Editorial

- Artificial Intelligence in Medicine
  Mahmud Hasan

Review Article

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Original Articles

- Anti-Covid Antibody Status in Health Care Professionals of Bangladesh after 3 Months of Completion of Two Doses of Covid-19 Vaccination
  Ayatun Nesa, Kazi Muhammad Mahbubur Rahman, Abdul Ali, Roksana Yesmin

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  Sahed Uddin Ahmed, Md. Abu Hanif Chowdhury, Md. Jaber Abedin, MA Sattar, Sujat Paul, Asok Kumar Dutta

- Effects of Intralesional Autologus Platelet Rich Plasma Therapy in Patients with de Quervain’s Tenosynovitis
  Mohammad Anisur Rahman, Abul Khair Mohammad Salek, Farzana Khan Shoma, Md. Ruhul Amin, Amitab Banik

- Intensive Rehabilitation is better When it is Combined with Tizanidine in Spastic Cerebral Palsy- A Randomized Clinical Trial
  Md. Ruhul Amin, Amitav Banik, Mohammad Anisur Rahman, Sohely Rahman

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  Durba Halder, Md. Yousuf Ali, Janesar Rahat Faysal, Farhana Nayeem, Abdur Rouf, Nabeela Tasnim, Mdhammad Ferdous Ur Rahman

Content continued in inside front cover
Comparison between Digital Subtraction Angiography and Magnetic Resonance Angiography in the Investigation of Acute Ischemic Stroke in a Tertiary Care Hospital in Bangladesh

Current Scenario of Poisoning and Snake Bite Patients Admitted in Sylhet MAG Osmani Medical College Hospital
Mrinal Saha, Sajjad Mahamud, Abu Kamran Rahul

A Clinical Utility of Neutrophil Lymphocyte Ratio as An Independent Predictor of Systemic Lupus Erythematosus Disease Activity
Mahmuda Abira, Mohammad Sirajul Islam, Rahnuma Ahmad, Farhana Sultana, Tahmina Akter, Md. Daharul Islam, Qazi Shamima Akhter

Case Reports
A Case Report of Takayasu’s Arteritis with Stroke as Initial Presentation

A Girl Presented with Learning Difficulty and Poor School Performance: A case report

A Young Girl With Granulomatosis with Polyangiitis: A Rare Case Report
Md Mahfuzer Rahman, Rana Shankor Roy, Md Golam Rabbani, Akter Banu, Md Jahangir Kabir, Md Abul Kalam Azad, Mohsina Akter, Yeasir Arafat

Post-COVID-19 Infection Tietze’s Syndrome in a Young Adult Patient
Sayeef Hossain Khan Mark, Rasif Hossain Khan, Shaima Rahman Mishu, Khan Abul Kalam Azad

A Deadly Tunnel: A Case Report of Atrial-Esophageal Fistulaafter Atrial Fibrillation Ablation
Farzana Hoque

A Case Report of Resistant Hypertension due to Renal Artery Stenosis: Long Term Sufferings of a Middle-Aged Gentleman
Homayra Tahseen Hossain, Nausabah Noor, Sharmin Akhter, Ishrat Binte Reza, Mahbub Mayukh Rishad, Quazi Tarikul Islam

If the Mind Doesn’t Know, the Eyes Cannot See: A Case Report of Localized Tetanus
Nausabah Noor, Homayra Tahseen Hossain, Mohammad Mohsin, Mahbub Mayukh Rishad, Mohammad Zahiruddin

Physician in Practice
God Must Be Crazy
Quazi Tarikul Islam

Clinical Images
Medical quiz: 1
AKM Monwarul Islam, Humaira Jesmin

Medical quiz: 2
Aminur Rahman
Answers to Medical Quizzes
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CONTENTS

Editorial

- Artificial Intelligence in Medicine  
  Mahmud Hasan 69

Review Article

- Non Alcoholic Fatty Liver Disease: A Silent Global Epidemic  
  Bimal Chandra Shil, Mohammad Kamal Uddin, Monirul Hasan 73

Original Articles

- Anti-Covid Antibody Status in Health Care Professionals of Bangladesh after 3 Months of Completion of Two Doses of Covid-19 Vaccination  
  Ayatun Nesa, Kazi Muhammad Mahbubur Rahman, Abdul Ali, Roksana Yesmin 80

- Predictive Value of Neutrophil to Lymphocyte Ratio and Sequential Organ Failure Assessment Score in Patient with Sepsis  
  Sahed Uddin Ahmed, Md. Abu Hanif Chowdhury, Md. Jaber Abedin, MA Sattar, Sujat Paul, Asok Kumar Dutta 86

- Effects of Intralesional Autologus Platelet Rich Plasma Therapy in Patients with de Quervain’s Tenosynovitis  
  Mohammad Anisur Rahman, Abul Khair Mohammad Salek, Farzana Khan Shoma, Md. Ruhul Amin, Amitab Banik 93

- Intensive Rehabilitation is better When it is Combined with Tizanidine in Spastic Cerebral Palsy- A Randomized Clinical Trial  
  Md. Ruhul Amin, Amitav Banik, Mohammad Anisur Rahman, Sohely Rahman 98

- Association of Vitamin-D Status with Ischemic Stroke and It’s Risk Factors in Bangladeshi Patients: A Case-Control Study  
  Md Abu Hanif Chowdhury, Sahed Uddin Ahmed, Md. Jaber Abedin, Md. Raihan Chowdhury, Sujat Paul, Asok Kumar Dutta 105

- Association of 99mTc- HMPAO SPECT Measured Regional Cerebral Blood Flow and Serum Vitamin D Level with Clinical Staging of Parkinson’s Disease  

- Pattern of Bone Mineral Density in Postmenopausal Women in a Tertiary Care Centre of Bangladesh  
  Durba Halder, Md. Yousuf Ali, Janesar Rahat Faysal, Farhana Nayem, Abdur Rouf, Nabeela Tasnim, Mammad Ferdous Ur Rahman 112

- Comparison between Digital Subtraction Angiography and Magnetic Resonance Angiography in the Investigation of Acute Ischemic Stroke in a Tertiary Care Hospital in Bangladesh  

- Current Scenario of Poisoning and Snake Bite Patients Admitted in Sylhet MAG Osmani Medical College Hospital  
  Mrinal Saha, Sajjad Mahamud, Abu Kamran Rahul 133

- A Clinical Utility of Neutrophil Lymphocyte Ratio as An Independent Predictor of Systemic Lupus Erythematosus Disease Activity  
  Mahmuda Abira, Mohammad Sirajul Islam, Rahnuma Ahmad, Farhana Sultana, Tahmina Akter, Md. Dahrul Islam, Qazi Shamima Akhter 137
Case Reports

- A Case Report of Takayasu’s Arteritis with Stroke as Initial Presentation

- A Girl Presented with Learning Difficulty and Poor School Performance: A case report

- A Young Girl With Granulomatosis with Polyangiitis: A Rare Case Report
  Md Mahfuzer Rahman, Rana Shankor Roy, Md Golam Rabbani, Akter Banu, Md Jahangir Kabir, Md Abul Kalam Azad, Mhosina Akter, Yeasir Arafat

- Post-COVID-19 Infection Tietze’s Syndrome in a Young Adult Patient
  Sayeef Hossain Khan Mark, Rasif Hossain Khan, Shaima Rahman Mishu, Khan Abul Kalam Azad

- A Deadly Tunnel: A Case Report of Atrial-Esophageal Fistula after Atrial Fibrillation Ablation
  Farzana Hoque

- A Case Report of Resistant Hypertension due to Renal Artery Stenosis: Long Term Sufferings of a Middle-Aged Gentleman
  Homayra Tahseen Hossain, Nausabah Noor, Sharmin Akhter, Ishrat Binte Reza, Mahbub Mayukh Rishad, Quazi Tarikul Islam

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  Nausabah Noor, Homayra Tahseen Hossain, Mohammad Mohsin, Mahbub Mayukh Rishad, Mohammad Zahiruddin

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Answers to Medical Quizzes
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ARTIFICIAL INTELLIGENCE IN MEDICINE

MAHMUD HASAN

The ability to learn, make decisions and solve problems is considered to be part of human thinking capacity. It called artificial intelligence (AI) when a machine can achieve these capacities autonomously. Storage capacity of computers have advanced so far that great parts of human knowledge can now be kept in store and accessed readily. Vast stores of information and much faster computing have enabled practical and real time relationships to be found in the data that was not possible in the past. Although the computers were much slower and the storage capacity much more limited in the early stages, it was possible to perform some repetitive human tasks that were prone to human error even in the 1990s and the early 2000s. Reading of ECGs, white cell counts, analysis of retinal photographs and skin lesions had been introduced in daily clinical practice. From the beginning of the development phase there was recognition by researchers and developers that AI systems in healthcare needed to recognize that perfect data is absent and the system should be based on the expertise of physicians. Development included fuzzy set theory, Bayesian networks and artificial neural networks in building up intelligent computing systems in medicine.

Machine learning is a type of AI where the computer can learn and improve its performance without programming. Deep learning is AI in which multiple layers of networks can continue to learn as it performs routine work. These systems have the ability to analyze much greater amount of data than humans. One application of AI in North London is being used to determine priorities in emergencies in one million patients. Such systems can analyze much more data than one physician can in his or her whole lifetime. Remarkable progress have been made by AI in the field of medical science, providing a powerful tool for improving healthcare delivery, patient outcomes, and disease prevention. AI has the potential to transform the way doctors diagnose and treat illnesses, and its impact is already evident in several areas of health care.

One of the most significant applications of AI in medical science is in disease diagnosis. AI algorithms can analyze vast amounts of medical data and identify patterns and anomalies that may be difficult for human doctors to detect. This technology can help doctors make more accurate and timely diagnoses, leading to better treatment outcomes for patients. In the interpretation of several imaging modalities, such as ECGs, plain radiographs, computed tomographic (CT) and magnetic resonance imaging (MRI) scans, skin images, and retinal photographs, the application of AI and machine learning has already become accepted. For instance, AI can analyze images of medical scans to identify tumors or lesions in the body, which can help doctors make more informed decisions about treatment options. That is true for processing of radiological and other images. AI has been shown to diagnose lung carcinomas in computerized tomography scans better than humans. Use of AI is also being made to diagnose polyps during colonoscopy. AI has been shown to make the diagnosis of skin cancer from photographs of skin lesions with equal efficiency compared to humans. Although these tasks often require oversight by a specialist, it does reduce the time needed for diagnosis in locations where expertise is not available. One AI system developed in China has been shown to make a diagnosis based on available clinical data in paediatric diseases with similar proficiency to clinicians. The use of wearable devices with smart phones using AI is being used to diagnose cardiac arrhythmias and epilepsy in real time and can give warning. In addition, AI has a significant role to play in personalized medicine. By analyzing a patient’s genetic data and medical history, AI algorithms can
help doctors develop customized treatment plans that are tailored to the patient's unique needs. This can lead to better treatment outcomes and fewer adverse reactions to medication.

Another area where AI is revolutionizing medical science is drug development. AI algorithms can help scientists identify potential drug candidates by analyzing large datasets of molecular structures and predicting their efficacy and safety. This can significantly reduce the time and cost required to develop new drugs, potentially leading to faster treatments for diseases.  

Potential for clinical trials to be simplified and speeded up by AI and machine learning has been created. This may be through more efficient recruitment and matching of participants of the study and more detailed analysis of data. Moreover, there is a potential for creation of synthetic control groups by matching historical data that will target trial enrollment criteria. Prediction of adverse events and patient subpopulations may be better understood by the application of AI and machine learning. It may also be possible to generate “synthetic patients” so that diagnostic and therapeutic outcomes can be simulated.

A computer program named Chatbot has been developed. In this programme, AI and natural-language processing is used to understand questions and automate responses to them, simulating human conversation. Chatbots are in use in many different areas besides medicine. Today's powerful computers, language models and the availability of a sea of data on the internet has made it possible to generate scientific compositions that are difficult to differentiate from human generated text.

The new generation of chatbots can help with medical documentation, thereby giving the clinician more time to spend with the patient. "Ambient Clinical Intelligence" is a programme that can analyze the conversation between a doctor and a patient and then prepare an electronic health record. A programme called “Babylon” in the United States makes appointments for patients and arranges for routine tests. Key questions about differential diagnosis can be answered by chatbots and thus help in making a diagnosis. The answers may not be based on appropriate facts and will need interpretation. If the user is not knowledgeable enough, mistakes can be made.

There are many other ways in which AI and machine-learning programs have also entered medicine. One of these areas is helping to identify infectious disease outbreaks that may have an impact on public health. AI can also be used to diagnose both common and rare conditions by combining clinical, genetic, and other laboratory outputs. Moreover, the AI simulation-based surgical training system that combines AI and simulation together for studying surgical techniques has created a new educational tool with objective feedback, which is beneficial for student learning.

AI is also being used to improve healthcare delivery by optimizing hospital workflows and resource allocation. For example, AI can help hospital administrators allocate staff and resources more efficiently, reducing wait times and improving patient outcomes. Additionally, AI can help doctors and nurses prioritize patient care by analyzing medical data and alerting them to patients who may require urgent attention.

However, AI in medical science is not without its challenges. One of the primary concerns is the potential for bias in AI algorithms. If the training data used to develop the algorithms is biased, the results may be skewed, leading to incorrect diagnoses or treatment recommendations. Additionally, the use of AI in medical science raises questions about patient privacy and data security.

There are concerns among some health professionals that AI and machine learning will reduce the need for doctors. Others think that AI will add to and expand the scope of work of doctors. The need for doctors who have knowledge about AI will continue to grow. Already some medical schools in developed countries have changed the curriculum to include relevant parts of physics, mathematics, computer science, coding and algorithm to prepare doctors better.

Development of AI and machine learning is advancing very fast. This has the potential to transform the field of medical science by improving disease diagnosis, drug development, personalized medicine, and healthcare delivery. While there are challenges that must be addressed, the benefits of AI in medical science are clear. As technology continues to evolve, we can expect to see even more innovative applications of AI in the field of medical science, leading to better health outcomes for patients worldwide.
References:


NON ALCOHOLIC FATTY LIVER DISEASE: A SILENT GLOBAL EPIDEMIC

BIMAL CHANDRA SHIL¹, MOHAMMAD KAMAL UDDIN², MONIRUL HASAN³

Abstract:
Nonalcoholic fatty liver disease (NAFLD) is a common liver disease worldwide affecting adult as well as children with an increasing prevalence. It is associated with insulin resistance and frequently occurs with features of the metabolic syndrome. NAFLD is a spectrum, with NAFL (Non-alcoholic fatty liver) being the initial mildest form, NASH and cirrhosis is being at the other end of the spectrum. Mostly NAFLD is asymptomatic but may present with elevated liver enzyme levels to cirrhosis with its complications and hepatocellular carcinoma. Standard ultrasound including elastography may be used to detect steatosis. Though, liver biopsy is the gold standard for diagnosis of NAFLD but it is not frequently performed. NAFLD patients with evidence of nonalcoholic steatohepatitis and advanced fibrosis are at increased risk of adverse outcomes, including overall mortality. Life style modification and weight loss remains the cornerstone of the management of NAFLD. There are no approved pharmacological drugs for the treatment of NAFLD till now. Although several promising drugs are on the horizon, more trials are needed to validate these medications.

Keywords: Nonalcoholic fatty liver disease, NAFLD, NASH, steatosis, steatohepatitis, treatment.

Introduction:
Nonalcoholic fatty liver disease (NAFLD) is now the most common chronic liver disease in our clinical practice causing major public health problem globally.¹ ³ ⁴Fatty liver disease occurs when excessive fat accumulates in the liver. Nonalcoholic fatty liver disease (NAFLD) refers to a condition where excess fat accumulates in more than 5% of liver cells in individuals who drink little or no alcohol (defined as <20 g/d for female or < 30 g/d for male) and absence of other secondary causes e.g.drugs, starvation & monogenic disorders.²

NAFLD is the term that includes a spectrum of progressive liver disorders that ranging from simple fatty liver (Steatosis) to nonalcoholic steatohepatitis (NASH) with presence of inflamations, fibrosis(with various degree of severity) leading to cirrhosis of liver & complications.² ³

Easy access to calorie rich food, lack of physical exercise together with current epidemics of overweight,obesity, insulin resistance and diabetes mellitus (DM) are responsible for NAFLD leading to a substantial health burden in Bangladesh as in the globe.⁴ ⁵ NAFLD is now becoming the leading cause of cirrhosis of liver, hepatocellular carcinoma (HCC) and liver transplant all over the world.⁵

NAFLD frequently coexists with metabolic syndrome and plays important role in causing hepatic and extrahepatic disorders like cardiovascular disease which is the leading cause of death in NAFLD.¹ ³

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Metabolic syndrome is defined if three or more of the following five criteria are present: waist circumference over 102 cm (40 inches) in male or 89 cm (35 inches) in female, blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl (National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III definition). 7, 8

We searched systematically in different published literatures at national and international level using various search engine like Google, PubMed and Bangladesh Journals Online (BanglaJOL) etc to collect recent knowledge on nonalcoholic fatty liver disease (NAFLD). The aim of this review is to present up to date information on prevalence, pathology, diagnosis and treatment of NAFLD.

### Prevalence:
NAFLD affects peoples of all ages and sex including adolescent and children. The prevalence of NAFLD in general population is about 25-30% but it varies with race, ethnicity, geographical and rural-urban differences. 2, 4 The prevalence of NAFLD was estimated between 17%-46% (on average about 25%) in western adults. 8 Prevalence in China, Japan, Korea and middle east is almost similar with western countries. 9 A recent meta-analysis of studies in India showed the prevalence of NAFLD is 38.6% in adults and 35.4% in children. 10 One study from India shows the prevalence of NAFLD is higher in urban populations (16-32%) than that of rural community (9%). 6 In Bangladesh an ultrasound based study observed that 18.5% of people had NAFLD. Among them it was detected in 36.93% of obese and 7.1% of non-obese persons. 11 Another study in Bangladesh showed the prevalence of NAFLD was 33.86% i.e. one-third of population and highest in between the age group of 31-60 years. 12, 13

### Pathophysiology of NAFLD and NASH:
Pathogenesis of NAFLD and NASH is multifactorial complex process. It has been suggested that progression of NAFLD to NASH is a two-step process. First step is hepatic fat deposition which will initiate the resistance to insulin. Second step of process is various cellular and molecular changes which includes oxidative stress and fatty acid oxidation in liver. These reactions are due to hyperinsulinemia, cytokine induced injury, change in immune functions etc. 14 When there is imbalance between nutrient intake and metabolic needs and proper disposal, carbohydrates like dietary sugars lead to excess production and accumulation of fat in liver cells from de novo lipogenesis (DNL). The saturated fat consumption is a higher risk to develop the disease than that of unsaturated fat. 2 Simple fatty liver (NAFL) i.e. only fat deposition in hepatocytes with no or minimal cellular inflammation does not usually do any harm. Majority of NAFLD patients have simple fatty liver. If NAFL is not managed properly, inflammation of hepatocytes will progress to nonalcoholic steatohepatitis (NASH) and cellular damage. These cellular damage can lead to accumulation of fibrous tissue in the liver (fibrosis) which can ultimately lead to cirrhosis of liver. 8 Among cirrhotic patient clinical decompensation develops in 3-20% of per year. 2

### Common causes of fatty liver:
6, 14, 15

<table>
<thead>
<tr>
<th>Macrovascularsteatosis</th>
<th>Excessive alcohol intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV infection (Genotype 3)</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Starvation</td>
<td>Total parenteral nutrition (TPN)</td>
</tr>
<tr>
<td>Intestinal bypass surgery</td>
<td>Medication:</td>
</tr>
<tr>
<td>Corticosteroids, Amiodarone, Methotrexate, Tamoxifen, Tetracycline, Vinyl chloride etc.</td>
<td>Microvascularsteatosis</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>HELLP syndrome</td>
</tr>
<tr>
<td>Reye’s syndrome</td>
<td>Inborn errors of metabolism</td>
</tr>
<tr>
<td>Medication:</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Anti-retroviral drugs</td>
<td></td>
</tr>
</tbody>
</table>

### Risk factors for NAFLD:
15

<table>
<thead>
<tr>
<th>Common conditions</th>
<th>Other conditions associated with NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Type 2 DM (T2DM)</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Metabolic syndrome (MetS)</td>
<td>Obstructive sleep apnea (OSA)</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome (PCOS)</td>
<td>Pancreatoduodenal resection</td>
</tr>
<tr>
<td>Psoriasis</td>
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</table>

Psoriasis
Clinical features:
NAFLD patients do not have any symptoms in majority cases but some of them may have mild right upper abdominal discomfort, weakness, hepatomegaly, acanthosis nigricans, lipomatosis. Diagnosis of NAFLD or NASH is very often made by getting abnormal LFTs like raised ALT & AST and finding bright liver on ultrasound image incidentally. A good number of patients present with chronic liver disease like cirrhosis and its complications.14

Laboratory findings:
In NAFLD, ALT and AST level may either normal or elevated commonly. ALT elevation is more common than AST elevation in the range of 2 to 3 times of upper limits of normal. Level of ALT tends to be higher in NASH than simple NAFL. The AST/ALT ratio typically less than 1 and this helps to distinguish NAFLD from alcoholic liver disease (ALD). Serum Ferritin is elevated in NAFLD in most of cases but transferrin saturation is elevated in fewer cases (6-11%).14,15 In NASH, in addition to ALT, AST level Alkaline phosphatase (ALP), ß-glutamyl-transpeptidase (GGT) may be elevated. NASH is more likely to have level of homeostasis model assessment of insulin resistance (HOMA-IR). (Normal Range of HOMA-IR is 0.5–1.4, above 1.9 indicates early insulin resistance and above 2.9 indicates significant insulin resistance).15 Antinuclear antibodies (ANA) are detected in 25-30% of NASH patients. There are no definite patterns of dyslipidemia, although high levels of triglyceride is usually found.6

Imaging in NAFLD:
Different imaging studies can be used to diagnose the fatty liver disease but none of them are routinely used to differentiate the subtypes of NAFLD or NASH.

