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CONTENTS

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The **title page** should carry 1) the title of the article, which should be concise but informative; 2) authors' name, with highest academic degree and institutional affiliation.

The abstract of original article should be structured and of no more than 250 words. The specimen of a structured abstract follows :

Title

Multiorgan failure in a cardiac surgical intensive care unit.

Abstract

Background/Context : To find out incidence and various risk factors associated with multiorgans failure in patient after cardiac surgery.

Materials and Methods : A prospective study of 935 consecutive admissions to cardiac surgical intensive care unit over a period of one year, April 1994 to March 1995. Cardiac surgical intensive care unit, National Institute of Cardiovascular Diseases, Dhaka. Nine hundred thirty five patients admitted to cardiac surgical intensive care unit after cardiac surgery.

Results : Mean age of patients was 29.6 years; males were 66.8%. As regards preoperative risk factors, 24.3% had systemic disease, 19.5% had cardiac dysfunction, 7.5% and 3.4% had hepatic and renal dysfunction respectively, 7.3% underwent emergency surgery, seventy percent of patients underwent surgery on cardiopulmonary bypass. Postoperatively 18.3% patients developed low cardiac output syndrome. Respiratory, acute renal and hepatic failure was seen in 7.5%, 4.6% and 2.9% respectively. 2.8% patients developed septicaemia and 2.2% developed multiorgan failure. Mean duration of intensive care unit stay was 1.9 days.

Conclusion : Cardiac surgical patients form a separate subset of multiorgan failure with different predisposing factors, pathophysiology and outcome. Pre-existing organ dysfunction, clinical status, surgery on cardio-pulmonary bypass, post-operative low cardiac output syndrome and septicaemia play significant role in causing multiorgan failure.

Three to six **key words** should be added to the bottom of the abstract.

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Preparing for weapons of mass destruction [editorial]. The Lancet 2003 January; 361 (9352):95.

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BrowelI DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitunour responses. Curr Opin Gen Surg 1993:325-33.

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Habib A. Effect of indomethacin on stomach and small intestine and its prevention by cimetidine in rat (Thesis). Dhaka Institute of Postgraduate Medicine and Research (IPGM&R); 1992: 20-30.

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Avoid **abbreviations** in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text, unless it is a standard unit of measurement.

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Manuscripts are examined by the editorial board and are sent to reviewers. Rejected manuscripts will not be returned. Proofs correction by the authors will be appreciated. No reprint will be provided.

The Editor reserves the customary right to style and if necessary shortens the material accepted for publication and to determine the priority and time of publication. **The editor assumes that all the works are based on honest observations. It is not the task of the editor to investigate scientific fraud paper**.

EDITORIAL

Strengthening and Integrating the Healthcare Referral System in the Government Health Sector of Bangladesh

The Ministry of Health and Family Welfare of Bangladesh is responsible for the health of the country's 171.5 million citizens. Both the public and private sectors contribute to the healthcare system in Bangladesh. The health care system at the government level is well-structured and encompasses primary, secondary, tertiary, and super specialized care. There are three tiers at the primary health care level, like Community Clinics (CC), Union Health and Family Welfare Centers (UHFWC) and Upazila Health Complexes (UHC). These primary care facilities are supported by district hospitals that provide secondary-level care, and various types of tertiary hospitals in large urban centers, and medical colleges.[1] There are also super specialized centers, such as different institutes and Medical universities.

For the health system reform, the Bangladesh government mainly focused on different service-related goals in different five-year sector plans. The first five-year plan emphasizes building infrastructure development, vaccination programs, etc. In the first five-year plan through different Population and Family Health Projects, the government established family planning programs, Maternal and Child Health programs, and different communicable disease control activities. Primary Health Care (PHC) is a vital component of overall healthcare and was established during the country's Second Five-Year Plan. During this period, the Health and Population Sector Program (HPSP) broadened the health services and focused on improving the health of the vulnerable population segment with a client-centered approach.[1,2,3]

An analytical framework used by WHO describes health systems by breaking them down into six core components: leadership and governance, service delivery, health system financing, health workforce, medical products, vaccines and technologies, and health information systems.[4] Bangladesh Government faces various challenges in proving efficient service delivery. Inefficient and ineffective referral system is one of the major concerns. According to the World Health Organization (WHO), referral is defined as a process in which a health worker at one level of the health system, lacking sufficient resources (such as medications, equipment, or skills) to manage a clinical condition, seeks assistance from a facility with better or different resources, either at the same level or a higher level, to help manage or take over the patient's case.[5]

A well-functioning referral system is essential for optimal patient care in any healthcare hierarchy[6]. It serves as a link for primary healthcare providers to connect patients with specialized healthcare resources and services beyond their immediate scope. It helps to reinforce the primary health care. Patients should be referred to higher-level facilities from primary care with proper referral notes from their attending physicians. These notes should indicate the patient's medical condition and the reason for the referral. However, the reality often differs; the limited resources available at these primary care centers frequently lead individuals to bypass them and seek healthcare directly at secondary or tertiary facilities. A study conducted in Bangladesh found that around 58% of participants were unaware of the referral system, and among patients visiting tertiary care hospitals, 59% were self-referred and the private facilities received a higher proportion of self-referred patients compared to government hospitals[7]. So, though Bangladesh has a good achievement in PHC but we need to do a lot to establish a structured referral system. Factors identified for referral in that study were

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inadequate treatment, inadequate facilities, critical cases, and lack of expert physicians[8]. It was also found that proximity to the referral hospital was also a significant factor in self-referral. Overcrowding in government facilities may also contribute to self-referral. In the secondary and tertiary healthcare facilities of Bangladesh, the bed occupancy ratios are almost 148.2% and 137% respectively, while the primary care facilities maintain a rate of only 79%.[9]

In a review study in Bangladesh identified four main themes and fourteen subthemes for successful implementation of referral system[10].

These include:

Themes	Subthemes
Improvement of Technology	Electronic referral
	Coordination
	Responsiveness
	Feedback
Improvement of delivering service Process	Effectivity
	Efficiency
Organization of health care delivery	Management, policy and planning
	Regulation
	Patient Centricity
Individual patient perspective	Insurance
	Social capital
	Transport
	Awareness, attitude, and satisfaction
	Social influence

Bangladesh has made remarkable achievements in the health sector in the last 50 years, such as improving life expectancy, reducing maternal and under-five mortality, increasing immunization coverage, implementing a TB control program, eradicating polio, and improving sanitation. All these are related to primary health care. Now, it is high time for Bangladesh to develop efficient and quality health care at the private and public levels.[11]

In the previous section, we discussed various themes and subthemes to improve and strengthen the referral system. We propose to conduct comprehensive research focused on identifying gaps in successfully implementing the referral system and developing appropriate strategies for a high-quality healthcare referral system. Our primary focus for strengthening and integrating the healthcare referral system in the Government health sector should be on enhancing infrastructure facilities, decentralizing healthcare services, improving patient transportation, implementing a web-based referral system, and addressing deficiencies in health information systems.

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Original Articles

Clinical Value of Serum Ca 19.9 Level As A Tumor Marker in Pancreatic Malignancy

Jahan SMS[1], Hussain MM[2], Islam T[3], Dewan MN[4], Das PK[5], Alam SI[6]

Abstract

Background: *Pancreatic cancer carries a poor prognosis; at operation approximately 25% of patients are found to have unresectable tumours even though CT has demonstrated that they are resectable. At our tertiary care centre, we intended to find out if there is an optimum cut-off value for the CA 19-9 level preoperatively that will indicate that the pancreatic cancer is unresectable despite radiologic imaging that suggests otherwise according to receiver operating characteristic (ROC) curve analysis.*

Objective: *To evaluate the clinical value of serum CA19-9 levels in predicting the resectability of pancreatic carcinoma according to receiver operating characteristic (ROC) curve analysis.*

Materials & Methods: *This study prospectively analyzed the clinical and imaging data including preoperative CA19-9 level in 25 patients with pancreatic cancer who underwent surgical resection in the department of surgery, DMCH from February 2012 to January 2013. Resectability of pancreatic cancer was evaluated at least by preoperative bolus-contrast, triple-phase helical computer tomography (CT) scan. ROC curve was plotted for the CA19-9 levels. The point closest to the upper left-hand*

corner of the graph were chosen as the cut-off point. The sensitivity, specificity values of CA19-9 at this cut-off point were calculated.

Results: *Resectable pancreatic cancer was detected in 09 (36%) patients and unresectable pancreatic cancer was detected in 16 (64%) patients. The cut-off point of CA19-9 level was calculated to be 188 U/mL and the sensitivity and specificity of CA19-9 at this cut-off point were 86.67% and 80.00% respectively.*

Conclusion: *Preoperative serum CA19-9 level is a useful marker for further evaluating the resectability of pancreatic cancer. Thus increased serum levels of CA19-9 (> 188 U/mL) can be regarded as an ancillary parameter for unresectable pancreatic cancer.*

Key words: *Serum CA 19.9, Tumor marker, Pancreatic malignancy.*

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Introduction:

Pancreatic carcinoma accounts for only 2.6% of all newly diagnosed malignancies.[1] It is the ninth most common malignancy and fifth most common cause for cancer related deaths.[2] Only 10% of patients have localized disease on presentation.[3] The prognosis of pancreatic cancer is extremely poor and its early diagnosis is difficult. Surgical resection is the best modality of treatment. However, local vascular

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involvement, nodal and distant metastases are frequently found at the time of diagnosis, thus losing the opportunity of operation.

Surgical resection represents the core of pancreatic cancer treatment but, unfortunately, at the time of diagnosis, only 15–20% of patients are detected with early-stage pancreatic malignancy and are eligible for resection.[4] Regrettably, up to 20–30% of radiological resectable malignancies show occult metastases at the moment of surgical exploration.[5] Furthermore, most of the resected patients die due to early local or distant recurrence. In recent years, the International Study Group of Pancreatic Surgery (ISGPS) and the International Association of Pancreatology (IAP) introduced the concept of biological resectability.[6] Since elevated preoperative serum levels of carbohydrate antigen 19.9 (CA 19.9)have been associated with both the intraoperative detection of occult metastases and worse disease-free survival, even in resectable pancreatic malignancy patients, CA 19.9 has become the main biological parameter to be used to assess biological resectability. CA19-9 was discovered in the serum of patients with colon cancer and pancreatic cancer in 1981.[7] CA19-9, also known as carbohydrate antigen 19-9 and cancer antigen 19-9 or sialylated Lewis a antigen is the most commonly used and best validated serum tumor marker for pancreatic cancer diagnosis in symptomatic patients and for monitoring therapy in patients with pancreatic malignancy.[7] Normally CA 19-9 is synthesized by normal human pancreatic and biliary ductal cells and by gastric, colon, endometrial and salivary epithelium. Usually CA 19-9 is present in small amounts in serum, but can be increased in several malignant gastrointestinal disorders too. Takahashi, in 2020, reported how preoperative CA 19.9 levels > 120 U/mL would allow one to define as "biologically" borderline resectable even tumors radiologically classified as resectable.[7] Therefore, the role of CA 19.9, already known and defined for diagnostic and prognostic purpose, has also acquired a preoperative staging role.In this study, we evaluated the clinical value of serum CA19-9 level in predicting the resectability of pancreatic carcinoma according to ROC curve analysis.

Objectives of the study

General Objective

Study the preoperative serum level of CA19.9 in evaluating resectability of pancreatic malignancy.

Specific Objective:

- To record preoperative assessment of serum CA19.9
- To correlate preoperative radiological findings & resectability of tumor with preoperative level of serum CA19.9
- To calculate a cut off value for serum CA19.9 level for resection of lesion.

Materials and Method:

The present study is a prospective cross sectional observational study which was conducted resection in the department of surgery, DMCH from February 2012 to January 2013. The study included 25 patients. Purposive sampling technique was used. Patient demographics, risk factors, associated symptoms including weight loss, jaundice and CA 19-9 values were the variables compared between the resectable & unresectable groups of pancreatic malignancy. A Receiver Operating Characteristic (ROC) curve was used in the estimation of cut off values for CA 19- 9 levels. Data was analyzed by SPSS version 24.

Result:

This study was carried out in 25 patients with pancreatic cancer who underwent surgical intervention at the department of surgery, DMCH from February 2012 to January 2013. Out of all patients 64% were male and 36% were female. Male and female ratio was 1.8:1.

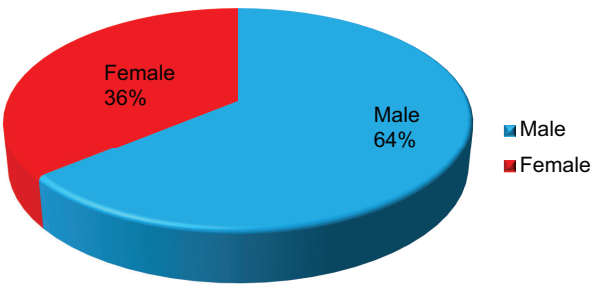

Fig-1: *Shows sex distribution of the patients*

Most of the patients (44%) belonged to 51 to 60 years age group.(fig-2) Almost all the patients presented with jaundice (88%).

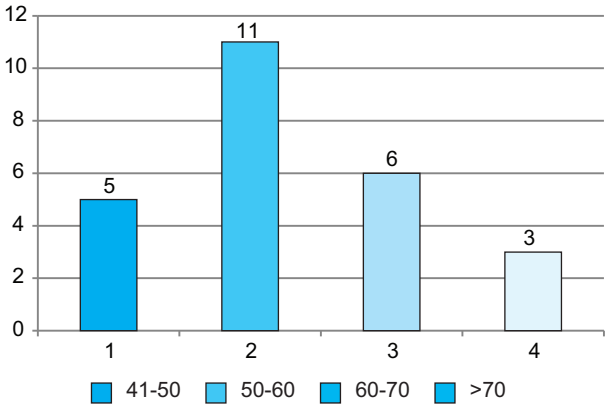

Fig-2: *Showing age distribution of patients*

Table-I

Shows clinical features of the patients

Symptoms	Frequency	Percent
Jaundice	22	88.0
Weight loss	18	72.0
Nausea	20	80.0
Loss of appetite	16	64.0
Pale stool	18	72.0
Pain	08	32.0
Vomiting	06	24.0

Out of them, 40% of the patient had serum bilirubin level more than 10mg/dl. 24(96%) patients was diagnosed with pancreatic adenocarcinoma confirmed by histopathogy. Among them 21(84%) patients had suspected carcinoma in CT scan as well as raised serum CA19-9 level.

Table-II

Shows CT scan, CA 19-9 and histopathological findings of the patients

Investigation	Frequency	Percentage
CT		
• Carcinoma	22	88.0
• OtherSerum Ca-19-9	03	12.0
• Raised	21	84.0
• Normal	04	16.0
Both CT scan and serum Ca 19-9		
• Suspected Carcinoma	21	84.0
• Other Histopathology	04	16.0
• Pancreatic adenocarcinoma	24	96.0
• Others	01	04.0

Peroperatively, 9(36%) patients had resectable cancer. On the other hand 16 (64%) patients had unresectable cancer among the 25 cases. According to the study serum Ca19.9 level found 0.6U/ml is lowest & 3006U/ml is highest. ROC curve revealed a cut off value of 188U/ml for CA 19-9 had sensitivity and specificity of 86.67% and 80.0% respectively which was highest to detect resectability of pancreatic cancer. Thus we concluded increased serum levels of CA19-9 (> 188 U/mL) can be regarded as an ancillary parameter for the unresectability pancreatic cancer.

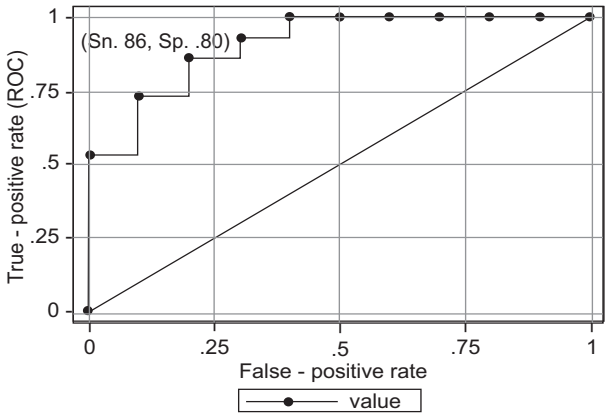

Fig-1: *Receiver Operating Characteristic (ROC) Curve of CA 19-9 level showing a value more than 188U/mL level has the highest sensitivity (86.67%) and specificity (80.00%) to detect the resectability of pancreatic malignancy*

Discussion:

Pancreatic cancer is one of the leading cause for cancer-related death. The overall five-year survival rate ranges from 0.4% to 4% being the lowest for any cancer.[8] Promt diagnosis of pancreatic cancer is difficult because it is asymptomatic in it's early stage. Local invasion and distant metastases are frequently found at the time of diagnosis.

