

BANGLADESH JOURNAL OF MEDICINE

September 2025

Volume 36

Number 3

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OFFICIAL ORGAN OF
THE ASSOCIATION OF PHYSICIANS OF BANGLADESH



BANGLADESH JOURNAL OF MEDICINE

ISSN 1023 - 1986
eISSN 2408 - 8366

Vol. 36 No. 3, September 2025

Official Journal of the Association of Physicians of Bangladesh (APB)

Room: 1701, Block: D, Dept. of Medicine

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PUBLISHED BY

Prof. Aminur Rahman
on behalf of the Association of Physicians
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PRINTED AT

Asian Colour Printing
130 DIT Extension Road, Fakirerpool
Dhaka, Bangladesh
Phone : +88 02 58313186, +88 01835180135
E-mail: asianclr@gmail.com
Web: asiancolourprinting.com

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EDITORIAL

CHIKUNGUNYA RESURGENCE AFTER 8 YEARS IN BANGLADESH: NEW DIMENSION AND NEW THREAT OF RECENT OUTBREAK

QUAZI TARIKUL ISLAM¹, NAJEEB MAHIYUDDIN²

Chikungunya is caused by an *alphavirus* belonging to the *Togaviridae* family.¹ It is transmitted by *Aedes* mosquitoes. The name is derived from a South Tanzanian language meaning “that which bends,” describing the contorted posture of a chikungunya patient with joint pain.²

The first case of chikungunya was identified in Tanzania in 1952. In Africa, the virus is maintained in a sylvatic cycle between non-human primates (bats or monkeys) and *Aedes* mosquitoes. However, during epidemics the virus can be transmitted to humans without the need for an animal reservoir. The virus caused sporadic outbreaks in several parts of Africa. The first reported outbreak in Asia was in the Philippines in 1954. During the 1970s, localized outbreaks occurred in Thailand, Vietnam, Cambodia, Laos, Burma, Sri Lanka, Pakistan, and India. After 2000, major outbreaks were seen in several parts of the world. Epidemics were described in the Democratic Republic of Congo, Indonesia, the Comoros Islands, and Reunion. The virus reemerged in India in 2005-2006 after a hiatus of 32 years, affecting around 1.3 million people in over 13 districts.³ Since August 2024, chikungunya virus transmission has been widespread, with over 47,500 cases being reported and 12 deaths as of May 2025 in Reunion, France.⁴ The most recent outbreak was observed in Foshan City of Guangdong Province in China, with over 7000 new cases being detected in the past month.⁵

The first cases of chikungunya in Bangladesh were detected in 2008 in Rajshahi and Chapai Nawabganj. Subsequently, another minor outbreak occurred in

2011 at Dohar, Dhaka. In 2017, the largest outbreak of Chikungunya occurred in Bangladesh, resulting in 13,176 clinically confirmed cases in over 17 districts. Since the last outbreak, chikungunya infection has been relatively absent, with few sporadic cases being reported. Few cases were detected in late 2024.⁶ A recent report by the Institute of Epidemiology, Disease Control and Research (IEDCR) confirmed 337 cases of chikungunya between January and May 2025, out of which 153 cases were PCR positive. This report admitted that the burden of the disease has been underestimated and warned that a large-scale outbreak may be imminent.⁷

Analysis of 2,467 multiplex PCR samples over two months from one laboratory revealed 1,456 (59.0%) chikungunya positives, while only 149 of 1,420 (10.5%) serology tests (IgM/IgG) were positive. The high PCR positivity highlights that clinicians are largely accurate in suspecting chikungunya early and selecting the appropriate diagnostic modality. In contrast, the low yield of serology reflects frequent false negatives arising from premature testing. This emphasizes the critical need for greater awareness of diagnostic timing, with serology performed only after at least seven days of illness to ensure reliability. However, in reality hospital admission is less than 5% of the total affected population in the country. Due to very low mortality and high morbidity, patients are not even admitting to the hospital until the pain is severe or there is a complication. Almost 90% of the patients are being treated at home, and this is not being documented in the national health registry. The Directorate General Health Services (DGHS) has a dengue dashboard but

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Date of submission: 23.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.82066>.

Citation: Islam QT, Mahiyuddin N. Chikungunya Resurgence after 8 Years in Bangladesh: New Dimension and New Threat of Recent Outbreak. *Bangladesh J Medicine* 2025; 36(3): 80-82.

does not show any updates regarding chikungunya. There is no active surveillance of chikungunya in Bangladesh in recent years. This is of great concern, as the enormous burden of this disease on society is high. The impact and burden of chikungunya is much deeper and higher than expected and previous outbreaks. The disability of people is not being considered by the DALY score, which is a measure of healthy life lost in a population.

Clinical presentation of chikungunya can be divided into 3 stages—acute phase (< 3 weeks), sub-acute phase (3 weeks to 3 months), and chronic phase (> 3 months).⁸ Symptoms of chikungunya infection are fever, rash, headache, myalgia, arthralgia, and back pain.⁹ However, most of these features overlap with another common endemic infection in Bangladesh, known as dengue fever. Therefore, it is imperative for a clinician to be able to differentiate between these two infectious diseases. Arthralgia and arthritis are more commonly seen in chikungunya. In contrast, myalgia, hemorrhagic manifestations, and shock are frequently seen in dengue infection.¹⁰

Accurate diagnosis of arboviral infections remains a major challenge in Bangladesh. Multiplex PCR within the first week of illness offers definitive detection of chikungunya, dengue, or Zika, yet its high cost and limited availability to tertiary centers render it inaccessible for most patients. The more affordable ELISA, detecting chikungunya antibodies, is useful only after seven days of symptom onset and is confounded by cross-reactivity with dengue, often leading to false positives. Dengue can be differentiated by NS1 antigen testing in the early febrile phase—the first 3–5 days of symptom onset¹¹—but no comparable antigen assay exists for chikungunya in Bangladesh. Clinically, features such as leucopenia, rising hematocrit, and thrombocytopenia are characteristic of dengue¹⁰, while a biochemical profile showing AST levels greater than ALT provides an additional clue.¹² These diagnostic gaps highlight the urgent need for affordable, widely accessible, and disease-specific testing strategies to support timely surveillance and patient care.

During the current outbreak, patients with chikungunya have presented with some atypical features like a brownie nose, pneumonitis, and coinfection with human coronavirus NL63. Other uncommon features or complications seen are myocarditis, Guillain-Barré syndrome, meningo-encephalitis, acute hepatitis, kidney failure, and hemorrhage.¹³

The treatment is usually supportive. Rest, hydration, paracetamol, and, if needed, weak opioids can be used

in the acute phase of the disease. If nonsteroidal anti-inflammatory drugs (NSAIDs) cannot control pain, then steroids may be prescribed in the subacute phase. During the chronic phase of the condition, disease-modifying antirheumatic drugs (DMARDs) may be needed.⁸

Live attenuated virus vaccine, IXCHIQ, and recombinant virus vaccine, VIMKUNYA, are available abroad. They are indicated for use when a person is travelling to a chikungunya-endemic or high-risk area. The live attenuated vaccine is contraindicated in pregnancy and older people (age >65 years).¹⁴

Halting chikungunya outbreaks requires a coordinated response from government, communities, and individuals to curb the spread of *Aedes* mosquitoes. At the household level, simple measures such as eliminating stagnant water, covering storage containers, and maintaining a clean environment are essential first steps. Larvicides and insecticides remain important tools for reducing adult mosquito density, while personal protection through repellents, mosquito nets, screened windows and doors, and full-cover clothing can limit exposure. Beyond these conventional strategies, innovative approaches—including the release of larvivorous fish like *Gambusia*, the introduction of *Toxorhynchites splendens* mosquitoes that prey on larvae, and the deployment of *Wolbachia* bacteria to reduce viral transmission capacity—offer promising adjuncts.¹⁵ Yet, without sustained political commitment, proper surveillance, and accountability, these measures risk remaining fragmented and reactive, allowing outbreaks to recur with devastating regularity.

Despite alarming positivity rates—71% in Chattogram and over 82% in Dhaka's fever cases during June—chikungunya remained excluded from routine disease reporting platforms, unlike dengue and COVID-19.¹⁶ The Institute of Epidemiology, Disease Control and Research (IEDCR) reported rising case counts up to May 2025 but flagged the absence of a formal nationwide surveillance mechanism, limited diagnostic capacity, and the likelihood of significant underreporting.^{17,18} Chikungunya virus infection, though rarely fatal, invariably leaves patients with prolonged arthralgia and disability, resulting in a substantial public health burden. Despite this, surveillance and reporting systems in Bangladesh remain inadequate, with little prioritization by the Directorate General of Health Services (DGHS), the Institute of Epidemiology, Disease Control and

Research (IEDCR), or even broader agencies like the CDC. Strengthening surveillance is crucial not only to quantify the true disease burden but also to guide timely outbreak response, allocate resources effectively, and implement preventive strategies. Without systematic monitoring, chikungunya continues to be underestimated, leaving patients to suffer silently and the health system unprepared for future epidemics.

Keywords: Chikungunya Resurgence, New Dimension, New Threat, Recent Outbreak

Acknowledgement:

Mr. Asadur Rahman, Laboratory Manager, Popular Diagnostic Centre Limited, Dhaka, Bangladesh

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ELISA: Enzyme-Linked Immunosorbent Assay, PCR: Polymerase Chain Reaction

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ORIGINAL ARTICLE

CLINICAL PROFILE, LABORATORY FINDINGS AND QUALITY OF LIFE IN 100 PATIENTS WITH CHIKUNGUNYA VIRUS INFECTION - 2025 OUTBREAK IN BANGLADESH

NAJEEB MAHIYUDDIN¹, REFAYA TASNIM², ASIF AHMED³, ZAZEBA HOSSAIN³, QUAZI TARIKUL ISLAM⁴

Abstract

Background: After a period of absence, a resurgence of chikungunya has been seen in Bangladesh. Therefore, this study aimed at to detect the clinical spectrum, laboratory parameters, and quality of life (QoL) of chikungunya patients during the 2025 outbreak. **Methods:** This observational study was carried out at Popular Medical College Hospital, Bangladesh, over a period of 3 months, including 100 adult chikungunya patients. QoL was assessed using the EQ-5D-3L (European Quality of Life 5 Dimensions 3 Level Version) tool. **Results:** The mean (SD) age was 50.6 (18) years with female (61%) predominance. Common manifestations were joint pain (96%), fever (86%), myalgia (57%), and rash (53%). Frequently involved joints were ankle (71%), proximal interphalangeal (60%), metacarpophalangeal (58%), and distal interphalangeal (54%) joints. Chikungunya was confirmed by polymerase chain reaction (59%) and anti-chikungunya IgM (41%). Laboratory findings showed leukopenia (19%) and thrombocytopenia (24%). QoL assessment revealed problems with mobility (62%), usual activities (71%), self-care (51%), pain/discomfort (64%), and anxiety/depression (27%). The mean (SD) and median (IQR) for EQ-VAS (EuroQol Visual Analogue Scale) score were 43.9 (22.2) and 40 (30-63), respectively. **Conclusion:** Common clinical presentations were fever and joint pain with a high preponderance to ankle and hand joints. Few patients had leukopenia and thrombocytopenia. Most patients suffered from poor QoL.

Keywords: clinical profile, laboratory findings, quality of life (QoL), chikungunya infection, 2025 outbreak, Bangladesh, EQ-5D-3L.

Date of submission: 20.08.2025 Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.84068>.

Citation: Mahiyuddin N, Tasnim R, Ahmed A, Hossain Z, Islam QT. Clinical Profile, Laboratory Findings and Quality of Life in 100 Patients With Chikungunya Virus Infection - 2025 Outbreak In Bangladesh. *Bangladesh J Medicine* 2025; 36(3): 83-90.

Introduction:

The name chikungunya is derived from a Kimakonde word of Tanzania called “kungunyala”, meaning “that which bends up” or “to become contorted” highlighting the stooped posture adopted by an effected person due to severe joint pain.^{1, 2} It is caused by a single stranded RNA arbovirus from the Alphavirus genus of Togaviridae family and mainly transmitted by the bite

of Aedes mosquitoes.^{1, 3} The first case of chikungunya infection was detected at Tanzania in 1952 and subsequently it has spread to >110 countries with the greatest prevalence in Southeast Asia, Africa and the Americas.^{2, 4} Before 2000 outbreaks of chikungunya virus were rarely seen but probably due to evolutionary changes and increased travel, frequent outbreaks are being reported after the year 2000.⁵ The latest outbreak

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was observed in La Réunion, France, where over 47,500 cases were detected with 12 deaths as of May, 2025.⁶ Foshan city of Guangdong Province in China recently reported 7000 new cases of chikungunya in the last month.⁷

In Bangladesh, there were two minor outbreaks of chikungunya in 2008 and 2011, followed by a major outbreak with more than 13,000 clinically confirmed cases being detected in 2017.⁸⁻¹⁰ Thereafter, the condition nearly disappeared before it resurged again in late 2024. From 474 patients with febrile illness, 55 cases of chikungunya were detected by reverse transcription-polymerase chain reaction (RT-PCR) at International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR).¹¹ This led to the current outbreak with detection of around 153 confirmed cases from 337 suspected cases of chikungunya in the first 5 months of 2025 before even the start of monsoon season.¹²

Clinical spectrum and laboratory parameters have been described during the 2017 outbreak in Bangladesh.^{3, 13-15} It was noted that features were different among adults and children.¹⁴ Moreover, there were variation of clinical features with respect to geographical location.¹⁵ While reports in Bangladesh showed fever and arthralgia as the most common symptoms of infection with particular involvement of small joints of the hands, other studies showed knee joint involvement as the most prevalent site in India and Colombia.^{3, 15-17} There is yet no study published regarding the current outbreak of chikungunya infection. Hence, this study aims to determine the clinical profile, laboratory findings and quality of life (QoL) of chikungunya patients during the 2025 outbreak in Bangladesh.

Methods:

The study was conducted under the leadership and supervision of Professor Quazi Tarikul Islam, who created a panel, called CHIKV Study 2025, with a group of expert doctors for the purpose of this research. This was a cross-sectional observational study conducted in consecutive 100 laboratory confirmed adult chikungunya patients that either admitted to hospital or presented to outpatient services at Popular Medical College Hospital over a period of 3 months from June to August, 2025, excluding those patients suffering from hyperuricaemia, rheumatoid arthritis, other connective tissue disease and unwilling to give consent. Ethical clearance was taken from the Ethical Review Committee of Popular Medical College.

Data regarding socio-demographic characteristics (age, gender, religion, marital status, occupation, residence, contact number) and clinical presentation (duration from symptom onset to first consultation, fever, joint pain, joint swelling, joint redness, rash, myalgia, nausea/vomiting, retro-orbital pain, conjunctivitis, diarrhoea, past history of dengue/chikungunya, recent

travel history, contact with suspected chikungunya patient, mosquito bite, comorbidities, length of hospital stay if admitted) were collected in a case record form by direct interview from suspected chikungunya patients that gave informed written consent to participate in the study during first contact with the patient. Based on the patients' presentations, appropriate laboratory investigations were sent. Chikungunya was confirmed either by PCR when patient visited within 7 days of symptom onset or by antibody test when patient presented after 7 days. Multiplex PCR of patient's serum was done to detect dengue, chikungunya or zika virus using Rotor-Gene Q PCR system by QIAGEN, Germany. Anti chikungunya IgM and IgG antibodies were detected using ELISA (Enzyme-Linked Immunosorbent Assay). The results of the investigations such as PCR for chikungunya, anti chikungunya IgM & IgG, complete blood count, erythrocyte sediment rate (ESR), C-reactive protein (CRP), blood sugar, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine were recorded once available during second contact with the patient. Considering the patients' symptoms, severity and duration of joint pain and laboratory parameters, adequate treatment was prescribed by an expert consultant and documented in the case record form. All information were kept confidential and used only in the purpose of research.

The QoL of a patient was assessed using the EQ-5D-3L (European Quality of Life 5 Dimensions 3 Level Version) instrument, which is a 2 part questionnaire. The first part is the EQ-5D descriptive system that assess 5 dimensions of health (mobility, usual activities, self-care, pain/discomfort and anxiety/depression) based on 3 problem levels (no problems, some problems and extreme problems). The patients were explained about the questionnaire. The interviewer read out the questionnaire in full and based on the patients' reply, ticked boxes that indicate problem levels the patients' experienced on each of the 5 dimensions. The second part consists of EQ VAS (EuroQol Visual Analogue Scale), which addresses the patients' overall assessment of their own health in a scale of 0 (worst health imaginable) to 100 (best health imaginable).¹⁸

All data were input into and analyzed using Statistical Packages for Social Sciences (SPSS) software version 26. Qualitative variables were presented as numbers and percentages while quantitative data were shown as mean (standard deviation) or median (interquartile range). All the results were expressed in tabular form except EQ VAS score, which was represented in a frequency distribution graph.

Results:**Table I***Sociodemographic and clinical characteristics of patients with chikungunya (n=100)*

Characteristics		Number (%)
Age (years)	18 – 64	75 (75%)
	> 64	25 (25%)
	Mean $\pm$ SD	50.6 $\pm$ 18
Gender	Male	39 (39%)
	Female	61 (61%)
Religion	Muslim	85 (85%)
	Hindu	13 (13%)
	Christian	2 (2%)
Marital status	Married	89 (89%)
	Unmarried	11 (11%)
Occupation	Government service	9 (9%)
	Private service	22 (22%)
	Businessman	7 (7%)
	Student	8 (8%)
	Unemployed	45 (45%)
	Self-employed	4 (4%)
	Others	5 (5%)
Residence	Urban	91 (91%)
	Rural	9 (9%)
Comorbidities	Diabetes Mellitus	44 (44%)
	Hypertension	51 (51%)
	Chronic Kidney Disease	6 (6%)
	Chronic Liver Disease	2 (2%)
	Ischaemic Heart Disease	12 (12%)
	Hypothyroidism	12 (12%)
	Past history of dengue or chikungunya	23 (23%)
	Recent travel history	8 (8%)
	Contact with suspected chikungunya patient	27 (27%)
	Mosquito bite	59 (59%)
Patient source	Clinical features of dengue	41 (41%)
	Duration to first consultation from symptom onset (days)(mean $\pm$ SD)	7.2 $\pm$ 9.1
Patient source	Outpatient	58 (58%)
	Hospital admission	42 (42%)
	Duration of hospital stay if admitted (days) (mean $\pm$ SD)	3.9 $\pm$ 2.3
Clinical presentation	Fever	86 (86%)
	Joint pain	96 (96%)
	Joint swelling	42 (42%)
	Joint redness	24 (24%)
	Rash	53 (53%)
	Muscle pain	57 (57%)
	Nausea/vomiting	53 (53%)
	Retro-orbital pain	8 (8%)
	Conjunctivitis	8 (8%)
	Diarrhoea	19 (19%)
	Paracetamol	78 (78%)
	Nonsteroidal anti-inflammatory drug	57 (57%)
	Steroid	20 (20%)

SD = Standard deviation

Around 100 laboratory confirmed chikungunya cases were included in the study. The mean age (standard deviation) of the study population was 50.6 (18) years with 75 % of the patients belonging between 18 to 64 years of age group. The median (interquartile range) age was 55 (35-64) years with female (61%) preponderance. Less than half (45%) of the chikungunya effected patients were unemployed. Most of the patients (91%) were living in the urban area. The common comorbidities in the study population were hypertension (51%) and diabetes mellitus (44%). Around 23% of the patients had past history of dengue or chikungunya and 27 patients had contact with suspected chikungunya patients. Clinical features similar to dengue were found in almost half of the patients (41%) and 59 patients could recall being exposed to recent mosquito bites. While most of the patient took outpatient service (58%), some patients had to get admitted to hospital (42%) for better management. The duration of hospital stay was around 3.9 $\pm$ 2.3 days. The most common presenting feature was joint pain (96%) and fever (86%). Almost half of the patients presented with joint swelling (42%), rash (53%), nausea/vomiting (53%) and myalgia (57%). Interestingly, 19 patients suffered from loose motion. Majority of the patients were treated with paracetamol (78%) followed by nonsteroidal anti-inflammatory drugs (57%) (Table I)

Table II*Pattern of joint involvement of chikungunya patients (n=100)*

Characteristics	Number (%)
Number of joints	
Single	13 (13%)
Multiple	83 (83%)
Type of joints	
Small joint	6 (6%)
Large joint	29 (29%)
Both	61 (61%)
Site of joints	
Distal interphalangeal joint	54 (54%)
Proximal interphalangeal joint	60 (60%)
Metacarpophalangeal joint	58 (58%)
Wrist joint	47 (47%)
Elbow joint	32 (32%)
Shoulder joint	33 (33%)
Hip joint	2 (2%)
Knee joint	36 (36%)
Ankle joint	71 (71%)
Spine	8 (8%)

Table II shows the pattern of joint involvement. Around 83 patients complained of multiple joint pain with involvement of both small and large joints (61%) being the common presentation. The most frequently effected joint was ankle joint (71%), followed by proximal interphalangeal joint (60%), metacarpophalangeal joint (58%), distal interphalangeal joint (54%) and wrist joint (47%).

Table III
Laboratory parameters of chikungunya patients (n=100)

Parameters	Number (%)
Chikungunya serology	
PCR positive	59 (59%)
Antibody positive	41 (41%)
Haemoglobin (g/dl)	12.1 ± 1.3 (mean ± SD)
White blood cell count (/mm ³)	6655.4 ± 2700.7 (mean ± SD)
Leucopenia (white blood cell < 4000/mm ³)	19 (19%)
Platelet count (/mm ³)	209809 ± 86865.2 (mean ± SD)
Thrombocytopenia (platelet < 150,000/mm ³)	24 (24%)
Haematocrit (%)	36.8 ± 5 (mean ± SD)
ALT (U/L)	39.1 ± 30.7 (mean ± SD)
Raised ALT (ALT > 40 U/L)	24 (24%)
AST (U/L)	37.1 ± 22.6 (mean ± SD)
Raised AST (AST > 40 U/L)	15 (15%)

SD = Standard deviation

Table IV
Quality of life assessment according to health dimensions and problem levels (n=100)

	Mobility	Self-care	Usual activities	Pain/Discomfort	Anxiety/Depression
	n (%)	n (%)	n (%)	n (%)	n (%)
No problems	38 (38%)	49 (49%)	29 (29%)	36 (36%)	73 (73%)
Some problems	59 (59%)	49 (49%)	66 (66%)	58 (58%)	26 (26%)
Extreme problems	3 (3%)	2 (2%)	5 (5%)	6 (6%)	1 (1%)
Any problems	62 (62%)	51 (51%)	71 (71%)	64 (64%)	27 (27%)

Around 59 patients were positive for chikungunya PCR and the rest (41%) showed presence of chikungunya antibody in their serum (Table 3). Leucopenia was seen in 19% patients and thrombocytopenia in 24% of the patients. Raised SGPT and SGOT were found in 24% and 15% of the patients respectively.

The QoL assessment according to health dimensions was presented in Table 4. Around 62% patients had problems with mobility, 51% faced issues with self-care, 70% had difficulties with usual activities, 64% suffered from pain/discomfort and 27% complained of anxiety/depression.

The mean (standard deviation) and median (interquartile range) for EQ-VAS (EuroQol Visual Analogue Scale) score was 43.9 (22.2) and 40 (30-63) respectively. The frequency distribution curve shows most of the patients had EQ-VAS score of ≥ 50 (68%), representing poor QoL (Figure 1).

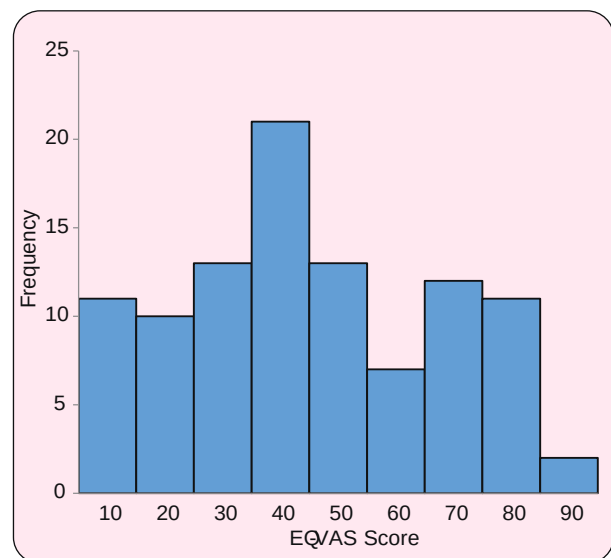


Figure 1. Frequency distribution of EQ-VAS (EuroQol Visual Analogue Scale) score of the study population (n=100)

Discussion:

This study aimed to look at the clinical spectrum, laboratory parameters and QoL of 100 chikungunya patients during the 2025 outbreak in Bangladesh. The mean and median age in the current study was found to be higher than the previous outbreak that occurred in Bangladesh back in 2017.^{3, 13-15} Additionally, chikungunya effected lower aged patients in India, Pakistan and Philippines as well.¹⁹⁻²¹ However, similar mean age to current study was reported in Thailand and Colombia.^{17, 22} None of the studies showed any specific predilection to a particular age group. The high incidence of chikungunya between the ages 18-64 years may just represent increased number of population in that particular age group in Bangladesh.²³

Majority of the women were effected in this study. Similar result was also seen in a study of 148 patients during the 2017 outbreak in Bangladesh and other studies as well.^{14, 17, 20, 22} This may be explained by the fact that most Bangladeshi women like to spend time inside the house and Aedes mosquitoes are more prevalent indoors.^{14, 24} In contrast, there are studies in Bangladesh and abroad with male preponderance.^{3, 25-27} Meanwhile, some research findings show unremarkable gender distribution.^{15, 16, 19}

The common comorbidities in the present case series were diabetes mellitus and hypertension, which was also similar in previous studies.^{3, 13, 16} Only 23% of patients with past history of dengue or chikungunya were effected, suggesting possible immunological protection due to previous infection. However, further research is required on this issue. Fever and joint pain were the most prevalent presenting features with almost 50% of patients having myalgia, rash and nausea/vomiting in this study. The trend has not changed with similar clinical features seen in other research works.^{3, 13-15, 19, 20} Interestingly, 19% patients had diarrhea. This finding was much lower compared to another study, showing 52.4% patients with dysentery-like symptoms.¹⁴

Multiple small and large joint pain, particularly in the ankle (71%) and small joints of the hand (>50%) were observed in the present study. Two other Bangladeshi studies during the previous outbreak showed similar joint pattern involvement but they also showed higher involvement of knee joint compared to current study.^{13, 14} Similarly, hand and ankle joints were commonly involved in Colombia.^{17, 28} Another large study of 685 patients in Bangladesh during the previous outbreak found wrist and small joints of the hand as the most effected joint with approximately 35% of patients having ankle and knee joint pain.³ An old Thailand

study described frequent involvement of small joints of the hand along with knee joint.²² A study in India during 2019-2020 reported maximum involvement in the knee joint (46%).¹⁶ Ankle joint seem to be frequently effected in this outbreak compared to the previous one in 2017.

There are no specific biochemical tests that can diagnose chikungunya infection. Results obtained can give a suggestive interpretation of the viral infection. Leucopenia was seen in 19% patients and almost one-fourth of the study population had thrombocytopenia. Previous Bangladeshi study found lower incidences leucopenia (10.4%) and thrombocytopenia (5.9%).³ Thus, showing a changing pattern from previous outbreak. Similar results were also seen in Thailand with 11.1% leucopenia and 13.3% thrombocytopenia but a study in Kerala reported almost 70% patients had leucopenia and 18% had thrombocytopenia.¹⁶ Another study in Thailand reported 11.1% of patients with leucopenia, 13.3% thrombocytopenia and 30% had elevated liver enzymes.²² Fewer patients had raised liver enzymes in the current study. However, the study conducted in Pakistan found normal levels of AST and ALT.²¹

While assessing QoL, most of the patients had difficulties with usual activities (71%) followed by pain/discomfort (64%) and mobility problems (62%). Almost half of the patients had troubles with self-care. The poor QoL was also representative in the EQ-VAS score, where most of the patients gave a low scoring. Similar results of poor QoL were seen in another study, which used QoL questionnaire endorsed by world health organization (WHO).¹³ Two other studies used visual analogue scale (VAS), where high score indicates more pain, to measure pain levels in patients with acute chikungunya infection. Most of the patients reported a high score.^{29, 30}

The changes in pattern of clinical presentation and laboratory parameters in different outbreaks may be difficult to explain. Different strains of chikungunya virus maybe the culprit. During the 2017 outbreak in Bangladesh, the East/Central/South African (ECSA) genotype was isolated.³¹ A recent phylogenetic analysis of the virus in 2024 revealed a new-sublineage within this ECSA genotype.²⁵

This study is not without its limitation. ELISA was used to detect antibody in the serum for some patients. In a country like Bangladesh, which is endemic to dengue infection, cross reactivity with ELISA may be a possibility, leading to false positive results. However, it is important to recall that tests were done during an outbreak with clinical features suggestive of chikungunya infection. EQ-5D-3L instrument used for

measuring QoL may have a high ceiling effect (most people report no problems in all the dimensions, reducing sensitivity to mild health issues) and have limited capability to detect moderate changes in health.³² Nevertheless, this tool is easy to use and recommended by professional organizations.³³ Since there was no follow-up, outcome could not be measured. While this report is an initial presentation of 100 patients, the study will continue and follow up will be done to detect outcome and long term sequelae.

Conclusion:

Despite limitations, the study provided an early knowledge regarding the 2025 chikungunya outbreak in Bangladesh. Most of the patients presented with fever and multiple joint pain, involving frequently the ankle joints and small joints of the hands. Patients may have leucopenia, thrombocytopenia with elevated liver enzymes, but the frequency of these findings is low. Majority of patients suffered from poor QoL.

Acknowledgments:

The authors thank all patients, health physicians, nurses and other health care providers involved in the care of these patients of Department of Medicine, Popular Medical College Hospital for their kind help and co-operation.

Funding:

This research did not receive any specific grant from any funding agencies

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Popular Medical College. Written informed consent was taken from all the patients before taking part of the study.

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ORIGINAL ARTICLE

CORRELATION OF RED CELL DISTRIBUTION WIDTH WITH STROKE SEVERITY AND SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

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Abstract:

Background: Red cell distribution width (RDW) has been proposed as an independent predictor of acute ischemic stroke (AIS) severity and outcomes. This study aimed to evaluate whether RDW alone can serve as a predictor of functional outcome at three months following AIS. **Methods:** In this prospective cohort study (July 2024–June 2025), patients with AIS were categorized into quartiles based on admission RDW values. Baseline characteristics were compared using Pearson's chi-square or Fisher's exact tests for categorical variables and the Mann–Whitney U test for continuous variables. Univariable and multivariable binary logistic regression analyses were performed to identify predictors of three-month functional outcome, assessed by the modified Rankin Scale (mRS 0–2 vs. 3–6). **Results:** Most patients had RDW values between 12% and 15%, with a small subset showing elevated RDW (>16%). At three months, the majority achieved good recovery (mRS 0–2). In univariable analysis, lower diastolic blood pressure was associated with greater odds of functional independence, whereas smoking, higher NIHSS score at admission, and severe baseline disability were significantly associated with lower odds. In the multivariable model, smoking and severe disability at admission remained significant, while the NIHSS score was significant at the 10% level of significance. **Conclusion:** In this prospective cohort study, admission RDW was not independently related with three-month functional outcomes following acute ischemic stroke. The findings suggest that RDW has limited value as a standalone prognostic biomarker in the early post-stroke period.