Ultrasound (US):
Ultrasound (US) is the cheapest method and most commonly used in clinical practice. US shows hyperechoic liver parenchyma or bright liver, sensitivity and specificity of US are 89% & 93% respectively.14 In the setting of morbid obesity sensitivity and specificity of US are reduced. It has low sensitivity for lesser degree of steatosis. Steatosis may have similar echogenicity as fibrosis.2

Grades of fatty liver on ultrasound:4

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade- I</td>
<td>Increased echogenicity of liver parenchyma in relation to spleen and kidney</td>
</tr>
<tr>
<td>Grade- II</td>
<td>Grade I + blurring of intrahepatic vascular structures</td>
</tr>
<tr>
<td>Grade- III</td>
<td>Grade II + deep attenuation of ultrasound waves. Diaphragm cannot be easily distinguished from the hepatic surface</td>
</tr>
</tbody>
</table>

CT, MRI imaging:
There are costly imaging modalities to detect the steatosis but are less sensitive to detect inflammation or fibrotic changes in liver. Magnetic resonance spectroscopy (MRS) & MRI proton density fat fraction (MRI-PDFF) have higher sensitivity and considered gold standard to quantify hepatic fat, but not yet widely available.2,6,14

Transient elastography (Fibroscan):
Fibroscan of liver is now the most commonly used method to estimate hepatic stiffness and the degree of liver fibrosis. Advanced fibrosis can be ruled out if liver stiffness measurement (LSM) is less than 8 KPa. LSM between 8 and 12 KPa indicates fibrotic NASH and greater than 12 KPa indicate advanced liver fibrosis. The controlled attenuation parameter (CAP) value can be used to assess stasis.2 A meta-analysis showed that the cut-off value for stasis> S0 was 248 dB/m and grade S1 was 268 dB/m.14 MR elastography (MRE) is more sensitive than fibro scan, thereby considered as most accurate imaging to detect fibrosis in NAFLD.4

Other noninvasive investigations:
Noninvasive tools to predict advanced fibrosis are NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, AST to platelet ratio index (APRI), serum biomarkers like enhanced liver fibrosis (ELF) panel, fibrometer, hepscore etc. But these are not sufficient to detect NASH and its severity and have various limitations.2,15

Liver biopsy:
This is the gold standard to diagnose the NAFL or NASH and fibrosis but it is controversial to perform biopsy of each patient with suspected NAFLD.4,14 The important limitations are sampling errors, variability, inter observer difference which may lead to
overestimation or underestimation of disease severity, fibrosis and risk with its complications. This is the only procedure which can distinguish between NAFL & NASH; it can provide prognostic information and can exclude coexisting conditions. This is the only procedure which can distinguish between NAFL & NASH; it can provide prognostic information and can exclude coexisting conditions. Histology shows cellular steatosis, balloon degeneration, inflammatory cell infiltrates, necrosis, Mallory hyaline and fibrosis with its degree. As liver biopsy is an invasive procedure, most of the patients do not prefer the modality and it’s not free of risk and complications.2,4,14

Management:
Management of NAFLD includes the treatment of liver disease and the associated metabolic disorders like obesity, dyslipidemia, insulin resistance & type 2 diabetes mellitus. The mainstay of NAFLD remains around lifestyle modifications to reduce the body weight and control of risk factors. Although the prevalence of NAFLD is increasing day by day but still now there are no reliable evidence based pharmacotherapy. Several emerging drugs are now in phase 2-3 trials.1-5

Life style modifications:
This is the initial approach to treat NAFLD & its advanced forms of the disease which includes weight loss, healthy hypocaloric food intake and physical exercise.1,2,17

Diet:
Diet containing refined carbohydrates, sugar-sweetened beverages, excess fructose and saturated fats are rich in calories and are associated with overweight, NAFLD and NASH. Low caloric diets (containing low carbs, low fat, unsaturated fat, omega-3 fatty acid, fibers, specific proteins like fish, poultry and Mediterranean food), intermittent fasting improve NAFLD and NASH.2,14 Calorie restriction by 30% per day i.e 500–1000 kcal/d appears to be more important to improve the condition than the type of food.4 Coffee consumption and polyphenol intake may also be useful in the treatment of NAFLD. Caffeine and polyphenols are strong antioxidant that reduce the oxidative stress and inflammation in liver.2,14 At least three cups of coffee consumption may be recommended to improve NAFLD, NASH and fibrosis.2 Polyphenols are present in high quantities in vegetables, cereals, fruits, spices etc.

Physical exercise:
Exercise has great beneficial effect on NAFLD, NASH and cardiovascular system irrespective of weight loss. Regular aerobic exercise of moderate intensity like brisk walking, jogging, running, swimming, or cycling etc. (about 150-200 minutes/week) can improve insulin resistance and NAFLD. Higher intensity exercises are required to improve NASH or fibrosis. Exercise also improves sarcopenia, easy fatiguability and quality of life in cirrhotic patients.2,4

Weight loss:
Loss of weight for 5 to 10% significantly improves NAFL or steatosis, NASH and liver fibrosis in a dose response relationship i.e 5% weight loss for steatosis, e 7% for NASH, e 10% for fibrosis improvement.2,4 Sustained weight reduction and maintenance is challenging but effective weight loss can decrease liver injury and improves insulin sensitivity.2,15

Bariatric surgery:
It’s a therapeutic option which can cure steatosis, NASH, Diabetes and liver fibrosis by increasing significant weight reduction upto 30%. Endoscopic bariatric procedure and metabolic surgery are minimally invasive options for weight loss and are promising in treatment of NAFLD.1,2,15,18 Current indication for bariatric surgery are severe obesity (BMI ≥40kg/m²) or obesity (BMI ≥ 35 kg/m²) with other comorbidities like T2DM, pre-diabetes, uncontrolled hypertension and osteoarthritis of knee or hip joints.1,2,6 There must be absence of liver cirrhosis or compensated cirrhosis without portal hypertension.2,6

Pharmacological treatment:
Till now there are no specific pharmacological drugs approved for the treatment of NAFLD and its other forms. However, different drugs have been investigated during the last decades including few hypoglycemic agents, lipid lowering drugs, antihypertensive and other molecules like obeticholic acid etc.

Summary of important drugs having histological benefits given below in table:
### Medications for treatment of NAFLD with their characteristics:

<table>
<thead>
<tr>
<th>Sl no</th>
<th>Medication with dosage</th>
<th>Mode of action</th>
<th>Indications</th>
<th>Benefits</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vitamin E 800 IU/d</td>
<td>Antioxidant</td>
<td>NASH except T2DM or cirrhosis</td>
<td>Improves Steatosis, NASH</td>
<td>Risk of stroke (haemorrhagic), Carcinoma prostate</td>
</tr>
<tr>
<td>2</td>
<td>Pioglitazone 30-45 mg/d</td>
<td>PPAR- gamma agonist</td>
<td>NASH with or without T2DM</td>
<td>Improves Steatosis, NASH, IR, Fibrosis</td>
<td>Weight gain, Risk of heart failure, Carcinoma bladder, Bone fracture</td>
</tr>
<tr>
<td>3</td>
<td>Liraglutide -1.8 mg sc/d in T2DM, -0.6 to 3 mg sc/d in obesity</td>
<td>GLP-1 RA</td>
<td>NASH without cirrhosis</td>
<td>Improves steatosis, NASH, IR, weight loss, No effect on fibrosis</td>
<td>Gall stone pancreatitis, Anorexia Nausea GI upset</td>
</tr>
<tr>
<td>4</td>
<td>Semaglutide 0.4mg sc/d</td>
<td>GLP-1 RA</td>
<td>NASH without cirrhosis</td>
<td>Improves steatosis, NASH, IR, weight loss, No effect on fibrosis</td>
<td>Gall stone pancreatitis, Anorexia Nausea GI upset</td>
</tr>
<tr>
<td>5</td>
<td>Empagliflozin, Dapagliflozin, Canagliflozin</td>
<td>SGLT 2 inhibitor</td>
<td>NAFLD &amp; T2DM</td>
<td>Improves steatosis, ALT level, IR, Modest weight loss</td>
<td>Risk of UTI Hypotension Bone loss</td>
</tr>
<tr>
<td>6</td>
<td>Obeticholic acid (Phase III trial)</td>
<td>FXR (FarnesoidX receptor ligand)</td>
<td>NASH, Liver fibrosis</td>
<td>Resolution of NASH, Improves fibrosis</td>
<td>Pruritis Increases LDL Cholesterol</td>
</tr>
<tr>
<td>7</td>
<td>Tirzepatide T2DM or Obesity with NAFLD</td>
<td>T2DM</td>
<td>Improves steatosis, NASH, IR, CV &amp; renal outcome, Prevent stroke</td>
<td>GI upset, Gall stones, Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Saroglitazar (Phase I trial)</td>
<td>Dual PPAR α/γ agonist</td>
<td>NAFL NASH T2DM</td>
<td>Decrease ALT level, TG, steatosis, NAS, Improve IR</td>
<td>Doubtful effect on fibrosis, Fatigue, GI upset</td>
</tr>
</tbody>
</table>

Above drugs are not approved for management of NAFLD or NASH but can be individualized and prescribed carefully with comorbidities like T2DM and obesity.¹²

**Some other drugs:**
Metformin does not have any role to reduce liver fat or inflammation but it improves IR. Statins have no beneficial effect on liver histology but it can improve cardiovascular morbidity. So it can be prescribed in patients with NAFLD with dyslipidemia.⁶ Several studies with ursodeoxycholic acid (UDCA) showed that it offers no histological benefit in NASH. According to AASLD guideline metformin, UDCA, statins and silymarin should not be given to treat NASH.²

**Choice of drugs and duration of treatment:**
Drug treatment should be given to patients with NASH with or without liver fibrosis. Choice of drug depends on patient’s age, sex, presence or absence of DM, dyslipidemia and other co-morbidities. So it should be individualized considering different factors. Drug efficacy and side effects also will come in consideration. Different scientific societies recommend only vitamin E (800 IU/d) and pioglitazone (30 mg/d) only for treatment of NASH. Suggested duration is two years for both the drugs. INASL recommends saroglitazar (4 mg/d) for one year as treatment of NASH. Assessment of treatment response is also problematic. However, ALT decrease of 17 U/L at 6 months of treatment may be used as improvement.⁴ Fibroscan of liver showing CAP and LSM values may also be used to monitor the treatment response.²⁴⁵

**NAFLD in children and adolescents:**
Though initially it was thought that it was a disease of adults but with increasing epidemics of obesity it is increasingly recognized in children and
adolescents. The prevalence in India is about 63% in obese and 12% in non-obese children.\textsuperscript{4,19} One study in Bangladesh showed 37.5% NAFLD in obese, 21.15% in overweight and 3.65% in normal weight children.\textsuperscript{20} Mostly they are asymptomatic. Genetic causes of fatty liver showed also be considered. Detailed discussion about pediatric NAFLD is not possible in this short context. However, lifestyle modification including healthy diet and weight loss is the mainstay of treatment. Vitamin E improves NAFL, NAS & NASH but long-term safety is unknown.\textsuperscript{2,4}

**NAFLD in lean subjects:**
Undoubtedly obesity is a major risk factor for NAFLD but it can also occur in lean individuals (Normal waist circumference and BMI). The prevalence of lean NAFLD is about 4.1% in USA and 19% in Asia.\textsuperscript{21} Genetic factors may play an important role in this group. In treatment consideration, weight loss will not be appropriate for them but physical exercise and healthy diet intake may be beneficial for them.\textsuperscript{2,4}

**MAFLD, a new term for NAFLD:**
Metabolic associated fatty liver disease (MAFLD) is the new nomenclature that had been proposed by a panel of experts instead of NAFLD mainly based on presence of metabolic dysfunctions.\textsuperscript{6,19} APASL also supported the new term as because this dysfunction is the key driver of NAFLD.\textsuperscript{6} As summary of proposal, MAFLD is diagnosed on presence of hepatic steatosis together with one of three criteria given below: 1) overweight or obesity 2) T2DM 3) clinical evidence of metabolic dysfunction like increased waist circumference and abnormal lipid or glycemic control.\textsuperscript{6} In contrary, NAFLD is a heterogeneous disease, only change of nomenclature to MAFLD will not make it homogenous. There is no recognized or accepted criteria for defining metabolic dysfunction.\textsuperscript{23, 24} However, there should be more evidence based study to change the name.

**Conclusion:**
NAFLD is a liver disorder requiring multidisciplinary approach. On initial evaluation possible causes of liver disease and risk factors should be sought out. To identify and early treatment of comorbid conditions like T2DM, dyslipidemia and cardiovascular diseases can significantly improve the prognosis. In spite of many advances in medical sciences there is no approved drug treatment for the disease. Currently lifestyle modifications with weight loss are the only effective treatment for NAFLD.

**Conflict of Interest:**
The authors declare no conflict of interest.

**Funding:**
This article received no external funding.

**References:**


ANTI-COVID ANTIBODY STATUS IN HEALTH CARE PROFESSIONALS OF BANGLADESH AFTER 3 MONTHS OF COMPLETION OF TWO DOSES OF COVID-19 VACCINATION

AYATUN NES A1, KAZI MUHAMMAD MAHBUBUR RAHMAN2, ABDUL ALI3, ROKSANA YESMIN4

Abstract

Background: Coronavirus 2019 (COVID-19) is a pandemic disease, where huge number of populations was infected, and massive death occurred worldwide for its rapid spread. Naturally produced antibody or artificially given vaccination can only give protection. This study evaluated the anti-Covid antibody status in health care professionals of Bangladesh after 21 days and 3 months of completion of two doses of Covid-19 vaccination. Methods: This study was conducted at the Department of Laboratory Medicine, BIRDEM, Dhaka. Total 100 respondents who had completed two doses of Covid-19 vaccination were enrolled according to inclusion criteria. After taking informed written consent a structured questionnaire was filled up for each subject. First sample (3 ml whole blood) was collected after 21 days of completion of 2nd doses of SARS-CoV-2 vaccination and a 2nd sample (3 ml whole blood) was collected again after 3 months. SARS-CoV-2 IgG was estimated by indirect chemiluminescence assay. Collected data were analyzed by SPSS 22. Results: The mean age of the study subjects was 32.09 ± 7.98. Study subjects were divided into two groups: those with history of past Covid infection (PCR positive) (n=33) and those with no evidence of past infection (n=67). SARS-CoV-2 IgG antibody level was found significantly reduced after 3 months of completion of vaccination, compared to the titer of 21 days of vaccination. A significant difference of mean SARS-CoV-2 IgG antibody level among subjects with and without previous history of Covid 19 infection was observed after 21 days of completion of 2nd dose of Covid 19 vaccination. However, after 3 months of 2nd dose of vaccination no significant differences of mean SARS-CoV-2 IgG antibody level were observed between the groups. Conclusion: SARS-CoV-2 IgG antibody level was significantly reduced after 3 months of completion of two doses of vaccination. Moreover, antibody level was found significantly higher among the study subjects with previous positive H/O of Covid 19 infection compared to subjects without any H/O previous Covid infection. Therefore, this study recommended that, a third booster dose would be necessary to maintain the effectiveness of vaccines.

Key words: Covid-19 vaccination, SARS-CoV-2 IgG antibody

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Introduction:
Coronavirus is an enveloped single stranded RNA virus of Coronaviridae family and Orthocoronaviridae subfamily.\(^1\) Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causative agent of Coronavirus disease 2019 (COVID-19) is a pandemic situation faced by the world. The World Health Organization (WHO) declared a Public Health Emergency on January 30, 2020, after COVID-19 had spread to other countries (Cascella et al., 2020) and declared COVID-19 a pandemic in March 2020 (WHO, 2020).\(^2\) According to the Institute of Epidemiology, Disease Control and Research (IEDCR) (22 March 2020), Bangladesh is the second most affected country in South Asia, after India.\(^3\) Fever, cough, loss of smell sensation, shortness of breath are the most common symptoms. In addition, gastrointestinal manifestations such as nausea, vomiting, anorexia, diarrhoea, and abdominal pain are more clinical manifestations.\(^4\)

COVID-19 has four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. Receptor-binding domain (RBD) of the spike protein acts as an antigen for identification of immune reactions.\(^5\) Transmission of COVID-19 occurs through respiratory droplets. The spike protein facilitates viral entry into host cells firstly by binding to a host receptor through the RBD in the S1 subunit and afterward fusing the viral and host membranes through the S2 subunit. Antibodies binding to the spike (S) protein RBD can neutralize SARS-CoV-2.\(^5\)

Body immune system responses to a pathogen with both innate and adaptive immunity. One aspect of the adaptive immunity is humoral response that features the production of antibodies recognizing specific antigens.\(^6\) Several follow-up studies of hospitalized patients in Sweden had reported about the development of IgG in majority of patients.\(^7\) A prospective study in Korea investigated antibody production in asymptomatic and mild COVID-19 patients and reported that neutralizing antibodies production was significantly lower in asymptomatic to mild symptomatic patients, compared to that of moderate to severe patients with pneumonia.\(^8\) But non hospitalized home treated patients developed antibodies by days 21–28, with a significant lower titer.\(^9\) In Southeast Asia, a cross-sectional study in India reported IgG antibodies appeared two weeks after infection and are sustained high for long time.\(^10\)

The presence of anti-spike or anti-nucleocapsid IgG antibodies was associated with a substantially reduced risk of SARS-CoV-2 reinfection in next 6 months.\(^11\) Vaccine against SARS-CoV-2, offer great promise for curbing the spread of COVID-19 infection. Since the vaccines have been developed, other important questions must be addressed, including the durability of protection over a long period after vaccination and the determination of the effect of a booster dose to extend the duration of immunity against SARS-CoV-2 infection. Bangladesh began administration of COVID-19 vaccines on 27 January 2021 while mass vaccination started on 7 February 2021.\(^12,13\) However, there are limited ideas about the duration of persistence of antibody after infection or vaccination. So, this study was done to know the quantitative antibody titer among the health care professionals who had completed two doses of SARS-CoV-2 vaccine.

Methods:
After taking informed written consent, a total 100 health care professionals, who had received both doses of the Covid 19 vaccination, were included according to inclusion criteria. This observational cohort study was conducted in the department of Laboratory Medicine, BIRDEM General Hospital, Dhaka. After taking informed written consent from each study subjects, a preset questioner had been filled up. All the base line characteristics along with personal history, clinical history, clinical examination findings and relevant investigation findings were included in the preset questioner. First sample (3 ml of venous blood in plain tube) was collected after 21 days of completion of 2nd doses of SARS-CoV-2 vaccine anda 2nd sample (3 ml of venous blood in plain tube) was collected again from each study subject after 3 months of 2nd dose of SARS-CoV-2 vaccination. Serum was separated after centrifugation on the same day of sample collection. The serum samples were stored at -80 degree Celsius till the antibodies were measured. SARS-CoV-2 IgG was estimated by indirect chemiluminescence assay. Statistical analysis was performed with the help of Statistical Package for Social Science 23, (SPSS 23) version. Descriptive statistics were presented as mean±SD score for normally distributed data. Continuous data were compared using parametric test (Student’s unpaired t-test, ANOVA, Chi square test). Statistical tests was considered significant at the level of d”5% and considered as test of significance when P<0.05.
**Results:**

Table 1 shows the baseline characteristics of the study subjects. The mean age of the study subjects was 32.09 ± 7.98. The study subjects were categorized into four different age group categories (<30, 31-40, 41-50, and 51-60 years) and majority (48%) of the study subjects were belong to 31-40 years age group (Figure 2). Mean BMI of the study subjects was 25.40 ± 2.82. In this study, among the health care professionals, 32% were Physician, 26 % Nurse/ Midwife, 8% Administrative Officer, 15% Cleaning staff and 19% were of other staffs. 32% study subjects were smokers (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong>†</td>
<td>32.09 ± 7.98</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong>†</td>
<td>25.40 ± 2.82</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
</tr>
<tr>
<td><strong>Occupation, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>32</td>
</tr>
<tr>
<td>Nurse/ Midwife</td>
<td>26</td>
</tr>
<tr>
<td>Administrative Officer</td>
<td>08</td>
</tr>
<tr>
<td>Cleaning staff</td>
<td>15</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
</tr>
<tr>
<td><strong>H/O Smoking, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
</tr>
<tr>
<td>No</td>
<td>70</td>
</tr>
</tbody>
</table>

† Values are Mean ± SD; BMI: Body mass index

Study subjects were divided into two groups: those with history of past Covid infection (PCR positive) (n=33) and those with no evidence of past infection (n=67) (Figure 1). Table 2 presents the demographic features of study subjects according to previous Covid 19 infection history. The mean age of subjects with and without previous H/O Covid infection were 36.67±8.59 and 29.84±6.64 respectively. There was significant difference in between the mean age of two groups. The mean BMI were 26.93±3.52 and 25.66±3.60 in subjects with and without previous Covid 19 infection, respectively, but no significant differences were observed. In this study, among the subjects with previous H/O covid 19 infection 39.4 % were male and 60.6 % were female. Moreover, 57.6 % of subjects with previous H/O Covid 19 infections were smoker.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Previous H/O Covid 19 infection</th>
<th>No Previous H/O Covid 19 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs) †</td>
<td>36.67±8.59</td>
<td>29.84±6.64*</td>
</tr>
<tr>
<td>BMI (yrs) †</td>
<td>26.93±3.52</td>
<td>25.66±3.60</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13(39.4)</td>
<td>32 (47.8)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (60.6)</td>
<td>35 (52.2)</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (57.6)*</td>
<td>11 (16.4)</td>
</tr>
<tr>
<td>No</td>
<td>14 (42.4)</td>
<td>56 (83.6)</td>
</tr>
</tbody>
</table>

† Values are Mean ± SD; *p<0.05 was taken as the level of significance

SARS-CoV-2 IgG antibody level after 21 days of 2nd dose of vaccination, among the subjects was 1622.63 (115.0-11525.4) and after 3 months of vaccination was 1151.12 (44.2-6617.5). It was found that, SARS-CoV-2 IgG antibody level was significantly reduced after 3 months of completion of vaccination, compared to the titer of 21 days of vaccination.
Table III

Comparison of SARS-CoV-2 IgG antibody level among the study subjects after 21 days and 3 months of completion of 2nd dose of Covid 19 vaccination

<table>
<thead>
<tr>
<th></th>
<th>21 days after 2nd dose of Covid 19 vaccination</th>
<th>3 months after 2nd dose of Covid 19 vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 IgG antibody level (AU/ml) †</td>
<td>1622.63 (115.0-11525.4)</td>
<td>1151.12* (44.2-6617.5)</td>
</tr>
</tbody>
</table>

† Values are Median (min-max); *p<0.05 was taken as the level of significance

Table IV

SARS-CoV-2 IgG antibody level after completion of 2nd dose of Covid 19 vaccination according to previous H/O Covid 19 infection

<table>
<thead>
<tr>
<th></th>
<th>Previous H/O</th>
<th>No Previous H/O</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 IgG antibody level (AU/ml)</td>
<td>Covid 19 infection</td>
<td>Covid 19 infection</td>
</tr>
<tr>
<td>After 21 days of 2nd dose of Covid 19 vaccination †</td>
<td>1945.3</td>
<td>1463.7*</td>
</tr>
<tr>
<td>After 3 months of 2nd dose of Covid 19 vaccination †</td>
<td>1377.5</td>
<td>1039.6</td>
</tr>
</tbody>
</table>

† Values are Mean; *p<0.05 was taken as the level of significance

A significant differences of the mean SARS-CoV-2 IgG antibody level after 21 days of completion of 2nd dose of Covid 19 vaccination (1945.3 AU/ml and 1463.7AU/ml) were observed among subjects with and without previous history of Covid 19 infection (Table IV). However, the mean SARS-CoV-2 IgG antibody level after 3 months of 2nd dose of vaccination were again estimated among the two groups but there was no significant differences were observed (Table IV).

Discussion:

The general regime in the vaccination against COVID-19 is administering the vaccines in two doses. This study aimed to measure the level of anti-SARS-CoV-2 IgG antibodies in health care professionals, who had completed 2nd dose of COVID-19 vaccination. The results of this study suggested two main outcomes: one is, anti-SARS-CoV-2 IgG antibody responses were significantly higher among the healthcare professionals with previous history of Covid infection compared to without history of any Covid infection. Another finding is, three months after a two-dose vaccination regime, anti-SARS-CoV-2 IgG antibody responses were relatively low compared to previously reported levels.