Recently, considerable improvements in radiological imaging make helps to make decision regarding surgery for patients. Contrast enhanced CT Scan is the choice of investigation to detect the resectability of pancreatic cancer. However, approximately 25%-50% of patients with resectable disease on CT Scan are found to have unresectable lesions during surgery.[9]

CA19-9 is a useful tumor marker for the diagnosis of pancreatic adenocarcinoma. Besides its prognostic value is also noteworthy.

Preoperative serum CA19-9 level is an important marker for determining the resectability of pancreatic carcinoma. When the cut-off value of CA19-9 was 188 U/mL according to the point closest to the upper left-hand corner of the graph, the sensitivity, specificity value was 86.67%, 80.00% respectively, indicating that increased serum levels of CA19-9 (> 188 U/mL) can be considered as an auxiliary denominator for the unresectability pancreatic cancer. In our study, pancreatic cancer was resectable only in 2 patients whose preoperative serum CA19-9 level was over 188 U/mL.

According to Kowalchuk et al. the sensitivity, specificity, positive and negative predictive values of CA 19-9 are 82.4%, 92.3%, 91.4% and 83.9%, respectively, in 51 patients, and the cut-off value of CA19-9 was 256.4 U/mL. Though the results are similar to our data, the cut-off value was lower in our study (256.4 U/mL vs 188 U/mL).[10]

The present study has some limitations. It was a single centre study. Besides the sample size was very small. So further large scale multi-centre study should be conducted to assess the role of CA 19-9 to predict the resectability of pancreatic malignancy.

Conclusion:

Preoperative serum CA19-9 level is a useful tool for management of pancreatic cancer. Never the less, serum levels of CA19-9 (>188 U/mL) can be used as an important marker to identify unresectable pancreatic cancer.

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The Diagnostic Role of Abductor Pollicis Brevis - First Dorsal Interosseous (APB-FDI) Index in Diagnosing Amyotrophic Lateral Sclerosis (ALS)

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Abstract

Background: *This study aimed to assess the diagnostic role of the Abductor Pollicis Brevis - First Dorsal Interosseous (APB-FDI) Index in the diagnosis of Amyotrophic Lateral Sclerosis (ALS) among the Bangladeshi population. It also compared its diagnostic performances with first dorsal interosseous first dorsal interosseous and abductor digiti minimi (FDI-ADM) and (ADM-APB) ratios measuring the split hand phenomenon.*

Methods: *This cross-sectional study was carried out in the Department of Neurology, Sir Salimullah Medical College & Mitford Hospital, and Dhaka Medical College Hospital, Dhaka, from March 2019 to September 2021. It also determined the APB-FDI index in ALS patients and compared the findings with age and gender-matched healthy control and disease control (Hirayama disease). The data was analyzed with receiver operating characteristic (ROC) curves and calculated area under the curve (AUC) for each ratio. Integrated discrimination improvement (IDI) and Decision Curve Analysis (DCA) to compare diagnostic accuracy over FDI-ADM and ADM-APB ratios.*

Results: *Total 43 people were studied with ALS, 30 healthy people, and 10 Hirayama patients. The cutoff values of APB-FDI Index, ADM-APB ratio, and FDI-ADM ratio are 4.27, 1.04, and 2.20 respectively. The APB-FDI Index has a high AUC of 0.9, with good sensitivity and specificity. However, for Hirayama disease, the APB-FDI Index cutoff value is 11.6. The APB-FDI Index is clinically effective with optimal threshold probabilities identified through the Youden-Index (APB-FDI Index-0.72, ADM-APB CMAP amplitude ratio-0.51, and FDI-ADM CMAP amplitude ratio-0.17). Its standardized net benefits exceed healthy control and Hirayama when risk thresholds are between 0.1 and 0.8. The IDI results showed that the APB-FDI Index was superior to the ADM-APB ratio and FDI-ADM ratio.*

Conclusion: *APB-FDI Index is the sensitive, specific, and early diagnostic marker for ALS.*

Keywords: *amyotrophic lateral sclerosis; compound muscle action potential; split hand; APB-FDI index.*

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Introduction:

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disorder[1] involving the motor neurons, a heterogeneous disease that begins focally and becomes widespread within a short period. The patient dies within three years of symptom onset due to respiratory muscle involvement.[2] The mechanisms of neuronal degeneration include oxidative stress, excitotoxicity, mitochondrial dysfunction, glial activation, RNA processing, and growth factor abnormalities. They may occur parallelly or in sequence.[3] There is no definitive diagnostic tool for diagnosing ALS. The progressive upper motor neuron (UNM) and lower motor neuron (LMN) findings in the history and examination may diagnose ALS with 95% accuracy.[4] For the uniformity of the diagnosis, El Escorial criteria were developed.[5,6] The sensitivity of these criteria is low in case of early stages of the

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disease.[7] Possible differentials like Spinal muscular atrophy (SMA), Hirayama disease, cervical myeloradiculopathy, and Multifocal motor neuropathy with conduction block (MMCB) are sometimes difficult to exclude.[8] The median diagnostic time from the symptom onset is 11.5 months, and about half of the patients received alternative diagnoses.[9] A dissociated pattern of muscle atrophy, first described as a split hand by Wilbourn[10], was observed in 60-70% of ALS patients.[9,11] Here the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles are involved more than the hypothenar muscles. The cause of differential muscle involvement in ALS is unknown; there are theories for cortical and peripheral mechanisms.[12] Among the postulated peripheral mechanism, higher nodal persistence of sodium currents in the APB and FDI than in Abductor Digiti Minimi (ADM) might be a mechanism.[13] Furthermore, the cortical mechanism involves preferential involvement of corticomotoneuronal input to the thenar muscles.[14] In our day-to-day activities, using a pincer grasp is essential (adductor pollicis, first dorsal interosseous and flexor pollicis brevis muscles.), making the spinal motor neurons innervating these muscles liable to more oxidative stress.

The corticospinal connections to FDI far outnumber those of ADM. It may produce more glutamate excitotoxicity in the FDI spinal neurons.[15] The APB-FDI index quantifies this preferential muscle involvement, which is derived by multiplying the APB and FDI CMAP amplitudes and dividing the product by the ADM Compound Muscle Action Potential (CMAP) amplitude according to the following formula: (APB FDI Index = $\frac{\text{ADM}_{\text{CMAP}} \times \text{FDI}_{\text{CMAP}}}{\text{ADM CMAP}}$ [16].

This index helps detect the early stages of ALS, not fulfilling the diagnostic criteria.[11] This phenomenon did not differ in different stages and certainty.[17] The cutoff value of this index is 5.2 and exhibits 74% sensitivity and 80% specificity in diagnosing ALS.[11] It is more sensitive than the two other ratios used to quantify the split hand phenomenon (ADM/APB CMAP amplitude ratio >1.7, 51% sensitive, and FDI/ADM less than 0.9 is 34 % sensitive).[16] This method was not examined among the Bangladeshi population, and the cutoff value is largely unknown among the Bangladeshi people. So, it was planned to assess the diagnostic role of the APB FDI Index, ADM/APB CMAP amplitude ratio, and FDI/ADM CMAP amplitude ratio in the diagnosis of Amyotrophic Lateral Sclerosis (ALS) and to determine their cutoff values for the Bangladeshi population. Their diagnostic performance was also cpmpared in diagnosing ALS.

Methods:

This cross-sectional study was done in the Department of Neurology at Sir Salimullah Medical College & Mitford Hospital, Dhaka, and Dhaka Medical College from March 2019 to September 2020. Ethical clearance was obtained from the ethical review committee of Sir Salimullah Medical College Mitford Hospital (SSMC/2019/224).

Participants:

All the probable, possible, and definite cases of Amyotrophic lateral sclerosis (ALS) were enrolled according to the revised El Escorial Diagnostic Criteria for ALS[5], presented in electrophysiology lab of the neurology department of Sir Salimullah Medical College & Mitford Hospital and Dhaka Medical College. Patients aged 18 years or more and of both sexes were included in this study. Patients with undetectable CMAP amplitude of any muscle (APB, FDI, and ADM), associated radiculopathy, peripheral neuropathy, or neuromuscular disease were excluded from the study. Healthy volunteers were recruited as the control. Patients diagnosed with Hirayama disease were also taken according to criteria outlined by Tashiro et al.[18] and confirmed with MRI cervical spine flexion and extension view as disease control. Both the cases and control participants gave Informed written consent. The calculated sample size was 30 for ALS and healthy-control, considering the abnormal split hand index proportion of 41% in the case and 5% in the healthy control group, according to Kuwabara et al. 2008.[19] With a 5% level of significance in the two-tailed test and 90% power, following formula was used to calculate the sample size

$$\text{Sample size} = \left(\frac{r+1}{r}\right)\frac{P(1-p)(z_\beta+Z_{\alpha/2})2}{(p_1-p_2)^2}$$

(Z_α=1.96 at 5% level of significance,

Z_β=1.28 at 90% power, P_1=0.41 P_2=0.05,

P= (p_1+p_2) ÷2=0.23).

The electrophysiology findings of 10 Hirayama patients were also compared with the ALS patients.

Study procedure:

The demographic profile and complaints were recorded in a preformed case record form. The expert neurologist did detail Neurologic examinations. The hemoglobin, total count, differential count, blood sugar, serum creatinine, brain CT scan, and MRI cervical spine were done to exclude the other diagnoses for all the included patients. Revised El Escorial Diagnostic Criteria for ALS diagnose patients with ALS.[5] The disability of ALS was assessed with ALS Functional Rating Scale-Revised (ALS-FRS-R).[20] The Hirayama disease was diagnosed with Tashiro criteria.[18]

NCS assessment:

The NCS was done with NIHON KOHDEN Neuropack MEB-7102 mobile unit with a two-channel evoked potential/EMG measuring system (Nihon Kohden Corporation, Tokyo, Japan) according to the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine and Rehabilitation guidelines. The temperature was maintained at 33-34 degrees centigrade. The neurophysiological study was done on the most affected hand and opposite lower limb in cervical onset MND, including the measurement of motor conduction velocity (MCV), distal motor latency (DML), and compound muscle action potential amplitude (CMAP), F-latency, sensory conduction velocity (SCV), distal latency and sensory nerve action potential amplitude (SNAP) of the examined nerves. In limb onset type MND, the electrophysiological study was done on the most affected lower limb and opposite upper limb, and in bulbar onset MND in the right hand and left leg.

Motor nerve conduction studies were performed on the median and ulnar nerves with compound muscle action potential (CMAP) responses recorded from the abductor pollicis brevis (APB), first dorsal interosseous (FDI), and abductor digit minimi (ADM) muscles. The responses were recorded by 10 mm gold disc electrodes positioned in a belly tendon arrangement over each muscle. Active electrode was placed over the midpoint of the respective muscle, ensuring a negative take-off of the CMAP response, while the reference electrode was positioned over the base of the thumb (APB and FDI CMAP recordings) and base of digit 5 (for ADM CMAP recordings). The distance was set between the stimulating cathode and active electrode for APB and ADM, CMAP to 5 cm, and for FDI CMAP to 8 cm. We set the filter at 3 and 10 kHz, the sweep speed at 20 msec, or 2 msec/division, and the sensitivity for recording CMAP responses at 5 mV. The pulse duration was 0.2 ms. Additional 25% current was increased to ensure the supramaximal stimulation. Measurements of the compound muscle action potential (CMAP) included latency (onset and peak) and conduction velocity (CV). In the study, belly tendon montage was used which gave the stimulation at the wrist using an orthodromic technique with a bipolar stimulator, and expressed the distal latency as a millisecond and conduction velocity as a meter per second.

The APB FDI index was calculated by multiplying the CMAP amplitude recorded over the APB and FDI muscles and dividing this product by the CMAP amplitude recorded over the ADM muscle, as follows: APB FDI sindex = APB CMAP X FDI CMAP /ADM CMAP. ADM/ APB CMAP amplitude ratio, and FDI/ADM CMAP amplitude ratio was also calculated. For the analysis, the values were taken from the most affected hand in case of ALS and Hirayama disease. In the case of control, generally right-hand parameters were used.

Statistical analysis:

Data were analyzed using SPSS 20 and R (v4.1.1). Qualitative data were expressed in number, percentage, normally distributed quantitative data as mean (±SD), and non-normal data as median (IQR). Comparisons between groups (continuous parameters) were made by Student's t-test and skewed parameters with Mann Whitney U test. The Chi-

Square test compared categorical parameters. Several indicators were used to measure the performance of the APB-FDI Index, FDI-ADM, and ADM-APB ratios. The prediction scoring systems were analyzed using the receiver operating characteristic (ROC) curve and the area under the ROC curves (AUC). DeLong's test was used to determine the statistical difference between AUCs. The Integrated Discrimination Improvement (IDI) indicator was also used to evaluate their performance. Decision Curve Analysis (DCA) was also performed to assess the clinical usefulness of these ratios. The significance of the results, as determined by a 95% confidence interval and a value of $p<0.05$, was considered statistically significant.

Results:

This cross-sectional study was conducted in the Neurology department of Sir Salimullah Medical College & Mitford Hospital and Dhaka Medical College, Dhaka, from March 2019 to March 2022. Total 57 suspected patients with ALS were screened and 43 patients were included after considering the patient's inclusion, exclusion criteria, and consent. There was 30 age and sex-matched healthy control (Figure 1) and 10 Hirayama patients also to compare the index and the ratios (APB-FDI Index, ADM-APB CMAP amplitude ratio, and FDI-ADM CMAP amplitude ratio)

Demographic and clinical profile of the participants:

The age of the ALS group was generally >40 years (88.4%), and the mean age (±SD) was 56.1(±14.8). The age of patients with ALS was comparable with the control. Whereas the Hirayama patients were generally < 40 years (90%), and the mean age was 24.7(13.7). The males were similarly frequent in ALS, 34(79.1%), and Hirayama groups, 7(70%). 15(34.4%) of the ALS patients were underweight. The mean (SD) weight of the ALS and Hirayama was 18.8(1.8) and 21.6(2.2), respectively (Table 1).