Keywords: Acute ischemic stroke; Functional Outcome; Red cell distribution.

Date of submission: 10.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.84213>.

Citation: Rahman A, Russel AHM, Yasmin S, Huq MN, Tasnim Z, Noni TK et al. Correlation of Red Cell Distribution Width with Stroke Severity and Short Term Functional Outcome in Acute Ischemic Stroke. *Bangladesh J Medicine* 2025; 36(3): 91-100.

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Introduction:

Red cell distribution width (RDW), which is frequently measured by automated cell counters¹, represents the volume of red blood cells. The circulating erythrocyte size variability measurement method is represented by the erythrocyte size variation coefficient². Previous research has found that RDW is associated with the incidence of all-cause mortality^{4,5} and the prognosis of patients with cardiovascular illnesses such as coronary heart disease³, heart failure^{6,7} and others. This study has been enrolled all individuals at high risk of acute ischemic stroke.

Red blood cell distribution width (RDW) is a widely used metric for determining the size distribution of erythrocytes and the cause of anemia. Its value can be high in a variety of different conditions, including chronic liver disease, autoimmune disorders, and cancer, as well as after a blood transfusion.³⁻⁵

RDW has recently received attention for its connections with a variety of cardiovascular diseases^{3,6-8}, as well as overall mortality.⁹ Higher RDW values have been linked to telomere shortening circumstances, including aging, oxidative stress, increased inflammatory biomarkers, dyslipidemia, and a high (≥ 2) CHA2DS2-VASC score in patients with atrial fibrillation (AF)¹⁰. and other disorders that can also be related to the etiology and prognosis of AIS, working as a potent biomarker associated with inflammation.

A large population-based prospective study found an independent association between elevated RDW and the risk of stroke in people with coronary disease over a median follow-up of five years.¹¹ Studies have indicated that elevated RDW levels may be a useful indication of severity and poor clinical outcome in patients with ischemic stroke, even though the precise underlying pathophysiology is yet unknown.¹²⁻¹⁴ There are still conflicting findings in the literature on this subject, specifically in relation to its relationship to functional outcome after a stroke. For example, in patients with ischemic stroke, a recent study demonstrated a correlation between greater RDW values and both the severity of the stroke and the functional prognosis at 3 months.¹² Additionally, research demonstrated that in patients with ischemic stroke, a larger RDW was a predictor of poor functional outcomes at three months^{13,14}, and increased mortality.¹⁵ Furthermore, ischemic

stroke patients with higher baseline RDW are more likely to have a poor long-term prognosis and to die.¹⁶ Recent research confirms this.

According to the World Health Organization, Bangladesh has the world's 84th highest rate of stroke-related mortality.¹⁷ Bangladesh has normalized stroke death rates by age and gender to 54.8 per 100,000, while stroke-adjusted life years lost are 888.1 per 100,000.¹³ Stroke victims inflict a substantial financial burden on themselves, their families, and the nation, with long-term implications.¹⁷

Given the high prevalence of stroke, identifying markers to determine clinical severity and prognosis is becoming increasingly important. There is a lack of research on the effect of RDW on stroke severity and functional outcomes in Bangladeshi people with ischemic strokes. Our aim is to investigate the relationship between RDW and stroke severity, as well as short-term functional outcomes in patients with ischemic stroke in the Bangladeshi population. Improve the quality of life for the elderly by incorporating greater plan management and stroke prevention.

Methods:

This prospective cohort study was conducted in the department of neurology, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh from July 2024 to June 2025 to examine the association between red cell distribution width (RDW) and both stroke severity and short-term functional outcomes in patients with acute ischemic stroke (AIS). The study was carried out at a tertiary care center, where patients were consecutively enrolled upon admission with a confirmed diagnosis of AIS based on clinical presentation and neuroimaging findings (CT or MRI). The duration of the study spanned a predefined period, during which eligible patients were recruited.

A total of 100 patients were included in the study. Inclusion criteria comprised adult patients (≥ 18 years) with radiologically confirmed AIS. Patients were excluded if they had hemorrhagic stroke, transient ischemic attacks, hematologic disorders, chronic systemic inflammatory conditions, advanced malignancies, or other medical conditions that could influence RDW levels. Written informed consent was obtained from all participants or their legal guardians before enrollment.

Clinical data were collected at three time points: at admission, during hospital stay, and at a follow-up visit three months post-stroke. A structured case record form was used to capture demographic information (age, sex, date of admission/discharge, and contact number), clinical presentation, comorbidities (e.g., hypertension, diabetes mellitus, atrial fibrillation, smoking status, previous stroke, MI/IHD), and vital signs including systolic and diastolic blood pressure. The timing and nature of stroke symptoms were also documented.

Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) at the time of admission.^{18,19} The NIHSS score ranges from 0 to 42 and assesses various neurological domains. Patients were categorized based on NIHSS scores as having minor (1–4), moderate (5–15), moderate to severe (16–20), or severe strokes (21–42). Functional status was assessed using the modified Rankin Scale (mRS) at admission and again at the 3-month follow-up.²⁰ The mRS score ranges from 0 (no symptoms) to 6 (death), and for analytical purposes, patients were dichotomized into functionally independent (mRS 0–2) and dependent (mRS 3–6).

At admission, venous blood samples were drawn to assess red cell distribution width (RDW, %), hemoglobin (g/L), random blood sugar (mmol/L), serum creatinine ($\mu\text{mol/L}$), and lipid profile parameters including total cholesterol, HDL, LDL, and triglycerides (mg/dL). RDW values were divided into quartiles: Q1 (11.3–12.7%), Q2 (12.8–13.3%), Q3 (13.4–13.9%), and Q4 (14.0–21.7%). Neuroimaging findings from CT or MRI scans were reviewed to identify infarct locations, including the frontal, temporal, occipital, frontoparietal, temporoparietal, thalamic, and basal ganglia regions.

Data analysis was performed using Stata version 16.0. Continuous variables were expressed mean value, and categorical variables were summarized as frequencies and percentages. Comparisons across RDW quartiles and between functional outcome groups were performed using the Pearson's chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. A correlation matrix was generated to explore

associations among RDW, NIHSS, mRS, and other variables. Univariable and multivariable binary logistic regression analyses were conducted to identify predictors of functional independence at 3 months. Variables that were statistically significant in the univariable model or deemed clinically relevant were included in the multivariable analysis. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were reported. The final model included variables such as diastolic blood pressure, smoking status, NIHSS score, baseline mRS score, RDW quartile, and basal ganglia involvement. A p-value of less than 0.05 was considered statistically significant.

Results:

A total of 100 patients with acute ischemic stroke were included, with a mean age of 66 years. The cohort consisted of 59 males (58.4%) and 41 females (41.6%). The mean systolic and diastolic blood pressures at admission were 131 mmHg and 84 mmHg, respectively. Hypertension was the most common comorbidity (64.4%), followed by diabetes mellitus (42.6%) and atrial fibrillation (36.6%). Nearly half of the patients (46.5%) were smokers, while 22.8% had a history of previous stroke and 16.8% reported myocardial infarction or ischemic heart disease. Stroke severity, measured by NIHSS, showed a mean score of 8.37. Based on severity categories, 35.6% of patients had minor stroke, 49.5% moderate stroke, 5.0% moderate-to-severe stroke, and 9.9% severe stroke. Functional status at admission, measured by the modified Rankin Scale (mRS), had a mean score of 3.62. Most patients presented with moderately severe disability (45.5%) or severe disability (27.7%), while smaller proportions had no significant, slight, or moderate disability. Neuroimaging revealed that the most frequently affected regions were the frontoparietal (43.6%) and temporal lobes (39.6%), followed by the frontal (28.7%) and occipital lobes (27.7%). Additional involvement was noted in the thalamus (20.8%), temporoparietal region (16.8%), and basal ganglia (10.1%). The lipid profile showed a mean total cholesterol of 199 mg/dL, LDL 156 mg/dL, HDL 44 mg/dL, and triglycerides 231 mg/dL (Table I).

Table I
Socio Demographic and Health characteristics of patients.

Characteristics	Categories	Frequency (%)
Age (years)		66
Gender	Male	59 (58.4%)
	Female	41 (41.6%)
Blood pressure	Systolic BP (mmHg)	131.08
	Diastolic BP (mmHg)	84.19
Medical History	Hypertension	65 (64.4%)
	Diabetes Mellitus	43 (42.6%)
	Atrial Fibrillation	37 (36.6%)
	Smoking Habit	47 (46.5%)
	Previous Stroke	23 (22.8%)
	MI/IHD	17 (16.8%)
NIH Stroke Scale (NIHSS)	Mean	8.37
	Minor Stroke	36 (35.6%)
	Moderate Stroke	50 (49.5%)
	Moderate to Severe Stroke	5 (5.0%)
	Severe Stroke	10 (9.9%)
Modified Rankin Scale (mRS) at admission	Mean	3.62
	No significant disability	16 (15.8%)
	Slight disability	7 (6.9%)
	Moderate disability.	4 (4.0%)
	Moderately severe disability	46 (45.5%)
	Severe disability	28 (27.7%)
Radiological Findings (CT/MRI)	Frontal Lobe	29 (28.7%)
	Temporal Lobe	40 (39.6%)
	Occipital Lobe	28 (27.7%)
	Frontoparietal	44 (43.6%)
	Temporoparietal	17 (16.8%)
	Thalamus	21 (20.8%)
	Basal Ganglia	10 (10.1%)
Lipid Profile and Blood Markers	Cholesterol (mg/dL)	199 (38)
	HDL (mg/dL)	44 (13)
	LDL (mg/dL)	156 (42)
	Triglycerides (mg/dL)	231 (102)

*Data presented as n (%) for categorical data and mean for continuous data. NIHSS score: Minor Stroke=NIHSS1-4; Moderate Stroke=NIHSS5-15; Moderate to Severe Stroke=NIHSS 16 -20; Severe Stroke = NIHSS 21- 42; mRS score: 1-No significant disability; 2-Slight disability; 3-Moderatedisability; 4-Moderately severe disability; 5-Severe disability; 6 - Dead.

Baseline Characteristics of Patients Stratified by Red Cell Distribution Width Quartiles

Table 2 summarizes the baseline characteristics across RDW quartiles. Age showed a progressive increase, with patients in Q4 being older on average than those in Q1 ($p = 0.048$). Sex distribution, blood pressure, and most comorbidities (hypertension, diabetes, smoking, prior stroke, MI/IHD) did not differ significantly between quartiles. However, atrial fibrillation was significantly more common in higher RDW groups, particularly Q3 (63.6%) compared to Q1 (18.5%) ($p = 0.008$). Stroke severity (NIHSS) ranged from 5.9 in Q1 to 10.6 in Q4, but this difference did not reach statistical

significance ($p = 0.223$). Similarly, functional status at admission (mRS) did not differ overall ($p = 0.182$), though patients in Q3 and Q4 more frequently presented with moderately severe or severe disability. Radiological findings demonstrated a notable difference in frontoparietal involvement, which was highest in Q4 (64%) compared to 26% in Q1 ($p = 0.009$). Other regions, including frontal, temporal, occipital, temporoparietal, thalamus, and basal ganglia, did not show significant quartile-specific differences. Lipid profiles and blood markers were largely comparable across quartiles, although LDL and triglyceride levels showed borderline variation, with lower LDL in Q4 and lower triglycerides in Q3 ($p = 0.057$ and $p = 0.071$, respectively).

Table II
Baseline Characteristics of the Study Population Stratified by RDW Quartile

	Red Cell Distribution Width Quartiles				
Variable	RDW-Q1	RDW-Q2	RDW-Q3	RDW-Q4	p-
	(n=27)	(n=27)	(n=22)	(n=25)	value
Demographic History					
Age (years)	63.14	68.74	62.31	70.64	0.048
Sex - Male	17 (63.0%)	16 (59.3%)	12 (54.5%)	14 (56.0%)	0.933
Systolic BP (mmHg)	134.81	127.22	132.95	129.61	0.635
Diastolic BP (mmHg)	88.11	82.59	85.68	80.4	0.381
Medical History					
Hypertension	18 (66.7%)	16 (59.3%)	17 (77.3%)	14 (56.0%)	0.435
Diabetes Mellitus	9 (33.3%)	12 (44.4%)	11 (50.0%)	11 (44.0%)	0.683
Atrial Fibrillation	5 (18.5%)	11 (40.7%)	14 (63.6%)	7 (28.0%)	0.008
Smoking Habit	13 (48.1%)	14 (51.9%)	10 (45.5%)	10 (40.0%)	0.856
Previous Stroke	6 (22.2%)	7 (25.9%)	6 (27.3%)	4 (16.0%)	0.786
MI/IHD	3 (11.1%)	4 (14.8%)	4 (18.2%)	6 (24.0%)	0.647
Stroke Severity and Functional Status					
NIHSS	5.88	9.29	7.81	10.56	0.223
mRS at Admission					
No significant disability	4 (12.5%)	4 (31.3%)	4 (31.3%)	4 (25.0%)	0.182
Slight disability	4 (57.1%)	1 (14.3%)	0 (0.0%)	2 (28.6%)	
Moderate disability.	2 (50.0%)	1 (25.0%)	0 (0.0%)	1 (25.0%)	
Moderately severe disability	16 (34.8%)	8 (17.4%)	11 (23.9%)	11 (23.9%)	
Severe disability	3 (10.7%)	12 (42.9%)	6 (21.4%)	7 (25.0%)	
Radiological Findings (CT/MRI)					
Frontal Lobe	6 (22.2%)	9 (33.3%)	8 (36.4%)	6 (24.0%)	0.584
Temporal Lobe	12 (44.4%)	11 (40.7%)	9 (40.9%)	8 (32.0%)	0.826
Occipital Lobe	7 (25.9%)	7 (25.9%)	10 (45.5%)	4 (16.0%)	0.154
Frontoparietal	7 (25.9%)	15 (55.6%)	6 (27.3%)	16 (64.0%)	0.009
Temporoparietal	3 (11.1%)	4 (14.8%)	4 (18.2%)	6 (24.0%)	0.647
Thalamus	8 (29.6%)	4 (14.8%)	6 (27.3%)	3 (12.0%)	0.308
Basal Ganglia	2 (7.4%)	4 (14.8%)	3 (13.6%)	1 (4.0%)	0.521
Lipid Profile and Blood Markers					
Cholesterol (mg/dL)	199 (36)	197 (45)	202 (46)	201 (56)	0.669
HDL (mg/dL)	44 (12)	44 (12)	46 (10)	40 (12)	0.181
LDL (mg/dL)	166 (31)	156 (41)	151 (73)	147 (44)	0.057
Triglycerides (mg/dL)	232 (98)	222 (104)	191 (75)	237 (71)	0.071

*Data presented as n (%) and mean for continuous data. The significance level was obtained by Mann-Whitney U and Pearson's Chi-Square tests, as applicable. The patients were stratified into four groups based on the Red Cell Distribution Width quartile distribution (Q1-11.3-12.7 %; Q2-12.8-13,3 %; Q3-13.4-13.9 %; Q4-14.0- 21.7 %)

Figure 1 demonstrates the distribution of modified Rankin Scale (mRS) scores stratified by quartiles of red cell distribution width (RDW). Patients in the lower RDW quartiles (Q1 and Q2) were more likely to have favorable functional outcomes (mRS 0–2), whereas those in the higher RDW quartiles (Q3 and Q4) showed a greater proportion of poor outcomes (mRS 3–6).

Table III summarizes patient characteristics stratified by 3-month functional outcome. Patients who achieved functional independence (mRS 0–2) had significantly lower diastolic blood pressure (77 vs. 87 mmHg, $p = 0.015$) and NIHSS scores at admission (mean 6.8 vs. 12.2, $p = 0.001$), while systolic BP was lower but borderline significant ($p = 0.067$). Smoking was significantly more frequent among dependent patients ($p = 0.004$). Admission functional status strongly predicted outcome ($p < 0.001$): severe disability (mRS = 5) was markedly more common in dependent patients (55.2%) compared to independent patients (16.7%). Among neuroimaging variables, basal ganglia infarction was significantly associated with dependency (56.1% vs. 20.7%, $p = 0.024$), whereas lesions in other regions (frontal, temporal, occipital, thalamus, parietal subregions) showed no significant differences. No significant variation was observed in lipid profiles (total

cholesterol, HDL, LDL, triglycerides) or in RDW quartile distribution between outcome groups.

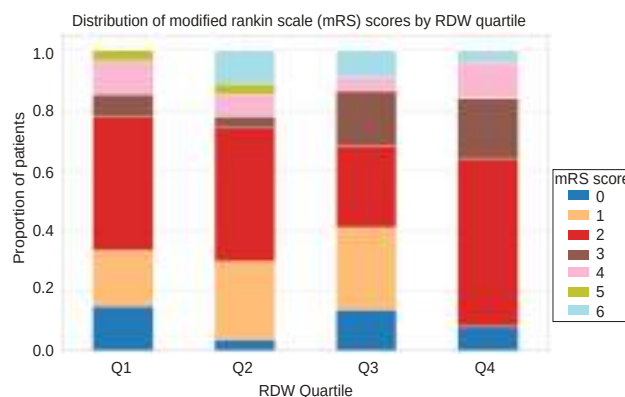


Figure 1: Distribution of after 3 months modified Rankin Scale (mRS) score stratified by Red Cell Distribution Width Quartile (RDW-Q1 to RDW-Q4).

Table-III

Characteristics	Categories	Functional Outcome		p value
		Independent (mRS 0 to 2)	Dependent (mRS 3 to 6)	
Age (years)		68.41	65.47	0.275
Gender	Male	18 (62%)	41 (56.9%)	0.636
	Female	11 (38%)	31 (43.1%)	
Blood pressure	Systolic BP (mmHg)	123.27	134.23	0.0669
	Diastolic BP (mmHg)	77.37	86.94	
Medical History	Hypertension	17 (58.6%)	48 (66.7%)	0.445
	Diabetes Mellitus	13 (44.8%)	30 (69.8%)	0.771
	Atrial Fibrillation	8 (27.6%)	29 (67.4%)	0.231
	Smoking Habit	20 (69.0%)	27 (62.8%)	0.004
	Previous Stroke	10 (34.5%)	13 (30.2%)	0.075
	MI/IHD	3 (10.3%)	14 (32.6%)	0.269
	Mean	12.17	6.84	0.0014
NIH Stroke Scale (NIHSS) Modified Rankin Scale (mRS) at admission	No significant disability	15 (20.8%)	1 (3.4%)	0.0001
	Slight disability	6 (8.3%)	1 (3.4%)	
	Moderate disability.	3 (4.2%)	1 (3.4%)	
	Moderately severe disability	36 (50%)	10 (34.5%)	
	Severe disability	12 (16.7%)	16 (55.2%)	
Radiological Findings (CT/MRI)	Frontal Lobe	5 (17.2%)	24 (58.5%)	0.205
	Temporal Lobe	12 (41.4%)	17 (41.5%)	0.817
	Occipital Lobe	10 (34.5%)	19 (46.3%)	0.335
	Frontoparietal	9 (31.0%)	20 (48.8%)	0.107
	Temporoparietal	3 (10.3%)	14 (34.1%)	0.269
	Thalamus	5 (17.2%)	24 (58.5%)	0.577
	Basal Ganglia	6 (20.7%)	23 (56.1%)	0.024
	Mean	12.17	6.84	0.0014
Lipid Profile and Blood Markers	Cholesterol (mg/dL)	199 (54)	199 (43.5)	0.2861
	HDL (mg/dL)	44 (14)	44 (11.5)	0.3745
	LDL (mg/dL)	159 (43)	156 (41)	0.7867
	Triglycerides (mg/dL)	230 (125)	231 (91)	0.6629
	Mean	12.17	6.84	0.0014
Red Cell Distribution Width	RDW-Q1	21 (29.1%)	6 (22.2%)	0.703
	RDW-Q2	20 (27.7%)	7 (25.9%)	0.75
	RDW-Q3	15 (20.8%)	7 (25.9%)	0.451
	RDW-Q4	16 (22.25)	9 (26.5%)	0.277

* Data presented as n (%) and mean for continuous data. The significance level was obtained by Mann-Whitney U and Pearson's Chi-Square tests, as applicable; Functional outcome was evaluated by dichotomization of the mRS, with patients with an mRS of 2 or below being considered independent and of 3 or above being considered dependent or dead.

Table IV
Binary logistic regression analyses for functional independence at 3 months.

Variable	OR [CI]	P value	Adjusted OR [CI]	P value
Diastolic BP (mmHg)	0.97 [0.94–0.99]	0.011	0.96 [0.92–0.99]	0.021
Smoking Habit (Ref: No)	3.70 [1.48–9.29]	0.005	7.67 [2.03–28.98]	0.003
NIHSS	1.11 [1.04–1.18]	0.001	1.09 [0.98–1.21]	0.096
mRS at Admission				
No significant disability (Ref)				
Slight disability	2.5 [0.13–46.8]	0.54	2.34 [0.05–112.6]	0.667
Moderate disability.	5 [0.24–104.1]	0.299	5.47 [0.15–204.3]	0.358
Moderately severe disability	4.17 [0.49–35.5]	0.192	5.09 [0.35–74.1]	0.233
Severe disability	20.0 [2.31–173.1]	0.007	28.36 [1.32–609.5]	0.033
Basal Ganglia	0.09 [0.01–0.66]	0.018	0.09 [0.01–0.66]	0.018
Red Cell Distribution Width				
RDW-Q1 (Ref)				
RDW-Q2	1.23 [0.35–4.28]	0.75	0.20 [0.03–1.37]	0.102
RDW-Q3	1.63 [0.46–5.85]	0.451	0.99 [0.16–6.06]	0.991
RDW-Q4	1.97 [0.58–6.67]	0.277	0.86 [0.15–4.82]	0.86

*Multivariate model Adjusted for Diastolic BP; Smoking habit; NIHSS at admission; mRS score at admission; Basal Ganglia. Ref indicates reference category. OR-Odds Ratio. AOR-Adjusted Odds Ratio;

Table IV presents factors associated with functional independence at 3 months after AIS. In univariable analysis, lower diastolic BP (OR: 0.97, $p = 0.011$), lower NIHSS scores (OR: 1.11, $p = 0.001$), and absence of basal ganglia infarction (OR: 0.09, $p = 0.018$) were significantly linked to favorable outcomes, whereas smoking (OR: 3.70, $p = 0.005$) and severe baseline disability (mRS = 5; OR: 20.0, $p = 0.007$) predicted poor recovery. In the multivariable model, smoking (AOR: 7.67, $p = 0.003$) and severe disability (AOR: 28.36, $p = 0.033$) remained strong independent predictors of poor outcome, while lower diastolic BP (AOR: 0.96, $p = 0.021$) and absence of basal ganglia involvement (AOR: 0.09, $p = 0.018$) independently predicted functional independence. Although NIHSS lost significance after adjustment ($p = 0.096$), its unadjusted association suggests it remains clinically relevant. RDW quartiles were not independent predictors, though RDW-Q2 showed a non-significant trend toward better outcomes (AOR: 0.20, $p = 0.102$).

Discussion:

In this prospective cohort study, we investigated the association between red cell distribution width (RDW) at admission and three-month functional outcomes among patients with acute ischemic stroke (AIS) in Bangladesh. Although higher RDW quartiles were initially associated with worse outcomes, this relationship did not persist after adjustment for

established clinical and neuroimaging predictors. Instead, smoking status, baseline functional disability (mRS), diastolic blood pressure, and basal ganglia infarction emerged as independent determinants of poor recovery.

The prognostic role of RDW in AIS has been increasingly explored in recent years. Several studies have suggested that elevated RDW reflects an underlying inflammatory and oxidative stress state that may worsen stroke outcomes through impaired microcirculatory flow, reduced red cell deformability, and endothelial dysfunction^{21,22}. However, consistent with our findings, other investigations have reported that RDW loses statistical significance after adjusting for confounding factors such as age, comorbidities, and stroke severity²³⁻²⁴. For example, a multicentre prospective study involving 416 AIS patients found that RDW was not an independent predictor of poor functional outcome after multivariate adjustment²⁵. Similarly, a large Chinese registry of 1,558 patients showed that while RDW predicted three-month mortality, its association with functional disability was attenuated in fully adjusted models²⁶.

Contradictory evidence also exists. A South Korean cohort of 1,901 stroke patients reported a modest but significant association between RDW and poor functional recovery (adjusted OR H⁺ 1.12 per 1% increase)²⁷. Meta-regression analyses pooling data

from over 15,000 participants have likewise demonstrated that RDW, when categorised, was associated with both mortality and poor functional outcomes, though its continuous association with disability remained inconsistent²⁸. These discrepancies may be explained by heterogeneity in study design, population characteristics, follow-up duration, and statistical adjustment strategies. Our null finding for RDW after adjustment suggests that in our setting, RDW may be more of a nonspecific marker of illness severity rather than an independent prognostic determinant.

Among the independent predictors identified, smoking status was strongly associated with adverse outcomes. This is consistent with prior work demonstrating that smokers have significantly worse neurological recovery after AIS²⁹⁻³⁰. Large prospective datasets, including analyses from the International Stroke Trial and the AHA registry, have challenged the so-called “smoking paradox” by demonstrating no protective effect of smoking and, in most cases, a detrimental impact on recovery³¹⁻³². The underlying mechanisms are likely multifactorial, involving pro-thrombotic effects, impaired endothelial repair, and chronic inflammatory activation.

Baseline disability, as measured by the admission mRS score, was another strong predictor, reinforcing existing evidence that pre-stroke functional status substantially influences the likelihood of regaining independence after an acute event³³⁻³⁴. Higher diastolic blood pressure at presentation was also associated with poorer outcomes. Although the optimal management of blood pressure in the acute phase of ischemic stroke remains debated, elevated diastolic values may worsen cerebral edema or impair collateral circulation, thereby limiting recovery potential³⁵⁻³⁶. Furthermore, the presence of basal ganglia infarction independently predicted adverse outcomes, in line with previous neuroimaging studies showing that lesions in this region disrupt key motor and cognitive pathways essential for functional recovery³⁷⁻³⁸.

Overall, our findings suggest that while RDW may be a useful adjunctive biomarker in the initial assessment of AIS patients, its prognostic value in functional recovery appears limited when robust clinical and imaging predictors are considered. These results highlight the need for composite prognostic tools that integrate laboratory, clinical, and neuroimaging variables to guide patient counseling and rehabilitation planning media.

Conclusion:

In conclusion, this prospective cohort study found that elevated RDW at admission was not an independent

predictor of short term functional outcomes in patients with acute ischemic stroke in a tertiary care hospital of Bangladesh. These findings challenge the assumption that RDW is a reliable early prognostic biomarker in AIS and suggest that its role may be limited to reflecting general illness severity rather than directly influencing recovery. The results underscore the importance of integrating RDW assessment with established predictors in comprehensive prognostic models and highlight the need for larger, multicenter studies with longer follow-up periods to better define its potential clinical utility.

Acknowledgments:

The authors thank all patients, health physicians, nurses and other health care providers involved in the care of these patients of Department of Neurology, Sir Salimullah Medical College Mitford Hospital for their kind help and co-operation.

Funding:

This research did not receive any specific grant from any funding agencies

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Sir Salimullah Medical College. Written informed consent was taken from all the patients before taking part of the study.

Authors' contributions:

Aminur Rahman contributed to the concept and design. Aminur Rahman, Abul Hasnat Md. Russel Ajoy Khetan, Shah Efrinul Kabir, Syed Sadib Islam, Mohammad Shahidul Islam Bhuiya performed data collection and compilation. Aminur Rahman, Sabina Yasmin, Mohammed Nazmul Huq contributed in data analysis and manuscript writing. All authors revised and approved the manuscript.

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ORIGINAL ARTICLE

PREDICTING THE ROLE OF ADMISSION BLOOD PRESSURE PARAMETERS FOR SHORT-TERM CLINICAL OUTCOME IN COMMUNITY-ACQUIRED PNEUMONIA AT A TERTIARY CARE HOSPITAL IN BANGLADESH

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Abstract:

Background: Community-acquired pneumonia (CAP) remains a life-threatening condition, especially in developing countries. On admission, blood pressure parameters can be crucial in assessing disease severity. The aim of the study was to identify hemodynamic predictors of for short-term Clinical Outcome in patients in CAP. **Methods:** This prospective observational study was conducted in the Department of Medicine at Dhaka Medical College Hospital from September 2022 to August 2023 and included 150 patients diagnosed with CAP. Blood pressure measurements were taken within four hours of admission. All patients received standard treatment as per hospital protocol. The attending physician decided to initiate inotropic support and need for mechanical ventilation. The primary outcomes assessed were 30-day mortality and the requirement for inotropic support or mechanical ventilation. Follow-up assessments were conducted on days 3 and 7 or at discharge, whichever occurred earlier. An additional follow-up was performed via telephone on day 30. Data were recorded on a structured data collection sheet. Multivariate logistic regression was performed to identify independent predictors. Moreover, receiver operating characteristic (ROC) curve analysis was conducted to evaluate predictive performance. **Results:** Fourteen percent of 150 patients died on admission and 23.3% needed ventilation/inotropes. At 30 days, mortality was 22.6% and 34.7% needed ventilation/inotropes. sBP<90 mmHg, dBP d"60 mmHg, pulse pressure ≤40 mmHg, and MAP <70 mmHg were significant for both outcomes ($p<0.001$). On multivariate analysis, systolic BP <90 mm Hg (OR 5.439; CI 1.565–18.895) and MAP <70 mm Hg (OR 4.465; CI 1.280–15.579) were found to be predictors of 30-day mortality. These also were predictive of the need for ventilation/inotrope (ORs 2.958 and 2.807). ROC analysis showed very good predictive power of systolic BP (AUC 0.852–0.922) and MAP (0.835–0.914), good-to-moderate of diastolic BP and pulse pressure. **Conclusion:** Upon admission, systolic blood pressure and MAP are strong predictors of short-term mortality and requirement of advanced support in CAP patients. On admission, Systolic and mean arterial pressure are key predictors of 30-day mortality and the need for mechanical ventilation or inotropic support in community-acquired pneumonia patients.

Keywords: Blood Pressure Parameters, Community-acquired Pneumonia,

Date of submission: 30.05.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.82066>.

Citation: Hossain MM, Islam MK, Haque N, Rashid MM, Zaman MMU. Predicting the Role of Admission Blood Pressure Parameters for short-term Clinical Outcome in Community-acquired Pneumonia at a Tertiary Care Hospital in Bangladesh. *Bangladesh J Medicine* 2025; 36(3): 101-108.

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Introduction:

The morbidity and mortality in community-acquired pneumonia (CAP) is a vital issue till now. Epidemiological studies suggest that the incidence of CAP is approximately 20% to 30% in developing countries, compared to 3% to 4% in developed nations.¹⁻³

Hemodynamic status is a core component of widely accepted pneumonia severity scoring systems, such as the Pneumonia Severity Index (PSI)⁴ and CURB-65.⁵ The PSI designates systolic blood pressure (SBP) <90 mm Hg as a high-risk feature, while the CURB-65 and CRB-65 criteria consider either SBP <90 mm Hg or diastolic blood pressure (DBP) $\leq$ 60 mm Hg as indicators of severity.⁶

Previous research has indicated that low DBP is independently associated with mortality, irrespective of SBP. Consequently, elevated pulse pressure (PP) may also be linked with poorer outcomes, as British et al. and the Public Health Laboratory Service reported in 1987. A subsequent study by Chalmers et al.⁷ further investigated this association.

