

BANGLADESH JOURNAL OF MEDICINE

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EDITORIAL

NOMOPHOBIA: THE EMERGING PHENOMENON

AMINUR RAHMAN

“No-MOBile PHone PhoBIA” is an acronym for nomophobia, which is the dread of not being able to use or be reachable through a smartphone¹. Because they are more accustomed to newer technology than older generations and have a greater drive to fit in, younger generations are more likely to develop nomophobia.

The term “nomophobia” was first used in 2009 and is short for “no mobile phone phobia.”²

Since 2005, there has been a significant growth in the use of mobile phones, particularly in European and Asian countries.³ Nomophobia is commonly seen as a behavioral addiction in young generations, with many similarities to substance addiction.⁴

In a 2008 survey conducted by the UK Post Office revealed that almost 53% of British mobile phone users report feeling anxious. The study, which included 2,163 participants, discovered that almost 58% of men and 47% of women experienced the phobia, with an additional 9% feeling disturbed when their mobile phones were turned off. 55% of those polled said that being unable to communicate with friends or family was the biggest reason they felt anxious when they couldn't use their phones.^{5,6} Another study found that the average occurrence of nomophobia caused stress levels comparable to “wedding day jitters” and appointments to the dentist.⁷

One of the causes contributing to nomophobia is the use of mobile phones to access the Internet. A need for comfort brought on by things like elevated anxiety, low self-esteem, insecure attachment, or emotional instability may be the cause of addiction symptoms. To feel more at ease in emotional relationships, some people use their phones excessively.⁷

Excessive cell phone use and a dread of disconnecting are common symptoms of this contemporary anxiety condition. Anxiety, panic attacks, and bodily symptoms like shaking and perspiration when the phone is not close by are some examples of symptoms.² Overuse of smartphones has been linked to problems in cognitive-

emotional management and cognitive performance.⁸

Since nomophobia can serve as a stand-in for underlying illnesses, it can be difficult to distinguish it from other mental disorders. Nomophobia can serve as a stand-in for other conditions.⁹ When separated or unable to use their digital gadgets because of low battery, out-of-service region, no connection, etc., people with an underlying social problem are likely to feel anxious, shivering, sweating, and experiencing anguish. These individuals will frequently insist on always having their gadgets with them, usually going back to their houses to pick up forgotten cell phones.¹⁰

Because of the concept's novelty, there are currently very few academically acknowledged and empirically verified treatments. However, promising therapies include cognitive-behavioral psychotherapy, EMDR, and pharmaceutical approaches. Part of the treatment option could include boosting the availability of mobile phone charging stations to address components of nomophobia connected to battery anxiety, hence improving consumers' sense of security about their device's power state.¹¹ Tranlycypromine and clonazepam were found to be effective treatments for nomophobia.¹²

Overuse of smartphones is becoming a bigger risk to one's physical, emotional, and social well-being. The younger generations who use smartphones have a serious problem with nomophobia, a behavioral disorder that is always changing and requires a variety of approaches to address. The varying severity levels are really concerning. It is essential to raise awareness of the negative consequences of smartphone addiction.⁹

Compared to the virtual world, we need to spend more time in the real one. Human-to-human interactions and face-to-face relationships need to be restored. We should limit, not outright forbid, our use of mobile phones because we cannot escape the power of technological growth.

Keywords: nomophobia, smartphone, emerging phenomenon

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REVIEW ARTICLE

THE MULTIFACETED ROLE OF EXTRACHROMOSOMAL DNA IN CANCER: FUNCTIONS AND CLINICAL IMPLICATIONS

Shafee Ur Rehman¹

Abstract:

The Extrachromosomal DNA (ecDNA) in cancer biology has emerged as a critical driver, enhancing the knowledge about tumorigenesis, progression and treatment. The current review article explores the multifaceted role of Extrachromosomal DNA, focusing on its ability to amplify oncogenes, enhance tumor heterogeneity, and support cancer cell survival and understanding therapeutics pressure. Moreover, the unique transcriptional and replication dynamics of ecDNA with linking the uneven segregation during cell division, create a significant environment for the understanding of genetic diversity and adaptive evolution in tumors. In clinics the ecDNA holds significant potential as a biomarker for cancer, diagnosis, treatment, therapeutic monitoring and progenies. The higher level of ecDNA correlates with poor clinical outcomes and resistance to therapies, emphasizing its prognostic value. The current therapeutic techniques targeting ecDNA specific vulnerabilities, such as disrupting replication stress pathways or silencing the transcriptional activity, represents promising ways for cancer treatment. This review also highlights the potential of circulating ecDNA in liquid biopsies as a non-invasive diagnostic and monitoring tool. Despite these advances, challenges such as standardizing detection methods and understanding ecDNA diverse roles across cancer types remain. Addressing these gaps will unlock new opportunities in precision oncology, making ecDNA a cornerstone of future cancer diagnostics and therapeutics.

Keywords: Extrachromosomal DNA, Cancer, diagnosis, biomarker, liquid biopsy and treatment.

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Introduction:

The extrachromosomal DNA (ecDNA) is a distinct form of DNA found outside the chromosomes in eukaryotic cells. The ecDNA is typically rare in normal cells, and prevalent in various cancers, where it initiates the amplification of oncogenes and enhances malignancy^{1,2}. The ecDNA lacks centromere, allowing unequal segregation during cell division which helps in tumor heterogeneity³. The current review article was conducted to investigate the biological applications of ecDNA and its growing demands in clinics for cancer

diagnosis and therapeutics⁴. The research on ecDNA is not novel, from decades research has been conducted on ecDNA. Although the role of ecDNA in cancer has recently emerged and gained attention⁵. The traditional genetic analysis of cancer was related to the study of chromosomes such as deletion, insertion, mutations, and translocation⁶. However, the current advances in genomic technologies have revolved role of ecDNA in cancer genomics, and provide an additional part in complexity.

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Extrachromosomal DNA is a circular molecule, lacking centromere and telomere which are the characteristics of chromosomal DNA⁷. Due to this structure, the ecDNA has unique replication and segregation dynamics that distinguish ecDNA from chromosomal DNA². Furthermore, the circular nature of ecDNA facilitates the accommodation of amplified oncogenes and regulatory elements, allowing high transcriptional activity without chromosomal context⁸. Additionally, the absence of centromeres contributes to its uneven

inheritance during cell division, driving genetic diversity within tumors⁹. The formation of ecDNA is thought to arise from chromosomal DNA through mechanisms such as double-strand breaks and faulty DNA repair pathways, including non-homologous end joining (NHEJ)¹⁰. These processes can excise segments of the genome, which circularize to form ecDNA. This phenomenon is particularly common in cancers with high genomic instability, where DNA repair mechanisms are frequently compromised (Figure 1).

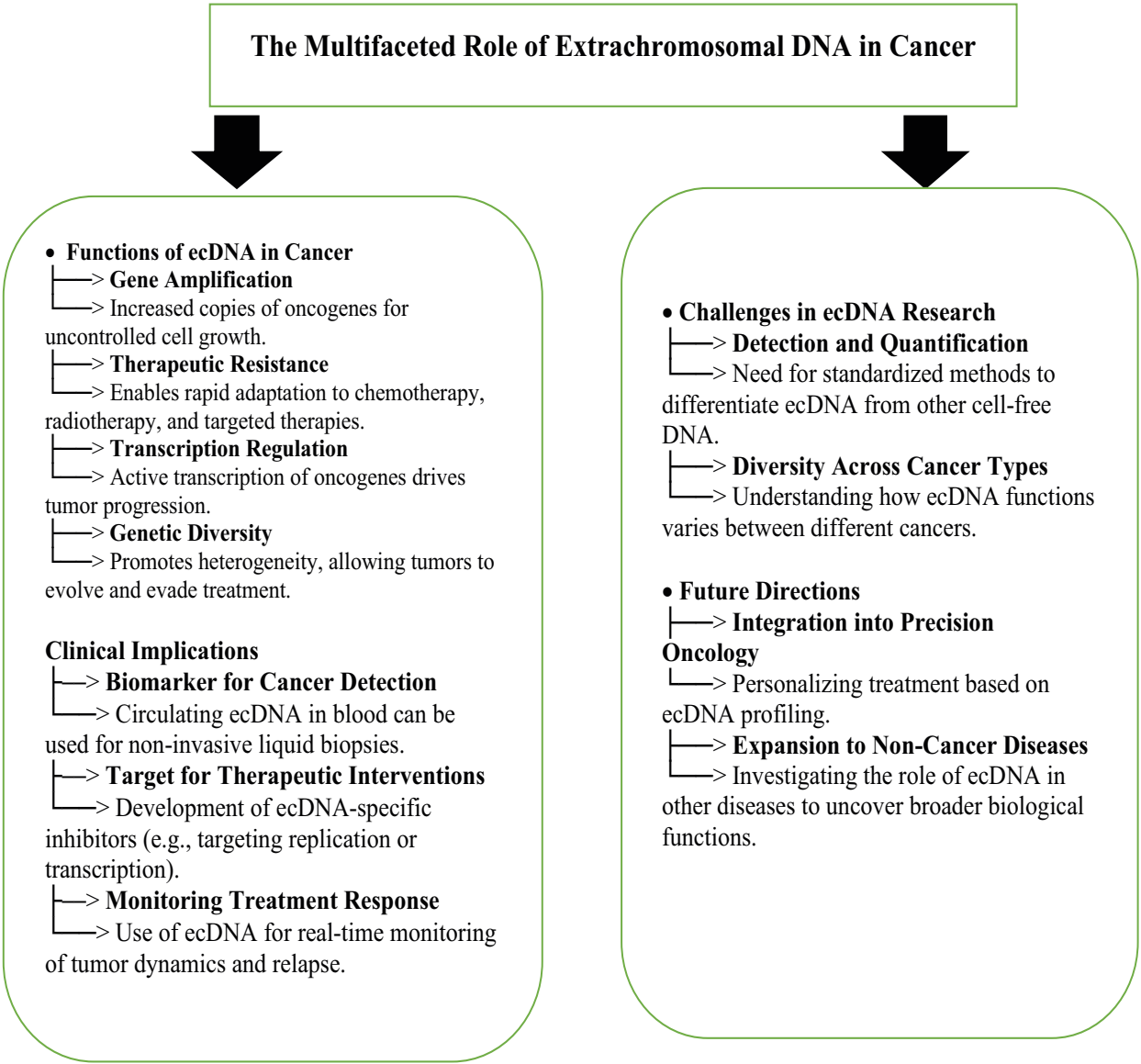


Figure 1. Flowchart provides a clear and concise overview of ecDNA’s role in cancer, from its biological functions to its clinical implications and future research directions.

EcDNA is present in a variety of cancers, including glioblastoma, lung cancer, and neuroblastoma, and is often associated with aggressive disease phenotypes³. Studies have shown that tumors with ecDNA amplification of oncogenes exhibit higher growth rates, metastatic potential, and resistance to therapy compared to those with chromosomal amplification¹¹. These properties underscore the clinical importance of ecDNA in cancer progression. The flexibility of ecDNA allows cancer cells to rapidly evolve and adapt to changing environmental and therapeutic conditions¹². For instance, ecDNA-mediated amplification of resistance genes can provide a survival advantage under targeted therapy, contributing to relapse and treatment failure¹³. Furthermore, the presence of ecDNA has been linked to increased tumor heterogeneity, a hallmark of cancer that complicates treatment¹⁴. Extrachromosomal DNA represents a powerful driver of cancer progression and therapy resistance. Its unique biological functions, coupled with its clinical potential, make it a compelling target for future research. By unraveling the mysteries of ecDNA, we can pave the way for novel diagnostic tools and

therapeutic strategies, transforming the landscape of cancer care. In this review we discuss the Multifaceted Role of Extrachromosomal DNA in Cancer: Functions and Clinical Implications

Functions of ecDNA in Cancer:

Extrachromosomal DNA (ecDNA) is circular DNA that plays an important role in the development and heterogeneity of cancer^{1,15}. The rapid evolution of methods to detect ecDNA, including microscopic and sequencing approaches, has greatly enhanced our knowledge of the role of ecDNA in cancer development and evolution¹⁶. Here, we review the molecular characteristics, functions, mechanisms of formation, and detection methods of ecDNA, with a focus on the potential clinical implications of ecDNA in cancer. Specifically, we consider the role of ecDNA in acquired drug resistance, as a diagnostic and prognostic biomarker, and as a therapeutic target in the context of cancer. As the pathological and clinical significance of ecDNA continues to be explored, it is anticipated that ecDNA will have broad applications in the diagnosis, prognosis, and treatment of patients with cancer (Figure 2).

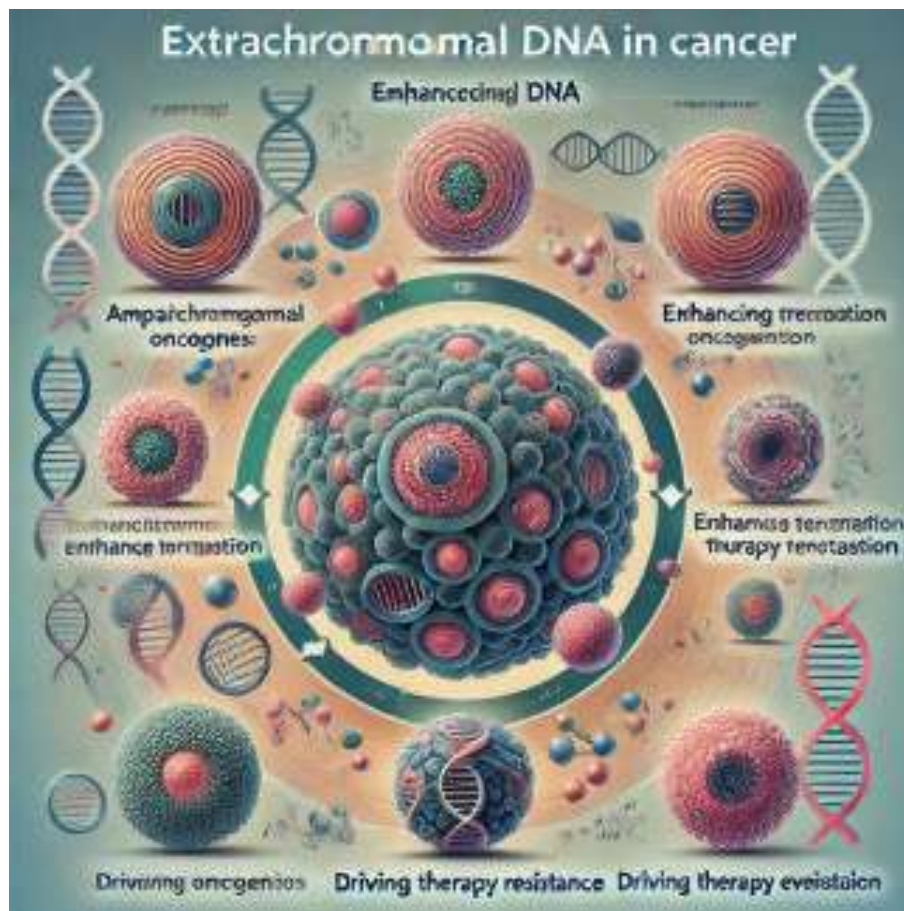


Figure. 2. Schematic overview of the functions of extrachromosomal DNA (ecDNA) in cancer

Oncogene Amplification:

Extrachromosomal DNA (ecDNA) has recently been recognized as a major contributor to cancer pathogenesis that is identified in most cancer types and is associated with poor^{17,18}. When it was discovered over 60 years ago, ecDNA was considered to be rare, and its impact on tumour biology was not well understood⁵. The application of modern imaging and computational techniques has yielded powerful new insights into the importance of ecDNA in cancer¹⁷. The non-chromosomal inheritance of ecDNA during cell division results in high oncogene copy number, intra-tumoural genetic heterogeneity and rapid tumour evolution that contributes to treatment resistance and shorter patient survival². In addition, the circular architecture of ecDNA results in altered patterns of gene regulation that drive elevated oncogene expression, potentially enabling the remodelling of tumour genomes¹⁹. The generation of clusters of ecDNAs, termed ecDNA hubs, results in interactions between enhancers and promoters in Trans, yielding a new paradigm in oncogenic transcription². One of the most prominent roles of ecDNA in cancer is the amplification of oncogenes such as **MYC**, **EGFR**, and **CDK4**^{3,20}. Unlike chromosomal amplifications, ecDNA-mediated amplification allows rapid and high-level oncogene expression, fueling aggressive tumor growth. For example, in glioblastoma, EGFR amplification via ecDNA correlates with poor prognosis and therapy resistance.

Tumor Heterogeneity and Evolution:

Extrachromosomal DNA (ecDNA) are circular regions of DNA that are found in many cancers. They are an important means of oncogene amplification, and correlate with treatment resistance and poor prognosis¹⁶. Consequently, there is great interest in exploring and targeting ecDNA vulnerabilities as potential new therapeutic targets for cancer treatment¹⁷. However, the biological significance of ecDNA and their associated regulatory control remains unclear. Light microscopy has been a central tool in the identification and characterisation of ecDNA¹⁸. The absence of centromeres in ecDNA facilitates its uneven distribution during cell division¹⁷. This unique property promotes genetic diversity within the tumor microenvironment, enabling adaptive evolution. Such heterogeneity poses significant challenges for targeted therapies, as subpopulations of ecDNA-enriched cells may evade treatment and drive relapse.

Transcriptional Regulation:

Enhancers are noncoding DNA sequences responsible for orchestrating gene expression programs by interacting with transcription factors and chromatin regulators within complex genome structures²¹. However, their fundamental functions can be disrupted by genetic and epigenetic alterations, leading to aberrant enhancer activation or rewiring that contributes to oncogenesis²². Analyzing dysregulated enhancer landscapes reveals new subtype-defining genomic features, such as enhancer hijacking, and identifies disease-relevant transcriptional regulators as potential targets for developing enhancer-targeting therapeutic strategies²³. EcDNA contributes to the transcriptional landscape of cancer cells by forming super-enhancers that boost oncogene expression²⁴. This burst-like transcriptional activity is often decoupled from chromosomal regulatory mechanisms, giving cancer cells a growth advantage. Moreover, the epigenetic plasticity of ecDNA enables dynamic responses to environmental and therapeutic pressures.

Replication and Segregation Dynamics:

Extrachromosomal DNA (ecDNA) presents a major challenge for cancer patients. ecDNA renders tumours treatment resistant by facilitating massive oncogene transcription and rapid genome evolution, contributing to poor patient survival²⁵. At present, there are no ecDNA-specific treatments²⁶. Here we show that enhancing transcription–replication conflict enables targeted elimination of ecDNA-containing cancers. Stepwise analyses of ecDNA transcription reveal pervasive RNA transcription and associated single-stranded DNA, leading to excessive transcription–replication conflicts and replication stress compared with chromosomal loci (Tang et al., 2024). Nucleotide incorporation on ecDNA is markedly slower, and replication stress is significantly higher in ecDNA-containing tumours regardless of cancer type or oncogene cargo. pRPA2-S33, a mediator of DNA damage repair that binds single-stranded DNA, shows elevated localization on ecDNA in a transcription-dependent manner, along with increased DNA double strand breaks, and activation of the S-phase checkpoint kinase, CHK1. Genetic or pharmacological CHK1 inhibition causes extensive and preferential tumour cell death in ecDNA-containing tumours²⁵. The replication of ecDNA occurs independently of the cell cycle, leading to rapid proliferation of ecDNA-bearing cells. During mitosis, ecDNA attaches to chromosomal regions or nuclear structures, ensuring its persistence in daughter cells. This mechanism underpins the sustained oncogene amplification observed in ecDNA-driven cancers.

Drug Resistance and Survival:

Recent research has unveiled fascinating insights into the intricate mechanisms governing tumor evolution²⁷. These studies have illuminated how tumors adapt and proliferate by exploiting various factors, including immune evasion, resistance to therapeutic drugs, genetic mutations, and their ability to adapt to different environments¹². Furthermore, investigations into tumor heterogeneity and chromosomal aberrations have revealed the profound complexity that underlies the evolution of cancer¹². Emerging findings have also underscored the role of viral influences in the development and progression of cancer, introducing an additional layer of complexity to the field of oncology²⁸. Tumor evolution is a dynamic and complex process influenced by various factors, including immune evasion, drug resistance, tumor heterogeneity, and viral influences²⁹. Understanding these elements

is indispensable for developing more effective treatments and advancing cancer therapies³⁰. A holistic approach to studying and addressing tumor evolution is crucial in the ongoing battle against cancer³¹. The main goal of this comprehensive review is to explore the intricate relationship between tumor evolution and critical aspects of cancer biology³². By delving into this complex interplay, we aim to provide a profound understanding of how tumors evolve, adapt, and respond to treatment strategies. EcDNA is a key contributor to therapeutic resistance. By harboring amplified oncogenes and stress-response elements, ecDNA enables cancer cells to survive targeted therapies. For instance, ecDNA-driven amplification of EGFR has been linked to resistance against tyrosine kinase inhibitors in non-small cell lung cancer (Figure 3).

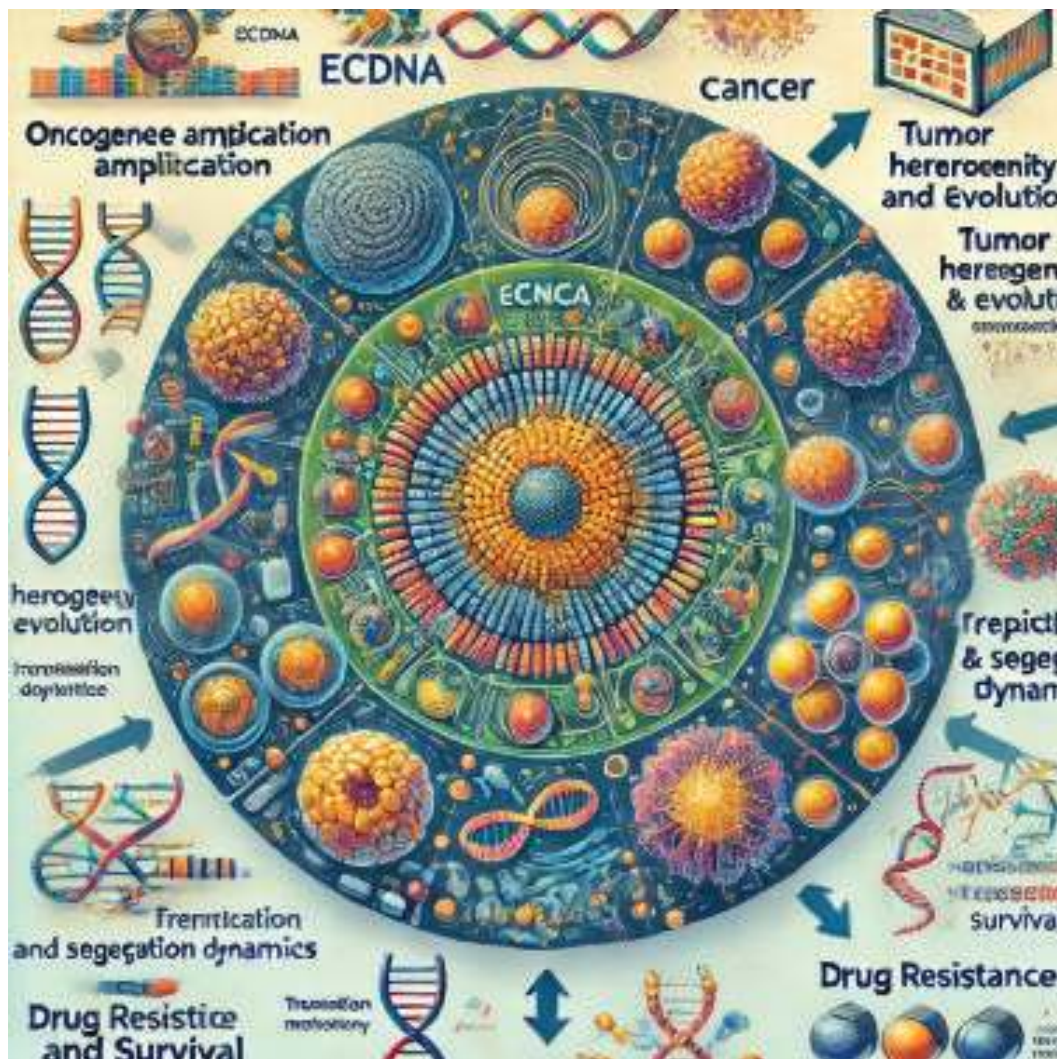


Figure. 3. Illustration depicting the roles of ecDNA in cancer, highlighting its five key functions.

Clinical Implications of ecDNA:

Diagnostic Potential

Nowadays, with the rapid development of sequencing and bioinformatics, the accuracy of eccDNAs detection has significantly improved³³. This advancement has consequently enhanced the feasibility of exploring the biological characteristics and functions of eccDNAs³³. This review elucidates the potential mechanisms of eccDNA generation, the existing methods for their detection and analysis, and their basic features. Furthermore, it focuses on the biological functions of eccDNAs in regulating gene expression under both physiological and pathological conditions. Additionally, the review summarizes the clinical implications of eccDNAs in human cancers and health. The presence of ecDNA is a hallmark of certain aggressive cancers. Advanced imaging techniques, such as fluorescence in situ hybridization (FISH), and sequencing technologies, including Circle-Seq, allow for the detection of ecDNA in tumor tissues³⁴. These methods have the potential to improve early cancer diagnosis and stratify patients based on ecDNA burden (Table 1).

Prognostic Value:

Extrachromosomal circular DNA (eccDNA) is defined as a type of circular DNA that exists widely in nature and is independent of chromosomes. EccDNA has attracted the attention of researchers due to its broad, random distribution, complex biogenesis and tumor-relevant functions. EccDNA can carry complete gene information, especially the oncogenic driver genes that are often carried in tumors, with increased copy number and high transcriptional activity²⁵. The high overexpression of oncogenes by eccDNA leads to malignant growth of tumors. Regardless, the exact generation and functional mechanisms of eccDNA in disease progression are not yet clear. There is, however, an emerging body of evidence characterizing that eccDNA can be generated from multiple pathways, including DNA damage repair pathways, breakage-fusion-bridge (BFB) mechanisms, chromothripsis and cell apoptosis, and participates in the regulation of tumor progression with multiplex functions³⁴. This up-to-date review summarizes and discusses the origins, biogenesis and functions of eccDNA, including its contribution to the formation of oncogene instability and mutations, the heterogeneity and cellular senescence of tumor cells, and the proinflammatory response of tumors. We highlight the possible cancer-related applications of eccDNA, such as its potential use in the diagnosis, targeted therapy and prognostic assessment of cancer. EcDNA abundance is often associated with poor clinical outcomes. Studies have demonstrated that high levels of ecDNA correlate with increased tumor aggressiveness, metastasis, and resistance to therapy. Monitoring ecDNA dynamics could provide insights into disease progression and recurrence risk (Table 1).