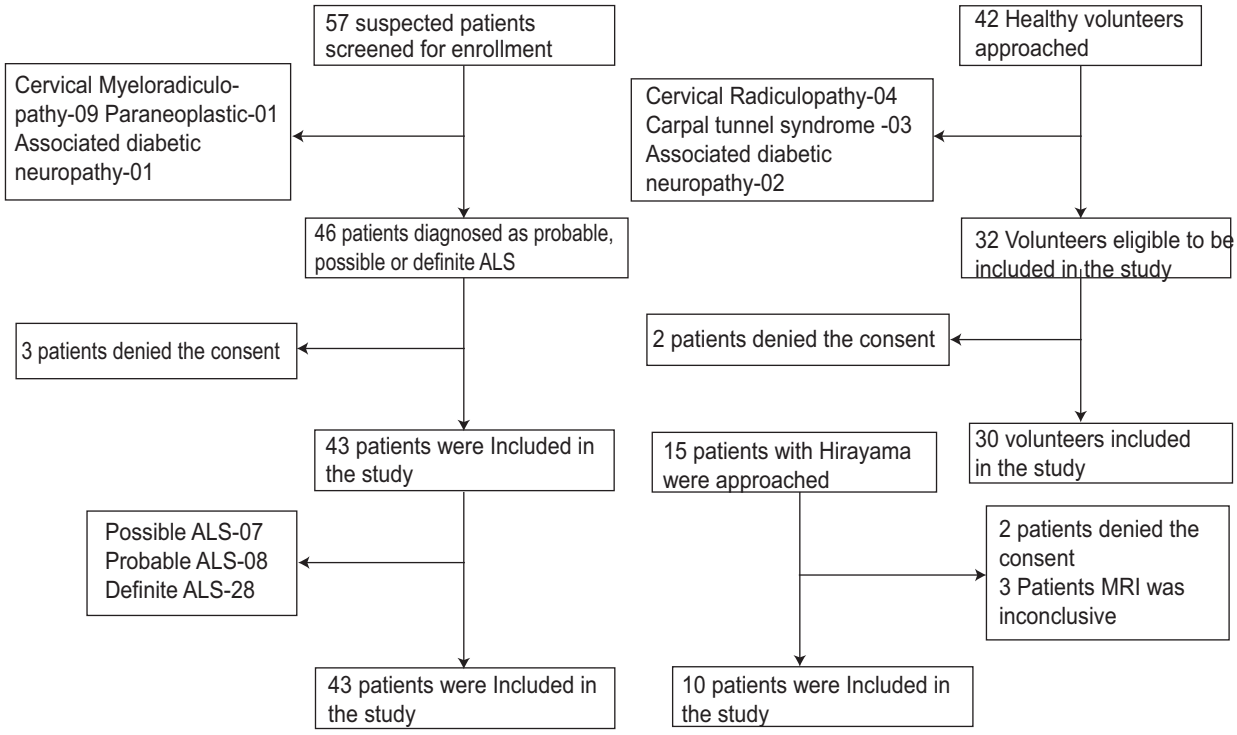


Fig.-1: *Patients and volunteer selection for this study. We screened 57 suspected patients with Motor Neuron Disease and included 43 patients after screening. We had 30 healthy volunteers and ten patients with Hirayama disease for comparison*

Table I

Demographic characteristics of the study participants

Trait	Group 1 (cases) N=43	Group II(Control) N=30	Group III (Hirayama) N=10
Age in years, mean (SD)	56.1(14.8)	57.7(9.7)	24.7(13.7)
Age groups, n (%)			
<40 years	5(11.6)	2(6.7)	9(90)
40-60 years	22(51.2)	21(70)	0(0)
>60 years	16(37.2)	7(23.3)	1(10)
Sex (Male), n (%)	34(79.1)	22(73.3)	7(70)
BMI, Mean (SD)	18.8(1.8)	22.8(1.65)	21.6(2.2)
BMI groups, n (%)			
Underweight (<18.5 kg/m^2)	15(34.9)	0(0)	1(10)
Normal weight (18.5-22.9 kg/m^2)	21(48.8)	18(60)	7(70)
Overweight (23-24.9 kg/m^2)	6(14)	11(36.7)	1(10)
Obesity (25-29.9 Kg/m^2)	1(2.3)	1(3.3)	1(10)

Table II

Clinical characteristics of the ALS patients

Clinical Characteristics	Results
Disease Categories according to El scorial criteria,	n (%)
Possible	7(16.3)
Probable	8(18.6)
Definite	28(65.1)
Age of onset, Median (IQR)	57(46-64)
Phenotype according to the onset	
Bulbar	3(7)
Cervical	31(72.1)
Lumbar	2(4.7)
Mixed	7(16.3)
Disease duration, months, median (IQR)	6(5-10)
ALS function rating score, median (IQR)	27(25-32)

In this study total of 28(65.1%) had definite ALS and presented with median (IQR), 6(5-10) months of illness. They were generally cervical phenotype, 31(72.1%), and they had ALS functional rating score, median (IQR) of 27(25-32). (Table II).

The median (IQR) CMAP amplitude of FDI, APB, and ADM, 2.8(0.8-5.3), 2.3(0.8-4.6), and 3.8(1.8-6.9) respectively were significantly low (p-value <0.001) than the healthy control. Among ALS patients amplitude of FDI and APB is lower than the amplitude of ADM. The median (IQR) of APB-FDI index, APB-ADM ratio and FDI-ADM ratio were 1.7(0.3-3.8), 0.6(0.3-1.1) and 0.8(0.4-1.1) were significantly lower than that of healthy control (p value<0.001, 0.016, 0.003 respectively). The ADM-APB ratio of 1.7(0.9-3.2) is significantly higher than the healthy control (p-value 0.016). (Table III).

Table III

Comparison of Electrophysiologic findings with the healthy controls and Hirayama disease

Muscle examined	Group in-30	CMAP amplitude in mV Group II, n=30	P value [a]	CMAP amplitude in mV Group III, n=30	P value [b]
FDI (CMAP amplitude in mV)	2.8(0.8-5.3)	10.4(8.5-12.6)	<0.001	1.3(0.9-4.9)	0.7
APB (CMAP amplitude in mV)	2.3(0.8-4.6)	7.9(6.5-9.3)	<0.001	6.4(5.3-8.1)	<0.001
ADM(CMAP amplitude in mV)	3.8(1.8-6.9)	9.7(6.2-11.8)	<0.001	0.7(0.4-3.6)	0.003
APB-FDI Index [c]	1.7(0.3-3.8)	9.9(6.1-13.1)	<0.001	13.6(6.9-15.7)	<0.001
APB/ADM	0.6(0.3-1.1)	0.8(0.7-1.2)	0.016	6.3(3.2-13,9)	<0.001
ADM/APB	1.7(0.9-3.2)	1.2(0.9-1.4)	0.016	0.2(0.1-0.3)	<0.001
FDI/ADM	0.8(0.4-1.1)	1.2(0.9-1.4)	0.003	2(1.2-2.7)	0.002

a-comparison between ALS and healthy control

b-Comparison between the ALS and Hirayama

c- calculated with the formula APB FDI index (SI) = APB_{CMAP} X FDI_{CMAP} /ADM_{CMAP}

APB-FDI Index, FDI-ADM, and ADM-APB ratios.

CMAP amplitude of the FDI did not differ between the ALS and Hirayama patients (p-value 0.7). Whereas the median (IQR) amplitude of the APB, 6.4(5.3-8.1), is significantly higher (p-value <0.001), and the amplitude of ADM, 0.7(0.4-3.6) was significantly lower (p value0.003) in the Hirayama than ALS.

The median (IQR) of APB-FDI index, and FDI-ADM ratio was 13.6(6.9-15.7), and 2(1.2-2.7) were significantly higher in Hirayama group than that of healthy control (p value<0.001, <0.001, 0.002 respectively). Whereas the ADM-APB ratio of 0.2(0.1-0.3) is significantly lower in the Hirayama group than in the ALS group (p-value <0.001).

There was no correlation between the disease severity of ALS and the APB-FDI index (r= -0.16, p-value 0.28) (Figure 2).

Comparison of ROC curves

To diagnose ALS, the APB-FDI Index, ADM-APB CMAP amplitude ratio, and FDI-ADM CMAP amplitude ratio are used with cutoff values of 4.27, 1.04, and 2.20, respectively. The APB-FDI Index has a high sensitivity and specificity with an AUC of 0.9. However, when differentiating Hirayama disease, the APB-FDI Index's cutoff value is higher at 11.6, but its specificity is lower at 0.7. In comparison, the APB-FDI Index is the most effective in diagnosing ALS compared to healthy individuals, but it has lower performance in differentiating Hirayama disease (Figure 2).

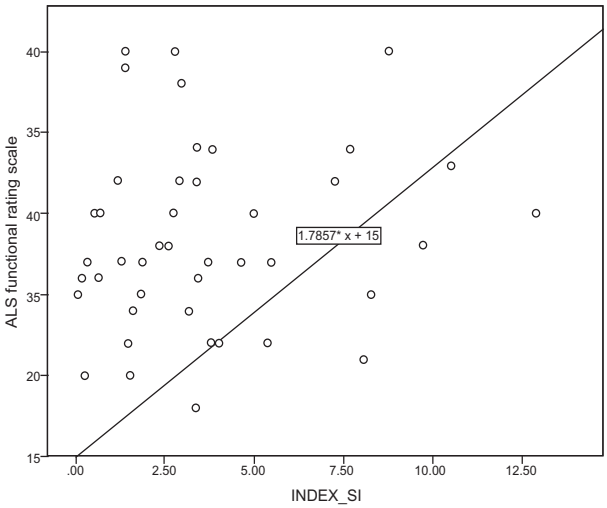
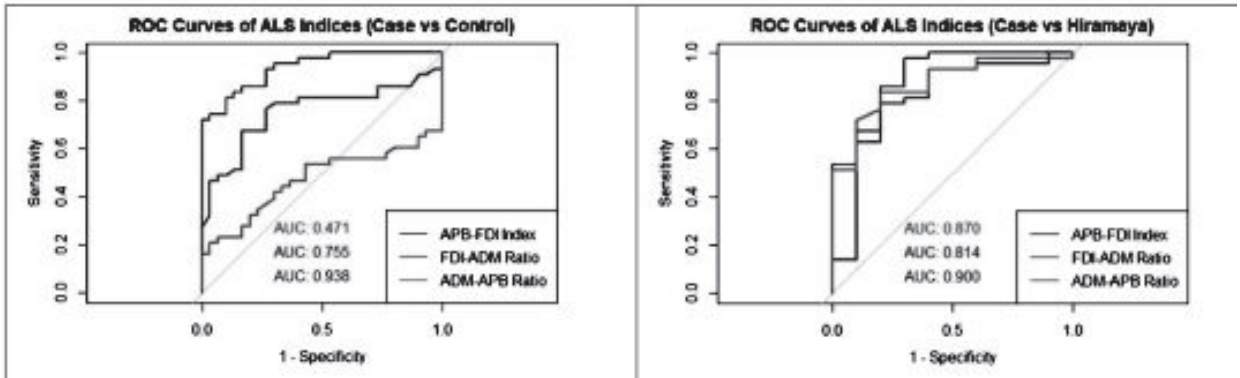


Figure 2: *Correlation between the disease severity of ALS assessed with ALS functional rating scale and the APB-FDI index (r= -0.16, p-value 0.28)*



Index/Ratio	AUC	95%CI	P-value	Optimal cut-off	sensitivity	specificity	Youden's index
FDI-APB index	0.938	0.889-0.987	<0.001	4.27	72.09	100	0.7209
FDI-ADM ratio	0.755	0.641-0.870	<0.001	1.04	67.44	83.33	0.5078
ADM-APB	0.471	0.336-0.606	0.67	2.205	20.93	96.67	0.1760

Index/Ratio	AUC	95%CI	P-value	Optimal cut-off	sensitivity	specificity	Youden index
FDI-APB index	0.900	0.786 – 1.0	<0.001	11.66	0.977	0.7	0.677
FDI-ADM ratio	0.814	0.643-0.985	0.0003	1.215	0.791	0.8	0.591
ADM-APB	0.870	0.758-0.982	<0.001	0.325	0.837	0.8	0.637

Figure 3: *Comparison of the ROC curve and diagnostic performances of APB-FDI Index, ADM-APB CMAP amplitude ratio, and FDI-ADM CMAP amplitude ratio*

Comparison of IDI

This evaluated the prediction performance of the scoring systems by calculating IDIs, corresponding P values, and confidence intervals using 1000 times bootstrap resampling (Table IV). The IDI results showed that the APB-FDI Index was superior to the ADM-APB CMAP amplitude ratio and FDI-ADM CMAP amplitude ratio in healthy control and Hirayama although p value is insignificant. The IDI for APB-FDI Index in comparison to ADM-APB CMAP amplitude ratio and FDI-ADM CMAP amplitude ratio was 0.55 (95% CI -0.661, -0.434; p=0.481) and -0.55 (95% CI -0.658, -0.440; p=0.504), respectively in healthy control. In Hirayama, the IDI for APB-FDI Index in comparison to ADM-APB CMAP amplitude ratio and FDI-ADM CMAP amplitude ratio was -0.228 (95% CI -0.416, -0.015; p=0.487) and -0.368 (95% CI -0.541, -0.172; p=0.465), respectively.

Table IV

Pairwise comparison of IDIs in overall patients

Comparison of models(New model VS reference model)	IDI	95% CI of IDI	*P*-value of IDI
For healthy control			
FDI-APB index vs FDI-ADM ratio	-0.549	-0.658, -0.440	0.504
FDI-APB index vs ADM-APB	-0.545	-0.661, -0.434	0.481
FDI-ADM ratio vs ADM-APB	0.007	-0.035, 0.051	0.495
For Hirayama			
FDI-APB index vs FDI-ADM ratio	-0.368	-0.541, -0.172	0.465
FDI-APB index vs ADM-APB	-0.228	-0.416, -0.015	0.487
FDI-ADM ratio vs ADM-APB	0.133	-0.028, 0.262	0.495

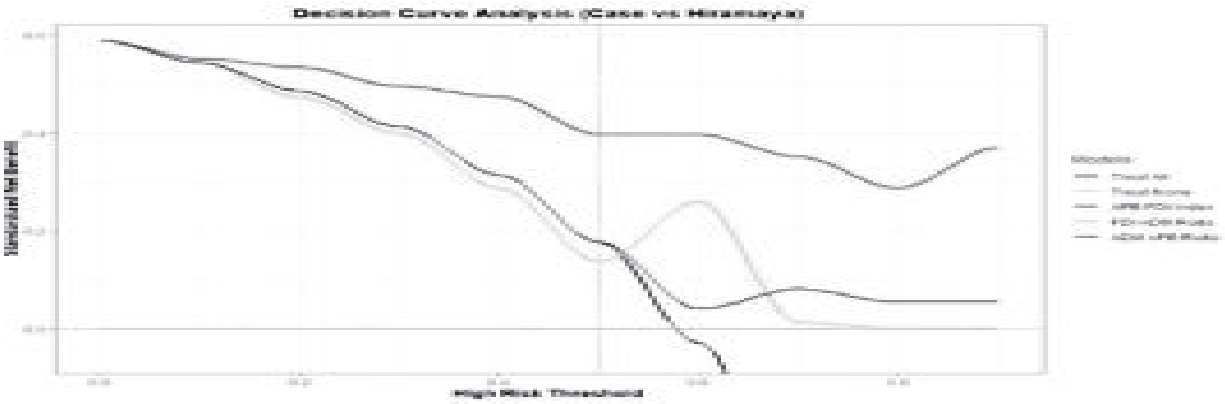


Figure 4. *DCA curves of APB-FDI Index, ADM-APB CMAP amplitude ratio, and FDI-ADM CMAP amplitude ratio*

Comparison of DCA curves

The results of DCA (Fig 4) demonstrate the clinical value of evaluating standardized net benefits (sNBs) and risk threshold probabilities using the APB-FDI Index, ADM-APB CMAP amplitude ratio, and FDI-ADM CMAP amplitude ratio. The sNBs of the APB-FDI Index were higher than the extreme curve for healthy control and Hirayama when the range of risk threshold probabilities was between 0.1 and 0.8. Compared to the ADM-APB CMAP and FDI-ADM CMAP amplitude ratios, the APB-FDI Index had higher sNBs when the range of threshold probabilities was between 0.1 and 0.8, indicating its broad clinical utility. Optimal threshold probabilities were also determined for each index using the Youden-Index (APB-FDI Index-0.72, ADM-APB CMAP amplitude ratio-0.51, and FDI-ADM CMAP amplitude ratio-0.17), and the DCA results show that the APB-FDI Index had higher sNBs than the other two ratios. Furthermore, the results and conclusions remained consistent for threshold probabilities between 0.45 and 0.80.

Discussion:

This study confirms the split hand phenomenon in ALS patients, where the CMAP amplitude of the ADM muscle is higher than that of the FDI and APB muscles. This phenomenon in measured using the APB-FDI index, APB-ADM ratio, and FDI-ADM ratio. The cutoff values for these measurements are 4.27, 1.04, and 2.20, respectively. The APB-FDI index is more sensitive and specific than the other two ratios, with a high AUC. However, for Hirayama disease, the APB-FDI index cutoff value is 11.6, and it shows broad clinical utility with standardized net benefits exceeding those of healthy controls and Hirayama patients when the risk thresholds are between 0.1 and 0.8. The IDI results indicate that the APB-FDI index is superior to the ADM-APB CMAP amplitude ratio and FDI-ADM CMAP amplitude ratio in healthy controls and Hirayama patients.

This study was done among a small number of Bangladeshi ALS patients. NCS parameters may differ in demography and physical factors[20]; we cannot generalize the findings to different races, ages, and physical traits. It needs a multicentered and multinational prospective study to generalize.