Chalmers et al.⁷ conducted an extensive prospective observational study in Edinburgh, UK, involving 1,007 patients with CAP. The study compared various hemodynamic parameters at admission—including SBP, DBP, mean arterial pressure (MAP), and PP—and assessed their associations with 30-day mortality and the requirement for mechanical ventilation and/or inotropic support. Their findings demonstrated that admission SBP <90 mm Hg, DBP $\leq$ 60 mm Hg, MAP <70 mm Hg, and PP $\leq$ 40 mm Hg were significantly associated with increased mortality and the need for advanced supportive measures. Their study also suggested that the CURB-65 score could be simplified to a modified CRB-65 by omitting the DBP criterion without compromising prognostic accuracy.

In another prospective observational study conducted by Aziz et al. in a similar setting, mortality in CAP was significantly associated with low DBP ($P = 0.04$)⁸.

These findings demand incorporating hemodynamic indicators into severity assessment tools to guide timely and appropriate clinical interventions. Prior studies have consistently shown that SBP <90 mm Hg or DBP $\leq$ 60 mm Hg correlates with adverse outcomes, and decreased MAP is also a predictor of mortality in acutely ill patients.

However, inconsistencies remain regarding the relative predictive value of different blood pressure indices. Moreover, to our knowledge, no study has yet been conducted in Dhaka Medical College Hospital (DMCH) or any other major hospital in Bangladesh to compare

various blood pressure parameters with CAP outcomes directly.

Therefore, the present study evaluated the association between admission pressure measurements and 30-day outcomes—including mortality and the need for mechanical ventilation or inotropic support—in patients with CAP admitted to a tertiary care hospital in Bangladesh. The findings may contribute to refining existing risk stratification models or developing a simplified, locally applicable severity scoring tool for CAP. We therefore hypothesized that admission blood pressure parameters—particularly systolic blood pressure and mean arterial pressure—would serve as independent predictors of short term mortality and the need for inotropic or ventilatory support in CAP patients.

Methods:

This prospective cohort study was conducted in the Department of Medicine, Dhaka Medical College Hospital (DMCH), Dhaka, from September 2022 to August 2023, primarily identifying hemodynamic predictors of short term clinical outcomes in patients with community-acquired pneumonia (CAP). Blood pressure measurements—including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP)—were recorded within four hours of hospital admission, prior to intravenous fluid administration or inotropic agents, except for patients who had received prehospital resuscitation. The following cut-off values, derived from previous studies, were used to define increased risk: SBP <90 mm Hg, DBP $\leq$ 60 mm Hg, MAP <70 mm Hg, and PP <40 mm Hg. All patients received standard CAP treatment per hospital protocol, and the attending physicians made decisions regarding inotropic or ventilatory support based on clinical judgment.

Although a larger sample size would have improved the power and external validity, the present sample of 150 patients was determined based on feasibility within the study period. Nonetheless, this cohort was sufficient to detect significant associations between blood pressure parameters and 30-day outcomes, as reflected in the narrow confidence intervals of our multivariate models. Inclusion criteria were age above 18 years, new infiltrates on chest radiographs, and at least three clinical features of pneumonia (e.g., cough, fever, dyspnea, or chest pain). Patients with hospital-acquired pneumonia, active malignancy, immunosuppression, pulmonary embolism, or those under palliative care were excluded. Baseline demographic data—including age, sex, comorbidities, and smoking status—were recorded. The study objectives were to compare admission blood pressure parameters with

disease severity and to evaluate their prognostic value in predicting 30-day mortality and the need for mechanical ventilation or inotropic support.

Patients were followed up on day 3, day 7, or at discharge, whichever occurred earlier. The need for inotropic support and/or mechanical ventilation was documented during these visits. Patients referred to intensive care units (ICU) or high-dependency units (HDU) were also included in outcome analyses.

A 30-day follow-up was conducted via telephone to assess post-discharge mortality, readmission, or the need for further inotropic support. If patients were unreachable, text messages were sent, and alternative contact numbers were attempted. The case was considered censored if no response was obtained for three consecutive days. All data were recorded using a structured data collection sheet.

Continuous variables were expressed as mean $\pm$ standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for skewed data. Categorical variables were presented as frequencies and percentages. The chi-square test was used to compare qualitative variables between groups. Logistic regression analysis was employed because the primary outcomes—30-day mortality and the need for mechanical ventilation—were binary in nature. Multivariate logistic regression allowed adjustment for potential confounders and identification of independent hemodynamic predictors.

Receiver Operating Characteristic (ROC) curve analysis was used to quantify the discriminatory power of systolic, diastolic, mean arterial, and pulse pressure in predicting outcomes. Area under the curve (AUC) values with 95% confidence intervals were reported.

This analytic strategy was chosen to align directly with the study objective of determining the predictive value of admission blood pressure parameters. Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 24.0. All analyses were performed at a 95% confidence interval, and a p-value <0.05 was considered statistically significant.

Results:

The mean age of participants was 53.93 ± 11.03 years, with most patients (77.6%) falling within the 45–65 age range. Males constituted 61.2% of the study population, while females comprised 38.8%. More than half of the participants (58.8%) were smokers. Regarding comorbidities, cardiovascular disease (26.3%) and chronic obstructive pulmonary disease (COPD) (23.8%) were the most prevalent, followed by diabetes mellitus (16.3%) and chronic kidney disease (6.3%), reflecting a complex clinical profile among the study cohort. (Table I)

The majority of patients had systolic blood pressure (SBP) in the 61–90 mmHg range (56.0%), followed by 28.7% with SBP ≤ 60 mmHg and 15.3% with SBP >90 mmHg. The mean SBP was 75.73 ± 14.48 mmHg, ranging from 61 to 90 mmHg. Most participants exhibited diastolic blood pressure (DBP) between 41 and 60 mmHg (85.3%), with fewer patients at the extremes (<40 mmHg, 10.0%; ≥ 61 mmHg, 4.7%). Pulse pressure (PP) was predominantly below 30 mmHg in 89.3% of subjects, with a reported interquartile range (IQR) of 8 to 31 mmHg (IQR = 23). Mean arterial pressure (MAP) was mainly distributed between 50 and 69 mmHg (63.3%), with a mean of 62.61 ± 8.47 mmHg, ranging from 54 to 71 mmHg. (Table II)

Table I
Demographic and Clinical Characteristics of the Study Participants (n = 150)

Variable	Subgroup	Frequency (n)	Percentage (%)	Mean $\pm$ SD
Age (years)	35–45	34	22.5	53.93 ± 11.03
	45–55	39	26.0	
	55–65	43	28.8	
	≥ 65	34	22.5	
Sex	Male	92	61.2	
	Female	58	38.8	
Smoking Status	Smoker	88	58.8	
Comorbidities	Diabetes Mellitus	24	16.3	
	Chronic Kidney Disease	9	6.3	
	Chronic Cardiac Failure	9	6.3	
	Cardiovascular Disease	39	26.3	
	COPD	36	23.8	
	Bronchial asthma	8	5.0	

Table II
Distribution of Blood Pressure Measurements Among Study Participants (n = 150)

Blood Pressure Parameter	Category (mmHg)	Frequency (n)	Percentage (%)	Mean $\pm$ SD / IQR	Range (mmHg)
Systolic Blood Pressure	≤ 60	43	28.7		
	61–90	84	56.0	75.73 $\pm$ 14.48	61–90
	> 90	23	15.3		
Diastolic Blood Pressure	≤ 40	15	10.0		
	41–60	128	85.3	56.03 $\pm$ 6.89	49–62
	≥ 61	7	4.7		
Pulse Pressure	< 30	134	89.3	IQR = 23 (8–31)	
	31–40	11	7.3		
	41–60	5	3.3		
	61–80	0	0		
	> 80	0	0		
Mean Arterial Pressure	≤ 50	17	11.3		
	50–69	95	63.3	62.61 $\pm$ 8.47	54–71
	≥ 70	38	25.3		

Most patients (86%) were discharged from the hospital, with varying lengths of stay: 13.3% were discharged within 24 hours, 26.0% within 3 days, 30.0% within 7 days, and 16.7% after more than 7 days. A notable proportion of patients required critical care interventions, with 23.3% needing mechanical ventilation—16.7% during hospitalization and 6.7%

after discharge but within 30 days. Similarly, 24.0% required inotropic support, with 22.7% receiving it during hospitalization and 8.0% after discharge but within 30 days. The overall mortality rate was 22.7%, including 14.0% who died during hospitalization and 8.7% who died after discharge but within 30 days. (Table III)

Table III
Distribution of Hospital Outcomes Among Study Participants (N = 150)

Outcome	Subgroup	Frequency (n)	Percentage (%)
Discharge	Within 24 hours	10	13.3
	Within 3 days	39	26.0
	Within 7 days	45	30.0
	More than 7 days	35	16.7
	Total discharged	129	86.0
Need for Mechanical Ventilation	During hospital stay	25	16.7
	After discharge (within 30 days)	10	6.7
	Total	35	23.3
Need for Inotropic Support	During hospital stay	34	22.7
	After discharge (within 30 days)	12	8.0
	Total	36	24.0
Death	During hospital stay	21	14.0
	After discharge (within 30 days)	13	8.7
	Total	34	22.7

Participants with systolic blood pressure (SBP) below 90 mmHg demonstrated a striking 91.2% 30-day mortality rate, revealing a highly significant association ($p < 0.001$). Similarly, all participants with diastolic blood pressure (DBP) ≤ 60 mmHg or pulse pressure (PP) ≤ 40 mmHg experienced 30-day mortality, with these associations also reaching statistical significance ($p < 0.001$). Additionally, 91.2% of participants with mean arterial pressure (MAP) below 70 mmHg succumbed within 30 days, emphasizing the critical prognostic value of blood pressure parameters in community-acquired pneumonia (CAP). These findings underscore the importance of vigilant monitoring and management of blood pressure to reduce mortality risk and improve clinical outcomes in CAP patients (Table IV).

Remarkably, participants with systolic blood pressure (SBP) below 90 mmHg demonstrated a substantial need for mechanical ventilation and/or inotropic support, with a prevalence of 94.2%, supported by a highly significant p-value (<0.001). Similarly, those with diastolic blood pressure (DBP) ≤ 60 mmHg and pulse pressure (PP) below 40 mmHg showed an even higher prevalence of 98.1% and 100%, respectively, requiring such critical interventions, both with highly significant p-values (<0.001). Furthermore, participants with mean arterial pressure (MAP) below 70 mmHg also exhibited a notable need for ventilation and inotropic

support at 94.2%, again with strong statistical significance ($p < 0.001$). These findings underscore the crucial role of blood pressure parameters as early predictors of the need for critical care interventions in patients with community-acquired pneumonia (CAP), emphasizing the importance of early detection and management of hemodynamic instability to improve patient outcomes Table V.

Multivariate logistic regression analysis demonstrated significant associations between blood pressure parameters and adverse outcomes in community-acquired pneumonia (CAP) patients. Specifically, systolic blood pressure (SBP) below 90 mmHg and mean arterial pressure (MAP) below 70 mmHg were independently associated with increased odds of 30-day mortality, with odds ratios (OR) of 5.44 (95% CI: 1.57–18.90, $p = 0.004$) and 4.47 (95% CI: 1.28–15.58, $p = 0.012$), respectively, highlighting their prognostic value in identifying high-risk patients. Similarly, low SBP and MAP were significantly linked to higher odds of requiring mechanical ventilation with ORs of 2.96 (95% CI: 1.01–8.69, $p = 0.018$) and 2.81 (95% CI: 1.00–8.22, $p = 0.025$), respectively. In contrast, diastolic blood pressure and pulse pressure did not show statistically significant associations with either 30-day mortality or the need for mechanical ventilation Table VI.

Table IV
Association of Blood Pressure Parameters with 30-Day Mortality (n = 34)

Blood Pressure Parameter	30-Day Mortality Frequency (n)	Percentage (%)	p-value
Systolic Blood Pressure < 90 mmHg	31	91.2	< 0.001
Diastolic Blood Pressure ≤ 60 mmHg	34	100	< 0.001
Pulse Pressure ≤ 40 mmHg	34	100	< 0.001
Mean Arterial Pressure < 70 mmHg	31	91.2	< 0.001

Table V
Association of Blood Pressure Parameters with Mechanical Ventilation at 30-Day Follow-Up (n = 52)

Blood Pressure Parameter	Frequency (n)	Percentage (%)	p-value
Systolic Blood Pressure < 90 mmHg	49	94.2	< 0.001
Diastolic Blood Pressure ≤ 60 mmHg	51	98.1	< 0.001
Pulse Pressure < 40 mmHg	52	100	< 0.001
Mean Arterial Pressure < 70 mmHg	49	94.2	< 0.001

Table VI
Multivariate Logistic Regression Analysis of Blood Pressure Parameters and 30-Day Outcomes in CAP Patients (N = 150)

Outcome	Blood Pressure Parameter	OR	95% Confidence Interval	p-value
30-day mortality	Systolic blood pressure < 90 mmHg	5.439	1.565 to 18.895	0.004
	Diastolic blood pressure < 60 mmHg	0.871	0.336 to 2.256	0.775
	Pulse pressure < 40 mmHg	0.756	0.090 to 6.377	0.797
	Mean arterial pressure < 70 mmHg	4.465	1.280 to 15.579	0.012
Ventilation	Systolic blood pressure < 90 mmHg	2.958	1.007 to 8.691	0.018
	Diastolic blood pressure < 60 mmHg	0.301	0.035 to 2.567	0.246
	Pulse pressure < 40 mmHg	0.939	0.225 to 3.917	0.931
	Mean arterial pressure < 70 mmHg	2.807	1.000 to 8.220	0.025

OR: Odds Ratio; CI: Confidence Interval; p-values obtained from multivariate logistic regression; significant values indicated.

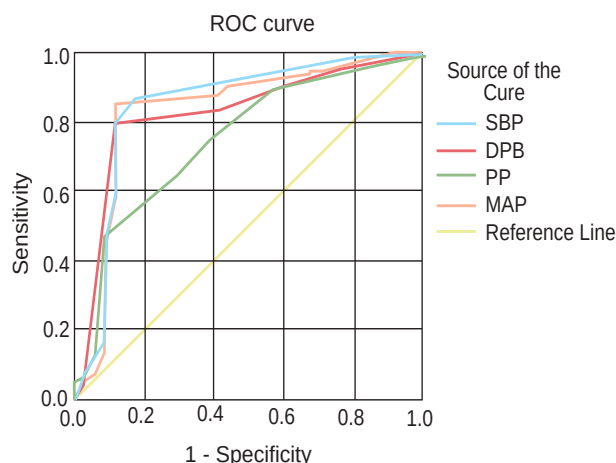


Fig.-1: Receiver Operating Characteristic (ROC) showing different blood pressure and prediction of 30-day mortality (N=150)

In Figure 1, ROC curve analysis showed that the area under the curve for systolic blood pressure was 0.852, diastolic blood pressure was 0.826, pulse pressure was 0.746, and mean arterial pressure was 0.835. In this study, systolic pressure, diastolic pressure, and mean arterial pressure had good discriminatory values, and pulse pressure had a moderate discriminatory value for predicting 30-day mortality.

In Figure 2, ROC curve analysis showed that the area under the curve for systolic blood pressure was 0.922, diastolic blood pressure was 0.856, pulse pressure was 0.831, and mean arterial pressure was 0.914. In this study, systolic pressure and mean arterial pressure had excellent discriminatory values, and diastolic pressure and pulse pressure had good discriminatory values for predicting 30-day need for ventilation.

Discussion:

Assessment of disease severity is a crucial component in managing community-acquired pneumonia (CAP). Most validated clinical scoring systems that predict 30-day mortality in CAP—such as CURB-65, PSI, and CRB-65—incorporate blood pressure measurements as key prognostic indicators. Hypotension is often a clinical manifestation of systemic inflammatory response and sepsis, which are associated with increased morbidity and mortality in CAP.

This prospective observational study evaluated the prognostic significance of early hemodynamic parameters in hospitalized CAP patients. We found that systolic blood pressure (SBP) <90 mmHg and mean arterial pressure (MAP) <70 mmHg, when measured within the first four hours of admission—prior to fluid or inotropic therapy—were independent

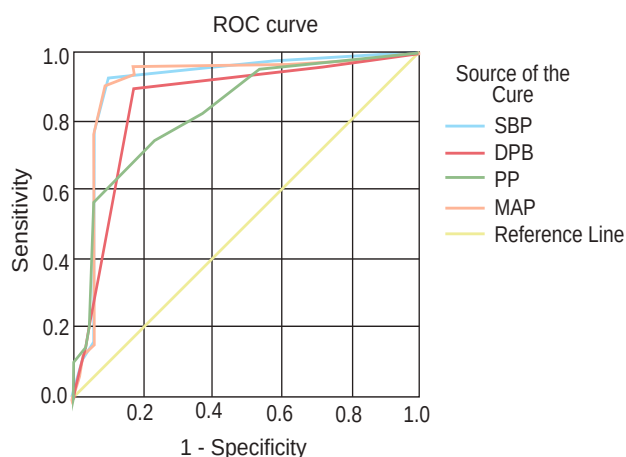


Fig.-2. Receiver Operating Characteristic (ROC) showing different blood pressure and prediction of 30-day ventilation (N=150)

predictors of adverse 30-day outcomes, including mortality and the need for mechanical ventilation or inotropic support.

In univariate analysis, all four parameters—SBP, diastolic blood pressure (DBP), pulse pressure (PP), and MAP—showed statistically significant associations with 30-day mortality and critical care interventions. However, in multivariate logistic regression, only SBP <90 mmHg and MAP <70 mmHg remained independently significant. This finding highlights the importance of early hypotension, particularly involving SBP and MAP, as strong indicators of poor prognosis in CAP.

A key strength of our study was the timing of the hemodynamic assessment, which was performed within four hours of hospital admission and before any therapeutic intervention. This methodology likely provides a more accurate representation of the patient's initial physiological derangement.

Our findings align with Chalmers et al.⁷, who reported that SBP is superior to other hemodynamic parameters (including MAP and PP) in predicting 30-day mortality in CAP. In their study, an SBP <90 mmHg was associated with an increased risk of death and a need for invasive support (Chalmers JD et al., 2008). Our observed rate of mechanical ventilation and inotropic support (34.7%) was notably higher than in the Chalmers study (10.2%), possibly reflecting differences in patient acuity, population characteristics, or healthcare system capacity.

In addition, Schulte-Hubbert et al.⁹ emphasized the prognostic importance of blood pressure drops within the first 24 hours after admission. Their retrospective

cohort study found that BP decline significantly increased the likelihood of requiring mechanical ventilation or vasopressor support (MVVS). Incorporating BP variability into existing scores improved predictive performance.⁹

Our study further supports the prognostic value of BP metrics. We observed a significant association ($p < 0.001$) between low SBP (<90 mmHg), DBP (≤ 60 mmHg), PP (<40 mmHg), and MAP (<70 mmHg) with both increased 30-day mortality and need for critical care interventions. On multivariate analysis, SBP <90 mmHg increased the odds of 30-day mortality by more than fivefold, and MAP <70 mmHg by over fourfold. Both parameters also significantly raised the risk of needing ventilation and inotropic support, underscoring their role as independent predictors of adverse outcomes. These findings are consistent with evidence from systematic reviews and meta-analyses of COVID-19 pneumonia, where hypertension and hemodynamic instability were strongly associated with increased mortality and disease severity.^{10,11} This reinforces the prognostic importance of blood pressure abnormalities across different forms of pneumonia

Our study's receiver operating characteristic (ROC) curve analysis revealed high predictive accuracy for mortality prediction in SBP, MAP, and DBP (AUC 0.852, 0.835, and 0.826, respectively). PP also demonstrated a moderate predictive value (AUC 0.746). SBP and MAP again demonstrated the highest AUC values for critical care needs, suggesting excellent discriminatory power.

While Chalmers et al.⁷ reported only moderate predictive value for SBP and lower predictive value for MAP and PP, these differences may reflect population-specific characteristics or evolving standards of care. Our study population, drawn from a tertiary care hospital in Bangladesh, may present later or with more severe illness than cohorts in high-income countries.

Taken together, our findings, in conjunction with existing literature, reinforce the utility of early blood pressure assessment—particularly SBP and MAP—as a simple, rapid, and non-invasive tool to stratify risk and guide the management of CAP. Incorporating these parameters into early warning systems or clinical decision-making algorithms could enhance patient triage and resource allocation. In addition to respiratory failure, CAP has also been associated with extrapulmonary complications, including cardiovascular events. Another study¹² demonstrated that cardiac complications are common in CAP and independently contribute to short-term mortality. This underscores the systemic impact of hemodynamic compromise and strengthens the rationale for close

monitoring of cardiovascular function in pneumonia patients presenting with hypotension

Conclusion:

Our study demonstrates that early systolic blood pressure and mean arterial pressure are strong, independent hemodynamic predictors of short term mortality and the need for advanced support in community-acquired pneumonia. These findings reinforce the prognostic value of basic vital signs and underscore their importance in early clinical decision-making, particularly in resource-limited settings.

Limitations of the Study:

However, several limitations should be acknowledged. Although a larger sample size would improve precision and external validity, our study included 150 patients based on feasibility within the study period. Nevertheless, this sample was adequate to demonstrate statistically significant associations, as evidenced by the multivariate models. Second, we excluded patients with hospital-acquired pneumonia and those with significant immunosuppression, which may affect external applicability. Third, we did not evaluate biomarkers such as serum lactate or procalcitonin, which could have added further depth to outcome prediction.

Acknowledgements:

The authors were grateful to the staffs of the Department of Internal Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh; We extend our sincere gratitude to the study participants whose generous commitment of time and candid responses have greatly enriched the quality and depth of our research.

Funding:

None.

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Dhaka Medical College. Written informed consent was taken from all the patients before taking part of the study.

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ORIGINAL ARTICLE

L-ASPARAGINASE ASSOCIATED TOXICITIES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A SINGLE-CENTER PROSPECTIVE COHORT STUDY

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Asparaginase has played a crucial role in improving the long-term survival. However, the administration of these agents may lead to multifactorial toxicities. So; the objective of this study is to identify the L- asparaginase associated toxicity in children with ALL. **Methods:** This Prospective cohort study was conducted from May 2023 to April 2025 in the Department of Pediatric Hematology and Oncology, Sir Salimullah Medical College Mitford Hospital, Dhaka. A total of 71 children diagnosed with ALL were included in this study. **Results** Patients aged ≥ 10 years, WBC count at diagnosis $\geq 50,000 \times 10^9 / L$, receiving Regimen B, body surface area (BSA) $> 1 m^2$ showed increased risk of toxicity in bivariate analysis. In multivariate analysis there was no significant association. Hyperglycemia was the commonest adverse reaction followed by hepatic transaminitis and elevated INR. Less frequent reactions included pancreatitis, hyperbilirubinemia, hypersensitivity and hypofibrinogenemia. **Conclusion:** Hyperglycemia was the commonest toxicities of L-asparaginase in children of more than 10 years, followed by hepatic transaminitis and elevated INR. The less frequent toxicities included pancreatitis, hyperbilirubinemia, hypersensitivity and hypofibrinogenemia.

Keywords: L-asparaginase, toxicities, Acute Lymphoblastic Leukemia

Date of submission: 30.05.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.82066>.

Citation: Jahan YT, Baten OS, Nargis W, Rahmam F, Kumer P, Shahidullah S. et al. L-asparaginase associated toxicities in children with acute lymphoblastic leukemia: A single-center prospective cohort study. *Bangladesh J Medicine* 2025; 36(3): 109-115.

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Introduction:

Acute Lymphoblastic Leukemia accounts for 72% to 75% cases of all childhood leukemia & one fourth of all malignancy in children with a peak prevalence in 2 to 5 years.^{1,2} There has been dramatic progress in the treatment of acute lymphoblastic leukemia due to combination chemotherapy which containing L-asparaginase. Literally, excellent outcomes have been observed in children with five-year overall survival (OS) of approximately 90%. This is thought to be due in part to the regimens used in the pediatric population, which generally include agents with more frequent and longer durations of administration. L-asparaginase is included as a main chemotherapeutic agents in several pediatric ALL chemotherapy protocol as a first-line treatment.^{3,4}

L-asparaginase is a highly effective chemotherapeutic agents that has become a cornerstone of combination chemotherapy for pediatric patients with ALL. Over the past few years, chemotherapy protocol of young and adolescent children with ALL has been studied closely. Overall survival have been improved due to high-intensity of L-asparaginase.^{5,6} L-asparaginase catalyzes the hydrolysis of L-asparagine to aspartic acid and ammonia, causing depletion of serum asparagines in the circulation. Normal cells are capable to synthesize asparagine and are therefore less susceptible to the action of L-asparaginase. On the other hand, tumor cells require an external source of asparagine due to their limited capacity to synthesize it.^{7,8}

Currently, three asparaginase preparations are available; two preparations are native, purified from bacterial sources, and one is modified from a native preparation. Thenative preparations are derived from *E. coli* or *Erwinia chrysanthemi*. The third preparation, PEG-asparaginase, is also derived from *E. coli* and is covalently conjugated to monomethoxy- polyethylene glycol, which improves the pharmacokinetics of asparaginase. The PEGylated form is better tolerated.⁸⁻¹⁰

Despite the effectiveness of asparaginase as an anti-cancer drug, its use has been associated with several toxicities. L-asparaginase associated toxicity can occur up to 25% of patients. The toxicities of asparaginase occurs due to immunologic sensitization to the foreign protein, and inhibition of protein synthesis. Common toxicities are allergic reactions, hyperglycemia, pancreatitis, hepatotoxicity, hypertriglyceridemia, diabetes, and coagulopathy. The coagulopathy occurs due to reduced synthesis of fibrinogen, plasminogen, antithrombin III, protein C, and protein S. These can result either bleeding or

thrombotic events. Thrombotic events include deep-vein thrombosis, pulmonary embolus and central venous thrombosis.¹¹⁻¹³

These can cause silent inactivation of L-asparaginase which may lead to treatment failure.¹⁴ Several risk factors are associated with L-asparaginase toxicity including age more than 10 years, increased BMI (body mass index), ALL risk categories, hypoalbuminemia, drug accumulation dose. Increase growth hormone secretion and other multifactorial mechanisms are responsible for toxicity in older age group.^{5, 15-18}

Results from several studies and clinical trial suggest that L- asparaginase is well tolerated in children and associated with less toxicity. Over the past few years which chemotherapy protocols of adolescent and young adult age group has been studied comprehensively which containing high dose of L- asparaginase and found that overall survival is better.¹⁹⁻²⁰

Several studies showed that children and adolescents less than 10 years of age have been suffered from pancreatitis and thromboembolic complication in comparison to hypersensitivity reaction.¹⁹ Other studies have found that there was no significant relationship of L- asparaginase-associated toxicity with age group.¹⁰⁻²⁰ However, L- asparaginase-associated toxicity in children with ALL has not been studied separately in Bangladesh. So, the aim of this study is to identify the L- asparaginase-associated toxicity in children with ALL.

Methods:

We performed a prospective cohort study that included 71 patients diagnosed with acute lymphoblastic leukemia at Department of Pediatric Hematology and Oncology in Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh from May 2023 to April 2025.

The inclusion criteria were a diagnosis of ALL according to the WHO criteria²², age 1–12 years, treatment according to the UKALL 2003²¹ protocol, and the administration of at least one dose of L-asparaginase. Children aged less than 1 year or ≥ 12 years were excluded from this study. All the information regarding the study was collected in a structured questionnaire after taking informed written consent. A total of 75 patients were evaluated for eligibility, but 04 were excluded either because they did not receive at least one dose of L-asparaginase (02 of them due to early death).

Diagnosis of ALL was done on the basis of clinical features, complete blood count with peripheral blood film and bone marrow study. Written informed consent was obtained before enrollment in the study from a parents or guardian.

All patients of ALL were treated with modified UKALL 2003 protocol, regimen 'A' or 'B' according to risk stratification. In addition to this treatment, general supportive care measures were administered to all patients.

The chemotherapy protocol used UKALL 2003²¹ provides 9 doses of L-asparaginase at 6000 IU/m² on days 04, 06, 08, 10, 12, 14, 16, 18, and 20 during the induction phase. During delayed intensification total four doses of L-asparaginase on days 128, 130, 132 and 134. All the L-asparaginase applications were with a native E. coli-derived preparation, were given intramuscularly.

All patients were monitored regularly from the start of chemotherapy up to 35 days of induction remission for development of toxicity of ALL.

Hypersensitivity skin test was done before giving first dose of L-Asparaginase. Laboratory studies including complete blood count, random blood sugar, activated partial thromboplastin time, prothrombin time, international normalized ratio (INR), alanine aminotransferase, aspartate aminotransferase, creatinine. The amylase and lipase level were tested only if the patients were symptomatic and adverse effects of L-Asparaginase were suspected. Complete blood count was performed in one day interval. Serum alanine aminotransferase, aspartate aminotransferase and creatinine were performed weekly. Activated partial thromboplastin time, prothrombin time, international normalized ratio (INR) were done after every three doses of L-Asparaginase. During this period Fresh frozen

Plasma and injection K-one were administered for patients with prolonged partial thromboplastin time, prothrombin time, international normalized ratio (INR).

Data collection included patient demographics, injection-related toxicity and laboratory parameters before administration and up to 35 days of induction of remission or until the resolution of abnormal events.

Statistical analyses were performed using IBM SPSS Statistics 26. Data were expressed as frequency, percentage. p-value was reached from Chi-square test. p<0.05 is considered level of significant.

Results:

Table I

Patient Demographics and Dosage Information

Characteristic	Patients (N = 71)
Median age, years (range)	8 (2 -13)
<'10' years	46 (64.8%)
≥'10' years	25 (35.2%)
Sex Male, N	59 (83.1%)
Female, N	12 (16.9%)
Body surface area (mean ± SD)	0.67 + 0.01

A total of 71 patients were included, most of the patients were < 10 years of age (64.8%) and remaining were >10 (35.2%) of age. In this study, 59 (83.1%) patients were male and 12 (16.9%) patients were female. Mean body surface area was 0.67 + 0.01 (Table-I).

Table II

Predictors of L-Asparaginase Toxicity in children with ALL (Bivariate analysis) (n=71)

Factors	Patient with toxicity (n=57)	Patient without toxicity (n=14)	OR	p value
Gender				
Male	48(84.2%)	11(78.6%)	1.46	0.614
Female	9(15.8%)	3(21.4%)	(0.34-6.24)	
Age at diagnosis of ALL (years)				
≥'10' years	24(42.1%)	1(7.1%)	9.45	0.014*
<'10' years		33(57.9%)	13(92.9%)	(1.16-77.3)
WBC at diagnosis of ALL				
WBC ≥50000 × 10 ⁹ /L	27(47.4%)	2(14.3%)	0.5.40	0.024*
WBC < 50000 × 10 ⁹ /L	30(52.6%)	12(85.7%)	(1.11-26.3)	
Immunophenotype				
B cell	47(82.5%)	12(85.7%)	0.783	0.771
T cell	10(17.5%)	2(14.3%)	(0.151-4.06)	
Regimen used during induction				
Regimen-B	25(43.9%)	1(7.1%)	10.16	0.011*
Regimen-A	32(56.1%)	13(92.9%)	(1.24-82.9)	
CNS disease at diagnosis				
Yes	8(14.0%)	0(0.0%)	-	0.137
No	49(86.0%)	14(100.0%)		
Body surface area				
≥ 1 m ²	21(36.8%)	1(7.1%)	7.58	0.031*
< 1 m ²	36(63.2%)	13(92.9%)	(0.93-62.2)	

Table III*Measurement of risk factors for L-Asparaginase Toxicity in children with ALL (Multivariate analysis)*

Factors	p value	OR	95% CI
Age group at diagnosis of ALL (>10 yrs)	.104	6.235	.688-56.472
WBC at diagnosis of ALL ($>50000 \times 10^9/L$)	.091	4.314	.792-23.493
Regimen used during induction (Regimen-B)	.057	8.305	.936-73.679
Body surface area (mean $\pm$ SD) ($>1m^2$)	.250	3.761	.394-35.877

Table II showed bivariate analysis of predictors of L-Asparaginase toxicity in children with ALL revealed several significant associations. Gender was not significantly associated with toxicity (OR 1.46, $p=0.614$). Age at diagnosis showed a significant association, with patients aged ≥ 10 years having higher odds of toxicity (OR 9.45, $p=0.014$). WBC count at diagnosis also demonstrated a significant association, with patients having $WBC \geq 50,000 \times 10^9/L$ being at increased risk (OR 5.40, $p=0.024$). Immunophenotype was not significantly associated with toxicity (OR 0.783, $p=0.771$). The induction regimen used was a significant predictor, with Regimen-B being associated with higher odds of toxicity (OR 10.16, $p=0.011$). CNS disease at diagnosis showed no significant association with toxicity ($p=0.137$). Lastly, body surface area $>1m^2$ was significantly associated with increased risk of toxicity (OR 7.58, $p=0.031$).