Therapeutic Resistance and Relapse:

Extrachromosomal DNA (ecDNA) plays a crucial role in cancer's ability to resist treatment and relapse after therapy⁵. This form of DNA exists outside the chromosomes, often carrying multiple copies of oncogenes or other genetic elements that drive tumor growth. When tumors are exposed to chemotherapy, radiotherapy, or targeted treatments, the presence of ecDNA allows cancer cells to rapidly adapt by amplifying key genes, mutating them, or altering their expression¹⁷. This makes it easier for the tumor to circumvent the effects of therapy, resulting in therapeutic resistance. The ability of ecDNA to rapidly evolve and provide genetic diversity within the cancer cell population makes it a major factor in treatment failure and relapse. To address this challenge, strategies that target ecDNA replication and transcription are being explored as potential therapies. By inhibiting the formation or replication of ecDNA, researchers hope to prevent tumors from adapting so quickly to treatment, ultimately improving the effectiveness of conventional therapies. Disrupting ecDNA's role in gene amplification and expression could significantly reduce the likelihood of resistance developing, thereby decreasing the chances of relapse. This approach is seen as a promising avenue for enhancing cancer treatment outcomes, particularly in cases where tumors have become resistant to existing therapies (Table 1).

Targeting ecDNA in Therapy:

Emerging therapeutic strategies are focused on exploiting the unique vulnerabilities of ecDNA to combat its role in therapeutic resistance. One promising approach involves targeting replication stress pathways, which are crucial for the replication of ecDNA. Inhibitors of proteins like ATR (ataxia telangiectasia and Rad3-related) and CHK1 (checkpoint kinase 1) are being investigated for their ability to disrupt the replication of ecDNA³⁶. These inhibitors work by inducing replication stress in cancer cells, preventing the efficient replication of ecDNA and reducing the ability of tumors to adapt to treatment. This approach holds promise in enhancing the effectiveness of conventional therapies and overcoming resistance mechanisms driven by ecDNA. Another strategy focuses on the epigenetic regulation of ecDNA³⁷. Since ecDNA often contains amplifications of oncogenes that are actively transcribed to promote tumor growth, silencing this transcription could inhibit the tumor's ability to survive and proliferate. Epigenetic modulators are being studied for their ability to alter the chromatin state of ecDNA, effectively silencing its transcription and reducing its contribution to cancer progression³⁸. By targeting the mechanisms that control ecDNA expression, these treatments aim to weaken the tumor's adaptive capabilities and improve the overall response to therapies, potentially reducing the likelihood of relapse (Table 1).

Liquid Biopsy and Non-Invasive Monitoring:

Circulating ecDNA in bodily fluids, such as blood, has emerged as a potential non-invasive biomarker for cancer detection and monitoring. Unlike traditional tissue biopsies, which can be invasive and difficult to perform regularly, liquid biopsies using blood samples allow for easier tracking of cancer’s presence and progression³⁹. EcDNA, released into the bloodstream as a result of tumor cell death or secretion, can contain genetic material that mirrors the tumor’s characteristics. By analyzing this circulating ecDNA, clinicians can gain valuable insights into the genetic makeup of a tumor, monitor its response to treatment, and detect early signs of relapse⁴⁰. However, distinguishing ecDNA from other forms of cell-free DNA (cfDNA), such as fragments from healthy cells, remains a significant challenge. The detection and isolation of ecDNA require highly sensitive and specific methods to avoid contamination from cfDNA that is not tumor-derived⁴¹. Advances in sequencing technologies are expected to overcome this hurdle, enabling more accurate and routine use of liquid biopsies for cancer detection. With improved sequencing techniques, it may become possible to differentiate ecDNA from other DNA fragments, making liquid biopsies a powerful tool in cancer diagnostics and treatment monitoring in the near future (Table 1).

Current Gaps and Challenges:

Despite the promising potential of ecDNA as a biomarker and therapeutic target, there are several hurdles that need to be overcome to fully realize its clinical applications. One major challenge is the lack of standardized methods for detecting and quantifying ecDNA. The sensitivity and specificity required to isolate ecDNA from other forms of cell-free DNA (cfDNA) are not yet fully established, making it difficult to use this biomarker in routine clinical practice³. The development of reliable, widely accepted protocols for ecDNA detection will be critical for its integration into cancer diagnostics and treatment monitoring. Additionally, ecDNA functions can vary significantly across different cancer types, adding another layer of complexity to its therapeutic targeting³. While ecDNA plays a role in promoting therapeutic resistance and tumor progression, its exact mechanisms and contributions can differ depending on the genetic landscape of the tumor. A deeper understanding of how ecDNA operates in various cancers is essential for developing targeted therapies that can effectively disrupt its function. Addressing these challenges will require interdisciplinary collaboration between researchers, clinicians, and technology developers, as well as innovative advances in sequencing, bioinformatics, and therapeutic approaches to unlock the full potential of ecDNA in cancer treatment.

Table 1
Summarizing the clinical implications of ecDNA in cancer, highlighting its role in tumor progression, resistance, and potential as a diagnostic and therapeutic target

Aspect	Implications	Description
Oncogene Amplification	Enhanced Tumor Progression	ecDNA enables rapid and high-level amplification of oncogenes, driving aggressive tumor growth and proliferation.
Tumor Heterogeneity	Increased Complexity of Tumors	ecDNA promotes genetic diversity within tumor cells, contributing to tumor heterogeneity and resistance to targeted therapies.
Therapy Resistance	Adaptation to Anti-Cancer Treatments	Tumors with ecDNA can bypass therapeutic stress by amplifying resistance genes or altering transcriptional programs.
Prognostic Marker	Association with Poor Prognosis	High levels of ecDNA correlate with worse clinical outcomes, including increased recurrence rates and lower overall survival.
Dynamic Evolution	Rapid Adaptation and Evolution	ecDNA allows tumors to adapt quickly to environmental pressures, including immune responses and therapeutic interventions.
Diagnostic Potential	Biomarker for Liquid Biopsies	Circulating ecDNA in blood or other bodily fluids can serve as a non-invasive biomarker for cancer detection and monitoring.
Target for Novel Therapies	Opportunities for Targeted Treatments	Inhibiting ecDNA replication, segregation, or transcription may provide novel approaches to limit tumor growth and resistance.
Metastatic Potential	Facilitated Spread of Cancer	ecDNA-related oncogene amplification can enhance cellular invasion and migration, increasing the likelihood of metastasis.
Epigenetic Regulation	Alteration of Gene Expression	The presence of ecDNA can modify the epigenetic landscape of cancer cells, influencing gene expression without changing the underlying DNA sequence.
Patient Stratification	Personalized Treatment Strategies	Profiling ecDNA content can help stratify patients for therapies tailored to their specific genetic and epigenetic tumor profiles.

Future Directions:

The future of ecDNA research holds great promise, particularly in the realm of precision oncology. As our understanding of ecDNA deepens, it is becoming clear that targeting this form of DNA could play a pivotal role in revolutionizing cancer treatment. Developing ecDNA-specific inhibitors to prevent its replication or transcription could provide a new class of therapies aimed at overcoming therapeutic resistance, while improving detection techniques will allow for more precise and non-invasive cancer monitoring through liquid biopsies³. By leveraging ecDNA as a biomarker, clinicians could gain real-time insights into the genetic evolution of tumors, enabling more personalized and timely treatment adjustments. This would not only improve cancer diagnostics but also optimize therapeutic strategies based on the tumor's specific genetic profile. Moreover, expanding ecDNA research beyond cancer could uncover broader biological roles for this enigmatic DNA form. While much of the focus has been on its involvement in cancer progression and resistance, ecDNA may play a role in other diseases as well, offering potential insights into its involvement in various pathological processes. This broader scope of study could reveal new therapeutic avenues for non-cancer diseases, expanding the potential impact of ecDNA research across the medical field. As research progresses, interdisciplinary collaboration and technological advancements will likely lead to significant breakthroughs that shape the future of both cancer treatment and our understanding of ecDNA's biological functions.

Conclusion:

Extrachromosomal DNA (ecDNA) has emerged as a powerful driver of cancer progression and therapy resistance, offering both challenges and opportunities for cancer treatment. Its ability to harbor and amplify oncogenes, as well as its role in enabling rapid genetic evolution within tumors, makes ecDNA a central player in the development of resistance to chemotherapy, radiotherapy, and targeted treatments. The unique biological functions of ecDNA—such as its involvement in gene amplification, transcription regulation, and rapid adaptation to environmental pressures—highlight its critical role in cancer survival and relapse. As a result, understanding and targeting ecDNA has the potential to significantly alter how we approach cancer therapy. Given its clinical significance, ecDNA presents an exciting frontier for future research, with the potential to lead to novel diagnostic tools and therapeutic strategies. Advances in detection methods, such as liquid biopsies, could enable non-invasive monitoring of cancer progression and response to

treatment by analyzing ecDNA in bodily fluids. Additionally, developing targeted therapies that disrupt ecDNA replication or transcription could overcome the challenge of therapy resistance, offering more effective and personalized treatment options for patients. By unraveling the mysteries of ecDNA, researchers and clinicians can transform the landscape of cancer care, offering new avenues for early detection, precision medicine, and the fight against resistant and relapsed cancers.

Author Contribution:

Shafee Ur Rehman design the idea, collect the information and wrote the manuscript.

Conflict of Interest:

The author declare that they have no conflict of Interest

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REVIEW ARTICLE

THE GLOBAL CHALLENGES OF TYPE 2 DIABETES: TRENDS, BARRIERS, AND FUTURE PERSPECTIVES

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Abstract:

Type 2 diabetes mellitus (T2DM) poses a considerable challenge to global health, with its incidence rising sharply, especially in low- and middle-income countries (LMICs). Epidemiological evidence indicates that T2DM constitutes more than 90% of all diabetes cases globally, influenced by factors such as urbanisation, an aging demographic, sedentary lifestyles, and changes in dietary habits. While high-income nations are experiencing a stabilisation in incidence rates, LMICs are witnessing an unprecedented surge, exacerbated by inadequate healthcare systems and unequal access to medical services. The management of T2DM is obstructed by various barriers, including socioeconomic inequalities, difficulties in adhering to lifestyle modifications and treatment regimens, and systemic shortcomings like inadequate screening processes and a shortage of trained healthcare professionals. These challenges not only hinder early detection but also worsen complications, leading to increased morbidity and healthcare expenditures. Nevertheless, progress in pharmacological and technological fields provides a glimmer of hope. Global initiatives, such as the WHO Global Diabetes Compact, stress the importance of collaborative efforts to improve prevention and management strategies. Tackling T2DM necessitates a holistic approach that includes healthcare reforms, the integration of technology, and international cooperation. This review analyses the worldwide trends associated with T2DM, highlights significant obstacles to effective management, and investigates new strategies aimed at alleviating its effects.

Keywords: Global Health, Socioeconomic Disparities, Low- and Middle-Income Countries (LMICs), Epidemiology, Urbanization.

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Introduction:

Diabetes mellitus is a common endocrine disorder worldwide. There are two common types of this condition: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T2DM accounts for approximately 90% of diabetes mellitus cases worldwide and is not dependent on the hormone insulin. This condition, which is characterised by hyperglycaemia, occurs as a result of insulin resistance. However, T1DM occurs due to autoimmune

destruction of insulin-producing beta cells in the pancreas.¹ Moreover, there are differences in the risk factors for both types. T1DM is more likely to develop in children and often there is a family history present. T2DM is more likely to affect overweight adults over the age of 45 and again, there is usually a family history present.²

Those with T2DM are also prone to various complications. There is an increased risk of heart

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conditions such as stroke, myocardial infarctions and peripheral artery disease. This is due to high levels of blood glucose damaging blood vessels. As mentioned, T2DM is associated with increased weight and age; both factors resulting in heart disease. Subsequently, heart disease is the leading cause of death for type 2 diabetics. Another major complication of T2DM is diabetic nephropathy leading to a gradual decline in kidney function. Diabetic retinopathy is another complication and can lead to gradual vision loss. Individuals may also experience diabetic neuropathy associated with nerve damage.³ It is clear that without preventive measures, T2DM can seriously reduce quality of life for affected individuals.

The incidence of diabetes is escalating at a concerning pace worldwide, posing a major public health dilemma. In 2021, approximately 537 million adults were diagnosed with diabetes, accounting for 10.5% of the global adult demographic. Forecasts suggest that this figure may rise to 783 million by 2045.⁴ Compounding the situation, nearly half of those affected remain undiagnosed, especially in low- and middle-income countries (LMICs), where access to healthcare is often restricted. Additionally, T2DM imposes a significant economic strain, with healthcare expenditures surpassing \$966 billion annually.^{5,6}

The global challenge encompasses not only the management of the increasing case numbers but also the need to rectify disparities in access to care, early diagnosis, and preventive measures. A high body mass index (BMI) continues to be the primary modifiable risk factor; however, initiatives to address this must take into account socioeconomic and structural obstacles, particularly in LMICs. Implementing policies that promote healthier lifestyles and strengthen healthcare systems is essential to mitigate this crisis.⁷

To confront these challenges, international health organizations, such as the World Health Organisation and the International Diabetes Federation, advocate for comprehensive strategies that prioritize prevention, early detection, and equitable healthcare access.⁷

This research aims to explore the global trends in T2DM prevalence, the obstacles to effective management, and the progress in therapeutic and technological innovations. The review concludes by underscoring the necessity for global collaboration to combat the disease and enhance healthcare equity.

Global Prevalence and Incidence of T2D:

Type 2 diabetes mellitus (T2D) has emerged as one of the most pressing global health challenges of the 21st century. According to the International Diabetes Federation,⁸ over 540 million adults (aged between

20-79) were living with diabetes as of 2021, with T2D comprising approximately 90% of these cases. This prevalence represents a significant increase from past decades, signalling an escalating global crisis. Without effective interventions, the IDF projects the number to exceed 783 million by 2045. The surge in T2D cases is driven by a complex interplay of factors, including aging populations, urbanization, and lifestyle changes such as dietary shifts and reduced physical activity.

The incidence of T2D also reflects disparities in socioeconomic conditions and healthcare systems. While high-income countries (HICs) report a stabilization of new cases, thanks to improved awareness, preventive measures, and better healthcare infrastructure; low- and middle-income countries (LMICs) are experiencing an alarming rise. These variations highlight the need for tailored approaches to prevention and management based on regional contexts and resources.

The prevalence and impact of T2D vary considerably between regions, revealing stark contrasts between high-income and low-income countries.

- **High-Income Countries (HICs):** Nations in North America, Western Europe, and parts of Oceania have historically reported higher T2D prevalence rates due to obesity, aging populations, and sedentary lifestyles. While the overall burden remains significant, the incidence in these regions has shown signs of plateauing. Enhanced public health initiatives, such as community-based interventions promoting physical activity and healthy diets, have played a critical role. Additionally, improved healthcare access and early diagnosis have mitigated the progression of the disease. Despite this stabilization, the economic burden remains disproportionately high, as managing diabetes-related complications requires substantial resources.
- **Low- and Middle-Income Countries (LMICs):** The sharpest increases in T2D cases are observed in regions such as Southeast Asia, Sub-Saharan Africa, and parts of South America. In 2013, LMIC contributed 77% of people living with diabetes and the prevalence is projected to increase.⁹

Urbanization, industrialization, and dietary transitions are major drivers of this trend. For example, the growing availability and affordability of energy-dense, nutrient-poor processed foods have contributed to higher rates of obesity and metabolic disorders in these regions.

Coupled with limited access to healthcare services and lack of awareness, many cases of diabetes go undiagnosed or are diagnosed late, resulting in severe

complications and increased mortality. Patients may not be able to manage their diabetes well and this can lead to preventable complications.¹⁰

Additionally, cultural factors, such as preferences for high-carbohydrate staple foods and reduced emphasis on physical activity, exacerbate the problem.

There is a trend in low income countries where increasing wealth and education correlate to increasing diabetes risk – this is in contrast to high income countries where lower levels of education increase risk of diabetes.¹¹

- **Genetic and Ethnic Considerations:** In regions like South Asia and the Middle East, genetic predispositions increase vulnerability to T2D, even at lower body mass indices.¹²

Individuals with a first-degree relative affected by type 2 diabetes exhibit approximately a threefold increased risk of developing the condition compared to those without a positive family history. It is possible that epigenetic changes such as histone acetylation, DNA modification and non-coding RNA are responsible for some of the heritability of T2D, and increased prevalence in these regions may lead to a cycle of greater risk.

The contrast between these regions underscores the inequities in health outcomes and the need for globally coordinated but locally tailored strategies to curb the rising burden of T2D.

Risk Factors for T2D:

Understanding the primary risk factors for T2D is essential for designing effective prevention strategies. While the interplay of genetic, environmental, and lifestyle factors varies, several universal drivers have been identified:

1. **Obesity and Sedentary Lifestyles:** Obesity is the leading modifiable risk factor for T2D. According to the World Health Organization global obesity rates in adults have doubled since 1990 and in adolescents it has increased by a factor of 4.⁵ The proliferation of sedentary lifestyles, characterized by reduced physical activity and increased screen time, further contributes to insulin resistance and glucose intolerance. Urbanization has amplified these issues, with many individuals adopting car-dependent transportation and desk-bound jobs.
2. **Dietary Changes:** The transition from traditional diets rich in fiber and plant-based foods to modern diets high in refined sugars, fats, and processed foods has significantly increased the prevalence of obesity and metabolic syndrome, both of which are precursors to T2D. This phenomenon is particularly pronounced in urban areas of LMICs.

Genetics and Family History: Genetic predisposition plays a pivotal role in T2D risk. Individuals with a family history of diabetes, particularly those of South Asian, Hispanic, or African ancestry, face heightened susceptibility. For example, South Asians exhibit a predisposition to abdominal obesity and insulin resistance, even at relatively low body weights. Certain genetic markers like TCF7L2 are risk factors for T2D however, it must be noted that traditional markers like BMI are more accurate predictors.¹³

3. **Socioeconomic and Environmental Factors:** Poverty and limited access to healthcare exacerbate T2D prevalence in LMICs. Poor communities are often “food deserts,” where nutritious options are scarce, and unhealthy processed foods dominate. Furthermore, inadequate healthcare systems delay diagnosis and treatment, leading to higher rates of complications. Programmes focused on tackling issues like poor diet and lack of physical activity in LMICs have shown promise in reducing T2 diabetic risk.¹⁴
4. **Aging Populations:** With increasing life expectancy, the proportion of older adults—a group inherently at higher risk for T2D—is growing. This demographic shift has been a significant driver of diabetes prevalence, particularly in HICs.¹⁵
5. **Urbanization:** As rural populations migrate to cities; lifestyle changes occur rapidly. Urban environments often encourage high-calorie diets and reduced physical activity, accelerating the risk of developing T2D. Moreover, urban settings frequently lack sufficient infrastructure to promote healthy behaviors, such as parks or safe walking paths.
6. **Other Emerging Factors:** Recent studies highlight the role of environmental pollutants, stress, and sleep disturbances in increasing T2D risk. These factors are becoming increasingly relevant as modernization and industrialization progress.

The interplay of these factors highlights the complexity of addressing the T2D epidemic. Multifaceted approaches combining public health policies, community education, and individual behaviour changes are necessary to mitigate the disease’s growing burden.

Healthcare Access and Systemic Issues

One of the biggest obstacles in managing T2DM is unjust access to health services, especially in LMICs. More than one in five people with diabetes lives in an

LMIC, according to the International Diabetes Federation (IDF), with medical systems lagging behind and drugs used to treat diabetes, including insulin, not readily available.¹⁶ Also, rising healthcare costs in developed countries perpetuate treatment disparities by making it difficult to access even in resource-constrained environments.

Socio-Economic Inequality:

Economic inequalities are important in affecting diabetes. There is evidence that poorer people are diagnosed later on due to financial barriers, at this point they present with severe side effects including neuropathy and retinopathy.¹⁷ Furthermore, good foods and opportunities for exercise may be limited for the poor, leading to more recourse to high-calorie, low-nutrient diets that make glycaemic control worse.

Diabetes Management: Cultural and Behavioural Factors

Cultural beliefs and practices affect the diabetes management. For instance, in many communities, diabetes diagnosis is stigmatized, and patients are told to keep it a secret or to not seek medical care.¹⁸ Other times, folk remedies take priority over scientific interventions and treatment is slacked off. Behavioural resistance (not taking medications and lifestyle changes prescribed) is another important factor, often caused by lack of knowledge about diabetes and complications.

Psychological Resilience:

Among the psychosocial issues, these include diabetes pain and depression, which are becoming more and more evident as major inhibitors of control. A meta-analysis revealed that depression affects diabetes care compliance in nearly one in three patients with T2D.¹⁹ The absence of mental health services in healthcare systems makes these difficulties only worse, leading to a demand for diabetes and mental health care together.

Lack of policies and awareness:

Despite the world's burden of diabetes, policy actions are not in place everywhere. National diabetes programmes are either not available or poorly funded in many LMICs due to a lack of economic resources. Furthermore, most public health initiatives are not extended to rural and underserved communities where diabetes rates are on the rise.²⁰ There needs to be more effective pressure on to put diabetes care first and allocate resources more justly.

Successfully treating Type 2 Diabetes Mellitus means closing the access to healthcare loopholes at multiple levels, from socioeconomic inequities to stigma. Mental health care should be integrated, and more robust

policy responses encouraged to address these barriers as well. Governments, health workers, and citizens need to collaborate in order to provide diabetes care that is both fair and sustainable.

Advances and Future Perspectives in Management:

Introduction

Diabetes currently has a broad range of treatment options; however each has their own complications, these can include side effects, application method, ease of access or associated costs. Development of treatments target reduction of diabetes incidence and reduce the implication of complications on quality of life.²¹

Pharmacological advances:

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of medications which treat type 2 diabetes by amplifying glucose-dependent insulin secretion, reducing glucagon secretion post-meal.²² Recent advancements focused on increasing compliance to the drug as well as ease of administration. Long-acting GLP-1 analogues, mainly semaglutide, are designed for once-weekly administration.²² Their prolonged action is achieved through increased albumin affinity as well as stability against metabolic degradation.²²

SGLT2 inhibitors

Sodium-glucose cotransported-2 inhibitors (SGLT2 inhibitors) block reabsorption of glucose in the kidneys, leading to increased glucose excretion via urine. This treats type 2 diabetes by lowering blood glucose independently of insulin.²³ Modern advancements have focused on improving cardiovascular and renal outcomes in patients who are prescribed SGLT2 inhibitors, where clinical trials demonstrated weight loss and reduced blood pressure.²⁴ Although SGLT2 inhibitors already provide renal and cardiovascular protection, maximising this and reducing side effects simultaneously enhances their therapeutic potential.²⁵

Metformin

Metformin is the preferred first-line management of type 2 diabetes and treatment with it begun in 1957.²⁶ Metformin is plagued with side effects and constraints to metformin bioavailability, leading to its underutilisation.²⁷

Fast-dissolving tablets provide an alternative route of administration for patients with difficulty swallowing, it allows for rapid disintegration and absorption of metformin in the mouth. To combat the low bioavailability of oral metformin, micro and nanoparticles were developed, allowing for enhanced metformin stability and bioavailability, this is essential

in allowing for its controlled and sustained release.²⁷

Microneedles are another invention which aims to improve compliance to metformin treatment, providing a minimally invasive transdermal delivery and bypassing the gastrointestinal tract (GI), avoiding any common GI side effects.²⁷ All these delivery systems aim to increase compliance of metformin, whilst also enhancing the bioavailability of metformin, meaning an improved pharmacokinetic profile.

Technological innovations:

Continuous Glucose Monitoring (CGM)

CGM is a technology allowing for real-time monitoring of glucose in the interstitial fluid, it is done using a subcutaneous sensor which measures glucose levels every few minutes.²⁸ It initially set out to work co-operatively with insulin pumps in patients with type 1 diabetes, however, has developed over time to work in patients with type 2 diabetes. In patients with type 2 diabetes, CGM allows for better self-management and compliance to their treatment.²⁸ Clinical studies demonstrated that CGM was more effective than self-monitoring of blood glucose, where HbA1c levels (average blood sugar over the last two to three months) were reduced with CGM.²⁸

Use of Artificial Intelligence in the Management of Type 2 Diabetes

Artificial Intelligence (AI) has a range of capabilities in improving management of type 2 diabetes. Even before onset, AI can be used to predict diabetes, enabling early intervention, important for public health.²⁹ AI driven tools can be a great asset for patients by adjusting medication dosages in real time based on CGM, further reducing risk of complications. Furthermore, AI can assist in managing modifiable risk factors, including diet and exercise plans, catering to individual needs.²⁹ In conclusion AI can have a great impact in improving patient outcomes, enhancing adherence to treatment protocols, as well as minimising overall costs.

Global initiatives and policy recommendations

The World Health Organisation (WHO) launched the Global Diabetes Compact aimed at reducing the risk of diabetes, whilst also ensuring unbiased, affordable and quality care across the world.³⁰ Its focus in integrating diabetes care into primary healthcare, utilising technologies such as CGM and promoting public health policies for the prevention of diabetes through lifestyle changes.³⁰ The initiative aims to utilising medical advancements and aims for collaboration with the hopeful outcome of a reduction in global diabetes burden.

NICE (National Institute for Health and Care Excellence) guidelines stress the requirement of personalised care plans based on individual preferences, comorbidities and risks from polypharmacy.³¹ Their recommendation is a structured education which can be used worldwide, aiming for improved adherence and self-management.³¹ These policies also promote the use of CGMs, and AI based tools to improve quality of care and reduce chances of long-term complications.

Discussion:

Key Findings and Interconnections

This paper has examined the multifaceted global challenge posed by type 2 diabetes mellitus (T2DM), highlighting critical aspects such as epidemiological trends, barriers to effective management, and recent advancements in treatment and prevention.

1. *Epidemiological Trends:* The global prevalence of T2DM has reached alarming levels, with over 540 million adults affected in 2021, a number projected to exceed 700 million by 2045.⁵ While high-income countries have seen stabilization in incidence rates due to improved public health measures, LMICs are witnessing rapid increases driven by urbanization, dietary transitions, and population aging.³²
2. *Barriers to Management:* Key challenges include the socioeconomic burden of treatment, healthcare system inefficiencies, and patient-level barriers such as medication non-adherence and low health literacy.³³ These barriers are interconnected, creating a cycle of poor disease management and adverse outcomes, especially in resource-limited settings.³⁴
3. *Advances in Management:* Innovations in pharmacological treatments, such as GLP-1 receptor agonists and SGLT2 inhibitors, have demonstrated efficacy in improving glycemic control and reducing cardiovascular risks.³⁵ Additionally, technological advancements like continuous glucose monitoring (CGM) systems and AI-driven tools are transforming diabetes management by enabling personalized care and early intervention.³⁶

Implications for Public Health and Clinical Practice

The findings underscore several implications for public health and clinical practice:

- *Strengthening Policies:* Governments and policymakers must implement robust policies to address the root causes of T2DM, such as obesity and sedentary lifestyles. Policies should promote

healthy eating, physical activity, and urban planning conducive to wellness.³⁷

- *Improving Healthcare Systems:* Investments in healthcare infrastructure, workforce training, and the availability of affordable medications are essential. Strengthening primary healthcare systems can enhance early diagnosis and long-term management.³⁸
- *Fostering Community Engagement:* Public health campaigns tailored to local cultural contexts can improve health literacy, reduce stigma, and empower communities to adopt healthier lifestyles. Engaging community leaders and leveraging grassroots efforts are critical for sustainable impact.⁶
- *Adopting Integrated Care Models:* Coordinated care models that link primary, secondary, and tertiary care settings are needed to streamline patient management and improve outcomes. Incorporating digital tools into these models can enhance efficiency and accessibility.³⁶
- *Equity in Care Delivery:* Addressing social determinants of health, such as poverty and education disparities, is crucial to reducing the disproportionate impact of T2DM on marginalized populations.³³

Future Directions:

Future strategies should emphasize:

- *Innovative Research:* Further research into the genetic and environmental factors driving T2DM can inform targeted preventive measures and therapies.³²
- *Sustainability:* Interventions must balance immediate needs with long-term goals, ensuring that programs remain adaptable and resource-efficient.³⁷
- *Global Collaboration:* International initiatives, such as the WHO Global Diabetes Compact, provide a foundation for addressing T2DM collectively. Cooperation between governments, NGOs, and the private sector is essential for scaling solutions and ensuring equitable distribution (WHO, 2021).³⁷

Conclusion:

The Urgent Need for Global Action

The escalating prevalence of T2DM underscores the need for coordinated, multi-sectoral action. Beyond being a medical condition, T2DM is a socioeconomic issue that exacerbates health disparities and imposes a heavy burden on individuals and healthcare systems globally. The disproportionate impact on LMICs further

highlights the need for targeted and equitable interventions.