In the present study, most ALS patients were 40 years or more, were generally male, and one-third had low body mass index. It is concordant with the demography and characteristics of ALS patients.[2,4,21] Most of the patients were a cervical onset phenotype. The predominant phenotype of ALS is bulbar in some studies[22], but in China dominant type is limb onset[23] in the case of sporadic ALS. As in this study, hand cervical phenotype is frequent here. The patients with Hirayama were generally young and male, as found in the other studies. [25,26]

The diagnosis of ALS is not always straightforward. There are no specific biomarkers of ALS, and it is mainly diagnosed

by criteria.[27,28] Accurate and early diagnosis is essential to increasing the life expectancy of ALS patients.[29] The most used diagnostic criteria are the revised El Escorial criteria (rEEC) and Awaji criteria (AC), has sensitivity ranges from 40-70%, which increases with the progression of the disease.[30] Electrophysiology may help diagnose early ALS, as some electrophysiologic findings may appear earlier. Spilt hand phenomenon is commonly found across all stages and degrees of certainty of ALS.[17,18]

The split hand phenomenon was first described by Wilbourn.[10] Satoshi Kuwabara [18], in their research electro physiologically confirmed the preferential involvement of APB and FDI among ALS patients. In their study, they elucidate APB-ADM, FDI-ADM, and FDI-APB ratio. Among the healthy control, the ratio of APB-ADM, FDI-ADM, and FDI-APB were 1(.3), 1.5(0.4), and 1.6(0.5), respectively.[10] Among the healthy subjects, the APB-ADM ratio was 0.8(0.7-1.2), FDI-ADM was 1.2(0.9-1.4) [18], and both were almost similar. In our study The cutoff values, ADM-APB CMAP amplitude ratio, and FDI-ADM CMAP amplitude ratio are 4.27, 1.04, and 2.20, respectively. In this study, among the ALS patients, the APB-ADM value was 0.6(0.3-1.1), and the FDI-ADM value was 0.8(0.4-1.1). The slight difference in the value might be due to different reporting parameters. Moreover, they used the mean, whereas we used the median. And in our study, the parameter was not normally distributed. They examined the ratio in lower motor neuron disorders (LMND), cervical spondylotic amyotrophy (CSA), and polyneuropathy. They found that the findings are specific to ALS.[18]

We found few studies comparing the findings in Hirayama disease, which also presents with the small muscle of hand wasting.[31] This study also found that the split hand phenomenon is unique to ALS. The ratio of APB-ADM and FDI-ADM is reversed in Hirayama disease 6.3(3.2-13,9) and 2(1.2-2.7), respectively. In the case of Hirayama disease, the reverse split hand phenomenon is described in some studies. One study reported APB-ADM ratio 0.89 ± 0.98.[17] APB amplitude of Hirayama in our study was 6.4(5.3-8.1), similar to Kalita et al.[32] They found CMAP ratio of ADM-APB was 0.43 (0.29), and in our study, the median value was 0.2(0.1-0.3). Moreover, we found wasting is more prominent in APB than in the FDI (.28 vs. 2.3).

In a study, an ADM-APB ratio >1.7 was found to be 51% sensitive and 99% sensitive [16]; in our study, we found the median ratio of 1.7of (0.9-3.2), and a value >2.2 can diagnose ALS with 21% sensitivity and 96% specificity.

The split hand index was first examined by Menon et al.[11]; they found the index in ALS was 3.5 ± 0.6, SI cutoff value of 5.2 exhibiting a sensitivity of 74% and specificity of 80%. Our study found that the median index was 1.7(0.3-3.8), and a cutoff value lower than 4.2 can diagnose ALS with 72% sensitivity and 100% specificity. In another study, the spilt hand index in Hirayama was found as 13.68 (9.39), whereas in our study, it was 13.6(6.9-15.7), and in ALS, they found it 2.13 (1.90)[32]. In this study, we affirmed the findings of other studies.

We evaluate which ratio performs better using indicators such as AUCs, IDIs, and DCAs. Based on DCA curve analysis, when the threshold probabilities were between 0.5 to 0.7, the order of performance was as follows: APB-FDI, FDI-ADM, and ADM-APB ratios. The APB-FDI index outperformed in all threshold probabilities, but FDI-ADM performed better than ADM-APB after threshold probabilities of 0.5.

Using decision curve analysis (DCA) has several advantages, including the consideration of patient and physician preferences and the use of a threshold probability metric. DCA helps in evaluating the benefits and harms associated with prediction models by assessing the value of correctly treating a positive case versus the risk of treating a false positive case. This makes it an essential tool in clinical decision-making. When determining the risk threshold, a model with a higher standardized net benefit (sNB) is deemed superior.[32]

This study found that the APB-FDI index is more effective than other groups, with an AUC of 0.93 and a 95% confidence interval of 0.99-0.98. However, the AUC for FDI-ADM and ADM-APB were only 0.75 and 0.47, respectively. The Youden Index, which summarizes the receiver

operating characteristic curve and places equal importance on sensitivity and specificity[33], showed a high score of 0.72 for the APB-FDI index and a very low score of 0.18 for ADM-APB.

This study found that the overall IDA was less than 0, meaning the model's performance could have been better. Nevertheless, the APB-FDI index performed slightly better than the other two ratios, although the difference was not significant.

This research has shown that the APB-FDI index is a more effective diagnostic tool than others, as it simultaneously considers all three muscles' involvement. Nevertheless, the APB-FDI test may be helpful in cases of severe muscle atrophy and concomitant entrapment neuropathy. It should still be routinely administered to evaluate small muscle wasting in the hands. This can help reduce unnecessary interventions for ALS patients, as research has shown that 5% of ALS patients undergo spinal surgery and 42% have lower back operations.[35]

In this study, a comprehensive analysis of the diagnostic performances. However, it is essential to note that this study was provided had certain limitations. The small sample size and the cross-sectional design are inherent limitations that may affect the generalizability of our findings. Additionally, as our data was obtained in real-time, the results may change throughout the disease. Future studies should establish whether this phenomenon is maintained in advanced disease stages through prospective analysis. Unfortunately, due to the limited sample size, subgroup analysis could not be conducted. Further studies are recommended comparing this phenomenon in different phenotypes of ALS while also considering the duration of the disease. It should be noted that most patients were evaluated during the routine diagnostic process.

Conclusion

APB-FDI Index, depicting the split hand phenomenon, is a highly sensitive and specific diagnostic marker and may be helpful in early and conflicting instances to diagnose ALS. Its diagnostic value is also higher than other diagnostic tests, like APB-ADM and FDI-ADM ratio, which reproduce the split hand phenomenon.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper

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Characteristics and Outcome of Headache in COVID-19 Patients in a Tertiary Care Centre of Bangladesh

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Abstract

Background: *Although the symptoms of coronavirus disease 2019 (COVID-19) are predominantly respiratory. Headache is one of the most frequent neurological symptoms. There is a wide variation in the prevalence of headaches, and little is known regarding the characteristics and outcomes of headaches in COVID-19 patients. So, this study aimed to determine the characteristics and headache outcomes among COVID-19 patients.*

Methods: *This was a hospital-based prospective cohort study conducted in Dhaka Medical College Hospital from January 2021 to December 2021. Confirmed COVID-19 patients with Reverse Transcription Polymerase Chain Reaction (RT-PCR) were enrolled in the study. The severity of the headache was assessed by the Numerical Rating Scale (NRS, 0-10). All the patients with headaches were followed up by telephonic interviews in the 2nd week and at the end of the 4th week of the onset of the headache. For patients who experienced persistent headaches after 4th week, the impact of headaches on quality of life was assessed with the Headache Disability Index (HDI).*

Results: *We included 362 patients in this study. The majority (52.5%) of the study population belonged to severe COVID-19 infection. Fever was the most common (63.81%) symptom among the study subjects. Headache was present in 19.06% of the patients. The mean (±SD) age of participants was 54(±14.7). Patients having headaches were younger 44.2±13.8 vs 56±13.8, p<0.05) than those have no headaches. Headache was more prevalent among the female (37[53.6%] vs 102[34.8%]). Tension-type headache (TTH) was the most common (60%) headache phenotype. The majority (68.12%) of the cases of headache occurred concomitantly with other COVID-19 symptoms. COVID-19-related headaches were, in most cases, bilateral, pressing, and of moderate intensity. Fever and pre-existing headaches were associated with significantly more frequency, duration, and intensity than COVID-19 headaches (p<0.05). Most patients (86.9%) recovered from headache within 4 weeks of onset. Median (IQR) recovery time was 10 (7.75) days. Nine patients (13.1%) did not recover from headaches in the 4th week of the survey. The Mean (±SD) HDI score was 24.4(±0.76) in patients who experienced headaches at the end of 4th week, which indicates mild disability.*

Conclusion: *This study revealed that headache was present in about one-fifth of the hospitalized patients with COVID-19. Younger age and female gender were significantly associated with headaches. Most of the patients recovered within four weeks of the onset of headache.*

Key words: Characrteristics, Headache, Outcome, COVID-19 patient.

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Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan City, Hubei Province, China.[1] On 30 January 2020, the World Health Organization (WHO) declared the coronavirus outbreak as a Public Health Emergency of International Concern and a pandemic on 11 March 2020.[2] In Bangladesh, the first patient was identified on 8 March 2020.

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Frequent symptoms of COVID-19 include fever, cough, shortness of breath, headache, malaise, muscle and joint pain, and loss of smell and taste.[3] Infrequent symptoms include abdominal pain, nausea, vomiting, and diarrhea.[4] The time from exposure to the onset of symptoms ranges from 5 to 14 days.[5]

The prevalence of headaches in patients with COVID-19 varies in different studies, ranging from 6% to 71%.[6,7] A possible pathophysiological mechanism of headache associated with COVID-19 is activating the trigeminovascular system.[8] At the meningeal level, its activation may be due to 1) systemic inflammation that may facilitate meningeal sensitization, leading to the local release of inflammatory peptides that stimulate trigeminal terminals 2) direct binding of SARS-CoV-2 from the blood stem on ACE2, which is expressed by the endothelium of meningeal vessels, causing endothelium and therefore inflammation. In the nasal cavities, both the specialized olfactory epithelium and the nasal epithelium are present, the latter being innervated by trigeminal nerve afferents. The olfactory neurons express ACE2, where the SARSCoV-2 may bind, causing anosmia, a symptom significantly associated with headache. At the level of nasal epithelium, the trigeminal system may be peripherally activated by the direct action of SARS-CoV-2 on the nasal epithelium or the trigeminal branches or by the indirect pathway involving the interaction between the olfactory and trigeminal innervation.[8,9] In Bangladesh prevalence of headache was 13.5% to 19.4%.[10,11] Little is known about the characteristics of these headaches.

One Spanish study reported headaches in about 75% of patients with COVID-19, of which 24.2% have migrainous features.[12] Another study reported headaches in 22.4% of patients, half of whom showed tension-type headache (TTH) features.[13] Patients having a pre-existing primary headache disorder had significantly more frequent COVID-19-related headaches.[14]

Few studies are available regarding the outcome of headaches, and they show different outcomes. In one study, the majority of patients recovered from headaches within two weeks[15], whereas Caronna et al.[12] reported that one-third of patients had persistent headaches after six weeks. Persistent headaches may adversely affect the quality of life. The Headache Disability Index (HDI) is a validated tool to assess the impact of headaches on quality of life.[16]

The International Classification of Headache Disorders, third edition (ICHD-3) requires a confirmed diagnosis of systemic viral infection without meningitic or encephalitic involvement to diagnose headaches attributed to systemic viral infections.[17] Headache is usually diffuse and bilateral, but some cases, it may be fronto-temporal or occipital with retroocular pain. It may be associated with conjunctival injection, nausea, vomiting, photophobia, or phonophobia[18] (Marinis and Welch 1992).

Information regarding headache characteristics and outcomes may be necessary for patient management and counseling in this pandemic. This study aimed to assess the characteristics and outcomes of headaches presented by COVID-19 patients.

Methods:

This was a prospective cohort study done in the Department of Neurology from January 2021 to December 2021. Ethical approval was obtained from the Institutional Review Board (IRB) of Dhaka Medical College Hospital. We obtained informed written consent from all the study participants.

Study participants:

We use consecutive sample methods. Our estimation sample size was 384, using the formula $n = \frac{z^2 pq}{d^2}$. We enrolled confirmed COVID-19 patients of both sexes and aged more than 18 years with RT-PCR from the in-patients and triage of Dhaka Medical College Hospital. Critical and unconscious patient and those who had other previous secondary headache were excluded from the study.

Operational Definition

We defined COVID-19 and its severity in patients according to WHO and Bangladesh COVID-19 guidelines.[19,20] We defined Headaches attributed to systemic viral infection according to the third edition of the International Classification of Headache Disorders (ICHD-3[13]).

The phenotypes of headaches associated with COVID-19 headache were classified as Migraine phenotype and Tension-type headache phenotype according to the third edition of the International Classification of Headache Disorders (ICHD-3).[13] Pain was quantified by the Numerical Rating Scale (NRS).[21] Score 0 is considered no pain, 1-3 is mild pain, 4-6 is moderate pain and 7-13 is severe pain.

The headache disability index (HDI) is a 27-item questionnaire used to assess the impact of headaches on quality of life.[16] The first two questions ask the patient to identify the frequency (1 per month, more than 1 per month but less than 4 per month, more than 1 per week) and intensity (mild, moderate, and severe) of their headache.

The remaining questions evaluate the quality of life issues to determine headache disability. Using this system, if 'Yes' is checked on any given line, that answer is given 4 points; a 'Sometimes' answer is given 2 points, and a 'No' answer is given 0 points.

Using this system, a score of 10 – 28 indicates mild disability, 30 – 48 indicates moderate disability, 50 – 68 indicates severe disability, and ≥72 indicates complete disability.

The outcome of headache was considered as Recovered (patients who recovered from headache within 4 weeks) and Not recovered (patients who experienced a headache after 4 weeks)

Study procedure

A total of 400 patients were included in this study according to defined inclusion and exclusion criteria. Informed written consent was taken from all participants after describing the aim, purpose, and procedure of the study. A structured questionnaire was filled up from the answers of the participants with the help of relatives to obtain information on demographic characteristics and headache-related questions. Adequate safety measures were ensured to prevent transmission of infection during data collection. The severity of the headache was assessed by the Numerical Rating Scale (NRS, 0-10). Headache phenotype was classified according to the International Classification of Headache Disorders third edition (ICHD-3). All patients with headaches were followed up by telephonic interview at the end of the 2nd week and 4th week of onset of headache to assess the outcome. Patients without headaches at the first survey were followed up by telephonic interview after 10 days of the first survey to document any new-onset headache. If a headache was present, then two further follow-ups were given at the end of 2nd and 4th week from the onset of the headache. The impact of headaches on quality of life was assessed with the Headache Disability Index (HDI) on patients who experienced headaches after 4th week. All the above information was recorded in a data collection form consisting of the relevant questionnaire.

Data Analysis Plan

All data was registered, documented and analyzed in the statistical program- Statistical Package for Social Science (SPSS) version 26.0. Each question was coded with a number and all alternative responses for each question were registered to enable a statistical analysis. The data was systematically described**,** summarized, and presented through descriptive statistics. Shapiro-Wilk test was done to see the distribution of data. For normally distributed data, continuous variables were expressed as means ± standard deviations (SD), while categorical variables were described as frequency and percentage. Non-normally distributed data was expressed as median (Inter Quartile Range, IQR). Student's *t* test was used for the continuous variables whereas Chi-square test for categorical variables to express association. Non-parametric test was done to see association between non-normally distributed data. P value ≤0.05 was considered as level of statistical significance.

Results:

A total of 400 RT-PCR positive patients admitted into DMCH were included initially based on inclusion and exclusion criteria. Among them 362 patients who completed follow-up at the end of 2nd and 4th week were finally included for analysis.

Table I

Demographic characteristics of the study subjects (n=362).

Variable	All patients	Headache present (n=69)	Headache absent (n=293)	p value
Age group (yrs)				
18-30	29 (8.01%)	16	13	
31-40	38 (10.50%)	13	25	0.001**
41-50	84 (23.20%)	18	66	
51-60	96 (26.52%)	14	82	
61-70	80 (22.10%)	8	72	
>70	35 (9.67%)	0	35	
(Mean±SD)	54.05±14.47	44.19±13.80	55.97±13.72	0.001*
Range	18-90	19-69	18-90	
Gender				
Male	223 (62%)	32 (46.37%)	191 (65.18%)	0.006 **
Female	139 (38%)	37 (53.63)	102 (34.82%)	

*= obtained by unpaired t test, **= obtained by Chi square test

Table I shows demographic characteristics of the study subjects. It was observed that majority (26.52%) of study subjects belonged to age 51-60 years. Mean age of the study subjects was 54.05±14.47 years. Headache was more common in younger age groups (p<0.001). Majority of study subjects were male (62%). Female gender was significantly associated with presence of headache (p=0.006).