Table III showed the multivariate analysis of risk factors for L-Asparaginase toxicity in children with ALL revealed no statistically significant independent predictors, although some factors approached significance.

Adverse Reactions in Patients receiving L-Asparaginase

Table IV showed that among patients receiving L-Asparaginase, the most common adverse reaction hyperglycemia (62.0%), followed by hepatic transaminitis (32.4%), and elevated INR (25.4%). Less frequent reactions included pancreatitis (11.3%), hyperbilirubinemia (8.5%), hypersensitivity (4.2%), and hypofibrinogenemia (4.2%).

Mortality Data in Patients receiving L-Asparaginase

Table IV*Adverse Reactions in Patients receiving L-Asparaginase (n=71)*

Adverse reaction	Number of patients	Percentage (%)
Hypersensitivity	3	4.2
Hyperglycemia	44	62.0
Pancreatitis	8	11.3
Hyperbilirubinemia	6	8.5
Hypofibrinogenemia	3	4.2
Elevated INR	18	25.4
Hepatic transaminitis	23	32.4

Table V*Mortality Data in Patients receiving L-Asparaginase (n=71)*

Outcome	Number of patients	Percentage (%)
Alive	56	78.9
Death	15	21.1
Total	71	100.0

Table V showed among 71 patients receiving L-Asparaginase, 78.9% (56 patients) were alive, while 21.1% (15 patients) death.

Table VI*Association of L-Asparaginase toxicity with mortality (n=71)*

Adverse reaction		Outcome			p-value
		Death (n=15)	Alive (n=56)	Total(n=71)	
Hypersensitivity	Present	3(20.0%)	0(0.0%)	3(4.2%)	0.001*
	Absent	12(80.0%)	56(100.0%)	68(95.8%)	
Hyperglycemia	Present	8(53.3%)	36(64.3%)	44(62.0%)	0.438
	Absent	7(46.7%)	20(35.7%)	27(38.0%)	
Pancreatitis	Present	5(33.3%)	3(5.4%)	8(11.3%)	0.002*
	Absent	10(66.7%)	53(94.6%)	63(88.7%)	
Hepatic transaminitis	Present	7(46.7%)	16(28.6%)	23(32.4%)	0.184
	Absent	8(53.3%)	40(71.4%)	48(67.6%)	
Hypofibrinogenemia	Present	0(0.0%)	3(5.4%)	3(4.2%)	0.360
	Absent	15(100.0%)	53(94.6%)	68(95.8%)	
Hypoalbuminemia	Present	1(6.7%)	5(8.9%)	6(8.5%)	0.780
	Absent	14(93.3%)	51(91.1%)	65(91.5%)	
Elevated INR	Present	5(33.3%)	13(23.2%)	18(25.4%)	0.424
	Absent	10(66.7%)	43(76.8%)	53(74.6%)	

p-value obtained by Chi-square, $p<0.05$ was considered as a level of *significant

Table VI showed the association between L-Asparaginase toxicity and mortality reveals significant relationships for specific adverse reactions. Hypersensitivity was significantly associated with mortality ($p=0.001$). Pancreatitis also showed a significant association ($p=0.002$), with 33.3% of deaths in patients who experienced pancreatitis. Other adverse reactions, such as hyperglycemia ($p=0.438$), hepatic transaminitis ($p=0.184$), hypofibrinogenemia ($p=0.360$), hypoalbuminemia ($p=0.780$), and elevated INR ($p=0.424$), did not show statistically significant associations with mortality.

Discussion:

Combination chemotherapy containing L-asparaginase has been shown to increase survival rates.

Asparaginase toxicity is common in children with ALL may lead to discontinuation of a pivotal component of a potentially curable disease and eventually decrease survival by 15% to 20%. The median age was 8 years.²³⁻²⁶

In this study, we evaluated the prevalence and nature of L-asparaginase related toxicities in 71 patients with acute lymphoblastic leukemia (ALL). Additionally, we compared our findings with previous studies to gain insight into the differences and similarities in toxicity profiles and potential risk factors.

In this study, patients aged ≥ 10 years having more toxicity in comparison to younger children. In some studies, older age is considered to be associated with an increased risk of asparaginase-related toxicity.²⁷ A study in Tehran showed that the mean age of children with ALL was 5.5 years and in Brazil,²⁸ the average age of children at initial diagnosis was 6.3 ± 0.5 years.²⁹ Kakajeet *al.* conducted an epidemiological study found that a higher proportion of boys with ALL (60.9%) compared to girls developed more hepatotoxicity.

We found that patients having $WBC \geq 50,000 \times 10^9 / L$, using Regimen-B during induction phase of chemotherapy, body surface area $\geq 1m^2$ having increased risk of L-asparaginase-related toxicity in bivariate analysis. In a retrospective cross-sectional study Awwadet *al.*¹⁰ found that, age, BSA, diagnosis, and PEG-ASP dose were associated with the development of toxicities. Patients diagnosed with high risk ALL and T-ALL displayed a significantly higher likelihood of developing toxicities.³⁰

In the multivariate analysis of risk factors for L-Asparaginase toxicity in children with ALL, none of the examined variables reached statistical significance at the conventional threshold ($p < 0.05$). However, several factors demonstrated high odds ratios (OR), suggesting potential clinical relevance.

In this study we found that patients receiving L-Asparaginase, the most common adverse reaction hyperglycemia followed by hepatic transaminitis and elevated INR. Less frequent reactions included pancreatitis, hyperbilirubinemia, hypersensitivity and hypofibrinogenemia. Awwadet *al.*¹⁰ found that Anaphylaxis/hypersensitivity (36.7%) was the commonest side effects followed by and hepatotoxicity (31.6%), by pancreatitis and hyperglycemia (12.7% each). In a retrospective study Schmidt *et al.* found the following incidence of asparaginase-associated toxicity: 24.1% clinical hypersensitivity, 19.4% hepatotoxicity, 6.7% hypertriglyceridemia, 4.2% hyperglycemia, 3.7% osteonecrosis, 3% pancreatitis, 2.4% thrombosis, and 1.2% cerebral thrombosis. In this study, we found 21.1% of patients were died. Hypersensitivity and pancreatitis were significantly associated with mortality. A retrospective chart review conducted by Ippoliti *et al.* found that a total of 17 patients died. 3 deaths were related to sepsis, 2 occurred during bone marrow transplant, 2 from multi-organ failure, and the cause of the other 10 deaths, which occurred during follow-up, could not be verified.³¹

Conclusion:

The risk factors for L-Asparaginase toxicity in children with ALL revealed no statistically significant independent predictors, although some factors approached significance. Hyperglycemia was the commonest adverse reaction followed by, hepatic transaminitis, and elevated INR. Less frequent reactions included pancreatitis, hyperbilirubinemia, hypersensitivity, and hypofibrinogenemia.

Acknowledgments:

The authors thank all patients, health physicians, nurses and other health care providers involved in the care of these patients of Department of Pediatric Hematology and Oncology, Sir Salimullah Medical College Mitford Hospital for their kind help and co-operation.

Funding:

This research did not receive any specific grant from any funding agencies

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Sir Salimullah Medical College. Written informed consent was taken from all the patients before taking part of the study.

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ORIGINAL ARTICLE

BRIDGING THE GAP: EVALUATING HEPATITIS B OCCUPATIONAL RISK PREPAREDNESS AMONG INTERN DOCTOR'S IN A BANGLADESHI MEDICAL COLLEGE

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Abstract:

Background: The incidence of HBV infection among health care workers is 2-4 times higher than general population and mostly occurred by percutaneous route. Lack of knowledge may lead to adverse professional outcome among healthcare workers in regions where the risk is high. This study was aimed to evaluate the knowledge, awareness and approach of our intern doctors towards occupational exposure of HBV in Bangladesh. **Methods:** This cross-sectional study was carried out on 100 working intern doctors from different departments of Rangpur medical college hospital, Bangladesh over a period of 06 months from January 2023 to June 2023. Data were collected using a self-structured questionnaire by personal interview. **Results:** Regarding mode of transmission of HBV, 38% of interns have overall good knowledge about HBV infection, 43% have average and 19 % have poor knowledge about HBV infection. Only 49% of interns know that both oral and injectable treatments are available for HBV infection, 76% knew that HBV has post exposure prophylaxis. In the area of practical measures for occupational safety, only 47% used sterilized instruments in every procedure and 60% of them used gloves in every procedure, 73% of them claimed needle prick or minor cut injury during their work, but only 44% took necessary measures. Only 17 interns took yearly Anti HBs titer check and 44% have full family vaccination coverage. **Conclusion:** The study highlights the need for better health education on safety measures to prevent infections in healthcare workers. Inadequate knowledge has led to negative attitudes towards HBV patients, impacting patient care.

Keywords: Hepatitis B Virus, Intern Doctors, Occupational Risk, Knowledge and Practice.

Received: 20-05-2025

Accepted: 25-08-2025

DOI: <https://doi.org/10.3329/bjm.v36i3.83078>

Citation: Hossain MS, Makunnahar, Anwar MMU, Jahan SMS, Chowdhury MS, Khan MMR et al. Bridging the Gap: Evaluating Hepatitis B Occupational Risk Preparedness among Intern Doctor's in a Bangladeshi Medical College. *Bangladesh J Medicine* 2025; 36(3): 116-122.

Introduction:

Hepatitis B virus (HBV) infection is a major concerning disease throughout the world and approximately 400 million people are infected with HBV at present.¹ The prevalence of HBV markedly varies among different

parts of world. About 60% of world population resides in highly endemic regions like Southeast Asia, China and Africa, of which 8% or more people are HBV infected.¹ Bangladesh is an intermediate endemic area having 5.4% HBV prevalence.² HBV is 50-100 times

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more infectious than HIV and 10 times than HCV.¹ Horizontal and perinatal transmissions are the main mode of transmission in majority of HBV cases. Other important routes are sexual contact, injectable drug abuse, blood and blood products. However occupational exposures in health care workers (HCWs) are also a major concern especially in countries where HBV infection is high. The incidence of HBV infection among health care workers is 2-4 times higher than general population and mostly occurred by percutaneous route. Globally annual HBV infection rate among HCW's is 5.9% on the other hand, in Bangladesh this figure is 8% found in a recent study.^{3,4} Knowledge of HBV as well as awareness among HCW's is very important in prevention of occupational exposure of this virus. Only standard infection control practice can prevent the hospital spread of HBV. Sound knowledge creates awareness, which ultimately lead to appropriate practical approach. Lack of knowledge may lead to poor professional safety among healthcare workers in developing regions that increase the risk.^{5,6} In Bangladesh, no study performed till date about knowledge and attitude of HBV infection among HCW's particularly young interns, as they are very prone to exposure in multidisciplinary tertiary care hospital. So, this study was aimed to evaluate the knowledge, awareness and approach of intern doctors towards occupational exposure of HBV in Bangladesh.

Methods:

This cross-sectional study was carried out on 100 intern doctors from different departments of Rangpur medical college hospital, Bangladesh over a period of 06 months from January 2023 to June 2023. All participants were asked permission before taking the interview with an informed written consent form. Data were collected using a self-structured questionnaire by personal interview, which was adapted from few previous studies.^{7,8} The reliability of the questionnaire was tested over 20 interns and they all can understand all questions. The questionnaire contains 03 parts and a total of 33 items. First part covers sociodemographic characteristics and personal status of HBV infection; second part contains 18 questions regarding knowledge such as transmission, investigation and treatment of HBV infection; and third part contains 09 question regarding their approach towards prevention of occupational exposure of HBV. Each variable from questions regarding knowledge was given 1 for yes and zero for no. The reliability of the questionnaire was tested by Cronbach's Alpha at acceptable level > 0.7. The Cronbach's Alpha of the 16 variable was 0.8. Quartile range was used to identify the cutoff points for knowledge levels. The scores of knowledge above 75% (≥ 14) was nominated as good knowledge, the scores between the inter-quartile, 50%-75% (14-10) was nominated as average, and the scores

below 50% (≤ 10) was nominated as poor knowledge.⁷ Statistical analyses were carried out by using the Statistical Program and Service Solution (SPSS) version 25.0 for Windows. Continuous variables expressed as mean & standard deviation and categorical variables as frequencies and percentages. Association between variable were described as high (>60%), moderate (50-60%), low (30-50%) and very low (<30%). Testing factors related to knowledge was carried by Chi-Square test at 95% confidence level and P-value less than 0.05 was considered as significant. Ethical permission was taken from Institutional Review Board of Rangpur Medical College.

Results:

Demographic profiles of the intern doctors showed that, 55 were male and rest 45 were female doctors. 30% of the intern doctors have not yet performed their screening test for HBV infection, whereas (70%) are screened. Of these 100 doctors, 19 are not vaccinated yet, though 55 are fully vaccinated, rests of 9 were on current vaccination (Table-I).

Table I
*Demographic and personal profile of Intern doctors:
(n=100)*

Profiles	Percentage (%)
Gender	
Male	55.0
Female	45.0
Department	
Surgery	24.0
Gynaecology	24.0
Medicine	37.0
Paediatrics	13.0
Dentistry	2.0
HBV screening status	
Done	70.0
Not done	30.0
Vaccination status	
Never received	19.0
Full dose	55.0
Incomplete dose	17.0
On schedule	9.0
Needle prick/cut injury during work	
Yes	73.0
No	27.0

Regarding mode of transmission of HBV, most of the intern doctors correctly answered that HBV can be transmitted by blood and blood products (100%), needle injury (91%), contact with open wounds (86%), sexual contact (96%) and during delivery of fetus (84%). However, only 46 % knew that HBV can be transmitted by breast feeding (Table-II).

Table II*Knowledge and practices regarding occupational exposure of HBV infection : (n=100)***Knowledge Domains :****A. Mode of Transmission*:**

Questions	Correct answers (%)	Wrong answers (%)
Blood and blood products	100	0
Sharing plate, glass, bed, hand shaking	68	68
Sexual contact	96	04
Contact with an open wound	86	14
Needle injury	91	09
Infected mother to child during delivery	84	16
During breast feeding	46	54
Feco oral route	75	75

B. Prevention of Transmission*:

Questions	Correct answers (%)	Wrong answers (%)
HBV screening	91	9.0
Effective vaccination	92	8.0
Safe sex	86	14.0
Provision of safe drinking water	73	73.0
Safe disposal of human excreta	78	78.0
Wearing gloves during work	83	17.0

C. Investigation of HBV:

Questions	Correct answers (%)	Wrong answers (%)
Preferable screening test		
HBsAg		60.0
Anti HBc total		11.0
Both	29	29.0
Effective vaccination status test		
Anti HBS	64	64.0
Anti HBc		24.0
Anti HBe		12.0

D. Treatment of HBV:

Questions	Correct answers (%)	Wrong answers (%)
Available treatment		
Only oral		37.0
Only injection		14.0
Both	49	49.0
HBV has post exposure prophylaxis		
Yes	76	76.0
No		24.0

Practice regarding prevention of occupational transmission of HBV:

Questions	Safe practice (%)	Unsafe practice (%)
Wear aprons in work places	91	09
Wear gloves in every procedures	60	40
Use of sterilized instruments in every procedures	47	53
Take necessary actions after accidental needle/ cut injury	44	56
Use mask or eye glass during procedures	32	68
Confident in treating/dealing HBV positive patients	36	64
Give health education to all HBV patients you treat	41	59
Yearly screening of HBV	17	83
Your family is vaccinated	44	56

*Multiple answers

Only 49% of interns know that both oral and injectable treatments are available for HBV infection. However, 76% knew that HBV has post exposure prophylaxis. (Table-II).

Thus, 38% of interns have overall good knowledge about HBV infection, 43% have average and 19 % have poor knowledge about HBV infection. (Figure-1).

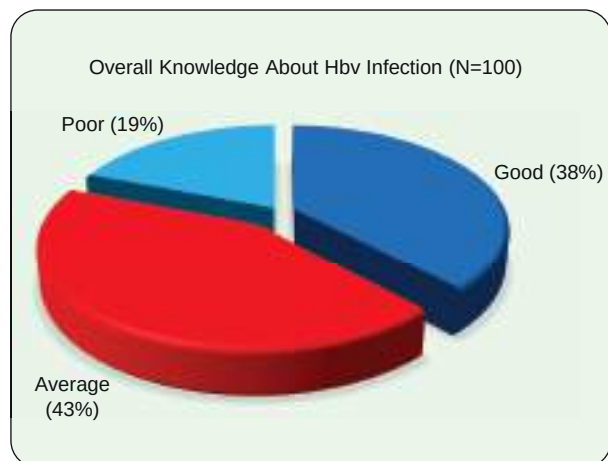


Fig.-1: Overall knowledge about HBV infection (n=100)

Majority of the interns were aware that, vaccine is safe and effective (96%), prevention & control is the mainstay of HBV infection (93%) and all healthcare workers should be vaccinated (98%), but 32% of doctors were not aware of risk of HBV infection (32%) (Figure-2).

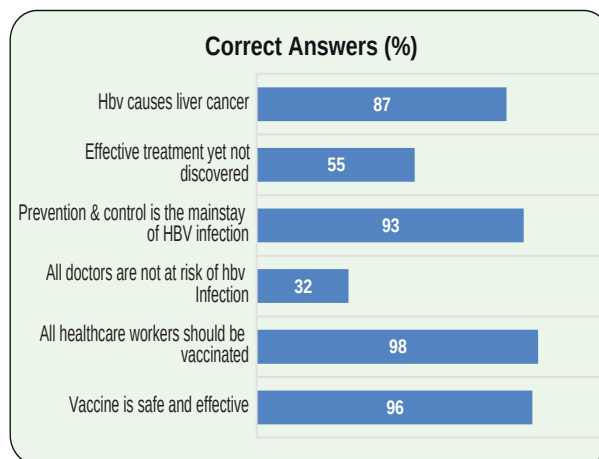


Fig.-2: Awareness about occupational risk of HBV infection (n=100)

During the interview 73 % of them claimed needle prick or minor cut injury during their work, while only 44% of interns took necessary measures after accident. Only 17 interns took yearly Anti HBs titer check and 44% have full family vaccination coverage (Table-II).

We have analyzed some key associations between demographic profiles and knowledge/practice among intern doctors in our study which were described in Table-III.

Table III

Associations between Demographic Characteristics and Knowledge and Practices among Intern doctors:

- Departmental Associations with Risk Exposure & Practices

(*Inferred from overall injury rate (73%) and procedural risk levels)

Department	Needle Injury Rate	Post-Injury Action Rate	Sterilized Instrument Use	Confidence in Treating HBV+
Surgery (24%)	High (Likely >80%)*	Low (<40%)	Low (Likely <45%)*	Low (<40%)
Gynaecology (24%)	High (Likely >80%)*	Low (<40%)	Low (Likely <45%)*	Low (<40%)
Medicine (37%)	Moderate (~70%)	Moderate (~50%)	Moderate (~50%)	Moderate (~50%)
Paediatrics (13%)	Lower (<60%)*	Higher (>60%)*	Higher (>60%)*	Higher (>60%)*
Dentistry (2%)	Variable*	Variable*	Variable*	Variable*

- Vaccination Status & Preventive Practices (*Inferred from aggregate practice patterns)

Vaccination Status	Yearly Screening	Family Vaccination	Post-Exposure Action	Risk Perception
Never (19%)	Very low (<10%)	Very low (<30%)	Very low (<30%)	High neglect
Incomplete (17%)	Low (<15%)	Low (<40%)	Low (<40%)	Moderate neglect
Full (55%)	Low (20-25%)*	Moderate (50-60%)*	Moderate (50-60%)*	Complacent
On schedule (9%)	Higher (>30%)*	Higher (>60%)*	Higher (>60%)*	Alert

Table III (Con'td)

• Knowledge Gaps vs. Critical Practices

Knowledge Deficiency	Affected Practice	High-Risk Groups
Breastfeeding transmission (54%)	Patient education (59% unsafe)	Non-medicine departments
Sanitation myths (73-78%)	PPE negligence (gloves: 40% unsafe)	All departments
PEP awareness gap (24%)	Post-injury inaction (56% unsafe)	Surgery/Gynaecology interns
Treatment options (51% incorrect)	Low confidence (64% unconfident)	Unvaccinated/incomplete interns

• Gender & Protective Practices(*Inferred from overall rates and typical behavioral patterns in medical literature)

Gender	Consistent Glove Use	Family Vaccination	Post-Exposure Action	PPE Compliance Trend
Male (55%)	Lower (<55%)*	Lower (<40%)*	Lower (<40%)*	Higher risk-taking
Female (45%)	Higher (>65%)*	Higher (>50%)*	Higher (>50%)*	Higher caution

Discussion:

Medical professionals are working in an area which can be compared with an active volcano filled with HBV, HCV and many other life-threatening germs. Intern doctors are the most vulnerable candidate for occupational exposure to this germ world, before their entry into the future world. By this study, we can measure the level of knowledge and preventive practice towards occupation exposure to HBV of our upcoming doctors. As Rangpur Medical College is one of the largest medical colleges in Bangladesh, this study may be the representative picture for the rest of the country. In this study, it was found that 64% of the interns are vaccinated, which is quite similar with a study in Saudi Arabia (KSA) where 69.5% had received HBV vaccine,⁹ but quite higher than another study in Bangladesh (40.7%).¹⁰ Regarding knowledge of HBV vaccines, 81% of students knew that carriers could transmit infection (89.5% of them said that it could not be spread by casual contact, 80% said it could be spread by contact with open wound, 96.5% knew it could be transmitted by contaminated blood and body fluids, 92.5% knew that HBV could be transmitted by unsterilized syringe, needle or surgical instruments and 79.5% said it could be transmitted by unsafe sex). The findings were in accordance with a previous study from Cameroon, which reported that its participants had a good knowledge of the study on HBV infection.¹¹ Our results indicate that levels of knowledge among medical students are not proportionate with acceptable levels of compliance with the vaccination. Few studies among Arab medical students showed lower HBV awareness in countries such as Syria¹² and Iran¹³. Our study found that most of the intern doctors lacked important information about cross infection control methods. It was found that, only 68% recognized that HBV is transmitted by sharing plate, glass, bed, hand shaking

and less than half 46% recognized that HBV could be transferred during delivery of fetus. However 84 % knew that HBV can be transmitted by breast feeding and only 46% knew about breast feeding transmission. Our study agrees with those internationally that have identified limitations in knowledge among al HCWs about HBV toward the occupational risk of the disease.¹⁴⁻¹⁷ For these specific modes of transmission (for example, saliva, maternofetal, breast milk) there were a confusions and misconceptions among the survey doctors. Only 29 % of interns correctly answered that, both HBsAg and Anti HBc (total) is the preferable screening test and 60 % preferred HBsAg as screening test. 64% interns exactly answered for Anti HBS as a test to see the effective vaccination status. Only 49% of interns know that both oral and injectable treatments are available for HBV infection. However, 76% knew that HBV has post exposure prophylaxis. In a study on medical students in KSA found that, 86.5% of students knew that vaccine could prevent HBV infection and 64% knew HBV had post exposure prophylaxis and only 55% knew that it could be cured.⁸ While findings regarding attitudes towards HBV, it was found only 36% of the respondents surveyed were willing to continue care for HBsAg positive patients, which is far low than a study in KSA (70.7%).⁸ During the interview 73 % of them claimed for needle prick or minor cut injury during their work, while only 44% intern took necessary measures after accident. However, a study in Sudan found, more than 60% of the HCWs do nothing for suspicious of being infected with HBV, 24.4% consider local dressing and 15% believe in self-testing when being suspicious.⁷ In another study among medical students; about 22% had a needle prick injury but 68% would report that injury.⁸ Regarding use of the barrier techniques such as gloves, facemasks or protective eye glasses provides

additional barriers against HBV transmission.¹⁴ In the area of safe practical approaches, only 47% interns' use sterilized instruments in every procedure, use of gloves in every procedure (60%), use of protective eye glasses (only 32%). We found some similarity with these findings in one study in KSA. In their study, only 34.1% reported of always using double gloves, 46.3% reported of wearing eyeglasses and 85.4% reported of using facemasks among dentists.¹⁸ This study reveals that, while interns have good foundational knowledge, departmental risks, complacency in vaccinated individuals, and myths about non-vector transmissions critically impact practices. Structural interventions are essential to bridge these gaps.

Conclusion:

Physicians must have proper knowledge, interest, and skills to ensure safety from occupational hazards. It is crucial for medical and dental students to be vaccinated against HBV before treating patients. The study highlights the need for better health education on safety measures to prevent infections in healthcare workers.

Recommendations:

Inadequate knowledge has led to negative attitudes towards HBV patients, impacting patient care. Changes in the medical college curriculum in Bangladesh are necessary, with a focus on early education and regular seminars to update knowledge on HBV prevention.

Acknowledgements:

The authors were grateful to the staffs of the Department of Gastroenterology, Rangpur Medical College Hospital, Dhaka, Bangladesh; We extend our sincere gratitude to the study participants whose generous commitment of time and candid responses have greatly enriched the quality and depth of our research.

Funding:

None.

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Rangpur Medical College. Written informed consent was taken from all the patients before taking part of the study.

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ORIGINAL ARTICLE

DEMENTIA SUBTYPES: A STUDY FROM DEMENTIA CLINIC IN A REFERRAL NEUROSCIENCE HOSPITAL, BANGLADESH

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Abstract:

Background: Dementia is one of the major causes of disability and dependency among older people globally but still it is not explored very well in most parts of the world particularly for low-income and middle-income countries. The aim of study was to explore the subtypes of dementia among patients attending the outdoor dementia clinic at a referral tertiary care hospital in Bangladesh.

Methods: This cross-sectional study was carried out in weekly dementia clinic of Department of Neurology at National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh from January 2020 to December 2023 for a period of 4 years. Consecutive patients attending this clinic with history suggestive of dementia were enrolled in this study. Data were collected through a predesigned questionnaire containing information about demography, clinical features, brain imaging and laboratory findings of patients. This study included all patients aged ≥ 18 years, both male and female, who attended with subjective memory and other cognitive impairment complaints. **Results:** The age range was from 25 to 100 years with mean age of 66.04 ($\pm$ SD 10.61) years with a male-to-female ratio of 1.54: 1. There was urban (67.4%) predominance. In 435 patients, the commonest subtype of dementia was Alzheimer's disease ($n= 219$, 50.3%). The second most common subtype was vascular dementia ($n= 75$, 17.2%) followed by mixed dementia ($n= 60$, 13.8%). Frontotemporal dementia, Parkinson's disease dementia, and dementia with Lewy bodies were diagnosed in 22 (5.1%), 13 (3 %) and 6 (1.4%) cases respectively. Most of the patients ($n= 141$, 32.9%) had mild dementia whereas 121 (27.8%) patients had moderate dementia. Only 35 (8%) patients had severe dementia, 72 (16.6%) patients had mild cognitive impairment (MCI). **Conclusion:** Dementia is a major morbidity with a higher prevalence among elderly males. Alzheimer's disease is the most common subtype of dementia in Bangladesh.

Keywords: Dementia, Bangladesh.

Date of submission: 02.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.83923>.

Citation: Hassan MS, Uddin MN, Shams S, Hossain S, Sarkar M, Sonia SF et al. Dementia Subtypes: A Study from Dementia Clinic in A Referral Neuroscience Hospital, Bangladesh. Bangladesh J Medicine 2025; 36(3): 123-128.

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Introduction:

Dementia is a syndrome characterized by decline in cognitive abilities, such as memory, thinking, and reasoning that is severe enough to interfere with daily functioning.¹ It is not a specific disease but rather a group of symptoms associated with underlying conditions.² Dementia is one of the leading causes of death worldwide and has 10 million new cases reported every year.³ Until 2018, the global number of people living with dementia has been estimated at 50 million, and the number will triple by 2050.⁴

Early signs and symptoms are forgetting things or recent events, losing or misplacing things, getting lost when walking or driving, being confused even in familiar places, losing track of time, difficulties solving problems or making decisions, problems following conversations or trouble finding words, difficulties performing familiar tasks, misjudging distances to objects visually.² Apart from memory loss, people with dementia may experience difficulty with language and communication, impaired judgment, changes in mood and behavior and a decline in the ability to perform basic day to day tasks.²

The cognitive symptoms of dementia relate to the area of the brain affected.⁵ The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines six key domains of cognitive function: complex attention, executive function, learning and memory, language, perceptual-motor control, and social cognition.⁶

Normally, symptoms must be present for at least six months to support a diagnosis.⁷ Cognitive dysfunction of shorter duration is called delirium. In comparison, dementia has typically a long, slow onset, slow decline of mental functioning, as well as a longer trajectory from months to years.⁷

Causes of dementia can be broadly classified as reversible causes and Irreversible causes. The most common irreversible types of dementia are Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson's disease, Frontotemporal dementia, Huntington's disease, Creutzfeldt-Jakob disease, Chronic traumatic encephalopathy, Pick's disease. The coexistence of more than one type of dementia is known as mixed dementia.^{8,9} Alzheimer disease is the most common form of dementia and may contribute to 60–70% of cases.⁴ Though reversible causes are less frequent, they carry good prognosis with prompt treatment of the underlying condition. The most frequently observed potentially reversible conditions are depression, adverse effects of drugs, alcohol abuse, space-occupying lesions, normal pressure hydrocephalus, and metabolic conditions and endocrine conditions like hypothyroidism and

nutritional conditions like vitamin B-12 deficiency. Depression is by far the most common of the potentially reversible conditions.

Diagnosis of dementia is usually based on history, clinical examination and cognitive testing laboratory testing and imaging. Various brief cognitive tests have reasonable reliability to screen for dementia.¹⁰ While many tests have been studied, presently the mini mental state examination (MMSE) is the best studied and most commonly used.^{11,12} The MMSE is a useful tool for helping to diagnose dementia if the results are interpreted along with an assessment of a person's personality, their ability to perform activities of daily living, and their behaviour.¹³

A CT scan or MRI scan is commonly performed to find structural lesions of brain such as stroke, normal pressure hydrocephalus, subdural hematoma or tumor.¹⁴ Imaging also helps to identify different degenerative causes of dementia.