Call to Action:

A unified response is required from healthcare professionals, policymakers, researchers, and community leaders:

1. *Healthcare Professionals:* Practitioners must integrate evidence-based approaches, such as personalized medicine and advanced technologies, into routine care. Patient education and empathetic communication are critical to fostering adherence and improving outcomes.³⁶
2. *Policymakers:* Governments must prioritize diabetes prevention and management through public health initiatives, subsidies for essential medications, and the establishment of supportive healthcare infrastructure.³⁷
3. *Researchers:* Continued exploration of the genetic, metabolic, and environmental underpinnings of T2DM is vital. Interdisciplinary research can bridge biomedical advances with social and behavioral insights.³²
4. *Community Leaders:* Local leaders and organizations must spearhead initiatives to address cultural and societal barriers, promoting awareness and early intervention in vulnerable populations.⁴

Building Sustainable Solutions:

To ensure long-term success, interventions must:

1. Focus on prevention, addressing root causes such as obesity and inactivity.
2. Be adaptable to demographic and cultural changes.
3. Leverage global frameworks like the WHO Global Diabetes Compact to foster international cooperation.³⁷

Final Thoughts:

The rising tide of T2DM demands immediate, comprehensive action. Advances in science, technology, and policy offer a roadmap for tackling this epidemic. By embracing equity and sustainability, the global community can mitigate the impact of T2DM, improve quality of life for millions, and build resilient healthcare systems for future challenges. The time to act is now.

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ORIGINAL ARTICLE

PREDICTING FACTORS FOR DELAYED HOSPITAL ARRIVAL OF ACUTE STROKE PATIENTS

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Abstract:

Background: Delayed hospital arrival following acute stroke is one of the important influencing factors for morbidity and mortality. The aim of the study was to identify the risk factors associated with hospital-delayed arrival among stroke patients. **Methods:** This cross-sectional study was carried out in the Department of Medicine, DMCH, for a 12-month period following ethical approval. After giving informed written consent, 311 patients with acute stroke were included in the study. Data were collected using a semi-structured questionnaire and direct interview and analyzed using SPSS-20. **Results:** Among 311 stroke patients, 134 were in the early arrival group, and 177 were in the late arrival group. In our cross-sectional study, age did not significantly impact arrival time ($p = 0.491$). A significant relationship was found between residence and arrival time ($p = 0.010$), with rural residents more likely to arrive late than semi-urban residents ($OR = 0.720$). Education level did not significantly affect arrival time ($p = 0.576$), but those with secondary education had higher odds of delayed arrival than those with higher education ($OR = 32.242$). Chronic conditions such as cardiac failure ($p = 0.523$), previous stroke ($p = 0.577$), diabetes ($p = 0.273$), hypertension ($p = 0.620$), and malignancy ($p = 0.677$) did not significantly influence arrival time. However, chronic obstructive pulmonary disease (COPD) was significantly associated with delayed hospital arrival ($p = 0.020$, $OR = 4.533$). Stroke symptoms played a critical role, with patients experiencing aphasia ($p = 0.061$, $OR = 3.759$) and dysarthria ($p = 0.002$, $OR = 2.814$) more likely to arrive late. At the same time, those with hemiparesis were less likely to arrive late ($p = 0.000$, $OR = 0.113$). Patients residing more than 15 km from the hospital were more likely to arrive late, and factors such as traffic jams, indecision about hospitalization, and mode of transportation contributed to delays. Notably, patients with knowledge about stroke were significantly less likely to arrive late ($p = 0.000$, $OR = 0.351$), and those living within 5 km from the hospital also had a reduced likelihood of late arrival ($p = 0.000$, $OR = 0.036$). Indecision about hospitalization significantly predicted late arrival ($p = 0.000$, $OR = 10.653$). Additionally, patients with hemianopia had lower odds of delayed arrival ($p = 0.014$, $OR = 0.074$), and those living within 5-15 km had reduced odds compared to those living more than 15 km away ($p = 0.010$, $OR = 0.364$). **Conclusion:** Symptoms of stroke, as well as sociodemographic factors, significantly affected hospital arrival on time. Proper strategy and planning should be applied to enhance people's knowledge of stroke to decrease the unfavorable outcome.

Keywords: predicting factors, delayed hospital arrival, acute stroke patients

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Introduction:

Stroke is a leading cause of death and disability worldwide. According to GBD 2019 stroke collaborators, stroke costs more than US\$891 billion globally (1.12% of global GDP).¹ The incidence of stroke is 11.39 per 1000 people in Bangladesh.²

Shortening the time between the onset of stroke symptoms and hospital admission can improve the likelihood that patients will get thrombolytic therapy or other critical treatments that can avert complications. Both ischemic and hemorrhagic strokes fall under this category. As a result, early intervention can lower the chance of morbidity and death. Previous research³⁻⁸ has examined the variables that may lead to delayed arrival times for stroke patients in several nations, including Bangladesh, Spain, and Nepal. These include things like living alone, the time the stroke started, age, gender, education, where the patient arrived at the hospital, income, the distance to the hospital, the symptoms of the stroke, risk factors, consciousness level, the method of transportation to the hospital, contacts with nearby medical professionals, and the general public's awareness of stroke.

Understanding and identifying these factors contributing to delayed arrival is important for optimizing pre-hospital and in-hospital stroke care protocols, ultimately improving patient outcomes and reducing the burden of stroke-related morbidity and mortality.

Little research has been done on the effects of delayed arrival variables on hospital outcomes for stroke patients. A new study looked at how stroke patients in Bangladesh responded to their symptoms, how soon they got to the hospital, and what was causing them to come later than expected.

Identifying and understanding the barriers to timely hospital arrival—whether they stem from patient characteristics, socio-economic factors, geographical challenges, or healthcare system inefficiencies—can inform targeted public health interventions, enhance emergency response systems, reduce mortality and morbidity, guide resource allocation, highlight healthcare disparities, and direct future research.

The study's objective was to determine the factors associated with delayed hospital arrival in patients with acute stroke.

Methods:

Study population:

The study was designed as a cross-sectional study conducted at the Department of Medicine, Dhaka Medical College, Dhaka, Bangladesh, from November 2022 to October 2023. The study population included stroke patients who attended the Department of Medicine at Dhaka Medical College Hospital. Consecutive sampling was employed to select participants. Given the lack of prior studies on the prevalence of factors contributing to delayed hospital arrival among acute stroke patients in Bangladesh, the prevalence was estimated at 56.4% based on similar international studies.⁸ Using the statistical formula for sample size calculation ($n = Z^2pq/d^2$) with a 95% confidence interval, a sample size of 378 was determined. However, 311 patients were ultimately enrolled during the study period. The study included participants who provided informed consent, were over 18 years of age, and were clinically diagnosed with stroke, confirmed by either Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI). Stroke mimics, intracerebral malignancies, and recurrent stroke were excluded from enrollment.

All patients admitted to the Medicine department of Dhaka Medical College Hospital from November 2022 to October 2023 presented with stroke symptoms compatible with neuroimaging and were diagnosed as having stroke were interviewed. Informed Written consent was taken from all patients or their attendants. Patients with in-hospital strokes and those with stroke mimics were excluded. In addition, if patients have communication deficits, a caregiver who resides with the patient has given consent and is interviewed.

Stroke onset time was noted as the time of appearance of stroke symptoms. In the wake-up strokes, the moment when the patient was last seen as healthy was evaluated as the stroke onset time. A questionnaire was filled in by face-to-face interview with each patient or the relative who agreed to participate in the study regarding stroke symptom onset, hospital arrival time, age, gender, level of education and financial status, and stroke severity at arrival.

The distance patients covered during hospital arrival was determined using regional road maps. The educational levels of the patients were classified as Primary, Secondary, Higher Secondary, Graduate, and Post Graduates. Income status was grouped as low income, lower middle income, upper middle income,

and high income according to the patient's perceived economic situation.

Whether the hospital arrival was direct or from another hospital, previous knowledge of the patients and their relatives about stroke was questioned about previous thrombolytic therapy. As part of the neurological examination, the consciousness levels of the patients were determined as Conscious, Semi-Conscious, and Unconscious (somnolence /stupor). Stroke symptoms were recorded as aphasia, dysarthria, hemi anopsia, hemiparesis, and hemi sensory loss. In addition, vascular risk factors, hypertension, diabetes mellitus (DM), hyperlipidemia, coronary artery disease (CAD), atrial fibrillation (AF), smoking, and family history of stroke were determined. Transportation to the hospital by ambulance or other private vehicles was questioned. Hospital arrival time is divided into two groups: early (4.5 hours) and late arrival (> 4.5 hours).

Statistical Package for Social Sciences version 20.0 for Windows was employed to conduct statistical analyses. Qualitative observations were represented in frequencies and percentages, and cross-tabulation was used to analyze the data through the Chi-Square test with Yates correction (95% CI). Logistic regression was utilized to evaluate risk factors. A *statistically significant difference* was defined as $P < 0.05$.

Operational Definitions:

Hospital Arrival Time:

The total duration in hours is counted from the onset of stroke symptoms to admission to the emergency department, where the patient is examined by the emergency team (doctor/nurse). Early arrival means admission within 4.5 hours, and late arrival means admission after 4.5 hours.¹⁰

Hospital Arrival Time:

Total duration in hours counted from onset of stroke symptoms to admission to the emergency department, where the patient is examined by the emergency team (doctor/nurse). Early arrival means admission within 4.5 hours, and late arrival means admission after 4.5 hours.¹⁰

Results:

Most of the patients were between the ages of 41 and 80, with 39.2% aged 41-60 and 47.3% aged 61-80. A significant number of patients were came from rural areas (59.5%), followed by urban areas (30.5%) and semi-urban areas (10.0%). The education level of the participants was mostly primary education (74.0%), followed by secondary education (24.1%), and very few

had education beyond secondary (1.9%). The occupation distribution shows that a significant portion of the participants were housewives (29.9%) and others (36.3%), while fewer participants were engaged in service (12.9%) or business (20.9%). A small proportion of patients reported living alone (8.0%), while the majority did not (92.2%). (Table 1)

Table-1

Socio-demographic factors of the participant (n=311)

Variables	Characteristics	Number (%)
Age	18-40	27 (8.7)
	41-60	122(39.2)
	61-80	147(47.3)
	>80	15 (4.8)
Gender	Male	192 (61.73)
	Female	119(38.27)
Residence	Urban	95 (30.5)
	Rural	185(59.5)
	Semi urban	31 (10.0%)
Education	Primary	230(74.0)
	Secondary	75 (24.1)
	Higher secondary or above	6 (1.9)
Living	Alone	25 (8.0)
	Joined	286(92.2)
Occupation	Service	40 (12.9)
	Business	65 (20.9)
	Housewife	93 (29.9)
	Others	113(36.3)
Distance from hospital	<5 km	25(8.03)
	5-15Km	46(14.8)
	>15Km	240(77.17)
Family type	nuclear	102(32.8)
	Joint	209(67.2)

It was found that Hypertension and Diabetes Mellitus were highly prevalent among the participants, both of which are known risk factors for stroke. A significant majority of participants (80.4%) were diagnosed with hypertension, while 50.2% of them had diabetes mellitus. However, other health conditions such as COPD, chronic cardiac failure, previous cardiovascular disease, and malignancy were less common among the participants. Table II

Table-II

Distribution of participant according to comorbidities (n=311)

Name	Total
Chronic Cardiac Failure	8 (2.6%)
Previous CVD	4 (1.3%)
Chronic Renal Failure	5 (1.6%)
COPD	18 (5.9%)
DM	156 (50.2%)
HTN	250 (80.4%)
Malignancy	2 (0.6%)

Upon arriving at the hospital, the majority of patients were conscious (73.0%), while a significant portion were semi-conscious (24.1%), and a small percentage were unconscious (2.9%). Language impairment, in the form of aphasia, was observed in 19.0% of patients, while 13.9% experienced speech difficulty known as dysarthria. Visual field loss, specifically hemianopia, was present in only 1.9% of patients. However, the most common symptom was weakness on one side of the body, or hemiparesis, which affected most patients (84.2%). In contrast, a small number of patients experienced loss of sensation on one side of the body, or hemisensory loss (1.6%). These clinical findings also give idea about acute stroke patients, which can aid in their diagnosis and effective management. Table 3

Table-III

Participant according to clinical presentation (n=311)

Variables	Total
Conscious	227(73.0%)
Semi-conscious	75 (24.1%)
Unconscious	9 (2.9%)
Aphasia	59 (19.0%)
Dysarthria	43 (13.9%)
Hemianopia	6 (1.9%)
Hemiparesis	262 (84.2%)
Hemisensory loss	5 (1.6%)

Among all, 77% had distance of hospital above 15 km followed by 15% had 5 to 10km and 8% had below 5 km.

Among all the patients, 134 were in Early arrival (within 4.5 hour) group and 177 were in Late arrival (after 4.5 hour) group. Fig 4

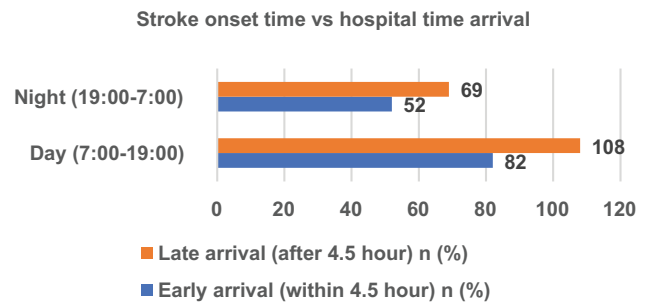


Figure 4: *Distribution of the patients according to time of hospital arrival (n=311)*

There was no significant impact of age on arrival time ($p=0.491$), although patients aged between 41-60 years and 61-80 years had a higher tendency to arrive late compared to those over 80 years ($OR=0.785$ and $OR=0.433$, respectively). In terms of residence, there was a clear relationship with arrival time ($p=0.010$), as rural residents were more likely to arrive late compared to semi-urban residents ($OR=0.720$). Although education level did not significantly influence arrival time ($p=0.576$), those with secondary education were more likely to arrive late than those with higher secondary education or above ($OR=32.242$). Family structure and living alone did not significantly affect arrival time ($p=0.378$ and $p=0.348$, respectively). Table 4

Chronic cardiac failure and previous stroke showed no significant association with arrival time ($p=0.523$ and $p=0.577$, respectively), with odds ratios of 5.073 and 0.577, respectively. Conversely, chronic obstructive pulmonary disease (COPD) demonstrated a significant association with delayed arrival ($p=0.020$, $OR=4.533$), indicating patients with COPD were more likely to arrive late. Diabetes mellitus (DM), hypertension (HTN), and malignancy did not exhibit significant associations with arrival time ($p=0.273$, $p=0.620$, and $p=0.677$, respectively), suggesting no substantial impact on arrival time. Table 5

Table-IV
Association of hospital arrival time with Socio-demographic factors of the study patients (n=311)

Variables	Early arrival (within 4.5 hour) n (%)	Late arrival (after 4.5 hour) n (%)	Total	p-value (*)	OR (95% CI)
Age (in years)				0.491	
18-40	11 (3.5%)	16 (5.1%)	27 (8.7%)		0.785 (0.081-7.584)
41-60	57 (18.3%)	65 (20.9%)	122 (39.2%)		0.740 (0.101-5.425)
61-80	62 (19.9%)	85 (27.3%)	147 (47.3%)		0.433 (0.061-3.056)
Male	77 (24.8%)	113 (36.5%)	190 (61.3%)	0.287	3.660 (0.639-20.950)
Residence				0.010 *	
Urban	52 (16.7%)	43 (13.8%)	95 (30.5%)		0.703 (0.193-2.564)
Rural	67 (21.5%)	118 (37.9%)	185 (59.5%)		0.720 (0.213-2.431)
Education				0.576	
Primary	98 (31.5%)	132 (42.4%)	230 (74.0%)		15.248 (0.599-388.157)
Secondary	32 (10.3%)	43 (13.8%)	75 (24.1%)		32.242 (1.33-779.60)*
Joint family	86 (27.7%)	122 (39.2%)	208 (66.9%)	0.378	1.853 (0.798-4.305)
Living alone	13 (4.2%)	12 (3.9%)	25 (8.0%)	0.348	1.069 (0.279-4.105)
Occupation				0.262	
Service	23 (7.4%)	17 (5.5%)	40 (12.9%)		0.175 (0.046 -0.671)*
Business	27 (8.7%)	38 (12.2%)	65 (20.9%)		0.230 (0.079-0.666)*
Housewife	39 (12.9%)	54 (17.4%)	93 (29.9%)		2.617 (0.676-10.137)

*Chi Square Test

Table-V
Association of hospital arrival with comorbidities (n=311)

Variables	Early arrival (within 4.5 hour) n (%)	Late arrival (after 4.5 hour) n (%)	Total	p-value (chi-square)	OR (95% CI)
Chronic Cardiac Failure	3 (1.0%)	5 (1.6%)	8 (2.6%)	0.523	5.073 (0.325-79.111)
Previous stroke	2 (0.6%)	2 (0.6%)	4 (1.3%)	0.577	0.577 (0.036-9.230)
Chronic renal Failure	1 (0.3%)	4 (1.3%)	5 (1.6%)	0.285	1.865 (0.145-24.053)
COPD	3 (1.0%)	15 (4.9%)	18 (5.9%)	0.020*	4.533 (0.774-26.567)
DM	72 (23.2%)	84 (27.0%)	156 (50.2%)	0.273	0.621 (0.295-1.308)
HTN	106 (34.1%)	144 (46.3%)	250 (80.4%)	0.620	1.586 (0.610-4.123)
Malignancy		1 (0.3%)	2 (0.6%)	0.677	0.722 (0.026-20.336)

*Chi Square Test

The symptoms of stroke were found to play a significant role in the timing of hospital arrival. Patients who experienced aphasia and dysarthria were more likely to arrive late (p=0.061, OR=3.759 and p=0.002, OR=2.814, respectively), while those

with hemiparesis were less likely to arrive late (p=0.000, OR=0.113). Interestingly, patients who experienced a loss of chemosensory function were significantly more likely to arrive late (p=0.629, OR=69.256). Table 6

Table-VI
Association of hospital arrival time according to clinical presentation (n=311)

Variables	Early arrival (within 4.5 hour) n (%)	Late arrival (after 4.5 hour) n (%)	Total	p-value (chi-square)	OR (95% CI)
BP				0.768	
90/60-120/80	9 (2.9%)	14 (4.5%)	23 (7.4%)		1.980 (0.443-8.846)
<90/60	1 (0.3%)	3 (1.0%)	4 (1.3%)		0.219 (0.013-3.652)
Consciousness level				0.825	
Conscious	100 (32.2%)	127 (40.8%)	227 (73.0%)		1.626 (0.181-14.593)
Semi-conscious	30 (9.6%)	45 (14.5%)	75 (24.1%)		0.735 (0.084-6.405)
Stroke symptoms					
Aphasia	19 (6.1%)	40 (12.9%)	59 (19.0%)	0.061	3.759 (1.273-11.097)*
Dysarthria	9 (2.9%)	34 (11.0%)	43 (13.9%)	0.002*	2.814 (0.877-9.030)
Hemianopia	3 (1.0%)	3 (1.0%)	6 (1.9%)	0.520	0.041 (0.004-0.475)*
Hemiparesis	124 (39.9%)	138 (44.4%)	262 (84.2%)	0.000*	0.113 (0.029-0.446)*
Hemisensory loss	2 (0.6%)	3 (1.0%)	5 (1.6%)	0.629	69.256 (1.342-3574.072)*

*Chi Square Test

More than 50% of stroke patients lived more than 15km away from a hospital, faced traffic jams, and experienced indecision about hospitalization. Most patients chose to use an ambulance and directly admitted themselves to the hospital. Late arrival at the hospital was significantly associated with various factors, including lack of knowledge about stroke, indecision about hospitalization, traffic congestion, choice of transportation, and method of admission.

Patients with knowledge about stroke were significantly less likely to arrive late to the hospital than those who lacked knowledge (OR = 0.351, 95% CI: 0.134-0.916),

and this result was statistically significant (p = 0.000). Patients less than 5km from the hospital were also significantly less likely to arrive late (OR = 0.036, 95% CI: 0.006-0.224), with a statistically significant result (p = 0.000).

Patients who experienced indecision about hospitalization had significantly higher odds of arriving late (OR = 10.653, 95% CI: 3.953-28.708), and this result was statistically significant (p = 0.000). Patients directly admitted to the hospital had slightly higher odds of arriving late than those referred (OR = 1.148, 95% CI: 0.519-2.539), but the result was not significant statistically (p = 0.000). table 7

Table-VII
Risk factors for late hospital arrival time of acute stroke patients (n=311)

Variables	Early arrival (within 4.5 hour) n (%)	Late arrival (after 4.5 hour) n (%)	Total	p-value (*)	OR (95% CI)
Knowledge about stroke	54 (17.4%)	33 (10.6%)	87 (28.0%)	0.000*	0.351 (0.134-0.916)*
Low income	72 (23.2%)	107 (34.4%)	179 (57.6%)	0.235	0.508 (0.241-1.068)
Distance from hospital				0.000*	
<5 km	22 (7.1%)	3 (1.0%)	25 (8.0%)		0.036 (0.006-0.224)*
5-10 km	32 (10.3%)	16 (5.1%)	48 (15.4%)		0.479 (0.172-1.338)
Indecision regarding hospitalization	65 (21.0%)	151 (48.7%)	216 (69.7%)	0.000*	10.653 (3.953-28.708)*
Traffic jam	79 (25.5%)	139 (44.8%)	218 (70.3%)		0.000*
Private Transport	51 (16.4%)	40 (12.9%)	91 (29.3%)	0.004*	0.634 (0.179-2.241)
Ambulance	73 (23.5%)	109 (35.0%)	182 (58.5%)		0.434 (0.148-1.276)
Direct admission	86 (27.8%)	76 (24.6%)	162 (52.4%)	0.000*	1.148 (0.519-2.539)

*Chi Square Test

Patients with hemianopia (partial blindness in half of the visual field of one or both eyes) are less prone to arriving late at the hospital following a stroke onset compared to those without this condition. (OR = 0.074, 95% CI 0.009- 0.584, $p = 0.014$),

Patients residing within 5-15 km from the hospital also display lowered odds (OR = 0.364) of delayed arrival when compared to those residing more than 15 km away. This result is statistically significant as well ($p = 0.010$). Tabe VIII.

Table-VIII

Final logistic regression model results for relative odds of late arrival to the hospital after onset of stroke (n=311)

Variables	OR	95% CI	p-value(*)
COPD	4.201	0.990-17.826	0.052
Hemianopia	0.074	0.009-0.584	0.014
Hemiparesis Distance	0.123	0.039-0.390	<0.001
Distance from hospital			
<5km	0.081	0.019-0.350	0.001
5-15km	0.364	0.168-0.788	0.010
Indecision regarding hospitalization	5.319	2.845-9.942	<0.001

*Step wise Logistics Regression.

*Chi Square Test.

Discussion:

Prehospital delays are a significant variable that can influence the hospital's outcome as well as long-term morbidity for stroke patients.

The current study enrolled 311 stroke patients, of which 134 arrived early (within 4.5 hours) and 177 arrived late (after 4.5 hours). The study found that only facial deviation or weakness and speech abnormalities were associated with a lower prehospital delay among all the primary stroke symptoms. Other symptoms like headaches, limb weakness, and sensory abnormalities can be confused with other illnesses or mental disorders, leading to delays in seeking treatment.

In this study, age did not significantly affect arrival time, although patients aged 41-60 and 61-80 tended to arrive late more than those above 80. Males tended to arrive later than females, but this was not statistically significant. Rural people were more likely to arrive late than semi-urban residents. Education level did not significantly influence arrival time, although patients with secondary education tended to arrive late more than those with higher secondary

education or above. Family structure and living alone were not associated with arrival time. However, the patient's occupation was associated significantly with arrival time, as patients in the service and business sectors were less likely to arrive late than others.

A previous study⁸ found that Patients from rural areas were more hesitant to seek help, whereas age and gender were similar in both groups. On the other hand, the previous study⁹ Found that age was significantly associated with late hospital arrival and living alone at home. However, one study found no significant association of sociodemographic factors with hospital arrival except for residence.¹⁰

Lack of knowledge and indecision about hospitalization of stroke symptoms is one of the most common factors causing delay in hospitalization. Previous studies have suggested that early detection of stroke, knowledge of stroke treatment, education beyond high school, and prompt visits to the emergency room upon onset of symptoms can help reduce prehospital delays (7 A previous study by Fladt et al. also revealed that the main factors causing a delay were not knowing the signs of a stroke, visiting a family doctor before being admitted to the hospital, and not using emergency medical services (Fladt et al., 2019). Another study found that 32% of patients experienced a delay due to their attendant's inability to comprehend stroke symptoms.¹⁰

Bangladesh has a diverse population with varying socio-demographic, educational, and cultural backgrounds. A patient's ability to access and choose between different levels of hospital care is determined by their socio-economic status, which ultimately affects where they seek consultation, whether a tertiary care hospital or an underqualified healthcare provider. A previous study found that rural patients tend to delay hospitalizations more frequently. This may be because underqualified healthcare professionals provide primary care for rural residents, leading to management delays.¹² Additionally, low levels of education, unemployment, and unfavorable economic conditions are significant predictors of longer prehospital delays.¹³

The study investigated the relationship between various comorbidities and the arrival time of acute stroke patients at Dhaka Medical College Hospital. The study found that chronic cardiac failure and previous stroke were not significantly associated with arrival time ($p=0.523$ and $p=0.577$, respectively). However, chronic obstructive pulmonary disease (COPD) showed a significant association with delayed arrival ($p=0.020$, OR=4.533), indicating that patients with COPD were more likely to arrive late.

The comorbidities such as diabetes mellitus (DM), hypertension (HTN), and malignancy did not show any significant associations with arrival time ($p=0.273$, $p=0.620$, and $p=0.677$, respectively), suggesting that they did not have a substantial impact on arrival time. However, Fladt et al., 2019 found no significant association between HTN, DM, and other comorbidities with hospital arrival. Nepal et al. (2019) also observed no significant difference between HTN and hospital arrival besides DM and history of stroke, which are significantly associated with late arrival at the hospital.

On the other hand, study observed that all comorbidities are statistically similar in both groups.¹³

Acute ischemic stroke can be treated effectively with tissue plasminogen activator within 4.5 hours of onset. However, more than half of the patients miss the optimal treatment window period due to delayed presentation. According to a recent study, the delay was due to a long distance from the hospital, indecision regarding hospitalization, and traffic jams. In particular, more than 50% of the patients lived more than 15km from the hospital. Most of them chose ambulance transportation and were directly admitted to the hospital.