Figure 1 shows the distribution of frequency of COVID-19 symptoms. The most Common symptom was fever (63.81%) followed by shortness of breath (56.08%), cough (53.87%) and changes in taste (31.77%). Headache was present in 19.06% patients

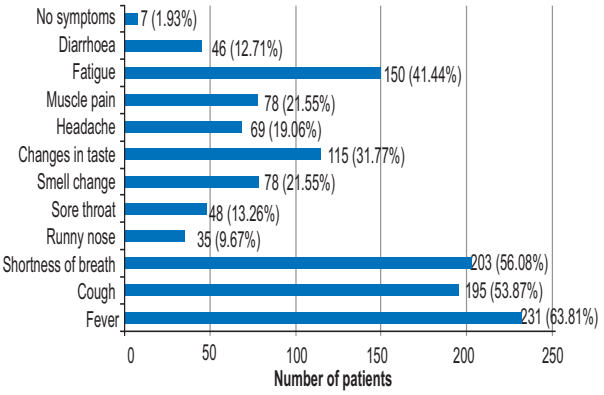

Figure 1: *Distribution of frequency of COVID-19 symptoms (n=362)*

Table II

Frequency of co-morbidities in the study subjects (n=362)

Co-morbidity	All patients (n=362)	Headache present (n=69)	Headache absent (n=293)	p value
HTN	125 (34.53%)	21 (30.43%)	104 (35.49%)	0.48*
DM	132 (36.46%)	25 (36.23%)	107 (36.51%)	0.81 *
IHD	48 (13.26%)	5 (7.2%)	43 (14.67%)	0.09 *
Asthma/COPD	35 (9.67%)	7 (10.14%)	28 (9.55%)	0.32 *
CKD	28 (7.73%)	4 (5.7%)	24 (8.1%)	0.12 *

*= Chi square test was done to see the level of significance

Table II shows the frequency of co-morbidities in the study subjects. DM was the most common (36.46%) co-morbidity followed by HTN (34.53%). Co-morbidities were not significantly associated with presence of headache (p>0.05).

Table III

Association of headache with severity of COVID-19

Severity	All patients (n=362)	Headache present (n=69)	Headache absent (n=293)	p value
Mild	83 (22.9%)	20 (28.9%)	63 (21.5%)	0.04[s*]
Moderate	89 (24.6%)	12 (17.5%)	77 (26.3%)	
Severe	190 (52.5)	37 (53.6%)	153 (52.2%)	

[s]= significant, *= Chi square test was done to see the level of significance

Table IV

Frequency and phenotypes of headache in COVID-19 patients (n=362)

	Number	Percentage (%)
Patients with headache	69	19.06
Tension type	41	59.4
Migraine type	23	33.3
Others	5	7.3
Patients without headache	293	80.94

Table III shows association of headache with severity of COVID-19. Severity of COVID-19 was significantly associated with presence of headache (p=0.04). Headache was more common in mild COVID-19 patients.

Table IV shows Frequency and phenotypes of headache in COVID-19 patients. Headache was present in 19.06% of study subjects and tension type headache was most common (59.4%).

Table V shows the characteristics of COVID-19 related headache. In most (68.12%) cases headache was concomitant with other COVID symptoms. Most cases headache was bilateral (60.87%), pressing (44.93%) and of moderate intensity in 56.52% cases. In 18.8% cases of COVID related headache had pre-existing primary headache.

Table V

Characteristics of COVID-19 related headache (n=69).

		Frequency	Percentage (%)
Onset	Before other COVID symptoms	14	20.29
	With other COVID symptoms	47	68.12
	After other COVID symptoms	8	11.59
Location	Unilateral	9	13.04
	Bilateral	42	60.87
	Diffuse	18	26.09
Characteristics of pain	Throbbing	23	33.33
	Pressing	31	44.93
	Dull	15	21.74
Headache intensity (NRS)	Mild (NRS 1-3)	13	18.84
	Moderate (NRS 4-6)	39	56.52
	Severe (NRS 7-10)	17	24.64
Duration of headache attack (hours/day)Median (IQR)		8 (7)	
Frequency of headache (attacks/week)Median (IQR)		5 (3)	
Pre-existing primary headache			
Present		13	18.8
Migraine		8	61.5
TTH		3	23.1
Others		2	15.4
Absent		56	81.2

Table VI shows the association of presence of fever with duration, frequency and intensity of headache in COVID-19 patients. Fever was significantly associated with increase in the duration, frequency and intensity of COVID-19 headache ($p<0.05$).

Table VII shows association of pre-existing primary headache with duration, frequency and intensity of COVID-19 headache. Duration, frequency and intensity of headache was significantly higher in patients with pre-existing headache ($p <0.05$).

Table VI

Association of presence of fever with duration, frequency and intensity of headache (n=69)

Characteristics	Headache with fever (n=59)	Headache without fever (n=10)	p value
Frequency/weekMedian (IQR)	7 (4)	3 (5)	0.004*
Duration (hours) Median (IQR)	11 (10)	6 (14)	0.001*
Intensity (NRS)Median (IQR)	7 (2)	6 (4)	0.03*

*= p value obtained by Mann Whitney U test

Table VII

Association of pre-existing primary headache with duration, frequency and intensity of COVID-19 headache (n=69)

Characteristics	Pre-existing primary headache present (n=13)	Pre-existing primary headache absent (n=56)	p value
Duration (hours) Median (IQR)	11 (10)	5 (9)	0.001*
Frequency/weekMedian (IQR)	7 (4)	3 (5)	0.001*
Intensity (NRS)Median (IQR)	7 (3)	5 (3)	0.012*

*=Mann Whitney U test was done to see the level of significance.

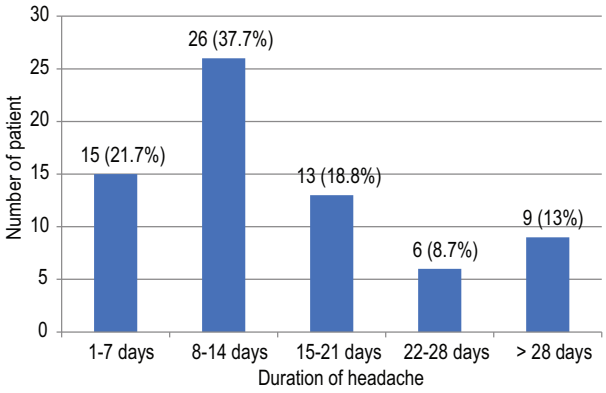

Figure 2: *Recovery time for patients with headache (9 patients did not recover after 4th week) (n=69).*

Figure 2 shows the recovery time for patients with headache. Maximum patients (37.7%) recovered between 8-14 days.

Table VIII

Recovery of headache (cumulative) at different survey period and median recovery time (n=69)

	At end of 2nd week		At end of 4th week	
	No.	%	No.	%
Recovered	41	59.42	60	86.9
Median recovery time Median (IQR) day	10 (7.75)			

Table VIII shows the recovery of headache at different survey period and median recovery time. Majority (86.9%) of the patient recovered within 4 week of onset of headache. Median (IQR) recovery time was 10 (7.75) days.

Table IX

Recovery time based on presence of pre-existing primary headache and severity of COVID-19 (n=60)*

	Number	Recovery time Median (IQR) days	p value
Pre-existing headache			
Present	9	18 (12.5)	0.032**
Absent	51	10 (8)	
Severity of COVID-19			
Mild	17	10 (11.5)	0.022***
Moderate	10	9 (5.5)	
Severe	33	14 (10)	

*= 9 patients who did not recover after 4 weeks are not included

**= Mann-Whitny U test was done to see the level of significance

***= Kruskal-Wallis test was done to see the level of significance

Table IX shows recovery time based on presence of pre-existing headache and severity of COVID-19. Recovery time was significantly higher in patients with pre-existing primary headache and severe COVID-19 patients ($p<0.05$).

Table X

HDI score for patients who did not recover after 4 weeks of onset of headache (n=9)

HDI score	Number	Percent
Mild disability (10-28)	7	77.77
Moderate disability (30-48)	2	22.23
Severe disability (50-68)	0	0
Mean HDI score (Mean±SD)	24.44±10.76	
Range	14-36	

Table X shows the HDI score for patients who did not recovered after 4 weeks of onset of headache. Maximum patient (77.77%) had mild disability. Mean HDI score was 24.44±10.76 SD

Discussion:

In the study, most of the patients had severe COVID-19 infection. Among them about one-fifth of patients presented with Headaches. Patients having headaches were younger than those have no headaches. Headache was more prevalent among the female. Tension-type headache (TTH) was the most common (60%) headache phenotype. COVID-19-related headaches were, in most cases, bilateral, pressing, and of moderate intensity. Fever and pre-existing headaches were associated with significantly more frequency, duration, and intensity than COVID-19 headaches. Most patients recover from headaches within 4 weeks of the onset. Headache is the most common neurological manifestation of COVID-19 infection. Previous studies show variable information regarding headaches' frequency, characteristics, and outcome.

Most (52.5%) of the study population belonged to severe COVID-19 infection because it was a hospital-based study and the maximum number of patients admitted to hospitals were in serious condition. Headache frequency is relatively low in this study. The frequency varies from 35-58%[22] in overall COVID-19 patients. Headache is more prevalent among the mild COVID patients.[23] This variation may be explained by the use of different methodologies in different studies and the genetic background of study populations, which may influence the prevalence of this neurologic symptom and the appearance of new SARS-CoV2 strains.[24,25] The mean age of the patient with headache was significantly lower in patients with headache than patients without headache ($p<0.05$). Membrilla et al.[26] and Caronna et al.[12] showed similar findings, but the mean age in patients with and without headaches was higher in a

later study. Like other studies, headache is common among females in our study.[12,27] Estrogen plays an important role in the neuroexcitability.[28]

TTH was the most common (60%) headache phenotype. Magdy et al. (2020) found TTH was present in 40.7% of cases.[29] Another study conducted by Rocha-Filho et al. (2020) showed that the majority of headaches (51%) were migraine-type.[30] This may differ in different populations based on the prevalence of pre-existing migraine headaches. In most cases, the headache was bilateral, pressing, and of moderate intensity. A study conducted by Magdy et al. (2020) showed almost similar findings, except the headache was severe in intensity.[29]

Pre-existing headaches were present in 18.8% of the cases of COVID-19 headaches, which were associated with significantly more frequency, duration, and intensity of headache. A similar finding was found in the study by Caronna et al.[12] This may be explained by derangement of the pain modulatory pathway, decreased pain threshold, and for migraine, cortical spreading depression may add to hyper-excitability of the trigeminovascular neurons.[31,32]

Most patients (86.9%) recovered from headaches within 4 weeks of their onset. A study conducted by Kacem et al.[33] reported complete recovery in 83.2% of patients after 1 month. Another study reported 62.2% recovery at 6 weeks of follow-up.[12] The median (IQR) recovery time was 10 (7.75) days. Patients with pre-existing headaches and severe COVID-19 had significantly longer recovery time.

Nine patients (13.1%) did not recover from headaches in the 4th week of the survey. Poncet-Megemont et al. (2020) reported that 3.6 % of patients had persistent headaches one month after fever and dyspnea remission. A post-COVID-19 condition may be responsible for such a condition.[34]

Neuroimaging, cerebrospinal ûuid tests, and ophthalmoscopy were not performed to rule out other causes of secondary headaches, such as meningitis, encephalitis, and cerebrovascular diseases, which may be complications of COVID-19. However, these patients had no meningeal or focal signs, confusional states, or impaired level of consciousness, which makes these complications less likely.

This study was conducted in a single center and involved only inpatients. This decreases the ability to generalize the study, and therefore, extrapolating the results to patients with mild forms of the disease who do not require hospitalization should be undertaken with caution.

Conclusion:

This study revealed that headache was present in about one-fifth of the hospitalized patients with COVID-19. Younger age and female gender were significantly associated with headaches. Most of the patients recovered within four weeks of the onset of headache.

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The Role of Early Pregnancy Serum Adiponectin Level in Predicting Development of Gestational Diabetes Mellitus (GDM)

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Abstract

Background: *Early prediction of GDM by measuring a biomarker at first trimester of pregnancy may prevent maternal and fetal complication. Adiponectin, which modulate insulin sensitivity, is secreted from adipose tissue and decreases blood glucose level. The objective of the study was to evaluate the association of maternal first trimester serum adiponectin with development of GDM.*

Methodology: *This longitudinal study was conducted in the BSMMU, Dhaka from June, 2021 to May, 2022 where pregnant women of first trimester were selected by purposive convenient sampling. At first 94 pregnant women were selected after excluding diabetes or previous history of GDM and their serum adiponectin level was measured. Then the participants were followed up at 24-28 weeks of gestation and OGTT was done to detect GDM. ROC was used to decide the best cut-off point of adiponectin level for detection of GDM. The respondents were divided into 'below cut-off' group and 'above cut-off' group. Differences between two groups were assessed by statistical test.*

Results: *A total 18 respondents developed GDM from both group. In below cut-off' group, out of 26 respondents 13 developed GDM and remaining 13 were euglycemic. Whereas in above cut-off group, out of 62 respondents, majority 57 were euglycemic and only 5 women developed GDM. ROC analysis of adiponectin level for detection of GDM, a AUC value 0.887 (95% confidence interval 0.802-0.972) was found which was statistically significant (p<0.001). A cut off value of ≤10.165 µg/ml showed the highest youden index (0.651) with 83.3% sensitivity and 81.4% specificity, the accuracy was 79.5%. Moreover a cut of value ≤10.165 µg/ml showed PPV and NPV of 50.8% and 92.8% respectively. A significant association was found between development of GDM and adiponectin level (P<0.001). The odds for developing GDM due to low adiponectin are 11.4 [95% CI: 3.45 – 37.64]. About 72.2% GDM patients had below cut-off adiponectin level.*

Conclusion: *Study finding revealed that maternal serum adiponectin level was lower at early pregnancy to those patients who subsequently developed GDM. So a low adiponectin level at early pregnancy may be a new risk factor for GDM.*

Key words: *adiponectin, gestational diabetes mellitus (GDM), pregnancy, insulin resistance.*

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Introduction:

The incidence of gestational diabetes mellitus (GDM) is increasing globally which affects 3-10% of pregnancies worldwide[1] with an increased risk of short and long term ill health for both mother and off spring. In Bangladesh, prevalence of

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GDM is quite high with frequencies around 7 - 14%.[2] Adipose tissue is a highly active endocrine organ and produces a number of adipocytokines like adiponectin, leptin, resistin, vispatin etc. Adiponectin is a physiologically active polypeptide hormone. Insulin is the main regulator of it's secretion from adipocytes. It stimulates glucose uptake and fatty acid oxidation by binding to it's receptor (typically adipoR1 and adipoR2) and activating AMP activated protein kinase (AMPK) and peroxisome proliferator activated receptor α (PPAR-α) in liver and skeletal muscle. It decreases glucose concentration by inhibition of gluconeogenesis. It reduces the use of insulin by stimulator effect in beta oxidation of fatty acid in skeletal muscle.[3] Plasma adiponectin is inversely correlated with body mass index (BMI), intra-abdominal fat and incidences of insulin resistance.

Low concentration of adiponectin has been reported in GDM subject during pregnancy. Some studies reported that risk of GDM is 5-6 times higher in women with low adiponectin level than women with normal or high level.[4] Adiponectin is not expressed nor produced by the placenta. Maternal adipose tissue is the major source of maternal plasma adiponectin, so it can be assessed as an independent biomarker.

If any association between early pregnancy adiponectin level and subsequent development of GDM can be evaluated then serum adiponectin level can be used as predictor of GDM in early pregnancy with subsequent interventions to minimize complications. The objective of this study was to find out the association of early pregnancy serum adiponectin level with development of GDM.

Methodology:

This prospective cohort study was conducted in outpatient department of both Feto-maternal Medicine and general Obs & Gynae, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka over a period of 1 year from June, 2021 to May, 2022. The study population included pregnant women at first trimester who were found non-diabetic (FPG < 7 mmo/L, 2 hour OGTT <11.1 mmol/L according to WHO criteria) and singleton pregnancy. A total 94 pregnant women were selected by purposive sampling who fulfilled the inclusion and exclusion criteria. Inclusion criteria was pregnant women who were non-diabetic (FPG <7 mmo/L, 2 hour OGTT <11.1 mmol/L according to WHO criteria) at their first trimester of pregnancy. Exclusion criteria were multiple pregnancy, pre-existing diabetes mellitus, diagnosed case of cardiovascular disease, chronic hypertension, previous history of pre-eclampsia, eclampsia or SLE. Data regarding demographic profile (e.g. age, BMI, educational status), previous history of GDM, family history were recorded in a semi structured questionnaire. Obstetrics history like gravidity, parity, gestational weeks, past history of any other medical disorders was documented. Then a physical examination was carried out by researcher including height, weight, BMI, BP etc. Written consent along with particulars of the participants was taken after explaining the procedure. Blood sample was collected on the same day at study place and sent to the microbiology laboratory of BSMMU for serum adiponectin assay by ELISA method. The participants were followed up between 24-28 weeks by doing OGTT to detect GDM according to WHO criteria. Six (6) patients were failed to follow up and 88 patients were finally selected for the study.

