (ER, PR and HER-2) of patients

Variables	Genotypes		Odds ratio (95% confidence interval)	Adjusted[a] odds ratio (95% confidence interval)
	Pro/Pro (CC)	Arg/Pro +Arg/Arg (GC+GG)		
Axillary lymph node metastasis				
No	35	70	6.5 (2.7–15.5)[b]	21.8 (7.0–67.9)[b]
Yes	7	91		
Estrogen Receptor expression status				
Negative	14	56	0.9 (0.5–1.9)	0.6 (0.3–1.4)
Positive	28	105		
Progesterone Receptor expression status				
Negative	21	119	0.4 (0.2–0.7)[b]	0.2 (0.1–0.6)[b]
Positive	21	42		
HER2 expressions status				
Negative	28	112	0.9 (0.4–1.2)	0.3 (0.1–0.9)[b]
Positive	14	49		

[a]Multivariate logistic regression was done for adjustment of age, tumour grade and tumour staging; [b]Statistically significant at 5% or smaller label

for prognosis. The significant association of this genotype with PR-negative and HER-2-negative tumours highlight the potential clinical relevance of this SNP in predicting breast cancer diagnosis and guiding personalised treatment strategies and outcomes. Further investigations in larger and more diverse cohorts are needed to validate our findings.

Limitations

Some FFPE archival samples were excluded due to poor performance in the DNA isolation procedure or the unavailability of all required data, including clinical data and histology reports. Due to the limited funds, the researchers had to restrict the number of cases analysed; as a result, more cases from around Bangladesh could not be included. Ultimately, the DNA sequencing of the 203 specimens in this research work could be more informative.

Conclusion

This study found that *p53* codon 72 polymorphism is significantly associated with histological and immunohistochemical features of IDC. However, for further association studies with this polymorphism and confirmation of clinical implication, the following recommendations can be considered: Case-control studies involving newly diagnosed, unilateral and bilateral breast cancer patients with age-matched healthy controls could provide more reliable information. Prognostic studies of various treatment regimens could further substantiate the evidence.

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Author contributions

Conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: MZR, MJA. *Drafting the work or reviewing it critically for important intellectual content:* MZR, MJA, AB, MARR, FBW, IIS, SRAS, LK, MAF. *Final approval of the version to be published:* MZR, MJA, AB, MARR, FBW, IIS, SRAS, LK, MAF. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* MZR, MJA, MAF.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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RESEARCH ARTICLE

Performance of two colposcopic indices for predicting premalignant cervical lesions

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Abstract

Background: Colposcopy is an essential tool for diagnosing premalignant cervical lesions in women. Colposcopic scoring systems, such as the Reid's colposcopic index (RCI) and Swede score, aim to improve diagnostic accuracy and reduce interobserver variability. This study compared the diagnostic performances of these two indices in predicting high-grade cervical intraepithelial neoplasia (CIN2+).

Methods: A cross-sectional study of 300 women aged ≥18 years with abnormal cervical screening results was performed at a tertiary care centre in Dahak, Bangladesh. All patients underwent colposcopic examination using both RCI and Swede scores, followed by biopsy, irrespective of colposcopic findings. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated considering histopathology as the gold standard. The agreement between the two scores was also examined.

Results: At a cutoff of 5, RCI showed a sensitivity of 37.0% and specificity of 94.5% (PPV, 40.1%; and NPV, 93.8%). For the Swede score, a cutoff of 5 yielded a sensitivity of 74.1% and specificity of 45.0% (PPV, 11.8%; and NPV, 94.6%), whereas a cutoff of 8 reduced sensitivity (11.1%) but increased specificity (92.3%). The RCI and Swede scores had a moderate agreement (κ=0.4).

Conclusion: Although RCI offers high specificity, its low sensitivity limits its screening utility. The Swede score is a flexible tool for screening at cutoff 5 and for "see and treat" management at cutoff 8.

Key messages

The Reid's colposcopic index and Swede score are used to diagnose premalignant cervical lesions. While Reid's colposcopic index remains a valuable tool with high specificity to rule out high grade cervical lesions, Swede score offers greater flexibility. Cutoffs 5 and 8 can be used for screening and treatment of high grade cervical lesions, respectively at the time of diagnosis.

Introduction

Cervical cancer ranks as the fourth most frequently occurring cancer in women globally and stands as the second most prevalent disease affecting women in Bangladesh [1]. Cervical cancer is often preceded by a lengthy premalignant stage of cervical intraepithelial neoplasia (CIN). This characteristic allows for early detection and prevent [2]. Commonly utilized screening techniques include visual inspection of the cervix with acetic acid (VIA), Pap smear, and human papillomavirus-DNA testing. Confirmation of the diagnosis then entails a biopsy. Colposcopy serves as a valuable tool for triaging and providing guidance for biopsy procedures. Reid and Scalzi introduced the Reid's colposcopic index (RCI) as a means to reduce subjectivity in colposcopic diagnosis, and it has become the commonest scoring system [3, 4]. The RCI is determined through an assessment of the margin of the acetowhite lesion, its color, the presence of atypical vessels, and iodine staining. Studies reported RCI's high sensitivity and specificity [4].

In 2005, Strander et al. introduced a novel colposcopic scoring system known as the Swede score. This system, built upon the four parameters of the RCI, includes lesion size as an additional variable [5]. The specificity of the Swede score was 95% for the detection of CIN2+ lesions [6].

As national cervical cancer screening programmes continue to expand, selecting the most effective and practical colposcopic scoring system is essential for improving early detection and treatment. The comparative analysis of the two indices is essential because each system has unique diagnostic capability. Additionally, the Swede score, being relatively new, has not been widely validated in Bangladeshi population. This study aimed to assess of RCI and Swede score in identifying premalignant cervical lesions considering histopathology as gold standard.

Methods

This cross-sectional study was conducted at the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (currently, Bangladesh Medical University), from August 2020 to September 2021. The sample size was calculated based on an expected sensitivity of 90%, 5% absolute precision, and a 95% confidence interval, resulting in 270 subjects. A final sample size of 300 was chosen to account for possible non-response.

Adult women, exhibiting various indicators such as positive VIA results, atypical squamous cells of undetermined significance or more severe findings on Pap smear, human papillomavirus DNA positivity, cervix abnormalities, and persistent pervaginal discharge, were selected for participation in the study via purposive sampling. The exclusion criteria included women with evident growth, prior cervical procedures (such as cold coagulation, cryotherapy, or conization), pregnancy, and unsatisfactory colposcopy. Prior to inclusion, all participants provided written informed consent, emphasizing the voluntary nature of their involvement.

Two colposcopic (RCI and Swede scores) tests followed by biopsy were taken in every participant. Biopsies were obtained from abnormal areas via Tischler forceps; in cases without evident lesions, a four-quadrant biopsy was taken from the squamocolumnar junction of the cervix. Hemostasis was ensured, and the speculum was then gently removed. Biopsy samples were preserved in 10% formalin and sent to the Department of Pathology for histopathological examination. For the RCI, four features were scored from 0 to 2: acetowhiteness, margins, vascular pattern, and iodine staining. A score ≥5 indicated high-grade CIN. The Swede score evaluates the same parameters and additionally includes lesion size, each graded from 0 to 2. A score ≥5 suggests CIN2+; ≥8 was used for "see and treat".

Statistical analysis

The qualitative variables were assessed for frequency (%). The RCI cutoff value ≥5 was regarded as high grade cervical lesion (CIN 2+) similarly Swede score at a cutoff value ≥5 is regarded as high grade cervical lesion and the cutoff value ≥8 indicated for offering treatment at the time of diagnosis. The sensitivity, specificity, positive predictive value, and negative predictive value were computed to compare the two indices in predicting premalignant lesions of the cervix considering histopathology findings as the gold standard. All data were analyzed using SPSS version 25.0.

Results

The study included 300 women (aged 18 to 71 years) with a mean age of 36.6 (9.1) years. Nearly half (49.7%) were aged 30–39, and most were multiparous homemakers from low to middle-income backgrounds. Most patients (66.7%) were referred for colposcopy due to a positive VIA test, while others had persistent vaginal discharge, abnormal Pap smears, or a suspicious cervix. Histopathological diagnoses showed that 64.3% had CIN1, while 18% were diagnosed with CIN2 and CIN3 lesions (Table 1). Others had invasive cancers (9.0%), chronic cervicitis (5.6%) and metaplasia (1.7%).

Table 1 Indications for colposcopy and histopathological diagnosis (n=300)

Variables	Number (%)
Indication of colposcopy [a]	
VIA positive	200 (66.7)
Abnormal pap test	13 (4.3)
Human papilloma virus DNA positive	4 (1.3)
Suspicious looking cervix	14 (4.7)
Others [b]	69 (23.0)
Histopathological diagnosis	
Cervical intraepithelial neoplasia 1	193 (64.3)
Cervical intraepithelial neoplasia 2	26 (8.7)
Cervical intraepithelial neoplasia 3	32 (10.7)
Invasive cervical cancer	27 (9.0)
Chronic cervicitis	17 (5.6)
Squamous metaplasia	5 (1.7)

[a] All patients were referred to the Colposcopy Clinic of Bangabandhu Sheikh Mujib Medical University (currently, Bangladesh Medical University); VIA indicates visual inspection of the cervix with acetic acid; [b] (per vaginal discharge, post-coital bleeding)

Table 2 Performance of the Reid's score and Swede score for the detection of high-grade[a] cervical lesions (n=300)

Test results		Disease		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		Yes	No				
Reid's score ≥ 5	Positive	10	15	37.0	94.5	40.1	93.8
	Negative	17	258				
Swede score ≥ 5	Positive	20	150	74.1	45.0	11.8	94.6
	Negative	7	123				
Swede score ≥ 8	Positive	3	21	11.1	92.3	12.5	91.3
	Negative	24	252				

[a] High-grade indicates a score of ≥5 in both tests; PPV indicates positive predictive value; NPV, negative predictive value

The colposcopic assessment using the Reid's score identified high-grade CIN (score ≥5) in 32.3% of patients, while the Swede score (cutoff ≥8) identified high-grade lesions in 16.7% of patients. Most women had some abnormal findings under both systems.

Table 2 presents the diagnostic performance of Reid's and Swede scores compared to histopathology. For a Reid's score ≥5, sensitivity was 37.0%, and specificity was 94.5%. Swede score ≥5 demonstrated higher sensitivity (74.1%) but lower specificity (45.0%). At a higher cutoff (Swede score ≥8), specificity improved markedly to 92.3%, but sensitivity decreased to 11.1%. NPV were persistently high (>91.0%) in all instances.

Analysis of lesion size in relation to histopathology showed a significant trend. Lesions larger than 15 mm were more frequently associated with CIN2+ outcomes (Table 3). This supports the inclusion of lesion size in the Swede scoring system.

The agreement between the Reid's Colposcopic Index and the Swede score was moderate (κ=0.4), indicating some diagnostic overlap, they remain complementary tools rather than interchangeable scoring systems.

Table 3 Performance of the Reid score and Swede score according to the size of the cervical lesions on histopathology (n=300)

Lesion-size	Histopathology report						Total
	CIN1	CIN2	CIN3	ICC	CC	SM	
0–5 mm	73	0	0	0	5	5	83
6–15 mm	119	18	1	4	0	0	142
>15 mm	1	8	31	23	12	0	75
Total	193	26	32	27	17	5	300

CIN indicates cervical intraepithelial neoplasia; ICC, invasive cervical cancer; CC, chronic cervicitis; SM, squamous metaplasia

Discussion

Colposcopy remains an essential tool for evaluating cervical premalignant lesions, particularly in low- and middle-income countries, where cytology and HPV testing may have limited availability. The development of colposcopic indices, such as the Reid's Colposcopic Index (RCI) and Swede score, aims to improve diagnostic objectivity and provide practical guidance for screening and treatment decisions. This study compared the performance of these two indices in predicting high-grade cervical intraepithelial neoplasia (CIN2+) considering histopathology as gold standard. Significant differences were found in their diagnostic profiles.

The four shared features allow for a valid head to head comparison of sensitivity, specificity, predictive value and clinical utility. However, it is acknowledged that the Swede score includes an additional parameter -lesion size-which is a critical predictor of high-grade disease. This makes the Swede score more comprehensive and objective. Moreover, its flexible use of dual thresholds (≥5 for screening and ≥8 for treatment) offers practical advantages, especially in resource-limited settings employing single-visit strategies. Therefore, while the scores are not interchangeable, their comparability remains appropriate for evaluating diagnostic accuracy, as was done in this study.

Our findings of high specificity but low sensitivity at a cutoff value of 5 are consistent with previous studies by Durdi *et al.* and Mousavi *et al.*, which reported that RCI is effective in ruling out high-grade lesions but may miss a significant proportion of CIN2+ cases [7, 8]. The high specificity of the RCI makes it suitable for confirming high-grade lesions, thereby minimizing overtreatment in "see and treat" programmes. However, its low sensitivity limits its effectiveness as a primary screening tool for this disease. Kushwah *et al.* and Hong *et al.* also observed similar trends, emphasizing the risk of underdiagnosis when relying solely on RCI in high-prevalence settings [9, 10].

In contrast, our findings of higher sensitivity but lower specificity of Swede score at a cutoff of 5 aligns with the findings of Strander *et al.* and Nessa *et al.*, who showed that the Swede score is a better screening tool because of its ability to detect more CIN2+ lesions, reducing the likelihood of missed diagnoses [5, 11]. However, its lower specificity may increase the risk of overtreatment, particularly in resource-limited settings, where follow-up can be challenging. Ranga *et al.* similarly concluded that while the Swede score improves sensitivity, it must be applied judiciously to avoid unnecessary interventions [12].