The study found that patients with hemianopia (a visual impairment affecting half the visual field) were less likely to arrive on time (OR=0.074, 95% CI 0.009-0.584, $p=0.014$). This could be due to the need for more awareness about sight loss and the fear of bringing patients to the hospital. However, the level of consciousness did not significantly affect arrival time ($p=0.825$). Patients with aphasia and dysarthria (speech and language impairments) were more likely to arrive late ($p=0.061$, OR=3.759 and $p=0.002$, OR=2.814, respectively). At the same time, those with hemiparesis (weakness on one side of the body) were less likely to arrive late ($p=0.000$, OR=0.113). Interestingly, patients with chemosensory loss (loss of smell or taste) were significantly more likely to arrive late ($p=0.629$, OR=69.256).

A previous study also found that several factors contributed to the delayed arrival of patients with acute ischemic stroke. According to multiple regression analysis, dysarthria, hemianopia, and hemiparesis were significantly associated with late arrival in the hospital.¹⁴

Patients with knowledge about stroke have significantly lower odds of late arrival compared to those without expertise (OR = 0.351, 95% CI: 0.134-0.916), and this result is statistically significant ($p = 0.000$).

Patients living less than 5 km from the hospital have significantly lower odds of late arrival compared to

those living more than 15 km away (OR = 0.036, 95% CI: 0.006-0.224), and this result is statistically significant ($p = 0.000$). Furthermore, individuals residing within proximity of less than 5 km from the hospital demonstrate substantially decreased odds (OR = 0.081, CI 0.019 to 0.350) of delayed arrival in comparison to those living over 15 km away. This finding holds statistical significance ($p = 0.001$).

A study by Ahsan et al. showed that patients who experience indecision about going to the hospital are significantly more likely to arrive late (delayed) than those who do not. The odds of delayed arrival are increased by a factor of 5.319 for patients indecisive about hospitalization. This outcome is highly statistically significant ($p < 0.001$). The study found that, on average, only 12% of patients arrive at the hospital within three hours. Of the causes of delayed arrival, indecision was the most significant factor, accounting for 40% of cases. Other factors included lack of transportation (22%), lack of resources (30%), traffic jams (10%), and consultation with rural doctors (30%).

Another study by Chowdhury and Chakraborty found that indecision and distance to the hospital were associated significantly with late arrival. Lack of public health measures, supply of ambulances, and low financial conditions were also contributing factors. Heavy traffic, which is common in densely populated areas, also plays a role in causing delays. The lack of awareness about stroke symptoms and their consequence was another reason for the delayed arrival. Some patients had not been taken to the hospital in an ambulance, had been alone when the stroke occurred, or were unaware that they had suffered a stroke, as also revealed by previous studies¹⁵.

Conclusion:

Prehospital delay is a major concern for stroke patients. In our study, there was a significant correlation found between late arrival at the hospital and residence, dysarthria, hemiparesis, hemianopia, indecision about hospitalization, and hospital distance. A person's knowledge of stroke, uncertainty about being admitted to the hospital, traffic congestion, mode of conveyance, and admission preference were all strongly linked to delay.

Conflict of Interest:

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

Funding:

This research received no external funding.

Ethical consideration:

The research protocol was presented to the Research

Review Committee (RRC) of the Department of Medicine, Dhaka Medical College. Subsequently, the protocol was submitted to the Ethical Review Board (ERB) for clearance. Before the commencement of the study, the Ethical Review Board of DMCH approved the thesis protocol.

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ORIGINAL ARTICLE

THE OUTBREAK OF DENGUE IN 2023 AT A PRIMARY HEALTH CARE CENTER, BANGLADESH

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Abstract:

Background: Dengue is an emerging arboviral infection caused by a flavivirus strain. All four serotypes are prevalent in Bangladesh. In 2023, Bangladesh experienced a severe upsurge of dengue resulting in high number of dengue-related deaths in Bangladesh. Several factors are associated with the increasing risk of the spread of the dengue epidemic in Bangladesh. **Methods:** This is a single-center, descriptive type of observational study. Total 940 confirmed dengue patients were considered the analytical sample for our study. The finalized data were imported into the statistical software (SPSS Version 25) for analysis and compared with clinical findings, measured BP level, IV fluid, antibiotic use, and outcome of the dengue patients. **Results:** In 2023, Bangladesh had the worst dengue outbreak including our study place. In our Upazila Health Complex, Mohammadpur, Magura, Khulna Bangladesh, in 2022 only 11 confirmed dengue cases were reported (0.2% of total admitted patients) and in 2024 the documented number was 101 (1.5% of total admitted patients) but in 2023 total of 1041 confirmed (940) and clinical dengue (101) patients (14% of total admitted patients) were treated as dengue. A total of 940 admitted confirmed dengue cases were included in the study. Male patients supersede females in number. All patients were symptomatic and 6.7% had co-morbidities. Out of 940 patients; 83.5 % (785) patients had dengue fever, 1.5 % (13) had dengue hemorrhagic fever, and 15 % (142) had dengue shock syndrome. Sex did not affect on clinical severity (p value=0.378). Most of the patients (64.1%) stayed less than 3 days in hospitals (CI at 95.0% level is 0.11). A total of 8.6% (81) patients developed complications during inpatients. Most (94.8%) of the admitted dengue patients were treated with IV fluids (p value=0.01). **Conclusion:** In 2023 Bangladesh faced a severe and unexpected outbreak of dengue infection. Male and young patients were mostly affected by dengue infection. Though there have been a large number of deaths in recent years, most of the patients recovered uneventfully.

Key words: Dengue fever, clinical severity, outcome, complication

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Introduction:

Dengue is an emerging arboviral infection caused by a flavivirus strain. The global incidence of dengue has markedly increased over the past two decades which leads to public health challenges. From 2000 to 2019, the World Health Organization (WHO) documented a ten-fold rise in reported cases worldwide increasing from 500,000 to 5.2 million. The year 2019 marked an unprecedented peak, with reported instances spreading across 129 countries. Several factors are associated with the increasing risk of spread of the dengue epidemic including, the changing distribution of the vectors (chiefly *Aedes aegypti* and *Aedes albopictus*), especially in previously dengue naïve countries and climate change leading to increasing temperatures and high rainfall, humidity among others; fragile health systems amid COVID-19 pandemic, political and financial instabilities in countries facing complex humanitarian crises and high population movements. These factors also challenge the response to the epidemic and the risk of further spread to other countries. “Weakness in the surveillance systems in many affected countries may have led to delayed reporting and response and missed identification of symptoms, contributing to increased severe dengue outcomes.” says WHO.

Dengue remains endemic since 2000 in Bangladesh. In 2023 Bangladesh faced a severe upsurge of dengue infection. Bangladesh witnessed a record-high number of dengue-related deaths in 2023.^{6,7} In 2023, over 320,000 confirmed dengue cases and 1,700 deaths reported in Bangladesh.⁹ Up to 31 December 2023, the Directorate General of Health Services (DGHS) website data revealed 321,179 hospitalizations and 1,705 deaths due to the *Aedes* mosquito-borne tropical disease outbreak and in the year of 2024 (January to 20 December 2024) a total of 99888 cases are detected in Bangladesh.^{10,11} *Aedes aegypti* is the primary vector. According to the WHO report published on 24 July 2024, increases in dengue cases were reported in Bangladesh. In Bangladesh overall, the total number of dengue cases for the period January to July 2024 remains lower than that reported for the same period in 2023 (4577 in 2024 as of 14 July compared to 20837 in 2023).

All four serotypes are circulating in Bangladesh. Infection with one serotype confers life-long immunity but a second infection with different serotypes is associated with an increased risk of severe disease. Previously it was thought that dengue was an urban disease but nowadays it is spreading everywhere in Bangladesh. Clinical case classification includes dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Definitive diagnosis of dengue

requires a positive NS1 or serologic examination (IgM, IgG antibody) in addition to clinical features.¹²

Magura is one among ten smallest districts of Bangladesh. Mohammadpur Upazilla of Magura district is also a smaller one in Bangladesh. People of this Upazilla also faced the Dengue epidemic with great surprise as Magura district of Bangladesh was regarded as a non-endemic for Dengue infection before 2022. Before the outbreak in 2023 Dengue was confined among the people coming from Dhaka and Saver areas but recent outbreak broke the trend, leading to disease among all kinds of local cultivating people of that area.

Methods:

This is a single-center; descriptive type of observational study conducted at Upazila health complex, Mohammadpur, Magura district of Khulna division, Bangladesh. Sampling technique was purposive and the inclusion criteria were all admitted clinical dengue patients who were positive NS1 or positive dengue IgM antibody. Data were collected from 1st August to 31 December 2023 and compared with previous and recent years. Information on all admitted confirmed dengue patients based on clinical features and positive NS1 or dengue IgM antibody in this facility were included in this study. The Authority/ institutional review board has approved this study and informed consent was taken from the patients. A total of 940 confirmed dengue patients out of 1041 admitted dengue patients (clinical and confirmed) were considered the analytical sample for our study. The information collected from the patients and their medical records were entered in the Microsoft Excel workbook by the researchers followed by reviewing the data for any necessary corrections. The finalized data were imported into the statistical software (SPSS Version 25) for analysis.

Patients were categorized into: age categories less than 15 years, 16-30 years, 31-45 years, 46-60 years, and more than 60 years. During the initial and subsequent consultations that were done on daily basis throughout their hospital stay, the patients also gave information related to comorbidities, duration of symptoms, and the in-hospital outcome of the patients. Clinical severity and grading were assessed by symptoms, hemorrhagic manifestations, documented measured blood pressure, and some laboratory parameters and categorized as dengue fever, dengue hemorrhagic fever, and dengue shock syndrome respectively. Clinical features including hemorrhagic manifestations, evidence of plasma leakage including rising Hct >20%, platelet count <100,000 cells/mm³, and measured blood pressure levels were categorized as dengue hemorrhagic fever or dengue shock syndrome.¹² Laboratory investigations were done on different time

of clinical presentations. Some patients were done on single time due to financial constraints and some patients were done several times. Hypotension by age, is defined as systolic pressure less than 80 mmHg for those aged <5 years or 80 to 90 mmHg for older children and adults and pulse pressure equal to or less than 20 mmHg with increased diastolic pressure.¹² We have also compared with clinical findings, measured BP level, IV fluid, antibiotic use, and outcome of the dengue patients.

To describe the characteristics of the study sample, we have categorized their demographic information, health status, and clinical findings associated with dengue fever, which were summarized as counts and percentages, and to assess their association using the significance level of $P < 0.05$ (in case of small sample size, less than 5, in the bivariate cells Fisher's exact test was used). Next, considered the measured blood pressure level and evidence of any kind of bleeding manifestation of the patient as a clinical severity marker and investigate a similar association between the results. We used SPSS, version 25, to perform the data management and statistical analysis.

Results:

A total of 940 confirmed admitted dengue patients out of total 1041 clinical (101) and confirmed (940) admitted dengue patients were evaluated. Among them 50.2 % (472) were male and 49.8 % (468) were female. 98.5 % (926) were Muslim and only 1.5 % (14) were Hindu. Age variation ranged from 1 to 90 years and the mean age was 34.19 ± 17.13 SD. Age groups were

divided into 1-15 years 13% (17), 16-30 years 35.5% (116), 31-45 years 28% (105), 46-60 years 16.5% (155) and more than 60 years 7% (66). Out of 940 patients, 6.7% (63) had comorbidities and the most common co-morbidities among the dengue patients were DM-38.09 % (24), HTN-15.87 % (10), IHD-9.52 % (6) and pregnancy were 23.8 % (15). 15.87% (10) patients had multiple co-morbidities. Co-morbidities affected hospital outcomes as referral to higher centre due to turn into severe dengue or development of complications though not statistically significant (p -value 0.132) but 7.9% of referred patients had co-morbidities and on the other hand, 3.4% of referred patients had no co-morbidities. All admitted patients were symptomatic and the most common symptoms during admission were fever (85%), nausea/vomiting (43.7%), bodyache (15%), headache (13.2%), diarrhea (10.2%). Out of 940 patients; 83.5 % (785) patients had dengue fever, 1.5 % (13) had dengue hemorrhagic fever, and 15 % (142) had dengue shock syndrome whose systolic blood pressure was <90 mmHg or pulse pressure equal or less than 20 mmHg. Interestingly age group more than 60 years had no hemorrhagic fever. 18.6% of clinically dengue shock syndrome patients were age group >31 to 45 years and 18.2 % were age group more than 60 years though age group had no significant relation on clinical severity (p -value=0.2). Sex did not affect on clinical severity (p -value=0.378). 15.3% of male and 15% of female patients were clinically dengue shock syndrome.

Age group and Grade: Cross tabulation

			Dengue fever	Dengue Haemorrhagic fever	Dengue shock syndrome	Total
Age group	1 to 15 years	Count	111	1	10	122
		% within Age_group	91.0%	0.8%	8.2%	100.0%
	16 to 30 years	Count	280	7	47	334
		% within Age_group	83.8%	2.1%	14.1%	100.0%
	31 to 45 years	Count	211	3	49	263
		% within Age_group	80.2%	1.1%	18.6%	100.0%
	46 to 60 years	Count	129	2	24	155
		% within Age_group	83.2%	1.3%	15.5%	100.0%
	>60 years	Count	54	0	12	66
		% within Age_group	81.8%	0.0%	18.2%	100.0%
Total	Count		785	13	142	940
	% within Age_group		83.5%	1.4%	15.1%	100.0%

Among the dengue hemorrhagic fever patients, 1.9% patients were male and 0.9% patient were female. Of those who presented with dengue shock syndrome, 15.9% had co-morbidities though statistically not significant $p=0.61$.

Comorbidity * Grade: Cross tabulation

			Dengue fever	Dengue Haemorrhagic fever	Dengue shock syndrome	Total
Comorbidity	no	Count	732	13	132	877
		% within comorbidity	83.5%	1.5%	15.1%	100.0%
	yes	Count	53	0	10	63
		% within comorbidity	84.1%	0.0%	15.9%	100.0%
Total	Count		785	13	142	940
	% within comorbidity		83.5%	1.4%	15.1%	100.0%

Regarding in-hospital stay, patients stayed from one to 15 days; most of the patients (64.1%) stayed less than 3 days and 33.7% of patients stayed from 4 to 7 days (Confidence Interval Level (95.0%) is 1.09). Male patients had more hospital stays than female patients (p value=0.04,).

Regarding in-hospital outcome, 86.5% (813) were recovered, 3.7% (35) were referred, 6.5% (61) were discharged on risk bond (DORB) and 1.5% (15) was discharged on request and 1.8% (17) was absconded. There was no death among the admitted patients during in hospital stay. Only 6.7% of admitted confirmed dengue patients had co-morbidities. Most of the patients (82.6%) were not been given antibiotics but 17.4% of patients were treated with antibiotics. The hospital documents showed the causes of antibiotic use were due to secondary infection and severe form of dengue fever with possible co-infection. Among the secondary infections, 26 patients had UTI, 13 patients had enteric fever, 7 patients had RTI, 2 patients had pneumonic consolidation and one patient had cellulitis. The result showed that 21.8% of dengue

shock syndrome, 15.4% of dengue hemorrhagic fever, and 16.7% of dengue fever patients were treated with antibiotics.

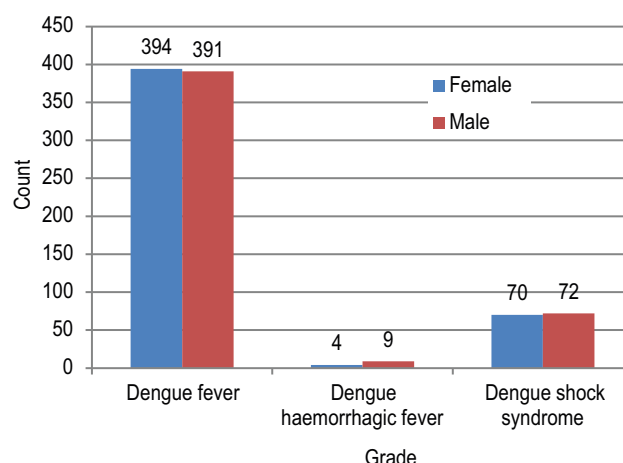


Fig 1: Grading of admitted dengue patients according to sex at UHC, Mohammadpur

Age group * Hospital Stay: Cross tabulation

			Hospital_Stay			Total	
			1 to 3 days	4 to 7 days	8 to 10 days	11 to 15 days	
Age group	1 to 15 years	Count	81	38	2	1	122
		% within Age_group	66.4%	31.1%	1.6%	0.8%	100.0%
	16 to 30 years	Count	227	102	5	0	334
		% within Age_group	68.0%	30.5%	1.5%	0.0%	100.0%
	31 to 45 years	Count	165	94	3	1	263
		% within Age_group	62.7%	35.7%	1.1%	0.4%	100.0%
	46 to 60 years	Count	93	57	3	2	155
		% within Age_group	60.0%	36.8%	1.9%	1.3%	100.0%
	>60 years	Count	37	26	2	1	66
% within Age_group		56.1%	39.4%	3.0%	1.5%	100.0%	
Total	Count		603	317	15	5	940
	% within Age_group		64.1%	33.7%	1.6%	0.5%	100.0%

Regarding in-hospital outcome, 86.5% (813) were recovered, 3.7% (35) were referred, 6.5% (61) were discharged on risk bond (DORB) and 1.5% (15) was discharged on request and 1.8% (17) was absconded. There was no death among the admitted patients during in hospital stay. Only 6.7% of admitted confirmed dengue patients had co-morbidities. Most of the patients (82.6%) were not been given antibiotics but 17.4% of patients were treated with antibiotics. The hospital documents showed the causes of antibiotic use were due to secondary infection and severe form of dengue fever with possible co-infection. Among the secondary infections, 26 patients had UTI, 13 patients had enteric fever, 7 patients had RTI, 2 patients had pneumonic consolidation and one patient had cellulitis. The result showed that 21.8% of dengue shock syndrome, 15.4% of dengue hemorrhagic fever, and 16.7% of dengue fever patients were treated with antibiotics.

Most (94.8%) of the admitted dengue patients were treated with IV fluids (p value=0.01) and only 5.2% of patients were treated without IV fluid. The age group had a significant relation ($p=0.05$) for requiring IV fluid; 98.5% of patients of the age group more than 60 years needed IV fluid, and 97.3 % of the age group 31-45 needed IV fluid. Due to the scarcity of IV fluid during the peak season of dengue, patients were managed with different types of fluids. 42% of patients were given only normal saline, and 28.3% were given 5% DNS only. 94.4% of female and 95.1% of male patients needed IV fluids. Regarding in-hospital complications; a total of 8.6% (81) patients had complications. Age group had an effect on complication though not statistically significant ($P=0.834$). Of those who belonged to the age group 46-60, 10.3% of patients developed complications. Complications are bleeding manifestations, ascites, pleural effusion, severe abdominal pain, acalculous cholecystitis, intestinal obstruction, electrolyte imbalance, and mumps. Six patients required blood transfusions due to active bleeding, severe anemia, and thrombocytopenia during in-hospital stay.

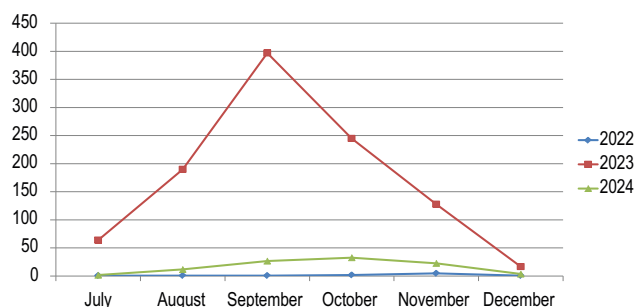


Fig.-2: The upsurge of dengue outbreaks in recent years at Mohammadpur Upazila health complex.

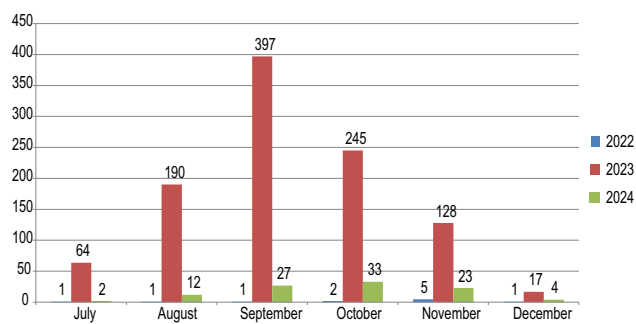


Fig.-3: Numbers of dengue cases detected at Upazila Health Complex in recent years

Discussion:

In 2023, Bangladesh experienced its worst dengue outbreak. My study place also had the outbreak of dengue in the year 2023. In 2022 from July to December only 11 patients (0.2% of total admitted) were confirmed dengue and in 2024 only 101 patients (1.5% of total admitted) were dengue patients but in 2023 total of 1041 (940 were confirmed and 101 were clinical dengue) patients (14% of total admitted) were treated as dengue patients.

In 2023 the highest number of dengue cases with the highest admission for the confirmed disease (n-940)

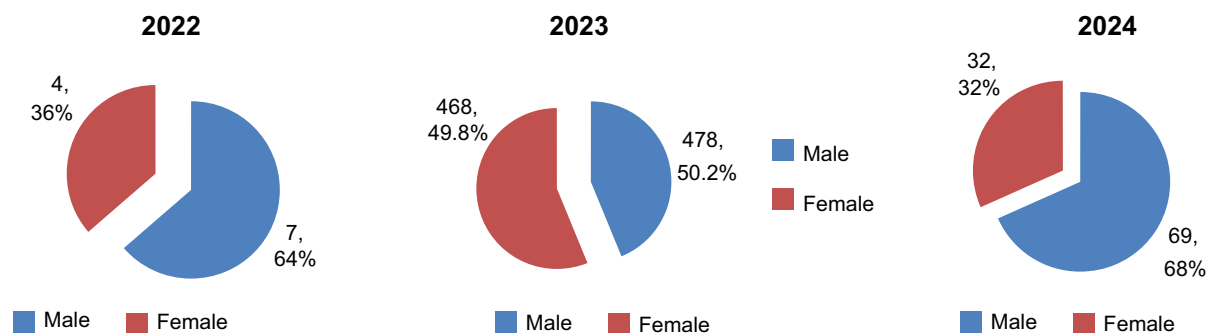


Fig 4: Number of dengue (Confirmed-940 and clinical-101) patients in recent years at UHC, Mohammadpur, Magura.

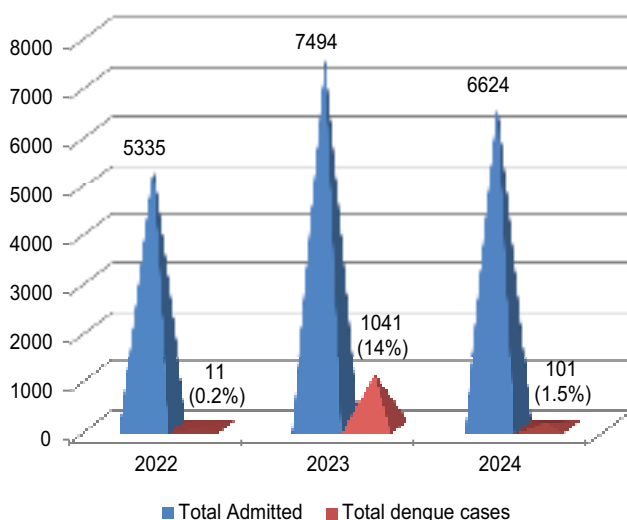


Fig.-5: Number of dengue patients (confirmed-940 and clinical-101) in relation to total admitted patients (July to December) at UHC, Mohammadpur, Magura

and the peak admission was in September and October, reflecting the similar finding of our national data of DHIS2 (District Health Information System). According to a review article by Samad et al all showed that the young adults were predominantly affected by dengue in Bangladesh.¹³ My study also showed that age groups 15-30 years are most affected (35.5%) followed by age group 31-45 years (28%) and age group >60 years are least affected (7%). Another study showed middle age group (21 to 30 years) was the most affected group followed by the 11 to 20 years age group and 31 to 40 years age group respectively and the older individuals (> 70 years) were found to be the least affected age group.¹ A study published in the BIRDEM journal showed that 7% had severe dengue² and my study found 16.5% had severe dengue classified as dengue hemorrhagic fever (1.5%) and dengue shock syndrome (15%). DSS was reported in up to 10% of cases (2023) compared to only 0.6% in the first outbreak in 2000- according to a review article on Dengue trends in Bangladesh by Samad et al.¹³ The proportion of males was persistently higher in all outbreaks but the recent outbreak is characterized by the presence of more female cases than the previous outbreaks. Trend analysis supports contracted male presence over time and it is statistically significant ($p = 0.0073$).³ Male predominance is also found in Indian studies and my study shows males predominance (52.8%).

Though antibiotics are not helpful for dengue patients a published article showed 547 (17.8%) out of 3078 patients that received antibiotics. In 10 (0.32%) cases the indication was due to recurrent shock and in 537

(17.5%) patients the indications of antibiotic administration were presumed concurrent bacterial infection.⁴ Our study shows 17.4% (164) were treated with antibiotics though it is a primary healthcare level where overuse of antibiotics is common. The most common causes of antibiotic use were secondary infection and severe forms of dengue fever. Regarding hospital stay, a study found out of 532 patients, two-thirds (72.6%) had stayed ≤ 3 days while one-third (27.4%) had stayed greater than 3 days⁵ and my study also shows most of the patients (64.15%) stayed less than 3 days. Male patients had more hospital stays than female patients.

Conclusion:

Dengue fever is no more an urban disease. Recently dengue presented as a fatal disease in Bangladesh and spreading to wide range non endemic areas of our country. Dengue fever is spreading to rural areas and affecting male and females equally. Young patients are mostly affected. Recent outbreak in rural areas presented with unusual presentation of systemic and abdominal symptoms. Commodities did not significantly affect the outcome in respect of hospital stay and severity

Limitations:

Study limitations include its observational nature. Additionally, patients admitted at different times of clinical presentation and outcomes of referred patients are not evaluated.

Conflict of Interest:

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

Funding:

No funding was received for conducting this study.

Ethical consideration:

The Institutional Authority/ institutional review board has approved this study and verbal informed consent was taken verbally from the patients.

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ORIGINAL ARTICLE

PREDIAGNOSTIC CLINICAL PRESENTATIONS AND ABNORMAL LABORATORY REPORTS IN PATIENTS OF COLORECTAL CARCINOMA: A 5 YEARS' EXPERIENCE FROM A TERTIARY CARE HOSPITAL OF BANGLADESH

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Abstract:

Background: Colorectal cancer (CRC) comprises a major public health issue globally. Understanding pre-diagnostic clinical features and abnormal laboratory reports in patients with Colo-rectal cancer could enlighten a way of opportunity for earlier diagnosis. This study was aimed to provide the pattern of relevant symptoms and abnormal laboratory results in patients with colorectal cancer before diagnosis. **Methods:** This cross sectional study held at department of gastroenterology of Rangpur medical College, Rangpur, Bangladesh from January 2019 to December 2023 over a 5 years period. Colonoscopy and histopathologically proven 1150 CRC patients were taken as study subjects. **Results:** Among the study subjects 73.47% (845) were male and 26.52% (305) were female. In the time before diagnosis of CRC, the most commonly observed symptom was abdominal pain 77.39%, (890) followed by altered bowel habit 46.95%, (540) among this study subjects. Other notable clinical features are Per rectal bleeding 20.69 % (238), abdominal lump 17.21% (198), Anemia/pallor 29.56 % (340) and weight loss in 23.21% (267). Laboratory reports of the patients before diagnosis were decreased hemoglobin in 47.04% (541) and high CRP in 65.56 % (754) and high ESR in 51.22%(589) patients. Stool examination shows RBC in 10.78 % (124) cases only. Ultrasonogram shows abdominal lump in 22.96% cases and SOL in liver in 12%. Plain X Ray abdomen shows acute and sub-acute intestinal obstruction in 11.30% cases. 217 (18.86%) patients presented within 6 months of symptom onset and 585 (50.86%) presented between 6 months to 02 years duration. About 35% of patients visited three or more physicians before diagnosis and rest (65%) of the study subjects consulted up to two physicians visit. **Conclusion:** From this study, it is evident that, if we will be aware of the CRC suggestive symptoms and laboratory reports, there is chance to promote referral for confirm diagnosis.