In this study, median (Inter Quartile Range, IQR) SARS-CoV-2 IgG antibody level were estimated after 21 days and 3 months of 2nd dose of vaccination, among the study subjects. It was found that, SARS-CoV-2 IgG antibody level was significantly reduced after 3 months of vaccination, compared to the titer of 21 days of vaccination. Bayram et al. investigated SARS-CoV-2 anti-spike antibodies in 1012 Turkish health care workers (HCWs) after two doses of CoronaVac (Sinovac). Antibodies were detected in 1008 of 1012 (99.6%) HCWs, 21 days after the second dose, and the median antibody titer of HCWs was calculated as 1022.40 AU/ml (range: 10.10–66 923.70 AU/ml). Yigit et al. investigated 678 Turkish HCWs 2 months after the second dose of CoronaVac using a semiquantitative method deployed a recombinant protein to represent the nucleocapsid (N) antigen of the virus (Elecsys Anti-SARS-CoV-2; Roche) and found titer in all participants after approximately four and a half months after the vaccination with a two-dose regime of CoronaVac before the vaccination with the third booster dose was 175.7 AU/ml (min: 10.90 AU/ml, max: 5201.60 AU/ml) and 11% of the participants were seronegative supporting the idea that antibody titers decrease over time sometimes in the degree of patients being seronegative. In a recent study, Yue et al. reported antibody titers fading after inoculation with two doses of an inactivated SARS-CoV-2 vaccine in a cohort of 355 volunteers participating in the development and production of inactivated vaccines. At 3 months after the second dose, the serum neutralizing antibody titers in this cohort decreased significantly. Their results suggested that a third booster dose was necessary to maintain the effectiveness of inactivated vaccines regardless of sex and two-dose immunization procedure.

BJM Vol. 34 No. 2
Anti-Covid Antibody Status in Health Care Professionals of Bangladesh

83
SARS-CoV-2 IgG antibody level were observed among the two groups of study subjects (subjects with and without previous history of Covid 19 infection). The mean SARS-CoV-2 IgG antibody level after 21 days of completion of 2nd dose of Covid 19 vaccination were estimated in this study and significant differences were observed between the groups. However, the mean SARS-CoV-2 IgG antibody level after 3 months of 2nd dose of vaccination were again estimated among the two groups but therewas nosignificant differences were observed. A recent study investigated quantitative SARS-CoV-2 anti-spike responses to two doses of BNT162b2 using Abbott’s assay and reported median IgG SP titers of 10 058 (6408–15 582) AU/mL in cases without evidence of previous infection and 18 047 (10 884–22 413) AU/ml in cases with known previous infection. Soysal et al. analyzed immunogenicity and reactogenicity of inactivated SARS-CoV-2 vaccine (CoronaVac) in both previously SARS-CoV-2 infected and uninfected Turkish HCWs and reported median SARS-CoV-2 IgG antibody levels of 1220 AU/ml (range: 202–10 328 AU/ml) and 913 AU/ml (range: 2.8–15 547 AU/ml) 28 days after the second vaccination in infected and uninfected HCWs, respectively.

**Conclusion:**
In present cohort study, anti-SARS-CoV-2 IgG antibody responses after completion of 2 doses of vaccination were found significantly higher among the health care workers with previous history of Covid infection compared to without history of any Covid infection. It was also found that, three months after a two-dose vaccination regime, anti-SARS-CoV-2 IgG antibody responses were relatively low compared with previously reported levels.

**Limitations:**
This study was conducted in a single centerwith limited time of span with a smaller number of samples. Primary antibody level, before vaccination could not be measured. Subject withmight had natural infection but had not undergone for PCR test could not be differentiated properly. Antibody responses according to different vaccine regime also could not be evaluated in this study. So, further prospective study with large sample size with long duration should be done. A third booster dose will be necessary to maintain the effectiveness of vaccines regardless of sex and two-dose immunization procedure.

**Conflict of Interest:**
There is no conflict of interest in this study

**Funding:**
This study was funded by Ministry of Science and Technology, Government of the people’s republic of Bangladesh, FY; 2021-22.

**Ethical consideration:**
The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

**Acknowledgements:**
Thankful to all doctors, nurses and medical stuffs of BIRDEM Women and Children Hospital, Segunbagicha, Dhaka, Bangladesh, for their best and kind support for collection of samples for this study.

**References:**


PREDICTIVE VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO AND SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE IN PATIENT WITH SEPSIS

SAHED UDDIN AHMED1, MD. ABU HANIF CHOWDHURY2, MD. JABER ABEDIN2, MA SATTAR3, SUJAT PAUL4, ASOK KUMAR DUTTA4

Abstract:

Background: Neutrophil to lymphocyte ratio calculated from white cell differential count provides a rapid indication of the extent of an inflammatory process. The aim of the study was to evaluate the predictive value of neutrophil to lymphocyte ratio and SOFA score in sepsis outcome.

Methods: Adult patients presenting to medicine department of CMCH with suspected sepsis by qSOFA score were considered for the present study. Baseline qSOFA, SOFA Score and NLR were calculated. Patients were followed until discharge or death to observe outcome. The primary outcome was in-hospital mortality. Secondary outcomes were ICU referral and ICU stay. All data were prospectively collected, coded and tabulated. ROC curves were constructed to evaluate the performance of NLR and SOFA in differentiating non-survivors from survivors. Multivariate logistic regression analysis was done to determine the independent predictors adjusted for the previously specified baseline covariates.

Results: The AUC for each indicator was compared. NLR had a modest power for predicting unfavorable outcome (death) as suggested by AUC of 0.705 (95% CI: .556-.854), which was greater than that of baseline qSOFA score (0.694). NLR >8.9 was proposed as the optimal cutoff value, which provided a sensitivity of 75.0% and a specificity of 67.7% for predicting mortality in sepsis. After adjusting for other variables NLR and SOFA remain as independent predictors of unfavorable outcome. Baseline NLR also had a modest power for predicting need for ICU referral than that of baseline SOFA score.

Conclusion: NLR is an easily calculated, simple, cost-effective index that could be used as a prognostic tool for clinicians when assessing sepsis patients in the emergency department and general ward.

Key words: NLR, SOFA score, Sepsis.

Introduction:

Sepsis is one of the most common causes of multi-organ failure and still a big challenge to both the developed and developing world. The reported morbidity of sepsis is constantly increasing, with sepsis and septic shock remaining among the major causes of death worldwide. Hospital mortality of early septic shock in ICU patient of developed world is 18.8%1 and hospital mortality in ICU patients of Bangladesh suffering from severe sepsis is 49.2%2.

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4. Professor (Rtd), Department of Medicine, Chittagong Medical College Hospital, Chattogram-4203, Bangladesh.

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Studies have found that one of the fundamental principles for the appropriate management of sepsis is early and accurate detection of the patients at high risk for death. This is generally dependent on the application of scoring systems. Although various clinical biomarkers are widely explored like CRP, Procalcitonin, Lactate, CRP albumin ratio & IL-6, only a few have been currently applied in the clinical practice.

Neutrophil lymphocytes ratio (NLR) has been the focus of several recent studies published as it is accessible, cheap and readily determined. The cause responsible for NLR elevations correlating with poor outcome in patients with sepsis remains unclear, although there are a variety of plausible explanations. One of the most convincing explanations is based primarily on the physiological link between neutrophilia and lymphopenia with systemic inflammation and stress. SOFA (sequential organ failure assessment) score is derived from six organ system functions; two clinical observations including GCS and mean blood pressure and four biochemical parameters. Total SOFA score is 24. According to SOFA calculator, if an initial SOFA scores are 9-11, predicted mortality is 40-50%. The SOFA score is a simple, but effective method to describe organ dysfunction/failure in critically ill patients. International Sepsis guideline recommends ‘SOFA score’ as diagnostic and monitoring tool for sepsis patient of ICU. In this prospective observational study, we have sought to evaluate the predictive value of NLR and SOFA score in sepsis outcome in a consecutive series of adult patients at medicine department of a tertiary medical college hospital.

**Methods:**

This prospective observational study was conducted at inpatient Department of Medicine, Chittagong Medical College Hospital (CMCH) from August 2017 to May 2018. Patient who was admitted with sepsis in medicine ward or those who developed new episode of sepsis within the hospital was enrolled within 12 hours. Patient was diagnosed as sepsis on the basis of suspected or documented infection plus (a) two of qSOFA parameters out of three and or (b) two points increased out of twenty four points of SOFA score. Sepsis with other known comorbidity like; inflammatory arthritis, SLE, Sarcoidosis, CLD, ESRD, COPD with type II respiratory failure, heart failure, hematological malignancy, HIV infection, pregnancy, patient with receiving steroid and other immunosuppressive therapy within 4 week, any acute insult within last fourteen days; like severe trauma, acute pancreatitis, major abdominal or cardiothoracic surgery, acute stroke, acute coronary syndrome, major burn were excluded from the study after initial screening with history, clinical examination and relevant investigations. Differential diagnosis of sepsis like severe malaria, severe dengue, viral meningo-encephalitis, and diabetic emergency were excluded from history, clinical examination and relevant investigations. From all eligible subjects after getting consent clinical history was taken and clinical examination was done to elicit findings related to sepsis and its complication. With all aseptic precaution 10 cc of venous blood was collected and blood analyzers (Sysmex, Xn-1000, Company- Ves- Matic) were used to give automated counts of WBC, neutrophils, lymphocytes, monocytes, eosinophil and basophils. Finally it was rechecked by hematologist microscopically. NLR was calculated from differential count of WBC result. Admission SOFA score, association between all these parameters and NLR were done later. Data were arranged into two groups according to survival status or death. Sequential Organ Failure Assessment (SOFA) score was calculated at baseline on day 1 to assess the severity of illness. ICU referral and nephrology referral was noted. The total duration of hospital stay, ICU stay was recorded. All patients of the study were monitored until discharge or death to observe the outcome. The primary outcome was in-hospital mortality. Secondary outcomes were ICU referral and ICU stay.

All data were prospectively collected, coded and tabulated. Data were analyzed using descriptive statistical measurements; continuous variables were reported as mean values ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were expressed as count and percentage. The ability of the variables to discriminate survivors from non-survivors was determined using receiver operating characteristic (ROC) curves. Multivariate logistic regression analysis to determine the independent predictors adjusted for the previously specified baseline covariates. Two- sided 50% value < 0.05 was considered to represent a statistically significant difference. All analyses were performed by the IBM SPSS Statistics software version 23.0.
**Results:**

Effective sample size was 51. Among them 31 patients (60.78%) survived (Survivors Group) and the other 20 patients (39.22%) died (Non-survivors Group) in hospital (Table-I).

<table>
<thead>
<tr>
<th>CBC parameters</th>
<th>Patients group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>Survivors</td>
</tr>
<tr>
<td></td>
<td>(n=51)</td>
<td>(n=31)</td>
</tr>
<tr>
<td>WBC count</td>
<td>15000 (10^9/L)</td>
<td>14000 (11660-22000)</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>12180 (9456-18000)</td>
<td>10356 (9300-17600)</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>1530 (1172-21000)</td>
<td>1568 (1200-1568)</td>
</tr>
<tr>
<td>NLR</td>
<td>8.6 (5.71-12.86)</td>
<td>7.7 (5.13-10.77)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD), or median (interquartile range, IQR) as appropriate. WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio. ^# = Not significant by independent sample t test or Mann-Whitney test as appropriate. ** = Significant by Mann-Whitney test.

**Value of SOFA score and NLR in predicting unfavorable outcome (Death):**

ROC curves were constructed to evaluate the performance of NLR and SOFA in differentiating non-survivors from survivors, and the AUC for each indicator was compared (Figure I).

NLR had a modest power for predicting unfavorable outcome as suggested by AUC of 0.705 (95% CI: 0.556-.854), which was greater than that of baseline SOFA score (0.694).

NLR ≥8.9 was proposed as the optimal cutoff value, which provided a sensitivity of 75.0% and a specificity of 67.7% for predicting mortality in sepsis (Table II).

**Table I : Distribution of the patients by their survival and laboratory parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>Survivors</td>
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<tr>
<td></td>
<td>(n=51)</td>
<td>(n=31)</td>
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<tr>
<td>WBC count (10^9/L)</td>
<td>15000 (12000-22000)</td>
<td>14000 (11660-22220)</td>
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<td>Neutrophil count (10^9/L)</td>
<td>12180 (9456-18000)</td>
<td>10356 (9300-17600)</td>
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<td>Lymphocyte count (10^9/L)</td>
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<td>1568 (1200-1568)</td>
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<tr>
<td>NLR</td>
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<td>7.7 (5.13-10.77)</td>
</tr>
</tbody>
</table>

**Table II : Distribution of the patients by NLR category and survival**

<table>
<thead>
<tr>
<th>Parameter: NLR category</th>
<th>Referred to ICU</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8.9</td>
<td>2 (77.8%)</td>
<td>21</td>
<td>(58.82%)</td>
</tr>
<tr>
<td>≥8.9</td>
<td>6 (22.2%)</td>
<td>9</td>
<td>(37.5%)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%); *: Significant by Chi-square test. NLR: neutrophil-to-lymphocyte ratio; OR: Odds ratio; CI: Confidence interval.

Table II shows that sepsis patients whose baseline NLR at admission was ≥8.9 had 3.66 times more chance to death in comparison to the patients whose NLR was <8.9.

**Table III : Distribution of the patients by NLR category referral to ICU**

<table>
<thead>
<tr>
<th>Parameter: NLR category</th>
<th>Referred to ICU</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8.9</td>
<td>2 (77.8%)</td>
<td>21</td>
<td>5.83 (.004*)</td>
</tr>
<tr>
<td>≥8.9</td>
<td>6 (22.2%)</td>
<td>9</td>
<td>15 (62.5%) (1.71-9.90)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%); *: Significant by Chi-square test. NLR: neutrophil-to-lymphocyte ratio; OR: Odds ratio; CI: Confidence interval.

Table III shows that sepsis patients whose baseline NLR at admission was ≥8.9 had 5.83 times more chance to require ICU support in comparison to the patients whose NLR was <8.9.
Table IV: Independent predictors of unfavorable outcome by multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>β value</th>
<th>Standard</th>
<th>Odds ratio</th>
<th>95% CI for OR Upper</th>
<th>Lower</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.058</td>
<td>1.060</td>
<td>.998</td>
<td>1.125</td>
<td>.057</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-.669</td>
<td>.512</td>
<td>.087</td>
<td>3.005</td>
<td>.458</td>
<td></td>
</tr>
<tr>
<td>Illness duration</td>
<td>.190</td>
<td>1.209</td>
<td>.976</td>
<td>1.497</td>
<td>.082</td>
<td></td>
</tr>
<tr>
<td>Interval of bloodcollection</td>
<td>-.250</td>
<td>.779</td>
<td>.566</td>
<td>1.072</td>
<td>.125</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>-.057</td>
<td>.945</td>
<td>.174</td>
<td>5.118</td>
<td>.947</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>.513</td>
<td>1.670</td>
<td>.087</td>
<td>32.076</td>
<td>.734</td>
<td></td>
</tr>
<tr>
<td>SOFA</td>
<td>.618</td>
<td>1.856</td>
<td>1.132</td>
<td>3.041</td>
<td>.014*</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>.174</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>.001</td>
<td>1.001</td>
<td>.999</td>
<td>1.002</td>
<td>.391</td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td>.305</td>
<td>1.357</td>
<td>1.017</td>
<td>1.810</td>
<td>.038*</td>
<td></td>
</tr>
</tbody>
</table>

The OR indicates the risk of obtaining unfavorable outcome. *Statistically significant.

Discussion:
The main finding of our study was that the baseline NLR measured at the time of admission to medicine ward was associated with in-hospital mortality and NLR was able to accurately stratify patients in terms of mortality and ICU referral as like as baseline SOFA score. These findings remained significant after adjusting for several potential covariates, suggesting that increased NLR was independently associated with unfavorable outcome in patients with sepsis. Non-survivors had significantly higher qSOFA and SOFA score in comparison to the survivor group. This finding was similar to finding of American study. No such study was found that included qSOFA and SOFA criteria in Bangladeshi literature.

Baseline laboratory parameters were revealed that NLR and neutrophil count were significantly higher and lymphocyte counts were significantly lower among non-survivors in comparison to survivors. Baseline NLR was 8.6 (5.71-12.86) in our study with significantly higher 11.06 (8.5-15.75) among Non-survivors (p= 0.014), (Table VII). The average value of NLR in American healthy adults was found 2.15 (2.11- 2.19) with significant racial difference. Normal NLR of Asian and Bangladeshi healthy adult population not yet studied. NLR of Bangladeshi type 2 DM patient was 1.56 (±.15), range was 1.23-1.74. NLR of Bangladeshi sepsis patients not yet known.

The cause responsible for NLR elevations correlating with poor outcome in patients with sepsis remains unclear, although there are a variety of provable explanations. One of the most convincing explanations is based primarily on the physiological link between neutrophilia and lymphopenia with systemic inflammation and stress. The evolution of these leukocyte subpopulations may differ based on their respective role in the inflammatory response. Increased numbers of neutrophil imply that infection is not eradicate, which further induce depression of lymphocyte. Neutrophilia caused by demargination of neutrophils, delayed apoptosis of neutrophils and stimulation of stem cells by growth factors. Lymphocyte plays a key role in the regulation of inflammatory response, and lymphocytopenia appears as a consequence of lymphocyte margination and redistribution in the lymphatic system with accelerated apoptosis may lead to the immune system suppression and non-resolution of inflammation. The sustainability of infection, inflammation and the incomplete eradication of infection are responsible for the increase of neutrophils production by the bone marrow and decrease lymphocytes counts by apoptosis and others mechanisms. Therefore, the resulting increase in NLR may identify patients who are in a state of non-resolution of inflammation, along with concomitant decreased survival rates. Zahorec R discovered the use of the NLR in septic and severe septic oncological ICU patients and
suggested that the ratio was associated with severity of disease. Zahorec investigated the differential white blood cell counts and the clinical course assessed by SOFA score in oncological ICU patients. They were found a correlation between the severity of clinical course and the grade of neutrophilia and lymphocytopenia was present. The author concluded that the ratio of neutrophil and lymphocyte counts was an easily measurable parameter which may express the severity of infections.

Receiver operating characteristic (ROC) curves for SOFA score and NLR in predicting unfavorable outcome (mortality) had shown that baseline NLR has higher sensitivity and specificity than baseline SOFA (AUC 0.705 Vs. 0.694 respectively). NLR e^{-8.9} was proposed as the optimal cutoff value, which provided a sensitivity of 75.0% and a specificity of 67.7% for predicting mortality in sepsis, (Figure 3).

Sepsis patients (n=21) of our study whose baseline NLR at admission was e^{-8.9} had 3.66 times more chance to death in comparison to the patients whose NLR was<8.9, (Table VII). Independent predictors of unfavorable outcome by multivariate logistic regression analysis had shown that both baseline NLR and baseline SOFA had significant predictive value. Varsha S. et al.\textsuperscript{13} were compared neutrophil to lymphocyte count ratio and SOFA score as prognostic markers in the setting of emergency medicine in a prospective observational cohort study. On comparing NLR with SOFA score, NLR has 100% sensitivity and 67.24% specificity. A more recent study\textsuperscript{14} showed that an initial value of NLR over ten could be correlated with an unfavourable prognosis, as assessed by the number of SIRS criteria, the presence of organ failures at admission. Xuan Liu et al.\textsuperscript{15} prospectively enrolled adult patients with sepsis admitted to the ICU of the department of emergency, xinhua hospital, Shanghai; was found increased NLR (SOFCU = 0.000) in the non-survivors compared to patients that survived.

Moreover, a retrospective study\textsuperscript{16} concluded that a value of NLR over seven on admission represented an independent increased mortality rate risk factor. Moreover, NLR was considered to be superior to other biomarkers such as CRP, leukocytes count or neutrophils count, as a predictor for bacteremia in patients admitted to emergency or intensive care units.\textsuperscript{17} Other studies attempted to establish threshold values for NLR to predict the severity and outcome of the disease. In a large study by Hwang et al.\textsuperscript{18}, with severe sepsis and septic shock, NLR measured at emergency department admission was independently associated with 28-day mortality. NLR was considered to be superior to other biomarkers such as CRP, leukocytes count or neutrophils count, as a predictor for bacteremia in patients admitted to emergency or intensive care units.\textsuperscript{19} Another prospective observational study\textsuperscript{20} was conducted in the emergency department of the university hospital of Patras, Greece, based on consecutively enrolled patients suffering from sepsis of multiple origin. They found that NLR was positively correlated with the sepsis severity prognostic score on admission (SOFA, rs=0.497, p<0.001). In an Egyptian study; Okashah A et al.\textsuperscript{21} highlighted NLR superiority regarding sensitivity, specificity to other parameters like lactate, CRP, neutrophils count, lymphocytes count, or leucocytes count. The same study showed the usefulness of NLR in prognostic evaluation by highlighting the statistically significant correlation with severity score SOFA (p=0.01). Bozkurt D et al.\textsuperscript{22} performed a retrospective study investigating whether NLR has prognostic significance in patients suffered from AKI. To predict mortality, they showed that, level of 9.90 point for final NLR has 73% sensitivity and 87% specificity as compared to value below in ROC curve analysis (HR: 7.31, CI 3.36-15.91; p < 0.001).Sepsis patients of our study whose baseline NLR at admission was e^{-8.9} had 5.83 times more chance to require ICU support in comparison to the patients whose NLR was <8.9.NLR was also superior to SOFA score in predicting need for ICU referral for the sepsis patient as suggested by area under the curve. There was no similar study that NLR can predict ICU referral because most of the study done at ICU.

We observed, both baseline NLR and SOFA score remained statistically significant predictors of the severity of sepsis upon presentation of the patient to the hospital. Patients with NLR e^{-8.9} had statistically significant (OR 3.66) in-hospital mortality (p<0.028) compared with those in NLR <8.9. After adjusted for other variables NLR and SOFA were remain as independent predictors of unfavorable outcome. However, in ROC curve analysis, NLR was superior to SOFA score to predict in-hospital mortality and ICU referral. Similar results were also found in the previous studies. In our study we demonstrated statistically significant relationship between baseline NLR and the sepsis prognostic scores SOFA upon medicine department presentation.

**Conclusion:**
The NLR is a biomarker easy to integrate in everyday clinical practice, as it is cost effective and easily calculated. The NLR could be a promising tool in the
initial assessment of patients with sepsis as we found significant relation between baseline NLR and SOFA score, the commonly used score of severity and prognosis of sepsis. In our opinion, the strength of the NLR is the possibility of implementing this parameter simply by using already available routine hematology count.

**Limitations of the study:**
Small sample size and selection of the cases from a tertiary level hospital might limit the generalize ability of the study results. Sepsis bundle management was not uniformly implemented in our setting that could have affected our result.

**Data Availability:**
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

**Conflict of Interest:**
The authors stated that there is no conflict of interest in this study.

**Funding:**
This research received no external funding.

**Ethical consideration:**
The study was approved by the Ethical Review Committee of Chittagong Medical College. Informed consent was obtained from each participant or caregivers of the patients.

**Author Contributions:**
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

**Acknowledgments:**
The authors were grateful to the staffs of the Department of Medicine wards in Chittagong Medical College Hospital, Bangladesh.