When the Swede score cutoff was increased to 8, specificity improved markedly (92.3%) with an associated reduction in sensitivity (11.1%), indicating its value in "see and treat" scenarios. This dual cutoff approach has also been supported by Suwanthananon *et al.*, who recommended using cutoffs of 5 and 8 for screening and treatment, respectively, to balance sensitivity and specificity [13]. Such flexibility offers practical advantages in diverse clinical contexts, particularly in settings where access to repeated follow-up visits is limited.

An important finding of this study was the significant association between lesion size and the likelihood of CIN2+ disease, which supports the inclusion of lesion size in the Swede score. Kierkegaard *et al.* previously demonstrated that larger lesions were more likely to be associated with high-grade histopathology, and our results are in agreement with this evidence [14]. By incorporating lesion size, the Swede score reduces interobserver variability and enhances diagnostic reproducibility. Similar findings by Ranga *et al.* suggest that while these two indices share common diagnostic features, they are not interchangeable in clinical practice [12]. Instead, they complement as indicated by a moderate agreement. The RCI may serve as a confirmatory tool owing to its high specificity, whereas the Swede score can be prioritized for initial screening.

From a public health perspective, the choice of scoring system depends on the balance between sensitivity, specificity, and feasibility. The adaptability of the Swede score is particularly valuable in high-burden, low-resource settings. Using a cutoff of 5 for initial screening can maximize detection, while employing a cutoff of 8 for treatment minimizes overtreatment. This dual strategy aligns with the recommendations of Nessa *et al.* and Suwanthananon *et al.*, providing a cost-effective and practical approach for cervical cancer prevention [11,13].

The current this study supports the complementary use of these two indices. Although the RCI remains reliable for confirming high-grade disease, the Swede score offers superior versatility for screening and treatment decisions. The implementation of these indices in combination, tailored to local resource availability, may enhance diagnostic precision and improve cervical cancer prevention outcomes. It is important to note the lack of generalizability of our findings because exclusively referred cases were included in this study at Colposcopy Clinic of a tertiary care hospital.

Conclusion

The Swede score, with its dual cutoff approach, provides greater flexibility than the Reid's Colposcopic Index for both screening and immediate treatment strategies. While RCI remains valuable for its high specificity, the Swede score offers superior adaptability in resource-limited settings.

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Author contributions

Concept or design of the work; or the acquisition, analysis, or interpretation of data for the work: JF, SR, NC, A, MSTJF, MMH. *Drafting the work or reviewing it critically for important intellectual content:* JF, SR, NC, A, MSTJF, MMH, KN, NA. *Final approval of the version to be published:* JF, SR, NC, A, MSTJF, MMH, KN, NA. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* MMH.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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RESEARCH ARTICLE

Effectiveness of the flipped classroom versus the traditional teaching method in enhancing learning among undergraduate medical students

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Abstract

Background: The flipped classroom is a form of interactive teaching strategy in which traditional learning is reversed by delivering core content outside the classroom and moving activities into the classroom. This study aimed to determine the effectiveness and medical students' perception of flipped classroom.

Methods: This quasi-experimental study included 100 first-year medical students who were divided into four groups (A, B, C, D), with 25 students in each group. Groups A and C received didactic lectures, while groups B and D participated in flipped classroom. Thereafter, there was a crossover for ethical purposes. All students took multiple-choice pre-tests and post-tests, and there was also a retention test two weeks after the flipped classroom sessions. Students were further divided based on their pre-test scores into two categories: the <50% and the ≥50% category. Wilcoxon and Mann-Whitney tests were used to analyse the data for statistical significance. Student perceptions were collected by Google questionnaire.

Results: The result showed a significant improvement in the post-test marks for both the teaching learning methods. However, the flipped classroom groups outperformed the didactic groups, with mean post-test scores of 82.2 (10.8) and 84.2 (10.3) for the <50% and ≥50% groups, respectively, compared to 63.2 (9.4) and 72.4 (14.9) for the traditional groups, with a P <0.001. Knowledge retention was also notably better in the flipped classroom groups. The students' feedback supported flipped classroom method.

Conclusion: The flipped classroom boosts students' performance and encourages active participation and higher order thinking in them. It can be adopted to make the MBBS students self-directed and lifelong learners.

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Key messages

The competency-based medical education for undergraduate medical students emphasises on interactive teaching learning methods like the flipped classroom. In our study, the flipped classroom strategy improved learning outcomes in undergraduate medical students, especially among those with poor baseline academic performance. This interactive, student-centred method excelled at stimulating knowledge retention, active participation, and engagement over traditional lectures.

Introduction

The introduction of the competency-based medical education (CBME) curriculum by the National Medical Council of India (NMC) has marked a paradigm shift to more interactive classes from the traditional didactic lecture class. The students participate actively in interactive classes, and higher-order thinking is encouraged [1]. Now, medical colleges all over our country are trying to bring modifications to the ongoing educational programs and various teaching-learning methods to inculcate the essence of self-directed learning to make them become lifelong learners. It will also help them to develop confidence to take "responsibility for their learning" [2]. One of the recent techniques adopted for interactive classes is the flipped classroom model (FCR) of teaching. The FCR potentially support student learning, so it is gaining momentum in medical education [3].

The FCR method is significantly adopted in the healthcare educational system to motivate and facilitate student participation in teaching and learning. In this method, students read the learning materials outside the class, giving more time for interactive activities in the class. This current medical education system aims to enable students to turn theory into practice [4]. In the previous traditional method of didactic lectures, the subject expert delivers the lecture to a large group of students. It consumed a lot of time, and the role of students in a lecture class was usually passive in the form of listening, understanding the concepts or taking notes, and having little opportunity to interact during the lecture hour [5]. The traditional didactic lectures helped to impart information to large groups of students. Still, they failed to develop the knowledge and problem-solving skills required in clinical practice in the students. "Flipped learning or the 'flipped classroom' is a strategy that reverses traditional learning by delivering core content outside of the classroom (often online), and moves activities more traditionally thought of as 'homework' into the classroom" [6].

The FCR is a type of "blended learning" where the students learn the "core" content of a topic before the lecture class either from the available resources, such as online resources or already circulated handout materials, books, class notes, etc. The main advantage of the FCR is that the students can learn in their environment and at their own pace, and it can be customised as per the difficulty level of the topic. It results in better and more effective time management of a class. This new teaching-learning method, the FCR method, was introduced to utilise the time available for teaching-learning fruitfully and help in the active participation of medical students to meet their learning needs [7]. Because the flipped classroom is a new education model in Indian medical education, so strong comparative studies are still required to determine its effectiveness compared with conventional teaching methods. With the CBME model, in particular, little data are available quantifying how this pedagogic change affects students' learning outcomes, satisfaction, and the acquisition of skills. In addition, an understanding of students' attitudes to this pedagogy is also necessary in order to quantify its acceptability and identify potential limitations to its broader implementation. So, this study aimed to determine the effectiveness of the FCR method compared to the traditional classroom method and to study students' perceptions of the newly introduced teaching-learning method.

Methods

This Study participants

This quasi-experimental study was conducted in the Department of Physiology, IMS and SUM Hospital, Bhubaneswar, India between January and June 2022. First-year medical students of the 2021-22 batch participated in the study. Students who were absent during the study period were excluded from the study. The study was undertaken after receiving the Institutional Ethical Committee clearance and obtaining informed consent from all the participants.

The calculated sample size from a batch of 150 medical students was about 109 at a 95% confidence level and 5% margin of error using the finite population correction formula (n=N/1+N.e2 where N=150 and e=0.05. Even though the calculated sample size was 109, 100 students (66.7% of the population) were included in the study based on logistical considerations. This was felt to be sufficient to ensure statistical power for quantitative analysis.

Study design

The participants were divided into four smaller groups (A, B, C, D) with 25 students each based on their roll numbers by convenient sampling. The entire FCR session was meticulously planned before implementation. The teachers were trained in FCR teaching. The process involved sensitising the students and faculty members about this new teaching-learning method, selecting pre-reading study materials, and forming a WhatsApp group of the faculties and students to share the pre-reading materials and collect feedback. Two topics in Endocrine Physiology with clinical application, actions of insulin and glucocorticoid, were selected. First, groups A and C attended the didactic lecture on actions of insulin, and groups B and D were assigned a flipped class on the same topic. Then, the two groups were swapped, and a crossover was done for ethical purposes. Groups A and C attended flipped class on actions of glucocorticoid, and groups B and D attended didactic lectures on same topic **(Figure 1)**. In the flipped class, students had come prepared with the topic from the resource materials, like pre-recorded lectures and videos provided to them a day before the class. The students were allowed to discuss their difficulties and doubts in the one-hour flipped class for about 15 minutes. Then, they were allotted four cases from the topic to discuss in groups. Each group presented the case allotted to them and discussed it with the other groups for about 10 minutes. The teacher's role was to facilitate and guide the students wherever required. The teacher summarised the topic at the end of the class.

Data was gathered through a mix of objective assessments and structured feedback. For each teaching session-Didactic and Flipped Classroom

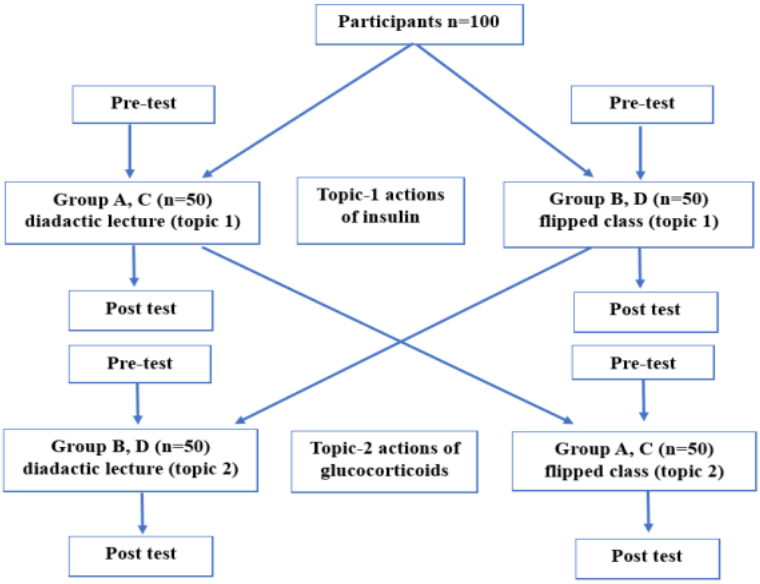

Figure 1 Distribution of students into traditional lecture class and flipped class groups

(FCR)-students took a multiple-choice question (MCQ) test of 10 marks. These test items were crafted to evaluate both their knowledge and problem-solving skills. Separate question papers were created for the pre-test and post-test, ensuring they were of similar difficulty. The MCQs were based on standard Physiology textbooks, and to ensure content validity, four subject experts and four faculty members from the Medical Education Unit (MEU) reviewed them. All students participated in both the pre-test and post-test evaluations that matched their instructional method. Moreover, a retention test (also 10 marks) using MCQs was conducted two weeks after the FCR sessions to evaluate the knowledge retention across both teaching methods. To gauge perceptions, student feedback on the FCR method was collected through a pre-validated structured questionnaire. This questionnaire included questions covering various aspects of the flipped classroom experience, as well as students' preferences for teaching and learning methods. The feedback form was developed based on a literature review, and its validity was confirmed by the same panel of subject experts and MEU members. The questionnaire was distributed digitally via google form.

Students were divided into two categories based on their pre-test marks: the <50% category and the ≥50% category. All marks were expressed in percentage. Analysis of their pre-test and post-test marks was done by applying appropriate statistics.

Table 1 Comparison of pre-test and post-test marks of didactic and flipped class groups (n=100)

Groups based on pre -test marks	Pretest marks (%)	Posttest Marks (%)	Difference in pre and post-test marks (mean improvement)	*P*
Didactic lecture classes				
<50%	36.6 (4.8)	63.2 (9.4)	26.6	<0.001
≥50%	52.8 (4.5)	72.4 (14.9)	19.6	<0.001
Flipped classes				
<50%	36.9 (4.7)	82.2 (10.8)	45.4	<0.001
≥50%	52.8 (4.6)	84.2 (10.3)	31.4	<0.001

Data presented as mean (standard deviation)

Statistical analysis

Statistical analysis was done using the SPSS software, version 18.0. Results were expressed in frequencies and percentages. The Wilcoxon signed-rank test was used to find the statistical significance between the pre-test and post-test marks in both categories. The post-test marks of both the T-L methods were compared by the Mann-Whitney U test between the categories. A p-value less than 0.05 was considered to be statistically significant.

Results

Out of 100 selected students, 62 were females and 38 were males. The mean post-test marks of both the T-L methods was significantly higher than the pre-test marks in the <50% marks and ≥50% category with a *P* <0.001 (Table 1). However, the post-test marks of flipped class [82.2 (10.8) and 84.2 (0.3)] were significantly higher than the didactic class marks [(63.2 (9.4) and 72.4 (14.9)] in the <50% and ≥50% category, respectively, with a *P* <0.001 (Table 2).

Analysis of students' perceptions indicated that they experienced improved recall, understanding, analytical skills, and knowledge application with the flipped method compared to the traditional didactic approach (Figure 2). 78% of students preferred a flipped class over a didactic lecture class. The students of FCR achieved higher marks than didactic class in the knowledge retention test in both the categories (Figure 3).

Discussion

This generation's medical students are losing interest in the didactic form of lectures [8], which is evident from their poor attendance and poor performance [9-12]. Students are lacking proper training in problem-solving and critical-thinking skills [13]. They are also not very much aware of self-directed learning. However, the students show interest in interactive learning [14]. The FCR fosters a student-centric approach, which helps students to develop lifelong learning skills [15]. Interactive learning like FCR gives a chance for individualised education. The students read the study materials conveniently and use face time more efficiently. The increasing role of FCR in enhancing the students' involvement and encouraging them to take responsibility for their learning has been broadly accepted by medical teachers [3]. As per Bloom's Revised Taxonomy, the classroom is for lecture classes, which helps in the acquisition of knowledge and comprehension of facts, whereas FCR helps in long-term learning of the topics as it focuses on the identification of the learning needs of the students and involves 'application, analysis, and evaluation' of the knowledge. It consists of the principle of 'learning by doing' [16, 17].