Keywords: Colorectal cancer (CRC), Pre diagnostic Clinical Presentations, Abnormal Laboratory Reports

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Introduction:

Colorectal cancer (CRC) comprises a major public health issue globally with an estimated 1.2 million new cases and with 630,000 deaths per year, reaches 8% amongst all cancer related mortality¹. Throughout the world this is the fourth most common cancer in male and the third most common in female². CRC is primarily known to be common in developed and Western countries. However, the clinico-pathological patterns of colorectal cancer have been shown to be different in various geographical regions of the world. Although in the western world colorectal cancer is a disease of elderly and presented at an earlier stages,^{3,4} colorectal cancer in Asian and African countries tends to present with advanced stages and shows poorer prognosis.^{5,6} The diagnostic stage of the CRC often destine the prognosis and survival rate of a patient, with the best outcomes seen when patients diagnosed at an initial stage. However, the consequences of treatment of colorectal cancer in our country have been poor because most of the patients present with advanced stage and only palliative care can be given at that time^{7,8}. This is partly due to lack of adequate data in this field as well as lack of public awareness about the significance of early diagnosis and treatment.

Throughout the world, at first most of the patients usually go to primary care physicians for their problem. Patients who experience alarm symptoms of colorectal cancer, including rectal bleeding, change in bowel habit, rectal or abdominal mass, and unexplained anemia can then be referred to a specialist for further evaluation.⁹ However, most patients do not face alarm symptoms before the diagnosis of colorectal cancer. Besides these many patients with colorectal cancer experienced non-specific symptoms such as bodyache, weight loss or fatigue before their diagnosis.¹⁰ They also visit other physicians for musculoskeletal, neurological, respiratory, endocrine dysfunction and for other non-specific symptoms.¹¹ These scenarios before diagnosis make a delay in timely diagnosis of CRC for most of the cases.

Based on previously reported data with colorectal cancer, blood test results for platelets, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and hemoglobin were analysed.¹² Reviewing of the literature, it was decided to take normal cut-offs values from reputed guidelines¹³

Understanding pre-diagnostic clinical features and abnormal laboratory reports in patients with CRC could enlighten a way of opportunity for early investigations and referrals and thus an earlier diagnosis of cancer could be possible.

Against this background, this study was aimed to provide a comprehensive and up-to-date description of the pattern of relevant symptoms and abnormal

laboratory results in patients with colorectal cancer before diagnosis, and to identify when first signals of possible colorectal cancer might occur, so that timely steps can be taken.

Methods:

This was a cross sectional study held at endoscopy unit of department of Gastroenterology of Rangpur medical College, Rangpur, Bangladesh from January 2019 to December 2023 over a 5 years period. Patients who were diagnosed as colorectal cancer on colonoscopy and confirmed by histopathology were taken as study subjects. A total of 1150 CRC patients aged between 18-90 years were included for the study during the study period by purposive sampling method. We excluded the patients who were negative on histopathological reports or who had a colorectal tumor as metastatic deposits. After enrolling the subjects, data were collected by a questionnaire mentioning previous clinical features and available laboratory investigations up to 02 years before diagnosis. The questionnaires were filled by a trained physician both by face to face interview and also reviewing of previous investigation reports.

Numbers and percentages are used to express qualitative data, and the chi-square test was performed to assess the relationship between variables. Quantitative data are expressed as mean $\pm$ standard deviation. Statistical analysis was performed using the SPSS (version 25; IBM Corp). Statistical significance was set at a p-value of ≤ 0.05 .

Ethical permission was taken from Ethical Review committee of Rangpur medical college(RMC/Rang/2024/2207-c). Informed written consent was also managed before enrolling each patient.

Results:

The study included 1150 patients with CRC, of whom 73.48% (845) were male and 26.52% (305) were female. More than half of the patients; 650 (56.52%) had an age at diagnosis ranging from 50 to 70 years. The majority of the CRC patient of this study have the following comorbidities; diabetes mellitus (10.17%), Hypertension(7.47%), IBS(20.17.%), IBD(2.08%), gall bladder diseases(3.05%) and hemorrhoids (7.73%). Family history were positive in 5.83 % of patients in our study. The duration of symptoms at presentation ranged from 06months to 2 years. 217 (18.86%) patients presented within 6 months of symptom onset and 585 (50.86%) presented between 6 months to 12 months duration. About 35% of patients visited three or more physicians visit before diagnosis and rest(65%) of the study subjects consulted up to two physicians visit.(Table-1)

Table-1
Clinico-demographic profile of the respondents:

Characteristics	Values	Number(n=1150)	Percentage(%)
Age at diagnosis(Years)	<50 years	189	16.43
	50-70 years	650	56.52
	>70 years	311	27.05
Gender	Male	845	73.48
	Female	305	26.52
Family History of CRC	Present	67	5.83
	Absent	1083	94.17
Comorbidities	Diabetes Miletus	117	10.17
	Hypertension	86	7.47
	Gall bladder diseases	35	3.04
	Irritable Bowel Syndrome	232	20.17
	Inflammatory Bowel Diseases	24	2.08
	Hemorrhoids	89	7.73
	None	567	49.30
Duration of symptom to diagnosis(Month)	<06	217	18.86
	06-12	585	50.86
	>12	348	30.26
Number of physician visits before diagnosis	≤02	748	65.04
	≥03	412	34.95

In the time before diagnosis of CRC, the most observed symptom was abdominal pain 77.39%, (890) followed by altered bowel habit 46.95%, (540) among this study subjects. Other notable clinical features are Per rectal Bleeding 20.69 % (238), abdominal lump 17.21% (198),

Anemia/pallor 29.56 % (340) and weight loss were in 23.21% (267). 11.65 % (134) of patients admitted in hospital with features of acute or subacute intestinal obstruction. (Figure-1).

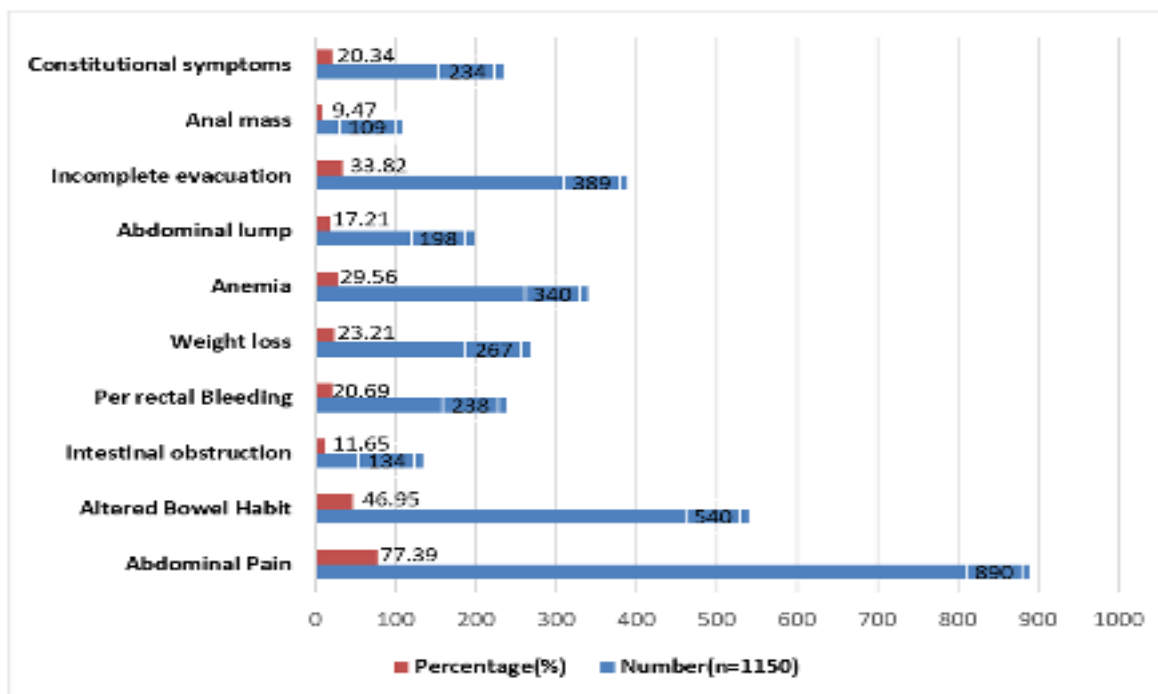


Figure-1: Pre diagnostic Clinical Presentations of the respondents (n=1150)

Table II
Association of age of the study subjects with pre diagnostic symptoms(n=1150)

Pre diagnostic symptoms	Total	Age (years)			p-value
		<50	50 - 70	>70	
Constitutional symptoms	234	52 (22.2)	126 (53.8)	56 (23.9)	0.024
Anal mass	109	32 (29.4)	45 (41.3)	32 (29.4)	<0.001
Incomplete evacuation	389	104 (26.7)	230 (59.1)	55 (14.1)	<0.001
Abdominal lump	198	52 (26.3)	113 (57.1)	33 (16.7)	<0.001
Anemia	340	97 (28.5)	165 (48.5)	78 (22.9)	<0.001
Weight loss	267	48 (18.0)	88 (33.0)	131 (49.1)	<0.001
Per rectal bleeding	238	94 (39.5)	91 (38.2)	53 (22.3)	<0.001
Intestinal obstruction	134	27 (20.1)	78 (58.2)	29 (21.6)	0.224
Altered Bowel Habit	540	131 (24.3)	309 (57.2)	100 (18.5)	<0.001
Abdominal Pain	890	147 (16.5)	510 (57.3)	233 (26.2)	0.463

Incomplete evacuation, abdominal lump is common among the age group 50-70 years and it is highly significant. Similarly weight loss is also significant among >70 years age group.(Table II).

Table III
Association of duration of symptoms with pre diagnostic presentations(n=1150)

Pre diagnostic symptoms	Total	Duration of symptoms			p-value
		<6	6 - 12	>12	
Constitutional symptoms	234	70 (29.9)	113 (48.3)	51 (21.8)	<0.001
Anal mass	109	72 (66.1)	21 (19.3)	16 (14.7)	<0.001
Incomplete evacuation	389	143 (36.8)	199 (51.2)	47 (12.1)	<0.001
Abdominal lump	198	155 (78.3)	33 (16.7)	10 (5.1)	<0.001
Anemia	340	212 (62.4)	71 (20.9)	57 (16.8)	<0.001
Weight loss	267	131 (49.1)	99 (37.1)	37 (13.9)	<0.001
Per rectal bleeding	238	163 (68.5)	50 (21.0)	25 (10.5)	<0.001
Intestinal obstruction	134	113 (84.3)	12 (9.0)	9 (6.7)	<0.001
Altered Bowel Habit	540	130 (24.1)	310 (57.4)	100 (18.5)	<0.001
Abdominal Pain	890	192 (21.6)	465 (52.2)	233 (26.2)	<0.001

Patients had presented within 06 months with abdominal lump, per rectal bleeding and intestinal obstruction. Whether patients with incomplete evacuation, altered bowel habit and abdominal pain had presented at later time.(Table III).

In our study, available previous blood reports of the most of the patient before diagnosis were decreased

haemoglobin in 47.04% (541) and high CRP in 65.35%(366/560) and high ESR in 51.22%(589) patients. Stool examination shows RBC in 10.74%(52/484) cases only. Ultra sonogram shows abdominal lump in 22.96% cases and SOL in liver in 12%. Plain X Ray abdomen shows acute and sub-acute intestinal obstruction in 11.30% cases.(Table-IV).

Table-1V

Investigation	Number(n=1150)	Percentage(%)	Mean ±standard deviation
Hemoglobin((<11 g/dL for males, <10 g/dL for females) ⁹	541/1150	47.04	Male:9.83±1.15 g/dL Female:8.56±1.34g/dL
Thrombocytosis(>400 × 10 ⁹ /L) ⁹	186/1150	16.17	(510±104)x10 ⁹ /L
Erythrocyte sedimentation rate (>40mm) ⁹	589/1150	51.22	70±11 mm
C Reactive protein(>10mg/L)	366/560	65.35	19±8 mg/L
Stool RME for RBC	52/484	10.74	
Ultrasonogram of Abdomen:			
Abdominal lump	264/1150	22.96	
SOL in liver	138/1150	12	
Plain X Ray Abdomen:			
Intestinal obstruction	130/1150	11.30	

Discussion:

In our study we have noticed a preponderance of left-sided tumors, especially rectum and recto-sigmoid junction, which is consistent with other studies in some developing countries ^{16,17}. Whereas in developed countries right-sided tumors are predominant. The reason for this anatomical difference among these countries is not clear. But studies from these countries showed that the more right sided tumor the more delayed presentation of cancer symptoms. ^{18,19}

Abdominal pain and altered bowel habit were the commonest symptom for colorectal cancer in our study which is in similarity with other study findings in Asian countries.²⁰ In our study, the next common clinical features were per rectal bleeding which were also predominant in other studies in African countries.^{5,21} It is evident by literature that, the more right sided tumor the late presentation and the more left sided tumor the earlier detection of CRC. Right sided tumors usually manifested with anemia and left side tumor presented with per rectal bleeding and intestinal obstruction. Hence, right sided tumor presented lately and left sided tumors presented at an earlier stage¹⁰. Weight loss, pallor and constitutional symptoms are also accounting a notable portion of clinical presentation in our study. These findings are nonspecific but common in CRC. That's why these findings should be kept in mind while clinical visit of a

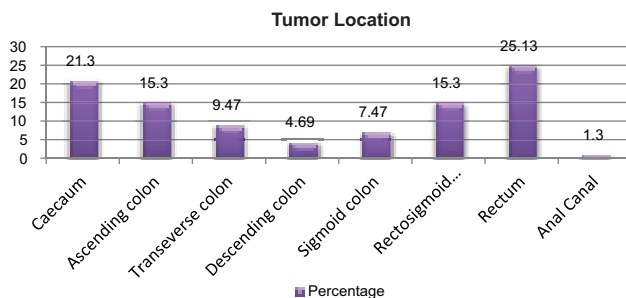


Figure-2: Site of the tumor at diagnosis

In our study, out of 1150 cases the most common histopathological variety were adenocarcinoma 74.43% (856). The remaining commoner varieties were Adeno-squamous (15.13%) and squamous cell carcinoma (9.39%). (Figure-3)

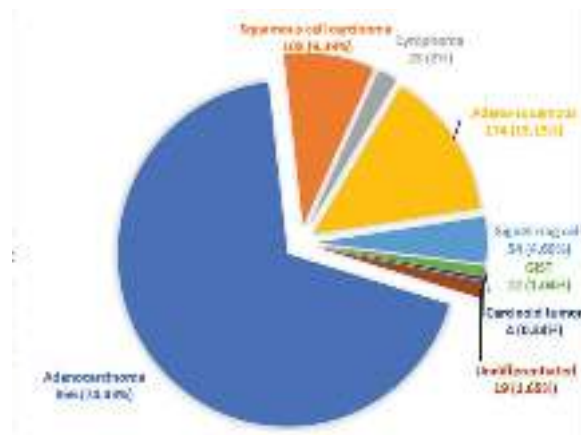


Figure-3: Histopathological varieties of the tumor of the respondents(n=1150)

patient. These data correlate with pre-diagnostic clinical feature study by Moullet et al. 2022¹⁸. If our primary care physicians and specialists are aware of these features, earlier search of CRC could be warranted.

Low hemoglobin were found in 47.04% of patients in this study which is consistent with previous studies elsewhere in the world.^{18, 24} Although high inflammatory markers and thrombocytosis are non-specific for cancer, the abnormality should prompt other investigation tools, especially when risk factors and suggestive clinical features or blood tests are positive.^{22,23} We found that, 10.74% patient had RBC in their stool test. This finding was not in consistent with study done by Abu- Freha et al.2022 in Israel (3.38%). This dissimilarity was possibly due to their population-based study and ours were CRC specific data.²⁴ Abdominal lump in Ultrasonogram were found in 22.69% in our study. Martinez-Ares et al.2005 found in 28.9% patients which was quite similar. Abdominal Ultrasonogram can be used as a screening tool for CRC suspected cases in general practice, though it is a highly subjective test.²⁵

In a retrospective study in Korea, 49.6% of colon cancer patients had e³ comorbidities.²⁶ The most common comorbidities we found in our study were IBS in 20.17% and DM in 10.17%. In a Taiwanese study showed 23% prevalence of IBS in CRC, which in concordance with this study.²⁷

In this study, a family history of colorectal cancer was reported in 5.83% of cases, a figure which is closely related to 4.10% in USA by Herkinsen et al. 2015²⁸ and 4.3% reported by Azadeh et al. ²⁹ in Iran. This finding suggests that genetic risk factors are also an important risk factor in the development of CRC throughout the world. Based on this important observation, it is suggested to start genetic screening for CRC patient's family in our country and all developing countries as well.

Similar to previous studies, we have found that about 35% of patients visited more than 03 physicians for consultation of relevant symptoms and abnormal tests in patients with colorectal cancer in the year before final diagnosis. These previous studies had analyzed number of physician consultations during the pre-diagnostic period.^{30,31} In our study, patients visited for gastrointestinal and other nonspecific constitutional symptoms indicates that if we can make awareness regarding those clinical features, we can make earlier referral for further investigations of CRC.

A recent study in England showed that GPs did not make adequate referrals for 82% of patients presenting

with per rectal bleeding. Other study also found that, lack of knowledge of standard referral criteria and concerns of over-referring leads to late referral of patients with CRC suggestive clinical features.³¹

Increasing primary care physicians' awareness of the less cancer-specific symptoms and abnormal blood tests (such as low hemoglobin and high CRP) may prompt convenient check-up of symptoms and abnormal laboratory reports. Moreover, the more employment of CRC specialized diagnostic points has the possibility to speed up diagnosis colorectal cancer.³²

Conclusion:

This study found evidence for increasing trends of physician visits for colorectal cancer-related clinical presentations and abnormal laboratory test results before diagnosis of CRC. From this study, it is evident that people who present with alarm symptoms such as rectal bleeding, change in bowel habit, and anemia will benefit from earlier referrals for cancer-specific investigations.

Limitations: This was a single center based study with limited numbers of patients and study subjects confined to only northern part of Bangladesh.

Conflict of Interest:

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

Funding:

This research received no external funding.

Ethical consideration:

The study was conducted after approval from the ethical review committee Rangpur Medical College, Rangpur, Bangladesh. The confidentiality and anonymity of the study participant was maintained.

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ORIGINAL ARTICLE

CORROSIVE INJURY TO ESOPHAGUS: A RUINOUS CURSE TO THE AFFECTED PATIENTS

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Abstract

Background: Corrosive, a harmful chemical substance, causes devastating tissue injury when contacts with body surface or ingested, is a common cause of poisoning in developing world. Prevention and early initiation of therapy after ingestion can reduce the morbidity and mortality. The aim of the study was to evaluate the demographic features, clinical presentations, endoscopic findings, complications, and the outcome of esophageal injury in corrosive ingestion. **Methods:** The cross-sectional study followed by prospective observation was carried out from 05/08/2019 and 15/03/2022 in the Department of Gastroenterology in Sir Salimullah Medical College Mitford Hospital. **Results:** Our study showed that from 105 patients, the dominating patients were female [n = 75 patients (71.4 %), p < 0.001] and significant number of the patients 84 (80%) were unemployed [p < 0.001]. In this series 37 (35.2%), 40 (38.1%) and 14 (13.3%) were students, housewives and service holders respectively. Of these only one (1%) and five (4.8%) were illiterate and graduate respectively. Most of the patients had monthly income ≤20,000 BDT [n = 81 (77.1%), p < 0.001] and total 91 (86.7%) cases were suicidal and 11 (10.5%) were accidental ingestion of corrosive [p < 0.001]. The most common ingested corrosive in our series was Harpic 91 (86.7%) [p < 0.001]. Most common clinical feature was dysphagia 72.4% (n=76). Endoscopy of upper GIT revealed injury 55 (52.4%) and 44 (41.9%) in esophagus and stomach respectively with significant difference of finding with age (p < 0.05). Follow up endoscopy showed 13.3%(n=14) patients developed complication like esophageal stricture and gastric outlet obstruction and significant number of patients [n=91(86.7%)] didn't develop any complication. Out of these 14 patients 57.1%(n=8) were managed by esophageal dilatation and 42.9%(n=6) were referred to surgery. **Conclusion:** Corrosive poisoning is a predominant and preventable condition in the developing countries. Preventive strategies should include regulation and packaging of corrosive substances, effective awareness program and strict legal action, decent psychosocial support system and counselling and proper education.

Keywords: Corrosive injury, Esophagus, Endoscopy

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Introduction:

Corrosive poisoning, often referred to as caustic ingestion, is a significant public health concern worldwide, encompassing the ingestion of substances capable of causing severe damage to tissues upon contact. It results in potentially life-threatening immediate complication like perforation within few hours and late complication like stricture formation in the gastrointestinal tract. The utmost commonly

affected body parts are the face, eyes, mouth, tongue, pharynx, epiglottis, larynx, upper gastrointestinal tract and extremities.^{1,2} Acids and alkalis are two primary categories of corrosive substances causing caustic injuries. Substances with pH values falling within the extreme acidic (less than 3) or extreme basic (greater than 11) ranges are particularly corrosive and pose a high risk of causing severe tissue damage upon ingestion or contact.³⁻⁶ Alkalis and acids cause tissue

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damage through distinct mechanisms. Alkalis induce liquefactive necrosis and saponification upon contact with tissues. They tend to cause more severe and penetrating injuries compared to acids due to their ability to dissolve lipids and proteins.^{6,7} Common alkalis include household bleaches, toilet cleaners, dishwashing agents, detergents. On the contrary, acidic substances donate protons (H⁺) to tissues, leading to disruption of cellular membranes, generation of free radicals, and activation of inflammatory cascades. This results in localized tissue destruction, edema, and inflammation, which can progress to ulceration, perforation, and stricture formation.^{2,6,7} Common acids include toilet cleaners, vinegar, formic acid etc. The most frequently ingested substance was Harpic in our country as it is cheap and easily available. Most of the corrosive ingestion are suicidal and commonly occur at second and third decade of age group among young adolescents.⁸ There are very limited epidemiological data worldwide because of under-reporting of corrosive ingestion.⁹ The prevalence of corrosive poisoning may vary across different regions and demographic groups. In some low- and middle-income countries, where access to safe storage and handling of corrosive substances may be limited, the prevalence of corrosive poisoning may be relatively higher compared to high-income countries with stricter regulations and better infrastructure for chemical safety. The prevalence of corrosive ingestion is decreasing gradually in developed world due to effective awareness program and strict legal action.¹⁰⁻¹³ Along with Indian data, popular ingestions were acids as these were cheaper and easily accessible. Corrosive ingestions are mostly under-reported so it is difficult to estimate their prevalence rate.¹⁴ Some recent study shows that prevalence of corrosive ingestion is 2.5–5% whereas the morbidity and the mortality are above 50% and 13% respectively.¹⁵ The intention corrosive ingestion may cause serious injuries in oropharynx, proximal part of the esophagus while it is taken as solid form, but in liquid form it may pass through the oropharynx and proximal part causing more injury to the middle and distal segments of the esophagus and stomach.¹⁶⁻¹⁸ Clinical features depend on how much corrosive was taken and type of corrosive agents. Most common acute complications of corrosive ingestion are pain, bleeding, stridor, dyspnea and perforation. Long term complication developed among the patients who survived from acute stage. Delayed complications of corrosive injury are esophageal stricture, bronco-esophageal fistula, gastric outlet obstruction, increased risk of cancer from which most common are esophageal stricture and gastric outlet obstruction.¹⁹ After history taking and relevant clinical evaluation, esophageal

complications are best assessed by upper GI endoscopy and CT esophagogram but upper GI endoscopy is more helpful because direct visualization is possible by this as well as dilation of stricture when indicated.^{19,20}

There is very limited study on corrosive injury to esophagus in our country. The purpose of this study was to evaluate the demographic features, clinical presentations, endoscopic findings, complications, and the outcome corrosive injury.

Methods:

One hundred and five patients over 12 years of age who were admitted to Sir Salimullah Medical College Mitford Hospital with the complaint of corrosive substance intake between the dates 05/08/2019 and 15/03/2022 were included in this study. Formal ethical approval was taken before starting the study. All patients were briefed about the purpose of the study and after their informed written consent data collection was started. The demographic characteristics of the patients included in the study, complaints while appearing to the emergency service, physical examination findings, the purpose of caustic intake, characteristics of corrosive substance taken were obtained from the patients and their attendants. Patients lacking information were excluded from the study. Upper gastro-intestinal (GI) endoscopy was performed by a single experienced endoscopist who had 10 years' experience in this field.

Endoscopy findings was graded according to Zargar classification were as follows-

Grade 0: Normal

Grade 1: Superficial mucosal edema and erythema

Grade 2a: Superficial ulcerations, erosions, exudates

Grade 2b: Deep discrete or circumferential ulcerations

Grade 3a: Focal necrosis

Grade 3b: Extensive necrosis

Data were analyzed using IBMSPSS Statistics Base 22.0 package program. Descriptive statistical methods (mean, standard deviation, frequency distributions) were used to evaluate the data.

Results:

Demographic findings: Demographic data have been showed in table 1. Total 105 patients, age from 13 years to 48 years (mean 21.51) were included and of these 30 (28.6% with mean age 27.5 years) and 75 (71.4% with mean age 18.54 years) were male and female respectively. Significantly greater number of females were observed ($p < 0.001$). In this series 51 (48.6%) were within 13-20 years age group. There is no significant difference concerning marriage; sixty (57.1%) were married, 45 (42.9%) were unmarried. Most of the patients 84 (80%) were unemployed [$p <$

0.001]. In this series 37 (35.2%), 40 (38.1%) and 14 (13.3%) were students, housewives and service holders respectively. Of these only one (1%) and five (4.8%) were illiterate and graduate respectively. Most of the patients in this series 81 (77.1%) had monthly income d"20,000 BDT [p < 0.001]. In this series 91 cases (86.7%) were suicidal and 11 (10.5%) were accidental ingestion of corrosive [p < 0.001]. The most common ingested corrosive in our series was Harpic 91 (86.7%) [p < 0.001].

Common underlying factors for corrosive ingestion were familial disharmony in 51 (48.6%) and Conflicts with parents 27(25.7%).