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EFFECTS OF INTRALESIONAL AUTOLOGOUS PLATELET RICH PLASMA THERAPY IN PATIENTS WITH DE QUERVAIN’S TENOSYNOVITIS

MOHAMMAD ANISUR RAHMAN¹, ABUL KHAIR MOHAMMAD SALEK², FARZANA KHAN SHOMA³, MD. RUHUL AMIN⁴, AMITAB BANIK⁵

Abstract

**Background:** To assess the effectiveness of intralesional Platelet Rich Plasma (PRP) therapy for the treatment of deQuervain’s tenosynovitis. **Methods:** The study was randomized controlled trial conducted in the Department of Physical Medicine and Rehabilitation, BSMMU, Dhaka, from April 2020 to March 2021. A total of 54 patients with lateral wrist pain were randomly allocated into two groups and were given interventions. Twenty six patients in group A were treated with 3 ml of autologous platelet rich plasma injection along the inflamed tendon sheath of Abductor Pollicis Longus (APL) and Extensor Pollicis Brevis (EPE) tendons while patients in group B were given conventional therapy in the form of rest, ice pack application, analgesics and anti-edema measures for 2 weeks and physical therapy in the form of soft tissue massage. Pain was assessed in VAS. Functional improvement was assessed by Patients Rated Wrist Evaluation (PRWE) scale. Twenty six patients in group A and twenty five patients in group B had completed the six month follow up schedule. **Results:** The mean age of the participants in group A and group B were 38.23 (± 10.47) and 40.76 (± 8.05) years respectively where >80.0% patients in both groups were female. From 1st month, the VAS scores significantly reduced in group A compared to group B which persisted up to 6 months (p<0.001). In group A, 85.0% reduction of pain score and in group B, 71.8% reduction of pain score was achieved after 6 month of treatment. From 1st month, the PRWE scores significantly reduced more in group A compared to group B (p=0.021) which persisted up to 6 months (p<0.001). In group A, 89.1% functional improvement while in group B, 72.6% functional improvement was achieved after 6 month of treatment. **Conclusion:** Intra-lesional platelet-rich plasma reduces pain and improves function in patients with de Quervain’s tenosynovitis.

**Key words:** deQuervain’s tenosynovitis, Platelet Rich Plasma (PRP), Visual analogue scale (VAS), Patients Rated Wrist Evaluation (PRWE)

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**Introduction:**
de Quervain’s tenosynovitis is classically defined as a stenosing tenosynovitis of the synovial sheath of tendons of the abductor pollicis longus and extensor pollicis brevis muscles in the first compartment of the wrist due to repetitive use. The incidence of de Quervain’s is not well-known in primary care, but the prevalence that found in people of UK as 0.52% of them is males and 1.32% in females.

Different treatment modalities for de Quervain’s disease has been assessed world wide. However, there is limited evidence that conservative treatment is effective in reducing moderate to severe symptoms of de Quervain’s tenosynovitis. Some literature has evaluated effectiveness of ice, nonsteroidal anti-inflammatory drugs (NSAIDs), heat, orthoses, strapping, rest, and massage but does not show these techniques to be very effective in the treatment of de Quervain’s tenosynovitis. Intralesional steroid injections has 83% cure rate, but benefit is usually short term and also associated with some potential complications.

Platelet rich plasma (PRP) is autologous blood derivative with enhanced platelet concentration which basically has properties of biologically enhancing the healing process naturally. A variety of potentially therapeutic growth factors are detected and released from the platelets in significant levels in platelet-rich plasma preparations. The first clinical study assessing the effect of Platelet Rich Plasma (PRP) on de Quervain’s tenosynovitis was published by Peck and Ely. They suggest that US-guided percutaneous needle tenotomy (PNT) and PRP injection may be a reasonable option to consider before surgery. Several studies showed that PRP injection is effective in reducing pain and disability who are resistant to conservative treatment. However, majority of these studies dealt with small sample size. Moreover, no study about the effect of PRP in patient with de Quervain’s tenosynovitis have been carried out in a sample of Bangladeshi population. Therefore, the present study had been conducted to assess the effectiveness of intralesional Platelet Rich Plasma (PRP) therapy for the treatment of de Quervain’s tenosynovitis. This research would be helpful to provide evidence based information to the physicians as well as patient groups about the efficacy of PRP injection in the management of de Quervain’s tenosynovitis for pain reduction and functional improvement.

**Methods:**
The present randomized controlled trial had been conducted at the Department of Physical Medicine & Rehabilitation (OPD, Indoor), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2020 to February 2021. A total of 54 patients with lateral wrist pain were randomly allocated into two groups (27 patients in each group) and were given interventions. Patients with haemoglobin <10 gm/dL and platelet count <10³ / µL, or patients with rheumatoid arthritis, gouty arthritis, seronegative arthropathies and reactive arthritis, patients with local infection at the site of the procedure, HIV, Hepatitis B or C, coagulation and bleeding disorders, septicaemia and other systemic disorders and who underwent surgical treatment for de Quervain’s tenosynovitis, were excluded from the study.

All the cases were clinically evaluated properly with detailed history and physical examinations which includes general physical examinations, MSK and neurological examinations and also Fienkelstien’s test. For pre procedure planning: CBC, Plain X-ray of wrist, HbsAg, HCV screening, BT, CT and other relevant investigations were done.

The patients were informed in details regarding the procedure of the study and informed written consent was obtained. Patients were randomly allocated in two groups named as group A and group B by block randomization.

**Group A:**
At first, patient was requested to sit with hand in semi-porone position. Then, the lateral side of the wrist was cleaned properly with povidone iodine solution. After that 3 mL of PRP was injected along the inflamed tendon sheath of APL and EPB tendons with a 22- gauge needle without local anesthetic. The sterile dressing was applied at the injection site. Immediately after the injection, the patient was kept in a supine position without moving the arm for 15 minutes. All patients were advised for resting the affected wrist with thumb spica splint for 24 to 48 hours post injection. During this period, patient was instructed to remove the splint 4 times daily for active range of motion exercises of the wrist and hand. Patient was sent home with instructions to limit their use of the wrist for approximately 24 hours and use cold compression and/or acetaminophen for pain. A formal strengthening program was initiated after stretching. At 2 weeks, the patient began supervised occupational therapy. At 4 weeks after the procedure, patients were allowed to proceed with normal regular activities as tolerated.

**Group B:**
In this group, patients were given conventional therapy in the form of rest, ice pack application,
analgesics and anti-edema measures for 2 weeks and physical therapy in the form of soft tissue massage. Semi-structured interviewer administered questionnaire was used to collect data regarding socio-demographic status. Pain was assessed in VAS. Functional improvement was assessed by Patients Rated Wrist Evaluation (PRWE) scale. VAS and PRWE score were charted pre-procedurally on day 0 and post-procedurally 1st, 3rd months and 6th months.

The statistical analysis was conducted using SPSS (statistical package for the social science) version 26 statistical software. The findings of the study were presented by frequency, percentage in tables. Means and standard deviations for continuous variables and frequency distributions for categorical variables were used to describe the characteristics of the total sample. Associations of categorical data were assessed using Chi square test while associations of continuous data were assessed using Independent Sample t test where p<0.05 was considered significant and p<0.001 was considered as highly significant. Here, all p-values were two sided.

Before starting this study ethical clearance was taken from Institutional Review Board (IRB) of BSMMU.

Results:
Twenty six patients in group A and twenty five patients in group B had completed the six month follow up schedule.

Table I: Baseline characteristics of the study participants (n=51)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (in years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 35</td>
<td>14 (53.8)</td>
<td>9 (36.0)</td>
<td>0.389</td>
</tr>
<tr>
<td>36-45</td>
<td>8 (30.8)</td>
<td>9 (36.0)</td>
<td></td>
</tr>
<tr>
<td>46-55</td>
<td>4 (15.4)</td>
<td>7 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>38.23±10.47</td>
<td>40.76±8.05</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (14.4)</td>
<td>5 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (84.6)</td>
<td>20 (82.4)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>17 (65.4)</td>
<td>10 (40.0)</td>
<td>0.214</td>
</tr>
<tr>
<td>Over weight</td>
<td>8 (30.8)</td>
<td>12 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1 (3.8)</td>
<td>3 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Affected hand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>19 (73.1)</td>
<td>14 (56.0)</td>
<td>0.249</td>
</tr>
<tr>
<td>Left</td>
<td>7 (26.9)</td>
<td>11 (44.0)</td>
<td></td>
</tr>
</tbody>
</table>

f=frequency, SD=Standard deviation, Body Mass Index (BMI)

The mean age of the participants in group A and group B were 38.23 (+ 10.47) and 40.76 (+ 8.05) years respectively. In group A, 22 (84.6%) were female while in group B, 20 (82.4%) were female. Right hand was affected in 19 (73.1%) and 14 (56.0%) patients in group A and group B respectively. No significant statistical difference was found between the groups regarding age, gender, BMI and affected hand as p>0.05 (Table I).

Table II: Comparison of study participants by Visual Analog Scale (VAS) score (n=51)

<table>
<thead>
<tr>
<th>VAS</th>
<th>Group A (Mean ± SD)</th>
<th>Group B (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At base line</td>
<td>7.3 ± 0.8</td>
<td>7.1 ± 0.6</td>
<td>0.264</td>
</tr>
<tr>
<td>At 1st month</td>
<td>3.4± 0.5</td>
<td>4.3± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 3rd month</td>
<td>1.5± 0.8</td>
<td>3.4± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 6th month</td>
<td>1.1± 0.3</td>
<td>2.0 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD=Standard deviation

There was no significant statistical difference between the groups regarding VAS scores at baseline as p=0.264. From 1st month, there was highly significant statistical difference between the groups regarding VAS scores which persisted up to 6 months (p<0.001) (obtained by Independent sample t test) (Table II).

Figure-1. Reduction of pain (in percentage) of study participants in VAS score (n=51)

In group A, 85.0% reduction of pain score was achieved while in group B, 71.8% reduction of pain score was achieved after 6 month of treatment (Figure 1).

Table III: Comparison of study participants by The Patient-Rated Wrist Evaluation (PRWE) score (n=51)

<table>
<thead>
<tr>
<th>PRWE</th>
<th>Group A (Mean ± SD)</th>
<th>Group B (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At base line</td>
<td>75.1 ± 3.8</td>
<td>73.0 ± 4.8</td>
<td>0.089</td>
</tr>
<tr>
<td>At 1st month</td>
<td>27.0 ± 8.3</td>
<td>32.8 ± 9.2</td>
<td>0.021</td>
</tr>
<tr>
<td>At 3rd month</td>
<td>17.0 ± 2.4</td>
<td>27.8 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 6th month</td>
<td>8.2 ± 2.9</td>
<td>20.0 ± 5.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD=Standard deviation
There was no significant statistical difference between the groups regarding PRWE scores at baseline as p=0.089. From 1st month, there was significant statistical difference between the groups regarding PRWE scores which persisted up to 6 months (p<0.001) (obtained by Independent sample t test) (Table III).

In group A, 89.1% functional improvement was achieved while in group B, 72.6% functional improvement was achieved after 6 month of treatment (Figure II).

**Discussion:**
The present randomized controlled trial had been conducted to assess the effectiveness of intraslesional Platelet Rich Plasma (PRP) therapy for the treatment of de Quervain’s tenosynovitis. A total of 54 patients with lateral wrist pain were randomly allocated into two groups (27 patients in each group) and were given interventions. Twenty six patients in group A and twenty five patients in group B had completed the six month follow up schedule. Intra-lesional platelet-rich plasma significantly reduced pain and improved function in patients with deQuervain’s tenosynovitis.

The results of the present study showed that the mean age of the participants in group A and group B were 38.23 (± 10.47) and 40.76 (± 8.05) years respectively. The typical age of occurrence of de Quervain’s disease are within 30 to 50 years. Studies conducted among Bangladeshi patients with deQuervain’s disease also found that the mean age of patients was around 40 years.

Most of the patients in both groups were female. It is thought to occur more frequently in women between the ages of 20 and 40, including the variant that occurs during pregnancy and the postpartum period. Other studies also found higher proportion of female patients compared to male.

There is no predilection for right versus left side for de Quervain’s disease. However, majority of the patients of the current study had de Quervain’s disease on right side which was consistent with the study of Haque, et al.

Before treatment, there was no significant difference between the groups regarding VAS scores. From 1st month, there was highly significant statistical difference between the groups regarding VAS scores which persisted up to 6 months (p<0.001). In group A, 85.0% reduction of pain score was achieved while in group B, 71.8% reduction of pain score was achieved after 6 month of treatment. The case report of Peck & Ely reported 63% reduction in pain from her preprocedure level at 6 months after the procedure. Bender & Elder retrospectively reviewed the charts of 8 patients who received at least one injection of PRP and analyzed the short and medium-term outcomes of ultrasound guided platelet-rich-plasma injections for the treatment of de Quervain’s tenosynovitis and observed that average VAS scores decreased an average of 87% and these results were maintained at all subsequent follow-up visits for all members of the cohort. The case series of Sikkandar & Sha also found that the VAS score decreased in all three patients. The prospective study of AL-Ardi found that at six month follow up, the VAS score significantly improve from 5.9 to 2.0 after injection with platelet-rich –plasma. Ramesh, et al. prospectively reviewed and compared the efficacy, feasibility and durability of conservative & physical therapy, and platelet rich plasma therapy and reported that from 1st month, there was highly significant statistical difference between the groups regarding VAS scores which persisted up to 12 months (p<0.001).

Functional improvement of wrist was evaluated by The Patient-Rated Wrist Evaluation (PRWE). From 1st month, there was significant statistical difference between the groups regarding PRWE scores which persisted up to 6 months. In group A, 89.1% functional improvement was achieved while in group B, 72.6% functional improvement was achieved after 6 month of treatment. The study of Ramesh, et al. also found that functional improvement was significant in PRP group compared to conventional group.

Three patients (11.5%) in group A complained for mild pain which subsided after application of ice and paracetamol. Minor bleeding occurred in one patient in group A which resolved spontaneously. PRP is prepared from autologous blood, so any concerns of allergic reactions or disease transfer are eliminated. PRP does not promote hyperplasia, carcinogenesis, or tumor growth.
It was mentionable here that within this follow up period, no patient needed second dose of injection and no patient had recurrence.

Some limitations were perceived while planning and conducting the study. Due to COVID-19 pandemic, only 54 patients were included in the study which might not be representing the population and long term follow up could not be done.

Conclusion:
This study concluded that intra-lesional platelet-rich plasma reduces pain and improves function in patients with de Quervain’s tenosynovitis. Further comparative studies with large sample size and long term follow up are required to evaluate the long-term outcomes.

Limitation of the study:
Although sample size was calculated statistically, this was small in relation to the huge number of population of our country. It was a single-center study done in tertiary care hospital. Since our study was not a prospective case-control study, we could not calculate the hazard ratios for CIMT values.

Conflict of Interest:
The author stated that there is no conflict of interest in this study

Funding:
No specific funding was received for this study.

Ethical consideration:
The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained

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Thankful to all doctors, nurses and medical stuff of Department of Physical Medicine & Rehabilitation, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh for their best and kind support.

References:


INTENSIVE REHABILITATION IS BETTER WHEN IT IS COMBINED WITH TIZANIDINE IN SPASTIC CEREBRAL PALSY- A RANDOMIZED CLINICAL TRIAL

MD. RUHUL AMIN¹, AMITAV BANIK², MOHAMMAD ANISUR RAHMAN³, SOHELY RAHMAN⁴

Abstract:
Background: To find out the combined efficacy of Tizanidine and intensive rehabilitation in the treatment of spastic cerebral palsy. Methods: This randomized clinical trial was conducted over 70 patients in Sir Salimullah Medical College Hospital from January 2022 to December 2022. The patient satisfying the inclusion and exclusion criteria was randomly enrolled into two groups; Group-A (Case) included 35 patients received only intensive rehabilitation and Group-B (Control) included 35 patients who received Tizanidine (2mg) orally at a dose of 1 mg given at bed time under 10 years and 2 mg 10 years or more, then after 1 week maintenance dose was 0.3 mg/kg/day three times daily in combination with intensive rehabilitation 1 hour daily five times a week for 24 weeks. All patients were followed up at 4 weeks interval and were evaluated for a total of 24 weeks. Combination of Tizanidine and intensive rehabilitation has superior efficacy in reducing tone in spastic cerebral palsy over only rehabilitation measured by using Modified Ashworth scale (p<0.001). Results: Combination of Tizanidine and intensive rehabilitation is improved in physician rating scale crouch (p<0.0001) and foot contact, (p<0.0001) and also improvement in gross motor function (p<0.01). Conclusion: Combination of Tizanidine and intensive rehabilitation group has superior efficacy than only rehabilitation group for reduction of generalized spasticity regarding muscle tone, range of motion of the joint and improvement of gait in cerebral palsy patients.

Key Words: Cerebral Palsy, Spasticity, Tizanidine, Intensive Rehabilitation

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Introduction:
Cerebral palsy is the most common disability of childhood that affects motor function as a result of injury to the developing brain. It is now well known that the prime risk factors for CP are delivery before 37 weeks and birth weight of less than 2.5kg; however, there are some other problems evident in the literature which are found to be some of the prominent reasons for brain damage, some of which includes malformation of the brain in the

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developmental period, genetic causes, in utero mother and fetus infections, and various other issues.

The presenting signs and symptoms of CP are diverse and mainly consist of motor disorders, sensory deficits, and associated comorbidities which occur due to a static lesion to the developing brain. These signs and symptoms change as the child ages and new features are added to the list. Thus, with advanced age, there is a worsening of the neuromuscular system and functional capability of the child even though the damage in the brain is static. The most common movement disorders seen in cerebral palsy are spastic muscles and dystonia with difficulties in coordination, strength, and selective motor control. Spasticity is the major challenge in the management of CP children. It causes spasticity-induced bone and joint deformity, pain, and functional loss. Commonly used medicines found in the literature to relieve spasticity are baclofen, diazepam, clonazepam, dantrolene, and tizanidine. Baclofen and diazepam help in relaxing the muscles but have many side effects. Treatment of spastic cerebral palsy includes physiotherapy along with antispastic medication. Tizanidine is similar to diazepam and baclofen in the effectiveness of tone reduction. Tizanidine is readily absorbed after oral administration and metabolized in the liver. Alpha 2 adrenergic agonists have an anti-nociceptive effect, which may assist in their tone-reducing abilities because pain is known to increase spasticity; it is possible that this effect is mediated through the release of substance P in the spinal cord. Tizanidine is possibly effective, but there are insufficient data on its effect on improvement of motor function and its side-effect profile. The tizanidine and baclofen are currently most promising drugs treated for cerebral palsy. Intensive rehabilitation may be defined as 1 hourly intervention, 5 days a week, as opposed to a therapy session once a week or once every second week. It consists of neurodevelopmental treatment (NDT), therapeutic exercises (TEs) and activities of daily living (ADL) training. The aim of this study was to find out the efficacy of Tizanidine in combination with intensive rehabilitation in reducing spasticity in cerebral palsy.

Methods:
Subjects:
A randomized controlled clinical trial was done in Sir Salimullah Medical College Hospital from January 2022 to December 2022. All the spastic cerebral palsy patients seeking treatment in outpatient department of Physical Medicine & Rehabilitation and Paediatrics were the reference population. From reference population, patients enrolled in the study who met the inclusion and exclusion criteria. Sample size estimates suggested that 35 subjects in each group would be sufficient to detect a 5% level of significance. Patients aged between 12 months to 12 years of both sexes; with disorder in the development of movement and posture presumably of cerebral origin started before 2 years of age, presence of spasticity associated with or characterized by increased tone reflexes, clonus or extensor plantar response, and delayed milestones of development which is improving over time were included in this study. Those with mixed type of cerebral palsy; receiving systemic anti-spastic medication or had received phenol and/or botulinum toxin type A injections; past surgical intervention that might interfere with ankle joint movement; neurodegenerative disorders, chromosomal abnormality such as Down syndrome, inborn errors of metabolism such as galactosemia and presence of comorbidity such as epilepsy were excluded.

Procedure:
A total number of 70 patients were primarily selected and were randomized into two groups (Group A and Group B), each of which included 35 patients. Complete history and clinical examination were done for all enrolled patients. After taking written informed consent they were finally selected for the study and randomization was done by lottery. In group A only intensive rehabilitation (1 hour daily for 5 days a week for 24 weeks) was given. In group B intensive rehabilitation (1 hour daily for 5 days a week) and oral Tizanidine (2mg) orally at a dose of 1 mg given at bed time under maintenance dose was 0.3 mg/kg/day three times daily was given for 24 weeks. Patients were first assessed with Modified Asworth Scale (MAS) based on muscle tone to determine the extent of spasticity. Then Physician Rating Scale to measure joint angle (crouch) especially by standard goniometer, knee recurvatum, foot contact and overall functional status by Gross Motor Functional Classification System. Then intervention was done by giving oral Tizanidine with intensive rehabilitation to reduce spasticity in Group B and Uniform intensive rehabilitation protocol was applied. After 4 weeks (1st follow up) during the continuation of drugs, patients were again assessed by principal investigator using previously mentioned 3 scales and adverse effect of oral tizanidine was recorded in follow-up sheet. After 8 weeks (2nd follow up) were again assessed by principal investigator using previously mentioned 3 scales and
adverse effect of oral baclofen was recorded in follow up sheet. Then follow up assessment was done every 4 weekly at 12th week, 16th week, 20th week and lastly 24th week for total with continuing the drugs using same scales by principal investigator. Both groups were given intensive rehabilitation by an experienced physiotherapist at the department of Physical Medicine & Rehabilitation, Sir Salimullah Medical College Hospital, Dhaka.

**Drug administration and titration:**
After group allocation, tizanidine was given according to following dose schedule. Oral Tizanidine (2mg) was started orally at a dose of 1 mg given at bed time under 10 years and 2 mg 10 years or more, then after 1 week maintenance dose was 0.3 mg/kg/day three times daily.

**Intensive rehabilitation:**
One hour intensive physiotherapy was done daily for 5 days a week. Activities included in each session were body alignment weight transfer in various positions, bimanual activities and facilitation sequences of movements.

**Data analysis:**
Data were collected through a pretested structured questionnaire. Data were processed and analyzed using SPSS (statistical package for social science) version 17. Test statistics used to analysis the data were chi square Test and student T test. The level of significance was set 0.05 and p-value of less than 0.05 was considered significant.

**Results:**
A total number of 70 cerebral palsy children were recruited for this study of which 35 patients were in Tizanidine and Intensive Rehabilitation group and 35 patients were in Intensive Rehabilitation group. Data on patient’s age was collected in months. Age range of patients was with a mean of 28.62. Thus the mean age in tizanidine group was 31.97 months with a standard error of 2.71. However, the mean age of Intensive Rehabilitation group was 25.27. Lower by about 7 months and relatively higher standard error (2.23) compared to tizanidine and Intensive Rehabilitation group (Table-1).

In this study about 46.0% of patients receiving Intensive Rehabilitation had AS score-3 before starting the treatment. In the 2nd and 3rd month the same trend was observed and the score remained within 40.0% to 50.0%. However, it was not until the 4th month that about 42.0% of the patients receiving Intensive Rehabilitation shifted to score 2 following improvement. This improving trend persisted till the final follow-up at 6 month after initiating treatment. It was noteworthy that 39.0% of patients receiving Tizanidine and Intensive Rehabilitation were also in AS score-3 before starting treatment. However, 46.0% of patients in this group later on began to show a lower Ashworth score which at 3rd month in 2nd follow up shifted to AS score-2 because of improvement. This improvement in the 4th month compared to the 3rd month within the Tizanidine and Intensive Rehabilitation group was also found to be highly significant (p < 0.0001) using paired sample t test. Moreover, by the end of the follow-up period (about 46.0%) of the Tizanidine and Intensive Rehabilitation group Ashworth score 1 step more putting them into the 1st category (Figure-1).