Our study reveals that the post-test marks of both the traditional class and flipped class were more than the pre-test marks and the post-test result in the Flip classroom method was significantly higher than that of the traditional classroom method, indicating an improvement in the teaching-learning outcome with the Flip classroom method compared to the traditional method. The improvement was more marked in the low achiever group (<50% group), indicating the

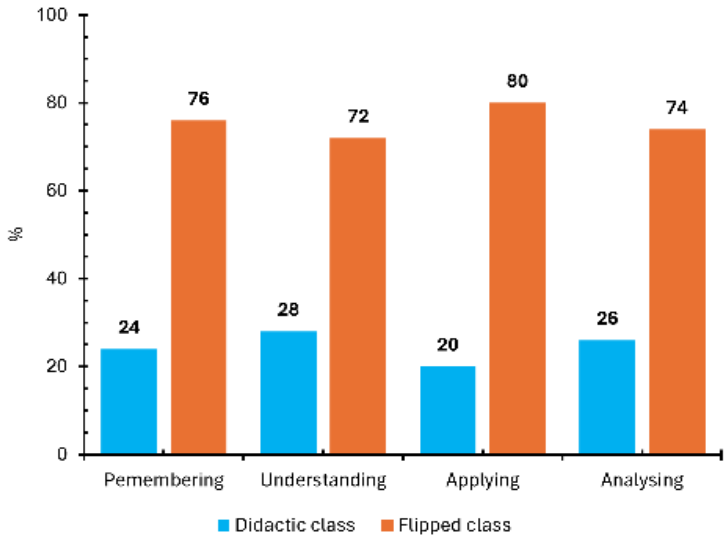

Figure 2 Cognitive domain of students based on various aspects of Bloom's Taxonomy according to didactic and flipped classes (n=100)

effectiveness of implementing FCR in the medical curriculum. In our study, the students whose score was less than 50% on the pre-test showed a significant increase in their post-test marks, indicating the effectiveness of the flipped class. Students could remember better, and there was better understanding, application, and analysis power in the flipped class than in traditional lecture methods. Our study also reveals that students preferred a flipped class over a traditional didactic lecture because students liked to learn at their own pace and an interactive lecture in the classroom, which was possible in a flipped classroom. Other studies that compared the flipped and traditional classroom methods showed that the flip class helps improve student learning process outcomes [18,19, 20]. A study by Viveka *et al.* [18] revealed that the passing percentage of students after intervention in the flipped classrooms was significantly more than that of students taught by the traditional method; they also found that students' perception was more in favour of the flipped classroom. Tune *et al.* [19] the study showed by adopting the flipped classroom model, there was an improvement in the performance of students in physiology. In their study, Christopher and Pound [20] said that students expressed massive satisfaction with introducing the Flipped class early in undergraduate medical education, which was preferred over lecture-based instruction. Whillier and Lystad's [21] study concluded that there was no significant difference in grades and satisfaction levels in a Flipped classroom of Neuroanatomy.

Table 2 Comparison of post-test marks of didactic lecture class and flipped class (n=100)

Group	Didactic posttest marks (%)	Flipped posttest marks (%)	Difference in marks (mean improvement)	*P*
<50%	63.2 (9.4)	82.2 (10.8)	19.0	<0.001
≥50%	72.4 (14.9)	84.2 (10.3)	11.8	<0.001

Data presented as mean (standard deviation)

The analysis of 82 papers by systemic review indicated that flipped class learning was a more favourable approach to motivating and engaging the students. However, there is little evidence about its effectiveness in retaining knowledge. In our study, we found FCR to be an interactive pedagogical tool that needs to be introduced early in medical education as it (i) helps the students to learn the subject assigned at their own pace, (ii) meaningfully use technology in learning the subject, (iii) helps in motivating students for self-directed learning, and (iv) enrich students with in-depth knowledge on the topic and facilitates conceptual learning. Memory retention was better for students of the flip class group than those who attended a didactic lecture in both groups. A meta-analysis of 46 papers with more than 9,000 participants revealed higher academic performance with flipped learning compared to a lecture-based approach [22]. Applying innovative methods like FCR in the teaching method can be rewarding. This type of student-centred approach enhances the lifelong learning ability of students. FCR promotes active learning by doing things and thinking about what they are doing. Based on Kolb's four learning styles, it was found that flipped sessions were more effective than the traditional method. In our study, students found FCR beneficial because it was student-friendly [23]. They reported that they could understand the basic concepts and that it was more active and provided an opportunity for one-on-one interaction within the group. Previous researchers have reported receiving a positive response to the FCR method from students and teachers' feedback. Zhao and Ho's analysis of students' feedback favoured FCR, although they did not find any improvement in students' academic performance following FCR in their studies. Studies have also concluded that students found FCR more beneficial because it engages them and facilitates interaction between students [24]. In our study, students showed that FCR improved their learning of the topic and their confidence to answer in the final exam. They also recommended teaching more topics using this method. In the studies of Veeramani *et al.* and Memon *et al.*, students' response to the FCR was hugely positive because the FCR approach met the learning objectives compared to didactic teaching [25, 26]. Buchner, in his article, pointed out that students were satisfied with this method as they got immediate feedback on their performance [27]. Szparagowski, in his project on flipped classrooms, mentioned some notes by students [28]. In this, students mentioned the benefits of FCR: it is less time-consuming than normal homework, and they can study from the videos at their convenience.

They mentioned that FCR is a beneficial method because they can access multiple links and get help, and it introduces the topic before learning in class. In our study, students liked FCR because of their interactive nature and application-based discussion. They also found reading from recorded lectures and videos more convenient at home. Our findings are similar to a study by Nouri, who stated low achievers significantly reported more positively than high achievers and their perceived increased learning [29].

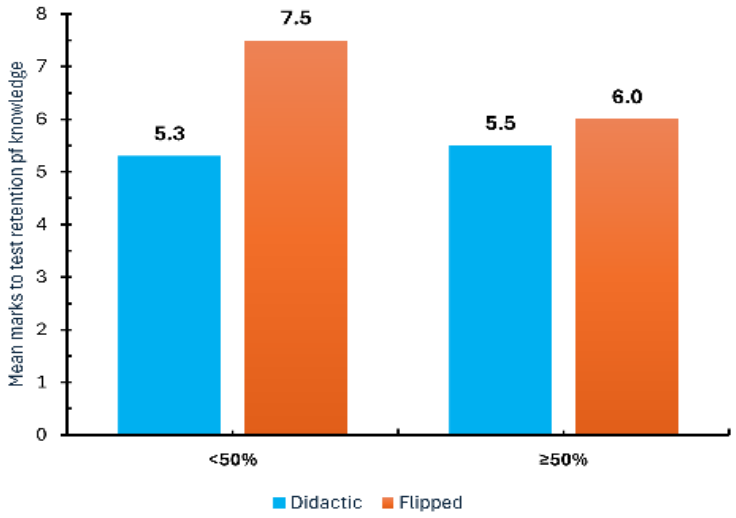

Figure 3 Retention of knowledge in didactic and flipped class group (n=100)

The significant challenges in implementing FCR are that, as almost all of us are acquainted with didactic lectures, a lot of preparation is needed both on the part of the students and teachers for its implementation. Increased workload and time constraints are other challenges. Students (i) have to be aware of self-directed learning; (ii) have to be ready for the class from the pre-reading material; (iii) have to know how to use smartphones and to access the internet; and (iv) need to be prepared with the assignments. Teachers (i) have to sort and list important pre-reading material, (ii) come prepared with lecture materials to the class in the form of MCQs, and (iii) provide the assignment materials like flowcharts, diagrams, etc. The strength of our study is that it employs a crossover design whereby each participant is exposed to both the conventional lectures and the flipped classroom approach. This not only amplifies the learning process but also ensures ethical integrity in providing equity of exposure to the learning strategies. We have divided the students into two groups, the <50% group and the ≥50% group, which helped us to identify the low achievers and to find out whether the new T-L method was useful for them or not. The major limitation of our study was the time constraint, under which we could do FCR only on a few topics with students of one batch and faculty members of the first phase only. A multicentric study involving multiple medical colleges and including a larger number of students and faculty members will help find out the actual effectiveness of the FCR.

Conclusion

Our study revealed that there is a marked improvement with FCR. The knowledge-retaining capacity was also better with students taught by the FCR method. It stands out as a promising strategy for cultivating self-directed, lifelong learners in the field of medical education. We recommend that FCR should be implemented in undergraduate medical teaching as it is an established teaching-learning tool that helps students gain a better understanding of the subjects compared to traditional Didactic lectures.

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Author contributions

Conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: DM, AM, TM, AM, PKS. *Drafting the work or reviewing it critically for important intellectual content:* DM, AM, TM, AM, PKS. *Final approval of the version to be published:* DM, AM, TM, AM, PKS. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* DM, AM, TM, AM, PKS.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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RESEARCH ARTICLE

Association of climate variability with hepatitis A and E infections in Dhaka (2016–2023)

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Abstract

Background: Acute viral hepatitis, predominantly caused by hepatitis A virus (HAV) and hepatitis E virus (HEV), remains a major global public health issue, especially in low- and middle-income countries. This study was conducted to determine the prevalence of acute hepatitis A and E infections in Dhaka city and to examine the influence of weather conditions on their transmission.

Methods: This retrospective study, based on laboratory data, was conducted at the Department of Virology, Bangladesh Medical University from 2016 to 2023. It analysed the test results for anti-HAV-IgM and anti-HEV-IgM antibodies from blood specimens of suspected acute hepatitis cases. The patients' details and laboratory results were retrieved using the Laboratory Information System, and climatic variables (temperature, humidity, and rainfall) were obtained from the Bangladesh Meteorological Department.

Results: In this study, test reports from 19,542 individuals for HAV and 23,249 individuals for HEV were analysed. HAV was detected in 29.5% of the population, and HEV was found in 20.6%. Males were predominantly seropositive for both HAV (65.1%) and HEV (76%). HAV was most common in those aged ≤10 and 11–20 years (37.9%), whereas HEV was most common in the 21–30 years group (40.6%). Higher HAV transmission was observed during autumn and late autumn, while HEV was more prevalent in summer and the rainy season.

Conclusion: Acute HAV and HEV infections are common in Dhaka city, and climatic factors affect their spread. Understanding these patterns can improve public health readiness and raise awareness of social health hygiene.

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Key messages

Acute viral hepatitis caused by hepatitis A and E viruses is heavily influenced by demographic factors. Age and gender play a crucial role in susceptibility to these infections. Climatic factors, including temperature, humidity, and rainfall, also affect disease transmission. Recognising these factors can support targeted public health measures.

Introduction

Acute viral hepatitis (AVH) is a pressing global public health issue due to its significant contribution to morbidity and mortality worldwide [1]. This is more apparent in low- and middle-income countries where the availability of proper sanitation infrastructure, access to clean water and safe hygiene practices are lacking [2]. Several hepatotropic viruses—including hepatitis A, B, C, D, and E—can cause acute viral hepatitis (AVH), but hepatitis A virus (HAV) and hepatitis E virus (HEV) are the most common enterically transmitted types. Both are primarily spread via the faecal-oral route, typically through contaminated food or water. Clinical symptoms include fever, nausea, vomiting, loss of appetite, abdominal pain, and jaundice, with severity ranging from asymptomatic to fulminant hepatic failure. An estimated 1.4 million new cases of HAV and approximately 20 million new cases of HEV are reported globally each year [3]. Addressing this morbidity and mortality burden remains a major public health challenge, especially in resource-constrained endemic settings.

Bangladesh, endemic for viral hepatitis and the transmission of HAV and HEV is influenced by socio-demographic and environmental conditions [4, 5]. The environment supports the persistence and transmission of enteric viruses due to poor sanitation, limited access to clean water, unhygienic practices, and widespread consumption of unsafe street food [6]. Moreover, distinct climatic variability due to the nature of Bangladesh's tropical climate–characterised by high humidity, heavy precipitation and temperature variation – is linked to changes in transmission dynamics [7, 8, 9]. Unplanned urbanisation, overcrowding further contribute to the sustained transmission of HAV and HEV [10].

A nationwide surveillance reporting hepatitis A in approximately 19% of cases and hepatitis E in about 10% [11] and several existing research on acute HAV and HEV-related viral hepatitis from the country has primarily focused on clinical and demographic risk factors, often overlooking the precise influence that meteorological variables, particularly within the local context [12]. This knowledge gap is especially critical given Bangladesh's climate vulnerability from the effects of climate change in the coming years [13]. Despite the established endemicity of HAV and HEV, there remains a gap in understanding how their prevalence correlates with demographic and climatic variability in Dhaka city. The city's dense population and rapid urbanisation have created major public health challenges, including poor sanitation, unsafe street food practices, inadequate drainage, and air pollution—conditions that facilitate frequent disease outbreaks [10]. Addressing such issues are paramount for developing effective disease forecasting, outbreak preparedness and evidence-based public health interventions within the epidemiological landscape of the city. Therefore, this study aimed to explore the seroprevalence of acute HAV and HEV infections in Dhaka city, with the intention of gaining a better understanding of how weather conditions influence the transmission of hepatitis A and E in a crowded city with numerous health risks.

Methods

Study design and place

This was a laboratory-based retrospective observational study carried out at the Department of Virology, Bangladesh Medical University, Dhaka, using data from 2016 to 2023.