Table-I

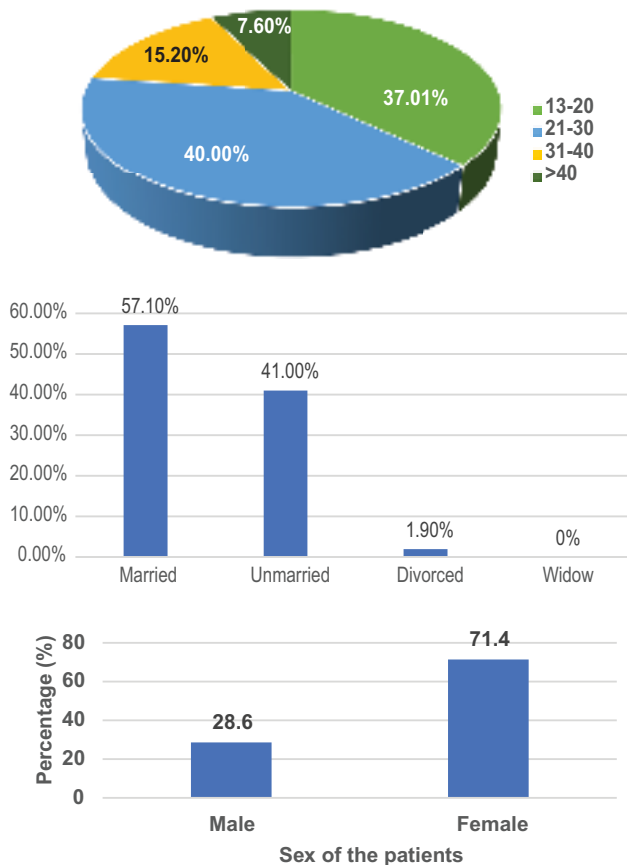
Variables	Number	Percentage	p-value
Sex			
Male	30	28.6	< 0.05
Female	75	71.4	
Marital status			
Married	60	57.1	> 0.05
Unmarried	45	42.9	
Occupation			
Unemployed	84	80	< 0.05
Service holder	21	20	
Address			
Rural	49	46.7	> 0.05
Urban	56	53.3	
Income			
<20000tk	81	77.1	< 0.05
>20000tk	24	22.9	
Nature of ingestion			
Suicidal	91	86.6	< 0.05
Accidental	11	10.5	
Homicidal	3	2.9	
Band of poison			
Harpic	91	86.6	< 0.05
Savlon	7	6.7	
Dettol	2	1.9	
Battery water	1	1.0	
Spirit	4	3.8	
Education			
Primary	76	72.4	< 0.05
Intermediate	23	21.8	
Graduate	5	4.8	
Illiterate	1	1.0	

Table-II

	Number of cases	Percentage
1 st Endoscopy done		
<48hrs	68	64.8
48-96hrs	24	22.9
>3weeks	13	12.3
Presentation		
Dysphagia	76	72.4
Odynophagia	21	20
Hoarseness of voice	5	4.8
Vomiting	46	43.8
Hematemesis	6	5.7
Chest pain	19	18.1
Abdominal pain	14	13.1
Respiratory distress	5	4.8
Esophageal endoscopic findings		
Grade 0	50	47.6
Grade 1	6	5.7
Grade 2A	28	26.7
Grade 2B	21	20
Gastric endoscopic Findings		
Grade 0	61	58.1
Grade 1	5	4.8
Grade 2A	14	13.3
Grade 2B	18	17.1
Grade 3A	3	2.9
Grade 3B	4	3.8

Most common clinical feature was dysphagia 72.4% (n:76). Other clinical features were vomiting (43.8%), odynophagia (20%), chest pain (18.1%), abdominal pain (13.3%), hematemesis (5.7%), hoarseness of voice (4.8%) and respiratory distress (4.8%).

Endoscopy of upper GIT revealed injury 55 (52.4%) and 44 (41.9%) in esophagus and stomach respectively with significant difference of finding with age (p < 0.05).

Age group**Table-III**

Parameters	Esophageal findings		P- value
	Normal	Abnormal	
Sex			
Male	12	18	.239
Female	38	37	
Age group			
13-20	27	24	.03
21-30	23	22	
31-40	0	7	
>40	0	2	
Brand of poison			
Harpic	39	52	.170
Savlon	6	1	
Dettol	2	0	
Battery water	1	0	
Spirit	2	2	
Nature			
Suicide	42	49	.761
Accidental	6	5	
Homicidal	2	1	

Table-IV

Parameters	Gastric findings		P-value
	Normal	Abnormal	
Sex			
Male	17	13	.851
Female	44	31	
Age group	13-20	34	17
.003			
21-30	27	18	
31-40	0	7	
>40	0	2	
Band of poison			
Harpic	50	41	.305
Savlon	6	1	
Dettol	2	0	
Battery water	1	0	
Spirit	2	2	
Nature			
Suicide	52	39	.415
Accidental	8	3	
Homicidal	1	2	

Frequencies and percentage of complication are shown in table V.

Follow up endoscopy showed 13.3%(n=14) patients developed esophageal stricture and among them 5 patients were associated gastric outlet obstruction and 86.7%(n=91) patients didn't develop any complication.

Table-V

Stricture	Number	Percentage
Present	14	13.3%
Absent	91	86.7%

Out of these 14 patients 57.1%(n=8) were managed by esophageal dilatation and 42.9%(n=6) were referred to surgery.

Discussion:

Previous studies showed the most common age group for corrosive substance intake is 18–25 years of age.^{21,22} In our study, the mean age of the patients was 21.51 years, with the majority belonging to the age group of 13-20 years with 48.6% that was compatible with previous studies and shows the vulnerability of adolescents and young adults to

corrosive ingestion. So targeted preventive measures and intervention is necessary. The higher prevalence of females (71.4%) compared to males (28.6%) in our study raises questions about potential gender-specific factors influencing the incidence of corrosive ingestion. While this gender disproportion aligns with some previous studies, it may warrant further investigation into underlying socio-cultural, psychological, or access-to-care factors contributing to this trend.²³ Different studies showed that corrosive ingestion is common in poor socioeconomic conditions and among the unemployed people.^{13,14,21} In our study we also found the same association. Eighty-one (77.1%) patients had monthly income $\leq$ 20,000 BDT and 84 (80%) participants was unemployed. These poor socioeconomic condition and unemployment create a vulnerable environment for corrosive induced suicidal intent. This underscores the importance of addressing social determinants like education, employment and economic stability to reduce such incidence. Suicidal intent accounted for the majority of cases (86.7%), emphasizing the need for psychological assessment and intervention in such cases. The high proportion of cases with suicidal intent points up the gravity of mental health issues and the need for comprehensive psychiatric assessments and interventions in individuals presenting with corrosive ingestion. Addressing underlying mental health concerns and providing appropriate support and counseling services are crucial components of holistic care for such patients. Some previous studies showed the similar results where one of the studies found suicidal intention of corrosive ingestion was 92%.^{22,24} Accidental corrosive ingestion occurs because of the mis-preservation of this substances. Corrosive injuries developing after accidental corrosive substance is preventable. In advanced countries, while accidental poisonings are declining, but in underdeveloped countries with low socioeconomic condition and illiteracy, the number of accidental ingestions is rising.^{10,25} In this study, the primary reason for suicidal corrosive ingestion was familial disharmony (48.6%), followed by conflicts with parents (25.7%) The association suggests the influence of interpersonal relationships on mental health outcomes. The association between corrosive ingestion and familial conflicts has been documented in previous research, highlighting the need for family-centered approaches in prevention programs.²⁶ Corrosive substances intake is an important problem, especially among uneducated persons with low socioeconomic position. Moreover, this education must ensure an awareness of the hazards of these substances. Another important observation of our study that suicidal ingestion of

caustic substances causes more grave health problems, and therefore, a decent psychosocial support system and counselling are needed to help for relieving of the anxieties or stresses that lead to suicidal tendencies.

The presence and intensity of symptoms can vary depending on factors such as the type and concentration of the ingested corrosive agent, the amount consumed, and the duration of contact with mucosal surfaces, so sometimes clinical presentation cannot predict gastrointestinal damage.^{4,13} Studies have found that despite burns or injury occurring in the oropharyngeal area, a portion of patients (up to 70%) did not exhibit significant damage to the esophagus and the severity of esophageal or gastric injuries observed in patients with lip and oropharyngeal damage tends to be relatively mild, typically not exceeding grade 1.^{4,27} In our study, we did not find any significant association between clinical presentation and degree of injury. So clinical symptoms should be interpreted in conjunction with other factors such as endoscopic findings, patients' history, and individual variability to ensure accurate diagnosis and appropriate management. Endoscopic evaluation plays a crucial role in assessing the extent and severity of mucosal injury in patients with corrosive ingestion. Esophageal injury was observed in 52.4% of cases, while gastric injury was seen in 41.9%. The findings of esophageal and gastric injuries in a significant proportion of cases indicates the need for early endoscopic intervention to guide therapeutic decision-making and prognostication. The correlation between advancing age and the severity of esophageal and gastric injuries highlights age as a potential risk factor for adverse outcomes in corrosive poisoning. This finding emphasizes the importance of age-specific risk stratification and management protocols in optimizing clinical outcomes for affected patients.

Follow up endoscopy showed 13.3%(n=14) patients developed complication like esophageal stricture and gastric outlet obstruction and significant number of patients [n=91(86.7%)] didn't develop any complication. Out of these 14 patients 57.1%(n=8) were managed by esophageal dilatation and 42.9%(n=6) were referred to surgery department. While another study carried out at Guangzhou, China concluded that out of 168 esophageal dilatation procedures done on patients of esophageal stricture, 26(60.5%) patients were categorized as in positive success rate and 17(39.5%) patients failed and referred for stent placement and/or surgery.²⁸

Future research directions may include multicentered longitudinal studies to assess long-term outcomes and

complications of corrosive poisoning, investigations into the efficacy of novel therapeutic interventions, and exploration of predictive factors for adverse outcomes in affected individuals.

Conflict of Interest:

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

Funding:

This research received no external funding.

Ethical consideration:

The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College. The confidentiality and anonymity of the study participant was maintained.

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ORIGINAL ARTICLE

SKIN DISEASE IN ELDERLY: A CROSS-SECTIONAL SURVEY IN A TERTIARY CARE CENTER OF BANGLADESH

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Abstract:

Background: Aging is a natural physiological process that affects various organs, including the skin. The elderly population in Bangladesh is rapidly increasing, necessitating an understanding of the common skin diseases affecting this demographic. The aim was to investigate the frequency, patterns, and associated factors of skin diseases among elderly patients attending a tertiary care center in Bangladesh. **Methods:** This cross-sectional survey was conducted during January 2024 to April-2024, at the department of Dermatology & Venereology in Mugda Medical College Hospital, Dhaka, Bangladesh. A total of 233 elderly patients aged 60 years and above were enrolled using consecutive sampling technique. Data were collected using a structured questionnaire capturing demographics, clinical presentations, and comorbidities, followed by clinical examinations. The data were analyzed using Statistical Package for Social Sciences (SPSS), version-23.0. **Results:** The mean age of the study patients was 65.64±5.54 years, with a nearly balanced gender distribution (48.92% male, 51.07% female). Common clinical presentations included itching (84.12%), redness (14.16%), and blistering (3%). Plaques (51.07%) and papules (46.35%) were the most frequent primary lesions, while scaling (53.21%) and erosion (36.05%) were common secondary lesions. Non-infectious skin diseases were more prevalent (58.79%) than infectious diseases (41.2%), with dermatitis (37.76%) and fungal infections (21.03%) being the most frequent conditions. A significant association was observed between educational level and infectious skin diseases with the study patients ($p=0.001$), with fungal infections more common among no formally educated patients. Similarly, diabetic-non-diabetic cases showed a significant association with infectious-non-infectious skin diseases ($p=0.001$). **Conclusion:** Skin diseases in elderly population can present with diverse clinical picture where dermatitis and fungal skin infections are more common. Patient's educational status and comorbidities may play a role in acquiring particular illnesses.

Keywords: Elderly, Skin, Disease, Infectious, Non-infectious, Association

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Introduction:

The global population is experiencing a significant increase in the proportion of elderly individuals, defined as those aged 60 years and above. In Bangladesh, this demographic shift is particularly notable, with projections indicating that by 2050, approximately 20% of the population will be elderly, up from 8% in 2020.^{1,2} This rapid growth presents unique health challenges, notably a rise in chronic conditions, including dermatological diseases, which substantially impact the quality of life among older adults.³ Aging induces several physiological changes in the skin, such as thinning of the epidermis, loss of elasticity, and decreased sebaceous gland activity, leading to conditions like xerosis (dry skin), pruritus, and increased susceptibility to infections.^{4,5} In South Asia, including Bangladesh, studies have highlighted a high prevalence of skin diseases among the elderly, with fungal infections, eczema, and pruritus being particularly common.^{6,7} In Bangladesh, the burden of skin diseases among the elderly is further exacerbated by socio-economic constraints, environmental factors, and limited access to healthcare, particularly in rural settings.^{8,9} Despite the growing elderly population, there remains a notable lack of recent, comprehensive research focusing on geriatric dermatological health in the country. The available studies are few, often geographically limited or outdated, failing to reflect the current disease patterns and healthcare needs of this age group.¹⁰ This lack of reliable and up-to-date data hampers the formulation of clinical guidelines and effective public health strategies tailored to the needs of older individuals. Moreover, underdiagnosis and undertreatment of skin diseases in this population can lead to prolonged discomfort, functional decline, and increased healthcare costs.¹¹ Addressing these challenges requires a thorough understanding of the prevalence and nature of skin diseases in the elderly within the local context. Therefore, the present study aims to evaluate the frequency, patterns, and associated factors of skin diseases among elderly patients attending a tertiary care center in Bangladesh. Understanding the spectrum of geriatric dermatoses is essential for developing targeted interventions, improving clinical care, and informing national health policy to better serve the growing elderly population.

Methods:

This cross-sectional survey was conducted from January to April 2024 at the Department of Dermatology & Venereology, Mugda Medical College Hospital, Dhaka, Bangladesh. Prior to enrollment, all participants were informed about the study's objectives, procedures, potential risks, and benefits,

and written informed consent was obtained. A consecutive sampling technique was followed and a total of 233 elderly patients aged 60 years and above, of all sexes, who presented to the outpatient department with dermatological complaints during the study period were enrolled in this study. Skin conditions were diagnosed based on established guidelines from the World Health Organization (WHO)(2020) and the National Guidelines for the Management of Dermatological Disorders in Bangladesh(2016).Data were collected using a structured questionnaire capturing demographic details, clinical symptoms, comorbidities, including diabetes, hypertension and relevant lifestyle factors.. Potential confounders, such as age, sex, and comorbid conditions, were documented to allow for stratified or adjusted analyses during statistical evaluation. The data were analyzed using Statistical Package for Social Sciences (SPSS), version 23.0. Descriptive statistics summarized the demographic and clinical characteristics of the skin diseases. Chi-square tests were performed to assess the association between education level and infectious skin diseases among the study patients. Association was also assessed between diabetic and non-diabetic cases and infectious skin diseases among the study patients, where $P < 0.05$ considered as the level of significance with 95% CI.

Results:

A total of 233 elderly patients aged ≥ 60 years, irrespective of sex, attending the OPD at the department of Dermatology & Venereology in Mugda Medical College Hospital for dermatological concerns were enrolled in this study. Regarding demographic characteristics distribution, the most frequent 212 (90.98%) were aged 60-74 years, with a mean age of 65.64 ± 5.54 years. The sex distribution was nearly balanced, with 114(48.9%) male and 119 (51.1%) female. The most frequent 125(53.65%) patients had no formal education, while 108(46.35%) patients had received any level of formal education. Occupationally, among males, 51 (44.73%) were retired, while 35(30.7%) worked in elementary jobs. Among the female patients, the majority (88.59%) were housewives, with smaller proportions in other occupations. Regarding the comorbidities distribution, the most frequent 106 (45.5%) patients had hypertension and 85 (36.5%) patients had diabetes. Among the study patients, 31 (13.3%) were smokers, while 61 (26.2%) patients consumed non-smoking tobacco (Table-1).

Table-I*Distribution of the study subjects by demographic characteristics (N=233).*

Age Group (years)	Frequency	
	N	%
60-74	212	90.98
75-89	21	9.02
Total	233	100
Mean age(years)	65.64±5.54	
Gender		
Male	114	48.92
Female	119	51.07
Educational Status		
Having no formal education	125	53.65
Having any level of formal education	108	46.35
Occupation by gender		
Male		
Retired	51	44.73
Businessman	20	17.54
Sales man	8	7.01
Elementary	35	30.70
Female		
Retired	10	8.77
Businessman	1	0.87
Sales man	2	1.75
Elementary	5	4.38
Housewife	101	88.59
Comorbidities		
Diabetes	85	36.5
Hypertension	106	45.5
Smoking Status		
Smoker	31	13.3
Non-smoke tobacco consumption	61	26.2

Age group: (60-74) years=older persons, (75-89) years=elderly persons (World Report on Ageing and Health-2015 by WHO).

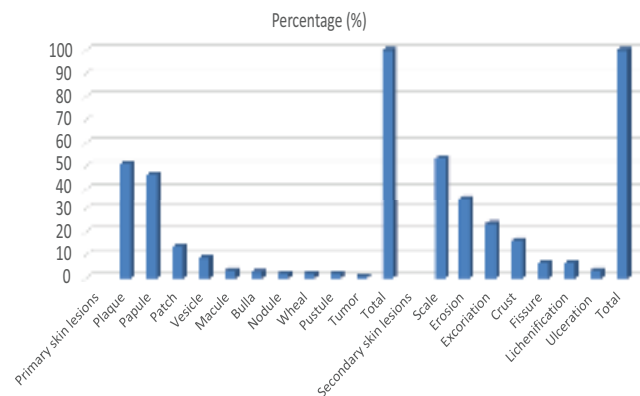
Regarding the distribution of clinical presentations, itching was the most commonly reported symptom, affecting 196(84.12%) patients. Redness was reported by 33 (14.16%) patients, while blisters were noted in 7 (3%) patients. Scaling and other unspecified symptoms each accounted for 24 (10.3%) patients. Pain was reported by 18 (7.72%) patients, followed by skin thickening in 16(6.89%) and pigmentary changes in 14 (6%) patients (Table-2). Regarding the distribution of primary and secondary skin lesions, plaques were the most commonly reported lesion, occurring in 119

(51.07%) patients, followed closely by papules in 108(46.35%) patients. Patches were noted in 32(13.73%) patients, while vesicles were observed in 20 (8.58%) patients. Less frequently reported lesions included macules in 8 (3.43%), bullae in 6 (2.57%), nodules, wheals, and pustules, each reported in 5 (2.14%) patients. Tumors were the least frequent skin lesion, seen in only 2 (0.85%) patients while, among the secondary skin lesions, scaling was the most frequently reported lesion, affecting 124(53.21%) patients. Erosion was noted in 84(36.05%) patients, while excoriation was observed in 55(23.60%) patients and crusting occurred in 38 (16.30%) patients. Less commonly reported lesions included fissures and lichenification, each present in 15 (6.43%) patients, and ulceration, which was the least frequent, occurring in 8(3.43%) patients (Fig-1).

Table-II*Distribution of clinical presentations among the study participants (N=233).*

Clinical Presentations	Frequency	
	N	%
Itching	196	84.12
Redness	33	14.16
Blister	7	3
Scale	24	10.3
Others	24	10.3
Pain	18	7.72
Skin thickening	16	6.89
Pigmentary change	14	6

Multiple responses were counted in clinical presentations of the study patients.

**Fig-1:** Distribution of skin lesions observed among the study patients (N=233).

Among the study patients, non-infectious skin diseases were the most commonly reported, affecting 137 (58.79%) patients, while infectious skin diseases were observed in 96 (41.20%) patients. Among the infectious skin diseases, fungal infection was observed the most common in 49(21.03%) patients and followed scabies 34 (14.59%), bacterial infection 12(5.15%) and viral infection 6(2.57%), while among the non-infectious skin diseases, 137(58.79%), dermatitis was the most frequent diagnosis, affecting 88 (37.76%) patients and followed psoriasis, 12 (5.15%) ,urticaria 7 (3%) , lichen planus and malignant skin tumors, each 6 (2.57%) , bullous diseases and pigmentary skin diseases, each in 4 (1.71%) , drug reactions 3 (1.28%) , discoid lupus erythematosus, psychiatric skin disease each 2(0.85%) and, acquired perforating dermatosis, benign skin tumors, chilblains, chronic arsenicosis, mycosis fungoides, and vasculitis, each affecting a single patient 1 (0.42%) respectively (Table-3).

Table- III

Distribution of patterns of skin diseases diagnosed among the study patients (N=233).

Patterns of skin diseases	Frequency	Percent
Infectious	96	41.20
Fungal infection	49	21.03
Scabies	34	14.59
Bacterial infection	12	5.15
Viral infection	6	2.57
Non-infectious	137	58.79
Dermatitis	88	37.76
Psoriasis	12	5.15
Urticaria	7	3.0
Lichen Planus	6	2.57
Malignant skin tumour	6	2.57
Bullous disease	4	1.71
Pigmentary skin disease	4	1.71
Drug reaction	3	1.28
Discoid Lupus Erythematosus (DLE)	2	0.85
Psychiatric skin disease	2	0.85
Acquired perforating dermatosi	1	0.42
Benign skin tumour	1	0.42
Chilblain	1	0.42
Chronic Arsenicosis	1	0.42
Mycosis fungoidis	1	0.42
Vasculitis	1	0.42

Association between educational level of the study patients with the infectious skin diseases among the study patients was observed statistically significant ($p=0.001$). Fungal infections were the most common, affecting 34(14.59%) of individuals with no formal education compared to 15(6.43%) with having any level of education. Scabies was also more prevalent in the no education group in 20(8.58%) patients than in the educated group 14(6.0%) patients. Similarly, bacterial infections were recorded in 8(3.43%) patients without having formal education, while only 4(1.71%) with having any level of education were affected. Viral infections were the least common but still showed a disparity, with 5(2.14%) patients occurring in the no education group versus only 1(0.42%) patients in the any level of educated group. The statistically significant difference suggests that lower education levels are associated with a higher prevalence of infectious skin diseases ($p=0.001$) (Table-IV).

Table-IV

Association of educational level with infectious skin diseases with the study patients (n=233).

Infectious skin diseases	Educational Level		P-value
	No formal education N (%)	Having any level of education N (%)	
Fungal infection	34(14.59)	15(6.43)	$P<0.001^s$
Scabies	20(8.58)	14(6.0)	
Bacterial infection	8(3.43)	4(1.71)	
Viral infection	5(2.14)	1(0.42)	

Chi-square test was performed to determine the association between educational status and pattern of skin diseases, where $P<0.05$ considered as the level of significance with 95% CI. S= significant.

Among the diabetic patients (n=85), the most frequent 45(52.94%) had infectious skin diseases and 40(47.05%) patients had non-infectious skin diseases, while, among the non-diabetic patients (n=148), the most frequent, 90(60.81%) patients had non-infectious skin diseases and 58(39.18%) patients had infectious skin diseases. The association between diabetic-non-diabetic cases and infectious-non-infectious skin diseases among the study patients also observed statistically significant ($p=0.001$) (Table-5).

Table-V

Association between diabetic-non diabetic cases and infectious-non-infectious skin diseases with the study patients (N=233).

Diabetic Status	Infectious Status		P-value
	Infectious (N)	Non-infectious (N)	
Diabetic cases	45	40	P<0.001 ^s
Non-diabetic cases	58	90	

Chi-square test was performed to compare the group frequencies, where P<0.05 considered as the level of significance with 95% CI. S= Significant.

Discussion:

The demographic characteristics of the study population reveals that the majority of the study patients were within the age group of 60-74 years (90.98%), aligning with the World Health Organization's classification of older adults¹². The mean age was 65.64±5.54 years, which is consistent with similar demographic patterns observed in aging populations in South Asia.¹³ However, this differs from the European scenario where life expectancy and health care advancements have led to a higher proportion of patients aged 75 years and above in dermatological studies.¹⁴ The gender distribution in this current study was nearly balanced, with a slightly higher presentation of females (51.1%) compared to males (48.9%). This gender pattern aligns with findings from Pakistan and Sri Lanka, where females slightly outnumber males in geriatric dermatological research due to longer female life expectancy.¹⁵ However, in African studies, male dominance has been more commonly observed, possibly due to healthcare access disparities.¹⁶ Educational status showed that 53.65% of the participants had no formal education, which could influence health literacy and health-seeking behaviors. This lack of formal education is similarly observed in rural settings of South Asia but contrasts with European countries where formal education levels among older adults are generally higher.^{17,18} Regarding occupation, a significant proportion of female participants (88.59%) were housewives, while the male group showed diversity with retired (44.73%), elementary jobs (30.7%), and businessmen (17.54%). These occupational patterns are partially align with another study in India.¹⁹ Comorbidities such as hypertension (45.5%) and diabetes (36.5%) were prevalent. Similar patterns are reported in South Asia where non-communicable diseases are rising.²⁰ A European study reported slightly lower hypertension rates due to better preventive healthcare services.²¹ The most common clinical presentation was itching (84.12%), followed by redness (14.16%) and scaling (10.3%). This distribution closely mirrors findings in

Nepal, where pruritic conditions dominated dermatological complaints.²² Another European study showed lower rates of pruritic disorders due to better dermatological care and awareness.²³ In terms of skin disease patterns, non-infectious diseases (58.79%) were more common than infectious conditions (41.20%). Dermatitis was the leading non-infectious disease, while fungal infections and scabies were the most common infectious diseases. These findings differ from African regions where infectious skin diseases like bacterial and parasitic infections often predominate due to limited sanitation.²⁴ Educational level and infectious skin diseases showed significant association (p<0.05). Infectious skin diseases were more prevalent among the patients with no formal education, reflecting health literacy disparities. Similar trends were also observed in rural African study.²⁵ A statistical significant association was also found between diabetic-non-diabetic cases and infectious-non-infectious skin diseases with the study patients (p<0.05), with fungal infections being more common among diabetic patients. This finding is align with another South Asian study.²⁷

Conclusion:

This study highlights a high prevalence of both infectious and non-infectious skin conditions among the elderly in Bangladesh, emphasizing the need for targeted dermatological care and preventive strategies, particularly for those with lower educational levels and comorbid diabetes.

Limitations:

Cross-sectional structure of this study limits causal interpretations, and the use of purposive sampling from a single tertiary care center restricts generalizability to the broader Bangladeshi elderly population. Reliance on self-reported data and basic clinical examinations without advanced diagnostics may have led to misclassification of skin conditions. Unexamined factors such as environmental exposures and medication use could influence the findings.

Conflict of Interest:

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

Funding:

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Ethical consideration:

The study was conducted after approval from the ethical review committee of Institutional Review Board, of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The confidentiality and anonymity of the study participant was maintained.

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CASE REPORT

HYPERKINETIC MOVEMENT CAUSED BY DIABETIC STRIATOPATHY: A CASE REPORT

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Abstract:

Hyperkinetic movement like chorea is rare in uncontrolled diabetic patients. Increased level of glucose affects the basal ganglia known as diabetic striatopathy. Synonym of this condition includes hemichorea-hemiballismus, chorea-hyperglycemia-hemiballismus syndrome, non-ketotic hyperglycemic hemichorea. We report a 65-year-old woman with uncontrolled diabetes who presented with unintentional ballistic movements of his right upper and lower extremities making her disabled. Magnetic resonance imaging of her brain demonstrated findings suggestive of diabetic striatopathy. Antipsychotics (eg. Haloperidol) helped to control her chorea-like movements. Strict glycemic control was advised to prevent recurrence.