Methods:

This cross-sectional study was carried out in weekly dementia clinic of Department of Neurology at National Institute of Neurosciences and Hospital (NINS&H), Dhaka, Bangladesh from January 2020 to December 2023 for a period of 4 years. Consecutive patients in dementia clinic during this study period were enrolled. Patients unwilling to give consent and patients without cognitive impairment were excluded from the study.

A preformed questionnaire was used containing information on age, sex, habitat, clinical history from patients and observers, examination findings, previous and current medications, result of laboratory and imaging studies for data collection.

This study included all patients aged ≥ 18 years, both male and female, who attended with subjective memory and other cognitive impairment complaints. The patients were recruited purposively, and consecutive patients were included in this study reporting to the dementia clinic.

The demographic profile details were recorded and evaluated per standard procedure in the dementia clinic, and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria were applied to diagnose dementia and to subtype dementia.⁶ In DSM-5, dementia is referred to as Major Neurocognitive Disorder. The core criteria involve significant cognitive decline from a previous level of performance in one or more cognitive domains (like memory, language, or executive function) that interferes with independence in everyday activities.⁶ This decline must be substantial and documented through both subjective complaints and objective cognitive testing.

The DSM-5 criteria for Alzheimer's disease, now categorized under "Major or Mild Neurocognitive Disorder due to Alzheimer's Disease," require evidence of cognitive decline from a previous level of performance in one or more cognitive domains (like memory, language, or executive function), alongside interference with independence in daily living.⁶ A diagnosis also necessitates that the cognitive deficits are not better explained by another mental disorder or delirium and that there's evidence of either probable or possible Alzheimer's disease based on clinical criteria.

The DSM-5 criteria for Dementia with Lewy bodies diagnosis requires insidious onset and gradual symptom progression, along with the presence of core features (fluctuating cognition, recurrent visual hallucinations, and parkinsonism) or a combination of core and suggestive features.⁶ The cognitive deficits should not be better explained by another mental disorder (e.g., major depressive disorder, schizophrenia), other medical conditions (e.g., stroke, traumatic brain injury) or another neurodegenerative disorder (e.g., Alzheimer's disease, Parkinson's disease).

The DSM-5 diagnostic criteria for Frontotemporal Dementia (FTD) primarily focus on behavioral variant FTD (bvFTD) and require a progressive decline in behavior and social cognition, or executive function, with relative sparing of memory and perceptual-motor function.⁶ A diagnosis of possible bvFTD necessitates at least three out of six specific behavioral symptoms, while probable bvFTD adds neuroimaging evidence or a known FTD pathogenic mutation. The core feature is prominent decline in social cognition and/or executive function with at least three of the following: behavioral disinhibition, apathy, loss of sympathy/empathy, perseverative, stereotyped, or compulsive/ritualistic behaviors, hyperorality and dietary changes. Memory and perceptual-motor functions are relatively spared, at least in the early stages of the disease.

The DSM-5 criteria for dementia in Parkinson's disease (PDD) require meeting the criteria for either major or mild neurocognitive disorder, occurring in the context of established Parkinson's disease, with an insidious onset and gradual progression.⁶ The cognitive decline must not be better explained by another medical condition or mental disorder, and there should be no evidence of mixed etiology.

In DSM-5, vascular dementia is categorized under Major or Mild Neurocognitive Disorder due to Vascular Disease. The criteria include evidence of cognitive decline from a previous level of performance in one or more cognitive domains (attention, executive function, memory, language, perceptual-motor, or

social cognition).⁶ This decline must be significant enough to interfere with independence in daily activities. Additionally, there must be evidence of cerebrovascular disease (through imaging or other means) and a causal link between the vascular disease and the cognitive deficits.

The DSM-5 does not have specific diagnostic criteria for "mixed dementia" as a distinct category. Instead, it focuses on the broader concept of Major Neurocognitive Disorder (which encompasses dementia) and allows for the specification of underlying etiologies. Mixed dementia, in the context of DSM-5, would be diagnosed when a patient exhibits cognitive decline that interferes with daily functioning and is attributed to more than one underlying neurodegenerative or cerebrovascular disease.⁶

Reversible causes of dementia, while not specifically listed as diagnostic criteria, are considered during the evaluation process. To exclude the reversible causes of dementia, we utilised different routine blood tests like blood sugar, serum creatinine, complete blood count, peripheral blood film, vitamin D, and thyroid function tests (Thyroid stimulating hormone, free triiodothyronine 3 and 4 levels), liver function test (LFT), Venereal Disease Research Laboratory (VDRL), serum vitamin B12, serum calcium, and chest X-ray. A neuroimaging test, like a computed tomography (CT) and MRI scan, was performed to find out infarct, hematoma, tumour, hydrocephalus, neurodegenerative causes of dementia. All these imaging tests were conducted in the Department of Neuroradiology and Imaging at the same institute using the same standard protocol.

Further, a MMSE was performed to score the severity of cognitive domains.¹³ Scores range from 0 to 30 points, with lower scores indicating more significant impairment. When the MMSE score is below 23, the patients are regarded as a case of dementia. MMSE scores of 19 to 22 are consistent with mild dementia, 10 to 18 with moderate dementia, and <10 with severe dementia. A score of 27 or higher classified as normal. If the score is 23 to 26, patients are considered to have mild cognitive impairment (MCI).

Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data were expressed as mean, standard deviation, minimum and maximum. Categorical data were summarized in terms of frequency counts and percentages. All consecutive dementia patients attended in this time period, were included in this study after fulfilling the inclusion and exclusion criteria.

Results:

A total number of 435 patients were recruited. The age range was from 25 to 100 years with a median of 66 years. The mean age was 66.04 years with Standard Deviation (SD) of 10.61 years (Table I). Out of 435 patients, 264 were male and 171 were female with a male-to female ratio of 1.54: 1. There was a male (60.7%) predominance (Table I).

Urban patients were residing in cities and in municipal corporations. All patients other than urban areas were labeled as rural patients. There was urban (67.4%) predominance (Table I).

Table I

Demographic Characteristics of patients

Characteristics	Values
Age in years (mean $\pm$ SD)	66.05 $\pm$ 10.61
Sex- N (%)	
Male	264(60.7%)
Female	171(39.3%)
Residence- N (%)	
Urban	293(67.4%)
Rural	142(32.6%)

Among the 435 patients, the commonest subtype of dementia was Alzheimer's disease (AD) (n= 219, 50.3%). The second most common subtype of dementia was Vascular Dementia (n= 75, 17.2%) followed by mixed dementia (n= 60, 13.8%). Parkinson's Disease Dementia was diagnosed in 13 (3%) cases. Frontotemporal Dementia was diagnosed in 22 (5.1 %) cases whereas Dementia with Lewy bodies was diagnosed in 6 (1.4%) cases. Reversible causes of dementia were identified in 40 (9.2%) cases. (Figure 1)

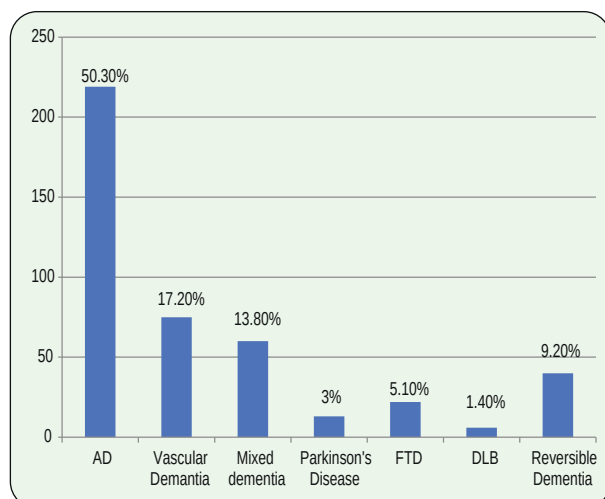


Fig.- 1: Types of Dementia (AD=Alzheimer's disease, DLB= Dementia with Lewy bodies, FTD= Frontotemporal Dementia, PDD=Parkinson's Disease Dementia)

Out of 40 cases of reversible dementia, depression was most commonly identified (n=17). Other reversible causes were Normal Pressure Hydrocephalus (NPH) (n=8), chronic kidney disease (CKD) (n=5), Vitamin B12 deficiency (n=3), brain tumor (n=3), hypothyroidism (n=2), paraneoplastic condition (n=1) and chronic liver disease (CLD) (n=1). (Figure 2)

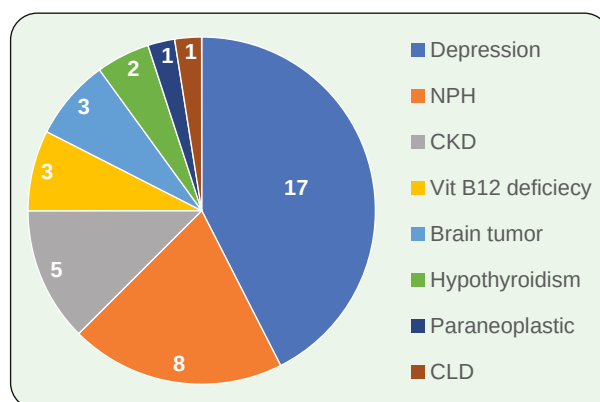


Figure 2: Reversible causes of Dementia (CKD= chronic kidney disease, CLD= chronic liver disease, NPH= Normal Pressure Hydrocephalus)

Among 435 patients, 64 (14.7%) patients had normal MMSE. 72 (16.6%) patients had mild cognitive impairment (MCI). Most of the patients had mild dementia (n=143, 32.9%) whereas 121 (27.8%) patients had moderate dementia. Only 35 (8%) patients had severe dementia. (Figure 3)

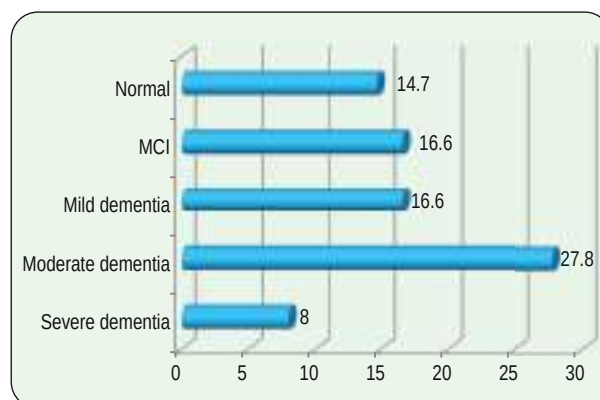


Figure 3: Severity of Dementia based on MMSE Score (27-30: No Dementia; 23-26: mild cognitive impairment (MCI); 18-22: Mild dementia; 10-17: Moderate dementia; < 9: Severe dementia)

Discussion

Dementia is a syndrome, characterized by a general decline in cognitive abilities that affects a person's ability to perform everyday activities.¹ This typically involves problems with memory, thinking, behavior, and motor control.¹

Things that increase the risk of developing dementia include age; more common in those 65 years or older.¹⁵ Although the greatest risk factor for developing dementia is aging, dementia is not a normal part of the aging process.¹⁶ In this study, the median age of patients was 66 years. The mean age was 66.04 years with Standard Deviation (SD) of 10.61 years. In a study in India among 347 consecutive dementia patients, the mean age of the group at presentation was 66.3 years, which is similar to our finding but nearly a decade younger than in developed countries.¹⁷

Women are disproportionately affected by dementia. Women experience higher disability-adjusted life years and mortality due to dementia.¹⁵ In this study, there was a male (60.7%) predominance with a male-to-female ratio of 1.54: 1 which is contrary to previous study which demonstrated that dementia prevalence was higher in females compared to males.^{18,19}

Alzheimer disease is the most common form of dementia and may contribute to 60–70% of cases.^{3,15} In this study, the commonest type of dementia was Alzheimer's disease (n= 219, 50.3%) followed by vascular dementia (n= 75, 17.2%) and mixed dementia (n= 60, 13.8%) respectively. So, our finding is similar to previous studies. In a study in India among 347 consecutive dementia patients, Alzheimer's disease was the most common subtype of dementia (38.3%), followed by a high proportion of vascular dementia (25.4%); Frontotemporal dementia syndromes were not uncommon (18.7%) and Dementia with Lewy bodies was encountered in 8.9% of the patients, and mixed dementia was found in 8.6%.¹⁷

Many neurocognitive disorders may be caused by another medical condition or disorder, including brain tumors and subdural hematoma, endocrine disorders, nutritional deficiencies, infections, immune disorders, liver or kidney failure.⁶ Some of the neurocognitive deficits may sometimes show improvement with treatment of the causative medical condition.⁶ These are reversible causes of dementia. In this study, 40 (9.2%) patients had reversible causes of dementia.

When compared to other countries, the prevalence of dementia reported in Bangladesh (8.0%) is like that reported across the world (range 5.5–11.3%).²⁰ The projected number of people living with dementia is expected to more than double by 2051.²¹ So early diagnosis and subtypes of dementia is warranted to tackle the vast number of current and future dementia cases in Bangladesh.

There are some limitations of the study. We looked for only a few reversible causes of dementia. Risk factors

for dementia were not evaluated. Genetic tests were not done.

Conclusion:

Dementia is more prevalent among elderly people. Alzheimer's disease is the most common subtype of dementia in Bangladesh. More effort is needed for early accurate diagnosis of dementia. Searching for reversible causes of dementia and appropriate treatment is also warranted.

Acknowledgments:

The authors thank all patients, health physicians, nurses and other health care providers involved in the care of these patients of Department of Neurology , National Institute of Neurosciences & Hospital for their kind help and co-operation.

Funding:

This research did not receive any specific grant from any funding agencies

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Consideration:

All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration 2013) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee (Ref: IRB/NINS/2020/393). Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and were analyzed using the coding system.

Authors' contributions:

Hakim M, Hassan MS and Uddin MN contributed to the concept and design. Uddin MN, Shams S, Hossain S, Sarkar M performed data collection and compilation. Hassan MS, Sonia SF, Mehrab R, Yusuf A and Rahman M contributed in data analysis and manuscript writing. All author revised and approved the manuscript.

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ORIGINAL ARTICLE

HYPOXEMIA WITH PNEUMONIA IN UNDER FIVE CHILDREN: A HOSPITAL-BASED STUDY IN DHAKA, BANGLADESH

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Abstract:

Background: Pneumonia causes significant child morbidity and mortality globally, especially in developing countries. Hypoxemia is a critical complication in pediatric pneumonia and a key indicator of severe disease needing urgent medical intervention. This study aimed to investigate the clinical predictors of hypoxemia in children with pneumonia. **Methods:** This is a cross-sectional comparative study was conducted at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh, from January to December 2022. A total of 394 children aged 2-59 months with pneumonia were purposively enrolled. Of these, 132 (33.5%) had hypoxemia, while 262 (66.5%) did not. All demographic, diagnostic, and clinical data were recorded and analyzed using SPSS version 22.0. **Results:** In univariate analysis, hypoxic status correlated significantly with vomiting, fast breathing, inability to drink, unusual sleepiness ($p < 0.05$), unconsciousness / lethargy, immobility during examination ($p < 0.001$), abnormal sleepiness, and palm pallor ($p < 0.05$). Indicators included nasal flaring, chest indrawing, head nodding, continuous grunting, diminished breath sounds ($p < 0.05$), and heart rate ($p < 0.001$). Sensitivity was higher for heart rate, fast breathing, palm pallor, and chest indrawing. Specificity was higher for vomiting, lethargy/unconsciousness, unusual sleepiness, head nodding, grunting, and nasal flaring. **Conclusion:** Among children with pneumonia, nearly one-third may be hypoxic, with a higher frequency in females. Sensitivity for predictors of hypoxemia is better in fast breathing, pallor of the palm, lower chest indrawing, and increased heart rate. Specificity is better in persistent vomiting, lethargy, unusual sleepiness, head nodding, grunting, and nasal flaring.

Keywords: Clinical predictors, Hypoxemia in Children, Pneumonia, Fast breathing, Nasal flaring

Date of submission: 02.06.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.82723>.

Citation: Islam MM, Qamruzzaman K, Islam MS, Azam MS, Shameem M, Tauhid SA et al. Hypoxemia with pneumonia in under five children: A hospital-based study in Dhaka, Bangladesh. Bangladesh J Medicine 2025; 36(3): 129-135.

Introduction:

Pneumonia is the leading cause of death in young children worldwide, with the highest number of cases occurring annually in the Asia-Pacific region.¹ Hypoxia, which is generally defined as a peripheral oxygen

saturation of less than 90%, is a frequent complication in childhood pneumonia and is an important marker of its severity.² Hypoxemia is partial arterial oxygen pressure below 8.0 kPa (60 mmHg) or SpO₂ less than 90% by pulse oximetry.³ It results from a ventilation-

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perfusion mismatch due to alveolar congestion from fluid or inflammatory cells caused by infection.⁴ Prolonged hypoxemia in children with pneumonia can worsen the illness duration and increase mortality.⁵ Oxygen therapy can reduce mortality in children with hypoxic pneumonia by 20%, but detecting hypoxemia is difficult where pulse oximetry is inconsistent.⁶ Case management helps identify severe cases in resource-limited settings for in-patient treatment.⁷ The revised Integrated Management of Childhood Illness (IMCI) guidelines of 2013 categorize pneumonia into two types: pneumonia with fast breathing and/or chest indrawing, treatable at home with oral amoxicillin, and severe pneumonia with any general danger sign, requiring hospital referral and injectable therapy.⁸ The WHO recommends using clinical signs to detect hypoxemia when pulse oximetry is unavailable.⁹ Children presenting to healthcare facilities are classified as having mild, moderate, or severe pneumonia based on clinical parameters.¹⁰ This classification, following IMCI principles with some variations, guides decisions on hospital admission, antibiotics, and oxygen therapy. While case management in resource-poor countries reduces overall and pneumonia-specific mortality, it has limitations, including over-referral and accurate recognition of hypoxemia.¹¹ The clinical criteria are designed to be highly sensitive to identify cases needing hospitalization and antibiotics. However, this can lead to unnecessary referrals, which are costly for parents and offer limited benefits to the child.¹² Studies have shown that detecting hypoxemia using clinical signs is sub-optimal, and pulse oximetry is the preferred method for assessing the need for and response to oxygen therapy.¹³

Methods:

This was a prospective observational study that was conducted at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh, from January 2022 to December 2022. A total of 394 children, aged between 2 and 59 months and diagnosed with pneumonia, were selectively enrolled in the study. Out of these, 132 children (33.5%) exhibited hypoxemia, while the remaining 262 children (66.5%) did not. The hospital's ethical committee approved the study, and informed consent was obtained from all participants before data collection. The entire intervention adhered to the principles of human research outlined in the Helsinki Declaration¹⁴ and was conducted following current regulations and GDPR provisions.¹⁵ The inclusion criteria encompassed children aged 2-59 months

suffering from pneumonia, based on the WHO guidelines of 2005, who were attending the Pediatrics OPD, Emergency Department, or In-patient Department of Sir Salimullah Medical College & Mitford Hospital in Dhaka. The exclusion criteria included children younger than 2 months or 60 months and older, any patient having precordial murmur, a history of repeated breathlessness improved with bronchodilators, and playful children with breathlessness and rhonchi. Data were collected and recorded using a structured questionnaire, with interviews conducted personally by the investigator. Oxygen saturation levels were measured with a pulse oximeter (NONIN Model 7500, USA). Sensitivity specificity and predictive values of the clinical findings significantly associated with hypoxemia in pneumonia were generated based on the standard formula. For data analysis, SPSS version 16.0 was utilized. In the statistical analysis, a P value of less than 0.05 was considered indicative of significance.

Results:

In this study, 394 subjects were interviewed and examined. Hypoxemia was diagnosed based on peripheral oxygen saturation measured via pulse oximetry, with 132 (33.5%) having hypoxemia and 262 (66.5%) not having it. Socio-demographic data and symptoms were collected through interviews, while general and respiratory signs were obtained through physical examination. Univariate analysis identified significant characteristics, that were further assessed for their predictive capacity using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)

Table-I
Socio-demographic characteristics (n=394)

Variables	Hypoxic (n = 132)	Non-hypoxic (n = 262)	X ²	p- value
Age group				
2-11 months	89(67.4)	172(65.6)	0.124	0.725
≥12 months	43(32.6)	90(34.4)		
Sex				
Male	62(47.0)	182(69.5)	18.841	0.000
Femnale	70(53.0)	80(30.5)		
Residence				
Rural	39(29.5)	87(33.2)	3.329	0.189
Urban	46(34.8)	105(40.1)		
Semi-urban	47(35.6)	70(26.7)		

Table I shows that there was no statistically significant difference in age distribution between hypoxic and non-hypoxic subjects. However, more females were hypoxic than males. Both groups were homogeneous in terms of place of residence.

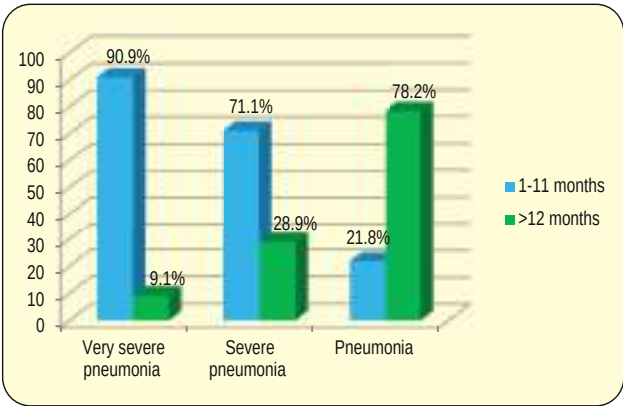


Figure 1: Distribution of hypoxemia and non-hypoxemia among the cases.

Among the 394 pneumonia cases, 132 (33.5%) had hypoxemia, while 262 (66.5%) did not (Figure 1).

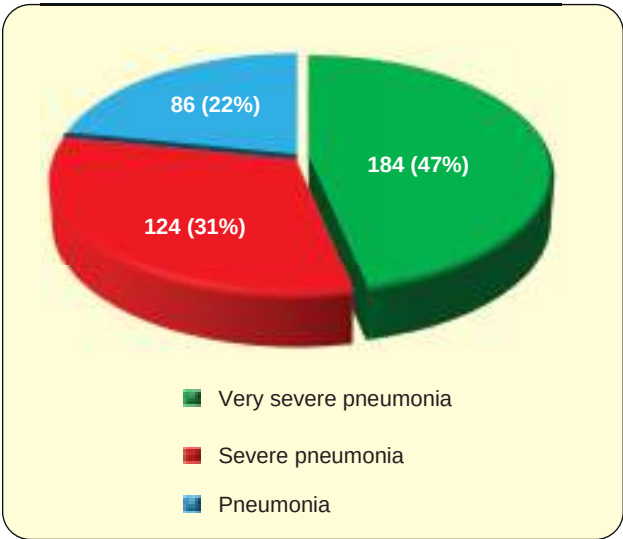


Figure 2: Distribution of pneumonia cases according to severity.

Figure 2 shows the distribution of pneumonia cases according to severity. Among the cases, very severe pneumonia accounted for 46.7% (184 cases), severe pneumonia for 31.5% (124 cases), and pneumonia for 21.8% (86 cases).

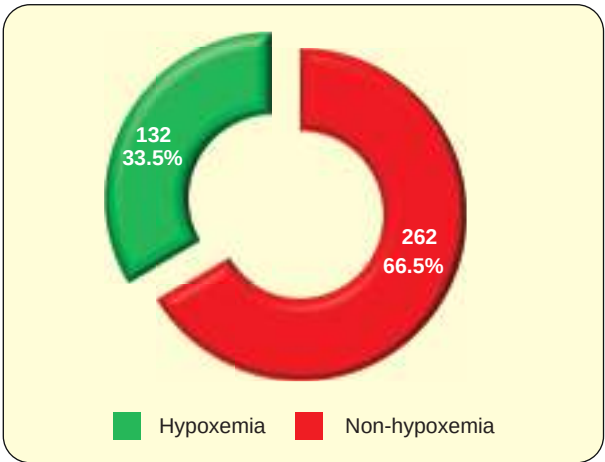


Figure 3: Distribution of children by age and classification (N=394)

Figure 3 shows the distribution of the study subjects by age and classification. Among the subjects with very severe pneumonia, 91% were less than 1 year of age. In children with severe pneumonia, 71.1% were less than 1 year old. In children with pneumonia, most (78.2%) were aged 12 months or older.

Table II
Comparison of symptoms reported between hypoxic and non-hypoxic subjects

Characteristics	Hypoxemic Non-hypoxemic		X2	p- value
	(n = 132)	(n = 262)		
	n(%)	(%)		
Cough		258(98.5)	2.036	0.154
Breathing difficulty		197(75.2)	2.205	0.138
Vomit everything		46(17.6)	10.291	0.001
Fast breathing		197(75.2)	4.075	0.044
Fever	132(100)	170(64.9)	0.154	0.695
Excess cry	108(81.8)	101(38.5)	2.129	0.145
	42(31.8)			
	111(84.1)			
	83(62.9)			
	61(46.2)			
	57(43.2)			
	60(45.5)			
	63(47.7)			
	33(25.0)			
Reduce feed		94(35.9)	1.681	0.159
Inability to drink		74(28.2)	11.584	0.001
Irritability		121(46.2)	0.084	0.772
Unusually sleepy		9(3.4)	42.862	0.000

Table II presents the univariate analysis of symptoms reported by informants. Symptoms such as vomiting everything($p=0.001$),fast breathing($p=0.004$),inability to drink($p=0.001$),and unusual sleepiness($p<0.001$) were significantly associated with the hypoxic status of children.

Table III

Comparison of signs revealed on general examination among subjects with or without hypoxia

Characteristics	Hypoxemic Non-hypoxemic (n = 132) (n = 262) n(%) (%)	X2	p-value
Unconscious/ Lethargic	60(45.5) 50(19.1)	30.332	0.000
Movement on examination	98(74.2) 258(98.5)	59.139	0.000
Abnormally sleepy	39(29.5) 4(1.5)	70.875	0.000
Ability to cry	112(74.2) 232(88.5)	1.085	0.298
Restless/ Irritable	79(59.8) 132(50.4)	3.163	0.075
Stridor in calm child	15(11.4) 25(9.5)	0.319	0.572
Pallor of palm	106(80.3) 179(68.3)	6.298	0.012
Temperature	50(37.9) 112(42.7)	0.86	0.354

Table III presents a comparison of signs revealed during the general examination of subjects with or without hypoxia. Univariate analysis indicates a significant association of the signs-unconsciousness or lethargy ($p<0.001$), absent movement during examination ($p<0.001$),abnormal sleepiness ($p<0.001$), and pallor of the palm ($p=0.012$)with hypoxic status.

Table IV presents a comparison of respiratory signs between subjects with and without hypoxia.Univariate analysis shows that nasal flaring ($p=0.016$), lower chest indrawing ($p=0.005$), head nodding ($p<0.001$), continuous grunting($p<0.001$), and diminished breath sounds ($p=0.04$)are significantly associated with hypoxic status.

Table V shows the distribution of study subjects by hypoxia status and respiratory rate across different age groups. In children aged 2-11 months, fast breathing was significantly morecommon in hypoxic subjects compared to non-hypoxic subjects($p<0.001$).

Similarly, in children aged 12-59 months, fast breathing was also significantly more frequent in hypoxic subjects than in non-hypoxic subjects ($p=0.009$).

Table IV

Comparison of respiratory signs between subjects with or without hypoxia

Characteristics	Hypoxemic Non-hypoxemic (n = 132) (n = 262) n(%) (%)	X2	p-value
Nasal flaring	43(32.6) 56(21.4)	5.854	0.016
Lower chest in drawing	105(79.5) 173(66.0)	7.718	0.005
Head nodding	20(7.6)	31.29	0.000
Continued grunt	31(11.8)	20.272	0.000
Crepitating	39(28.8) 221(84.4)	1.881	0.170
Wheeze	40(30.3) 31(11.8) 104(78.8) 21(15.9) 34(25.8) 54(40.9)	1.274	0.259
Rhonchi	68(26.0)	0.002	0.966
Diminish breath sound	80.(30.5)	4.210	0.040
Bronchial breath sound	32(24.2) 57(21.8)	0.310	0.577
Stridor in calm child	15(11.4) 25(9.5)	0.319	0.572

Table V

Comparison of the presence or absence of fast breathing between subjects with or without hypoxemia

Charac- teristics	Hypoxemic (n=132)	Non- hypoxemic (n=262)	X2	p-value
Age:2-11 months				
<50/min	21(23.6)	82(47.7)	14.20	0.000
≥50/min	68(76.4)	90(52.3)		
Age:≥12 months				
<40/min	19(44.2)	61(67.8)	6.76	0.009
≥40/min	24(55.8)	29(32.2)		

Table VI*Comparison of non-respiratory physical signs in children with or without hypoxia*

Charac- teristics	Hypoxemic (n=132)	Non- hypoxemic (n=262)	X2	p- value
Heart rate				
≥100	124(93.9)	262(100)	16.208	0.000
<100	8(6.1)	0(0.0)		
Capillary refill time				
<3 second	117(88.6)	240(91.6)	0.908	0.341
≥3 second	15(11.4)	22(8.4)		
Hepatomegaly				
<2cm	104(78.8)	199(76.0)	0.397	0.529
≥2cm	28(21.1)	63(24.0)		

Table VI presents a comparison of physical signs in children with and without hypoxia. The analysis indicates that hypoxic status is significantly associated only with heart rate ($P<0.0001$)

Table VII*Sensitivity, specificity, and predictive values found to have a significant association with hypoxia*

Clinical predictors	Sensitivity %	Specificity	Predictive value Positive	Negative
Symptoms				
Vomit everything	31.8	82.4	47.7	70.6
Fast breathing	82.4	24.8	36.3	75.6
Inability to drink	45.5	71.8	44.8	72.3
General sign				
Lethargy	45.5	80.9	54.5	74.6
Movement	74.2	1.5	27.5	10.5
Unusually sleepy	29.5	98.5	90.7	73.5
Pallor of palm	80.3	31.7	37.2	76.2
Heart rate	93.9	0.0	35.4	0.0
Respiratory sign				
Nasal flaring	35.6	78.6	43.4	69.8
Chest indrawing	79.5	33.9	37.8	76.7
Head nodding	28.8	92.3	65.5	72.0
Continued grunting	30.3	88.2	56.3	71.5

Table VII analyzes the predictive capacity of clinical signs and symptoms in terms of sensitivity, specificity, and predictive values for hypoxemic and non-hypoxemic children. Sensitivity was higher for heart rate, fast breathing, pallor of the palm, and lower chest indrawing, while specificity was higher for symptoms like vomiting everything, lethargy/unconsciousness, unusual sleepiness, head nodding, grunting, and nasal flaring. No single characteristic excelled in both sensitivity and specificity.