Data analysis:

Data was analyzed by SPSS statistical software. ROC analysis was used to detect the best cut-off point of adiponectin level for detection of GDM. Youden index was used to find out the accuracy and best threshold value for adiponectin as a marker. Normal distribution of the continuous variables was checked first before comparing the means between below and above cut off value of adiponectin patients and between GDM and normal patients. Then according to the result parametric and non-parametric test (Mann Whitney test) were selected for comparing means of the two groups.

Results :

ROC analysis of adiponectin level for detection of GDM among pregnant women found an AUC value of 0.887 (95% CI 0.802-0.972) which was statistically significant (P <0.001) (Figure:1 and Table I).

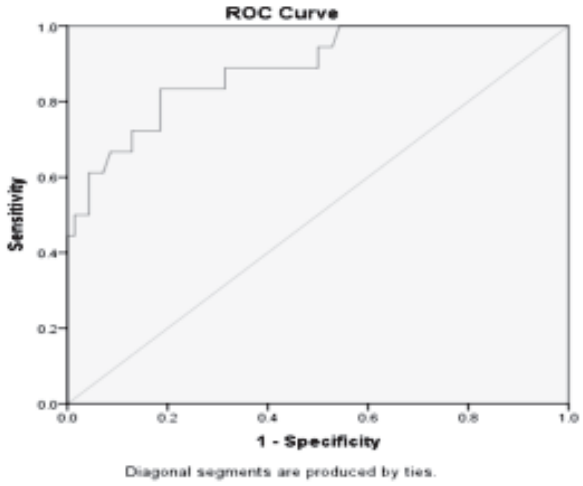

Figure 1: *ROC curve for first trimester serum adiponectin level*

Table II shows a cut-off value of ≤10.165 showed the highest Youden index (0.651) with 83.3% sensitivity and 81.4% specificity. In addition, the accuracy was 79.5%. Moreover, A cut-off value of ≤10.165 showed, PPV and NPV of 50.8% and 92.8%.

A significant association was found between development of GDM and adiponectin level (P<0.001). The odds for developing GDM due to low adiponectin are 11.4 [95% CI: 3.45 – 37.64]. About 72.2% GDM patients had below cut-off adiponectin level. However, only 18.6% normal patients had low adiponectin level (Table-IV).

Table I

Area Under the Curve

Test Result Variable(s): adiponectin

Area	Std. Error[a]	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.887	0.043	<0.001	0.802	0.972

Table II

Determination of cut off value with youden index

Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy	youden index (j=sen+spe-1)
10.115	0.722	0.814	0.486	0.889	0.784	0.541
10.165	0.833	0.814	0.508	0.916	0.795	0.651
10.230	0.833	0.801	0.474	0.928	0.772	0.632

Table III

Cross tabulation of GDM with adiponectin level based on derived cut-off value

Adiponectin (µgm/ml)	GDM	Non-GDM	Total
≤10.165	True positive 13	False positive 13	26 (TP+FP)
>10.165	False negative 5	True negative 57	62 (FN+TN)
	All patients with GDM (TP+FN) 18	All patients without GDM (FP+TN) 70	88 (TP+FN+FP+TN)
	All patients with GDM (TP+FN) 18	All patients without GDM (FP+TN) 70	88 (TP+FN+FP+TN)

Table IV

Association of GDM with low adiponectin.

		GDM		OR	P value
		Yes	No		
Adiponectin(ig/ml)	below cut-off (≤10.165)	13 (72.2%)	13 (18.6%)	11.4	<0.001
	above cut-off (>10.165)	05 (27.8%)	57 (81.4%)		
Total		18	70		

Here, P value obtained from chi square test.

Discussion:

This prospective longitudinal study was carried out among 88 women with singleton pregnancy at their first trimester of pregnancy, having no evidence of GDM. The responders were divided into two groups. One group with below cut-off of adiponectin (≤10.165 igm/ml) and another group with above cut-off of adiponectin level (>10.165 μgm/ml). Among them, 26 women (29%) were in below cut-off of adiponectin group and 62 (71%) women were in above cut-off of adiponectin group. During follow up 18(20.5%) women developed GDM and 70 (79.5%) were diagnosed as non GDM.

ROC analysis of adiponectin level for detection of GDM among pregnant women found an AUC value of 0.887 (95% CI 0.802-0.972) which was statistically significant (P <0.001). A cut-off value of ≤10.165 igm/ml showed the highest Youden index (0.651) with 83.3% sensitivity and 81.4% specificity. In addition, the accuracy was 79.5%. Moreover, A cut-off value of ≤10.165 μgm/ml showed, PPV and NPV of 50.8% and 92.8%. In a study by Madhu et al (2019), ROC curve revealed a cut-off value of adiponectin was 9.1 μgm/ml in the first trimester with 100% sensitivity and 95.6% specificity in prediciting GDM.[5]

In this study, the levels of serum adiponectin were significantly lower in GDM subjects (8.24±2.31) μgm/ml than healthy pregnant women (11.83±1.76) μgm/ml and related adversely to blood glucose level. Moreover, a significant association was found between development of GDM and adiponectin level (P<0.001). The odds for developing GDM in below cut-off of adiponectin group were 11.4 [95% CI: 3.45 – 37.64]. About 72.2% GDM patients had below cut-off of adiponectin level. However, only 18.6% normal patients had below cut-off of adiponectin level. Saini et al (2015) showed that adiponectin concentration was lower in pregnant women with GDM and found an inverse relationship between adiponectin level and fasting blood sugar.[6] Results of the study by Pala et al (2005) were similar to this study; adiponectin levels were significantly lower than the control group.[7] Tsai et al (2005) reported that the concentration of serum adiponectin was lower in GDM group.[8] A systematic review and meta-analysis have demonstrated a significant decline in adiponectin levels in GDM group vs. control group.[9]

Conclusion:

In this longitudinal study, the level of adiponectin in early pregnancy was evaluated. The results of this study show that adiponectin has the potential to be used as an important screening biomarker for the early pregnancy which strongly predicts GDM in Bangladesh women. Apart from diagnosis, adiponectin levels can help in stratifying pregnant women so that measures to prevent GDM can be instituted in the early pregnancy to the at-risk patients. In country with growing burden of GDM and inadequate resources, such information can significantly improve maternal and fetal outcomes in women at risk for GDM.

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Outcome of Ischemic Stroke with or without Left Ventricular Systolic Dysfunction

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Abstract

Background: *Patients experiencing stroke with Left Ventricular Systolic Dysfunction (LVSD) face elevated mortality rates, heightened dependency, prolonged hospitalization, increased ICU referrals, and greater complication risks compared to those without LVSD.*

Objective*: This study aims to evaluate the outcomes differences of ischemic stroke patients with and without LVSD, as well as within subgroups of LVSD severity.*

Materials and Methods: *The study was Conducted in the Department of Neurology, Dhaka Medical College and Hospital (DMCH) from January 2022 to December 2023. In this prospective cohort study we enrolled 117 acute ischemic stroke patients meeting predetermined inclusion and exclusion criteria. LVSD diagnosis was established through echocardiography. Patient outcomes, including hospital duration, ICU necessity, mortality, and modified Ranking Scale (mRS) scores, were assessed and compared.*

Results: *Among the 117 patients, 61 were classified under stroke with LVSD, while 56 were without LVSD. The mean(SD) age was 65.50(9.94) years for LVSD and 63.78(10.85) years for non-LVSD patients. Male predominance was observed in both groups, with 83.6% males in the LVSD group and 67.9% in the non-LVSD group.*

Mortality rates at hospital and the first month were 5.4 times higher in LVSD patients compared to non-LVSD patients (9.8% vs. 1.8%, p- value 0.029). Total 3-month mortality was nearly three times higher in LVSD patients (27.9% vs. 10.7%, p <0.05). mRS scores indicated significantly poorer functional outcomes at 1 and 3 months for LVSD patients compared to non-LVSD patients. (mRS >2 in 95.1% vs 83.9%) at 1 month and mRS >2 in 68.9% vs 39.3% at 3 months). Length of hospital stay was longer for LVSD patients (median [IQR] 10 [8-15] days) compared to non-LVSD patients (median [IQR] 7 [4-11] days). Need for ICU referral of the ischemic stroke patients with LVSD was 2.3 times more than non-LVSD patients (32.8% vs 14.3%, p- value 0.029).

Conclusion: *Ischemic Stroke patients with LVSD exhibit poorer clinical outcomes, higher mortality rates, increased dependency, prolonged hospital stay and greater need for ICU referral compared to those without LVSD.*

Key words: *Ischemic stroke, left ventricular dysfunction, outcome.*

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Introduction:

Globally, stroke is a significant health issue and the second leading cause of mortality and the third leading cause of morbidity.[1] The prevalence of stroke is also high in Bangladesh, about 11.4 per thousand population.[2] Asymptomatic and even milder degrees of left ventricular dysfunction also increase the risk of stroke.[3] Left ventricular dysfunction is also a predictor of poorer clinical outcomes, even in patients with thrombolysis.[4] Wei, N et al. found that, he presence of left ventricular dysfunction in patients with stroke increases risk of death.[5] Other studies with short-term outcomes also

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revealed similar outcomes.[6-8] Stroke severity is also associated with left ventricular dysfunction.[9] The pathophysiology of adverse outcomes involves increased stroke severity, dysregulated cerebral autoregulation, and increased risk of recurrent stroke due to cardioembolic phenomenon.[10,11] Left ventricular dysfunction also increases the healthcare cost and hospital stay.[12]

There is a paucity of research in Bangladesh about the impact of left ventricular dysfunction on the outcome of stroke. In this study, we aimed to compare mortality, hospital stay, and morbidity outcomes.

Materials and methods:

Study Design and patient demographics

Prospective cohort study conducted from January 2022 to December 2023 at Dhaka Medical College Hospital (DMCH), focusing on patients with ischemic stroke, both with and without left ventricular systolic dysfunction (LVSD), admitted to the Neurology ward. Ethical approval was obtained from the DMCH ethical review board prior to the study. Patients were selected based on specific inclusion and exclusion criteria, including age (≥45 years) and diagnostic criteria for exposure (EF<50%) and control (EF >50%) cohorts. After subject selection, detailed explanations of the study's nature, purpose, and benefits were provided to each participant, encouraging voluntary participation. Informed written consent was obtained from all participants. Detailed personal, family, and medical histories were collected, and routine neurological and cardiovascular assessments were conducted for all patients. Diagnosis of ischemic stroke was initially based on positive lesions observed on brain CT scans or diffusion-weighted imaging (DWI) with corresponding ADC sequences on brain MRI.

Echocardiographic data acquisition and analysis

The presence and severity of LVSD were determined using 2D echocardiography with the Philips EPIQ 7 cardiac ultrasound machine, and LV ejection fraction (EF) was calculated using the Modified Simpson's method. Patients were divided into two categories: those with and those without LVSD. LVSD was defined as LVEF < 50%. An LVEF of 50% was chosen, as this value is still clinically relevant according to the American College of Cardiology guidelines. Additionally, routine electrocardiography (ECG) was performed to diagnose atrial fibrillation (AF) and ischemic heart disease (IHD).

Data collection and evaluation

Data collection involved face-to-face interviews, physical examinations, and investigations using a pre-designed data collection sheet. For patients unable to provide informed consent, consent was obtained from their families. Demographic, clinical, and biochemical variables were noted, and necessary blood workups were performed. Patients were followed up at the hospital, stroke clinic at one month and three months' post-admission

Evaluation of outcomes

Outcome determinants included mortality and morbidity measured using the modified Rankin Scale (mRS), with scores of 3, 4, and 5 considered poor outcomes and scores of 0-2 considered good outcomes. The primary concern of this study was to find the difference in mortality, disability, length of hospital stay, and need for ICU referral in an ischemic stroke patient with or without left ventricular systolic dysfunction and according to the severity of LVSD among the Bangladeshi population.

Statistical analysis

All collected information was stored in separate data record forms, checked for accuracy, inputted into Microsoft Excel, and transcribed into statistical software. Statistical analyses were performed using SPSS version 26.0, including means, standard deviations, and percentage frequencies. Significance was determined by a p-value of less than 0.05. Various statistical tests such as unpaired t-test, Mann–Whitney U test, Kruskal-Wallis test, Chi-square test, Fisher's exact test, and multivariable logistic regression analysis were conducted as applicable. Survival analysis using Kaplan-Meier graphs and log-rank tests measured significance, and Hazard ratios with 95% confidence intervals were calculated.

Results

The present study was undertaken to compare the outcome of ischemic stroke with or without LVSD. For this study 61 patients with ischemic stroke with LVSD and 56 ischemic stroke without LVSD patients admitted in the Neurology Department of Dhaka Medical College and Hospital, Dhaka were included. Flowchart of patient selection in Figure-1.

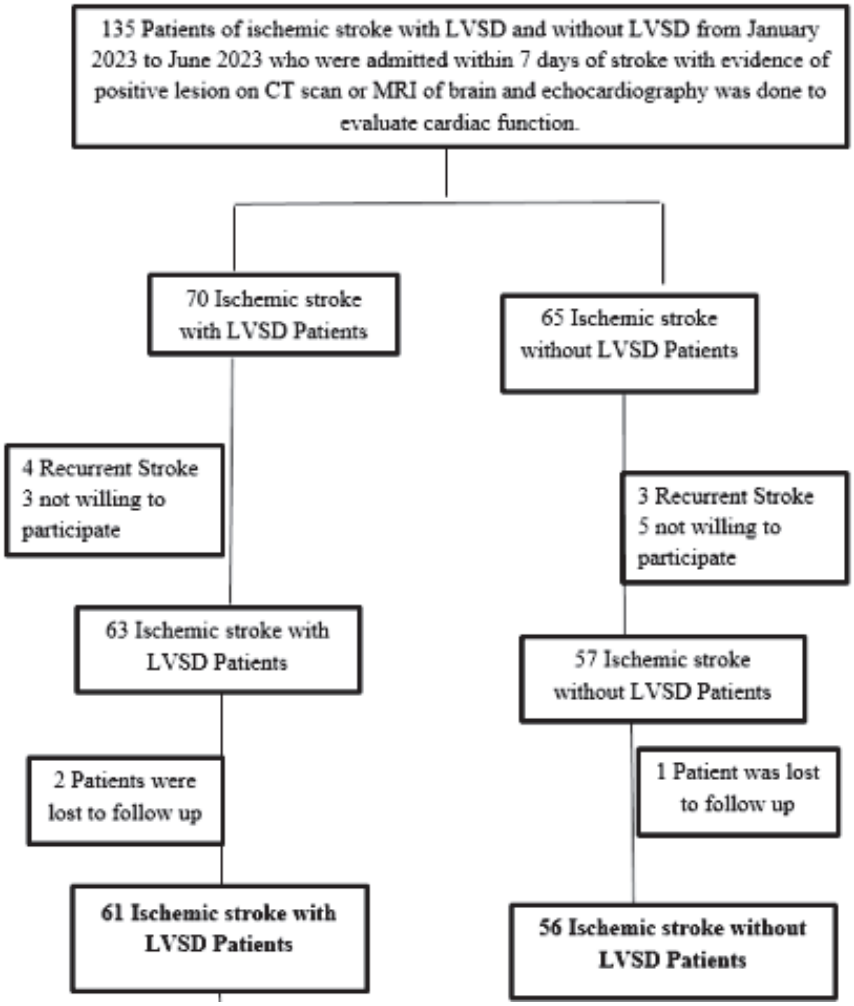

Figure 1. *Flowchart of patient selection.*

Baseline characteristics: In patients with LVSD, the mean age was 65.50 years (± 9.94 years), while among those without LVSD, the mean age was 63.78 years (± 10.85 years). In terms of gender distribution, 51 (83.6%) individuals with LVSD were male, whereas among those without LVSD, 38 (67.9%) were male. The relationship between comorbidities and stroke among patients with and without LVSD. For diabetes mellitus (DM), 23 (37.7%) stroke patients with LVSD had DM, compared to 21 (37.5%) stroke patients without LVSD. Hypertension (HTN) was present in 38 (62.3%) patients with LVSD and 28 (50%) patients without LVSD. Ischemic heart disease (IHD) was present in 23 (37.7%) patients with LVSD and 6 (10.7%) patients without LVSD. Dyslipidemia was present in 12 (19.7%) patients with LVSD and 8 (14.3%) patients without LVSD. Additionally, smoking prevalence was 44.25% in LVSD patients and 37.5% in non-LVSD patients.