Study population

The study population comprised individuals with clinical suspicion of acute hepatitis from both outpatient and inpatient departments of the university hospital, whose blood samples were submitted for laboratory testing. The analysis was conducted using test results obtained from these blood specimens. A total of 19,542 and 23,249 specimens were tested for anti-HAV-IgM and anti-HEV -IgM, respectively, during the study period and the resulting serological data were utilised. The demographic profiles (age and gender) of the study populations were retrieved from the Laboratory Information System (LIS), and other details were kept anonymised to ensure patients' confidentiality.

Climatic data collection

The climate data of Dhaka city from January 2016 to December 2023 (average monthly temperature in °C, average monthly humidity %, and total monthly rainfall in mm) were collected from the climate and weather data portal of Bangladesh Meteorological Department (BMD), Agargaon, Dhaka 1207, Bangladesh and matched temporally to the laboratory testing results. For the seasonal analysis, they were classified into the following periods: Spring runs from mid-February to mid-April, summer from mid-April to mid-June, the rainy season from mid-June to mid-August, autumn from mid-August to mid-October, late autumn from mid-October to mid-December, and winter from mid-December to mid-February [14].

Statistical analysis

The collected data were rechecked, coded, and analysed using SPSS (version 21). Descriptive statistics were used to summarise demographic data, and age groups were categorised into ≤10 years, 11–20 years, 21–30 years, 31–40 years, 41–50 years and >50 years. A multivariable logistic regression model was constructed to identify predictors of HAV and HEV infections. The model included: demographic variables (age, gender), environmental variables (temperature, humidity, rainfall), and temporal variables (month and season). Significance was set at $P<0.05$. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate each variable's effect on the odds of infection.

Ethical considerations

All patient data were anonymised before analysis, and no personal identifiers were used during the interpretation of results.

Results

Between 2016 and 2023, a total of 19,542 and 23,249 suspected AVH patients were tested for anti-HAV-IgM and anti-HEV-IgM, respectively. Among these, 5,767

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Table 1 Patients' demographics and hepatitis A and E virus infection

Characteristics	Total samples (n)	Negative n (%)[a]	HAV infection n (%)[b]	HEV infection n (%)[b]	HAV and HEV infection n (%)[b]
	42791	32244 (75.3)	5767 (29.6)	4780 (20.5)	85 (0.6)
Gender[c]					
Male	29756	22369 (69.4)	3755 (65.1)	3632 (76.0)	62 (72.9)
Female	13035	9875 (30.6)	2012 (34.9)	1148 (24.0)	23 (27.1)
Age group in years[c]					
≤10	7198	4675 (14.5)	2183 (37.9)	340 (7.1)	10 (11.8)
11–20	10477	7046 (21.9)	2186 (37.9)	1245 (26.0)	41 (48.2)
21–30	10828	7990 (24.8)	898 (15.6)	1940 (40.6)	27 (31.8)
31–40	5539	4596 (14.3)	230 (4.0)	713 (14.9)	5 (5.9)
41–50	3786	3368 (10.4)	115 (2.0)	303 (6.3)	2 (2.4)
>50	4963	4569 (14.2)	155 (2.7)	239 (5.0)	0 (0)

[a]n= number of participants, % in bracket; [b]Total samples tested for HAV infection=19452, HEV infection=23249 and both HAV and HEV infection = 13997; [c]Percentages for the HAV, HEV and both (HAV and HEV) infection were calculated from the total tested samples, respectively. The percentages within the group in the gender and age categories were calculated.

(29.6%) tested positive for anti-HAV-IgM, and 4,780 (20.5%) for anti-HEV-IgM. A breakdown by gender showed that males accounted for the majority of positive cases in both infections. The prevalence of dual HAV and HEV infection was 85 (0.6%), with a male predominance of 72.9%. Age categorisation by each decade of life showed that anti-HAV-IgM was most frequently detected among younger individuals. In contrast, anti-HEV-IgM was predominantly observed among young adults, with the highest proportion (40.6%) occurring in the 21–30 age group. For dual infections, those aged 11 to 30 years were the most affected group (Table 1).

This study investigates the month-wise (Figure 1) and season-wise (Figure 2) infection patterns of HAV and HEV in relation to meteorological variables—temperature (°C), humidity (%), and rainfall (mm). Monthly analysis reveals that fluctuations in humidity coincide with both HAV and HEV (Supplementary Figure 1) cases, with HEV showing a stronger association. Both infections exhibit a proportional rise and fall throughout the year, with rainfall emerging as a key environmental driver. In July, the peak month, HAV and HEV cases reached 10% and 11%, respectively, alongside a rainfall level of 345 mm. HAV transmission was most prominent during the warmer months with moderate rainfall, particularly from July to November, while HEV transmission peaked during months characterised by high humidity and precipitation, spanning March through September. Seasonal climatic analysis further affirmed these trends (Supplementary Figure 2). HAV infections were most prevalent in autumn (19%) and late autumn (20%), despite declining temperature (27.8°C), humidity (69.8%), and rainfall (62.3 mm). In contrast, HEV infections peaked during the summer (18%) and rainy season (19%), aligning with elevated humidity levels (75.6–78.7%) and high rainfall (287–289 mm).

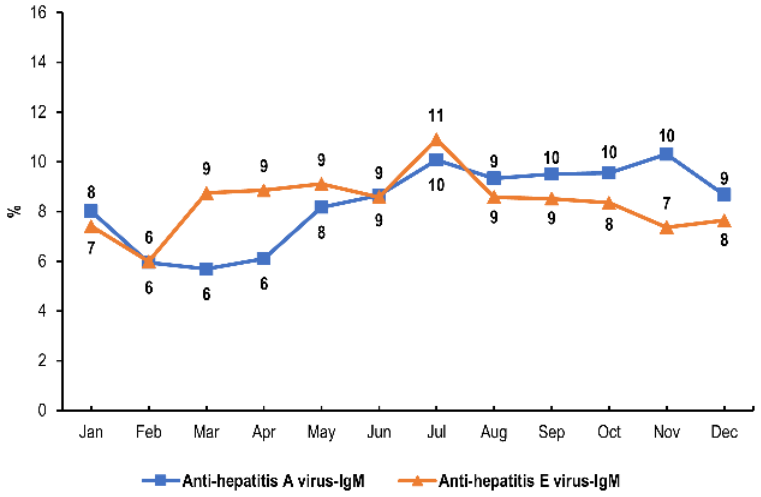

Figure 1 Monthly distribution of anti-hepatitis A virus-IgM and anti-hepatitis E virus-IgM positive among all the tested samples

A multivariable logistic regression model using continuous predictors identified several significant associations (Table 2). Demographic and temporal factors were identified as significant predictors of infection. Compared to males, females had slightly higher odds of HAV infection (OR 1.1; 95% CI 1.1–1.2) but were significantly less likely to test positive for HEV (OR 0.8; 95% CI 0.8–0.9). When age groups were compared against the reference category of ≤10 years, the odds of HAV infection declined with increasing age. However, HEV showed the opposite trend, with the 21–30 age group demonstrating the highest risk (OR 2.5; 95% CI 2.0–3.1). Temporal trends were also evident. Compared to January, the odds of HEV infection increased sharply between April and September, with the highest risks recorded in June (OR 15.5; 95% CI 11.6–20.7). HAV did not exhibit such pronounced monthly fluctuations, although the odds were lowest from February to May ($P<0.05$) compared to other months. In terms of seasons, late autumn was associated with significantly lower odds of HEV infection (OR 0.8; 95% CI 0.7–0.9), while no seasonal variation reached statistical significance for HAV.

Discussion

AVH, especially those caused by HAV and HEV represent a substantial global public health concern that disproportionately impacts low- and middle-income countries. In Bangladesh, the persistence of these viral infections is exacerbated by poor sanitation, unsafe water and unhygienic food practices, particularly due to the presence of unregulated street vendors and emerging climate variability. Bangladesh is one of the countries that will be most severely impacted by climate change. It is believed that climate factors may influence disease transmission dynamics– an area we aimed to investigate in this study for HAV and HEV. This study is the first of this kind from Bangladesh in observing the integration of laboratory-confirmed sero-prevalence data with temporal meteorological parameters like temperature, humidity and rainfall on an extensive dataset aimed to illuminate the interplay between environmental conditions and disease dynamics in an endemic setting from a dense population residing in a city.

Our findings regarding age and gender patterns in AVH cases align with previous reports. Consistent with earlier studies, we observed that HAV infections predominantly affected children and adolescents, whereas HEV infections were more common among young adults [2, 11]. A male predominance was noted for both viruses, although it was more pronounced for HEV. Previous studies have reported that males

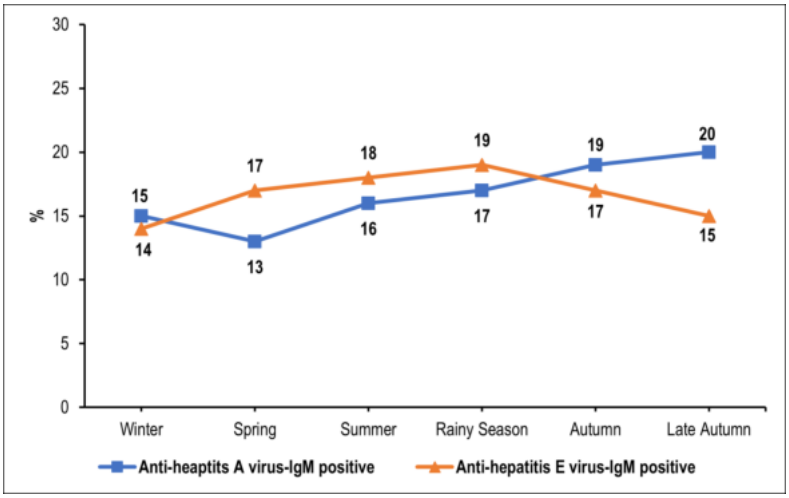

Figure 2 Seasonal distribution of anti-hepatitis A virus-IgM and anti-hepatitis E virus-IgM positive among all the tested samples

comprise approximately >60% of HAV cases and >70% of HEV cases [15, 16], findings that closely parallel our results. Additionally, prominent age- and gender-specific susceptibilities were observed, children and adolescents (≤20 years) were predominantly affected by HAV, while HEV was more common in young adults (21–30 years). Notably, males contributed to the majority of the positive cases for both viruses, possibly reflecting gender-based differences in exposure risks, such as outdoor occupations or dietary practices, due to their engagement in job-related activities [17]. Similar gender-age patterns were also observed in dually infected cases. Still, earlier studies have mentioned that it may have an impact on the prognosis of fulminant failure in some cases [18].

Table 2 Odds ratios of factors linked to hepatitis A virus and hepatitis E virus infection in relation to patients' demographics, month and seasonal weather data (n=42791)

Characteristics	Odds ratio (95% confidence interval)	
	HAV infection[a]	HEV infection[a]
Gender		
Male	1	1
Female	1.1 (1.1–1.2)[a]	0.8 (0.8–1.0)[a]
Age group in years		
≤10	1	1
10–20	1.0 (0.9–1.1)	2.0 (1.8–2.4)[a]
21–30	0.5 (0.4–0.6)[a]	2.5 (2.0–3.1)[a]
31–40	0.4 (0.3–0.5)[a]	1.6 (1.2–2.1)[a]
41–50	0.4 (0.2–0.6)[a]	0.8 (0.6–1.3)
>50	0.7 (0.4–1.7)	0.4 (0.3–0.8)[a]
Month		
January	1	1
February	0.6 (0.5–0.7)[a]	2.8 (2.2–3.5)[a]
March	0.4 (0.3–0.5)[a]	8.3 (6.4–10.8)[a]
April	0.6 (0.5–0.8[a]	13.1 (10.1 –17.0)[a]
May	0.8 (0.6–1.0)[a]	13.7 (10.4–18.0)[a]
June	1.0 (0.8–1.3)	15.5 (11.6–20.7)[a]
July	1.0 (0.8–1.3)	14.5 (10.6–19.8)[a]
August	1.0 (0.8–1.3)	14.1 (10.5–18.9)[a]
September	0.9 (0.7–1.7)	13.1 (9.7–17.7)[a]
October	0.8 (0.7–1.0)	9.8 (7.6–12.8)[a]
November	0.9 (0.7–1.1)	4.4 (3.4–5.5)[a]
December	0.9 (0.8–1.1)	1.6 (1.4–2.0)[a]
Season[b]		
Winter (mid–December to mid–February)	1	1
Spring (mid–February to mid–April)	1.1 (1.0–1.3)	1.0 (0.9–1.2)
Summer (mid–April to mid–June)	1.1 (1.0–1.3)	1.0 (0.8–1.2)
Rainy Season (mid–June to mid–August)	1.0 (0.8–1.1)	1.1 (0.9–1.3)
Autumn (mid–August to mid–October)	1.1 (1.0–1.3)	0.9 (0.8–1.1)
Late Autumn (mid–October to mid–December)	1.1 (1.0–1.3)	0.8 (0.7–0.9)[a]

[a]$P<0.05$; [b]As per Bangla calendar (Winter: *Poush–Magh*; Spring: *Falgun–Chaitra*; Summer: *Boishakh–Joishtho*; Rainy Season: *Aashar–Shrabon*; Autumn: *Bhadro–Ashwin*; Late Autumn: *Kartik–Ograhayon*)

This study also demonstrates that climatic factors play a significant role in the transmission patterns of HAV and HEV. HAV infections peaked during the late autumn months, coinciding with moderate temperatures and humidity, while HEV incidence was highest during the rainy season characterised by peak precipitation and high moisture. Comparison with previous literature corroborates our findings. Earlier studies have shown a significant association between temperature and HAV infections. A positive association was observed, particularly in China [8, 19]. Sun *et al.* identified both positive and negative associations within different regions of China, emphasising the regional variation within the same country [20].