Keywords: Hyperglycemia, Striatopathy, Hemichorea- hemiballismus syndrome, Chorea-hyperglycaemia-basal ganglia syndrome

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Introduction:

Diabetic Striatopathy (DS) is a rare cause of acute onset hemichorea-hemiballismus and it becomes a good differential when a patient is diabetic with uncontrolled blood sugar and presents with abnormal movement¹. To establish a diagnosis of DS, other acute causes of movement disorder need to be excluded which include stroke, and Sydenham's chorea². Basal ganglia lesions of different etiology can present in a similar way (3). Magnetic resonance imaging (MRI) is the key mode of investigation linked with the medical history for accurate diagnosis².

Case Report:

This 65-year-old right-handed diabetic woman presented with involuntary movement of her right upper and lower limbs for 5 days. Her past medical history was unremarkable except for uncontrolled diabetes for about 20 years and an ischemic stroke 10 years back. She was not on her regular follow-ups and was not compliant with her medication.

Her abnormal movements started insidiously but deteriorated rapidly. Her movement persisted when she was awake but dampened when sitting still in one place. Initiating movement of any sort made her

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abnormal movement worse. Her relatives observed very little to no jerks in her limbs during her sleep. Her movements became violent very quickly and seriously affected her physically and mentally. She could not able to hold herself quiet at one place. It was also tiring due to exhaustion caused by the movements.

The findings of her physical examination showed hemiballismus localized to her right upper and lower extremities. Her blood pressure record showed 136/80 mm Hg, her pulse was regular at 80 beats/ min, and other vital parameters were unremarkable. A neurological examination revealed that she was alert, oriented, cooperative, and communicating well. Her cranial nerve functions were intact including normal fundoscopy examination and normal speech. Her gait was violent, not following any specific pattern and we were unable to perform a Romberg's test on her. Regarding her limb examinations, there was no pronator drift. Tone, power, and deep tendon reflexes were normal. The plantar reflex was bilaterally flexor. Her sensory findings were also unremarkable.

Her blood parameters revealed hyperglycemia of 15 mmol/L and corresponding urine sugar was 4+, HbA1c 13.3%, S. creatinine 1.4 mg/dl. Serum electrolytes were within normal limits. Her blood lipid profile revealed dyslipidemia (Cholesterol 180 mg/dl, LDL 80 mg/dl, TG 470 mg/dl). We have done brain imaging on her, which showed hyperintensity at the left lentiform nucleus in the T1 sequence (Figure:1). There was also a hypo-intensity at pons suggestive of an old infarct. There was no evidence of acute infarction, intracranial hemorrhage, parenchymal mass lesion, mass effect, midline shift, or sign of herniation.



Fig.-1: Sagittal T1 weighted magnetic resonance imaging of the brain

Her violent movements were treated with haloperidol 2.5 mg twice daily and hyperglycemia was managed with basal-bolus insulin regimen. The patient responded very well to the mentioned therapy and dramatic improvement of symptoms was observed.

Discussion:

DS is a rare condition that was first coined a decade back for patients of abnormal movement in patients of hyperglycemia¹. Because of the uncommon nature

of the condition, there are only a few case reports and the nomenclature is not consistent in the articles due to a poor understanding of this condition^{2,3}. Any lesion at the basal ganglia can produce similar symptoms, however, high blood glucose in the absence of an infarct or mass lesion makes the condition unique and labeled as DS. This condition is often known by other names like hyperglycemic nonketotic hemichorea/hemiballismus, diabetic hemichorea/hemiballismus, and hyperglycemic basal ganglia syndrome⁴. Only a clinical picture is not sufficient to make this diagnosis⁵.

On review of the available literature, we have found that most patients with hemichorea/ hemiballismus had uncontrolled diabetes and their imaging showed evidence of contralateral basal ganglia involvement⁶. This condition is mostly treatable with typical or atypical antipsychotics combined with control of blood glucose.

A meta-analysis published in 2020 showed that putamen is the most involved striatal area (about 78.6%), and MRI is way more sensitive (95.33%) than CT (78.9%) for identifying the lesion⁷. This analysis also recognized the benefit of antipsychotic medication combined with glycemic control compared with those managed with glycemic control alone, showing a response rate of 76.25 in earlier cohort compared with 25.6% in the later cohort^{7,8}.

There are few analyses done pathologically and radiologically as attempts to identify the mechanism behind this. Though definite pathogenesis has yet not been discovered, the proposed mechanism includes disruption of the blood-brain barrier, demyelination, mineral deposition, petechial hemorrhage, and microinfarction with astrocytosis⁸.

DS is less common in non-Asian descent, making it highly underdiagnosed among them. This article could raise awareness among clinicians to think of DS as a differential whenever they encounter a patient with acute chorea/hemiballismus-like movement disorder in a hyperglycemic patient. This will alert the clinicians to screen those subjects for DS changes on MRI. As this is a treatable condition and has a great impact on patients' quality of life, early diagnosis is important.

Conclusion:

One uncommon neurological symptom in DM patients is DS. Despite the paucity of treatment guidelines and the possibility of potentially life-threatening consequences, it is curable and has a favorable prognosis if treated appropriately.

Conflict of Interest:

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Funding:

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Consent:

For the purpose of publishing this case report and any related photos, the parents are written informed consent was acquired.

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CASE REPORT

ENCAPSULATING PERITONEAL SCLEROSIS SECONDARY TO PERITONEAL DIALYSIS

FOREST RIEKHOF¹, FARZANA HOQUE²

Abstract

Encapsulating peritoneal sclerosis (EPS) is a rare and morbid complication of peritoneal dialysis, characterized by peritoneal thickening, fibrosis, and encasement of the bowel. Here, we report a 37-year-old man who presented with encapsulating peritoneal sclerosis complicated by a significantly large, loculated fluid collection several months after discontinuation of peritoneal dialysis. The case, overall, highlights a lesser-known complication of peritoneal dialysis and provides clinical pearls for clinicians to optimize patient care.

Keywords: Encapsulating peritoneal sclerosis, EPS, Peritoneal dialysis, Peritoneal fibrosis, Thickened peritoneum, Bowel cocooning, Bowel encapsulation, Peritoneal calcification

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Introduction:

Encapsulating peritoneal sclerosis (EPS) is a poorly understood entity that can lead to encasement of the bowel leading to bowel obstruction and malnutrition. It is a life-threatening complication of long-term peritoneal dialysis (PD). Clinicians should remain vigilant to ensure a timely diagnosis, as the rarity of this disease and variable symptoms often contribute to delays in diagnosis. To describe a case of encapsulating peritoneal sclerosis which is a rare but fatal complication of peritoneal dialysis.

Case report:

A 37-year-old man, with a past medical history of hypertension, asthma, and end-stage renal disease (ESRD) secondary to congenital obstructive uropathy, underwent a living donor renal transplant in 2004. Unfortunately, the transplant failed in 2012, leading to the reinitiation of hemodialysis (HD). He transitioned to peritoneal dialysis (PD) from 2018 to 2023 but returned to HD six months before presentation due to tumoral calcinosis of his left thigh. He presented to

our emergency department (ED) due to two weeks of anorexia, non-bloody diarrhea, non-bloody non-bilious emesis, abdominal distention, and right upper quadrant abdominal pain.

In the ED, the patient's temperature was 37°C, heart rate 110/min, and blood pressure was 88/45. Laboratory test results showed leucocytes $17 \times 10^9 / L$ ($4.1-11.1 \times 10^9 / L$), lactic acid 2.9 mmol/L (less than 2 mmol/L), creatinine 16 mg/dL (0.7-1.3 mg/dL), calcium 10.0 mg/dL (8.6-10.3 mg/dL), and phosphorus 7.2 mg/dL (3-4.5 mg/dL). A CT scan of the chest, abdomen, and pelvis was significant for calcified peritoneum, a large loculated peritoneal fluid collection with rim calcification, mild colonic wall thickening/fat stranding with pseudo pneumatosis (air surrounding fecal content), no evidence of acute bowel obstruction (Figures 1-3). A CT scan of the chest, abdomen, and pelvis 1 year ago revealed mild peritoneal calcification. Given symptoms, abdominal findings, and imaging, encapsulating peritoneal sclerosis (EPS) was higher in our differential.

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A paracentesis was performed draining approximately 1 Liter of serosanguinous fluid. He was started on empiric antibiotics (piperacillin-tazobactam) for presumed bacterial peritonitis. Hemodialysis was continued during hospitalization. Blood cultures and peritoneal fluid analysis were negative. The patient improved significantly with the resolution of symptoms. He was switched from piperacillin-tazobactam to 2 weeks of oral Augmentin at discharge.

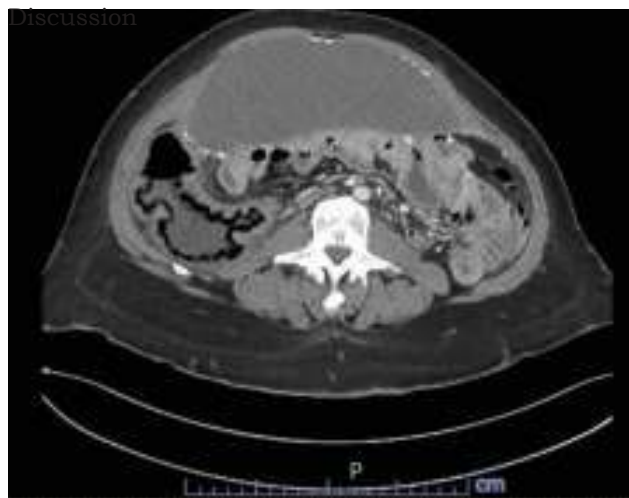


Fig.-1. CT abdomen axial cut showing peritoneal calcification, large fluid collection, pseudo-pneumatosis of ascending colon, bowel loops drawn into center.



Figure 3. CT abdomen sagittal cut showing peritoneal calcification and large abdominal fluid collection.



Fig.-2. CT abdomen axial cut showing peritoneal and bowel wall calcification, large fluid collection, and calcified kidney graft.

Our patient developed encapsulating peritoneal sclerosis, a rare complication of long-term peritoneal dialysis.

Discussion:

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome within the spectrum of peritoneal fibrosis. It is characterized by the encasement of the bowel due to a diffusely thickened peritoneum and is associated with high morbidity and mortality (1). Risk factors for EPS include younger age at PD onset, increased duration of PD, prior episodes of peritonitis, and dialysate makeup (e.g. increased glucose concentration) (2). This patient's risk factors include younger age at PD onset, six years duration of PD, and previous peritonitis episodes. The pathogenesis of EPS is not well understood but inflammation leading to fibrosis and calcification is considered multifactorial because of prolonged contact between dialysate and peritoneum (3,4). Laparoscopic findings suggest that peritoneal degeneration is associated with the duration of peritoneal dialysis and frequent episodes of peritonitis. EPS is slowly progressive and often asymptomatic early in the disease course. It commonly presents after cessation of peritoneal dialysis and the time frame can vary (5). Our patient had PD six months before this presentation. Clinicians may notice serosanguinous dialysate or decreased ultrafiltrate if the patient still receives peritoneal dialysis. As EPS progresses to later stages, the disease can present with signs and symptoms of obstruction including abdominal pain, constipation, vomiting, palpable abdominal mass, or ascites. Diagnosis remains challenging due to diagnostic criteria that rely largely on clinical symptoms and variable radiographic

findings. CT scan of the abdomen is the most common modality used for imaging in EPS currently. Radiographic findings include peritoneal calcification, bowel and peritoneal thickening, bowel dilatation, loculated ascites, and bowel cocooning (bowel loops clustered in the central abdomen with tethering) (6).

EPS is a life-threatening complication of long-term PD. Prevention efforts have been primarily aimed at reducing glucose and glucose degradation product concentrations in dialysis fluid using icodextrin and neutral pH solutions (7,8). Length of peritonitis episodes have also been associated with EPS (9). Early recognition and treatment have been reported to improve outcomes. Nutritional status should be regularly assessed and optimized in all patients. Effective treatment with glucocorticoids, tamoxifen, or other immunosuppressive agents has been described, but no randomized controlled trials have been performed due to disease rarity (10,11). Tamoxifen is the most widely used anti-fibrotic treatment due to inhibition of TGF $\alpha 1$, which is thought to halt progression and lead to collagen degradation in EPS. Laparotomy is only recommended for surgical enterolysis in cases of complete bowel obstruction at presentation or cases of medical management failure.

In summary, we describe a rare case of encapsulating peritoneal sclerosis (EPS) following peritoneal dialysis. A high index of suspicion is warranted in patients experiencing symptoms such as abdominal pain, constipation, vomiting, palpable abdominal mass, or ascites, given the associated high morbidity and mortality.

Conclusion:

Clinicians should be vigilant for signs of encapsulating peritoneal sclerosis (EPS) in long-term peritoneal dialysis patients. Recognizing prolonged dialysis, recurrent peritonitis, and high-glucose dialysate as risk factors is crucial for early detection. Management of EPS involves medical treatments like glucocorticoids and tamoxifen, with surgery for severe cases.

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 the purpose of publishing this case report and any related photos, the parents are written informed consent was acquired.

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CASE REPORT

ACUTE HEPATITIS OF UNKNOWN ORIGIN (AHUO) IN AN INFECTIOUS DISEASE REFERRAL HOSPITAL: A CASE REPORT

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Abstract

The World Health Organization (WHO) reported Acute Hepatitis of Unknown Aetiology (AHUA) occurred in children in several countries, including Indonesia. Before this study was conducted, the cause and treatment were unknown. The Ministry of Health reported 91 cases in less than 16 years old children which spread across 22 provinces in Indonesia. This is a case report which was part of a surveillance program at Sulianti Saroso Infectious Disease Hospital (SSIDH) in 2023. The treated probable AHUA case was 16 years and 10 months old, while other studies reported probable AHUA cases <16 years old. Of the 17 patients suspected AHUA who were treated at SSIDH, one case was categorized as probable AHUA. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin levels were elevated. Tests for hepatitis B (HBsAg), hepatitis C virus (HCV) antibodies (Ab), hepatitis A IgM, and hepatitis E IgM were all negative. Length of Stay (LoS) hospitalisation was 12 days, and the patient has recovered. Adequate identification and management of cases were carried out by paediatricians so that severe conditions do not occur.

Keywords AHUA, Probable, Surveillance, Case report

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Introduction:

The World Health Organization (WHO) reported a mysterious case of Acute Hepatitis of Unknown Origin (AHUO) in children younger than 16 years in the United Kingdom and Northern Ireland on April 15, 2022^{1,2}. Similar cases have been reported in Central Scotland, the United States, Israel, and Japan^{2,3}. On July 8, 2022, the WHO reported 479 cases of mysterious acute hepatitis spread across Europe (23 countries), the American (eight countries), the Western Pacific Region (one country), Southeast Asia (two countries), and the Eastern Mediterranean (three countries). Meanwhile, as of August 26, 2022, the number of similar cases had increased dramatically to 1115 cases that spread across 35 countries worldwide. Most were female (52%) and aged six or older (76%)⁴.

The agent of this hepatitis case is still unknown. Hepatitis A, B, C, D, and E tested negative¹, while some cases were confirmed for SARS CoV-2 or adenovirus⁵. The literature mentions the presence of adenovirus or SARS-CoV-2 in children with mysterious acute probable hepatitis, as well as the role of microorganism agents and other risk factors⁶.

AHUO definition varies in several countries; however, the patient's clinical symptoms and age are the most important criteria, as well as the exclusion of hepatitis A, B, C, D and E infection⁷. Clinical signs are characterized by increased AST or ALT levels (>500 U/L)^{8,9}, along with jaundice⁹ and sometimes with gastrointestinal symptoms⁷ such as nausea, vomiting, abdominal pain, and diarrhea⁹. For cases with a poor prognosis, consultation with a pediatric hepatologist is required as some cases are treated with liver transplantation^{5,10} and some others cause death¹¹. Of there was no history of international travel¹⁰.

The Ministry of Health reported 91 cases in less than 16 years old children which spread across 22 provinces in Indonesia. Jakarta Metropolitan Area was the province that contributed the most cases, with 12 cases¹². SSIDH, an infectious disease referral hospital, reported there were 17 suspected cases of AHUO admitted to the hospital, one of them was included as probable AHUO. In this study, we described the case, its symptoms, clinical signs, laboratory, and findings management of AHUO in SSIDH.

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Case report:

A 16-year-old Javanese boy was referred from PHC with suspected AHUO. He was admitted due to persistent abdominal pain for 7 days. The Javanese boy also experienced jaundice for 4 days (Fig. 1), malaise, vomiting only once but felt nauseous, poor appetite, dark urine and acholic stool. He had a history of diarrhoea two days before admission and no history of fever. He was previously healthy and denied taking any prescription, over-the-counter or herbal medications. He had no exposure history to patients with COVID-19 and received the second dose of inactivated COVID-19 vaccine nine months before admission. He also had no history of hepatitis. He lives with his parents and an older sister. The other family members don't experience the same symptoms. The family consume bottled drinking water for drinking and cooking.



Fig.-1: Jaundice and icteric sclera appearance

Physical examination revealed that the teenager had normal vital signs, low weight-for-height, scleral icteric, jaundice, and hepatomegaly (2 cm below the rib edge). While the spleen was not palpable, he had upper abdominal tenderness. He was hospitalized for 10 days and discharge in good condition (Table 1).

Data was gathered from investigational forms of AHUO and electronic medical records. Laboratory supporting data, such as PCR EBV, ENT, CMV, ADV, leptospira, and whole genome sequencing (WGS) of Hepatitis E, were examined at the Research Laboratory for Infectious Diseases Prof. Dr. Sri Oemijati, Health Ministry of Indonesia.

The biochemical tests showed high levels of ALT (1005 U/L), AST (1276 U/L), gamma-glutamyl transferase [(GGT) 112 U/L], total bilirubin [(TB) 16.7 mg/dL] and direct bilirubin [(DB) 10.3 mg/dL]. The coagulation function was within the normal range and the albumin level was slightly low (3.2 mg/dL). No abnormality was found in the blood routine and acute phase reactant (Table II). The patient underwent infectious pathogen screening. Evidence of hepatitis A, B, C, and E virus infection was not found. PCR examination on blood and nasopharynx specimens showed Cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus (AdV), enterovirus, and leptospiral infection were not found. *Klebsiella Oxytoca* and *Staphylococcus aureus* were detected in the blood.

Abnormal transaminase enzymes total and direct bilirubin, Gamma GT, INR and IgG Covid-19 were detected. Filmarray/Nested-Multiplex examination used Filmarray BioFire Gastrointestinal Panel 2.1 to detect *Campylobacter*, *Clostridium difficile* toxin, *A/B. Plesiomonas shigelloides*, *Salmonella*, *Vibrio*, *Vibrio Cholera*, *Yersinia enterocolitica*, *Enterogregretative Escherichia coli* (EAEC), *Enteropathogenic E. coli* (EPEC) *lt/st*, *Shiga-like-toxin-producing E.coli* (STEC), *E.coli* O157, *Shigella/Enteroinvasive E.coli* (EIEC), *Cryptosporidium*, *Cyclospora cayetanensis*, *Entamoeba histolytica*, *Giardia lamblia*, and *Adenovirus F40/41*, *Astrovirus*, *Norovirus GI/GII*, *Rotavirus A* and *Sapovirus*. The patient didn't undergo a liver biopsy due to parental rejection.

Abdominal ultrasound indicated hepatosplenomegaly with increased intrahepatic vascular (Fig.-2). Chest X-rays showed normal heart and lungs.

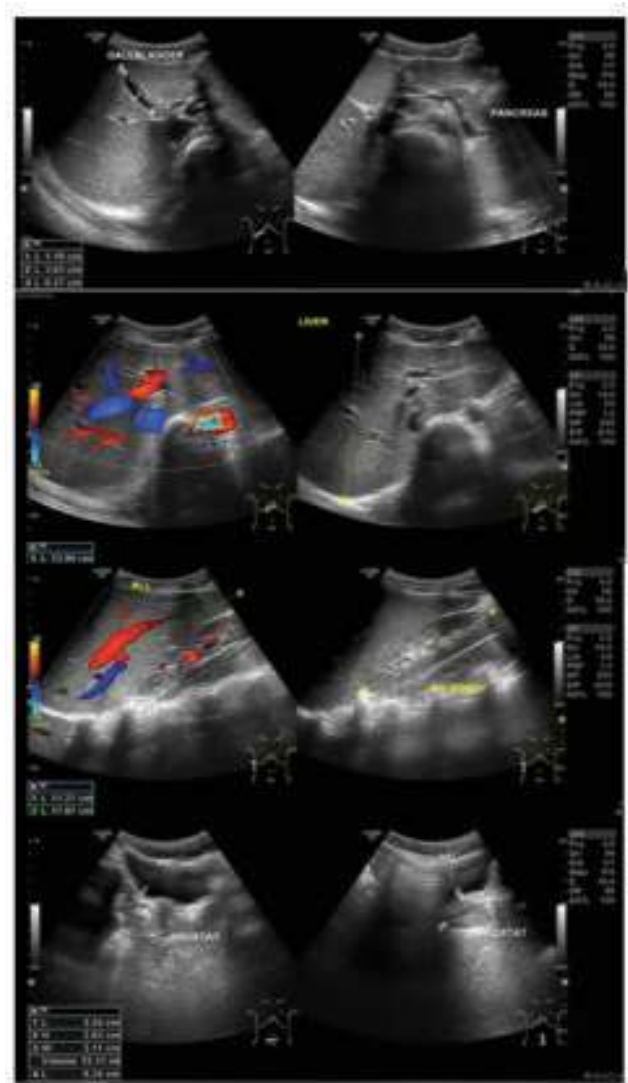


Fig. 2. The Abdominal Ultrasound results show normal descriptions of the gallbladder, pancreas, kidney, and prostate. The liver's measurement shows a craniocaudal size of 17.87 cm, inhomogeneous echotexture, and increasing intrahepatic vascularization, which indicates acute hepatitis.

Table I
Clinical sign and symptoms

Day	Signs and Symptoms										
	Fever	Abdominal Pain	Nausea	Vomit	Diarrhoea	Acholic faeces	Urine color	Headache	Icteric	Jaundice	Hepatomegaly
Day -9	-	+	-	-	-	-	Clear-Yellow	-	-	-	N/A
Day-8	-	+	+	-	-	-	Clear-Yellow	-	-	-	N/A
Day -5	-	+	+	-	-	-	Clear-Yellow	-	+	+	N/A
Day-3	-	+	+	-	-	+	Clear-Yellow	-	+	+	N/A
Day-1	-	+	+	-	+	+	Clear-Yellow	-	+	+	N/A
Day 0*	-	+	+	+	+	+	Brown	-	+	+	+
Day 1	-	+	+++	+	+	+	Brown	+	+	+	+
Day 2	-	-	+	-	-	-	Brown	+	+	+	+
Day 3	-	-	-	-	-	-	Brown	-	+	+	+
Day 4	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 5	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 6	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 7	-	-	-	-	-	-	Dark yellow	-	+	+	+
Day 8	-	-	-	-	-	-	Clear-Yellow	-	+	+	+
Day 9	-	-	-	-	-	-	Clear-Yellow	-	+	+	+
Day 10	+	-	-	-	-	-	Clear-Yellow	-	+	+	+
Day 11	+	+	-	-	-	-	Clear-Yellow	-	-	+	+
Day 12	-	-	-	-	-	-	Clear-Yellow	-	-	-	+
Day 21	-	-	-	-	-	-	Clear-Yellow	-	-	-	-

*Day 0 marks hospital admission

Table II
Laboratory parameter

Date	Laboratory Parameter									
	Leucocyte (10 ³ /μL)	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Indirect Bilirubin (mg/dL)	Albumin (g/dL)	CRP (mg/L)	Procalcitonin (ng/mL)	Gamma GT
Day 0*	4.4	453	1005	16.7	-	-	-	-	--	-
Day 1	4.8	556	1276	13.5	10.3	3.2	3.0	2.55	0.21	-
Day 6	-	59	506	4.9	4.2	0.7	-	-	-112	-
Day 11	6.8	37	251	3.2	2.5	0.7	-	-	--	-
Day 21	-	35	99	1.8	1.4	0.4	-	-	--	-

*Day 0 marks hospital admission

Treatment:

During hospitalisation, the patient received supportive treatment. Ranitidine, a lipid-soluble vitamin, compound glycyrrhizin injection, and ursidoxycholic acid were given. Treatments were intravenous fluids that contained electrolytes and carbohydrates based on body weight, regular diet 1700 kcal, and supplementary milk; enteral nutrition specifically for liver dysfunction has a tailored composition, with carbohydrates contributing 62%, protein 13%, and fat 35%. It is also supplemented with specific nutrients such as BCAAs (Branched-Chain Amino Acids) to improve the Fischer ratio and support muscle protein recovery processes. Additionally, it contains MCTs (Medium-Chain Triglycerides), a type of fat that is easily digested and metabolized, serving as an alternative energy source 1 × 200 cc. Hepatoprotector drugs were given two times one ampule per day, ranitidine injection two times per day, antipyretic three times one tablet a day, vitamin E 400 IU per day, and ursodeoxycholic acid 2 times 500 mg were given to treat. On day 12, the patient was discharged. Post-discharge follow-up was done seven days after discharge, there was no complaint.

Discussion:

More than 30 countries reported a new disease that infects children aged < 16 years with AHUO. After a cluster of unexpected cases of pediatric AHUO was identified in Scotland in March 2022¹, WHO announced an outbreak alert with more than 1010 probable cases of mysterious acute hepatitis spread across 35 countries (1 October 2021 to 18 July 2022)^{1,13}.

Gastrointestinal complaint was the most common symptom. Icteric sclera and jaundice were seen, and laboratory tests showed an increase in liver enzymes. Some patients experience complications of acute liver failure that require liver transplantation. Between March and August 2022, 17 patients were referred with a suspected diagnosis of acute hepatitis of unknown cause in SSIDH.

Seventeen of these suspected referral cases of acute hepatitis were characterised by elevated liver enzyme levels (more than 500 U/L), and the majority were icteric. Most patients experience other intestinal symptoms. All patients receive the same treatment, SARS CoV-2 examination is always carried out on in-patients as a strategy to identify COVID-19 cases^{14,15}. In addition, other laboratory tests, such as adenovirus¹⁶, immune-serology hepatitis virus test, AST-ALT, total bilirubin, rapid dengue/NS-1, and leptospirosis, were performed. Of 17 cases, 16 were discarded, and one case was probable cases of AHUA.

Our case was experienced by a 16 year 10 months-old boy. According to some investigations, infection occurs in all sexes^{1,17}. However, there is a difference with cases reported in Europe where most cases occur in younger children, less than 5 years old^{1,18}. The research of Chen et al, 2022 stated that there is no relationship between hepatitis of unknown cause and travel history¹⁹. The patient experienced jaundice symptoms, nausea, vomiting, lower abdominal pain, diarrhoea and no history of fever²⁰. Laboratory tests revealed AST or ALT levels >500 IU/L, negative hepatitis tests, and adenovirus-negative results¹. Several research stated one of the possible causes of AHUO is adenovirus. Adenovirus infection is a cause of fulminant hepatitis but is rare in immunocompetent children in only a few cases⁴ in a few countries^{1,18,21-24}, which states the possible cause of AHUO is adenovirus.

Some other hypothesis mentioned involvement of Covid-19 mRNA vaccine as the cause of AHUA. However, this theory was easily ruled out as most children with AHUO were too young to receive the vaccine at the time they were sick²⁵. In July 2022, covid-19 immunization rate in China was 92.1% for the first dose, 89.7% for the full course and 71.7% for the booster. However, the reported AHUO was 0²⁶.