Discussion:

In this study, 394 pneumonia cases were examined, and hypoxemia was confirmed in 132 cases (33.5%). This prevalence aligns well with Basnet et al.'s¹⁶ finding of a 38% prevalence of hypoxemia. Very severe pneumonia was more frequent in the 2-11 months age group than in children aged 12 months or older, consistent with findings from other studies.^{16,17} Additionally, this study showed that hypoxemia was more prevalent among young children aged less than 12 months, similar to another previous study², which also found a higher frequency of hypoxemia in infants compared to children aged 12 months or older. In the present study, symptoms reported by informants that showed a significant association with hypoxemia included persistent vomiting, fast breathing, and inability to drink, aligning with observations by Odeyemi et al.¹⁸ Among these symptoms, the inability to drink had the highest sensitivity (45.5%) and specificity (71.8%) in this study. Among the general signs considered, lethargy, absent movement during examination, unusual sleepiness, pallor of the palm, and altered heart rate showed significant associations with hypoxemia. These findings are consistent with those of Basnet et al.¹⁶, who also reported significant associations with lethargy and unresponsiveness. In the present study, lethargy exhibited a sensitivity of 45.5% and a specificity of 80.9%, making it a better predictor of hypoxemia in children with pneumonia than other general signs. This aligns with Usen et al.¹⁹, who reported a sensitivity and specificity of 49% and 77%, respectively. Respiratory signs significantly associated with hypoxemia in the present study included nasal flaring, lower chest indrawing, head nodding, diminished breath sounds, tachypnea, and grunting. Similarly, Basnet et al.¹⁶ identified nasal flaring, lower chest indrawing, cyanosis, tachypnea, crepitation, and grunting as significant predictors. In the present study, nasal flaring had a sensitivity of 35.6% and a specificity of 78.6%, comparable to Dyke et al.²⁰, who reported a sensitivity and specificity of 56% and 84%, respectively. In the present study, although the sensitivity of nasal flaring was low, its specificity was comparable to other studies. Lower chest indrawing demonstrated better sensitivity (79.5%) and specificity (33.9%) in our findings. Lozano et al.¹⁷ reported similar results with a sensitivity of 83% and specificity of 40%. Only two cases of cyanosis were identified in this study. Consequently, the significant clinical predictors of hypoxemia were inability to drink, lethargy, nasal flaring, and lower chest indrawing. Among these, lethargy emerged as the best clinical predictor of hypoxemia in children with pneumonia aged 2-59 months, with a sensitivity

of 45.5% and specificity of 80.9%. Clinical signs that predict hypoxemia can help identify children who need supplemental oxygen and should be referred to larger hospitals, thereby reducing morbidity. In centers where hypoxemic children are screened using physical signs for referral to higher facilities, these predictor signs can facilitate quicker and more accurate referrals.

Limitation of the study:

The study faced several limitations: not all patients could be recruited during emergency admissions, which could have enhanced the results. It was conducted at a single center and had a short duration due to time constraints, limiting its generalize ability. Additionally, confounding factors such as bronchiolitis, asthma, and other related conditions were inadequately addressed.

Conclusion:

Among children with pneumonia, nearly one-third may experience hypoxia, with a higher frequency observed in females. Predictors of hypoxemia show better sensitivity in the presence of fast breathing, pallor of the palms, lower chest indrawing, and increased heart rate. In contrast, specificity for hypoxemia is higher when symptoms such as persistent vomiting, lethargy, unusual sleepiness, head nodding, grunting, and nasal flaring are present.

Recommendations:

Inability to drink, lethargy, nasal flaring, and lower chest indrawing are clinical predictors of hypoxemia in pneumonia, though their sensitivity and specificity do not meet optimal expectations. Further studies with greater methodological rigor and consideration of all limitations are recommended to provide more conclusive evidence regarding hypoxemia in pneumonia. This can help improve diagnosis and treatment protocols, enhancing patient care in resource constrained settings

Acknowledgements:

The authors were grateful to the staffs of the Department of Pediatrics, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh; We extend our sincere gratitude to the study participants whose generous commitment of time and candid responses have greatly enriched the quality and depth of our research.

Funding:

None.

Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are

responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Sir Salimullah Medical College. Written informed consent was taken from all the patients before taking part of the study.

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ORIGINAL ARTICLE

A SHORT-TERM FOLLOW-UP STUDY ON HORMONAL CHANGES AFTER THREE TO SIX MONTHS OF SARS-COV-2 INFECTION

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Abstract:

Background: Long-COVID symptoms may develop following coronavirus disease 2019 (COVID-19) and mimic various endocrine dysfunctions. Hormonal assessment during and after COVID may be necessary to distinguish between these conditions. This study evaluated hormone status during active infection and after three to six months post-COVID-19 infection. **Methods:** This prospective study initially included ninety-one noncritically ill hospitalized patients with COVID-19 infection (18-65 years, m/f: 37/54). The participants were reassessed three to six months after their hospitalization. Eight patients died during their hospital stay, and we were able to collect follow-up data for only fifteen [age (years): 47.3±13.3, m/f: 6/9] out of eighty-three survived patients. Thyroid (TSH, FT4, and FT3), adrenal (basal cortisol and ACTH), and sex-steroid (total testosterone and dehydroepiandrosterone sulfate) axes were evaluated and compared with laboratory cut-offs at diagnosis and three to six months later. All the hormones were measured by chemiluminescent microparticle immunoassay. **Results:** At baseline, six participants (40.0%) had normal values for all the studied hormones, five (33.3%) exhibited one abnormality, and four (26.7%) displayed two abnormalities. After three months of COVID-19 infection, four had normal values (26.7%), six (40.0%) had one abnormality, three (20.0%) had two, and two (13.3%) had three abnormalities in the studied hormone status. **Conclusion:** Endocrine dysfunctions are not uncommon during short-term follow-up after COVID-19, and hormonal evaluations may be necessary, particularly for symptomatic patients.

Keywords: Coronavirus disease 2019, Post-COVID, Hormone, Thyroid, Adrenal, Testosterone, Dehydroepiandrosterone sulfate

Date of submission: 14.05.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.81503>.

Citation: Arafat SM, Banu H, Morshed MS, Sultana N, Hasanat MA. A short-term follow-up study on hormonal changes after three to six months of SARS-CoV-2 infection. *Bangladesh J Medicine* 2025; 36(3): 136-141.

Introduction:

The devastating pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) still exists, but in a milder form.¹ So, the importance has shifted from acute infection to prolonged and persistent long COVID syndrome. The long-term effects of post-COVID

syndrome comprise several overlapping features of endocrine dysfunctions including fatigue, reduced libido, menstrual irregularity, palpitations, etc.² Endocrine glands are vulnerable to destructions and dysfunctions by COVID-19 due to the expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) which

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are located on the cell membrane and facilitate viral entry. Androgens are known to regulate the TMPRSS2 receptors.³ Despite these, the effects of COVID-19 on endocrine glands are mostly acute and usually not related to direct damage; instead, they are affected by inflammatory cytokines and hypercoagulable states, depending on the severity of the illness.^{4,5} Furthermore, the use of steroids during an acute illness might impair different hormonal axes, making it challenging to assess hormonal levels.⁶ Follow-up hormone evaluation data are unavailable among Bangladeshi patients in the literature.

Regardless of steroid treatment during their acute phase of infection, we sought to evaluate the adrenal, thyroid, and sex hormone levels in non-critically sick individuals three to six months following COVID-19 infection.

Methods:

The study was carried out in compliance with the Helsinki Declaration. Before being included in the study, all individuals gave written informed consent. The Institutional Review Board of Bangladesh Medical University gave ethical permission for this study (No. BSMMU/2021/557).

This prospective study recruited participants from a cohort of patients admitted to two tertiary hospitals in Dhaka city. These patients had been RT-PCR positive for COVID-19 between three and six months before enrolment in the study. All patients between 18 and 65 with a nasopharyngeal swab real-time RT-PCR test confirming their COVID-19 diagnosis were eligible for inclusion. The study excluded patients who were on other medications known to impact cortisol-binding globulin, such as oral estrogens, or who had taken steroids (oral, inhaled, topical, or intra-articular) after recovering from COVID-19. Similarly, those patients with known chronic diseases or states known to influence cortisol-binding globulin (e.g., pregnancy, end-stage renal failure, or underlying malignancy) were also excluded.

Two fasting blood samples (eight ml on each occasion), at diagnosis and three to six months of diagnosis were taken from participants for assaying of cortisol, thyroid-stimulating hormone (TSH), free thyroxine (FT4), free tri-iodothyronine (FT3), total testosterone (TT), dehydroepiandrosterone sulfate (DHEA-S), and adrenocorticotrophic hormone (ACTH, the sample was collected within icepack and centrifuged in 2-8 degree centigrade) by chemiluminescent immunoassay method. All the samples were analyzed on the same

day at the Department of Microbiology and Immunology of BMU. The inter- and intra-assay coefficient of variation was $\leq 10\%$ for all the measured hormones. The reference values of all the hormones were taken as per the cut-offs provided by the laboratory. The presence of comorbidities was recorded by taking history and laboratory investigations as part of a routine check on admission. The diagnosis and classification of COVID-19 (mild, moderate, and severe) were done according to the World Health Organization's interim guidance.⁷

Data were expressed in mean $\pm$ SD or median (inter-quartile range, IQR) for numerical data and frequency (percent, %) for qualitative data. Statistical analysis and comparison of variables between baselines and three to six months after infection were done by paired t-test and Wilcoxon signed-rank test. A p-value below 0.05 was considered statistically significant.

Results:

Among ninety-one noncritically ill hospitalized patients with COVID-19, eight (8.8%) died during their hospital stay, and eighty-two survived. Among the surviving patients, we collected follow-up data in only fifteen patients (Figure-1). Only three were above 60 years old; six were males, and nine were females. Diabetes mellitus was the most common (60.0%) comorbidity. None of them had severe COVID-19 during admission (Table I). All the baseline characteristics are available elsewhere.⁸⁻¹⁰

The frequency of all the COVID-related symptoms improved after three months of admission. While the median pulse rate values were reduced, blood pressure increased. Body mass index remained almost similar.

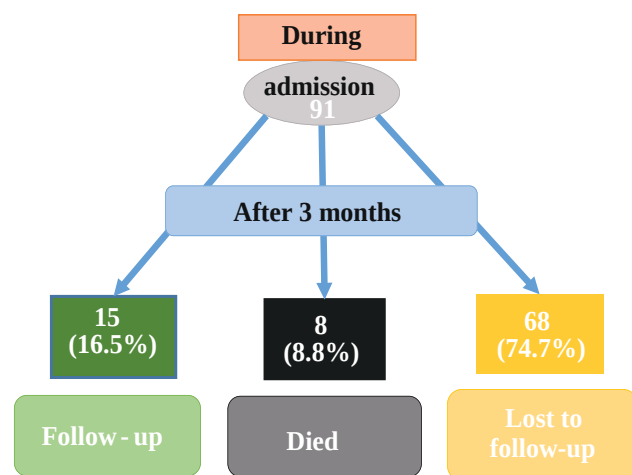


Fig.-1: The study flow chart

Table-I*Baseline characteristics of the study participants (n=15)*

Variables	Values
Age, years	47.3±13.3
Age ≥60 years	3 (20.0)
Age <60 years	12 (80.0)
Sex	
Male	6 (40.0)
Female	9 (60.0)
Comorbidities	
Hypertension	6 (40.0)
Diabetes mellitus	9 (60.0)
Obstructive lung disease	2 (13.3)
Severity of illness	
Mild	10 (66.7)
Moderate	5 (33.3)
Investigations	
Hemoglobin, g/dL	11.7±1.7
Total leukocytes, ×10 ³ /μL	8.5 (6.5-8.5)
Total platelet count, ×10 ³ /μL	242.4(200.0-250.0)
Neutrophils/lymphocytes ratio	1.9 (1.9-3.0)
Platelets/lymphocytes ratio	90.5(86.9-108.8)
S. Na ⁺ , mmol/L	132.4±2.7
S. K ⁺ , mmol/L	4.0±0.5
S. ALT, U/L	45.6 (40.0-50.0)
S. creatinine, mg/dL	0.9±0.2
C-reactive protein, mg/L	33.6 (12.0-60.5)
D-dimer, mg/L	0.5 (0.1-1.5)
S. ferritin, ng/dL	609.0 (461.0-630.0)

Out of the fifteen individuals, only one had adrenal insufficiency at admission (serum basal cortisol <276 nmol/L) and continued to be such. However, among the rest, six patients developed new adrenal insufficiency three-sixto six months after hospital admission. They all had normal plasma ACTH levels (>46 pg/mL), indicating central adrenal insufficiency. So, during follow-up, we found seven (46.7%) patients with adrenal insufficiency (Table-II).

Eight patients (53.3%) had normal thyroid function tests (TFTs) during admission and remained euthyroid after three to six months of admission. One patient with subclinical thyrotoxicosis returned back to euthyroid status. Another three out of five patients from isolated hyperthyroxinemia also became euthyroid. One patient with isolated hyperthyroxinemia developed the biochemical feature of the nonthyroidal illness. Two patients became hypothyroid- one from isolated hyperthyroxinemia and one from subclinical hypothyroidism. Three of seven patients with abnormal TFTs remained abnormal (Table-II).

All six males had normal TT levels, but one developed low TT status after three months. On the other hand, two females with higher TT levels remained high during the follow-up. Another two out of seven females with normal TT levels also became high after three to six months of admission (Table-II). One male had low, and the other five had normal DHEAS during admission.

Table-II*Individual hormone status of the study participants (n= 15)*

Age (years)	Sex	Adrenal reserve		Thyroid status		TT status		DHEAS status		No. of gland involvement	
		During	F/U	During	F/U	During	F/U	During	F/U	During	F/U
19	M	A	A	N	N	N	N	N	N	0	0
31	M	A	A	IH	N	N	N	L	L	2	1
45	M	A	A	N	N	N	L	N	N	0	1
51	M	A	I	IH	N	N	N	N	L	1	2
64	M	A	A	N	N	N	N	N	N	0	0
65	M	A	A	ST	N	N	N	N	N	1	0
28	F	A	I	IH	ESS	N	N	N	N	1	2
38	F	A	A	N	N	N	N	N	N	0	0
47	F	A	A	SH	PH	N	N	N	N	1	1
47	F	A	I	IH	N	N	N	L	N	2	1
51	F	A	I	N	N	H	H	H	H	2	3
53	F	I	I	IH	PH	N	H	N	N	2	3
54	F	A	I	N	N	N	N	N	N	0	1
57	F	A	A	N	N	H	H	N	N	1	1
60	F	A	I	N	N	N	H	N	N	0	2
Total abnormality		01	07	07	03	02	05	03	03	13	18

Table-III
Hormones in COVID-19 during and 3-6 months after infection (n= 15)

Hormones	During infection	3-6months after inf.	p
TSH, mIU/mL	1.2 (0.8 – 2.8)	2.4 (1.9 – 5.4)	0.001
FT4, ng/dL	1.4 (1.3 – 3.0)	1.1 (1.0 – 1.3)	0.002
FT3, pg/mL	2.9 (2.5 – 3.2)	3.1 (2.6 – 3.2)	0.798
Cortisol, nmol/L	495.0 (327.0-615.0)	280.0 (218.2 – 448.7)	0.017
ACTH, pg/mL	21.2 (17.5 – 27.1)	26.0 (23.5 – 29.6)	0.156
Total testosterone, ng/dL			
Male (n=6)	329.5 (283.3 – 483.8)	343.5 (270.0 – 452.8)	0.917
Female (n=9)	32.0 (21.4 – 44.9)	40.5 (31.3 – 53.0)	0.343
DHEAS, ig/dL			
Male (n=6)	84.6 (45.9-194.0)	73.0 (49.6 – 126.3)	0.225
Female (n=9)	41.0 (28.5 – 74.5)	98.4 (62.5 – 109.0)	0.021

Data were expressed in median (IQR)

Wilcoxon-signed rank test was done

During follow-up, the male with low DHEAS maintained the same status, and another male developed low DHEAS from a normal DHEAS status. One female with low and another seven with normal DHEAS at admission had a normal DHEAS status during follow-up. One female with high DHEAS remained the same during the follow-up (Table II).

Overall, six(40.0%) had normal values for all the studied hormones, five(33.3%) had one abnormality, and four(26.7%) had two abnormalities at baseline. After 3 months of admission, four had normal (26.7%), six(40.0%) had one, three(20.0%) had two, and two(13.3%) had three abnormalities of the studied hormone status (Table-II).

Elaborations: M (male), F (female), A (adequate), I (insufficiency), N (normal), IH (isolated hyperthyroxinemia), ST (subclinical thyrotoxicosis), SH (subclinical hypothyroidism), ESS (euthyroid sick syndrome), PH (primary hypothyroidism), L (low), H (high)

Reference levels: Cortisol cut-off 10 ig/dL, ACTH: 0 – 46 pg/mL; TSH: 0.35 – 5.5 iIU/mL, FT4: 0.8 – 1.8 ng/dL, FT3: 1.4 – 4.2 pg/mL; total testosterone: Male (Age, years: 18-49: 2.7 – 17.3, ≥50: 2.1 – 7.6, ng/mL), Female (Age, years: 18-49: 0.1 – 0.5, ≥50: 0.1 – 0.4, ng/mL); DHEAS: Male (Age, years: 18-20: 24.0 – 537.0, 31-40: 106.0 – 464.0, 41-50: 70.0 – 495.0, 51-60: 38.0 – 313.0, 61-70: 24.0 – 244.0, µg/dL), Female (Age, years: 18-20: 51.0 – 321.0, 21-30: 18.0 – 391.0, 31-40: 23.0 – 266.0, 41-50: 19.0 – 231.0, 51-60: 8.0 – 188.0, 61-70: 12.0 – 133.0, µg/dL)

The TSH levels significantly increased, the FT4 levels decreased, and the FT3 levels remained unchanged. While the cortisol levels significantly reduced, plasma ACTH levels were statistically similar. Except for the significant increase in DHEAS levels in females, TT and DHEAS levels remained statistically identical in both sexes (Table-III).

Discussion:

COVID-19 is a multi-organ infectious disease, and complications may occur even after recovery. Limited studies are available in our country to evaluate short-term follow-up endocrine function in individuals following COVID-19 infection. In a recent investigation by us, 19%-40% of patients were found to have adrenal insufficiency in an acute setting (depending on various cut-offs).⁸ We intended to see if individuals who recovered from COVID-19 had any symptoms of hormone imbalances at a later time. Unfortunately, only fifteen treated cases came to us for follow-up, eight cases died during the hospital course, and the rest didn't come back for a follow-up. Seven of the fifteen individuals still lacked sufficient adrenal reserves. All received standard doses of steroids during their hospital course. Those who developed new insufficiencies after COVID-19 remission may have a contributory factor that leads to post-COVID fatigue. Among the seven persons who had inadequate adrenal reserve, at least one person is likely to have definite adrenal insufficiency, as his serum DHEAS was also low.¹¹ In contrast to our study, Clarke SA, et al. (2021) found that all the participants had a normal adrenal

function, which was confirmed after the synacthen test.¹² However, we couldn't do the standard synacthen test to confirm adrenal insufficiency, which is a significant drawback of our study and might have diluted the impact of observed cortisol level at follow-up, and our sample size was also low. In agreement with our study, Sunada N, et al. (2022) found that symptomatic long-term COVID patients had lower serum cortisol levels without altering plasma ACTH.¹³ Almost all of the symptoms in the study participants improved after three months; however, four people still had fatigability, and five people had postural dizziness, both of which are signs of adrenal insufficiency.

The clinical impact of thyroid dysfunction in the context of COVID-19 is still unknown, and it has been observed in a remarkable number of people with SARS-CoV-2 infection from the early months of the COVID-19 outbreak.¹⁴ Subclinical thyrotoxicosis was routinely described in COVID-19 hospitalized patients.¹⁵ A prospective study demonstrated that 96% of thyrotoxicosis patients became euthyroid after 30-120 days.¹⁶ We also looked for thyroid dysfunction and found five out of fifteen had isolated hyperthyroxinaemia, and another two had subclinical hypothyroidism during their admission to the hospital. After three months, among the five patients with thyroid dysfunction, three became normal, one of them became frank hypothyroid, and another had biochemical features of euthyroid sick syndrome. Most of our cases turned to euthyroid state, which was in agreement with other previous studies.^{12,17} Only one had subclinical thyrotoxicosis during the acute infective phase, which became normal during the follow-up.

A growing number of studies have suggested that the viral infection may lower the production of testosterone and is associated with more severe clinical outcomes.¹⁸ In a seven-month follow-up study, over fifty percent of men who recovered from COVID-19 infection still had low circulating testosterone levels, indicating hypogonadism.¹⁹ Meanwhile, a systematic review and meta-analysis showed that testosterone levels fall immediately after infection and rebound during recovery.²⁰ However, the findings were inconsistent and inconclusive. Over half of the trials examined reported no significant change in testosterone levels in the recovery period, even those comparing severe vs. moderate COVID-19. In the current study, among six men who recovered from COVID-19, only one (16.6%) developed hypogonadism after 3-6 months, and others became normal, which was compatible with the findings of several other

prospective studies.²⁰ Of the nine female participants, two had baseline high levels of testosterone; however, during a follow-up period, the levels of serum testosterone rose in two more individuals, two of whom had chronically elevated levels. The majority of the afflicted females were menopausal, and we were unable to measure their gonadotropin or estradiol levels, making it impossible to determine their sex hormone status accurately.

This study has several limitations, including a small number of participants, a short follow-up period, and inadequate etiological evaluation for persistent hormone abnormalities.

Conclusion:

Endocrine dysfunction as a result of SARS-CoV-2 infection is prevalent. In the current prospective study, almost one-third of infected people had signs of involvement of more than two endocrine glands; thus, endocrine function may be examined during the post-COVID state in symptomatic patients.

Ethical approval: IRB, BMU (No. BSMMU/2021/557)

Conflict of interest: None

Acknowledgement:

Department of Microbiology and Immunology, BMU, for technical support

Funding:

Partial funding by the Bangladesh Medical Research Council and Research & Development, BMU

Authors' contributions:

HB, MSM, NS, HAH, SMA (Conceptualization, Methodology, Software); MAH (validation); HB, MSM (Investigation, Data curation); HB, MSM, NS (Formal analysis, Writing- Original draft preparation, Visualization); MAH, SMA (Supervision, Writing- review & editing, Project administration, Funding acquisition). All authors read and approved the final manuscript.

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SHORT COMMUNICATION

CIS-REGULATORY ELEMENTS AND TRANS-ACTING FACTORS MODULATING POST-TRANSCRIPTIONAL SPLICING IN CANCER: A SHORT COMMUNICATION

SHAFEE UR REHMAN

Abstract

The key post-transcriptional process of alternative splicing (AS) generates transcriptomic and proteomic diversity through its mechanism. The precise regulation of AS depends on cis-regulatory RNA elements together with trans-acting protein factors whose alterations frequently occur in cancer cases. Cancer progression occurs through the generation of abnormal isoforms which emerge from mutations together with altered splicing factors and epigenetic transformations. The combination of modern sequencing approaches with computational tools allows scientists to study cancer-specific splicing patterns which enables both biomarker development and targeted therapeutic applications. This paper discusses the basic molecular mechanisms behind AS control as well as cancer-related abnormalities and new precision oncology therapeutic approaches through splice-switching oligonucleotides and small-molecule modulators and CRISPR-based strategies.

Keywords: alternative splicing, cis-regulatory elements, trans-acting factors, cancer, spliceosome

Date of submission: 10.06.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.82174>.

Citation: Rehman SU. Cis-Regulatory Elements and Trans-Acting Factors Modulating Post-Transcriptional Splicing in Cancer: A Short Communication. *Bangladesh J Medicine* 2025; 36(3): 142-146.

Introduction:

The process of alternative splicing (AS) extends protein diversity because it produces multiple isoforms from a single gene^{1, 2}. Splicing processes depend on cis-elements including exonic and intronic enhancers/silencers and trans-acting splicing factors that consist of SR proteins and heterogeneous nuclear ribonucleoproteins (hnRNPs) for their regulation³. Cancer progression and therapy resistance and immune evasion occur due to disruptions in these networks when they alter isoform proportions⁴. Precision oncology depends on cancer-specific splicing codes to develop biomarkers and targeted treatments. The spliceosome functions as an assembly of U1, U2, U4/U6 and U5 snRNPs to perform two

transesterification reactions that remove introns. ESEs, ISEs, ESSs, and ISSs located in the cis-elements determine whether exons will be included or excluded from the final transcript while SR proteins (e.g., SRSF1, SRSF2) and hnRNPs (e.g., hnRNP A1) function as either activators or repressors^{5, 6, 7}. The cancer-specific isoforms emerge from somatic mutations that affect splice sites along with mutations in splicing factors including SF3B1, U2AF1 and SRSF2 which disrupt the spliceosome's ability to be faithful⁸. DNA methylation along with histone modifications function as epigenetic regulators to control co-transcriptional splicing processes (Figure 1).

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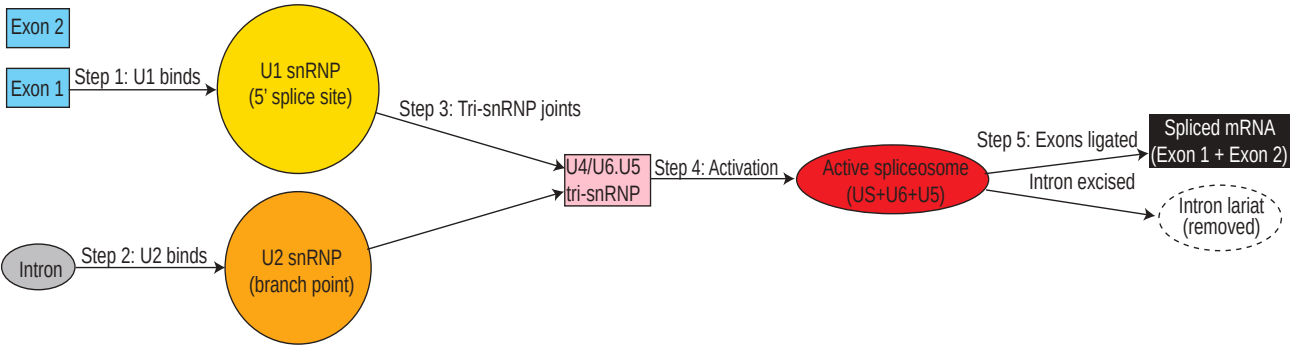


Figure 1. The spliceosome’s gradual construction and activation during pre-mRNA splicing is depicted in this image. The recruitment of the U4/U6.U5 tri-snRNP complex follows the binding of U1 and U2 snRNPs to the 52 splice site and branch point, respectively. The ensuing active spliceosome removes the intron as a lariat, ligates the exons, and creates mature spliced mRNA.

Oncogenic Splicing Events and Isoforms:

The process of alternative splicing produces cancer-causing isoforms which promote tumor growth and make tumors resistant to treatment and lead to metastasis¹. BCL-XL functions to protect cells from chemotherapy while BCL-XS triggers programmed cell death and PTBP1 drives the transition from FGFR2-IIlb to FGFR2-IIlc which leads to increased metastasis potential and MDM2-S accelerates p53 degradation and CD44v isoforms enable stemness and invasion.

The Wnt/ β -catenin signaling pathway becomes active through RAC1b while TP53 and BRCA1 and RB1 undergo aberrant splicing which disrupts tumor suppression and DNA repair and cell-cycle regulation^{9, 10, 11}. The therapeutic approach includes antisense oligonucleotides to restore isoform balance and SF3B1-targeting H3B-8800 for leukemia treatment and CRISPR-based exon editing to fix mutations¹². The research demonstrates that splicing functions as both a cancer biological mechanism and a therapeutic opportunity (Figure 2).

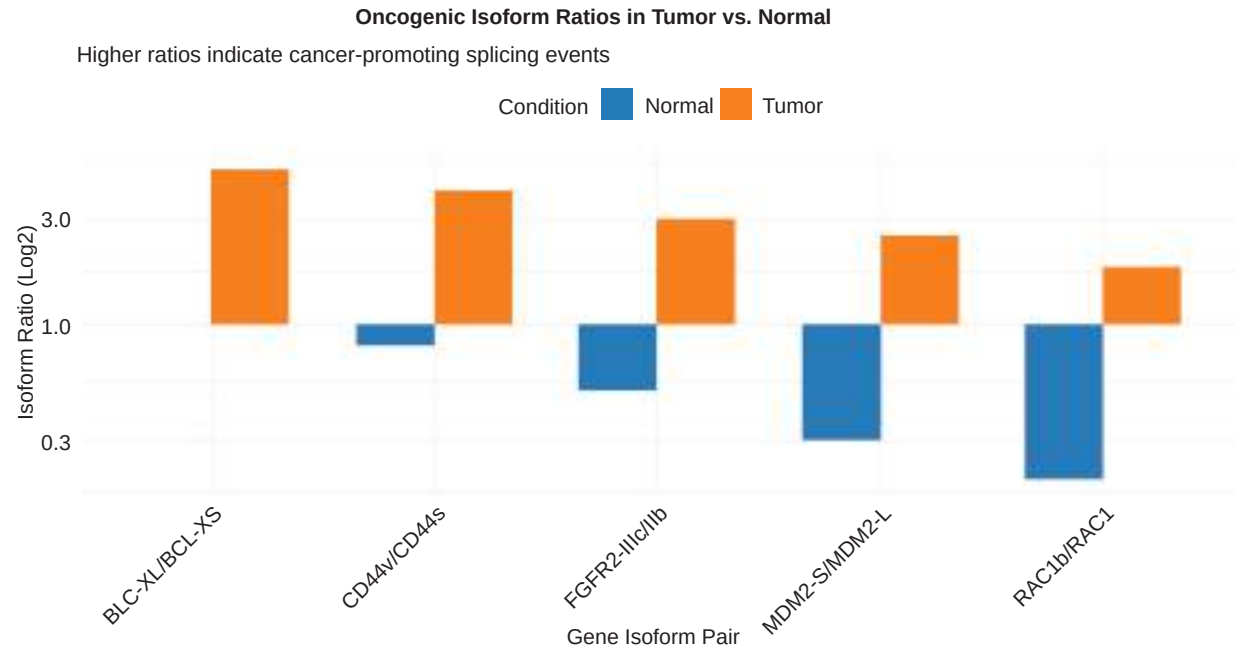


Figure 2: The expression ratios of splice isoforms linked to cancer (such as FGFR2 variations and BCL-XL/ BCL-XS) in tumor and normal tissues are contrasted in this bar plot. Tumor-specific overexpression of carcinogenic isoforms is indicated by higher log2-transformed ratios (orange bars), whereas normal splicing patterns are reflected by lower ratios (blue bars). Important isoform transitions that promote tumor growth and could be targets for treatment are highlighted in the figure.

Table I
Therapies Targeting Splicing in Cancer

Therapy Type	Mechanism of Action	Examples	Clinical Applications
Splice-Switching Oligonucleotides (SSOs)	Bind to pre-mRNA to redirect splicing decisions	Eteplirsen, SSOs for BCL2L1	Alter oncogenic isoform balance
Splicing-Modulating Small Molecules	Inhibit components like SF3B1 to alter splicing in cancer cells	H3B-8800, E7107, Spliceostatin A	Myelodysplastic syndromes, leukemias
Antisense Therapy / CRISPR Correction	Target abnormal transcripts or correct splice sites using genome or RNA editing tools	Antisense drugs, CRISPR/Cas9/13	Rare cancers with defined splice mutations
Isoform-Based Biomarkers	Use tumor-specific splicing isoforms for detection or immune targeting	AR-V7, CD44v6, FGFR2 IIIc	Diagnosis, prognosis, immunotherapy targeting

Therapeutic Targeting of Splicing in Cancer:

The therapeutic approach of targeting aberrant splicing presents new possibilities for cancer treatment. BCL2L1-targeting SSOs function as splice-switching oligonucleotides to change BCL-XL into its pro-apoptotic form BCL-XS. The small-molecule modulators H3B-8800, E7107 and spliceostatin A target SF3B1 to produce selective cell death in SF3B1-mutant cancer cells. CRISPR-based editing provides exact modifications to splice sites and intronic mutations and regulatory elements and CRISPR/Cas13 enables RNA-guided modulation for treating rare cancers. The clinical relevance of isoforms such as CD44v6, FGFR2 IIIc and AR-V7 enables their use as biomarkers for both prognosis and therapy monitoring¹³⁻²⁰. The abnormal splicing products create neoantigens which serve as targets for vaccines and immunotherapy while uniting diagnostic and therapeutic approaches to enhance precision oncology (Table I).