In Intensive Rehabilitation group, before starting treatment 58% patient was in moderate variety. At final follow-up, 6 months after treatment with Intensive Rehabilitation the measured angle for crouch gait did not improve (58% VS. 60%). Before starting treatment no patient was in mild variety but after 6 months follow up 28% patient was found in mild variety. But this improvement in month wise follow up is not statistically significant. Tizanidine and Intensive Rehabilitation group showed remarkable variation in scores and accordingly change in severity of angle compared to patients receiving Intensive Rehabilitation. For example, 49% the patients had severe spasticity in the first month. However, in the second month 61% patient had moderate angle, although the mean score improvement was not statistically significant (p = 0.21) from the 4th month another shift of improvement was observed.

![Figure-1. Monthly change of muscle tone by modified ash worth scores between two treatment groups.](image-url)
among patients receiving Tizanidine and Intensive Rehabilitation and without any notable statistical significance ($p = 0.33$). 46% of the patients in the 4th month had mild variety, the condition lasting through the end of the follow up and with statistical significant change in mean scores at 5th month ($p = 0.03$) but nonsignificant from 5th to 6th month ($p = 0.14$) (Figure-2).

Another component of physician rating scale of Intensive Rehabilitation group is foot contact score ranging from 0 grade (patient walk on toe) grade 4 (patient starts walking contact the ground first by heel and end by toe). It was found that patients receiving Intensive Rehabilitation showed detrimental trend in toe-walking on subsequent follow-up, which changed from base line (79%) to subsequent follow-up at 2nd and 3rd month, 64% and 52% respectively. It was not until the 4th month that 60% patients receiving Intensive Rehabilitation had a score of 1 (starts walking with toe then heel). The change in mean scores from 3rd to 4th month was statistically significant ($p = 0.04$). The pattern of change continued till the last month of follow-up ($p = 0.12$). Patients receiving Tizanidine and Intensive Rehabilitation had a score of 0 in month 1 and 2 (about 70% and 52% respectively), a change in score was seen in 3rd month (about 61% had score 1) of the follow-up, however, the change in mean score from 2nd to 3rd month was not statistically significant ($p = 0.67$). Statistically significant improvement ($p < 0.0001$) in mean score began between 3rd to 4th month and the trend continued till the end of the follow-up (Figure-3).

Table-I

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age in Month</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Rehabilitation</td>
<td>25.27±12.81</td>
<td>0.048</td>
</tr>
<tr>
<td>Tizanidine &amp; Intensive Rehabilitation</td>
<td>31.97±15.63</td>
<td></td>
</tr>
</tbody>
</table>

Figure-2. Monthly change of joint angle measured by crouch scores of physician rating scale between two treatment groups.

Figure-3. Monthly change of gait measured by foot contact scores of physician rating scale between two treatment group.
Before starting treatment, the majority of patients in the Intensive Rehabilitation group were in level-4 and level-5 (42% VS. 39% respectively). At 5th month (4th follow-up) the proportion of patients in level 4 increased to 67% whereas proportion of level-5 patients decreased to 8% but this improvement in gross motor function from level-5 to level-4 was not significant monthly follow-up was not statistically significant in any month. Tizanidine and Intensive Rehabilitation group: before starting treatment 52% patients were at level 5% and 32% patient were at level 4. In Month 4 follow-up it was found that over half the patients receiving Tizanidine and Intensive Rehabilitation (56.0%) improved to Level 3. The difference in mean score was statistically highly significant (p = 0.001). Although a large proportion of these patients eventually improved towards level 2 (30.0%) or level 1 (9.0%), the majority of the sample remained in level 3 in the 4th (56.0%), 5th (56.0%) and 6th month (46.0%) of follow up time (Figure-4).

**Discussion:**

The syndrome of spastic hypertonia develops when the supra segmental control over the spinal cord segmental reflexes is lost. Spasticity It can range from mild muscle stiffness to severe, painful, and uncontrollable muscle spasm. It is associated with some common neurological disorders: Multiple sclerosis, stroke, cerebral palsy, spinal cord and brain injuries, and neurodegenerative diseases affecting the upper motor neuron, pyramidal and extrapyramidal pathways. First we planned for a double blind comparative study between Intensive Rehabilitation and tizanidine with Intensive Rehabilitation for reducing spasticity in CP but due to unavailability of same dose formulation and non-convenience we compelled to do uniblind study. The minimum age for both the group was equal, although the maximum age differed by 6 months yielding a wider range of age among tizanidine with Intensive Rehabilitation group and therefore a larger mean compared to Intensive Rehabilitation. Mean age of tizanidine with Intensive Rehabilitation group was 31.97 months with SE 2.71. Mean age of Intensive Rehabilitation group was lower by about 7 months relating higher standard error (2.25). Independent t test showed that mean age of tizanidine with Intensive Rehabilitation was significantly higher (p = 0.048). This difference cannot be ruled out due to randomization process.

Nikkhah et al. found mean age of 7.3 ± 3.4 years and Adam et al. found mean age of 7.4 ± 2.3 years. The difference between this study and other study is that patient not coming to physician after 5 years due to socioeconomic condition & false belief.

Nikkhah et al. found the mean Ashworth score decreased in 50% of the patients receiving tizanidine versus 6.7% of patients receiving the placebo (p < 0.0001). In a previous study by Vasques et al. found that in the group receiving tizanidine 78.8% reported having reduced spasticity compared with only 76% patients receiving the placebo (p < 0.0001). Alper et al. found that the mean score of gross motor function measure is highly significant and modified Asworth is significant. This study suggests that adjuvant treatment with oral tizanidine is more effective than baclofen in combination with botulinum toxin for spastic equines foot deformity due to cerebral palsy. Significant improvement was demonstrated using gross motor and modified Asworth scale (p < 0.05). In present study in gross motor function score, it was found that the mean gross motor function score among tizanidine with Intensive Rehabilitation receiving patients was lower compared to the gross motor function score of patients receiving Intensive Rehabilitation. But the difference by independent t test was non-significant (p > 0.05).
Physician ratings scales comprise crouch measure and foot contract score. Mean crouch score of patients receiving tizanidine with Intensive Rehabilitation and Intensive rehabilitation was tested for difference using independent t test. A higher mean crouch score for patients receiving tizanidine with Intensive Rehabilitation compared to Intensive Rehabilitation and the difference was statistically highly significant (p < 0.0001).

Wagstaff et al. found improvement in muscle tone occurred in 60% to 82% of tizanidine recipients compared with 60% to 65% of baclofen. Adam et al. using Tardiew score found that score was 4.4 for baclofen and placebo. Data from this research shows that majority of the patients (about 46%) receiving Intensive Rehabilitation were in a score of 3 of Asthwoth scale. It was not until the 4th month that the majority about 42% of the patient receiving intensive Rehabilitation improved to score 2. It is noteworthy that majority of the patients receiving tizanidine with Intensive Rehabilitation (about 39%). In the first month also were in Asthwoth some categories 3. However, majority of this later group began to show a lower Ashworth score in the 3rd month that is one month earlier than its Intensive Rehabilitation counterpart.

This improvement in the 3rd month to the 2nd month within the tizanidine with Intensive Rehabilitation group was also found to be statistically highly significant (p < 0.0001) using paired sample t test. During measuring crouch, majority (60% - 72%) of the patient in the Intensive Rehabilitation group had moderate angle based on crouch score. Also it is notable that no more than two patients improved from moderate to mild score in any given month time. Tizanidine with Intensive Rehabilitation group on the other hand showed remarkable variation in scores and accordingly change in severity of ankle compared to patients receiving intensive rehabilitation. For example majority of (about 49%) of the patients had severe spasticity in the first month. However in the second month majority of patient (about 61%) had moderate Ankle measure, although the mean score improvement was not statically significant (p = 0.21). Statically significant improvement of spasticity by change of mean score, using MAS score it is at 4th month in Intensive Rehabilitation compared to tizanidine with Intensive Rehabilitation is at 3rd month. Using GFMS, there is no significant change in Intensive rehabilitation group but at 3rd month there is significant change in Intensive Rehabilitation group. Using foot contract Intensive Rehabilitation group has significant change at 4th month same as well tizanidine with Intensive Rehabilitation group.

Conclusion:
Analytical results of this study shows that basic motor abilities and self-care improved after intensive physiotherapy with Tizanidine is effective for reducing generalized spasticity regarding muscle tone and joint angle stiffness and gait improvement in cerebral palsy patients over intensive rehabilitation.

Data Availability:
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

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

Funding:
No specific funding was received for this study.

Ethical consideration:
The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College. The confidentiality and anonymity of the study participants were maintained.

Acknowledgments:
The authors were grateful to the staffs of the Outpatient Department(OPD) of Physical Medicine & Rehabilitation and Paediatrics in Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh.

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Intensive Rehabilitation is Better When it is Combined with Tizanidine in Spastic Cerebral Palsy

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ASSOCIATION OF VITAMIN-D STATUS WITH ISCHEMIC STROKE AND IT’S RISK FACTORS IN BANGLADESHI PATIENTS: A CASE-CONTROL STUDY

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Abstract:
Background: Vitamin D (VD) shortage and inadequacy are serious global health issues affecting people of all ages. Several studies have shown a link between VD insufficiency and ischemic stroke. Unfortunately, VD is rarely measured, diagnosed, or treated, especially in patients with severe neurological disorders like stroke in our context. The study aimed to explore the association between VD and the risk of acute ischemic stroke along with its risk factors in Bangladeshi patients. Methods: Forty-four patients with ischemic stroke and 44 age and sex-matched healthy subjects were included in this study from Chittagong Medical College Hospital. Demographic and clinical data were collected with a structured interview questionnaire. Fasting 25(OH) VD, calcium, lipid profile, and blood sugar were measured. VD levels classified the individuals in sufficient (VDSe"30.0 ng/mL), insufficient (VD: 20.0–29.9 ng/mL), and deficient (VDD<20.0 ng/mL) status. Results: Out of 44 stroke patients, 27 (61.4%) were men, and the mean age was 54.6±11.0 years (age range: 18-70 years). The frequency of hypertension, diabetes mellitus, obesity, and dyslipidemia were 68.2%, 31.8%, 52.3%, and 81%, respectively, among stroke cases. VDD and VDI was observed in 29 (65.9%), 9 (20.5%) stroke patients and 5 (11.4%), 12 (27.3%) controls respectively. Multiple logistic regression analysis showed an independent association of 25(OH)D deficiency or insufficiency with ischemic stroke (odds ratio: 10.71, 95% confidence interval: 2.21-51.88, p=0.003). Conclusions: This study shows that low VD levels may be associated with an increased risk of ischemic stroke.

Keywords: Ischemic stroke, Vitamin D, Chattogram, Bangladesh.

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Introduction:
Data from the World Health Organization in 2021 indicates that stroke is at the top of the list of ‘leading causes of death in Bangladesh,’ which ranks mortality due to stroke in Bangladesh as number 41 in the world.1 Increasing burden of stroke in Bangladesh is primarily driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors.2 Without the urgent implementation of effective primary prevention strategies, the stroke burden will probably continue to grow across the world, particularly in low to middle-income countries like Bangladesh.3

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Hypertension, diabetes mellitus, dyslipidemia, sedentary lifestyle, obesity, smoking are the common risk factors of stroke. However, plenty of epidemiological studies are being done to spot novel emerging risk factors and their role in reducing the incidence of stroke and their exact nature of association with stroke. In the recent past, researchers have given much emphasis to one such risk factor i.e., VD deficiency (VDD), but the results were inconclusive and conflicting. While some studies reported an association between low levels of VD and stroke, as well as its relationship with outcome and prognosis, but some studies failed to establish such association.

VD is an organic compound consisting of fat-soluble secosteroids mainly responsible for regulation of calcium and phosphorous levels, among other physiological functions. VD is measured by levels of a metabolically inactive precursor, 25-hydroxyvitamin D3[25(OH)D3] since the serum concentration of 1,25(OH)2D3 is significantly lower than 25(OH)D3. Deficiency can cause bone demineralization and is associated with obesity, diabetes, hypertension, and cancer. 25(OH)D3 levels have been associated with regulating cardiac myocyte, systolic blood pressures, glycemic control, vascular function, high-density cholesterol, and metabolic syndrome, which all influence cerebrovascular and cardiovascular events.

Given these discrepancies and biological plausibility, the current study was undertaken to assess the association between VD status and risk of ischemic stroke based on a population from southeastern Bangladesh.

**Methods:**

We conducted a case control study over a period of one year (January 2018 to December 2018). The study was conducted at Chittagong Medical College Hospital, Chattogram, Bangladesh and subjects were recruited from medicine and neurology wards.

A total of 44 patients with acute ischemic stroke were chosen in the study. An equal number of age- and sex-matched healthy controls were taken from normal healthy individuals. Sample size was calculated with reference to a previous study, where the proportion of VD deficiency was 43% and 5% respectively in stroke cases and controls. By using above reference values, sample size was calculated by formula for calculating sample size for case-control study by comparing two proportion at 95% confidence interval and 80% power, 5% level of significance.

Clinically and Radiologically (C.T scan of Head/MRI of brain) documented new case of Ischaemic stroke, duration of stroke within 7 days, and ages 18 to 70 years were included in the study. Known case of other comorbid conditions like, chronic liver disease, chronic hepatitis, chronic kidney disease, severe sepsis, malabsorption syndrome, systemic sclerosis, chronic obstructive pulmonary disease, bronchial asthma, nephrotic syndrome, bone diseases including fracture were excluded. Patients with ongoing drug history of steroid, oral contraceptive pill, Bisphosphonate antiepileptic and calcium & vitamin-D supplements were also excluded.

All relevant demographic and clinical data were collected using structured case record form. After keeping fasting for 8-12 hours, with all aseptic precaution 8cc venous blood was collected from median cubital vein at morning. Then blood was taken into two sealed sterile red tube, each of 4cc and immediately sent to the laboratory with proper care. For fasting lipid profile and serum calcium, blood samples were centrifuged at 3000 RPM for 5 minutes. Separated serum samples for mentioned investigations, were analyzed by auto analyzer (SIEMENS-Dimension® EXL™-200). VD levels were classified as sufficient (VDS≥30.0 ng/mL), insufficient (VDI: 20.0–29.9 ng/mL), and deficient (VDD<20.0 ng/mL) status.

Data were analyzed by using SPSS version 23. Categorical variables were expressed as frequency and percentage and continuous data were either in mean (±SD) or median (Interquartile range) as appropriate according to their distribution. To see the association of demographics, laboratory parameters and risk factors of ischemic stroke between case and control groups Fisher’s exact or Chi-square test were used for categorical variables and independent sample test or Mann-Whitney U test for quantitative variables. Logistic regression model was used to estimate adjusted effect of VD and to determine the independent predictors of ischemic stroke. Additionally, binary logistic regression analysis done for same purpose and also the odds ratios (ORs) with 95% confidence interval for OR to see the association between risk factors of stroke with VD status by dividing the all-study subjects (n-88) by VD level e30ng/dl versus <30ng/dl. P <0.05 was considered statistically significant.

**Results:**

The mean age of the stroke patients was 54.6 (±11.0) years and 61.4% were male. Most prevalent risk factor in stroke patients was dyslipidemia (80%), followed by hypertension (68.2%), obesity (52%), smoking (38%) and diabetes (32%).
Vitamin D status in stroke cases and controls

Study subjects were categorized according to their vitamin D level as vitamin D sufficient (VDD), insufficient (VDI), deficient (VDD) and severely deficient. Majority of the stroke patients (56.8%) are vitamin D deficient whereas majority of the control (61.4%) have sufficient vitamin D. Deficient & severely deficient vitamin-D status are significantly different between cases & controls.

Finally, to determine the independent predictive factor for stroke a binary logistic regression analysis is done, vitamin D level <30 ng/ml is remained as an independent factor associated with acute ischemic stroke (OR 10.71, 95% CI: 2.21–51.88; p=0.003). Relation with smoking also significant (OR 5.43, 95% CI: 1.135-25.989; p=0.034) (Table III).

**Fig.-1:** Distribution of the cases and controls according to their VD status.
Table III

<table>
<thead>
<tr>
<th>Variables</th>
<th>P value</th>
<th>Odds ratio (OR)</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D (e³0 vs. &lt;30 ng/ml)</td>
<td>0.003</td>
<td>10.71</td>
<td>2.21-51.88</td>
</tr>
<tr>
<td>Age, in years</td>
<td>0.210</td>
<td>0.95</td>
<td>0.89-1.02</td>
</tr>
<tr>
<td>Sex, (male vs. female)</td>
<td>0.394</td>
<td>0.49</td>
<td>0.10-2.47</td>
</tr>
<tr>
<td>Smoking (Never/Ex vs. current)</td>
<td>0.034</td>
<td>5.43</td>
<td>1.13-25.98</td>
</tr>
<tr>
<td>Hypertension (Absent vs. present)</td>
<td>0.143</td>
<td>3.21</td>
<td>0.67-15.32</td>
</tr>
<tr>
<td>Diabetes (Absent vs. present)</td>
<td>0.440</td>
<td>1.78</td>
<td>0.40-7.83</td>
</tr>
<tr>
<td>Obesity (Absent vs. present)</td>
<td>0.136</td>
<td>0.34</td>
<td>0.08-1.39</td>
</tr>
<tr>
<td>Dyslipidemia (Absent vs. present)</td>
<td>0.408</td>
<td>0.46</td>
<td>0.07-2.85</td>
</tr>
</tbody>
</table>

CI: Confidence interval

All of the study subjects (both case and control) are classified according to their vitamin D status (e³0 ng/ml and <30ng/ml) and association with the risk factors of stroke are observed in Table IV. Among them hypertension is significantly associated with vitamin D status ((OR 4.73, 95% CI: 1.86-12.0; p=0.003).

Table IV

<table>
<thead>
<tr>
<th>Variables</th>
<th>Vitamin D status (n=88)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufficient (≥30ng/ml)</td>
<td>Deficient (&lt;30ng/ml)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Absent (n=33)</td>
<td>23 (69.7%)</td>
<td>4.73(1.86-12.0)</td>
</tr>
<tr>
<td></td>
<td>Present (n=55)</td>
<td>18 (32.7%)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>Absent (n=33)</td>
<td>28 (84.8%)</td>
<td>2.29(0.75-7.1)</td>
</tr>
<tr>
<td></td>
<td>Present (n=55)</td>
<td>39 (70.9%)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Absent (n=33)</td>
<td>19 (57.6%)</td>
<td>1.88(0.18-2.17)</td>
</tr>
<tr>
<td></td>
<td>Present (n=55)</td>
<td>23 (41.8%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Absent (n=33)</td>
<td>4 (12.1%)</td>
<td>0.62(0.18-2.17)</td>
</tr>
<tr>
<td></td>
<td>Present (n=55)</td>
<td>10 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Never/Ex (n=33)</td>
<td>23 (69.7%)</td>
<td>0.94(0.37-2.42)</td>
</tr>
<tr>
<td></td>
<td>Current (n=55)</td>
<td>39 (70.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as frequency and percentage. * Chi-square test

Discussion:
In this study, we investigated whether vitamin D status was associated with ischemic stroke in Bangladeshi patients admitted to a tertiary level hospital. The study demonstrated that VDD may be considered an independent factor associated with acute ischemic stroke and here individual with vitamin D level <30ng/dl was 10.71 times more likely to have acute ischemic stroke when compared to those with vitamin D level ≥30ng/dl.

A large body of evidence from epidemiological studies indicates that VDD is associated with an increased risk of stroke, and stepwise decrease in plasma 25(OH)D concentrations were associated with stepwise increasing risk of ischemic stroke.8,12-14 To the best of our knowledge, the present study is one of the few published reports that has focused on the association between 25(OH)D and acute stroke in Bangladeshi population.6 Majumder et al.6 first reported from their cross-sectional study that VDD is an important risk factor for ischemic stroke in a group of Bangladeshi patients. The present study affirms this association with a superior study (case control study) design.
In our study, the mean of serum 25(OH)D level in the 88 adult subjects examined was 25.03 (±10.1) ng/dl, the VDI (<30ng/dl) was as high as 62.5%. The results indicated that inadequacy of VD was prevalent in Chattogram as in other areas of Bangladesh and other countries. We found significantly higher rates of VDI, and VDD in the stroke patients than control group. The serum 25(OH)D levels of stroke cases were even lower than controls 19.0 (±7.79) ng/mL versus 31.05 (±8.46) ng/mL. Similar findings have been shown in previous observational studies on ischemic stroke.

In the present study, most prevalent risk factor in stroke patients was dyslipidemia (80%), followed by hypertension (68.2%), obesity (52%) and DM (32%). The corresponding figures in the study of Majumder et al. was hypertension (44.8%), obesity (12.9%) and DM (32.8%) and dyslipidemia (30.2%). Among the modifiable risk factors of ischemic stroke, only hypertension was found statistically significant (p=0.005). It agrees with others, where a significant association between hypertension and VDD were reported. On the contrary, though previous studies, found associations between VDD, and other modifiable risk factors including DM were not found to be associated with VDD in the present study. This insignificant association of risk factors of stroke might be due to mechanism other than VD status or small sample size. As hypertension is established modifiable risk factors of stroke and that regulate RAAS and as it was found more prevalent among VDD groups, so maintenance of optimal VD level is crucial. Moreover, both hypertension and VDD are controllable and treatable parameter; worldwide stroke burden can be reduced by effective health care program.

**Conclusion:**
The current study shows that ischemic stroke patients are more common of VDD than age-sex matched control. Among the risk factors of ischemic stroke, hypertension might have association with VDD. In the context of our observations, VDD may be a risk factor for acute ischemic stroke.

**Limitations:**
Small sample size and selection of the cases from a tertiary level hospital might limit the generalizability of the study results. More sensitive method for vitamin-D estimation by HPLC could not be used in this study due to unavailability of laboratory support in our context.

**Data Availability:**
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

**Conflict of Interest:**
The authors stated that there is no conflict of interest in this study.

**Funding:**
This research received no external funding.

**Ethical consideration:**
The study was approved by the Ethical Review Committee of Chittagong Medical College. Informed consent was obtained from each participant or caregivers of the patients.

**Author Contributions:**
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

**Acknowledgments:**
The authors were grateful to the staffs of the Department medicine and neurology wards in Chittagong Medical College Hospital, Bangladesh.

**References:**


ASSOCIATION OF 99MTC- HMPAO SPECT MEASURED REGIONAL CEREBRAL BLOOD FLOW AND SERUM VITAMIN D LEVEL WITH CLINICAL STAGING OF PARKINSON’S DISEASE

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Abstract:

Background: Parkinson’s disease (PD) is the most common neurodegenerative movement disorder. Diagnosis of PD can be made through Single-photon emission computed tomography (SPECT). Vitamin D deficiency has recently been proposed as a potential risk factor for PD. This study aimed to evaluate the association of 99mTc- HMPAO SPECT image findings and vitamin D status with clinical staging of PD.

Methods: This cross-sectional study was conducted in Department of Neurology, Sir Salimullah Medical College Mitford Hospital for a period of 12 months. Total 66 diagnosed PD patients were included after taking informed written consent. Detailed demographic history and neurological examination were done. The severity of PD was assessed using the modified Hoehn and Yahr (H & Y) scale. Serum 25-Hydroxyvitamin D level was measured for each participant.