Demographic characteristics, co-morbidities, Baselines information and Investigations profile of the patients appear in Table 1

In LVSD, the median (IQR) pulse rate was 86 (83-94), and the systolic and diastolic blood pressures were 150 (132-160) mmHg and 90 (80-100) mmHg, respectively. In the non-LVSD group, the median (IQR) pulse rate was 80 (72-88), with systolic and diastolic blood pressures of 140 (120-150) mmHg and 80 (77-90) mmHg, respectively.

Table I

Demographics, Co-Morbidities, Investigations profiles and Baseline information of Acute Ischemic Stroke patients with or without Left Ventricular Systolic Dysfunction.

Variables	LVSD (N=61)	No LVSD (N=56)	p Value
Age Mean±SD (years)	65.50 ± 9.94	63.78 ± 10.85	0.372
Gender (n,%)			
Male	51 (83.6)	38 (67.9)	0.053
Comorbidities			
Diabetes Mellitus (DM)	23 (37.7%)	21 (37.5%)	0.459
Hypertension (HTN)	38 (62.3%)	28 (50%)	0.017
Dyslipidemia	12 (19.7%)	8 (14.3%)	0.439
Ischemic Heart Disease (IHD)	23 (37.7%)	6 (10.7%)	0.001
Smoking status			
Current smoker	11(18%)	4(7.14%)	0.221
Former-smoker	16(26.25%)	17(30.36%)	
Non-smoker	34(55.75%)	35(62.5%)	
Admission GCS			
Total (Median, IQR)	11(9-14)	13(10-14)	0.069
Initial NIHSS			
Total (Median, IQR)	15(12-20)	14(13-16)	0.186
Investigation biomarker Profile			
Hb%	12(10-13)	12(11-12)	0.261
Total count	9.8(8.18-12)	8.7(7.25-11.66)	0.450
Neutrophil	79(70-84)	77.5(70-82)	0.452
Platelet count	241(205-317)	241.5(240-280)	0.959
RBS	6.9(5.8-8.8)	7.9(6.23-9.48)	0.118
S. Creatinine	1.08(0.9-1.2)	1.02(0.88-1.2)	0.937
Sodium	138(135-145)	138(136-142.8)	0.539
Potassium	4.1(3.8-4.5)	4.1(3.7-4.2)	0.243
LDL (mg/dl)	108(86-152)	85(79-122)	0.019
HDL (mg/dl)	38(31-42)	38(35-42)	0.622
TG (mg/dl)	128(105-177)	152(109-135)	0.182
Total cholesterol (mg/dl)	197(157-219)	178(144-191)	0.010
NT pro BNP	848.5(540-1755)	32(23-56)	<0.001
EF%	38(33-42)	63(60-65)	<0.001

For the GCS, 44.3% of the LVSD group had a score of 9-12, while 53.6% of the Non LVSD group had 13-15(Moderate). NIHSS score on admission was higher for participants with LVSD (Median, IQR; 15(12-20)) compared to those without LVSD (Median, IQR; 14(13-16)). The baseline mRS at admission, the table shows that both LVSD and without LVSD group had mRS >2 in majority patient, 98.3% of LVSD and 98.2% of the non-LVSD group.

In investigation profile the individuals with Left Ventricular Systolic Dysfunction (LVSD) and those without LVSD across various clinical variables. The variables include hemoglobin (Hb%), total count, neutrophil count, platelet count, random blood sugar (RBS), serum creatinine, sodium, potassium, LDL cholesterol, HDL cholesterol, triglycerides (TG), total cholesterol, NT pro BNP levels, and ejection

fraction (EF%). P-values indicate the statistical significance of the differences observed between the two groups. Notable differences include significantly lower EF% and higher NT pro BNP levels in the LVSD group compared to the non-LVSD group, suggesting impaired cardiac function. Additionally, differences in LDL cholesterol, total cholesterol, and Hb% are statistically significant, indicating potential differences in lipid metabolism and hemoglobin levels between the two groups.

Clinical outcomesTop of Form:

Early mortality (up to one month) was significant in LVSD than non-LVSD (p 0.029) and at 3 month follow up the mortality is almost equal (p= >0.99).

The mean survival times of each group were presented based on the Kaplan–Meier estimates. The cumulative incidence of death was significantly different among LVSD groups and Non-LVSD group (log-rank P =0.016; Figure 2)

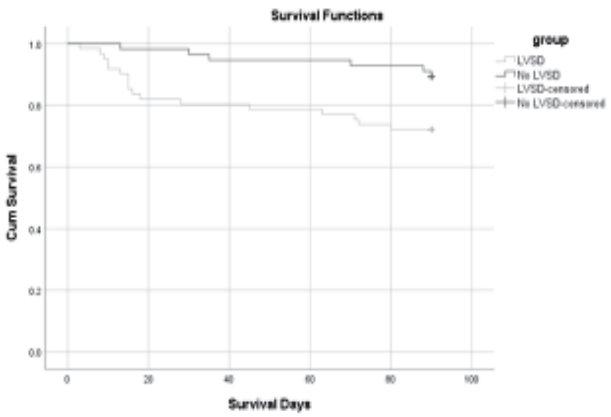

Figure 2: *Kaplan–Meier curves of with or without LVSD level on mortality. LVSD, left ventricular systolic dysfunction.*

Table III shows Total mortality 3.314 times more mortality in LVSD group than in non LVSD group.

Table II

Total Mortality in AIS Patients with or without LVSD

	No of patients in the analysis					
Group	Day 1	Day 20	Day 40	Day 60	Day 80	Day 90
LVSD (censored)	61	53	51	49	45	44
No-LVSD (censored)	56	56	54	53	52	50
LVSD (Death)	00	8	2	2	4	1
No-LVSD (Death)	00	01	2	00	1	2

Table III

Total Mortality in AIS Patients with or without LVSD

Events	Total study subjects (n=117)	LVSD (n=61)	Non- LVSD (n=56)	HR (95%CI)	p Value
Death	23 (19.7%)	17 (27.9%)	6 (10.7%)	3.134 (1.036 to 9.475)	0.016

Table IV shows at 1 month, 95.1% of the LVSD group scored >2 on the mRS, while 83.9% of the non-LVSD group shared this score. For an mRS score of 0-2 (indicating good functional outcome), 4.9% of the LVSD group achieved this score, compared to only 16.9% of the non-LVSD group. At 3 months at 31.1% of the LVSD group achieved an mRS score of 0-2 (indicating good functional outcome), whereas 60.7% of the non-LVSD group obtained the same score. Conversely, for an mRS score >2 (indicating poor functional outcome), 68.9% of the LVSD group scored this, compared to only 39.3% of the non-LVSD group. Stroke-related disability (as described by mRS) at discharge and at 3 months worsened significantly among the LVSD groups (Figure 2)

Table IV

Disability(mRS) in Stroke Patients with or without LVSD

Outcome scales	LVSD (n=61)	No LVSD(n=56)	p value
At 1 month			
Good functional outcome (mRS 0-2)	3 (4.9%)	9 (16.1%)	0.067
Poor functional outcome (mRS >2)	58 (95.1%)	47 (83.9%)	
At 3 month			
Good functional outcome (mRS 0-2)	19 (31.1%)	34 (60.7%)	**<0.001**
Poor functional outcome (mRS >2)	42 (68.9%)	22 (39.3%)	

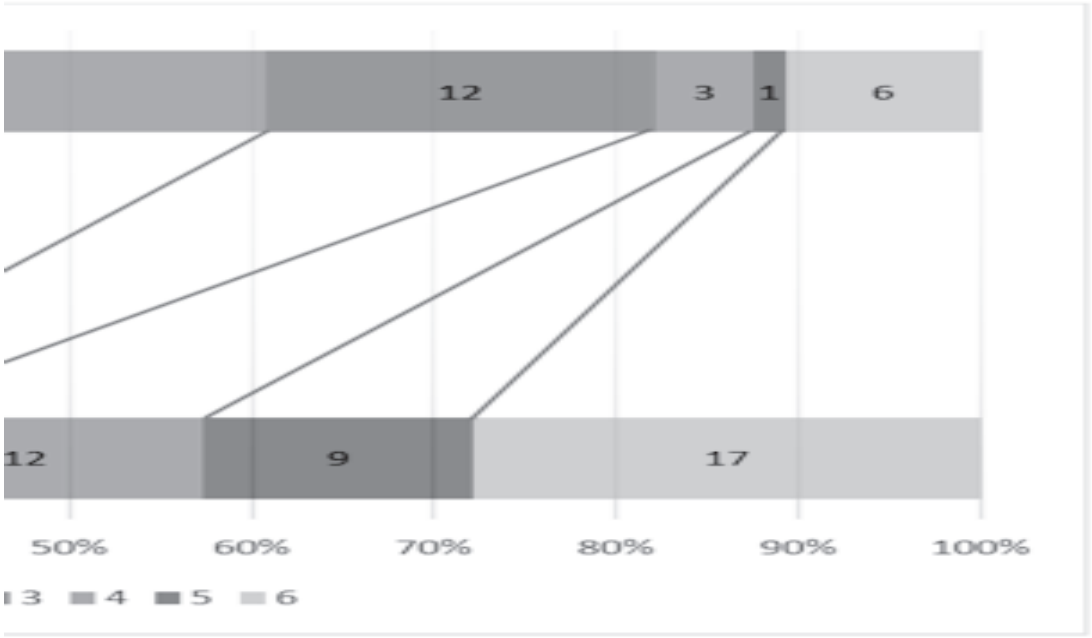

Figure 2. *Distributions of modified Rankin Scale at 3 month*

Table V shows Length of hospital stay of the stroke patients with the LVSD was 10 days with a IQR of 8-15 and without the LVSD was 7 days with a IQR of 4-11. Need for ICU referral of the ischemic stroke patients with the LVSD was 32.8% while and without the LVSD was 14.3%. also in Table V.

Table V

Length of hospital stay and Need for ICU Referral in AIS Patients with or without LVSD

Outcome scales	LVSD (n=61)	No LVSD(n=56)	p value
Length of hospital stay			
Median (IQR)	10 (8-15)	7 (4-11)	<0.001
Need for ICU Referral			
Yes	20 (32.8%)	8 (14.3%)	0.029

Table VI

Multivariable logistic regression model for poor functional outcome at 3 months

	p-value	OR	95% CI for OR	
			Lower	Upper
Diabetes Mellitus	0.606	0.670	0.146	3.064
Hypertension	0.751	0.770	0.153	3.867
Ischemic Heart Disease (IHD)	0.004	4.781	1.668	13.698
Dyslipidemia	0.719	1.395	0.227	8.566
Smoking	0.452	0.536	0.106	2.720
Gender (male)	0.031	2.833	1.098	7.310
Initial NIHSS	0.116	3.383	0.739	15.479
Duration of Hospital stay	0.201	2.804	0.577	13.619

Table VI shows Multivariable logistic analysis showed that male gender (OR:2.833; 95%CI: 1.0988 to 7.310), IHD (OR:4.781, 95%CI: 1.668 to 13.698), in the LVSD group were independently associated ($p<0.05$) unfavorable outcome.

Discussion:

In terms of financial, social, and health costs, stroke is one of the most common diseases in Bangladesh. This is the first-ever study in this institute to demonstrate the outcome of stroke patients with or without LVSD. This study provides essential information about the disability and mortality of stroke in the LVSD, non-LVSD groups and sub-group of LVSD. Stroke patients who were enrolled in this study were examined on admission and followed-up at hospital, after one month and 3 months to see the outcomes.

During the study period, 117 patients admitted to this institute with Ischemic stroke were enrolled for this study. Among them, 61 patients had strokes with LVSD, and 56 had strokes without LVSD. In our study, the incidence of stroke was higher in male patients in both the LVSD and non-LVSD groups, which is 51 (83.6%) and 38 (67.9%), respectively. The mean age of stroke in the LVSD group was 65.50 ± 9.94 years, and stroke without LVSD was 63.78 ± 10.85 years. According to this study, older male patients; either LVSD or non-LVSD; had a higher risk of stroke, similar to previous studies done by some Bangladeshi researchers.[4] Another stroke registry gathered data from 679 stroke patients in BIRDEM General Hospital, Dhaka, Bangladesh. Mean age of the stroke patients was 60.6 years; the majority of patients (67.7%) were male.[13] Consistent with earlier research, this study indicated that patients with a prior history of coronary heart disease had a higher risk of developing stroke among LVSD patients (37.7%) compared with non-LVSD patients (10.7%). A prior study found that the incidence of IHD in stroke with LVSD was 32.11%, and stroke without LVSD was 7.9%, which supports this study.[11] The LVSD group comprised 62.3% hypertensive patients. In contrast, 50% non-LVSD patients had hypertension, indicating a higher prevalence in LVSD group. this study shows hypertensive is more common risk factor in both LVSD and non-LVSD group. a Study in Bangladesh informed that hypertension was the most common risk factor observed among the stroke patients 79.2%.[4] Another previous study found that hypertension in the LVSD stroke group was more 93.3% than in the non-LVSD group 74.1%, similar to this study.[14] The incidence of diabetes more in the LVSD group 37.7% than in the non-LVSD group 37.5%, which was comparable to a previous study 39.4% in LVSD group and 29.7% in non-LVSD group.[11] In our study, 44.25% in LVSD and 37.5% in non-LVSD stroke patients were smoker, this result was supported by a study where smoker in LVSD group was 56.3% and in non-LVSD group was 37.4%.[15] Pulse rate was considerably higher in

LVSD groups during examinations of stroke patients 86(83-94) vs 80(72-88), p-0.161). a previous study showed that pulse rate in LVSD 87.38 (67.06-98.32) and in non-LVSD 80.32 (62-89) group[15] However, systolic blood pressure was higher in LVSD group patients 150(132-160) vs 140(120-150),p 0.007), (median, IQR) which was supported by a study where SBP in LVSD group was 140.9± 16.7 vs non-LVSD group 134.2±16.4.[14] The stroke patients were assessed by the Glasgow Coma Scale, National Institutes of Health Stroke Scale (NIHSS), and Modified Rankin Scale (mRS) on admission. According to the GCS scale, patients who had LVSD had a higher severe score (GCS 3-8, 14.8%,)) than patients who did not have LVSD (GCS 3-8, 7.1%)) which is statistically significant (p=0.037). But GCS 13-15 more frequent in non-LVSD patients about 53.6% whereas LVSD patients had 41% which is also statistically significant (p=0.042). Baseline NIHSS on arrival was not significant between LVSD and non-LVSD patient group (5-15 NIHSS, 52.5%% vs 66.1%, p =0.188; 16-20 NIHSS 26.2% vs 17.9%, p=0.374; and NIHSS 21-42, 21.3% vs 16.1%, p=0.489). This study shows that NIHSS score on admission was higher for participants with LVSD (Median, IQR; 15(12-20)) compared to those without LVSD (Median, IQR; 14(13-16)), and this difference was not statistically significant (p=0.293). a retrospective study on 937 stroke patient with or without LVSD found that LVSD patients had NIHSS Median, IQR; 18 (11-22) and on non-LVSD patients had Median, IQR; 15 (08-21) [16]. This study shows that at hospital mortality and 1st month mortality, both are 5.4 times higher in LVSD than non-LVSD, 9.8% vs 1.8% (p=0.029). another study found that early mortality was 3 times higher in the LVSD group than Non-LVSD.[15] A prior shudy showed that in hospital mortality for stroke patients with LVSD were 2 times higher than those without LVSD.[12] This result was remarkably comparable to our findings. At 3rd month follow up the mortality is slightly higher in LVSD group than non-LVSD group (8.2% vs 7.14%) which is not statistically significant (p >0.99). Total mortality at 3 months is almost 3 times greater in LVSD than non-LVSD patients (27.9%vs 10.7%, p<0.05). another study showed that total mortality at 3 months is more in LVSD than non-LVSD group (26.10% vs 12.40%) which was also similar to our findings.[17] Modified Rankin Scale (mRS) assessed the outcome. at 1 month follow up mRS was ≤2 in 4.9% vs 16.1%), mRS was >2 in 95.1% vs 83.9%) in LVSD group vs non-LVSD group. its showed that unfavorable outcome has identified in both group but more unfavorable in LVSD group than non-LVSD group. No study was found to compare our 1 month findings due to different methodology. Functional outcome at 3 months follow up mRS was ≤2 in 31.1% vs 60.7%)), mRS was >2 in 68.9% vs 39.3%) in LVSD group vs non-LVSD group. its showed that favorable outcome has identified in non-LVSD group than LVSD group. So, at 3 months 68.9% of LVSD patients and 39.3% of non-LVSD patients showed unfavorable outcome. The difference was statistically significant with a p-value of <0.001. From the study of Acute Stroke Registry and Analysis of Lausanne (ASTRAL) registry, stroke-related disability was worse in the LVSD group. another previous study found that dependency/ poor functional outcome at 3 months was 60% in the LVSD group, but 37.7% in the non-LVSD group. that supports this study's findings.[17]

Length of hospital stay of the stroke patients with the LVSD was 10 days with a IQR of 8-15 and without the LVSD was 7 days with a IQR of 4-11. That results show that stroke patients with LVSD had a longer in-hospital Length of hospital stay (LOS) compared to those without LVSD. a earlier work showed that stroke patients with LVSD had a longer in-hospital stay (LOS) compared to those without LVSD about 5.9 days (95% CI: 5.8-6.1) with LVSD and 4.6 (95% CI:4.6-4.7) days without LVSD.[12]

Need for ICU referral of the ischemic stroke patients with LVSD was 2.3 times more than non-LVSD patients (32.8% vs 14.3%, p 0.029**)** hospital stay was statistically significant in both group.