The complex interplay between temperature, human behaviour, sanitation systems and other environmental factors likely contributes to these variations in disease patterns across different geographical contexts. Previous studies have indicated that moderate humidity is conducive to HAV transmission, a finding that reflects our study [21, 22]. However, it might vary with different humidity [19, 20, 23]. Hepatitis A demonstrates notable seasonal variation across different geographical regions. Some observed spring and summer peaks [24], while others observed peaks during the rainy season [5, 8, 25]. Our study did not find any consistent seasonal association with HAV despite absolute cases peaking during late autumn.

Heavy rainfall and delayed wastewater clearance were significant factors for predicting the HEV incidence during the rainy season in our study. Similar observations were also made by many in different regions [24, 26, 27]. In China, HEV exhibits a high-incidence season in spring [28], while other studies report increased incidence during rainy seasons [29]. Recent research from the Democratic Republic of Congo found a strong association between HEV cases and the dry season, with significantly higher seropositivity [30]. These complex seasonal patterns underscore that effective HEV prevention requires consideration of the combined effects of multiple environmental factors rather than focusing on single variables.

As mentioned earlier, both HAV and HEV infections are transmitted through the faecal-oral route, exposing individuals of all ages to the same risk. Often, these infections spread from individuals who are asymptomatic or immune. In addition to transmission through contaminated food or water sources, other methods have been documented. HAV transmission was thought to occur from person to person, involving high-risk behaviours, such as sharing needles; this was not observed for HEV transmission. HEV is associated with transfusion-related transmission and can also infect the fetus when transmitted from the mother [31]. Due to the complex interplay of age, gender, climate, sanitation, hygiene practices, and viral genetic factors, predicting the transmission route and timing remains a challenging task.

The strength of the study was its examination of a large number of individuals from Dhaka city, with data reported to a single tertiary care centre and analysed in relation to the local climate. However, this study had several limitations. First, the laboratory-based, hospital-centric, retrospective design of data collection from a single tertiary care hospital in Dhaka introduces selection bias, potentially omitting asymptomatic or mild cases that did not seek medical attention. Consequently, the data may not represent the general population and the findings might not be generalisable to the entire country. Second, the meteorological data collected on a city level may mask localised patterns of short-term, extreme weather events and hinder understanding of hyper-localised disease-climate interactions. Third, the study lacked data on potential confounders such as socioeconomic status, access to healthcare, sanitation practices, water source quality, HAV vaccination history, and environmental exposures like proximity to contaminated water bodies or flooding events. Lastly, we did not have access to viral genotype data which is a crucial factor in transmission dynamics, particularly for HEV.

Future research should focus on multicenter, community-based prospective studies with a representative cohort, the integration of high-resolution, localised meteorological data, a systematic assessment of key confounders, and the incorporation of viral genotyping to more accurately elucidate transmission dynamics.

Conclusion

This study confirms the high burden and endemic nature of both acute HAV and HEV infections throughout the year. More importantly, it provides strong evidence that climatic variability significantly impacts the occurrence of these infections. These findings highlight the vital need to incorporate climate data and demographic information into public health strategies seasonally, such as targeted awareness campaigns to promote hygienic practices or vaccinations for high-risk groups. Improving water safety and sanitation infrastructure, along with implementing climate-aware solutions, will be essential to reducing the burden of enteric hepatitis in Bangladesh.

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Author contributions

Conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: SMRUI, AAM, AAMi, RA, MAB, SUM, AN. *Drafting the work or reviewing it critically for important intellectual content:* SMRUI, MAB, AN. *Final approval of the version to be published:* SMRUI, AAM, AAMi, RA, MAB, SUM, AN. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* SMRUI, AAM, AAMi, MAB, AN.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

Supplementary file 1: Hepatitis A and E infection based on temperature, humidity, and rainfall according to months and seasons

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RESEARCH ARTICLE

Clinical audit of medical referral notes at Bangladesh Medical University Hospital

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Abstract

Background: Medical referral notes are essential for smooth patient care transitions between healthcare providers. Poorly organised or incomplete referrals can cause delays in treatment, miscommunication, and risk to the patients. This clinical audit assessed the quality of medical referral notes at Bangladesh Medical University (BMU) Hospital regarding their compliance with established standards.

Method: A cross-sectional study was carried out on 113 referral notes gathered from various departments in April 2025. Eight audit standards were adapted from BMU's existing referral notes. Trained auditers collected the completed referral notes and extracted data from the notes.

Result: About seven in ten (71.7%) of referral notes had date and time written properly. Most referrals (81.4%) were sent to faculty members, 65.5% having clear justification and 46.9% having full clinical information. About six in ten (58.4%) responded timely with proper explanations (61.1%), and a follow-up plan (65.5%). The study revealed considerable deficiencies. Overall, 46.9% of them met all required standards.

Conclusion: More than half of the referral notes did not meet the required standards. We recommend the introduction of an electronic referral system with a provision of periodic audits to maximise healthcare quality.

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Key messages

More than half of the referral notes at Bangladesh Medical University Hospital did not meet required standards, highlighting a large gap in medical referral documentation in Bangladesh's top tertiary care hospital. Response from the concerned clinicians also was inadequate. By introducing an electronic system for referral and periodic evaluation, Bangladesh Medical University can improve referral quality to improve patient care.

Introduction

Clinical audits are systematic reviews of clinical practice aimed at assessing and enhancing the quality of patient care by comparing current practices against established standards [1]. Medical referral notes act as a vital communication tool among healthcare providers, ensuring continuity of care, accurate diagnosis, and prompt treatment [2]. Poorly written referral notes can cause delays in patient management, miscommunication, and suboptimal clinical outcomes [3]. Therefore, evaluating the quality of referral documentation by the service providers are crucial for improvements of healthcare. The success of medical referrals depends on the completeness, clarity, and relevance of the information provided [4]. Studies have indicated that incomplete or vague referral letters contribute to diagnostic mistakes, unnecessary tests, and increased healthcare costs [5,6].

A well-organised referral note should include patient demographics, clinical history, examination findings, provisional diagnosis, and clear referral objectives [7]. However, audits across different healthcare settings show significant variation in the quality of referral documentation, with key elements often missing [8]. In low- and middle-income countries, these challenges are intensified by limited resources, high patient volumes, and insufficient training in medical documentation [9,10]. Even in high-income settings, variability in referral quality continues, emphasising the need for standardised templates and ongoing professional training [11]. Clinical audits provide a systematic way to assess compliance with best practices, pinpoint deficiencies, and apply corrective measures. [12]. Previous studies have demonstrated that audit-driven quality improvement initiatives result in improved patient outcomes and more efficient healthcare systems [13].

Anecdotal reports from clinicians at Bangladesh Medical University (BMU) indicated frequent issues with referral quality, such as missing information and ambiguous instructions. This audit was initiated to objectively examine the completeness and accuracy of referral notes, identify common deficiencies, and suggest evidence-based improvements.

Methods

This clinical audit was conducted on referral notes written in April 2025. One hundred thirteen referral notes were collected from the Medicine and Allied departments and the Surgery and Allied departments located in the blocks C and D. The inclusion criteria were inter-departmental referrals. Duplicate referrals were excluded.

Referral notes

BMU's existing referral note format was considered the audit standards, having following eight indicators:

Referral side

Referral date and time

The referral should specify the date and time it was composed. Proper documentation ensures accountability and facilitates tracking delays in response. An absence of a clearly written referral date and time makes it difficult to evaluate timelines.

Referral recipient

Specifies the recipient's designation (e.g., Faculty/ Medical Officer/Student) and helps to determine whether the referral reached the appropriate level of expertise.

Type of referral

There are two options: urgent and routine. Urgent referral requires immediate attention within an hour (e.g., life-threatening conditions). Routine referral can be responded within 24 hours.

Clinical information

The referral format includes relevant history (symptoms, duration, medical history, etc.), physical findings (vitals, examination notes), and lab/imaging results (if available) to support the referral.

Reason for referral

There is a large space for writing a clear justification and expected action from the respondent. Explain why the patient is referred (e.g., specialist opinion, further tests), and what action is anticipated (e.g., surgical assessment, diagnostic confirmation).

Referral respondent

This indicates who acknowledged or acted upon the referral and helps evaluate whether the responder had sufficient expertise.

Response side

Response date and time

The responding clinician should record the date and time in the format.

Response duration

It was calculated by subtracting the response time for the referral time. Perfect timing indication if the response was within the expected timeframe (e.g., urgent < 1 hour, routine < 24 hours).

Response quality

A proper explanation includes assessment, treatment plan, and a clear instruction.

Data collection and analysis

Data were extracted by trained auditors using a standardised checklist. The auditors were physicians who had completed structured training to understand referral standards (e.g., required clinical elements, urgency criteria), apply audit tools consistently (e.g., checklists), and reduce bias (e.g., avoiding subjective interpretations of "adequate" documentation). Auditor training was conducted by the authors at the Department of Internal Medicine of BMU covering referral standard criteria defining a "complete" referral (e.g., history, examination, labs), checklist utilisation, and maintaining confidentiality and objectivity. Descriptive statistics (numbers and their corresponding percents) were used to analyse compliance.

Results

In this clinical audit, we found that the 71.7% referral notes had properly written referral dates and times. The referrals were mostly (88.5%) sent to the faculty members. Routine referrals (within 24 hours) accounted for 73.5% of the instances. Fully documented clinical information was present in 46.9% of cases. The reason for referral with a clear justification was provided in 65.5% notes (Table 1).

Referrals were responded mostly by faculty members (81.4%), with a perfect response time (58.4%) and proper explanations (61.1%). There was no date or time in case of 28.3% of the notes. In 55.8% referral notes, response time and dates were not written. Only 46.9% met all required standards.

Table 1 Clinical audit standard-based findings in referral notes (n=113)

Clinical audit standards	Number (%)
Referral side	
Referral date and time written	
Date and time	81 (71.7)
Date only	28 (24.8)
No date and time	4 (3.5)
Type of referral notes	
Routine	83 (73.5)
Urgent	13 (12.4)
Not specified	5 (4.4)
Clinical information written in referral notes	
History	108 (95.6)
Physical examination	53 (46.9)
Lab investigation	79 (69.9)
Reason written in referral notes	
Clearly	74 (65.5)
Unclearly	39 (34.5)
Type of respondent who responded to the referral notes	
Faculty	92 (81.4)
Student	6 (5.3)
Not specified	11 (9.8)
Response side	
Response date and time	
Date and time	50 (44.2)
Date	42 (37.2)
No date and time	21 (18.6)
Response duration	
Perfect time	66 (58.4)
Delayed response	25 (22.1)
Not responded	5 (4.4)
Response with proper explanation	
Written	69 (61.1)
Not written	44 (38.9)

In addition, we explored whether there was any follow-up plan in the referral reply although it was not in the list of the standards. Such a plan was mentioned by 65.5% of the responding clinicians (Figure 1).

Discussion

The audit revealed a large variability in referral quality, with critical omissions that could impact badly patient care. The absence of date and time, incomplete clinical information, delayed response time, lack of proper explanation, and lack of follow-up plans were particularly concerning, as they may lead to inappropriate and delayed management. Less than half of referral notes met all required standards.

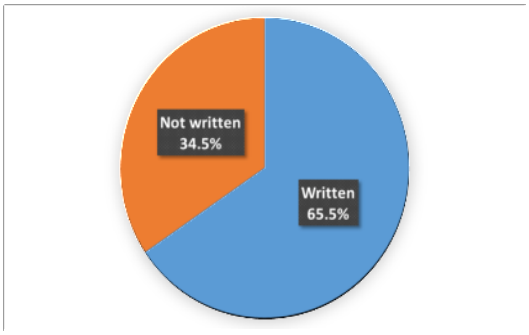

Figure 1 Follow-up plan suggested by the responding clinicians

The BMU currently uses a paper-based referral note. Transitioning to electronic systems for documentation and referrals may enhance the quality and legibility of medical notes, reduce errors and improve compliance with standards. Our compliance with proper date/time documentation, aligns closely with the finding of Johnston *et al* (68%) [1]. Similarly complete clinical information aligns almost exactly with the findings of Pronovost *et al.* (47%) on the adherence standards [14]. Our finding of 65.5% referrals with clear justification remains below the 82% standard reported by Wright and colleagues [13].

Perfect response time in our analysis (58.4%) was lower than that reported by others (61.1% - 78.0%) [15,16]. Follow-up plan documentation (65.5%) failed to reach the 80% standard demonstrated in Shojania and Grimshaw's optimal practice model [17].

Most concerning was our finding that less than half of referrals met all standards. This gap underscores the need for systemic interventions like those proposed by Dixon-Woods and Martin, whose framework achieved 89% sustained improvement through continuous quality monitoring [18].

Our results support WHO's recommendation for standardized referral protocols in low-compliance settings [19]. Moreover, this study supports global efforts to strengthen healthcare systems through ongoing quality improvement and patient-centred care. Given the increasing focus on interdisciplinary collaboration in modern healthcare, optimising referral processes is essential for reducing errors and enhancing clinical efficiency [20].

This study has limited generalisability as it was done at Bangladesh's top academic hospital for a short period. However, we presume the situation is similar or even worse in other tertiary-level hospitals, such as medical college hospitals and specialised institutes.

Conclusion

The clinical audit identified large gaps in referral documentation and processing, including incomplete clinical information, delayed responses and lack of follow-up plans. We recommend introduction of an electronic system for referral notes with an alert system, periodic training, and audits for maximizing the benefits.

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We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

Supplementary file 1: Bangladesh Medical University Referral Notes format.