Results: The mean age of the studied respondents was 71±8.72 (SD) years wherein maximum were male (59.1%) and aged above 70 years. The most common symptoms among the patients were tremor (78.8%) and bradykinesia (75.5%). The mean duration of PD was 5.74±2.22 (SD) years. Majority of the patients were diagnosed to have stage-2 (30.3%) followed by stage-2.5 (24.2%), stage-3 (16.7%), stage-4 (7.6%), stage-1 (4.5%), and stage-5 (3%). As the clinical stage of PD advanced from stages 1-5, the HMPAO uptake reduced significantly in the basal ganglia (p=0.006). Vitamin-D level decreased significantly as the disease severity progress from stage-1 (27.8 ng/ml) to stage-5 (19.5 ng/ml) (p-value=0.008).

Conclusion: Serum Vitamin-D level was inversely associated to severity of PD and decreased regional cerebral blood flow in basal ganglia in advanced stages of PD patients. However, further larger study is recommended.

Keywords: Parkinson’s disease, 99mTc HMPAO SPECT, Regional cerebral blood flow, Serum vitamin D level.

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**Introduction:**

Parkinson’s disease (PD) is a common neurodegenerative disorder that can cause major incapacity and lessened class of life \(^1\). It is the second most common neurodegenerative disease worldwide with incidence and prevalence on the rise along with changing population demographics \(^2\). The prevalence of PD in industrialised countries is generally estimated at 0.3% of the entire population and about 1% in people over 60 years of age \(^3\). PD is rare before 50 years of age, but the incidence increases 5-10-fold from the sixth to the ninth decade of life \(^4\). It is found that relative risk in first-degree relatives of PD cases increases by approximately two- to three-fold \(^5\).

There are several proposed mechanisms for neuronal death in PD; however, not all of them are well understood. Five proposed major mechanisms for neuronal death in Parkinson’s disease include protein aggregation in Lewy bodies, disruption of autophagy, changes in cell metabolism or mitochondrial function, neuroinflammation, and blood-brain barrier (BBB) breakdown resulting in vascular leakiness \(^6\).

At present, the diagnosis of PD still depends mainly on clinical criteria. But the insidious onset and multifarious presentations often interfere with the accuracy of PD diagnosis, therefore, a considerable misdiagnosis in PD patients is inevitable \(^7\). The pathophysiological changes in PD start to occur before the onset of clinical symptoms. Motor disturbances are known to occur only after about 50% to 60% of striatal dopamine is lost. Brain single-photon emission tomography (SPECT) imaging with specific radioligands provides a useful tool of in vivo investigation of the pathogenesis of PD, and it is a sensitive method for examining the integrity of the presynaptic dopaminergic system \(^8\). 99mTc HMPAO is a lipophilic compound that easily crosses the blood brain barrier and is therefore taken up on first pass through the brain where it is retained for several hours. It is distributed in proportion to regional cerebral blood flow \(^9\). SPECT is an imaging modality that is capable of differentiating between PD and essential tremor \(^10\). SPECT imaging can also distinguish between PD and drug-induced Parkinsonism \(^10,11\). However, any disease that causes loss of the presynaptic dopamine neurons will appear as abnormal compared with normal controls in SPECT. Thus, SPECT is not able to differentiate among PD, progressive supranuclear palsy, multiple system atrophy, and other neurodegenerative disorders that affect the dopamine neurons \(^12\). SPECT is now well recognized and documented thoroughly in terms of its sensitivity in detection of PD. But there still remains paucity of data on correlation of SPECT imaging with clinical staging of PD \(^13,14,15\).

Recently, vitamin D is not only considered as a vitamin, but also as a hormone with autocrine and paracrine functions well beyond those of regulating calcium homeostasis and bone health. Optimal balance, muscle strength, and innate immunity require sufficient vitamin D levels, and its deficiency is correlated with increasing risk for various types of cancer, as well as autoimmune and cardiovascular disorders \(^16\). Recently, chronic inadequacy of vitamin D intake has been suggested to play a remarkable role in the pathology of Parkinson’s disease \(^17\). Related to the role of vitamin D and PD, there are some cross-sectional studies in Japan indicating that serum levels of 25-hydroxyvitamin D (25OHD) as well as 1, 25-hydroxy-vitamin D (1, 25OHD) may have an inverse correlation with the severity of PD \(^18,19\), and higher circulating 25OHD levels are significantly related to milder form of PD \(^20\). This observation has been confirmed in a European Caucasian population showing a significant decline in vitamin D levels in patients with PD compared with healthy controls \(^21\). In a post hoc analysis of more than 3000 participants in Finland, higher serum vitamin D level was associated with lower risk for PD \(^17\). Fahmy et al. found that there was an association between low vitamin D levels and PD \(^22\). It seems that the distribution of vitamin D receptors in the substantianigra is widely known to be affected in PD, and the involvement of this vitamin has been revealed in the regulation of tyrosine hydroxylase gene expression and consequently dopamine biosynthesis \(^17,23\). However, the epidemiological evidence of an association between vitamin D and Parkinson’s disease is limited. Therefore, considering the circumstances this study was taken for evaluation of 99mTc- HMPAO SPECT image findings and vitamin D status with clinical staging of Parkinson’s disease.

**Methods:**

Study design, population and settings:

This study was carried out in the Department of Neurology at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh, from July 2021 to June 2022. The study included 66 patients with Parkinson’s disease (PD) . Subjects were selected based on inclusion and exclusion criteria. The patient was incorporated after receiving written approval. Aged 18 years or older, the included patients underwent a neurologist’s examination, and Parkinson’s disease was diagnosed clinically by MDS clinical diagnostic
criteria. Patients with parkinsonism other than Parkinson's disease, osteoporosis or taking a vitamin D supplement, pregnant women or lactating mothers, carcinoma, chronic kidney disease, chronic liver disease, and hypoparathyroidism were all excluded from the study. The study protocol received approval from the ethical council of the Sir Salimullah Medical College in Dhaka, Bangladesh.

A total of 66 patients with Parkinson’s disease attending the outpatient department and indoor department of neurology at Sir Salimullah Medical College Mitford Hospital were enrolled in this study. The patient’s parkinsonism was diagnosed by the primary physician in the outdoor and indoor departments. Then patients with Parkinson’s disease were diagnosed clinically by the researcher himself using MDS clinical diagnostic criteria for Parkinson’s disease. Each participant provided written, informed consent. Then patients were subjected to a detailed neurological examination, and a modified Hoehn and Yahr (H & Y) scale was used for the clinical staging. Then, serum vitamin D levels were measured for all the patients using the enzyme-linked immunosorbent assay (ELISA) technique. Venous blood samples were collected and then centrifuged to get serum. The quantitative measurement of total 25-OH vitamin D3 in serum was done using the competitive immunoassay technique (Advia CentaurR XPT Immunoassay System, Siemens). After that, all the patients underwent a SPECT scan at the Institute of Nuclear Medicine and Allied Sciences, Dhaka Medical College Hospital campus, Dhaka. A brain perfusion study was performed 30 min after intravenous administration of a 10 mci dose of 99 mTc Medi-Exametazime (HMPAO). Dynamic sequential SPECT images were taken from the vertex through the skull base for 30 minutes in 28 seconds/frame, Matrix: 128×128. Image interpretation was done by visual and quantitative analysis in transaxial, coronal, and sagittal slices by the Siemens-Symbia T16 dual headed SPECT-CT. Semi quantitative analysis was performed by comparing uptake in the area under investigation with uptake in the area unaffected by the disease process. The cerebellum is pathologically relatively spared in Parkinson’s disease, and therefore it is usually used as the reference region in SPECT studies in Parkinson’s disease. We expressed HMPAO uptake for each region as the ratio of uptake in that region to that in the cerebellum. All the collected information was stored in separate data records.

Data collection and laboratory procedures:
Data on the patient’s sociodemographics, clinical features, stroke risk factors, and pertinent laboratory tests will be performed and recorded when the patient is included in the study.

All information was collected and documented, including demographic data (age and gender), DSA and MRA were given for each case; the neurorlogist was blind to the modality of angiography; and the order of DSA and MRA results were randomized. Case Report Forms were used to collect and record all of the data (CRF).

Data management and analysis:
Data were collected, tabulated, and analyzed by SPSS version 24.0. Socio-demographic characteristics, laboratory parameters, and 99mTc-HMPAO SPECT Imaging findings were reported. Continuous data were expressed as mean and standard deviation, and categorical data were expressed as frequency and percentage. Associations were assessed by student t-tests and one-way ANOVA tests for continuous variables, where applicable. Probability (p) values of < 0.05 were considered statistically significant. The correlation was seen by Pearson’s correlation coefficient test.

Results:
This study was a cross-sectional study conducted in Department of Neurology, Sir Salimullah Medical College. A total of 66 patients diagnosed to have PD by the generally accepted clinical criteria were included in this study.

Table-4.1
Distribution of socio-demographic characteristics among the patients with Parkinson’s disease (PD) (n=66).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency N</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>11</td>
<td>16.7</td>
</tr>
<tr>
<td>61-70</td>
<td>14</td>
<td>21.2</td>
</tr>
<tr>
<td>70-80</td>
<td>34</td>
<td>51.5</td>
</tr>
<tr>
<td>&gt;80</td>
<td>7</td>
<td>10.6</td>
</tr>
<tr>
<td>Age Mean ±SD</td>
<td>71±8.72</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>59.1</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>40.9</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>36</td>
<td>54.5</td>
</tr>
<tr>
<td>Urban</td>
<td>30</td>
<td>45.5</td>
</tr>
</tbody>
</table>

More than half of the patients with PD were from the age group above 70 years(51.5%) and the mean age was 71±8.72 years and majority of the patients with PD were male (59.1%),54.5% patients were from rural area and 45.5% patients were from urban area (Table-I).
Table-II
Distribution of co-morbidities, family history and duration of PD among the study population (n=66)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency N</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of PD(in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>5.74±2.22</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>14</td>
<td>21.2</td>
</tr>
<tr>
<td>HTN</td>
<td>16</td>
<td>24.2</td>
</tr>
<tr>
<td>Family history of PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>9.1</td>
</tr>
<tr>
<td>No</td>
<td>60</td>
<td>90.9</td>
</tr>
<tr>
<td>History of exposure to insecticides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>7.5</td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>92.5</td>
</tr>
</tbody>
</table>

The mean duration of PD was 5.74±2.22 years and 24.2% and 21.2% of the patients had HTN and DM respectively. About 9.1% were reported to have a family history of Parkinson’s disease in their family and 7.5% have been exposed to some sort of insecticides (Table II).

Figure-1: Distribution of cardinal symptoms among the PD patients in addition of bradykinesia (n=66)

The most common symptoms were tremor (78.8%) along with bradykinesia. Rigidity and postural instability was observed in 60% and 30% of the patients respectively (Figure 1).

Table-III
Exposure to sun and 7 days dietary recall chart of vitamin –D rich foods (n=66)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with normal vitamin-D level(n=26)</th>
<th>Patients with vitamin-D insufficiency/deficiency (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sun exposure &gt; 30 minutes/day</td>
<td>21(80.8)</td>
<td>22(55)</td>
<td>0.032</td>
</tr>
<tr>
<td>sun exposure &lt; 30 minutes/day</td>
<td>5(19.2)</td>
<td>18(45)</td>
<td></td>
</tr>
<tr>
<td>Vitamin-D rich foods(_&gt;2 days per week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat</td>
<td>14(53.8)</td>
<td>18(45)</td>
<td>0.482</td>
</tr>
<tr>
<td>Organ meat</td>
<td>18(69.2)</td>
<td>17(42.5)</td>
<td>0.033</td>
</tr>
<tr>
<td>Fish</td>
<td>16(61.5)</td>
<td>15(37.5)</td>
<td>0.056</td>
</tr>
<tr>
<td>Milk and dairy products</td>
<td>16(61.5)</td>
<td>17(42.5)</td>
<td>0.131</td>
</tr>
<tr>
<td>Eggs</td>
<td>14(53.8)</td>
<td>13(32.5)</td>
<td>0.085</td>
</tr>
<tr>
<td>&gt;_2 vitamin-D rich foods&gt;2 days within last 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20(76.9)</td>
<td>19(47.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>No</td>
<td>6(23.1)</td>
<td>21(52.5)</td>
<td></td>
</tr>
</tbody>
</table>

*p-value obtained by chi-square test

Figure-2: Distribution of the patients of Parkinson’s disease according to clinical stages. (n=66)

Out of 66 PD patients, 12 patients were diagnosed with stage-1 and 1.5 (stage-1:4.5% and stage1.5-13.6%), 36 patients were diagnosed with stage-2 and 2.5 (stage-2:30.3% and stage-2.5:24.2%), 11 patients were diagnosed with stage-3(16.7%), 5 patients were diagnosed with stage-4 (7.6%) and 2 patients were diagnosed with stage-5(3.0%) (Figure 2).

Figure-3 Distribution of 25(OH) D level among the PD patients (n=66)

Among the PD patients majority of the patients had vitamin D insufficiency (n=33,50%) and 10.6% (n=7) had vitamin D deficiency .39.4%(n=26) was reported to have vitamin D within normal level (Figure 3).
PD patients who were less exposed to sun (45%) and lower intake of vitamin-D rich foods (52.5%) had higher in vitamin-D insufficiency/deficiency in compared to patients with normal vitamin-D level (Figure 3).

**Figure-4** Distribution of serum 25 (OH) D level among the patients of different clinical stages of PD (n=66)

Figure 4 depicts the number of PD in each clinical stage with vitamin D insufficiency, deficiency and normal level. Out of 12 patients with PD stage 1-1.5, 3 had vitamin D insufficiency and 9 had normal level of vitamin D. Out of 36 patients with PD stage 2-2.5, 22 had vitamin D insufficiency and 14 had normal level of vitamin D. Among stage 3 PD patients, 2, 6, 3 had vitamin D deficiency, insufficiency and normal respectively. Moreover among stage 4 and 5, 3 and 2 patients had vitamin D deficiency respectively.

It is seen from figure-5 that the 25(OH) D levels has a inversely proportional relationship with the severity in different clinical stages of PD patients. The median (IQR) vitamin D level (expressed in ng/ml) was 30(24-31), 28(25.5-31), 28(27-29), 28.7(25.4-31), 24.9(24-28.8), 19.8(19-21.9) and 19(18.5-19.5) for stage-1 stage-1.5, stage-2, stage-2.5, stage-3, stage-4 and stage-5 respectively.

Logistic regression analysis revealed that age, sex and sun exposure <30 minutes/day did not contribute significantly to the serum vitamin D status, whereas lower intake of vitamin D rich foods affected significantly as negative factors (Table IV).

**Table-V: Mean ±SD of serum vitamin 25(OH)D level among the patients with different clinical stages of PD (n=66)**

<table>
<thead>
<tr>
<th>Clinical stage of PD</th>
<th>25(OH)D level Mean ±SD(in ng/ml)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-1</td>
<td>27.8±3.96</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage-1.5</td>
<td>27.6±3.31</td>
<td></td>
</tr>
<tr>
<td>Stage-2</td>
<td>27.5±3.57</td>
<td></td>
</tr>
<tr>
<td>Stage-2.5</td>
<td>26.4±3.16</td>
<td></td>
</tr>
<tr>
<td>Stage-3</td>
<td>25.9±3.53</td>
<td></td>
</tr>
<tr>
<td>Stage-4</td>
<td>20.6±2.41</td>
<td></td>
</tr>
<tr>
<td>Stage-5</td>
<td>19.5±1.07</td>
<td></td>
</tr>
</tbody>
</table>

*p-value obtained by one way ANOVA

From table-III it was observed that the mean 25(OH) D level was the higher in the earlier stages of patients of PD, which is (stage-1-2.5:27.8-26.4 ng/ml) and lower in more advanced stages of PD (stage-4-5:20.6-19.5 ng/ml). Stages of PD was significantly associated with the level of 25(OH) D level (p-value: 0.001) (Table V).
Table VI: Mean (SD) regional cerebral blood flow measured by HMPAO SPECT in different cerebral regions.

<table>
<thead>
<tr>
<th>Cerebral regions</th>
<th>Right Mean ±SD</th>
<th>Left Mean ±SD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td><strong>0.83±0.07</strong></td>
<td>0.82±0.08</td>
<td>0.473</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.81±0.06</td>
<td>0.82±0.04</td>
<td>0.983</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.77±0.12</td>
<td>0.76±0.10</td>
<td>0.446</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.71±0.06</td>
<td>0.72±0.07</td>
<td>0.500</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.75±0.12</td>
<td>0.74±0.10</td>
<td>0.221</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.74±0.22</td>
<td>0.73±0.23</td>
<td>0.967</td>
</tr>
</tbody>
</table>

*p-value obtained by student t-test.

**Ratio of regional cerebral blood flow in comparison to cerebellum

There were no significant differences between HMPAO uptake in the right and left hemispheres in all the regions (Table VI).

Table VII: Comparisons of mean (SD) regional cerebral blood flow measured by HMPAO SPECT in different regions with clinical stages of PD.

<table>
<thead>
<tr>
<th>Cerebral regions</th>
<th>Stage-1-1.5 Mean±SD</th>
<th>Stage-2-2.5 Mean±SD</th>
<th>Stage -3 Mean±SD</th>
<th>Stage-4-5 Mean±SD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td><strong>0.86±0.06</strong></td>
<td>0.83±0.08</td>
<td>0.77±0.05</td>
<td>0.70±0.05</td>
<td>0.006</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.84±0.04</td>
<td>0.82±0.55</td>
<td>0.81±0.09</td>
<td>0.76±0.14</td>
<td>0.254</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.80±0.08</td>
<td>0.76±0.11</td>
<td>0.73±0.13</td>
<td>0.68±0.15</td>
<td>0.238</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.74±0.06</td>
<td>0.72±0.06</td>
<td>0.67±0.06</td>
<td>0.67±0.56</td>
<td>0.995</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.75±0.11</td>
<td>0.77±0.09</td>
<td>0.71±0.13</td>
<td>0.67±0.11</td>
<td>0.773</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.72±0.24</td>
<td>0.76±0.22</td>
<td>0.71±0.25</td>
<td>0.72±0.15</td>
<td>0.922</td>
</tr>
</tbody>
</table>

*p-value obtained by one-way ANOVA.

**Ratio of regional cerebral blood flow in comparison to cerebellum

From table-V it is seen that as the clinical stage of PD advanced from stages 1-5, the HMPAO uptake reduced significantly in the basal ganglia (p=0.006). There was no significant reduction in the occipital, parietal, frontal, temporal region and thalamus (Table VII).

Table VIII: Comparisons of mean (SD) regional cerebral blood flow measured by HMPAO SPECT in basal ganglia with clinical stages of PD.

<table>
<thead>
<tr>
<th>Clinical stage of PD</th>
<th>Ratio of regional cerebral blood flow in comparison to cerebellum (Mean ±SD)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-1-1.5</td>
<td>0.86±0.06</td>
<td>0.006</td>
</tr>
<tr>
<td>Stage-2-2.5</td>
<td>0.83±0.08</td>
<td></td>
</tr>
<tr>
<td>Stage -3</td>
<td>0.77±0.05</td>
<td></td>
</tr>
<tr>
<td>Stage-4-5</td>
<td>0.70±0.05</td>
<td></td>
</tr>
</tbody>
</table>

*p-value obtained by one way ANOVA

From table-4.8 it is seen that as the clinical stage of PD advanced from stages 1-5, the HMPAO uptake reduced significantly in the basal ganglia (p=0.006) (Table VIII).
From figure-6, It is observed that there was an insignificant correlation between the 25(OH) D level and the regional blood flow in basal ganglia (p-value:0.054).

Discussion:
In recent years, PD has undergone the fastest growth in prevalence and disability among neurological disorders, and it has become one of the leading causes of disability worldwide. The Global Burden of Disease study reported that incident cases of PD were 1.02 million in 2017 (James et al. 2018). The aim of this study was to assess the influence of different clinical stages of Parkinson’s disease on the vitamin D levels and correlation 99mTc-HMPAO SPECT Imaging findings with different clinical stages.

In the present study it was observed that most of the study population was above the age of 50 years with highest number of patients in the age group 70-80 years and male (59.1%) were predominantly reported to have Parkinson’s disease than females (40.9%) in this study. The incidence of Parkinson’s disease increases steeply with age especially after age 60 years, and men have higher incidence than women, except for ages 80-99 years making age one of the crucial risk factor for the disease. PD data collected from global burden of disease 2019 also agreed with the findings of our study where it was reported that the largest number of PD patients was seen in the groups aged more than 65 years, and the percentage rapidly increased in the population aged more than 80 years.

Family history is another strong risk factor for development of PD. Balestrino et al. reported that familial forms of PD accounts for only 5%–15% of patients with Parkinson’s disease. A cross-sectional study among 100 PD patients reported 6.3% of the PD reported family history of Parkinson’s disease, 23.9% reported diabetes mellitus and 21.7% reported history of hypertension among Parkinson’s disease patients (Sarkar et al. 2019). The current study was in agreement with these findings since 9.1% of study population reported a family history of PD, 24.2% and 21.2% of the patients had HTN and DM respectively.

In this study most of the patients were in stage 1 (72.6%), followed by stage 3 (16.7%), and stage 4-5 (10.6%). In a previous clinical study of 135 patients, 55.56% were in stage 1-2, 31.11% patients were in stage 3 and 13.33% patients were presented at stage 4-5.

In our study, majority of patients had vitamin D insufficiency (n=33, 50%) and deficiency. Previously in a double-blinded cross-sectional study among 109 PD 38.4% of the patients showed deficiency level of 25(OH)D and 72.8% showed 25(OH)D level insufficiency. This study observed that PD patients who were less exposed to sun (45%) and lower intake of vitamin-D rich foods (52.5%) had higher in vitamin-D insufficiency/deficiency in compared to patients with normal vitamin-D level. In a previous case-control study PD patients who were less exposed to sun had decrease vitamin D level. In the present study, we observed that the more advanced stage of PD was significantly associated with lower level of 25OHD (stage-1-27.8ng/ml vs stage-5-19.5ng/ml). On the other hand, Fahmy et al. found that mean serum vitamin D level was significantly lower in PD patients compared to healthy controls (p-value= 0.029) however no significant difference was found between disease stages as regards to mean serum 25 vitamin D level (p-value= 0.372).

In the current study it was observed that HMPAO SPECT indicated a significant decrease in regional blood flow in the basal ganglia (p-value: 0.006) with the advancement of PD from stages1-5. This is consistent with a cross-sectional study conducted among 21 Parkinson patients and 11 controls were it was reported that the uptake of HMPAO by the basal ganglia (p-value: 0.004) was significantly decreased in the PD patients compared with normal controls. In contrast another study conducted among 16 Parkinson’s patients failed to demonstrate consistent alteration in blood flow in the basal ganglia (Spampinato et al. 1991). The discrepancies in the findings may be due to the fact that basal ganglia uptake was measured visually resulting on underestimation of the reduction in uptake. A study conducted in South Korea among 10 Parkinson’s disease patients showed a significant reduction in ratio of uptake of HMPAO of frontal region (p<0.05) which was not similar with the finding in the present study. In this study, we found insignificant correlation between serum vitamin D level and regional cerebral blood flow in parkinson’s disease patients. But there is a previous study, where positive correlation between vitamin D deficit and impaired regional cerebral blood flow was seen in neurodegenerative disease.

Conclusion:
This study concludes that serum vitamin D level was inversely associated to severity of PD.99mTc HMPAO SPECT image findings showed significantly decreased regional cerebral blood flow in basal ganglia in advanced stages of PD patients. No significant correlation was found between serum vitamin D level and regional cerebral blood flow in basal ganglia.
Limitations:
All samples were collected from a single centre. DaTscan based SPECT is now widely used for detection of PD. Which is not available in our country.