The patient had positive blood cultures of klebsiella and staphylococcus. Klebsiella, as it a common bacteria found in hospital, and staphylococcus, as it a common bacteria of skin, both could cause jaundice in patients with sepsis²⁷. Given the high morbidity and mortality linked to *Staphylococcus aureus* bacteremia (SAB), the presence of even a single *S. aureus*-positive blood culture bottle (SPBCB) in blood culture sets is often regarded as clinically significant. Notably, there have been no studies to date examining the clinical significance of a single *S. aureus*-positive blood culture bottle (SPBCB) in patients with SAB, despite its frequent recognition in clinical microbiology. Local anecdotal experience shows that antibiotic therapy is often initiated, even though it is recognized that *S. aureus*, like other commensal bacteria, can colonize the skin and lead to contamination in blood cultures²⁸. It is noteworthy that coagulase-negative staphylococci are well-known as skin flora and a frequent source of blood culture contamination, often appearing in only a single blood culture bottle²⁹.

The probability of bacterial infection in this case could be ruled out because clinical signs did not indicate infection, and the patient had a borderline procalcitonin level; therefore, he did not receive any antibiotics.

Study strength: This study describes that examinations of all suspected AHUO cases were

performed during treatment. One of the unique features of this case is that the patient was 16 years and 10 months old. While other studies reported probable AHUO cases of 16 years old^{30,31}. The clinical symptoms (experienced jaundice symptoms, nausea, vomiting, lower abdominal pain, diarrhoea and no history of fever) were consistent with the results of the supporting examination of ALT 1276 and AST 556 and this indicated symptoms of acute hepatitis. Supportive examinations up to genomic sequencing were performed on all AHUO suspect patients.

The working definition of probable is established after all the results of the supporting examination are negative / no specific microorganism agent is identified that causes AST, ALT, and bilirubin to increase^{31,32}. So that the diagnosis of the disease in this case cannot be established. The contribution of this study is the recommendation of adequate treatment (Hepatoprotector drugs) immediately given to patients with impaired liver function. This study also confirms that there is no link to the administration of the COVID-19 mRNA vaccine as a cause of AHUO because in this study the history of the COVID vaccine was 1 year before this case was reported.

There are some limitations to the exploration of aetiology in this study. Some investigations, such as multiplex PCR for respiratory virus and faecal cultures for common bacterial entero-pathogens were not performed. Also, pathology and histology examinations were carried out after stable conditions, which is not proper for aetiology investigation. The patient underwent infectious pathogen screening. Evidence of hepatitis A, B, C, and E virus infection were not found. PCR from blood and nasopharynx swabs showed Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Adenovirus (AdV), Enterovirus, and leptospiral infection were not found. Abdominal ultrasound indicated hepatosplenomegaly with increased intrahepatic vascular. Any manifestations of the acute phase in the liver biopsy also were not found. Comprehensive follow-up is needed for further clarification of clinical characteristics and aetiology of AHUO in children.

A history of risk factors and transmission was not obtained from anamnesis. Therefore, the authors could not determine the source of the transmission. Case identification was easily screened based on clinical symptoms and ALT and AST levels of >500 U/L. Adequate management by treated with hepatoprotector was done in this case.

Conclusion:

We identified one probable case of mysterious acute hepatitis out of the 17 cases we observed at SSIDH.

The case was a 16-year 10-month-old boy, AHUO. We recommend liver biopsy for patients with severe acute hepatitis of unknown origin and trial steroid therapy when liver damage is similar to autoimmune hepatitis. With this case report, we hope to add information that immune dysfunction may be the leading cause of liver damage in children with acute hepatitis of an unknown origin.

Declaration:

Ethics approval and consent to participate

Ethics approval:

This study was reviewed and approved by the Health Research Ethics Committee of Sulianti Saroso Hospital, Number. 13/XXXVIII.10/II/2023.

Consent for publication:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest:

The authors declare that they have no conflict of interest

Funding:

None.

Author's contributions:

S.M. was responsible for data collection, data analysis and research conceptualisation. E.S. and N.A. were responsible for data collection. A.D.W. and V.S. were responsible for overseeing the write-up. L.D.R. was refining the methodology.

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CASE REPORT

POST DENGUE ACUTE MOTOR AXONAL NEUROPATHY (AMAN): AN UNUSUAL CASE REPORT

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Abstract:

Dengue virus, an RNA virus linked to a wide range of neurological symptoms that causes less than 5% of patients experience neuromuscular complications. A less frequent neurological sequel to dengue fever is Guillain-Barre syndrome (GBS). Six days after recovering from dengue fever, a 25-year-old woman with the illness presented with acute-onset flaccid paraplegia of both lower limbs. Dengue NS1 antigen testing was used to diagnose dengue. In the NCS test, an acute motor axonal neuropathy (AMAN) variant was found. Thrombocytopenia (36,000/cmm), hypoalbuminemia (2.30 g/dL), and a low hemoglobin level (Hb-10.3 gm/dL) were among the laboratory results, which most likely indicated post-dengue symptoms and nutritional inadequacies. The significance of early neurophysiological and CSF tests in detecting GBS variations is highlighted by this instance, which also identifies dengue as an AMAN variant.

Keywords: Dengue virus, Guillain-Barré Syndrome, Acute Motor Axonal Neuropathy, AMAN

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Introduction:

An estimated 390 million cases of dengue fever, a virus spread by female *Aedes aegypti** and rarely *Aedes albopictus** mosquitoes, occur worldwide each year, with Asia accounting for the majority of cases (about 70%)¹. Asian nations with the greatest infection rates in 2019 included Bangladesh (101,000 cases), Malaysia (131,000), the Philippines (420,000), and Vietnam (320,000)². Although the precise prevalence of dengue-related neurological problems is unknown,

there has been an increase in recent years³. In 1976, Thailand reported the first known neurological sign of dengue as an unusual presentation³. The most common neurological conditions are encephalopathy and encephalitis, which affect 0.5% to 6.2% of patients⁴.

Acute disseminated encephalomyelitis, optic neuritis, myelitis, and Guillain-Barré syndrome (GBS) are among the additional neurological consequences⁵. GBS

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is a rapidly progressive peripheral neuropathy characterized by symmetrical muscle weakness that begins in the lower limbs and progresses upward, as well as decreased or absent reflexes. In severe situations, respiratory muscles might be damaged, with 10-30% of patients requiring mechanical ventilation due to respiratory failure [5]. Common infections that precede GBS include *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and viruses such Cytomegalovirus, Epstein-Barr, and Influenza (6). This report describes a rare instance of GBS linked with dengue illness.

Case report:

A 25-year-old normotensive, non-diabetic lady came with severe weakness in both lower limbs lasting 10 days. She comes from a lower socioeconomic background and works as a homemaker with two children. She had no substantial medical or surgical history and denied smoking or consuming alcohol. Sixteen days before admission, she had a high-grade intermittent fever and was diagnosed with dengue. The fever subsided after four days of medication. Two days after being afebrile, she felt acute weakness in both lower limbs but no upper limb involvement, sensory impairments, or autonomic symptoms. She reported no swallowing problems, nasal regurgitation, double vision, seizures, or bowel/bladder malfunction.

According to her general examination, she was ill-looking yet focused patient steady vital signs. There was no evidence of lymphadenopathy, thyromegaly, anemia, or jaundice. Examinations of the respiratory and cardiovascular systems revealed nothing unusual. A neurological evaluation revealed normal fundoscopy and healthy cranial nerves. Upon motor testing, both lower limbs showed normal muscular size but decreased tone. Both legs' proximal and distal muscle power was rated at 1/5, and both feet dropped. Plantar reflexes were non-responsive, and deep tendon reflexes (knee and ankle jerks) were reduced. Due to significant weakness, gait and coordination could not be evaluated. The sensory examination was intact and romberg's test could not be performed. Cerebellar and autonomic functions were normal.

Her blood investigation showed thrombocytopenia with a platelet count of 36,000/cmm, and the WBC count (8,400/cmm) was within normal limits. She had a low hemoglobin level of 10.3 g/dL and a hematocrit level of 31.1%. She had mild hyponatremia with a sodium

level of 132 mmol/L. Thyroid function (TSH 2.91 uIU/mL, Free T3 2.40 pg/mL, Free T4 1.12 ng/dL) and random blood sugar (5.7 mmol/L) were normal. Serum albumin was low (2.30 g/dL), suggesting nutritional deficits. Dengue NS1 antigen was positive, confirming recent dengue infection (Table I).

Table I
Biochemical and serological reports

Hb%	10.3 gm/dL
WBC count	8400/cmm
Platelet count	36000/cmm
S. Electrolyte	Normal
TSH	2.91uIU/mL
FT3	2.40pg/mL
FT4	1.12ng/dL
S.Albumin	2.30 g/dL
RBS	5.7 mmol/L
Dengue NS1 antigen	Positive

An LP was performed, and CSF analysis showed albuminocytological dissociation: protein 75 mg/dL with 2 lymphocytes/cmm. CSF glucose (4.5 mmol/L) was normal, and infectious etiologies (bacterial, TB) were ruled out via Gram stain, Z-N stain, and Gene Xpert (Table-II).

Table II
CSF analysis

Cell count	2 cells/cmm; 100% lymphocyte
Glucose	4.5 mmol/L
Protein	75 mg/dL
Gram stain	No bacteria seen
Ziehl-Neelsen Stain	No AFB found
GeneXpert	MTB not detected

Nerve conduction studies (NCS) of cross limbS showed CMAP amplitudes of both peroneal nerves are reduced to absent with normal SNAP of all the examined nerves, which was consistent with the AMAN variant of Guillain-Barré Syndrome (GBS). A diagnosis of dengue fever complicated with GBS, AMAN variant, was made (Table III & IV).

She was closely monitored for ascending muscle weakness and respiratory involvement. The patient did not receive any immunotherapy, as her neurological deficit was over-plateaued and showed improvement. She underwent physiotherapy.

Table III
Motor Nerve conduction Study

Site	Latency (ms)	Amplitude (mv)	Segment	NCV ms ⁻¹
Rt Median (Wrist)	3.64	15.05	Wrist	59.6
Rt Median (Elbow)	6.66	14.46	Wrist-Elbow	
Rt Ulnar (Wrist)	2.32	7.43	Wrist	61.7
Rt Ulnar (Elbow)	5.4	6.82	Wrist-Elbow	
Left Tibial (Ankle)	5	10.38	Ankle	48.3
Left Tibial (Popliteal)	10.8	8.16	Ankle-Popliteal	
Rt Tibial (Ankle)	3.45	7.21	Ankle	42.1
Rt Tibial (Popliteal)	10.1	6.03	Ankle-Popliteal	
Left Peroneal (Ankle)	3.75	440.00 μ V	Ankle	43.2
Left Peroneal (head of Fibula)	10	210.00 μ V	Ankle-Head of Fibula	
Left Peroneal (Popliteal)	11.6	200.00 μ V	Head of Fibula-Popliteal	43.8
Rt Peroneal (Ankle)	00	00	Ankle	44
Rt Peroneal (head of Fibula)	00	00	Ankle-Head of Fibula	
Rt Peroneal (Popliteal)	00	00	Head of Fibula-Popliteal	

Table IV
Sensory Nerve Conduction Study

Site	Latency	Amplitude (μ V)	Segment	NCV ms ⁻¹
Right Median (Wrist)	2.66	46.00	Wrist	52
Rt Ulnar (Wrist)	2.04	52.00	Wrist	53
Left Sural	2.02	25	Sural	45
Right Sural	2.62	20	Sural	44

Discussion:

Dengue fever, a prevalent mosquito-borne disease in tropical and subtropical regions, exhibits a broad range of clinical symptoms. While neurological complications are rare, affecting only 1–5% of dengue cases, they can include encephalopathy, encephalitis, myelitis, myositis, Guillain-Barré syndrome (GBS), and polyneuropathy. Dengue is caused by four related serotypes (DEN-1 to DEN-4), with DEN-2 and DEN-3 most commonly linked to severe neurological outcomes⁷. Murthy JM has proposed the classification of neuropathogenesis of dengue infection into (1) metabolic disturbances - encephalopathy; (2) direct viral invasion - encephalitis, meningitis, myelitis; and (3) autoimmune reactions - acute disseminated encephalomyelitis, neuromyelitis optica, optic neuritis, myelitis, post-infectious encephalopathy, GBS^{4,7}.

GBS, a peripheral nervous system complication of dengue, occurs in 0.6–1.9 cases per 100,000 people

and is marked by ascending paralysis, loss of reflexes, and sensory changes. It typically emerges during the recovery phase of dengue. A rare variant, acute motor axonal neuropathy (AMAN), is identified through nerve conduction studies. Case reports highlight diverse GBS manifestations in dengue patients, ranging from mild weakness to severe quadriparesis and respiratory failure requiring mechanical ventilation. Early recognition of GBS in dengue cases is crucial for effective management.

This case of AMAN following dengue fever aligns with emerging evidence highlighting arboviral infections as triggers for immune-mediated neuropathies. Dengue-associated GBS, though rare, has been increasingly reported in endemic regions, with AMAN being the predominant variant due to molecular mimicry between dengue viral antigens and peripheral nerve gangliosides (8). The patient's CSF profile—albuminocytological dissociation (protein 75 mg/dL, 2 cells/cmm)—mirrors

findings in prior AMAN cohorts, where elevated protein without pleocytosis is common but typically less pronounced than in AIDP⁹. The temporal onset of weakness 6 days post-dengue mirrors the classic “post-infectious” interval seen in GBS, as described in the Brighton Collaboration criteria¹⁰. A case review of neurological manifestations of dengue infection by Guo et al. reported that the average time it takes for neurological signs of GBS to develop was one to 19 days after the onset of dengue¹¹.

The thrombocytopenia (36,000/cmm), a common dengue effect, underscores the importance of selecting IVIG over plasmapheresis, as endorsed by the 2017 GBS Consensus Guidelines, which caution against plasma exchange in thrombocytopenic patients due to bleeding risks¹². This aligns with a 2020 case series where IVIG achieved functional recovery in dengue-associated AMAN without exacerbating thrombocytopenia¹³. The patient presented to us during plateau phase and thus not requiring immunotherapy. She subsequently improved clinically and was discharged with minimal deficit followed by gradual recovery with rehabilitation.

Hypoalbuminemia (2.30 g/dl) and mild anemia (Hb 10.3 g/dl) likely reflecting nutritional deficiencies compounded by her lower socioeconomic status, echo findings from a 2018 Indian study linking hypoalbuminemia to prolonged GBS recovery¹⁴. While AMAN often exhibits faster motor recovery than AIDP, malnutrition may delay rehabilitation, emphasizing the need for multidisciplinary care in resource-limited settings.

The absence of sensory or autonomic involvement in this case parallels prior AMAN reports, which associate “pure motor” phenotypes with anti-GM1/GD1a antibodies¹⁵. The normal serum electrolytes and thyroid function argue against metabolic mimics, reinforcing the role of post-dengue autoimmunity.

This case reinforces dengue’s emerging role in precipitating AMAN and highlights the utility of early NCS and CSF analysis to differentiate axonal from demyelinating variants, guiding prognostication. Future studies should explore socioeconomic determinants of GBS outcomes, particularly in dengue-endemic regions, to optimize resource allocation and recovery pathways.

Conclusion:

The importance of recognizing post-infectious GBS, particularly in dengue-endemic regions. Early

diagnosis, appropriate immunomodulatory therapy, and supportive care are crucial for optimizing outcomes in AMAN.

Conflict of Interest:

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

Funding:

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Consent:

For the purpose of publishing this case report and any related photos, the parents are written informed consent was acquired.

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CASE REPORT

GASTROINTESTINAL HISTOPLASMOSIS: A CASE REPORT AND LITERATURE REVIEW

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Abstract:

A 33-year-old female with a history of renal transplant 18 months prior was transferred to our hospital with acute kidney injury after presenting with acute gastrointestinal symptoms. Computed tomography (CT) imaging suggested diffuse colitis. Her symptoms persisted on empiric antibiotics, and she developed hematochezia. Colonoscopy revealed discontinuous ulcers, and Histoplasma urine antigen was positive. Grocott's methenamine silver (GMS) staining of a large intestine biopsy revealed narrow-based budding yeast compatible with Histoplasma capsulatum. Itraconazole was initiated, and her symptoms improved within two days. This case demonstrates the importance of suspecting histoplasmosis in immunocompromised patients presenting with gastrointestinal symptoms.

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Introduction:

Histoplasmosis is an infection caused by the dimorphic fungi *Histoplasma capsulatum*, which primarily occurs in endemic areas worldwide, including the Ohio and Mississippi river basins.^{1,2} Inhaled spores from soil containing bat and bird droppings are phagocytosed by macrophages within the respiratory tract, where they can divide and disseminate to other tissues.^{1,3} Individuals living in endemic areas have high estimated exposure rates; however, illness severity depends on the host's immunological status and exposure level. Immunosuppressed populations are at higher risk for severe infections, including disseminated disease.⁴ Gastrointestinal histoplasmosis (GIH) is an uncommon

manifestation of disseminated histoplasmosis (DH), occurring along any part of the gastrointestinal tract. GIH occurs in only 3-12% of DH cases.⁶ Patients commonly present with diarrhea, abdominal pain, weight loss, and fever.⁵

Objective We present this rare case of histoplasmosis with isolated gastrointestinal symptoms to emphasize the importance of evaluating for *Histoplasma* infection using antigen tests or special stains, such as GMS, particularly in immunocompromised patients residing in endemic regions.

Case Report:

A 33-year-old female with a history of renal transplant 18 months prior was transferred to our hospital with acute kidney injury after presenting with acute onset abdominal pain, non-bloody diarrhea, nausea, and vomiting. The patient denied recent travel or known sick contacts. Upon arrival, she was tachycardic (101 beats/minute), afebrile (99.8°F), with blood pressure of 136/82 mmHg. Initial laboratory findings are summarized in Table I.

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Table I

A summary of blood test results upon arrival to our hospital

White blood cell count	2.5 x 10 ⁹ /L
Neutrophils	2.13 x 10 ⁹ /L
Lymphocytes	0.13 x 10 ⁹ /L
Hemoglobin	7.5 g/dL
Hematocrit	22.9 %
Platelets	221 x 10 ⁹ /L
Sodium	132 mmol/L
Potassium	5.2 mmol/L
Blood urea nitrogen	47
Creatinine	2.62
eGFR	24 mL/min
Lactic acid	1.2 mmol/L
Creatinine kinase	29 U/L

Empiric antibiotics with ciprofloxacin and metronidazole were initiated. Transplant nephrology managed immunosuppression; mycophenolate was held, while tacrolimus and prednisone continued. One year earlier, the biopsy of the transplanted kidney revealed budding yeast compatible with *Histoplasma capsulatum*, though urine and serum antigens were negative at that time. Itraconazole was discontinued previously due to gastrointestinal side effects. Initial infectious investigations, including COVID-19, influenza, blood cultures, stool ova and parasites, cytomegalovirus (CMV), *Clostridium difficile*, and gastrointestinal pathogen panel, were negative except for mildly elevated quantitative plasma CMV PCR (33 IU/mL). Elevated inflammatory markers included erythrocyte sedimentation rate (49 mm/hr), C-reactive protein (11.9 mg/dL), and fecal calprotectin (925 µg/g). CT imaging showed diffuse colonic wall thickening suggestive of colitis. Symptoms persisted, and hematochezia developed on day six, accompanied by nightly fevers up to 101.9°F. Colonoscopy revealed discontinuous ulcerations in the sigmoid and descending colon (Figure 1).

Initial colon biopsy indicated active colitis without CMV infection, granulomas, or inflammatory bowel disease. Further infectious investigations revealed negative HIV testing, but urine *Histoplasma* antigen was significantly elevated (13.23 ng/mL). GMS staining confirmed *Histoplasma capsulatum* infection (Figure 2).



Figure 1: Endoscopic imaging of the sigmoid colon showing multiple ulcerated lesions (arrows).

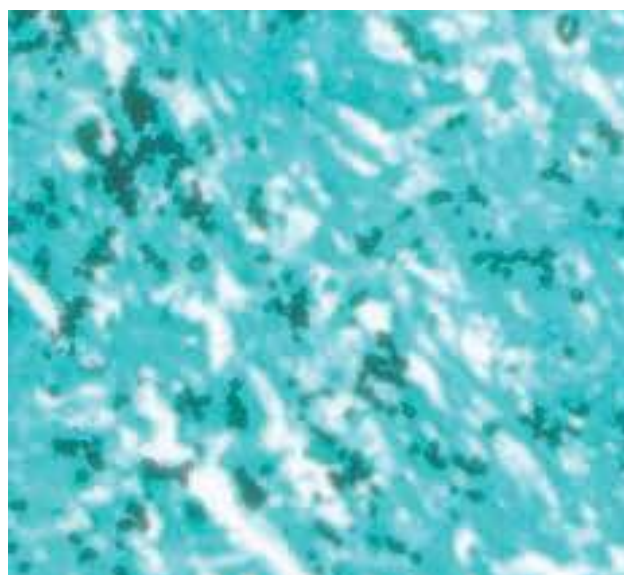


Figure 2: Colon biopsy showed narrow based budding yeast consistent with *Histoplasma capsulatum* (GMS stain, 40x).

Subsequent fungal blood cultures, serum *Histoplasma* antigen (0.97 ng/mL), brain MRI, and chest CT were negative for additional dissemination sites. Infectious disease consultation recommended itraconazole therapy despite previous intolerance, initiated at 200 mg orally three times daily for three days, then twice daily. Tacrolimus dosage was reduced. The patient tolerated itraconazole well, with significant symptom improvement within two days, normalization of creatinine, and discharge on treatment day four. Lifelong itraconazole therapy was planned due to the high risk of reinfection or reactivation, with close follow-up arranged.

Discussion:

Histoplasmosis is the most common endemic mycotic infection among solid organ transplant (SOT) recipients, although rare, with a one-year incidence of 0.1%.^{7,8,9} Disseminated disease frequently presents as moderate to severe.^{7,8,9} Symptomatic gastrointestinal histoplasmosis, as observed in this case, occurs in only 3-12% of DH cases.^{6,9} Overlapping symptoms with more common gastrointestinal diseases can delay diagnosis. This patient's clinical presentation was typical of GIH yet also aligned with common gastrointestinal diseases.⁵ Given her immunosuppressed state, a broad differential diagnosis was essential. Her previous history of histoplasmosis and poor initial treatment response guided further investigation, ultimately leading to the diagnosis. While tissue biopsy and fungal cultures are gold standards for diagnosis, antigen testing provides less invasive and timely alternatives. Serum and urine antigen testing should be included early in the workup when histoplasmosis is suspected.¹¹ Histological confirmation via PAS or GMS staining offers better visualization compared to hematoxylin and eosin staining.¹⁰ Proper communication with pathology to ensure appropriate staining is vital. Recommended GIH treatment includes itraconazole for at least 12 months, with or without initial Amphotericin B, based on symptom severity.⁹ Immunosuppressive regimen adjustments should be collaboratively decided through shared decision-making.^{11,12} Regular monitoring of antigen levels at baseline, two weeks after therapy initiation, and every three months thereafter for 6-12 months is recommended.¹⁰ Antigen levels may persist at low levels but discontinuation after completing therapy is considered safe in SOT patients.^{13,14}

This case highlights a rare presentation of GIH in SOT recipients, underscoring the necessity of broad differential diagnoses and the consideration of histoplasmosis in immunocompromised patients with gastrointestinal symptoms, particularly with prior histoplasmosis exposure. Prompt antigen testing and appropriate tissue staining facilitate timely diagnosis and effective treatment.

Conflict of Interest:

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

Funding:

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Consent:

For the purpose of publishing this case report and any related photos, the parents are written informed consent was acquired.

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CLINICAL IMAGE

MEDICAL QUIZ : IMAGES

Aminur Rahman

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A 60-year-old woman presented with low back pain of 2 months duration, which increased in severity over the last 15 days. The pain was radiating to the left lower limb and was associated with tingling and numbness. The patient had a history of low-grade fever,

weight loss, and malaise over the last 2 months. There was a history of cough with expectoration. On examination, there was mild pallor and no other significant findings. There was localized tenderness over the lumbosacral spine.

An MRI of the lumbosacral spine was done.



Figure-1: MRI of lumbosacral spine T1-weighted and T2-weighted and T1+C sagittal images of the patient

Please answer the question as above scenarios

- What are the findings of MRI of lumbosacral spine?
- What is the most likely diagnosis?
- How can you confirm the diagnosis?
- What is the gold standard treatment?

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Answer to Medical Quiz

Answer:

- i) Destruction and signal alteration involving L1 and L2 bodies,
- ii) Altered signal intensity involving L1-2 disc and destruction, and
- iii) Thecal sac compression
- iv) Paravertebral and prevertebral collection extending from L1 to L2 level.
- b) Lumbar spinal tuberculosis/ Pott's disease
- c) computed tomography-guided Fine needle aspiration cytology (FNAC)/ fine needle biopsy
- d) Antituberculosis drugs (four-drug therapy)

Overview:

Spinal infections can be classified by the anatomical location involved: the vertebral column, intervertebral disc space, the spinal canal and adjacent soft tissues.¹ Infection may be caused by bacteria or fungal organisms, and can occur after surgery. Pott's disease, often called spinal TB or tuberculous spondylitis, is a type of tuberculosis that affects the spine.² Mycobacterium tuberculosis causes a bacterial infection that travels from the lungs to the spine.³ The infection harms the vertebrae, potentially causing pain, stiffness, and spinal deformity. Untreated, Pott's disease can lead to serious problems such as spinal instability, neurological impairments, and even paralysis.⁴ Approximately 10% of patients with extrapulmonary tuberculosis have skeletal involvement. The spine is the most common skeletal site affected, followed by the hip and knee. Spinal tuberculosis accounts for almost 50% cases of skeletal tuberculosis.⁴ Infection starts in cancellous bone usually adjacent to an inter-vertebral disc or anteriorly under the periosteum. Site of involvement in spinal tuberculosis: thoracic (65%) lumbar (20%), cervical (10%), thoraco-lumbar (5%), and atlanto-axial region (< 1%).³ There may be multiple vertebrae; Two (<90%), Three (50%) vertebrae and Paraspinal abscess 55-90%. Characteristics features in MRI of spine: T1+C : Rim enhancement of abscess on MRI is suggestive of tuberculous spondylitis, however, rim enhancement can be observed in both tuberculous and pyogenic spondylitis :TB Spondylitis: Thin and smooth enhancement of the abscess wall and well-defined paraspinal abnormal signal.⁵ Pyogenic Infections: Thick and irregular enhancement of abscess wall and ill-defined paraspinal abnormal signal. Hyperintense signal on T2 is more common in tuberculous spondylitis. Subligamentous spread to three or more vertebral levels was frequent in tuberculous spondylitis. Involvement of the posterior element has been reported in tuberculous spondylitis and very

uncommonly in pyogenic spondylitis.⁶ CNS tuberculosis is categorised under TB treatment category I by WHO. Initial phase therapy (2 months) with isoniazid, rifampicin, pyrazinamide and streptomycin or ethambutol followed by continuation phase (7 mths) with isoniazid and rifampicin. The BTS and IDSA/ATS recommend 9-12 months of ATT. Therapy should be extended to 18 months in patients who do not tolerate pyrazinamide. Short duration therapy (6 months) might be sufficient if the likelihood of drug resistance is low.⁷ However as the emergence of neurological deficit has been seen in some of the studies so a minimum of 12 months treatment would be worthwhile.⁸

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