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RESEARCH LETTER

Bridging early clinical exposure in basic science with clinical years to reinforce medical education

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Medical education in India is currently undergoing a significant transformation. There is a need to align it with international standards, improve healthcare outcomes, and address challenges like the imbalance between patient and doctor ratios [1]. Historic reforms like Flexner Report and Hopkins Circle laid the groundwork for medical education [2,3]. However, quality of education and patient care has since declined [4]. To address this, the Medical Council of India, under Vision 2015, introduced early clinical exposure (ECE) as a foundational component of competency based medical education. This initiative was further institutionalised by the National Medical Commission in 2019 [5,6]. Although the strategy by the National Medical Commission regarding ECE is clear, concerns still remain among the teaching community regarding its implementation and effectiveness in achieving desired goals. Consequently, there is a lack of clarity and acceptance of this teaching-learning methodology in medical education.

ECE is a student-centric teaching-learning method that encourages medical students to bridge the gap between theoretical and clinical knowledge by exposure to actual patients/ human exposure as early as the first year of MBBS [7]. It facilitates cognitive, psychomotor, and affective domain development [8]. This study aims to assess the effectiveness of ECE in enhancing the knowledge and attitude of first year MBBS students. It will increase the confidence of students and faculty members to implement and utilise ECE in their curriculum.

The quasi-experimental study was conducted at a tertiary care teaching hospital after obtaining ethical clearance and written informed consent. A total of 244 first year professional MBBS students were randomly divided into two groups: A and B. Group A participants underwent ECE sessions on Parkinson's disease, which included video clippings, case scenarios, and clinical inputs from a neurologist. A teacher-centered didactic lecture was given to Group B students on the same topic by a neurologist. Both groups underwent pre-and post-tests with validated case-based MCQs administered via Google Forms to assess the knowledge domain. Additionally, a five-point Likert scale-based questionnaire was used to evaluate student perceptions and attitudes towards teaching methodologies. In the subsequent week, roles of both groups were reversed for the second clinical topic, cerebellar disorders, to ensure equal exposure. Data were analysed using SPSS version 28. Paired and independent *t* test were conducted, and $P < 0.05$ was considered statistically significant.

Knowledge level of post-test scores showed statistically significant improvement in the ECE group compared to the traditional teaching group for both topics ($P < 0.001$). For cerebellar disorders, the mean (standard deviation) post-test score of the ECE group was 6.4 (1.4), compared to 2.8 (1.0) in the traditional group. Similarly, for Parkinson's disease, the mean (standard deviation) post-test score of the ECE group was 6.0 (1.3), compared to 1.9 (0.7) in the traditional group (Table 1). Feedback from students revealed overwhelmingly positive responses as 92% felt confident in handling clinical cases, 93% reported increased motivation to study basic sciences, 95% found ECE helpful for recalling theoretical knowledge, 84% felt reduced anxiety in clinical assessments, and 92% reported a better understanding of disease physiology.

Key messages

Early clinical exposure improved recall, understanding, and clinical application compared to traditional teaching methods. It was also a more acceptable teaching method by the students. Early clinical exposure is an effective teaching strategy that should be integrated across institutions to strengthen foundational learning and foster competent, patient-centered medical professionals.

Table 1 Knowledge pre and post-test scores of two teaching methods (n=122)

Topic	Teaching method	Pre-test score	Post-test score	Difference (post minus pre-test scores)	*P*
Cerebellar disorder	Traditional teaching	1.2 (0.9)	2.8 (1.0)	1.6	<0.001
	ECE	1.2 (0.9)	6.4 (1.4)	5.2	<0.001
Parkinson's disease	Traditional teaching	1.2 (0.9)	1.9 (0.7)	0.7	<0.001
	ECE	1.2 (0.9)	6.0 (1.3)	4.8	<0.001

ECE indicates early clinical exposure. All values expressed as mean (standard deviation)

Traditional didactic lectures in medical education often lack clinical relevance, leading to fragmented learning experience. In contrast, the present study demonstrated that ECE significantly enhances post-test knowledge compared to pre-test levels. This aligns with Kolb's theory, where learners cycle through observation, reflection, conceptualisation, and application. Thus, it fosters deeper insight and real-life application, enhances higher-order thinking and bridges the gap between theory and clinical practices. It motivates student to learn standardized skills to examine and communicate with a patient in a professional manner. Our findings indicate that ECE significantly improved knowledge comprehension, clinical reasoning, recall, and student motivation. Findings are consistent with previous studies by Tayade and Warkar [9], which reported enhanced learning outcomes and student satisfaction with ECE [10,11]. Exposure to clinical cases created an opportunity to make the theoretical classes interesting and understand concepts of knowledge for more extended periods and enhanced higher-order thinking within the students.

ECE, the teaching-learning methodology introduced by National Medical Commission in 2019 as an essential component of the medical curriculum, improved the relevance and understanding of basic science concepts. ECE ensured a student's patient-centric and behavioural attitude towards the patient and facilitated clinical skill development, confidence, and competence in communicating with the patient in future clinical classes. To optimise ECE effectiveness faculty members should focus on improving case presentation and discussion methods to ensure clarity and student engagement. This study will encourage other institutions willingness to adopt this new teaching-learning method for the betterment of students.

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Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

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RESEARCH LETTER

Clinical profile of patients with pulmonary hypertension

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Once considered an orphan disease, pulmonary hypertension is now recognized as a major contributor to morbidity and mortality, yet it continues to receive limited attention in clinical practice worldwide [1]. Currently, pulmonary hypertension affects over 70 million people worldwide, with a 10% incidence among those over 65 in both developed and developing countries. Pulmonary hypertension was defined as a mean pulmonary arterial pressure of more than 20 mmHg at rest by the sixth world symposium on pulmonary hypertension in 2018 [2]; however, the guidelines of the European Respiratory Society and European Society of Cardiology consider a threshold of 25 mmHg at rest [3].

In Bangladesh, pulmonary hypertension patients experience delayed or missed diagnosis due to non-specific symptoms, which sometimes lead to early preventable death. This study investigates the clinical characteristics of pulmonary hypertension in Bangladeshi adults, offering valuable insights for enhancing management approaches.

The study was conducted in the Department of Cardiology, Bangladesh Medical University, and included 60 patients (29 men and 31 women) with previously diagnosed pulmonary hypertension, confirmed by echocardiography, from November 2023 to April 2024. A 12-lead resting electrocardiogram (10 mm/mV, 25 mm/s) and echocardiography using a Simens GE Vivid E9 machine were performed. Transesophageal echocardiography was done when needed. Right ventricular systolic pressure and mean pulmonary artery pressure were measured according to the 2022 the European Society of Cardiology pulmonary hypertension guidelines. Right heart catheterization was performed in three idiopathic pulmonary hypertension cases with elevated RVSP, preserved left ventricular function, and no significant valvular disease on echocardiography. As per the 2022 guidelines of the European Society of Cardiology and European Respiratory Society, right heart catheterization was necessary for definitive hemodynamic confirmation. Pulmonary hypertension is categorized into five groups based on etiology, while its severity is evaluated using right ventricular systolic [4].

The mean age of the participants was 49.6 (14.6) years, with 31 females (52%) and 29 males (48%). Type 2 pulmonary hypertension was the most frequent type (45.0%) with a mean pulmonary artery pressure of 46.0 (7.6) mmHg, followed by Type 1 pulmonary hypertension (31.6%). Pulmonary hypertension was mild in 46.7%, moderate in 36.7%, and severe in only 16.7%. Common symptoms were dyspnea (93.3%), chest pain (91.6%), and fatigue (93.3%). Right heart catheterization in three idiopathic pulmonary hypertension cases showed a mean pulmonary artery pressure of 56.7 (10.7) mmHg, a mean pulmonary vascular resistance of 9.3 (0.8) Wood units, and a mean pulmonary capillary wedge pressure of 10.9 (1.0) mmHg.

In our study, most patients were comparatively younger to middle-aged. Krishna and Venu reported a higher mean age of 51.9 (11.5) years [5]. The younger age distribution in our cohort may reflect demographic differences and progressiveness of the disease.

Key messages

Pulmonary hypertension remains under-recognized in Bangladesh. Dyspnea, chest pain and fatique were the most common manifestations in this series; 16.7% were severe cases. These are different from other populations worldwide. Therefore, pulmonary hypertension in Bangladesh deserves special attention.

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Table 1 Severity, types and clinical features of patients with pulmonary hypertension (n=60)

Variables	Results
Number (%)	
Sex	
Male	29 (48.0)
Female	31 (52.0)
Symptoms	
Dyspnea	56 (93.3)
Chest pain	55 (91.7)
Fatigue	55 (91.7)
Leg oedema	47 (78.3)
Palpitation	49 (81.6)
Cough	27 (45.0)
Hoarseness of voice	3 (5.0)
Hemoptysis	5 (8.3)
Syncope	3 (5.0)
Cyanosis	3 (5.0)
Severity of pulmonary hypertension	
Mild	28 (46.7)
Moderate	22 (36.7)
Severe	10 (16.7)
Types of pulmonary hypertension	
Type 1	19 (31.6)
Type 2	27 (45.0)
Type 3	7 (11.7)
Type 4	3 (5.0)
Type 5	4 (6.7)
Mean (SD)	
Age (years)	49.6 (14.6)
RVSP (mmHg) by severity of pulmonary hypertension	
Mild	43 (7.0)
Moderate	58 (5.0)
Severe	80 (7:0)
mPAP (mmHg) of type of pulmonary hypertension	
Type 1	54 (28.9)
Type 2	46 (7.6)
Type 3	47.4 (11.0)
Type 4	53 (2.0)
Type 5	49.5 (16.2)

SD indicates standard deviation; RVSP, right ventricular systolic pressure; mPAP, mean pulmonary artery pressure. RVSP 36–49 mmHg is mild, 50 –69 mmHg is moderate, and ≥70 mmHg is severe pulmonary hypertension. Types of pulmonary hypertension are based on etiology as per reference[4].

Regarding gender distribution, female patients were predominantly more. For instance, females comprised 59% of cases in the Swiss registry [6] and 65.3% of cases in the French registry [7]. In contrast, Bansal *et al.* [8] found somewhat more males (54%) than females (46%). In Bangladesh, women often have limited healthcare access, and our study found a greater number of female participants. This also reflects the known female predominance in pulmonary hypertension.

Similar to Dzudie *et al.*, pulmonary hypertension due to left heart disease (Type 2) was the most common type found in our study [9]. Type 1 pulmonary hypertension was our second most prevalent type and exhibited the highest mPAP on echocardiography. This is likely due to progressive vascular remodeling, increased pulmonary vascular resistance, and absence of left-sided pressure overload. The predominance of type 2 pulmonary hypertension indicates that it arises from the chronicity of left heart disease. This condition is amenable to prevention and treatment.

Most participants presented with mild to moderately severe pulmonary hypertension based on RVSP measurements. Krishna and Venu found a similar distribution, with 32% having mild, 38% having moderate, and 30% experiencing severe pulmonary hypertension [5]. This distribution suggests that many patients had mild to moderate disease, which may reflect disease progression or clinical presentation differences.

The most frequently reported symptoms were shortness of breath, fatigue, and chest pain. Bansal et al. reported dyspnea (86.4%) and cough (77.5%) as the most common symptoms [8]. These findings are commonly seen in pulmonary hypertension, and symptoms become more pronounced with the progression of the disease.

Right heart catheterization in three idiopathic pulmonary hypertension cases confirmed pre-capillary pulmonary hypertension with significantly elevated pulmonary vascular resistance and preserved wedge pressures, suggesting that it was pre-capillary. AL-Kinani observed similar mean pulmonary artery pressure values [10].

This study highlights the clinical profile and hemodynamic characteristics of pulmonary hypertension in Bangladeshi adults, with left heart disease (Type 2) emerging as the most common type. The majority of cases were mild in severity. Fatigue and dyspnea were the predominant presenting symptoms.

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Conflict of interest

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Data availability statement

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Supplementary file

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CASE REPORT

Surgical retrieval of a migrated peripherally inserted central catheter guidewire in an acute myeloid leukaemia patient: A case report

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Introduction

Acute myeloid leukaemia (AML) treatment typically involves intensive chemotherapy regimens, often necessitating the placement of central venous access devices. Peripherally inserted central catheters (PICCs) are frequently utilised for this purpose [1]. Although PICC lines are generally considered safe and effective, complications may arise during insertion or management, including rare instances of guidewire dislodgement. Retaining a guidewire during interventional procedures can lead to serious complications if not addressed promptly. Thrombosis, embolisation, sepsis, and perforation are the potential risks associated with retained guidewires [2]. In some instances, guidewire retention can result in acute coronary thrombosis [3]. This case report describes an unusual complication of PICC line insertion in a patient with AML, emphasising the importance of vigilance during central venous access and managing preventable mishaps.

Case description and management

A 45-year-old man was admitted to the Al Helal Specialised Hospital in Mirpur, Dhaka, on 4 October 2024 with suspected dislodgement of the PICC guidewire. The patient was transferred from Lab One Hospital, Uttara, Dhaka, where he had to receive a second cycle of chemotherapy for AML. During the insertion of a PICC line into the patient's left hand for chemotherapy, an unexpected complication occurred at the Lab One Hospital. The guidewire of the introducer sheath migrated into the patient's body, necessitating emergency transfer to Al Helal Specialised Hospital for guidewire removal, as such facilities were unavailable at Lab One Hospital. The patient was haemo-dynamically stable upon admission. Chest radiography revealed a clear path of the dislodged guidewire extending from the medial one-third of the clavicle to the inferior vena cava along the PICC line (Figure 1). Initially, an attempt was made to remove the PICC line, anticipating that the guidewire would be extracted simultaneously with the catheter. However, this approach was unsuccessful, as the guidewire remained in situ. Subsequently, a right anterolateral thoracotomy for guidewire removal was proposed. The patient and his relatives were consulted regarding the potential benefits and risks of the procedure, and written informed consent was obtained.