Data Availability:
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

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

Funding:
Funding from research grant from Bangladesh Medical Research Council (BMRC) was received for this study.

Ethical consideration:
The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College. The confidentiality and anonymity of the study participants were maintained.

Acknowledgments:
The authors were grateful to the staffs of the Department of Neurology in Sir Salimullah Medical College Mitford Hospital, Bangladesh and Institute of Nuclear Medicine and Allied Sciences, Dhaka Medical College Hospital, Dhaka, Bangladesh.

References:
PATTERN OF BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN IN A TERTIARY CARE CENTRE OF BANGLADESH

DURBA HALDER1, MD. YOUSUF ALI2, JANESAR RAHAT FAYSAL3, FARHANA NAYEEM4, ABDUR ROUF4, NABEELA TASNIM4

Abstract:

Background: Incidences of osteoporosis and diabetes have dramatically increased in recent decades and they have become one of the major health problems. Osteoporosis is a skeletal condition characterized by decreased density (mass/volume) of normally mineralized bone. The reduced bone density leads to decreased mechanical strength, thus making the skeleton more likely to fracture. This study aimed to assess the pattern of bone mineral density in Bangladeshi postmenopausal women.

Methods: This descriptive cross-sectional study was conducted at the Department of medicine, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh. The study duration was 1 year; from January 2021 to January 2022. A total of 100 women attending the Outpatient Department of Medicine were included in this study as per inclusion criteria. A convenience sampling technique was applied for this study. A pre-formed questionnaire was used for necessary data collection containing general characteristics, presence or absence of risk factors, BMI status, and BMD. Qualitative data were analyzed by Chi-square test & quantitative data were analyzed by student’s t-test. All statistical analyses were performed by using SPSS Software version 20. Informed written consent was obtained from all subjects.

Results: In this study, a maximum (of 36, 36.0%) patients belonged to the age group of 50-59 years, followed by (33, 33.0%) 60-69 years age group. Regarding education, most patients (70, 70.0%) had a secondary school certificate or below that level, followed by higher secondary level (25, 25.0%). Concerning years since menopause, 27.0% of patients had menopause since 20-29 years, followed by 25.0% of subjects had menopause since 10-19 years. Regarding BMI, 20.0% of patients had <23 kg/m², 24.0% 23.1-25.99 kg/m², 25.0% 26-29.99 kg/m², and 31.0% ≥30 kg/m². Concerning risk factors, 45.0% of patients had a history of taking medication containing estrogen, 40.0% of patients had DM, and 18.0% of patients had a history of taking thyroid hormone. Prevalence of osteopenia and osteoporosis was seen in 33.0% and 8.0% of patients respectively concerning BMD proximal femur and spine DXA. Moreover, concerning DXA at the lumbar spine, hip, and total body osteopenia and osteoporosis were 50.0% and 30.0% respectively.

Conclusion: This study suggests that advancing age and menopausal condition are an important risk factor for the occurrence of low BMD.

Keywords: Osteopenia, Osteoporosis, BMD, BMI

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**Introduction:**

Osteoporosis is the most prevalent disease in menopausal women, and is strongly associated with low quality of life. Osteopenia is a term to define bone density that is not normal but also not as low as osteoporosis. By definition from the World Health Organization osteopenia is defined by bone densitometry as a T score of *1 to “2.5.* Osteoporosis is a skeletal condition characterized by decreased density (mass/volume) of normally mineralized bone. The reduced bone density leads to decreased mechanical strength, thus making the skeleton more likely to fracture. Postmenopausal osteoporosis (Type I) and age-related osteoporosis (Type II) are the most common primary forms of bone loss seen in clinical practice. Secondary causes of osteoporosis include hypercortisolism, hyperthyroidism, hyperparathyroidism, alcohol abuse, and immobilization. Osteoporosis and its related complications are one of the major healthcare problems around the globe. It is estimated that osteoporosis affects about 200 million women worldwide and is a substantial cause of morbidity and mortality. Fifty-four percent of postmenopausal white women are osteopenic and 30% are osteoporotic, and by the age of 80, 27% of women are osteopenic and 70% are osteoporotic. Atherosclerotic vascular disease (AVD) and osteoporosis or osteopenia are common conditions among postmenopausal women and appear to be linked in a manner that is not fully understood. Osteoarthritis (OA) and osteoporosis (OP) are two age-related degenerative diseases, both common in middle-aged and older women. The generally held opinion is that the incidence of OP is inversely associated with the incidence of OA. However, during total hip arthroplasty (THA) it is not uncommon to encounter postmenopausal female patients who have fragile cancellous bone both in the proximal femur and in the acetabulum. Osteoporosis is a condition in which the ratio of bone mass to its volume is decreased. When bone tissue is reduced, the likelihood of fracture increases. Low bone mass with an increased risk of subsequent fracture is one of the most prevalent community health problems. The amount of bone mineral present in the skeleton of adult women is primarily a function of the amount gained during the phase of skeletal development and maturation. Although skeletal development begins before birth (particularly during the last trimester), many factors influence a woman’s peak bone mass: these include genetics, nutritional status, exercise, and hormonal factors. In adulthood, skeletal mass is 10–15% higher in men than in women. There are several factors affecting the prevalence of osteoporosis in postmenopausal women, such as age, age at menarche, duration of menopause, dietary or nutritional intakes, lifestyle and level formal education. Although the risk of fracture is higher in patients with a low bone mass, the best predictor of an osteoporotic fracture is a previous fracture either in the vertebrae or in the hips. Hence, 20% of women who have had a recent vertebral fracture will have a new fracture within a year. Having had one or more vertebral fractures has been related to poorer quality of life, and higher long-term mortality. Osteoporosis is a major public health problem through its association with age-related fractures. Although fracture risk at any skeletal site depends upon a complex interaction between bone strength and trauma, recent epidemiologic studies confirm that bone density is currently the best single predictor of future fracture. This study aimed to assess the pattern of bone mineral density in Bangladeshi postmenopausal women.

**Methods:**

This descriptive cross-sectional study was conducted at the Department of medicine, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh. The study duration was 1 year; from January 2021 to January 2022. A total of 100 women attending the Outpatient Department (OPD) of Medicine were included in this study as per inclusion criteria. A convenience sampling technique was applied for this study. Healthy PMW aged above 50 years of age and above with a history of complete cessation of menstruation over more than 1 year and bone density in women who consulted a participating physician when a densitometer was available in their practice (usually 1+wk) and who were able to give a detailed fall history were included for the study. The patients below 50 years of age and Menstruating women are excluded from the study. All data were kept confidential and used only for the study purpose. A pre-formed questionnaire was used for necessary data collection containing general characteristics, presence or absence of risk factors, BMI status, and BMD. Qualitative data were analyzed by Chi-square test & quantitative data were analyzed by student’s t-test. All statistical analyses were performed by using SPSS Software version 22. Informed written consent was obtained from all subjects.
Results:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>36</td>
<td>36.0</td>
</tr>
<tr>
<td>60-69</td>
<td>33</td>
<td>33.0</td>
</tr>
<tr>
<td>70-79</td>
<td>24</td>
<td>24.0</td>
</tr>
<tr>
<td>≥80</td>
<td>07</td>
<td>7.0</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school and below</td>
<td>70</td>
<td>70.0</td>
</tr>
<tr>
<td>Higher Secondary</td>
<td>25</td>
<td>25.0</td>
</tr>
<tr>
<td>Graduate</td>
<td>05</td>
<td>5.0</td>
</tr>
<tr>
<td>Years since menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>22</td>
<td>22.0</td>
</tr>
<tr>
<td>10-19</td>
<td>25</td>
<td>25.0</td>
</tr>
<tr>
<td>20-29</td>
<td>27</td>
<td>27.0</td>
</tr>
<tr>
<td>≥30</td>
<td>26</td>
<td>26.0</td>
</tr>
</tbody>
</table>

In this study, a maximum (of 36, 36.0%) patients belonged to the age group of 50-59 years, followed by (33, 33.0%) and 60-69 years age group. Regarding education, most patients (70, 70.0%) had a secondary school certificate or below that level, followed by higher secondary level (25, 25.0%). Concerning years since menopause, 27.0% of patients had menopause since 20-29 years, followed by 25.0% of subjects had menopause since 10-19 years. [Table 1]

![Figure 1: Distribution of subjects according to BMI (N=100).](image)

Regarding BMI, 20.0% of patients had <23 kg/m², 24.0% 23.1-25.99 kg/m², 25.0% 26-29.99 kg/m², and 31.0% ≥30 kg/m². [Figure 1]

Table II

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal H/O osteopenia</td>
<td>11</td>
<td>11.0</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>18</td>
<td>18.0</td>
</tr>
<tr>
<td>Cortisone</td>
<td>03</td>
<td>3.0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>17</td>
<td>17.0</td>
</tr>
<tr>
<td>Estrogen</td>
<td>45</td>
<td>45.0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>00</td>
<td>0.0</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>00</td>
<td>0.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Concerning risk factors, 45.0% of patients had a history of taking medication containing estrogen, 40.0% of patients had DM, 18.0% of patients had a history of taking a thyroid hormone, and in 11.0% of patients there was a positive maternal history of osteopenia. [Table 2]

Table III

<table>
<thead>
<tr>
<th>Method of diagnosis</th>
<th>Osteopenia Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD proximal femur</td>
<td>33.0% 8.0%</td>
</tr>
<tr>
<td>and spine-DXA</td>
<td></td>
</tr>
<tr>
<td>DXA at the lumbar spine, hip, and total body</td>
<td>50.0% 30.0%</td>
</tr>
</tbody>
</table>

In this study, the prevalence of osteopenia and osteoporosis was seen in 33.0% and 8.0% of patients respectively concerning BMD proximal femur and spine DXA. Moreover, concerning DXA at the lumbar spine, hip, and total body osteopenia and osteoporosis were 50.0% and 30.0% respectively. [Table 3]

Discussion:

This study showed a maximum (of 36, 36.0%) patients belonged to the age group of 50-59 years, followed by (33, 33.0%) 60-69 years age group. Regarding education, most patients (70, 70.0%) had a secondary school certificate or below that level, followed by higher secondary level (25, 25.0%). Concerning years since menopause, 27.0% of patients had menopause since 20-29 years, followed by 25.0% of subjects had menopause since 10-19 years. The average age of the women was 64 years (range 50–87 years) according to...
a study by Sanfélix-Genovés J, Reig-Molla B. et al. In another study, Siris ES, Miller PD et al. observed that the mean (SD) age was 64.5 (9.3) years (range, 50–104 years) which was quite relatable to the present study. Osteoporosis was determined in 10.6% and 16.2% of women with menopause duration of 0–3 years and 4–7 years, respectively, whereas this rate was 31.9% in women with menopause duration of over 7 years (p = 0.001). The percentages for osteopenia remained constant among the three different menopause durations (0–3 years: 37.2%, 4-7 years: 42.1%, and >7 years: 40.9%) in a study conducted by Demir B, Haberal A et al. Another study done by Bijelic R, Milicevic S et al. found that, the prevalence of osteoporosis was significantly greater among women with low educational levels than women with high educational status (18.0% vs 3.8% P < 0.0001). Concerning risk factors, 45.0% of patients had a history of taking medication containing estrogen, 40.0% of patients had DM, 18.0% of patients had a history of taking medication containing estrogen, and 11.0% of patients had similar degrees of osteoporosis. Moreover, concerning DXA at the lumbar spine, hip, and total body osteopenia and osteoporosis were 50.0% and 30.0% respectively and this result was quite relatable to another study conducted by Siris ES, Miller PD et al. 

Conclusion: This study concluded that osteoporosis has become more prevalent in postmenopausal women and an important risk factor for the occurrence of low BMD.

Limitation of the study: Although sample size was calculated statistically, this was small in relation to the huge number of population of our country. It was a single-center study done in tertiary care hospital.

Data Availability: The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

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

Funding: No specific funding was received for this study.

Ethical consideration: The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College. The confidentiality and anonymity of the study participants were maintained.

Acknowledgments: The authors were grateful to the staffs of the Outpatient Department (OPD) of Medicine in Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh.

References:


COMPARISON BETWEEN DIGITAL SUBTRACTION ANGIOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY IN THE INVESTIGATION OF ACUTE ISCHEMIC STROKE IN A TERTIARY CARE HOSPITAL IN BANGLADESH

MUHAMMAD JAMIL AHMED¹, AMINUR RAHMAN², ZAHED ALI³, ABUL HASNAT MD. RUSSEL³ SHAHJADA MOHAMMAD DASTEGIR KHAN³, MOHAMMAD MOSHIUR RAHMAN³, BIPLAB PAUL³, PALLAB KANTI SAHA² MD. ALAMGIR HOSSAIN⁵, AJAY KUMAR AGARWALLA⁶

Abstract:

Background: Ischemic stroke is the most common type of stroke. Digital subtraction angiography (DSA) is a definite method for demonstrating vascular lesions, while High-resolution Magnetic Resonance Angiography (MRA) imaging has recently been introduced as a promising diagnostic modality in intra-cranial artery disease. This study aimed to compare between DSA and MRA as the modality of investigation of ischemic stroke. Methods: This quasi-experimental study was conducted at the department of Neurology, Sir Salimullah Medical College & Mitford Hospital, Dhaka, for one year following ethical approval. Total of 30 patients with acute ischemic stroke were enrolled in this study. DSAs and MRAs of all patients were analyzed and reported by two experienced neurologists. Collected data will be recorded into the separate case-record form and analyzed by SPSS 24.

Results: The mean age of the studied respondents was 47.50±10.42 (SD) years with male predominance (63.3%). Among the male patients, 73.7% were smoker and female patients 81.8% were non-smoker. Among the total patients 80.0% had HTN and 73.3% DM, 24.1% had history of other cardio-vascular diseases and 36.7% of the patients had family history of stroke. Maximum patients had arm weakness (66.7%), leg weakness (60.0%), self-reported speech disturbance (53.3%) and dysphasia or dysarthria (53.3%). Hypertension and diabetes mellitus were present in 80% and 73.3% cases, respectively. For the majority of the patients the affected artery was MCA (Middle cerebral artery) and it was among 17 out of 30 patients. The aetiology based on TOAST diagnosis was similar by both MRA and DSA in 16 (out of 30). All the DSAs and 22 out 30 MRAs revealed abnormalities.

Conclusion: MRA has significant agreement with DSA to identify etiology of acute ischemic stroke. Hence, it is better to use MRA in ischaemic stroke considering its non-invasiveness and cost-effectiveness.

Key words: Digital Subtraction Angiography, Magnetic Resonance Angiography, Acute Ischemic Stroke.

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**Introduction:**

Over 10%, or 5.7 million deaths per year, are caused by strokes, which are the second biggest cause of mortality globally. Over the next several decades, more cases of stroke are expected to occur. Vigorous control of blood pressure has reduced stroke mortality in affluent nations, but the burden of stroke is still increasing because of an aging population. Furthermore, the rising stroke prevalence in middle-income countries is a direct result of longer life expectancies in developing nations. Among the two major types of stroke, hemorrhagic and ischemic. The ischemic stroke is more common, representing approximately 85% of all stroke cases, and has a much lower 30-day mortality rate at approximately 12%. In recent times, digital subtraction angiography (DSA) is being used for detection of type of lesion of occlusive arterial disease, but it is an invasive and time-consuming modality and the procedure needs to be performed by well experienced experts.

DSA can detect intracranial branch arterial lesions even in the absence of identifiable sources of embolism. DSA is the most cases can identify stroke in the young patients and critically assess stroke etiology. The popularity of DSA can be attributed to its good spatio-temporal resolution which is not easily matched by other acquisition techniques such as magnetic resonance imaging (MRI) and computed tomography (CT). Vascular abnormalities such as narrowing, blockage, or malformations can be visualized precisely in DSA. In addition, DSA is invasive and is readily available in interventional suites of modern intensive care units (ICUs). Minimal cost, low risks, and rapid acquisition time are other features in favor of DSA. DSA is a method of choice to visualize blood flow and guide endovascular interventions. DSA provides high-resolution spatio-temporal images that have mostly been used qualitatively through the manual review of raw gray scaled video.

On the other hand, magnetic resonance-angiography (MRA) is a method that improves imaging protocol in both diagnosis and clinical management. MRA can track the changes in the vessel lumen with time. Imaging of the vessels can reliably answer questions about the mechanism of the stroke, whether it is thrombotic, embolic or homodynamic. It also assesses the risk of future events by identifying whether there is occlusive arterial disease.

Localizing the exact site of occlusion and by determining the pathology underlying the stroke such as atherosclerosis or dissection. MRA can also identify other vascular lesions such as malformation, aneurysms and arterial compression. In addition to that, DSA is an invasive procedure with the risk of neurologic complications and radiation exposure. In contrast, MRA is an noninvasive, relatively less complicated method in acute phase of stroke, which provides early positive diagnosis of occlusive intracranial arterial disease that has a potentially important role in appropriate patient selection for intra-arterial fibrinolysis, by providing a relatively easy, non-invasive, time-efficient in screening procedure for the determination of the site of intracranial occlusion. So this study is designed to compare the usefulness between Digital Subtraction Angiography and Magnetic Resonance Angiography in the investigation of acute ischemic stroke in a tertiary Care hospital in Bangladesh.

**Methods:**

**Study design, population and settings:**

This study was carried out in the Department of Neurology at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh from July 2021 to June 2022. The study included 30 patients with acute ischemic stroke. According to inclusion and exclusion criteria, subjects were chosen. Following written consent, the patient was included. Aged e18years or older, the included patients underwent a neurologist’s examination, and acute ischaemia was clinically and CT scan / magnetic resonance imaging of the brain-evidently identified. Patients with Transient ischemic attack, intracerebral hemorrhage, primary or secondary brain tumor, any malignancy were all excluded from the study.

All of the patients had undergone clinical and neurological evaluation, electrocardiogram, hemogram, blood biochemistry, lipid profile, erythrocyte sedimentation rate, immunologic and coagulation testing and cranial computed tomography. These patients had also received high-resolution MRA and DSA within 7 days or less of the initial investigation. All collected information was stored in separate data record form.

The Sir Salimullah Medical College in Dhaka, Bangladesh, ethical committee gave its approval to the study protocol.

**Data collection and laboratory procedures:**

Standard imaging protocols was used where MRA was performed with a 1.5 T system with unenhanced 3D time-of-flight (TOF) multiple overlapping thin-slab acquisition (MOTSA) sequences, three-dimensional maximal intensity projection (MIP) images (TR/TE 33.3/3 ms, flip angle 20°, thickness=0.8 mm, matrix 256x192, field of view from 13x13 to 22x22 cm, 0 mm interval) with a smart preparation technique.
Intra-arterial 4-vessel selective DSA was performed via the femoral artery, starting with imaging of the aortic arch followed by selective injections of contrast material into both carotid and vertebral arteries. DSA (GE Medical Systems) was performed in the antero-posterior, lateral and oblique projections. Non-ionic contrast of low osmolarity (Iopamiron®, Schering) was administered in the common carotid and subclavian arteries (volume: 8 ml) and a rate of 4 ml/s in the internal carotid and vertebral arteries (6 ml). Hydrophilic coated guide wires and 4 or 5-F sheaths will be used. Sheaths were intermittently flushed with heparinized saline (5000 IU of heparin in 1000 ml of normal saline). Manual compression at the puncture site was usually performed for 10 minutes after the end of the procedure.

Each patient was referred to an experienced neurologist for diagnosis of acute ischaemic stroke by symptom and CT scan and classified according to TOAST criteria. Results of DSA and MRA were given for each case; neurologists were blind to the modality of angiography and the order of DSA and MRA results were randomized. Treatment of each patient (anti-platelet drugs/ anticoagulants/ other) was defined, considering clinical and laboratory investigation as well as results of MRA or DSA. Therefore, the two methods of neuro-imaging was compared the finding including arterial occlusions, stenosis, dissection, aneurysm in a descriptive way.

Data management and analysis:
After collection of all the required data, these were checked, verified for consistency and tabulated using the SPSS version 24. Statistical significance was set as 95% confidence level at 5% acceptable error level. Socio-demographic, clinical and neuroimaging profile were reported. Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and percentage. To determine the level of agreement between MRA and DSA to detect stenosis, kappa statistic was done. Statistical significance was set as 95% confidence level at 5% acceptable error level (p<0.05). Data were analyzed by the SPSS 24.

Results:
The majority of the studied patients (66.7%) were belonged to 41-60 years of age group. The mean ages for the studied participants were 47.50±10.42 (SD) year’s age. Regarding gender distribution, 63.3% (n=19) of the studied patients were male and 36.7% (n=11) were female.

Among the male patients, 73.7% were smoker and 26.3% were non-smoker whereas among the female patients 18.2% were smoker and 81.8% were non-smoker. A significant difference was seen in terms of smoking history when compared based on gender (p<0.05) (Table-I).

<table>
<thead>
<tr>
<th>Smoking habit</th>
<th>Male (n=19)</th>
<th>Female (n=11)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>14 (73.7)</td>
<td>2 (18.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>5 (26.3)</td>
<td>9 (81.8)</td>
<td></td>
</tr>
</tbody>
</table>

*p-value was determined by chi-square test

In terms of co-morbidities and risk-factors, 80.0% of the total patients had HTN and 73.3% had DM, 24.1% had history of other cardio-vascular diseases, 36.7% of the patients had family history of stroke (Table II).

<table>
<thead>
<tr>
<th>Co-morbidities and risk factors</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>24</td>
<td>80.0</td>
</tr>
<tr>
<td>DM</td>
<td>22</td>
<td>73.3</td>
</tr>
<tr>
<td>Other cardio-vascular diseases</td>
<td>7</td>
<td>24.1</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>11</td>
<td>36.7</td>
</tr>
</tbody>
</table>

Among the clinical presentations, arm and leg paresis was the most common and they were present among 83.3% of the total patients followed by decreasing order arm weakness (66.7%), leg weakness (60.0%), self-reported speech disturbance (53.3%), dysphasia or dysarthria (53.3%), facial weakness (36.7%), arm and leg paresthesia (23.3%), hemiparetic or ataxic gait (16.7%), eye movement abnormality (10.0%) and visual field defects (10.0%) (Table III).

<table>
<thead>
<tr>
<th>Clinical presentations*</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm weakness</td>
<td>20</td>
<td>66.7</td>
</tr>
<tr>
<td>Leg weakness</td>
<td>18</td>
<td>60.0</td>
</tr>
<tr>
<td>Self-reported speech disturbance</td>
<td>16</td>
<td>53.3</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>11</td>
<td>36.7</td>
</tr>
<tr>
<td>Arm paresthesia</td>
<td>7</td>
<td>23.3</td>
</tr>
<tr>
<td>Leg paresthesia</td>
<td>7</td>
<td>23.3</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>23.3</td>
</tr>
<tr>
<td>Non-orthostatic dizziness</td>
<td>9</td>
<td>30.0</td>
</tr>
<tr>
<td>Arm paresis</td>
<td>25</td>
<td>83.3</td>
</tr>
<tr>
<td>Leg paresis</td>
<td>25</td>
<td>83.3</td>
</tr>
<tr>
<td>Dysphasia or dysarthria</td>
<td>16</td>
<td>53.3</td>
</tr>
<tr>
<td>Hemiparetic or ataxic gait</td>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>Eye movement abnormality</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>Visual field defects</td>
<td>3</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Multiple responses considered
Table: 4.4 showing the affected territories, MRA findings, DSA findings and TOAST diagnosis considering MRA and DSA findings according to cases. For the majority of the patients the affected artery was MCA (Middle cerebral artery) and it was among 17 out of 30 patients. TOAST diagnosis was similar for both MRA and DSA in 17 (out of 30). All the DSAs and 22 out 30 MRAs revealed abnormalities.