Computational tools for alternative splicing analysis:

Computational and Multi-Omics Approaches for Alternative Splicing Analysis The precise identification and measurement of cancer-related alternative splicing (AS) requires sophisticated computational methods together with integrated omics approaches^{21, 22}. The

tools rMATS and SUPPA2 and MAJIQ and LeafCutter enable sensitive detection of differential and novel splicing events through their ability to model exon inclusion across replicates and detect major splicing types and quantify transcript levels for large-scale multi-condition studies and model local splicing variations directly from splice junction reads and perform annotation-free clustering of junction usage²²⁻²⁶. Bulk RNA sequencing (RNA-seq) delivers wide-ranging information yet fails to show cellular diversity which single-cell RNA-seq (scRNA-seq) addresses through its ability to detect infrequent isoforms and cell-type-specific patterns despite its limited coverage and technical noise²⁷. The advancement of computational pipelines enhances scRNA-seq resolution while combining bulk and single-cell data provides a more detailed understanding of tumor splicing dynamics. The combination of genomics with transcriptomics and epigenomics through multi-omics analysis shows how DNA methylation and histone modifications and chromatin remodeling and somatic mutations work together to control splice site recognition and cancer development. These approaches work together to improve biomarker discovery and therapeutic development which drives progress in precision oncology (Table II).

Table III
Key Tools and Approaches for Splicing Analysis

Category	Tool/Approach	Description	Applications
Alternative Splicing Tools	rMATS	Statistical detection of differential splicing with replicate support	Cancer vs normal splicing comparisons
	SUPPA2	Fast transcript-based quantification and differential splicing analysis	Large-scale multi-condition studies
	MAJIQ	Annotation-free detection of local splice variations	Discovery of novel splice junctions
	LeafCutter	Clustering of splice junctions to identify differential splice site usage	Rare or complex splicing event detection
Transcriptomics Approaches	RNA-Seq	Bulk sequencing to measure gene and isoform expression	Tumor-wide splicing profiling
	Single-Cell RNA-Seq	High-resolution transcriptomics capturing cell-specific splicing events	Tumor heterogeneity and microenvironment
Multi-Omics Integration	Genomics +Transcriptomics+ Epigenomics	Integrates splice site mutations, splicing profiles, and chromatin modifications to elucidate mechanisms	Comprehensive mechanism and biomarker studies

Summary of the study:

The process of aberrant alternative splicing functions as a key driver of cancer development and its progression and metastasis and therapy resistance while providing valuable diagnostic and prognostic and predictive biomarkers such as SF3B1 mutations in myelodysplastic syndromes and CD44 variant isoforms in metastasis and BRCA1/TP53 exon skipping. The precise detection of these alterations becomes possible through high-resolution RNA sequencing and nanopore sequencing and PCR assays and single-cell transcriptomics which receive computational support from tools such as rMATS, SUPPA2, MAJIQ. The multi-omics approaches reveal regulatory mechanisms that include somatic mutations together with epigenetic changes and splicing factor dysregulation. The advancement of therapeutic strategies includes splice-switching oligonucleotides and small-molecule modulators (H3B-8800) and CRISPR-based exon editing yet tumor heterogeneity and off-target effects and delivery limitations continue to be challenges. The integration of splicing modulation into personalized oncology advances through emerging solutions which include AI-driven models (SpliceAI, Pangolin) and base/prime editing and cancer-specific splicing codes that enhance biomarker discovery and therapeutic precision.

Acknowledgments:

The author is thankful to Ala-Toos International University for financial support and rewards for publication.

Author Contributions:

Shafee Ur Rehman collected the data and wrote the manuscript.

Conflicts of interest:

The author has no conflict of interest

Funding Sources:

No grant was available for this study.

Data Availability:

All the data is available in the manuscript.

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CASE REPORT

ATYPICAL PRESENTATION OF TWO CHIKUNGUNYA CASES: A CASE SERIES DURING 2025 OUTBREAK

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Abstract

Bangladesh is experiencing a sharp rise in viral infections, particularly during the current monsoon season. Dengue, chikungunya, and COVID-19 are now posing a triple threat to public health. As their symptoms are overlapping, a strong diagnostic support is pivotal in severe cases. Here, we describe two older male chikungunya virus patients who, in addition to their typical symptoms, have significant organ involvement. Pneumonia caused by chikungunya affecting the lungs occurred in the first patient. The second case had similar lung involvement with encephalitis. Both had diabetes and hypertension, two co-morbidities that increase the chance of developing serious illness. The second case was also a known case of chronic kidney disease (CKD), old cerebrovascular disease (CVD) and ischaemic heart disease (IHD). He was transferred to the critical care unit and eventually passed away. These cases demonstrate how crucial it is that Chikungunya PCR tests be made available across the country at a reasonable cost in order to prevent needless treatment and investigations as well as early case diagnosis.

Keywords: Chikungunya, Pneumonia, Encephalitis

Date of submission: 21.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.84071>.

Citation: Hossain Z, Ahmed A, Raka FA, Quazi Tarikul Islam QT. Atypical presentation of two Chikungunya cases: A case series during 2025 outbreak. *Bangladesh J Medicine* 2025; 36(3): 147-154.

Introduction:

Chikungunya virus (CHIKV) infection is a neglected tropical disease, caused by an RNA virus (genus: Alphavirus; family: Togaviridae). With the spread of Aedes mosquito vectors, chikungunya is therefore regarded as a significant re-emerging public health issue in both tropical and temperate nations. The disease was first described in Tanzania in 1952, and the virus was first isolated in Thailand in 1958. The term “chikungunya” refers to the twisted posture of infected individuals who experience excruciating joint pain and is derived from a word in the southern Tanzanian Kimakonde language that means “that which bends up”¹. This RNA virus is known to have three genotypes: West African, East/Central/South African (ECSA), and Asian². In the Americas, there were more than 2.6 million probable cases of chikungunya by the end of 2017. Since then, the virus has spread around the world, causing occasional outbreaks and sporadic cases in Asia, the Americas, and Africa. In two recent outbreaks more than 50,000 suspected cases were found in Ethiopia in 2019 and 160,000 in Paraguay in 2023. In 2024 and 2025 multiple outbreaks were reported on the island of Réunion in

the Indian Ocean³. Bangladesh is habituated in facing periodic outbreak of dengue fever, but chikungunya outbreak is rarely seen. It may be because of the prolonged presence of antibody and cross immunity against genotypes⁴. The last known outbreak of chikungunya happened between April 1, 2017 to Sept 7, 2017, and the Bangladeshi Ministry of Health reported 984 cases confirmed by real-time PCR assay. More than 13176 clinically confirmed cases in 17 of 64 districts⁵. Apart from typical presentation in acute phase and chronic debilitating arthritis may also be seen. Some systematic manifestations like cardiac complications was reported in 37% (myocarditis and arrhythmia)^{6,7}, neurological complications has been reported in 16-25% of patients. These include encephalitis, facial paralysis, sensorineural deafness, and Guillain-Barré syndrome (GBS)⁷⁻⁹. Upto 17% reports of pneumonia with 8% respiratory failure was also reported⁷, and rarely, ocular complications (conjunctivitis, optic neuritis, iridocyclitis, episcleritis, retinitis and uveitis)¹⁰ has also been reported. Herein, we will discuss two elderly male patients with multiple co-morbidities who had with chikungunya fever with atypical presentation that was seldom reported before.

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Both Chikungunya cases were confirmed by VIASURE Mosquito-Borne (Zika, Dengue and Chikungunya virus) multiplex RT-PCR detection Kit (Spain). This test is performed using the Rotor-Gene Q PCR system by Qiagen, Germany. The clinical specificity of this PCR kit is 100% and the analytical sensitivity is up to 20 Copies/reaction.

Case 1:

Chikungunya and bilateral pneumonia, a rare presentation

A 64-year-old diabetic, hypertensive male, got admitted to our hospital with the complaints of fever for 3 days, which was high grade, highest recorded temperature was 105°F which was not associated with chills and rigor. Fever was preceded by frontal headache for one day. He also developed severe ankle and low back pain which made him unable to walk without limping or support. On query he further complained of intermittent dry cough for 2 days. There was also history of dengue fever twice before. He was not vaccinated against influenza or pneumococcus before.

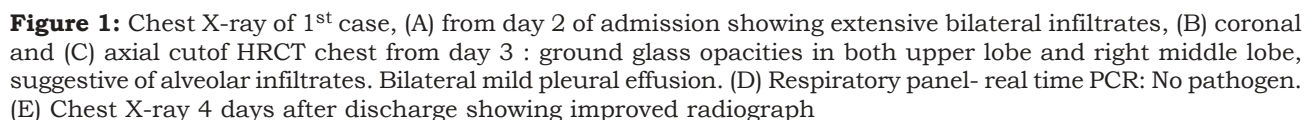
He took oral hypoglycemic medications (Gliclazide 30mg, metformin 500mg, empagliflozin 5mg) for diabetes control. Beta blocker (bisoprolol 2.5 mg), calcium channel blocker (amlodipine 5mg) with angiotensin receptor blocker (olmesartan 20mg) all in once daily dose for hypertension. He was compliant to medications and maintained regular follow up with good control of comorbidities. There was no history of asthma, osteoarthritis or other connective tissue disease. On the day of admission, he had flushed face, temperature was 102°F, pulse 84 b/min with regular rhythm & volume, blood pressure :110/70mmHg, SpO2: 98% in room air, There was grade II tenderness and swelling of both his ankle joints. There was no anemia, jaundice, oedema, dehydration or clubbing. Precordium, abdomen and lungs were unremarkable on examination. No conjunctival congestion or rash. He was kept on conservative management and his anti-diabetic and antihypertensive medications were kept on hold. Dengue-chikungunya-zika multiplex PCR was sent (detected Chikungunya) along with other lab parameters (Table 1). On his peripheral blood film there was microcytic hypochromic anemia.

Table I

Clinical scores and laboratory parameters of the case 1

Clinical and Lab Parameters	Normal range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
qSOFA	0	1	0	0	0	0	
NEWS	2	11	6	3	0	0	
MEWS	3	4	1	1	0	0	
Hemoglobin(g/dL)	13-17	10.6	10	11.2	12.9	12.4	12.4
HCT %	39-51	31.5	31	33.6	39.3	38.2	37.5
Total WBC(k/ μ L)	4-10	4.31	3.4	5.5	5.6	6.4	6.74
Platelet Count(k/ μ L)	150-410	70	90	50	50	40	50
N:L ratio		8	8.2	8.6	4.9	6.9	12.6
ESR (mmHg 1 st hour)	0-14	09	07	10	14	05	10
SGOT (U/L)	<40	23				57	
SGPT (U/L)	<41	17				32	
CRP (mg/L)	<5	8.85		50.12		10.37	
S. Creatinine (mg/dL)	0.7-1.2		1.13				
S. Sodium(mmol/L)	136-145		123			133	134
S. Potassium(mmol/L)	3.5-5.1		4.3			3.9	4.35
S Chloride(mmol/L)	98-107		95			100	102
S. Bicarbonate(mmol/L)	24-30		20			20	
D-Dimer(μ g/mL)	<0.5		1.46			1.28	
Ferritin (ng/mL)	21-274					1730	
Procalcitonin(ng/mL)	<0.5 sepsis unlikely		0.16			0.05	
Cardiac Troponin I (ng/mL)	<0.034		0.016				
NT pro BNP (pg/mL)			2548				
pH			7.42	7.37			
pCO2 (mmHg)			28.5	22.7			
pO2 (mmHg)			35.3	80.8			
HCO3 (mmol/L)			20.1	16.1			
PO2/FIO2			168	384.7			

Day 1 signifies first day of admission; qSOFA: quick sequential organ failure assessment; NEWS: National early warning score; MEWS: Modified early warning system; HCT: hematocrit; WBC: White blood cells; N:L ratio (neutrophil lymphocyte ratio), ESR: erythrocyte sedimentation rate; SGOT: serum glutamic oxaloacetic transaminase test; SGPT: Serum glutamic pyruvic transaminase; CRP: C reactive protein; NT pro BNP: N terminal pro B type Natriuretic Peptide.



On second day morning, he developed restlessness, severe shortness of breath with worsening cough and mild mucoid expectoration but no orthopnea. There were bilateral coarse crepitations from mid chest. His SpO₂ dropped to 75% on room air, respiratory rate was 44 breaths per minute, GCS 14. Blood pressure was 110/70 mmHg, Heart rate came down to as low as 46 beats per minute. He still had a temperature of 101°F. His saturation was maintained to 94% on 15L O₂ (non-rebreathable mask). Immediate Chest Xray was done at bedside, which revealed bilateral lung infiltrates from mid to lower zone (FIG- 1A). Arterial blood gas showed marked hypoxia suggesting ARDS (Table I). ECG revealed sinus bradycardia, troponin-I, NT pro BNP and procalcitonin unremarkable. D-dimer was slightly raised. His HRCT chest non-contrast (Fig 1B,C) showed ground glass opacities in both upper lobe and right middle lobe, suggestive of alveolar infiltrates. Bilateral mild pleural effusion. Coronary artery calcifications were also noted. Bedside ECHO revealed No abnormality (Ejection fraction 62%). Before adding further treatment, we did a respiratory panel (Fig -1D, sputum for Gram's stain and culture sensitivity, Gene xpert and fungal culture which excluded all other pathogens. Blood culture came out negative.

He was managed with high dose intravenous hydrocortisone 200mg stat and 100mg 8hrly for Day 1, then gradually tapered off by day 5. He also received antibiotics (IV meropenem and oral moxifloxacin for 7 days), nebulization with budesonide with bronchodilators and symptomatic propantheline bromide for bradycardia. After initiating steroids his oxygen dependency came down to 8L on day 3. On day 4, he maintained on 2L with nasal cannula and became afebrile. Thereafter on day 5, he was free from oxygen. He was discharged on day 6 without any oxygen support. Four days after he came for follow up with normal CBC, negative dengue IgM/IgG antibodies and Chest radiograph was also normal (Fig- 1E).

Day 1 signifies first day of admission; qSOFA: quick sequential organ failure assessment; NEWS: National early warning score; MEWS: Modified early warning system; HCT: hematocrit; WBC: White blood cells; N:L ratio (neutrophil lymphocyte ratio), ESR: erythrocyte sedimentation rate; SGOT: serum glutamic oxaloacetic transaminase test; SGPT: Serum glutamic pyruvic transaminase; CRP: C reactive protein; NT pro BNP: N terminal pro B type Natriuretic Peptide.

Case 2:

Chikungunya encephalitis and respiratory failure

A 75-year-old diabetic, hypertensive male, known case of CKD, old CVD (11 years back) and IHD, complained of continued high-grade fever for 2 days. His highest recorded temperature was 105°F. Fever was associated with severe bodyache, increased pain in both knees,

ankle and small joints of hand and feet. There was no cough, abdominal pain or vomiting. He developed altered consciousness the next day and admitted to this hospital for better management. After admission, we found him to be disoriented. Not obeying commands. GCS was 9 (E1M5V3). There was no neck rigidity. Kernig's Sign was negative. Pupil was bilaterally equally reacting to light. Temperature was 101°F, blood pressure was 130/70mmHg, heart rate was 100beats per minute, respiratory rate was 20 breaths per minute. He had mild bipedal edema. His Spo₂ was 92% on Room air (99% on 1L o₂). There was grade II tenderness over his both knee and ankle joints, but no swelling or significant erythema seen. Heart, lungs and abdomen was normal on examination. On investigation: His CBC was normal except mild anemia and thrombocytopenia (110k) and hyponatremia, serum creatinine was slightly high, arterial blood gas showed respiratory alkalosis (Table-II). Dengue NS1 antigen came out negative, Urine RME revealed trace albuminuria and sugar otherwise normal, Liver function test, Bedside Chest Xray and Echocardiography (EF: 61%) was normal. Multiplex PCR (Dengue-Zika-Chikungunya) detected chikungunya. CSF study was done which showed Clear fluid, total WBC was 03/Cumm (100% lymphocytes), high protein (74.9 mg/dL) and glucose (111.96 mg/dL), ADA was also normal (1.1 U/L). Gram's stain, AFB stain, Gene xpert for mycobacterium tuberculosis and culture was negative. CSF PCR for Neuro-9 panel was negative (Fig- 2A). CT scan of brain was done which revealed generalized cerebral atrophy and tiny hypodense lesion in left frontal lobe and left thalamus (Fig-2 C,D). MRI brain (with MRA) was also done which showed chronic bilateral periventricular ischaemic changes with mild generalized cerebral atrophy. He was on conservative management with NG tube feeding, intravenous paracetamol one gram for fever and pain, oral correction of hyponatremia, high dose hydrocortisone injection and management of comorbidities.

The following day of admission he developed shortness of breath which was progressive upto day 4 of admission. We had to transfer him to critical care unit for better management. GCS was not improving, respiratory rate went up to 44 breaths per minute, and heart rate was 154 beats per minute. On auscultation of lungs there was bilateral coarse crepitation on both lungs, more on the right side. He was needing 15L on non-rebreathable mask to maintain 94% oxygen. On investigation (Table-2) total count WBC was normal throughout, thrombocytopenia was progressive upto day 3 then began improving. D dimer, procalcitonin and fibrinogen was not significantly high. Sputum culture, Gram's stain, AFB

stain, fungal stain, Gene xpert for mycobacterium tuberculosis was negative. Blood culture also showed no growth. NT pro BNP was high but bedside echo was normal. ECG showed only sinus arrhythmia. ABG revealed persistent hypoxia from day 4. On day 5, he developed metabolic acidosis due to deteriorated renal function. Respiratory panel from nasopharyngeal swab was unrevealing (Fig 2 A), There was bilateral lung

infiltrates more on the right side (Fig-2B). He was Intubated on day 4 upon shifted to ICU, where he was managed with inj. meropenem 1g(12hourly), inj. dexamethasone 5 mg (8 hourly) with other conservative management. Unfortunately, his family members took him home after 4 days of treatment in ICU. He succumbed to death after 2 days at home.

Table II
Laboratory parameters of case 2

Lab Parameters	Normal range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Hemoglobin(g/dL)	13-17	11.5	12.3	11.3	12.1	12.2	10.8	11.0
MCV (fL)	81-94	68.4	67.9	68.8	70.5	69.2	70.3	73.3
HCT %	39-51	36.4	39.1	37.3	40.3	40.3	36	37.9
Total WBC(k/ μ L)	4-10	6.95	6.5	3.67	4.99	4.99	7.02	7.89
Neutrophil (%)	40-80	87	80	72	80	80	81	82
Platelet Count(k/ μ L)	150-410	110	80	70	75	80	70	105
N:L ratio		12.4	5.3	3.1	5.3	5.3	5.4	6.3
ESR (mmHg 1 st hr)	0-14					32	41	52
SGOT (U/L)	<40	23		28		30	77	53
SGPT (U/L)	<41	15		22		37		50
S. Albumin (g/dL)	3.5-5.2	3.62					3.09	
CRP (mg/L)	<5					55		193.4
S. Urea(mg/dL)	16.6-48.5	42.8		38	30.6	28	47.4	68.48
Uric acid (mg/dL)	3.5-7.2	7.30						
S. Creatinine (mg/dL)	0.7-1.2	1.77	1.62	1.55	1.47	1.67	2.13	1.91
S. Sodium (mmol/L)	136-145	132	133	139	138	136	140	
S. Potassium(mmol/L)	3.5-5.1	3.7	3.9	3.93	3.9	3.6	3.86	
S Calcium (mg/dL)	8.8-10.6	8.8					7.75	
S.Magnesium(mg/dL)	1.6-2.3	1.6					1.6	
D-Dimer(μ g/mL)	<0.5				1.32			
Procalcitonin(ng/mL)	<0.5				0.45			3.22
Fibrinogen (mg/dL)	200-400				512			
PT (sec)/INR	12-17				17/1.47			
APTT(sec)					32			
S. Ammonia (μ mol/L)	9-33			09			10	
Cardiac Troponin I (ng/mL)	<0.034	0.09	0.10		0.08			0.11
NT pro BNP (pg/mL)	<125				4054			
pH	7.35-7.45	7.5	7.4	7.5	7.45	7.36*	7.30*	7.34*
pCO ₂ (mmHg)	35-45	23.2	24.2	23.8	25	41.1	31.7	36.8
pO ₂ (mmHg)	75-100	71.8	75.4	71.6	56.4	79.6	92.3	86
HCO ₃ (mEq/L)	22-26	23.2	22.3	22.9	20.7	22.6	16.7	21.4

MCV : mean corpuscular volume, N:L ratio (neutrophil lymphocyte ratio), HCT: hematocrit; WBC: White blood cells; ESR: erythrocyte sedimentation rate; SGOT: serum glutamic oxaloacetic transaminase test; SGPT: Serum glutamic pyruvic transaminase; CRP: C reactive protein; NT pro BNP: N terminal pro B type Natriuretic Peptide. *after intubation.

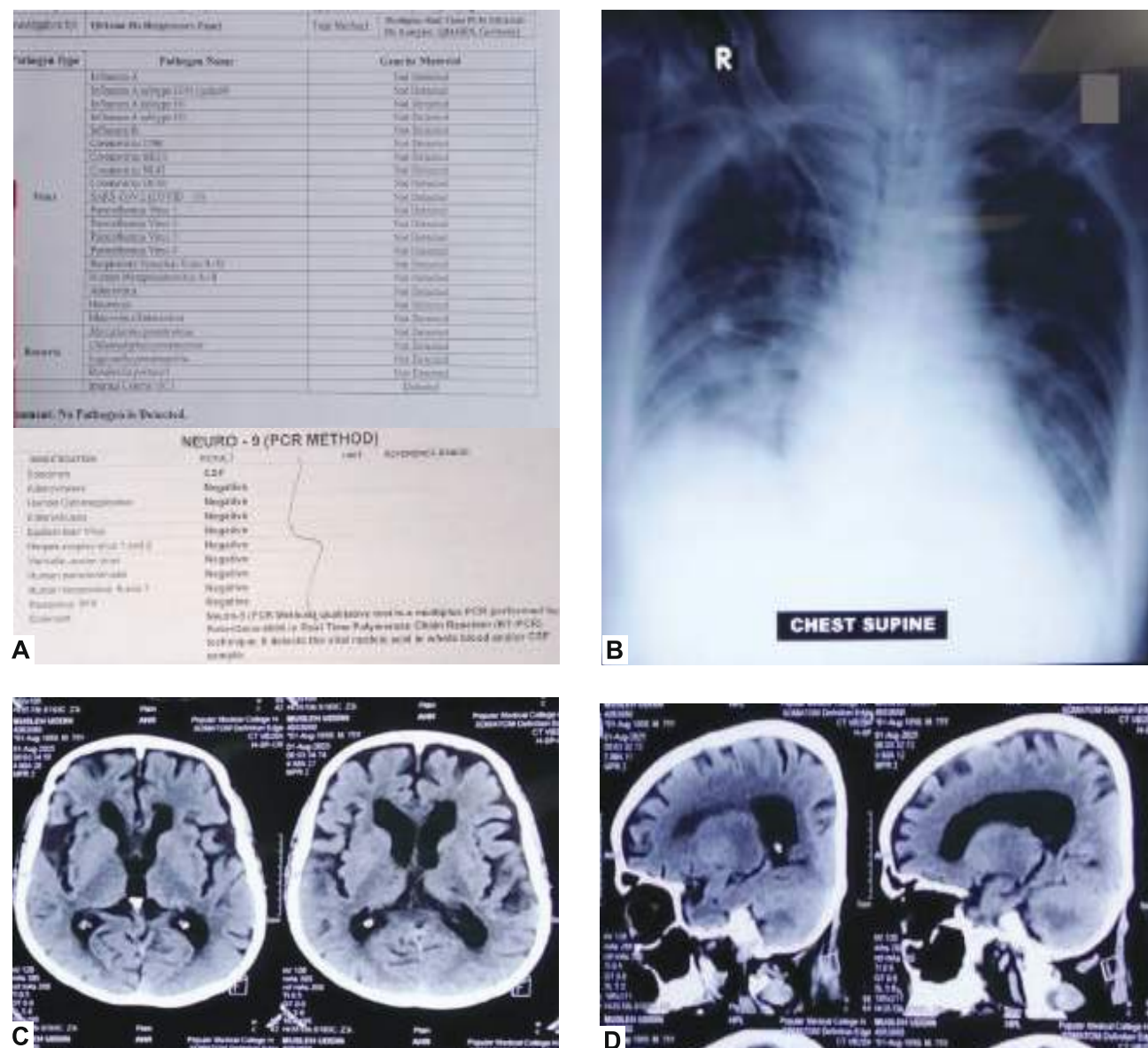


Figure 2 : A) Showing negative nasal swab for Respiratory panel (above) and CSF for Neuro-9 PCR panel, B) CXR supine view after respiratory distress showing bilateral (right > left) pulmonary infiltrates, C) & D) showing CT brain Axial and sagittal view respectively showing, tiny hypodense lesion in left frontal lobe and left thalamus generalized cerebral atrophy and ventriculomegaly

Discussion:

Reappearance of chikungunya cases have been reported in Bangladesh in 2024, following a seven-year hiatus. From 19th October to 31st December 2024, 138 Chikungunya positive cases were reported. These cases were mostly male and over 30-years old.¹¹ This is by far the fifth outbreak happening in Bangladesh. The first three were in 2008 (Rajshahi), 2009 (Pabna), 2012 (Tangail) and 2017 (Dhaka) respectively¹². In 2025 the cases still continue to rise. Up to May 28th, 2025 IEDCR alone reported 153 PCR confirmed

cases out of 337 suspected patients from both Dhaka North and South City Corporation¹³. These numbers are just the tip of iceberg as there is lack of national surveillance data.

Pneumonia in Chikungunya is not a rare entity. About 17% patients presented with pneumonia in a report from 2005-2006 from Reunion⁷. In previous outbreak of 2017, from Dhaka Bangladesh, there was no pulmonary involvement reported in any of the 690 participants¹⁴. Khare et al. reported a similar case like ours in 2022, from India. He described an elderly male

with diabetes and hypertension suffering from bilateral consolidation. However, he had no pleural effusion like our case¹⁵. They had successfully treated the patient with steroids. There has been reports of co-infection of chikungunya with respiratory syncytial virus, influenza and adenovirus especially in elderly and diabetics¹⁶ which was excluded in both of our cases by respiratory panel. Bacterial Infection was also excluded by sputum and blood culture. The pattern of lung involvement was different in both cases, upper lobe and perihilar region being more involved in case 1 and lower lobes, predominantly right lung being more involved in case 2. In both cases bilateral involvement was a common feature. How CHIKV infects the lung is still understudied. Presence of previous respiratory disease, co-infection with other respiratory viruses may predispose the condition. Additionally, viral respiratory infections mainly show up as a Th1 response, in which IFN- α , CD8 T cells, and NKC's all contribute to viral clearance, a process that is also observed for CHIKV in other organs¹⁷.

Our 1st case also suffered from bradycardia, which was resolved on follow up after discharge, may be a presentation of chikungunya myocarditis. We excluded that by ECG and cardiac enzymes¹⁸. He also showed delayed platelet recovery, even after 3rd afebrile day which may be explained by increased platelet activation due to the inflammatory process¹⁹.

Encephalitis was reported to be the most common neurological presentation. In 2017, the largest cohort reported from Bangladesh documented 11 (out of 690 suspected cases) with neurological impairment. Most of these cases were in elderly age group, All of them except one presented with altered consciousness and diagnosed as encephalitis. Although PCR from CSF was not done in all cases. The common co-morbidities reported was diabetes, hypertension and less commonly CKD and IHD²⁰. Other neurological manifestations were encephalopathy, GBS, myelitis, ADEM (Acute demyelinating encephalomyelitis), brainstem encephalitis, cranial neuropathy²¹. Unfortunately, we could not do chikungunya PCR from CSF due to unavailability of test kit. But we excluded other possible viral (Neuro -9 PCR from CSF, Fig-2A) and pyogenic causes (by cytology, biochemistry and culture). Tuberculosis was also excluded by ADA and Gene xpert MTB/RIF. A similar case report in India has documented bilateral numerous small punctate lesions in the white matter with periventricular diffusion-restricted spots in MRI brain. That patient underwent intravenous immunoglobulin (IVIG) therapy for approximately 7 days²². Although there are reports of good response to IVIG therapy²³, more evidence base is needed to prove it's cost-effectiveness in a low income

country like Bangladesh. In our encephalitis case, we only found cerebral atrophy and features of his old CVD in brain imaging. CHIKV appears to enter the brain by first infecting the brain vasculature's endothelial cells, which makes it easier for the brain parenchyma to become infected and may result in encephalitis. Cytokine profiling of neurologically ill patients during CHIKV infection revealed elevated levels of TNF- α , IFN- α , and IL-6 in CSF samples, which is indicative of a type I IFN response^{17,24}.

From the first outbreak of chikungunya in 2008 to the fifth one in 2025, chikungunya virus has changed its molecular characteristics. The evolution and emergence of a novel sub-lineage within the previously prevalent ECSA genotype of the virus in Bangladesh was demonstrated by recent phylogenetic research in late 2024. Given the strong kinship between these outbreak strains, it is probable that their most recent common ancestor developed from the local strains that were previously in use in early 2019¹¹. Unfortunately, we are still relying on 2017 national guidelines which lacks the treatment outline of organ involving severe cases. We need urgent measures to learn from our experience in this outbreak, generate evidence base for rational treatment of atypical presentations of chikungunya fever and update management plan to avoid fatalities and implement prompt management throughout the country.

Conclusion:

The actual burden of the chikungunya fever is underestimated because there is no regular national surveillance system for Chikungunya, diagnostic capacity is low, and there is clinical overlap with Dengue, especially during the monsoon season. Even if the acute infection resolves on its own, if there is neurological and respiratory involvement, it could become fatal. Preventive actions are encouraged for the general population to minimize mosquito breeding grounds and prevent mosquito bites, especially in and around dwellings.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study.

Funding:

This research received no external funding.

Consent for publication:

Informed written consent was taken from the parents of the patient to publish details relevant to the disease and management.

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CASE REPORT

RECURRENT CHOLANGITIS FROM COMMON BILE DUCT STONES AFTER CHOLECYSTECTOMY IN A PATIENT WITH DUODENAL PERIAMPULLARY DIVERTICULA

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Abstract:

Choledocholithiasis is a commonly encountered hepatobiliary disease. The gallstones may migrate into the common bile duct (CBD) or develop de novo in the CBD. Endoscopic Retrograde Cholangiopancreatography (ERCP) is the primary treatment for choledocholithiasis with reduced morbidity and similar efficacy compared to surgical exploration of the common bile duct. Some anatomic factors that promote biliary stasis include CBD dilation, periampullary diverticulum, and CBD stricture. We reported on a 61-year-old patient who underwent multiple ERCPs for recurrent cholangitis due to CBD stones. Each time she had fever, abdominal pain and jaundice. Periampullary duodenal diverticula were a risk factor for recurrent stone formation. Choledochoduodenostomy was performed to prevent recurrent CBD stone formation. At endoscopic follow-up, healed diverticula were noted.

Key words: Recurrent cholangitis, duodenal periampullary diverticula, ERCP, choledochoduodenostomy

Date of submission: 29.07.2025

Date of acceptance: 30.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.84038>.