A thoracotomy was performed through the 5th intercostal space. The superior vena cava was controlled proximally and distally. Manual palpation of the superior vena cava was performed to locate the guidewire precisely. Surgical measure was taken to remove it (Figure 2). A small incision was made over the superior vena cava, and the guidewire was successfully removed using a skin hook. The thoracotomy was closed in layers, and a water-sealed chest drain tube was inserted. A cardiac anaesthesiologist, cardiovascular and thoracic surgeon and haemato-oncologist were involved in this procedure. Postoperative radiography confirmed

Key messages

Guidewire dislodgement and migration during peripherally inserted central catheter line insertion can be life-threatening through embolism, thrombosis, or vascular injury. Such a dislodgement was promptly detected and surgically removed by a multidisciplinary team in a 45-year-old Bangladeshi man. An initial attempt at nonsurgical removal was unsuccessful.

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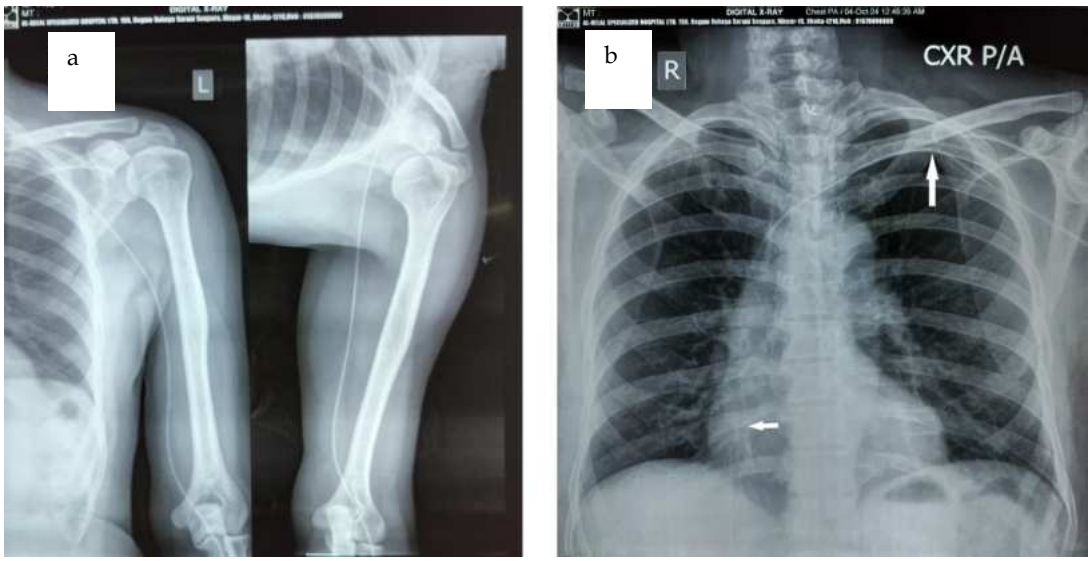

Figure 1 Preoperative X-ray showing peripherally inserted central catheters with the retained guidewire: a) left arm, b) chest (arrows indicate guidewire's position)

the complete removal of the guidewire. There were no complications during the patient's recovery, and the chest drain tube was removed the following day. The patient was subsequently transferred back to the original hospital in stable condition to continue treatment of AML.

Discussion

PICC lines are widely used in oncology for stable venous access, though complications like infection and thrombosis are common [4]. Guidewire dislodgement and migration are rare, but these serious complications can occur during the PICC line placement [5]. Retrieving a migrated guidewire is technically challenging and requires thorough knowledge of vascular anatomy and potential complications. Literature suggests prompt intervention is crucial to prevent further complications, such as embolism or vascular injury [6], including a case from Bangladesh[7]. Established techniques for a dislodged guidewire removal include endovascular approaches and surgical explorations. Our case report highlights the challenges of surgical retrieval, especially in patients with compromised vascular integrity.

Research supports the efficacy of surgical extraction for complications arising from retained guidewires, as demonstrated in various case studies. These cases underscore the critical role of surgery where non-invasive interventions prove ineffective [8]. Healthcare professionals should implement standardised protocols for PICC placement, using checklists to ensure all components are accounted for post-procedure [9].

This case report presents a rare but potentially serious complication associated with PICC line insertion in a patient undergoing treatment for AML. It also emphasises the need for the importance of multidisciplinary approaches in managing such iatrogenic complications.

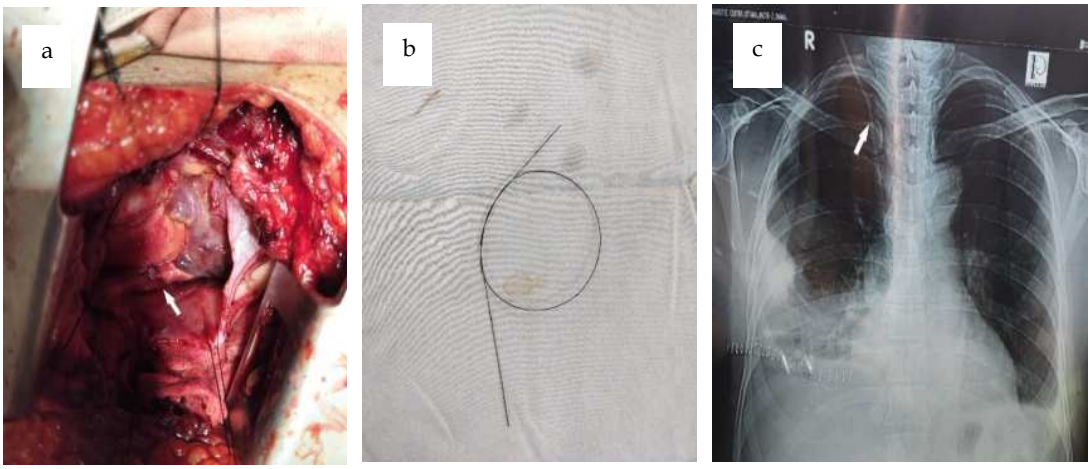

Figure 2 Operative and postoperative images: a) closed stoma over superior vena cava, b) removed guidewire, and c) postoperative X-ray after removal of the guidewire central venous catheter in situ.

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Author contributions

Manuscript drafting and revising it critically: SKS, MSS, HS. *Approval of the final version of the manuscript:* SKS, MSS, HS, MAU, MAH. *Guarantor accuracy and integrity of the work:* SKS, MSS, HS, MAU, MAH.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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CASE REPORT

Delirious mania in an adolescent with Bardet-Biedl syndrome : A case report

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Introduction

Bardet-Biedl syndrome is a multisystemic autosomal recessive disorder characterised by a range of phenotypic manifestations. Its frequency is 1 in 120,000 in North America, 1 in 160,000 in Europe, and 1 in 36, 000 in Kuwait [1]. Bardet-Biedl syndrome is marked by a set of core features as retinal dystrophy, obesity, polydactyly, hypogonadism and cognitive impairment historically referred to as the "Bardet-Biedl syndrome pentad." These manifestations are commonly attributed to underlying defects in primary cilia function [2, 3].

It is often associated with psychomotor slowness, infantile behaviour, and emotional instability in response to stimuli [3]. Delirious mania has been rarely documented [4, 5], although other mental symptoms of Bardet-Biedl syndrome have included hallucinations, delusions, depressed mood, manic symptoms, and catatonic features [4]. Delirious mania is regarded as a variant form of classical bipolar disorder [6]. This severe but frequently undiagnosed neuropsychiatric illness is characterised by the abrupt development of psychosis, manic symptoms, and delirium [5].

This example illustrates the challenge of recognising and treating a patient exhibiting perplexity and manic excitement, particularly in those with complex comorbidities.

Case description and management

A 17-year-old girl, the first child of consanguineous parents presented at Bangabandhu Sheikh Mujib Medical University (currently, Bangladesh Medical University), Dhaka, Bangladesh with characteristics that were typical of Bardet-Biedl syndrome. Phenotypically, the diagnosis was determined based on the presence of distinctive clinical characteristics such as developmental delay, post-axial polydactyly, obesity, and retinal degeneration (Figure 1). She had significant mental symptoms, hypertension, diabetic renal disease, hypothyroidism, and type-2 diabetes mellitus also, among other comorbidities for last 2-years.

The patient had auditory hallucinations, affective disturbances like mood swings, increased energy, crying spells, and emotional instability, cognitive impairment, and behavioural issues like irritability, self-harm, insomnia, treatment non-adherence, violent behaviour, and refusal of medical intervention, which worsened over the past week. Her psychiatric symptoms worsened, deteriorating her overall health and complicating her comorbidities. Her severe psychiatric symptoms and refusal of treatment necessitated an urgent referral to psychiatry. The patient was irritable, talkative, aggressive, had poor eye contact, and was agitated during the mental state examination. Speech was disorganised and incoherent. She was easily distracted and skipped topics, making sustained attention and sequencing tasks difficult. Although her extremities showed negativism, a motor examination did not find any catalepsy, echophenomena, grimacing, or stereotypies. Although denied, she

Key messages

Psychiatric issues in adolescents with conditions like Bardet-Biedl Syndrome and neurodevelopmental delay can be challenging to diagnose because symptoms like mood swings, hallucinations, and aggression can mix with their existing cognitive and behavioral problems. Delirious mania is often hidden by this overlap. Early detection and multidisciplinary care are crucial for accurate diagnosis, effective treatment, and improved health and compliance.

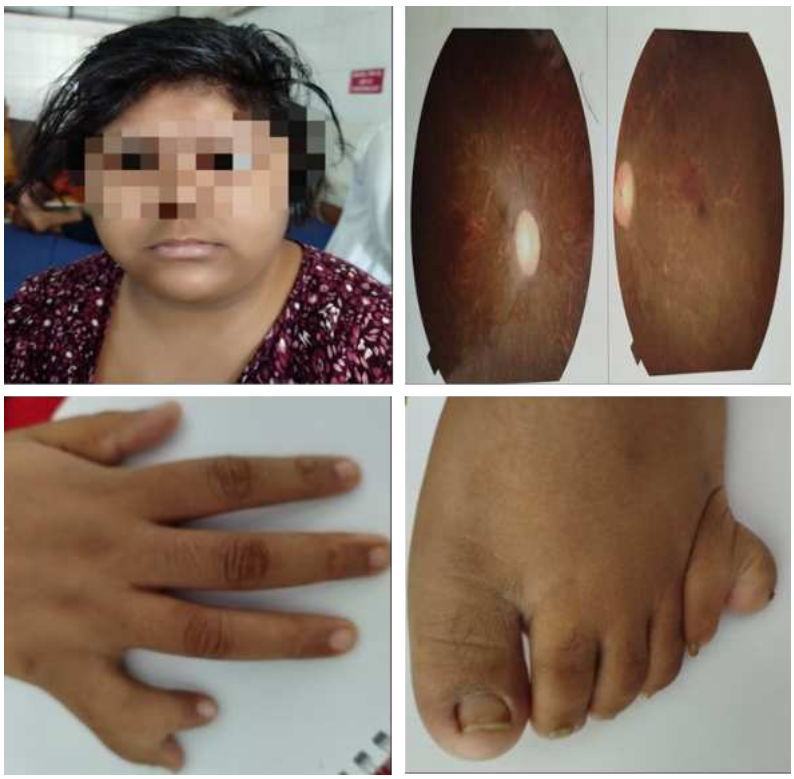

Figure 1 An adolescent girl with Bardet-Biedl syndrome

demonstrated active symptoms of hallucinations, such as self-laughing and self-muttering, indicating a lack of insight. Her attention was poor, and she was disoriented to time and place. Previous records showed that her IQ was 65. Mini–mental state examination score was 22. She had epilepsy managed with valproate for six years, remained seizure-free for five years, and had been off medication for the past year. There was no family history of Bardet-Biedl syndrome. Her medical conditions were treated according to standard protocols by the endocrinologist and nephrologist. Laboratory investigations and organic delirium or catatonia were ruled out on clinical grounds. The psychiatric diagnosis was clinical delirious mania, characterised by the simultaneous presence of both delirium and manic symptoms. Interventions, including rapid tranquilisation, de-escalation strategies, pharmacological management, and psychoeducation for the caregivers, were initiated.

She was prescribed lorazepam (2 mg), quetiapine (100 mg), aripiprazole (10 mg), topiramate (25 mg), and melatonin (3 mg), resulting in significant improvement in her psychiatric symptoms. Over the course of a three-month follow-up, including an initial two-week inpatient stay, her agitation, hallucinations, and disorientation resolved, as confirmed by mental state examination. Her mini–mental state examination score increased from 22 to 26, behavioural disturbances lessened, and treatment adherence improved. Despite experiencing mild mood symptoms, her attention, insight, and cooperation were enhanced, allowing her to safely transition to outpatient psychiatric and endocrinological care.

Discussion

She exhibited mixed delirious symptoms (both hyperactive and hypoactive) [6] along with mixed manic symptoms. When cases of delirious mania arise at the convergence of psychiatry and medicine, it can be difficult to balance the needs of behaviour, mental health, and medicine [6]. Delirium, which can have infectious or metabolic causes, was included in the differential diagnosis for this illness. However, relevant investigations and clinical examinations ruled out these. Confusion, increased hallucinations, and a noticeable escalation of manic symptoms are characteristics of the shift from mania to delirious mania [7]. Abruptly stopping medication raises the risk of mania in people with Bardet-Biedl syndrome and concomitant chronic diseases, particularly chronic kidney disease [6] as occurred here. The extremely quick onset of delirious mania is especially common among children and adolescents [7]. Literature showed the majority of patients with delirium and mania were female, younger, and had a history of bipolar disorder [8]. Of all individuals with acute mania, 5–20% exhibit delirium symptoms [7].