In the multivariable logistic regression analysis in LVSD group Patients shows that IHD (OR: 4.781, 95% CI: 1.668 to 13.698), and male gender (OR: 2.833; 95%CI: 1.0988 to 7.310), in the LVSD group were independent predictors

of poor functional outcomes (mRS >2) at 3 months. an existing literature showed that in the multivariable analysis, poor functional outcomes at 3 months were significantly associated with IHD (OR:3.25, 95% CI: 1.82–5.81; P-value <0.001) [18]. Wei *et al*,.2023 a prior research found that male gender in low EF was significantly associated with poor functional outcome (OR: 1.64; 95%CI: 1.28 to 2.10, P-value <0.001).[19]

Patient with declining ejection fraction (LVSD) had high left ventricular filling pressure that led to decrease in the stroke volume. Reduced ejection fraction has shown to have a role in causing decreased of brain blood vessels reactivity which subsequently leads to cerebral hypoperfusion. Left ventricular ejection fraction was a determinant factor for clinical outcomes in ischemic stroke patients.[20]

Moreover, this study leads us to the conclusion that stroke patients with LVSD have worse clinical outcomes, severe strokes, higher mortality rates, Longer hospital stay. A greater need for ICU referral and more stroke-related complications. The findings of the thesis warrant further research into the management and prevention of ischemic strokes in patients with LVSD to improve their long-term outcomes. The study also highlights the importance of early diagnosis and intervention of LVSD to minimize the risk of ischemic stroke and reduce the associated morbidity and mortality.

Conclusion:

Our study demonstrated that Ischemic Stroke patients with LVSD have worse clinical outcomes, higher mortality rates, excessive dependency, longer hospital stay time and greater need for ICU referral than patients without LVSD. The outcome was measured by mRS score which was significantly higher in LVSD group than non-LVSD group, after the end of 1st month and 3rd month follow up.

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Case Report

A Case Report on Diabetic Striatopathy; A Diagnostic Dilemma

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Abstract

Diabetic striatopathy (DS) is an acute hyperkinetic movement disorder characterized by hemiballismus-hemichorea (HBHC) due to nonketotic hyperglycemia. Diabetic striatopathy occurs due to striatal (putamen, caudate nucleus, globus pallidus) pathology. The exact pathogenesis and mechanism remain unclear but may involve hyperviscosity, ischemia, and alterations in basal ganglia neurotransmitters. We present here a case of HBHC syndrome with right-sided neuroimaging findings and contralateral chorea due to uncontrolled type 2 diabetes mellitus. She had a history of poorly controlled type 2 diabetes and presented with involuntary movements of her left limb suggestive of chorea. Laboratory tests confirmed hyperglycemia, with an elevated hemoglobin A1c level. Neuroimaging revealed T1-hyperintensity in the right putamen. The patient was diagnosed with diabetic striatopathy and responded well to insulin therapy and haloperidol with a rapid resolution of symptoms. The striking features on imaging such as computed axial tomography (CT) scan of the brain and T1-weighted magnetic resonance imaging (MRI) of the brain can mislead the clinician to an erroneous diagnosis of a cerebral hemorrhage and/or ischemic infarct, especially in an acute setting. With careful and thoughtful analysis, an accurate diagnosis can spare the patient unnecessary anxiety and medical costs.

Keywords: *hyperkinetic movement disorder, hemichorea, hemiballismus, diabetes mellitus, diabetic striatopathy.*

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Introduction

Diabetic striatopathy (DS) is a condition occurring in individuals with type II diabetes mellitus (T2DM). It is an acute hyperkinetic movement disorder secondary to nonketotic hyperglycemia. DS is a rare disorder with an estimated prevalence of 1 in 100,000, which is likely an underestimation due to unfamiliarity and missed diagnosis.[1] This syndrome was first described by Bedwell in 1960.[2] It is more prevalent in females, and the greatest risk factor is old age.[3] It is presented as development of hemiballismus-hemichorea (HBHC) associated with hyperintensity on T1-weighted magnetic resonance imaging (MRI) of the putamen, caudate nucleus, and globus pallidus in various combinations, with the putamen being most involved.[4,5] Imaging usually shows an absence of mass effect or contrast enhancement, indicating an intact blood-brain barrier. The internal capsule is normally spared.[6] The most likely pathology of DS involves myelin destruction caused by swollen reactive astrocytes called gemistocytes.[7] This hyperkinetic movement disorder is usually improved with judicious glucose control, sometimes necessitating treatment with anti-chorea agents such as dopamine antagonists (haloperidol), vesicular monoamine uptake (VMAT-2) inhibitors (tetrabenazine), or gamma-

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aminobutyric acid (GABA) agonists (clonazepam).[8]

Case Presentation

We present the case of 60-year-old woman with poorly controlled diabetes mellitus and one month history of sudden, involuntary, rapid, jerky, irregular movement of the left upper and lower extremity, sparing the tongue, face, and the neck which got worsened over 2 weeks. These movements did not abate with sleep. Her speech was unaffected, but her gait was interrupted by the motion. Past medical history showed 10-year history of diabetes mellitus with non-compliance to anti-diabetic medication. She had no previous history of trauma, no history of similar symptoms. There was no family history of chorea, and she did not smoke cigarettes or drink alcohol. She only used to take metformin for diabetes but irregularly. There was no significant occupational or environmental exposure to toxins. On examination, her blood pressure was 130 mmHg systolic and 80 mmHg diastolic with a pulse of 76 beats per minute. On initial inspection, examination was notable for high amplitude involuntary dyskinesia of the axis (trunk), left upper extremity, and left lower extremity. The movement was rapid, involuntary, jerky, random, irregular, large amplitude, purposeless, flinging, sometimes forceful. On gait examination, the patient's left foot and lower leg jerked during the swing phase, making her gait irregular and unsteady. Her speech was normal. Her extraocular muscles were intact with normal-amplitude eye motion in all directions without nystagmus. The rest of the cranial nerve examination was normal. Blinking frequency was also normal. Kayser-Fleischer rings were not detected. There were no stigmata of connective tissue disease or metabolic or nutritional disorders.

Motor strength was preserved in the upper and lower extremities. Coordination examination with left finger-to-nose test and left heel-to-shin test demonstrated sinuous movements due to the choreoathetosis, but the target was reached. Patient's deep tendon reflexes were normal. Sensory examination was generally preserved to small and large fiber modalities in the fingers and toes except for a diminished vibration sense bilaterally. Plantar responses were flexor. The patient's random glucose level was 301 mg/dL (normal range: 70-115 mg/dL), and his hemoglobin A1c was 12% (normal range: 3.8-5.6%). The basic metabolic panel was otherwise normal.

Table -I

Investigations.

Investigations.			
Full Blood Count	White Blood Cells (× 10^9 /L)	8.4	4.5 – 11
	Haemoglobin (g/dL)	11.5	11-13
	Platelets (x 10^9/L)	239	150 – 400
Liver Biochemistry	Alanine Transaminase (U/L)	17	< 40
	Aspartate Transaminase (U/L)	22	< 40
	Serum Albumin (g/L)	39	35 - 50
Renal Profile	Serum Creatinine (mg/dl)	89	20 - 275
	Blood Urea (mg/dl)	16	6 - 24
Electrolytes	Serum Sodium (mmol/L)	139	135 – 145
	Serum Potassium (mmol/L)	3.9	3.5 – 5.5
	Serum Calcium (mmol/L)	2.4	2.2 to 2.7
	Serum Magnesium (mg/dl)	1.7	1.6 – 2.5
Thyroid Function Test	Thyroid Stimulating Hormone (mIU/L)	3.95	0.5 to 5.0
Urine	Urinary Ketone	Absent	
Other Investigations	Serum Ceruloplasmin (mg/dl)	16	14 - 20

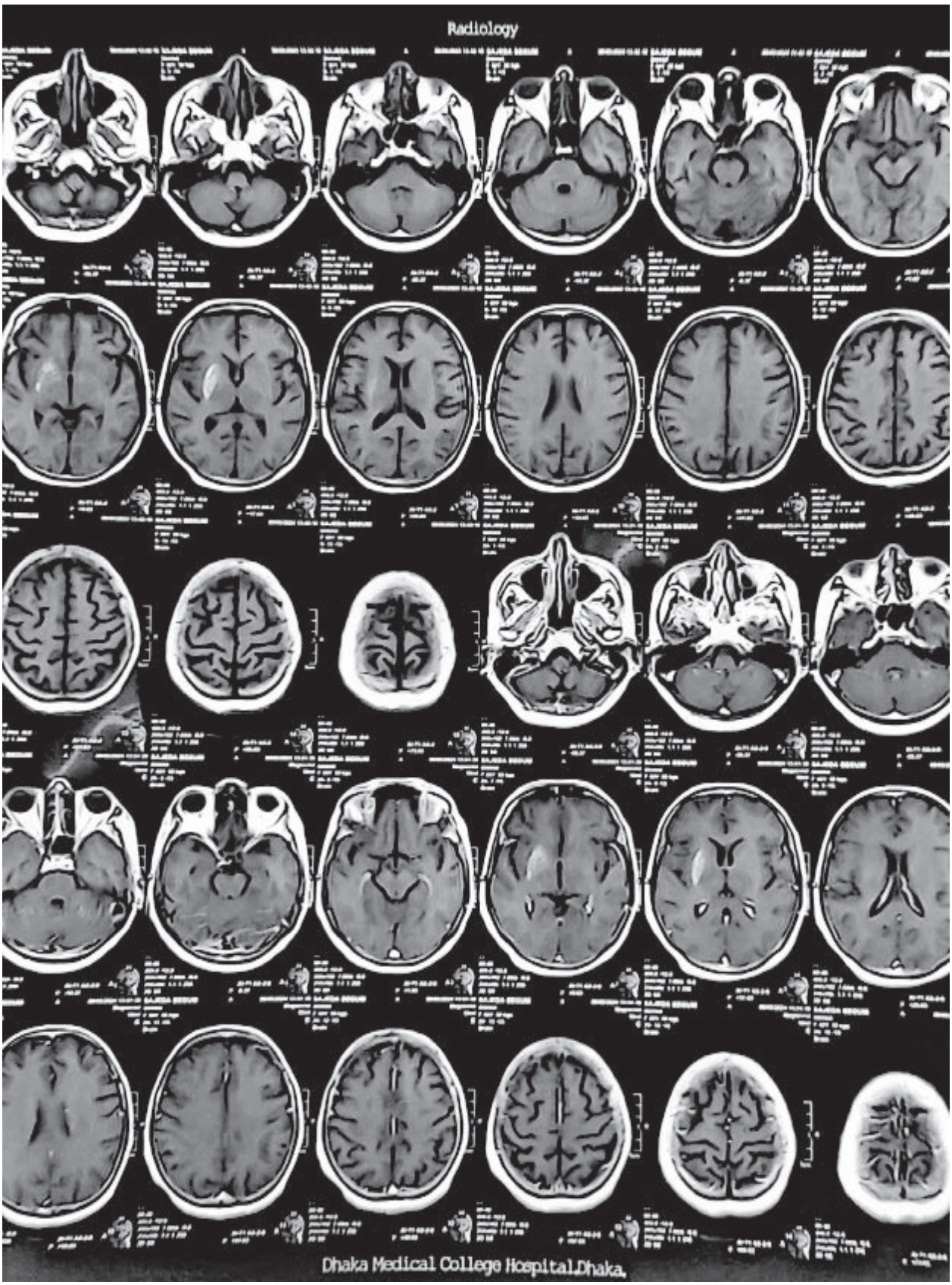

Fig.-1:*T1-weighted MRI of the brain showing hyperintensity in the right putamen*

Based upon the absence of a family history of chorea, the characteristic clinical history of chronic poorly controlled diabetes, and the characteristic MRI brain findings, probable diagnosis of Diabetic Striatopathy was made. The patient was treated with insulin for hyperglycemia and a trial of haloperidol daily was prescribed to reduce the amplitude and frequency of the disabling choreoathetosis. The patient demonstrated substantial improvement of the movement disorder following the treatment within a week.

Discussion

Acute HBHC is a defining clinical characteristic of DS. However, diagnosing DS is not always straightforward as there are many differential diagnoses of HBHC. Common clinical presentations of DS include HBHC involving unilateral limbs, progression from upper to lower extremities with suppression of HBHC during sleep.[8] In our case, the patient's acute onset of unremitting characteristic unilateral A1c HBHC and the hemoglobin 12% raised suspicion for DS. Based on the principles of T1-weighted MRI sequences, T1-shortening resulting in hyperintensities can be caused by various factors, including melanin, subacute haemorrhage with methaemoglobin, fat, slow-velocity blood flow, high protein content, and the presence of paramagnetic transition metals such as manganese, iron, zinc, and copper, which have unpaired electrons.[14] The clinical features observed in this patient can exclude certain causes of T1 hyperintensity. For example, disorders related to copper deposition (i.e. Wilson disease) and other similar conditions typically present as chronic diseases with a gradual onset.[15] Early subacute blood on an MRI brain demonstrates hypodensities on both susceptibility-weighted imaging (SWI) and apparent diffusion coefficient (ADC) sequences, and late subacute blood shows hyperintensity on diffusion-weighted imaging (DWI) sequences.[11,12] An ischemic infarct would show high signal intensity on DWI sequence and low signal intensity on ADC sequence.[13]

According to a meta-analysis published in 2020, 96.6% of the patients reported had type 2 diabetes, and the average hemoglobin A1c was 13.1%. In total, 97.7% of patients presented with chorea/hemichorea, and the striatal area mostly involved (78.6%) was putamen. It was also noted that MRI had a greater sensitivity (95.33%) of detecting abnormalities associated with DS, compared with that of CT (78.9%)[14]. In this case, MRI showed the typical feature in putamen which is the most common site. Greater successful treatment rate (76.2%) was noted in patients treated with combined glycemic control and antichorea medications, compared with 25.6% in those treated only with glycemic control. In this case, insulin and haloperidol together helped to make rapid recovery within a week.

There also have been multiple meta-analyses to understand the phenomenon. However, the limited number of case data was a major limitation to explain the pathogenesis and phenomenon[15]. We believe our case report will contribute to current available data in the literature.

DS can mimic other movement disorders and strokes, which can be challenging. This report creates awareness to physicians as well as mid-level providers that DS is a good differential diagnosis to consider when confronted with a movement disorders, especially in patients with uncontrolled diabetes. Acute-onset chorea in poorly controlled hyperglycemia in type 2 diabetes should alert the providers to screen with MRI for DS.

Conclusion

In conclusion, physicians need to be alert of possibility of DS, as its timely-bound condition and prognosis partially depend on the time window of detection and management. Nevertheless, the radiologist needs to pay attention to the distinct features of this condition and should not dismiss other possibilities, such as haemorrhage in patients with atypical presentation. Further study of its pathophysiological mechanisms is needed to guide better management.

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