Citation: Shrestha R, Shrestha M, Bhattarai K, Jha IK, Khadka D. Recurrent Cholangitis from Common Bile Duct Stones after Cholecystectomy in a patient with Duodenal Periampullary Diverticula. *Bangladesh J Medicine* 2025; 36(3): 155-159.

Introduction:

The presence of stones in the common bile duct (CBD) defines choledocholithiasis. Stones can either form in the CBD or migrate to it from the gallbladder. Symptoms include episodic right upper quadrant (RUQ) abdominal pain, nausea, fever, jaundice, and weight loss. The patient may also develop biliary pancreatitis and cholangitis with increased morbidity and mortality due to severe complications. They may also develop within the CBD de novo due to bacterial infections of the bile ducts and biliary stasis.¹

Since its introduction in 1974, initially as a procedure of choice for elderly unfit patients for surgical

management of CBD stone (CBDS), ERCP with endoscopic sphincterotomy has become the procedure of choice for the treatment of CBDS in all categories of patients worldwide². Although the procedure is usually considered safe and effective, it is not an innocuous one, and complications (4-16%), either early or late, may develop.

Periampullary diverticulum (PAD) refers to a mucosal or submucosal outpouching of the duodenum commonly caused by a defect of the local muscular layer and arising within a 2-3 cm radius of the major papilla^{3,4}. Prevalence of PAD increases with age, and

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overall prevalence among the elderly is reportedly 65%⁵. The presence of duodenal periampullary diverticulum had also been reported as a risk factor for CBDS recurrence. Duodenal diverticulum, firstly recognized in 1710 by Chomel, is uncommon, with an incidence rate of 15-22% by post-mortem studies^{6,7}. Periampullary diverticula are the most common type of duodenal diverticulum, usually located within two to three centimeters from the papilla of Vater⁸. Three different types of periampullary diverticulum are known, depending on the location of the major papilla: type 1 - inside the diverticulum, type 2 - adjacent to the diverticulum, and type 3 - outside the diverticulum.

Case report:

A sixty-one-year-old lady with a history of cholecystectomy one week prior presented to the Gastroenterology Department of National Academy of Medical Sciences, Kathmandu with a history of fever, abdominal pain, and jaundice. She had undergone open choledocholithotomy with cholecystectomy. Common bile duct exploration with T-tube exploration was done. Operative findings revealed multiple stones in the common Bile duct and dilated cystic duct. Postoperative T-tube cholangiogram showed a filling defect, near the tip of the T-tube in the common bile duct. Total leukocyte count was 13000 with neutrophilia. Her liver function test revealed total bilirubin: 3.1mg/dl, direct 1.4mg/dl, SGOT (AST):184 U/L, alkaline phosphatase 853 IU/L, Hb% %:12gm/dl. Amylase and lipase were within normal limits. Abdominal ultrasound demonstrated a dilated biliary tree with the presence of calculi in the distal common bile duct, along with upstream dilatation of the biliary tree. Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed. Periampullary diverticula noted. Initially, cannulation was difficult. Two diverticula, one on each side of the ampulla of different sizes. Larger diverticulum was around 1.5 cm in diameter and smaller diverticulum of 5 mm in diameter. Cholangiogram showed few filling defects. After selective cannulation over a guide wire technique, sphincterotomy was done. Two stones measuring up to 1 cm were extracted with the extraction balloon. A temporary plastic stent was placed in the common bile duct. T-tube cholangiogram showed no filling defect. She was discharged home. After two months of follow-up, her symptoms resolved, and the comprehensive metabolic panel was normalized (Bilirubin (total): 0.8 mg/dl, conjugated 0.3 mg/dl, SGPT:37 U/l, Alkaline phosphatase:

111IU/l. During repeat ERCP, the previous stent was removed, and a few debris and sludge were successfully extracted. Distal balloon occlusion cholangiogram revealed no remaining stone. On subsequent follow-up, the patient was symptom-free with no calculus in imaging. Her comprehensive metabolic panel was within normal range.

Two years later, the patient presented to the hospital with symptoms suggestive of cholangitis in the form of fever, abdominal pain, and yellowish discoloration of the body and high colored urine. Patient had conjugated hyperbilirubinemia along with transaminitis and raised alkaline phosphatase (Bilirubin was 8.7 mg/dl with Conjugated bilirubin 3.9mg/dl, aspartate transaminase 148 IU/l, and alanine transaminase:240 U/l. Alkaline phosphatase 366 U/l. She also showed a raised total leukocyte count with neutrophil predominance. MRCP again showed a CBD (1.2cm) with recurrence of choledocholithiasis. During ERCP, a single stone was extracted. No filling defects were confirmed on occlusion cholangiogram. Free flow of bile noted, and the common bile duct was not stented. Three days later, the patient had fever and abdominal pain, suggestive of cholangitis. It was thought that there might be retained stone, and decompression was done with the placement of a double pigtail stent.

Within nine months, she had recurrent cholangitis four times and was admitted at ICU. During her last ERCP, the patient had multiple stones (largest one 1 x 0.5 cm) and was extracted with mechanical lithotripsy. Frank discharge of pus was noted suggesting cholangitis. Double pigtail plastic stent deployed. The patient was referred to surgical Gastroenterology for the surgical management. The patient was re-evaluated along with radiological imaging and had normal tumor markers, with evidence of periampullary diverticula and choledocholithiasis. ECBD with choledochoduodenostomy was done for biliary decompression with no diverticulectomy. Operative findings revealed dense omental adhesion. CBD diameter is approximately 2 cm. CBD stent in situ. Few microliths were present in CBD. Liver and peritoneum were normal during the operative evaluation.

The patient was followed up for five years with a six-monthly interval. The latest endoscopic image showed choledochoduodenostomy in the first part of the duodenum. The papilla was intact with no evidence of diverticula [Figure 5,6]. Diverticula healed spontaneously after decompression.



Fig.1: Filling defects (stones)
On cholangiogram



Fig. 2: Extraction of stones



Fig.3: Papilla with two diverticulum



Fig.4: Papilla with diverticulum



Fig.5: Choledochoduodenostomy in the
first part of duodenum diverticula



Fig.6: Papilla with healed

Discussion:

Five to thirty percent of patients have cholelithiasis along with choledocholithiasis (common bile duct stones (CBDS)) at the time of diagnosis⁹. CBDS are usually classified as primary when detected two years or more following cholecystectomy. When CBDS are detected up to two years following cholecystectomy, it is labelled as secondary CBDS. Recurrent CBDS are defined as stones found six months or more following initial endoscopic retrograde cholangiopancreatography (ERCP) with complete duct clearance^{10,11}.

Deng et al⁹ found that the risk of common bile duct stone recurrence after ERCP was 1.599 times higher for patients with a stone diameter ≥ 10 mm compared to those with a stone diameter < 10 mm. A study involving 1148 patients found that stone diameter > 12 mm was more likely to recur.¹²

Several risk factors have been reported in various studies¹³⁻¹⁸. This study showed that advanced age more than 65 years, history of choledocholithotomy, endoscopic papillary balloon dilatation (EPBD), endoscopic sphincterotomy (EST), CBD stent

implantation, multiple ERCP procedures (more than two), stones in the intrahepatic bile duct, periampullary diverticulum, choledocholithiasis diameter ≥ 10 mm, bile duct-duodenal fistula, biliary tract infection, and no preoperative antibiotic use were independent risk factors for the recurrence of choledocholithiasis after ERCP.

Duodenal diverticulum was diagnosed radiologically by Case in 1913¹⁹. Duodenum is the second most common site of diverticula in the alimentary tract after colon, followed by jejunum, ileum, and stomach^{20,21}. Several studies confirmed that the second part is the most common site, followed by the third and fourth parts of the duodenum. Periampullary diverticulum is usually asymptomatic, with only five percentage of patients presenting with complications. These complications include pancreatitis, biliary obstruction, choledocholithiasis, and, rarely tumors. PAD was classified as type 1, 2, or 3 according to the position of the major papilla from the endoscopic view: type 1, the major papilla was located inside of the diverticula; type 2, the major papilla was located at the edge of the

diverticula; type 3, the major papilla was located outside of the diverticula. PAD, especially type 1 PAD, is associated with an increased risk of acute pancreatitis as well as the occurrence and recurrence of CBD stones²². The relatively high prevalence of PAD (around 5–23%) documented in previous studies underscores the significant influence of these luminal defects on pancreaticobiliary diseases or the procedure of endoscopic retrograde cholangiopancreatography (ERCP)⁷. In a study by Lapin et al. perampullary diverticulum was reported as the cause of massive gastrointestinal bleeding [23]. Venishetty N, et al. (July 20, 2023) reported perampullary diverticula causing recurrent pancreatitis²⁴. Grant Boileau identified two diverticula in 11 female subjects, compared to 13 in 122 male subjects²⁵. Mackenzie et al. have also reported a female preponderance in the ratio from 1.6 to 1²⁶.

In cases of biliary obstruction, excision of the diverticulum (diverticulectomy) is an appropriate procedure, but it can be difficult and is associated with significant mortality and morbidity²⁷. Bypass procedures such as choledcho-duodenostomy, Roux-en-Y choledcho-jejunostomy, and procedures such as duodenal diverticulization and duodenojejunostomy, aiming at duodenal decompression and inversion or reconstruction of the diverticular sac through aduodenotomy, may also be useful²⁸.

Conclusion:

Primary recurrent choledocholithiasis is usually uncommon. Frequent episodes of primary choledocholithiasis post-cholecystectomy increase the likelihood of future recurrence. Several risk factors are well known. In the absence of therapeutic consensus, a multidisciplinary team management approach is highly recommended. The patients with risk factor like perampullary diverticulum should be identified and referred for early surgical intervention if a second symptomatic episode cholangitis develop.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study.

Funding:

This research received no external funding.

Consent for publication:

Informed written consent was taken from the parents of the patient to publish details relevant to the disease and management.

Acknowledgments:

The authors were grateful to the staffs of the Department of Gastroenterology, National Academy of Medical Sciences, Kathmandu, Nepal

Authors' contributions:

All authors were involved in the management of the patient and all authors contributed to the conception, writing, and editing of the case report.

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CASE REPORT

PERIPHERAL ARTERIAL THROMBOSIS AS AN ATYPICAL INITIAL PRESENTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS IN A YOUNG MALE: A CASE REPORT

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Abstract:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous clinical manifestations and a predilection for affecting women of childbearing age. Thrombotic events, particularly venous thrombosis, are well-documented complications of SLE, often associated with antiphospholipid syndrome (APS). However, arterial thrombosis, especially involving large peripheral vessels, is a relatively rare initial manifestation, and even more unusual in young males without traditional cardiovascular risk factors. We report the case of an 18-year-old previously healthy male who presented with acute peripheral arterial thrombosis of the superficial femoral artery. Comprehensive laboratory evaluation showed positive antinuclear antibody (ANA) and anti-double stranded DNA (anti-dsDNA) antibodies, with negative antiphospholipid antibodies and a normal thrombophilia panel. CT angiogram confirmed a long-segment thrombotic occlusion of the right superficial femoral artery. The diagnosis of SLE with vascular involvement was established in the absence of APS. The patient was successfully managed with immunosuppressive therapy and antiplatelet agents. This case highlights the diagnostic complexity of SLE in atypical presentations and emphasizes the importance of considering SLE in young patients with thrombotic events, even in the absence of classic risk factors.

Keywords: Systemic Lupus Erythematosus, Young Male, Arterial Thrombosis, Rare Case Report

Date of submission: 11.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.83738>.

Citation: Khan R, Nobl MA, Faruque AA, Ahsan HMN. Peripheral Arterial Thrombosis as an Atypical Initial Presentation of Systemic Lupus Erythematosus in a Young Male: A Case Report. Bangladesh J Medicine 2025; 36(3): 160-163.

Introduction:

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disorder characterized by the production of autoantibodies and immune complex deposition, leading to inflammation and tissue damage¹. The disease predominantly affects women, with a female-to-male ratio of approximately 9:1, and commonly presents between the ages of 15 and 45 years². Clinical manifestations vary widely, ranging from mild cutaneous lesions to severe organ involvement

including lupus nephritis, central nervous system disease, and hematological abnormalities³.

Vascular complications are a significant cause of morbidity and mortality in SLE patients. These include accelerated atherosclerosis, vasculitis, and thrombotic events. Venous thrombosis, especially deep vein thrombosis and pulmonary embolism, are well documented and are often associated with the presence of antiphospholipid antibodies, collectively known as antiphospholipid syndrome (APS)^{4,5}. Arterial

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thrombosis, particularly involving large peripheral vessels, is much less common and typically occurs in the setting of APS or traditional cardiovascular risk factors such as hypertension, diabetes, or smoking⁶.

Arterial thrombosis as an initial presentation of SLE, especially in young males without conventional risk factors or APS, remains exceedingly rare and poses a diagnostic challenge. Here, we report such a case with detailed clinical, laboratory, and imaging findings, emphasizing the importance of considering SLE in atypical vascular presentations.

Case report:

An 18-year-old male, with no significant past medical or family history, presented to our clinic with a 2-month history of pain, numbness, and progressive weakness in his right lower limb. He described the limb as cold and noted difficulty in walking. There was no history of trauma, fever, rash, joint pain, oral ulcers, photosensitivity, or weight loss. He denied smoking, alcohol consumption, or use of illicit substances. There was no history of chest pain or palpitation.

Vital signs were within normal limits. Examination of the right lower limb revealed absent dorsalis pedis, anterior tibial, and popliteal artery pulsations. The limb was cooler compared to the left side with mild muscle wasting noted in the calf region. Sensory and motor

examination revealed decreased power (4/5) in the ankle dorsiflexors and plantarflexors. The left lower limb exhibited normal peripheral pulses and no wasting. Initial laboratory investigations were largely unremarkable (Table 1). The complete blood count was within normal limits. Renal function tests, liver function tests, and electrolyte levels were all normal. Urinalysis revealed no proteinuria or hematuria. The coagulation profile, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR), was within normal range.

Immunological testing showed a positive antinuclear antibody (ANA). Anti-double stranded DNA (anti-dsDNA) antibodies were also positive, with levels exceeding 50 IU/mL. Antiphospholipid antibodies were negative, including lupus anticoagulant, anticardiolipin IgG and IgM, and anti- β_2 glycoprotein I antibodies.

Tests for rheumatoid factor (RF), perinuclear ANCA (p-ANCA), and cytoplasmic ANCA (c-ANCA) were negative. The complement levels showed a normal C4 level of 0.12 g/L (normal 0.10-0.40 g/L) but a low C3 level of 0.68 g/L (normal 0.90-1.80 g/L). D-dimer was elevated 1.98 μ g/mL (normal <0.50 μ g/mL).

A thrombophilia screen, including Protein C, Protein S, Antithrombin III, homocysteine levels, and testing for the Factor V Leiden mutation, showed all parameters within normal limits.

Table I
Laboratory results

Investigation	Result	Normal Range
WBC count	$7.46 \times 10^9/L$	$4-10 \times 10^9/L$
Platelet	210 K/ μ L	150-410 K/ μ L
Haemoglobin	13.50 g/dL	13-17 g/dL
ESR	32 mm in 1 st hour	0-10 mm in 1 st hour
CRP	21 mg/L	<5.00 mg/L
Procalcitonin	0.02 ng/mL	<0.05 ng/mL
ALT	31 U/L	Upto 41 U/L (Male) Upto 33 U/L (Female)
S. Creatinine	1.08 mg/dL	0.70-1.20 mg/dL
Urea	32.90 mg/dL	16.60-48.50 mg/dL
Serum Albumin	4.11 g/dL	3.50-5.20 g/dL
Calcium	8.78 mg/dL	8.80-10.60 mg/dL
p-ANCA	<2.50 AU/mL	Nonreactive: <16AU/ml Reactive: >24 AU/ml
c-ANCA	<2.00 AU/mL	Nonreactive: <16AU/ml Reactive: >24 AU/ml
Anti-phospholipid IgG	2.35 U/mL	<10: Negative >10: Positive
Anti-phospholipid IgM	2.88 U/mL	<10: Negative >10: Positive
Anti Cardiolipin IgG	2.42 GPLU/mL	Nonreactive: <8GPLU/mL Reactive: >12 GPLU/mL
Anti Cardiolipin IgM	2.73 GPLU/mL	Nonreactive: <8 GPLU/mL Reactive: >12 GPLU/mL



Figure 1: CT angiogram of abdominal aorta and both lower limbs revealed thrombotic occlusion of the right superficial femoral artery (Indicated by circle & arrow)

CT angiography of the abdominal aorta and lower limbs was done (Figure 1). It showed a thrombotic occlusion of the right superficial femoral artery extending for approximately 17.6 cm. There was reconstitution of moderate blood flow distally in the lower superficial femoral, popliteal, and posterior tibial arteries. Narrowing with thin flow was noted in the right anterior tibial and peroneal arteries. Echocardiogram and electrocardiogram were normal, ruling out cardiac embolic sources.

Based on the clinical presentation of acute limb ischemia, serological positivity for ANA and anti-dsDNA, negative antiphospholipid antibody panel, and exclusion of inherited thrombophilia, a diagnosis of SLE with large vessel arterial thrombosis was established. Since this case receives two (2) points for fever, three (3) points for low C3, and six (6) points for a positive anti-dsDNA antibody, it satisfies the 2019 EULAR/ACR criteria for diagnosing SLE. So, we have classified this case as SLE with a score of 11 and it also fulfills the entry criterion which is positive ANA.

The patient was initiated on high-dose corticosteroids (oral prednisone 1 mg/kg/day) alongside hydroxychloroquine (400 mg daily) to control underlying autoimmune activity. Given the absence of antiphospholipid antibodies and stable distal limb perfusion, antiplatelet therapy (aspirin 75 mg daily)

was started without full anticoagulation. The vascular surgery team advised conservative management as the limb was viable and surgical thrombectomy carried high risks.

The patient was monitored closely for symptom progression and potential development of further SLE manifestations.

At 3 months, the patient reported improvement in pain and functional use of the affected limb. On physical examination, peripheral pulses remained diminished but there was no progression of ischemia or tissue loss. Repeat imaging demonstrated partial recanalization of the occluded segment.

At 6 months, the patient remained clinically stable without new SLE symptoms or thrombotic events. The pain subsided and functional capacity is improved. On physical examination, popliteal pulsation was found to be sluggish. There was no progression of ischemia or tissue loss and corticosteroids were gradually tapered. He continues hydroxychloroquine therapy and is under regular rheumatology follow-up.

Discussion:

Vascular complications in SLE are predominantly due to accelerated atherosclerosis and antiphospholipid syndrome (APS)-related thrombosis⁷. However, the occurrence of large-vessel arterial thrombosis in the absence of APS remains uncommon and poorly understood. The pathogenesis likely involves multiple mechanisms such as immune complex-mediated endothelial injury, complement activation, inflammatory cytokine release, and vasculitis, which together promote a prothrombotic state^{8,11}.

This case is unique given the patient's young age, male gender, and lack of traditional cardiovascular risk factors or APS antibodies, highlighting the heterogeneous and sometimes atypical presentations of SLE. Arterial thrombosis without APS in SLE patients is often under-recognized and can delay diagnosis and treatment⁹. Recent studies have emphasized the role of neutrophil extracellular traps (NETs) in SLE-associated vascular damage, further supporting immune-mediated endothelial dysfunction as a key mechanism for thrombosis¹².

Clinicians should maintain a high index of suspicion for autoimmune etiologies in young patients presenting with unexplained arterial occlusion, particularly when conventional risk factors are absent. A comprehensive autoimmune panel, including ANA and anti-dsDNA, is crucial for early diagnosis and appropriate management.

Therapeutic strategies focus on immunosuppression to control lupus activity and prevent further vascular injury. Hydroxychloroquine has been shown to have antithrombotic properties and reduce SLE flare rates, while corticosteroids help control acute inflammation. Antithrombotic therapy should be individualized; anticoagulation is recommended in patients with APS, but in APS-negative patients, antiplatelet therapy may suffice¹⁰. Surgical or endovascular interventions are reserved for critical ischemia or limb-threatening cases.

Early recognition and prompt immunosuppressive treatment are essential to minimize ischemic complications and improve long-term outcomes. Our case underscores the importance of considering SLE as a differential diagnosis for arterial thrombosis even in atypical demographics and presentations.

Conclusion:

This case exemplifies an atypical presentation of SLE in a young male patient manifesting as peripheral arterial thrombosis without antiphospholipid syndrome. Awareness of such rare presentations is critical for timely diagnosis and management.

Funding:

This research received no external funding.

Consent for publication:

Informed written consent was taken from the parents of the patient to publish details relevant to the disease and management.

Acknowledgments:

The authors were grateful to the staffs of the Department of Medicine, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh.

Conflict of interests: None

Authors' contributions:

All authors were involved in the management of the patient and all authors contributed to the conception, writing, and editing of the case report.

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CLINICAL IMAGE

CLINICAL IMAGE-1

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Date of submission: 22.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.84070>.

Citation: Tasnim R, Islam QT. Clinical Image-1. Bangladesh J Medicine 2025; 36(3): 164.

A 61-year-old hypertensive, non-diabetic male presented with a history of fever for 4days, rash and arthralgia of small joints of hands, wrists and both ankles for the last 13 days.

On examination, he was afebrile, tender and swollen PIP, MCP, wrists and both ankles. He also had a hyperpigmented rash over his nose (Figure-01), which he noticed to develop during this course of illness.



Fig.-1:

His full blood count showed, leucopenia.

Follow-up visit after 3 weeks, showed improvement of the hyperpigmentation over his nose (Figure-02).



Fig.-2:

Question 01: Describe the lesion of Figure-01 and Figure-02.

Question 02: Name the lesion.

Question 03: What is the clinical diagnosis?

Question 04: What is the mechanism of this condition?

Question 05: Enumerate the treatment options for this condition?

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CLINICAL IMAGE

CLINICAL IMAGE-2

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Date of submission: 18.08.2025

Date of acceptance: 25.08.2025

DOI: <https://doi.org/10.3329/bjm.v36i3.84228>.

Citation: Rahman A. Clinical Image-2. Bangladesh J Medicine 2025; 36(3): 165.

A 52-year-old woman visited a tertiary care hospital's neurology outpatient department, complaining of severe headaches and insomnia for the previous six to seven months. The patient reported the headaches' gradual development and severity, including a traffic collision in 2018. She also complains about hazy vision. She had also recently noticed deterioration in her diabetes control despite being on a basal-bolus insulin regimen. She had no obvious cushingoid characteristics other than central obesity, and she had no family history of pituitary tumors or related illnesses.

She is a mother of four who stays at home. All of the children are the result of uneventful pregnancies and

normal deliveries. She had been married to a doctor for twenty years. She was not an alcoholic or smoker. It was suggested that she be admitted to the department of neurology. A visual perimetry test and a brain MRI had been performed.

Please answer the following question

1. What is the imaging protocol?
2. What are the findings of MRI?
3. What is the finding of perimetry?
4. What are the 3 important differentials?
5. How can you differentiate them?
6. What is treatment plan?

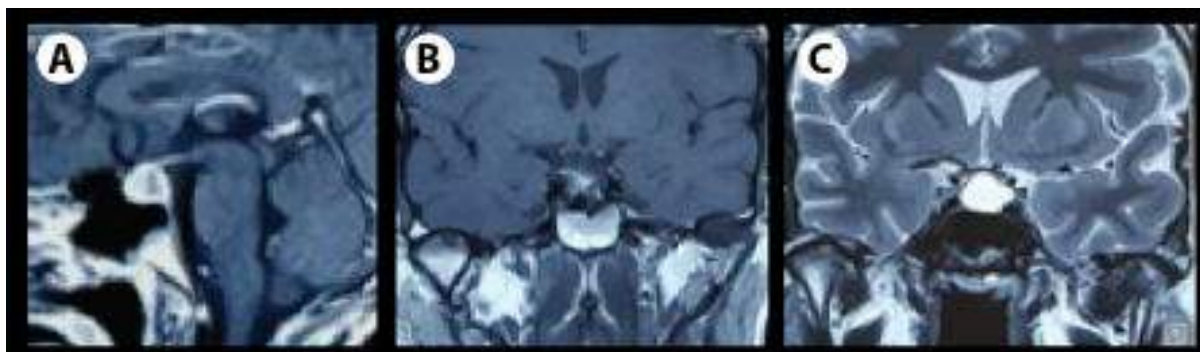


Fig.-1 :

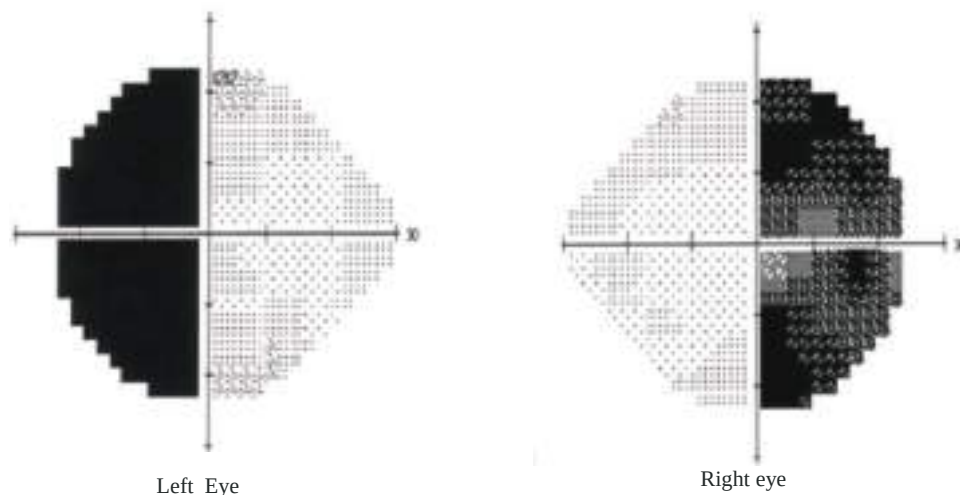


Fig.-2: A visual perimetry test

Answer to Clinical Image - 1

Answer 01:

Figure-01: A diffuse, hyperpigmented, flat patch over the tip, nasal bridge and the alae of the nose with brown to black discoloration.

Figure-02: Faded brownish pigmented macules over the tip and thenasal bridge.

Answer 02:

Chik sign of Chikungunya / Brownie nose

Answer 03:

Convalescent phase of Chikungunya virus infection

Answer 04:

- Post-inflammatory hyperpigmentation leads to melanocyte stimulation
- Photosensitivity
- The Chikungunya virus may directly affect melanocyte activity or induce dermal inflammation that alters pigmentation.

Answer 05:

Treatment is mainly reassurance and photoprotection. The pigmentation is self-limiting, but topical depigmenting agents (hydroquinone, azelaic acid, tretinoin) and sunscreen may be used if persistent.

Discussion:

Chikungunya, transmitted by *Aedes* mosquitoes, manifests with fever, debilitating arthralgia, and various mucocutaneous features. Cutaneous manifestations of Chikungunya include pigmentary changes, maculopapular eruptions, intertriginous aphthae-like lesions, transient nasal erythema, vesicobullous and lichenoid eruptions, exacerbation of preexisting dermatoses, and subungual hemorrhage. Pigmentary changes usually develop one to three weeks after the fever subsides and may present as centrofacial freckle-like macules, diffuse pigmentation over the face, pinna and extremities, flagellate pigmentation on the face and limbs, mucosal pigmentation involving the tongue and palate, melasma-like pigmentation on the face, lichen planus pigmentosus-like lesions over the neck and flexures, periorbital hypermelanosis, and pigmentation of preexisting acne lesions¹.

The characteristic centrofacial post-inflammatory hyperpigmentation, known as the *Chik sign* or *brownie nose*, may persist for up to six months. It is thought to result from increased intraepidermal melanin dispersion or retention triggered by Chikungunya fever².

Studies suggest the Chik sign may act as a clinical marker of severe Chikungunya, with patients showing this facial hyperpigmentation more likely to have prolonged fever, persistent arthralgia, systemic complications, functional disability, and higher hospitalization rates. Although the exact mechanism remains unclear, it may reflect heightened immune activation or viral load burden³. Chik sign is usually asymptomatic and self-limiting but may persist for months; management is mainly conservative with sun protection, moisturizers, and topical depigmenting agents⁴.

Recognition of this sign can help clinicians anticipate prolonged morbidity, guide early rheumatologic intervention, and prioritize close monitoring, particularly in resource-limited endemic settings³.

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Disclaimer:

Pictures are taken with the permission of the patient in July 2025.

Answer to Clinical Image - 2

Answers:

1. MRI of the brain with pituitary protocol
2. Magnetic Resonance Imaging (MRI) T1 and T2-weighted images in the sagittal and coronal planes, confirmed the presence of a large, lobulated mass involving the sella and suprasellar region
3. Bitemporal hemianopia: most common lesion produced by chiasmal compression.
4. Pituitary macroadenoma
5. 3 important differentials:
 - a) Craniopharyngioma: MRI of Pituitary region demonstrates a suprasellar mass which is predominantly cystic with a small enhancing posterosuperior nodule. The mass elevates and distorts the optic chiasm but does not extend into the pituitary fossa.
 - b) Rathke cleft cyst (if cystic) : intracystic mural nodule is specific but not very sensitive , fluid-fluid levels are rare, more likely to be midline, less likely to have a dark T2 rim
 - c) Meningioma :separate pituitary is usually identifiable, dural tail usually visible, enhancement more vivid, hyperdense on non-contrast CT
6. Treatment for pituitary macroadenomas involves surgery (typically transsphenoidal surgery), radiation therapy, and medication,

Discussion:

Pituitary macroadenomas produce a complex therapeutic dilemma since they can induce both hormonal dysfunction and compressive symptoms. Early detection and effective care are critical for preventing neurological impairments and improving patient outcomes ¹.

Medical management approaches can be tried first in prolactinomas, somatotroph, and thyrotroph adenomas.² Dopamine agonists, such as bromocriptine and cabergoline, have been shown to diminish prolactinoma growth and reverse hyperprolactinaemia ³. Dopamine agonist therapy has been shown in patients with macroprolactinomas to reduce tumor size in 50-90% of instances and normalize serum prolactin levels in 60-95% of cases ⁴. Previous imaging studies have also found that the greatest reduction in tumor size and serum prolactin levels occurs during the first 3-6 months of treatment, and the absence of significant

improvement during this time is a strong predictor of pharmacological resistance to dopamine agonist therapy . ⁵

The mainstay of treatment for pituitary macroadenomas is still surgery, which aims to relieve symptoms and decompress surrounding structures. Because it is less intrusive and has a lower rate of morbidity than conventional methods, the trans-nasal trans-sphenoidal endoscopic approach has become the method of choice ^{6,7}. In this instance, the patient experienced symptom relief following the successful trans-nasal trans-sphenoidal endoscopic excision of the pituitary macroadenoma. Postoperative problems, however, are prevalent and need to be carefully managed. In this instance, supportive care and antibiotic treatment were required after the postoperative CT scan showed hyperdense lesions and mixed-density collections ⁸. To properly handle complications and guarantee the best possible outcome, careful postoperative monitoring and the right kind of intervention are crucial.

Radiation therapy should be considered in the management of patients with pituitary adenomas, particularly when medical and surgical options have been exhausted.⁹ Success of radiation therapy in controlling tumor growth is high, 90-100% in most series, regardless of radiation technique and adenoma subtype. Success in achieving hormonal normalization in secretory tumors is more variable because of differences in patient population, radiation technique, and doses employed and variation of the definition of success. ¹⁰ Complete biochemical remission is generally achieved in 50% of patients at 10 yr after treatment for most adenomas.

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