Bardet-Biedl syndrome genes may affect cortical development and cause major mental illness, with over 30% prevalence in psychiatric conditions [9]. Increased dopamine activity and decreased acetylcholine may affect melatonin release, circadian rhythms, and sleep patterns. These symptoms improved with the above-mentioned pharmacological treatment, which targets neurotransmitter imbalances [5, 8].

No diagnostic classifications or treatment guidelines exist for delirious mania, which makes diagnosis and treatment challenging. Given a history of Bardet-Biedl syndrome with psychosis, along with current symptoms of delirium and mania, the symptom profile and medical history can assist in therapeutic decision-making.

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We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

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COMMENTARY

Lewy body dementias: One spectrum or two diseases?

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Lewy body dementias, encompassing dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), are the second most common form of neurodegenerative dementia following Alzheimer's disease. Although both syndromes are unified by the pathological hallmark of α–synuclein deposition, their clinical classification remains bifurcated, defined not by distinct mechanisms but by the order in which cognitive and motor symptoms emerge [1]. This longstanding convention, based on an arbitrary temporal rule, is increasingly challenged by overlapping presentations and shared pathophysiological features. The central question remains: Are DLB and PDD distinct entities or phenotypic variants within a broader, continuous disease spectrum? The current diagnostic framework distinguishes DLB and PDD based on a one-year rule: if cognitive impairment precedes or appears within a year of Parkinsonism, DLB is diagnosed; if dementia occurs later in the course of Parkinson's disease, PDD is assumed. However, this artificial cutoff has little biological basis and often fails in real-world clinical contexts, where symptom onset may be subtle, fluctuating, or ambiguously reported [2]. As a result, many patients fall into diagnostic grey zones, impacting both prognosis and treatment decisions. Clinically, both forms of LBD share core features: fluctuating cognition, REM sleep behaviour disorder, visual hallucinations, and parkinsonism-supported by converging evidence from neuroimaging, biomarker studies, and therapeutic response.

Structural and functional imaging studies have identified overlapping patterns of cortical and subcortical involvement, particularly in dopaminergic and cholinergic networks. Post-mortem studies consistently demonstrate widespread α–synuclein pathology in both DLB and PDD, often accompanied by Alzheimer-type changes such as β–amyloid plaques and tau tangles [3]. These shared pathologies correlate with cognitive decline, psychiatric symptoms, and disease progression in both conditions.

Despite these parallels, the temporal distinction remains entrenched in diagnostic criteria issued by the DLB Consortium and the Movement Disorder Society [4]. While useful for clinical categorisation, this model fails to capture the heterogeneity observed across patients and may hinder research by segregating patients with biologically similar diseases. For instance, patients with early psychiatric symptoms and later motor dysfunction may be mislabeled, resulting in suboptimal treatment strategies and exclusion from relevant clinical trials [4]. Importantly, the therapeutic landscape for LBDs also reflects a spectrum-based reality. Both DLB and PDD respond to cholinesterase inhibitors for cognitive and neuropsychiatric symptoms, while dopaminergic agents address motor features [5]. To better understand the distinction between the two diagnostic approaches and their clinical implications, refer to **Table 1**, which contrasts the conventional model with the emerging continuum model, emphasising how a unified approach can guide more personalised therapies. However, the risk of exacerbating psychosis with dopaminergic therapy in

Key messages

Recognising Lewy body dementias as a singular, heterogeneous spectrum rather than as two distinct diagnoses aligns with current neuropathological and biomarker evidence. Abandoning rigid temporal classifications could enhance diagnostic precision, optimise therapeutic decisions, and facilitate inclusion in targeted clinical trials, paving the way for biologically driven, individualised approaches in neurodegenerative disease management.

Table 1 Conventional versus emerging models in Lewy body dementias

Aspect	Conventional dichotomous model	Emerging continuum model
Disease Classification	Dementia with lewy bodies (DLB): Cognitive decline manifests prior to or within 12 months of motor symptom onset. Parkinson's disease dementia (PDD): Dementia emerges after at least one year of established Parkinsonism.	Disease is conceptualised as a spectrum with overlapping onset of cognitive, motor, psychiatric, and sleep disturbances. No distinct temporal order governs the presentation of symptoms.
Neuropathology	Predominantly characterised by α-synuclein deposits. DLB often demonstrates more prominent cortical involvement, while PDD predominantly affects subcortical structures.	Extensive cortical and subcortical involvement of α-synuclein pathology in both DLB and PDD. Coexistent Alzheimer-type pathologies (β-amyloid plaques, tau tangles) observed across both entities, suggesting shared neurodegenerative processes.
Clinical Features	Cognitive impairment follows motor symptom onset in PDD, whereas DLB exhibits early cognitive symptoms. Both conditions feature Parkinsonism, visual hallucinations, fluctuating cognition, and REM sleep behaviour disorder (RBD).	A broader clinical continuum of cognitive, motor, psychiatric, and sleep disturbances with no rigid sequence, indicating that cognitive and motor symptoms may emerge simultaneously or in varying order. Common pathophysiological markers overlap between both forms of LBD.
Diagnostic Thresholds	Clear temporal distinction based on the onset of dementia relative to motor features, specifically the one-year cutoff rule for PDD.	Diagnostic boundaries are fluid, guided by clinical, pathological, and molecular markers rather than an arbitrary time frame. Both phenotypes represent variations within a spectrum.
Therapeutic Implications	Cholinesterase inhibitors and dopaminergic therapies are commonly employed, but treatment regimens are often stratified based on the temporal progression of symptoms, without regard for underlying pathophysiology.	A unified therapeutic approach tailored to individual patient profiles using biomarkers. Both cholinesterase inhibitors and dopaminergic agents are employed but with careful consideration of the individual patient's symptomatology and the risk of treatment-related side effects.
Clinical Trial Design	Clinical trials often restrict inclusion based on rigid diagnostic criteria, such as the one-year temporal cutoff, potentially excluding individuals with early cognitive or psychiatric symptoms and misclassifying patients.	Clinical trials are designed to accommodate the full spectrum of disease, focusing on biomarker-based phenotyping rather than rigid temporal criteria, allowing for more inclusive patient selection and better representation of disease variability.

both groups underscores the need for a nuanced approach. As research moves toward disease-modifying treatments, particularly those targeting α–synuclein aggregation, rigid classifications based solely on symptom chronology could limit therapeutic reach and precision. Increasingly, experts advocate for a unified model of Lewy body disorders that integrates clinical, pathological, and molecular data. Biomarker studies-spanning cerebrospinal fluid analysis, PET imaging, and genetic profiling-are beginning to delineate shared and subtype-specific signatures [6]. A shift toward biologically informed classification could enhance diagnostic accuracy, guide personalised therapy, and improve clinical trial design by accommodating the true complexity of disease presentation. Revisiting the current nosology is not simply a matter of semantics but a call for a paradigm shift in neurodegenerative disease research and care [7]. Recognising LBDs as a spectrum-rather than two arbitrarily separated diseases-aligns classification with emerging biological understanding and paves the way for more tailored, effective interventions.

A spectrum-based model of Lewy body dementia can improve diagnostic clarity, personalise therapeutic strategies, and reflect the complex neurobiology of the disease.

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COMMENTARY

First global guideline of the World Health Organization on pregnancy care in sickle cell disease: Balancing maternal equity and ethical accountability

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The June 2025 release of the World Health Organisation (WHO)'s first global guideline on managing sickle cell disease (SCD) in pregnancy marks a milestone in maternal and public health [1]. As an inherited haemoglobinopathy, SCD imposes physiological, psychological, and social burdens on women of reproductive age. Yet maternal health frameworks have long lacked clinically comprehensive and ethically grounded guidance. This new WHO guideline is not only a scientific advancement—it is an ethical imperative. SCD affects more than 7.7 million people globally, primarily in sub-Saharan Africa, the Middle East, South Asia, and the Caribbean. Improved childhood survival has led to more women with SCD reaching reproductive age, who face a four- to eleven-fold higher risk of maternal mortality compared to their peers. They are also at increased risk for severe anaemia, pre-eclampsia, thromboembolic events, infections, and adverse fetal outcomes such as growth restriction, preterm birth, and stillbirth. Existing guidance has largely been based on high-income contexts, with limited relevance to low- and middle-income countries (LMICs), where the disease burden is highest.

The WHO guideline addresses this critical gap with over 20 evidence-based recommendations tailored for resource-constrained settings. It combines clinical science with a focus on equity, improving pharmacological management: up to 5 mg of folic acid is advised in non-malaria regions, and 400 µg in areas receiving sulfadoxine-pyrimethamine. Routine iron supplementation is discouraged unless deficiency is confirmed. Prophylactic transfusions are recommended for women with severe or frequent crises, subject to careful risk-benefit evaluation.

Importantly, the guideline revises the traditional recommendation to avoid hydroxycarbamide (hydroxyurea) during pregnancy. It now supports use after the first trimester under a shared decision-making model—prioritising autonomy and individualised risk-benefit dialogue [2]. Pain management, which has historically been neglected, is emphasised through personalised plans that may include paracetamol, NSAIDs, and opioids, based on gestational age and clinical history. Hospitalised patients should receive fluid balance management, prophylactic anticoagulation, and structured fetal monitoring with growth scans every four weeks from 24 to 32 weeks, and every three weeks thereafter.

Delivery planning is individualised. Vaginal delivery is preferred unless medically contraindicated. The timing of delivery should balance maternal and fetal risk while centring informed maternal choice [3]. Postnatal care includes surveillance for thrombosis, newborn screening, contraception counselling, breastfeeding support, and timely re-initiation of hydroxyurea when clinically appropriate. The integration of SCD-specific services into reproductive healthcare ensures continuity throughout the life course.

The guideline's ethical foundation is as important as its clinical content. WHO explicitly calls for stigma-free, respectful, and culturally competent care. Women with SCD often face systemic bias, pain

Key messages

The WHO's first global guideline on sickle cell disease in pregnancy (2025) provides both clinical clarity and ethical accountability, offering a pathway toward safe, equitable, and dignified maternal care, especially in resource-limited settings. However, the challenges of turning the recommendations into actions need political will and strategic investments.

Table 1 Summarising the World Health Organization 2025 guideline's key clinical interventions, ethical principles, and system-level requirements

Clinical focus area	Key WHO recommendations	Public health and ethical rationale
Antenatal pharmacological care	• Daily folic acid: 5 mg (non-malaria zones); 400 µg with sulfadoxine–pyrimethamine • Iron only if deficiency documented • Prophylactic transfusion for women with prior severe crises	• Prevents adverse effects of excess folate • Preserves antimalarial efficacy • Minimizes crisis recurrence while balancing transfusion risks
Hydroxycarbamide use	• May continue/reinitiate after first trimester • Shared decision-making approach	• Promotes autonomy and individualized care • Moves beyond outdated blanket contraindications
Pain management strategy	• Individualized pain plans • Paracetamol, NSAIDs, opioids as per gestational stage/history	• Counters undertreatment of SCD pain • Respects patient preferences, reduces stigma, avoids misuse
Inpatient management protocols	• Careful fluid monitoring • Thromboprophylaxis unless contraindicated • Serial fetal scans: 24 wks (4-weekly to 32 wks), then 3-weekly	• Prevents pulmonary edema • Reduces thromboembolic risk • Enables early detection of fetal growth restriction
Labour and delivery planning	• Vaginal birth preferred unless contraindicated • Birth timing based on maternal–fetal risk and maternal preference	• Reduces unnecessary cesarean sections • Promotes safe, dignified, patient-centered delivery
Postnatal and interpregnancy care	• Monitor thrombotic complications • Newborn SCD screening • Breastfeeding support, contraception, early hydroxyurea reintegration	• Ensures maternal–newborn continuity of care • Supports safe reproductive planning • Promotes long-term disease control and parenting goals
Health system strengthening	• Invest in diagnostics, safe blood access, multidisciplinary teams, antenatal infrastructure	• Addresses systemic inequities • Calls for sustainable policy action in LMICs
Global health equity and research inclusion	• Frame SCD in pregnancy as maternal equity issue • Include pregnant/lactating women in SCD trials	• Corrects historical research exclusion • Advances reproductive justice and global accountability

dismissal, and delayed interventions. By emphasising shared decision-making, patient dignity, and provider training, the guideline affirms reproductive justice as a core value. To support implementation, a concise Table 1 summarising the WHO 2025 guideline's key clinical interventions, ethical principles, and system-level requirements is presented below. This framework clarifies the intersection between medical evidence, patient rights, and health system capacity, facilitating practical translation into care pathways. Nonetheless, implementation barriers persist. Many LMICs lack safe blood supplies, diagnostics, multidisciplinary teams, and routine antenatal monitoring. The WHO guideline must be viewed not only as a clinical roadmap but as a call for systemic reform. Investments in training, supply chains, and health infrastructure are essential [1].

This guideline also marks a paradigm shift. As the first in WHO's forthcoming series on noncommunicable diseases (NCDs) during pregnancy, it recognises chronic illness—long overlooked—as a significant contributor to maternal mortality [4, 5]. Future guidance on diabetes, cardiovascular disease, mental health, and respiratory conditions should adopt this equity-focused model.

Finally, it closes a long-standing ethical gap: excluding pregnant and lactating women with SCD from clinical trials. Their inclusion in future therapeutic studies is vital for ensuring safe, effective, and fair care.

In conclusion, WHO's guideline on SCD in pregnancy is more than just a clinical protocol; it is a transformative blueprint for maternal health equity. Rooted in autonomy, dignity, and inclusion, it sets a new global standard. The challenge now is to turn these recommendations into action, particularly in high-burden settings. With political will and strategic investment, it can become a cornerstone of safe and equitable motherhood for women living with SCD.

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Conflict of interest

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Data availability statement

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Supplementary file

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