Table IV: Distribution of the studied patients by the affected territories, MRA findings, DSA findings and TOAST diagnosis considering MRA and DSA findings (n=30)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Affected area</th>
<th>MRA findings</th>
<th>DSA findings</th>
<th>TOAST by MRA</th>
<th>TOAST by DSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>R MCA</td>
<td>R MCA branch stenoses</td>
<td>R MCA branch occlusion#</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>02.</td>
<td>R MCA</td>
<td>R clICA dissection</td>
<td>R clICA dissection, R iiICA occlusion</td>
<td>4(D)</td>
<td>4(D)</td>
</tr>
<tr>
<td>03.</td>
<td>L MCA</td>
<td>L MCA stenoses</td>
<td>L iCA, LAC stenosis, LMCA occlusion#</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>04.</td>
<td>LICA</td>
<td>L clICA occlusion</td>
<td>L clICA FMD, LiICA, LS occlusion</td>
<td>1</td>
<td>4 (FMD)</td>
</tr>
<tr>
<td>05.</td>
<td>R ICA, L PCA</td>
<td>Normal</td>
<td>Diffuse lesion in cortical arteries</td>
<td>5</td>
<td>4 (V)</td>
</tr>
<tr>
<td>06.</td>
<td>BA</td>
<td>L MCA branch stenoses</td>
<td>LVA dissection</td>
<td>5</td>
<td>4 (D)</td>
</tr>
<tr>
<td>07.</td>
<td>L MCA</td>
<td>L MCA stenoses</td>
<td>L clICA dissection and LMCA branch occlusion</td>
<td>1</td>
<td>4 (D)</td>
</tr>
<tr>
<td>08.</td>
<td>L MCA</td>
<td>L clICA dissection, L iiICA occlusion</td>
<td>L clICA dissection, L iiICA occlusion</td>
<td>4 (D)</td>
<td>4 (D)</td>
</tr>
<tr>
<td>09.</td>
<td>R MCA</td>
<td>R clICA dissection</td>
<td>R clICA dissection, R iiICA occlusion</td>
<td>4 (D)</td>
<td>4 (D)</td>
</tr>
<tr>
<td>10.</td>
<td>R PICA</td>
<td>Normal</td>
<td>R PICA occlusion#</td>
<td>4</td>
<td>4 (D)</td>
</tr>
<tr>
<td>11.</td>
<td>L MCA</td>
<td>L clICA dissection, L iiICA occlusion</td>
<td>L clICA dissection, L iiICA occlusion</td>
<td>4 (D)</td>
<td>4 (D)</td>
</tr>
<tr>
<td>12.</td>
<td>L PCA, R MCA, L MCA</td>
<td>Normal</td>
<td>R MCA posterior parietal branch occlusion#</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>13.</td>
<td>R PICA</td>
<td>Normal</td>
<td>R PICA occlusion#</td>
<td>4 (D)</td>
<td>4 (D)</td>
</tr>
<tr>
<td>14.</td>
<td>BA</td>
<td>R/L VA and BA occlusion</td>
<td>R/L VA dissection and BA occlusion</td>
<td>4 (D)</td>
<td>4 (D)</td>
</tr>
<tr>
<td>15.</td>
<td>L MCA</td>
<td>R/L ACA, L MCA stenoses</td>
<td>LACA and LMCA stenoses</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>16.</td>
<td>R PCA</td>
<td>Normal</td>
<td>R calcarine artery occlusion#</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>17.</td>
<td>R ICA</td>
<td>Normal</td>
<td>R ICA dissection and stenosis at LVA</td>
<td>5</td>
<td>4 (D)</td>
</tr>
<tr>
<td>18.</td>
<td>L MCA</td>
<td>L MCA stenoses</td>
<td>L MCA angular branch occlusion#</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>19.</td>
<td>MCA</td>
<td>L MCA branch stenoses</td>
<td>LVA dissection</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>20.</td>
<td>L MCA</td>
<td>LMCA stenoses</td>
<td>L iiCA, LAC stenoses, L MCA occlusion</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>21.</td>
<td>L MCA</td>
<td>L MCA stenosis</td>
<td>LMCA angular branch occlusion#</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>22.</td>
<td>R PICA</td>
<td>Normal</td>
<td>R PICA occlusion</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>23.</td>
<td>BA</td>
<td>Normal</td>
<td>L MCA parietal branch occlusion#</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>24.</td>
<td>R ICA, L ICA</td>
<td>Stenosis of R ICA</td>
<td>90% stenosis R ICA and 70% stenosis at LICA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25.</td>
<td>L MCA</td>
<td>L MCA stenoses</td>
<td>L MCA branch occlusion#</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>26.</td>
<td>RICA</td>
<td>Stenosis at both ICA</td>
<td>40% Stenosis at R ICA, 30% stenosis at LICA</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>27.</td>
<td>L MCA</td>
<td>LMCA stenoses</td>
<td>L MCA branch occlusion#</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>28.</td>
<td>R MCA</td>
<td>R MCA branch stenoses</td>
<td>R MCA branch occlusion</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>29.</td>
<td>L PCA, L MCA, R MCA</td>
<td>L MCA stenosis</td>
<td>R MCA posterior parietal branch occlusion#</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>30.</td>
<td>R ICA</td>
<td>R ICA stenoses</td>
<td>&gt;95% stenosis of R ICA after bifurcation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

L- Left, R-Right, MCA- Middle Cerebral Artery, PICA- Posterior inferior cerebellar artery, BA- Basilar artery, PCA- Posterior Cerebral artery, ICA- Internal Carotid Artery, clICA- Cervical ICA, iiICA- Intracranial ICA, ACA- Anterior Cerebral Artery, FMD- Fibromuscular dysplasia, V- vasculitis, #Lesion suggestive of embolism
**Discussion:**
Currently, cerebrovascular disease is the third most commonest causes of death following malignant tumors and cancer, especially ischemic cerebrovascular disease, which has a high risk of paralysis. There are nearly 7.5 million Transient Ischemic attacks (TIAs) worldwide each year. TIA carries a particularly high short-term risk of stroke, and approximately 15% of diagnosed strokes are preceded by TIAs. Due to the negligence of TIA management, TIAs eventually evolved to stroke, which has brought huge economic losses and left the patients with disability and dependence. Clinicians tend to diagnose TIA with the collection of imaging evidence and duration of cerebral ischemia. With the increased recognition of TIA, update diverse imaging techniques have been used to improve the early diagnosis rate and location of TIA. The largest obstacle for the clinicians must to overcome is how to confirm the evaluation and management of TIA with multiple neuroimaging technologies. For example, cranial Doppler ultrasonography can be used for the acute attack as a minimally invasive method to identify large vessels occlusion or monitor stroke response. Compared with Digital subtraction angiography, four-dimensional CTA and MRA provide a less invasive alternative to determine the degree of vascular obstruction and collateral blood flow during macrovascular obstruction. When there is substantial disagreement regarding TIA diagnosis, patients may miss the best treatment window and get the unnecessary treatment. This study aimed to Compare Digital Subtraction Angiography and Magnetic Resonance Angiography in the Investigation of Acute Ischemic Stroke in A Tertiary Care Hospital in Bangladesh

This current study found that nearly two-thirds of the studied patients (66.7%) belonged to 41-60 years of age group followed by decreasing order 26.7% were with 21-40 years age group and only 6.6% were from 61-80 years age group. The mean age for the studied participants was 47.50±10.42 (SD) years in this current study. A study by Cotter et al. found that the mean age for the stroke patients was 63.2 and another study of 679 patients done by Bhowmick et al. found the mean age 60.4 years. In Nepal, Shakya et al, conducted a study where the mean age was 62.68±13.27 (SD) years.

In terms of gender distribution, this study found that 63.3% of the studied patients were male and 36.7% were female. A study was done by Palm et al., to see the gender differences for ischemic stroke; they also found the male predominance in the ischemic stroke although the difference wasn't significant.

Among the male patients of this present study, 73.7% were smoker and 26.3% were non-smoker whereas among the female patients 18.2% were smoker and 81.8% were non-smoker. A significant difference was seen in terms of smoking history when compared based on gender (p<0.05). Ischemic stroke is a complex disease state with structural and functional perturbations at the tissue, cellular and molecular levels. The vascular pathophysiological mechanism involved in ischemic stroke include peripheral thrombus formation, changes in cerebral blood flow, breakdown of the blood-brain barrier, and alterations in the cerebrovascular endothelium and it is evident that smoking adversely affects all of these characteristics and that nicotine is a major contributing factor in some of these effects.

In terms of co-morbidities and risk factors, 80.0% of the total patients had HTN and 73.3% had DM, 24.1% had a history of other cardiovascular diseases. 36.7% of the patients had a family history of stroke. A study by Fekadu et al., showed that, patients with ischemic stroke, 83.7% of them had HTN, 10% of them had a family history of stroke and 75% of them had Diabetes Mellitus.

In this present study, for the majority of the patients the affected artery was MCA (Middle cerebral artery) and it was for 17 patients out of 30. The final diagnosis was completely in concordant for 10 patients out of 30 in this present study.

The aetiologies according to TOAST diagnosis were similar by both MRA and DSA in 18 (out of 30) cases and different in 12 cases. In case 1, diagnosis was large-artery atherosclerosis by MRA but DSA showed cardioembolism. In case 3, MRA diagnosed large artery atherosclerosis but DSA showed undetermined aetiology. In case 4, MRA found large artery atherosclerosis but DSA revealed fibro-muscular dysplasia (FMD). Case 18 showed large artery atherosclerosis by MRA and undetermined aetiology by DSA findings. In case 21 large artery atherosclerosis was diagnosed by MRA and cardioembolism by DSA was found. For case 23, undetermined aetiology by MRA and cardioembolism by DSA, for 25 and 26, large artery atherosclerosis was diagnosed by MRA but for 25 undetermined aetiology and for 26 cardioembolism was diagnosed by DSA. For case 29, large artery atherosclerosis was diagnosed by MRA but cardioembolism by DSA. All the DSAs and 22 out 30 MRAs revealed abnormalities in this present study. This study
showed that, MRA didn’t reveal a posterior cerebellar inferior artery (in case 10, 22) lesion, Fibro-muscular dysplasia (FMD) in case 4.

Digital subtraction angiography (DSA) is the gold standard for evaluating arterial stenosis but it has some disadvantages like it’s an invasive procedure, costly and complicated. On the other hand, MRA is non-invasive and cost-effective for the patients. This was a single-centered study so the findings may not represent the true scenario. Multi-centered studies are recommended to corroborate these research findings.

**Conclusion:**
This study found that both MRA and DSA can effectively identify etiology of acute ischemic stroke. However, DSA is an invasive, costly and complicated procedure. Therefore, the application of MRA is suggested as practical tools to evaluate the etiology of ischaemic stroke individuals as MRA is non-invasive and cost-effective, especially for third world countries, like Bangladesh.

**Limitations:**
Small sample size and this single hospital based study did not reflect exact scenario of the whole community. Patients from all socioeconomic status and all parts of the country did not come to seek medical attention in the study place.

**Data Availability:**
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

**Conflict of Interest:**
The authors stated that there is no conflict of interest in this study

**Funding:**
Funding from research grant from Bangladesh Medical Research Council (BMRC) was received for this study.

**Ethical consideration:**
The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College.. The confidentiality and anonymity of the study participants were maintained.

**Acknowledgments:**
The authors were grateful to the staffs and management of the Department (OPD) of Neurology in Sir Salimullah Medical College Mitford Hospital, Bangladesh.

**References:**


CURRENT SCENARIO OF POISONING AND SNAKE BITE PATIENTS ADMITTED IN SYLHET MAG OSMANI MEDICAL COLLEGE HOSPITAL

MRINAL SAHA¹, SAJJAD MAHAMUD², ABU KAMRAN RAHUL³, MOHAMMAD FERDOUS UR RAHMAN⁴

Abstract:

Background: Poisoning cases are still neglected in our society. Recent studies have revealed the increasing trend of poisoning and snake bite patients, which may be a big challenge shortly. This study was carried out to observe the epidemiological profile of acute poisoning and snake bite in northeastern Bangladesh and to evaluate the risk factors, patterns and mortality. Methods: Data was collected from the emergency admission registrar of Sylhet MAG Osmani Medical College Hospital with a history of poisoning or snake bite from 1st January 2022 to 30th September 2022. Then indoor ward registers were used to see the outcomes. Results: 774 patients were admitted in the last nine months. Among them, 707 were poisoning cases (406 males and 301 females), and 67 (48 males and 19 females) were snake bites. We found 201 (28%) patients with unknown poisoning, and 167 (24%) were OPC poisoning. Other poisoning types were drug overdose (sedative, paracetamol, antipsychotic, anti-depressant and anti-hypertensive) and corrosive poisoning (Herpic, Dettol, Savlon, Detergent, Soap, Household Cleaning Materials, and paraquat). Though less frequent (11 cases), parquet poisoning was the most fatal. Regarding, Snakebite, 16 (24%) were venomous, and 44 (66%) were non-venomous. At last, we observed 45 deaths (Poisoning 40 and Snakebite 5). Conclusion: Both poisoning and snake bite cases are important in the clinical context of every tertiary care hospital like ours. To reduce this burden, we should focus on the risk factors. At the same time, proper treatment guideline is necessary even in the rural setup to ensure initial life-saving care.

Keywords: Poisoning, Snakebite, Outcome

INTRODUCTION:

Our healthcare system continues to ignore incidents of poisoning and snake bites. In rural places where widespread beliefs prevent patients from receiving appropriate medical attention, it is more difficult. A global issue that is getting worse every day is acute poisoning. The majority of fatal poisoning cases, according to the World Health Organization, take place in developing nations. Acute poisoning is an issue in developed nations as well. 10–20% of all acute medical hospitalizations in the UK are due to it ¹. It is a frequent medical emergency and the ninth most frequent cause of in-hospital mortality in Bangladesh. The most frequent causes of poisoning are pesticides, herbicides, rodenticides, chemicals, medications, alcohol, travel-related poisoning, and various kinds of bites. The first two days are extremely important and can call for high-dependency care. It is

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particularly challenging for Bangladesh’s tertiary care hospitals to treat those patients due to the shortage of segregated wards.

According to recent research from several Asian nations, there may be 300,000 intentional pesticide ingestion suicides per year. Adult females make up about 44% of all fatalities in Bangladesh, and medical wards at tertiary hospitals account for 8 to 10% of all fatalities 2,3. In Bangladesh, a tropical nation, snake bites are extremely typical. Rain is nearly always a given in Sylhet. Flooding is a common, natural tragedy in this area. These two elements help explain why snake bites are on the rise during a given season. In addition, the forests and tea gardens of Sylhet are home to a few unique venomous snakes. So, it is important for us to get ready for the early care of snake bites. National statistics from the 1999 Bangladesh Health and Injury Survey (BHIS) showed that the annual incidence of snake bites was 10.98/100000 people. An estimated 15,372 people are bitten by snakes each year, and 1,709 deaths have been reported. According to a national mortality survey conducted in India, roughly 4.1/10,000 people each year pass away from snakebites 4.

In order to determine the pattern and frequency of poisoning in a tertiary care level government hospital, this study counted all poisoning and snake bite cases. Additional specific goals were classifying venomous and non-venomous snake bites and locating lethal poisonings. Lastly, the results were recorded by adding the number of discharges, deaths, and ICU support requirements.

**Methods:**

Data was collected from the Emergency Admission registrar because all the poisoning and snake bite patients were admitted through the emergency department. Every patient was counted with a history of poisoning and snake bite from 1st January 2022 to 30th September 2022. After initial data collection, indoor ward registers were used to see the outcomes. A semi-structured questionnaire form was filled with previous data and information from a short telephone interview with the patients or their attendants.

**Results:**

In this study total of 774 (male 454 and female 320) patients were observed who was admitted with a history of either poisoning or snake bite from January to September. In Table 1 showed that 707 were poisoning cases (406 males and 301 females), and 67 (48 males and 19 females) were snake bites. In poisoning cases, 406 (57%) were male, and 301 (43%) were female. Besides this, 48 (72%) were male, and 19 (28%) were female among the snake bite cases. Urban habitats were 113 (poisoning 101, snake bite 12), whereas 661 patients were from the rural (606 and 55 for poisoning and snake bite, respectively). The observation is clear that most cases are from the countryside due to inadequate treatment facilities. The number of male patients was more than the female, and most cases were from 18-30 years old (poisoning 430, 61% and snake bite 16, 24%). In Table: 2 observed that in March 2022, the highest number of poisoning cases (131) was admitted, whereas the lowest number of patients was admitted in June 2022. Surprisingly, no snake bite patient was hospitalized till May 2022, and in July, the number rose to its maximum (44). It was probably due to the flood. In Table 3: showed that the distribution of cases regarding their age, the number of cases more in the age 18-30 years as they were the main working force. InTable:4 demonstrated that suicidal poisoning is more common in male (261), and female (223). In Table: 5 demonstrated that there are 12 major categories of poisoning, among which unknown poisoning cases are 201 (28%), and the second highest is OPC poisoning, which is 167(24%). Patients used different medications, likely antipsychotic, antihypertensive, aspirin, beta-blocker, etc., to harm. The lowest number came from the alcohol intoxication group, and the no is 5(0.7%). In Table-VI observed that types of bites regarding venom potentialities. There were different types of snake bites. Most snakes were non-venomous (44, 66%). Of the venomous snakes, 16 (24%), whereas 7(10%) cases were locally venomous. In Table-VII demonstrated that outcome of poisoning patient admission in terms of cure and death.

In the case of poisoning, 667 (94%) patients were cured, 40 (06%) died, and 45 needed ICU admission. We saw 62 (93%) patients with snake bites get cured, 5(7%) die, and 9 need ICU support. Regarding total mortality, the number was 45. Among them, 40 cases were poisoning and five from snake bites. Most of the poisoning cases are paraquat; other causes are OPC and unknown poisoning. All the deaths from snake bites were venomous snake bites.

<table>
<thead>
<tr>
<th>Table I: Summary of total observed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Urban</td>
</tr>
<tr>
<td>Rural</td>
</tr>
</tbody>
</table>
Table II: Monthly distribution of patients according to their admission

<table>
<thead>
<tr>
<th>Month</th>
<th>Poisoning</th>
<th>Snake Bite</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>98</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>February</td>
<td>102</td>
<td>0</td>
<td>102</td>
</tr>
<tr>
<td>March</td>
<td>131</td>
<td>0</td>
<td>131</td>
</tr>
<tr>
<td>April</td>
<td>64</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>May</td>
<td>97</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>June</td>
<td>49</td>
<td>5</td>
<td>54</td>
</tr>
<tr>
<td>July</td>
<td>50</td>
<td>44</td>
<td>94</td>
</tr>
<tr>
<td>August</td>
<td>55</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>September</td>
<td>61</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>707</td>
<td>67</td>
<td>774</td>
</tr>
</tbody>
</table>

Table III: Distribution of cases regarding their age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Poisoning</th>
<th>Snake Bite</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>119</td>
<td>12</td>
</tr>
<tr>
<td>18-30</td>
<td>430</td>
<td>28</td>
</tr>
<tr>
<td>31-50</td>
<td>105</td>
<td>16</td>
</tr>
<tr>
<td>&gt;50</td>
<td>53</td>
<td>11</td>
</tr>
<tr>
<td>Grand Total</td>
<td>707</td>
<td>67</td>
</tr>
</tbody>
</table>

Table IV: Mode of poisoning.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Male (707)</th>
<th>Female (301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal (484)</td>
<td>261</td>
<td>223</td>
</tr>
<tr>
<td>Homicidal (141)</td>
<td>95</td>
<td>42</td>
</tr>
<tr>
<td>Accidental (81)</td>
<td>45</td>
<td>36</td>
</tr>
</tbody>
</table>

Table V: Types of poisoning cases

<table>
<thead>
<tr>
<th>Types</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>201</td>
</tr>
<tr>
<td>OPC</td>
<td>167</td>
</tr>
<tr>
<td>Drug</td>
<td>134</td>
</tr>
<tr>
<td>Harpic</td>
<td>77</td>
</tr>
<tr>
<td>Sedative</td>
<td>44</td>
</tr>
<tr>
<td>Corrosive</td>
<td>30</td>
</tr>
<tr>
<td>Household Products</td>
<td>14</td>
</tr>
<tr>
<td>Paraquat</td>
<td>11</td>
</tr>
<tr>
<td>TCA</td>
<td>10</td>
</tr>
<tr>
<td>Rat Killer</td>
<td>7</td>
</tr>
<tr>
<td>Street</td>
<td>7</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>707</td>
</tr>
</tbody>
</table>

Table VI: Types of Bites regarding venom potentialities.

<table>
<thead>
<tr>
<th>Types</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally Venomous</td>
<td>7</td>
</tr>
<tr>
<td>Non-Venomous</td>
<td>44</td>
</tr>
<tr>
<td>Venomous</td>
<td>16</td>
</tr>
<tr>
<td>Grand Total</td>
<td>67</td>
</tr>
</tbody>
</table>

Table VII: Outcome of poisoning patient admission in terms of cure and death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Poisoning</th>
<th>Snake Bite</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>667</td>
<td>62</td>
<td>729</td>
</tr>
<tr>
<td>Death</td>
<td>40</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>ICU</td>
<td>45</td>
<td>9</td>
<td>54</td>
</tr>
</tbody>
</table>

Discussion:

In this study, poisoning in men was more than the women; this finding was very similar to some Bangladeshi and Indian studies. On the other hand, women’s predominant findings were seen in Turkey and Japan. The higher incidence of poisoning in men may be due to stress following the financial crisis and job-related pressures. Most patients were from 18 to 30 years old, which is similar to a study by Chowdhury et al. in Bangladesh. Studies in other countries also showed a similar pattern of age distribution. Moreover, young adults are more vulnerable to this health problem due to emotional and social disharmony and occupational problems. The majority of poisoning cases were found suicidal, where males are slightly more in number than females. However, Chowdhury et al. also observed a higher suicidal tendency among females. Here, we found that the highest number of snake bites occurs during the rainy season and the flood (June to September). This is probably because most agricultural activities occur during this season. These changed conditions are likely to force snakes to come out of their shelters, which might cause an increased risk of a snake bite during the monsoon season. Similar findings were reported from other studies. We observed 16 (24%) venomous, 7 (10%) locally venomous snake bites, and the rest, 44 (66%), were non-venomous. Krait and Cobra were the commonest snakes, and green pit viper was the most commonly locally venomous. Most patients had tight tourniquets during admission, and some had local maltreatment. Some of the venomous snake bites...
had a local invasion. There were some unknown snakes that the patient could not identify. This study had a similarity to the study done by Mymensingh Medical College, Bangladesh. Regarding total mortality, the number was 45. Among them, 40 cases were poisoning and five from a snake bite. Most of the poisoning cases are paraquat poisoning, a herbicide commonly found in Sylhet. Despite having ICU support for a long period patient expired of respiratory and renal complications. The proper management protocol is still elusive regarding this issue. Again, the death rate from unknown street poisoning is also higher because of late presentation and proper initial management. Our observation was that if poison could not be identified earlier, the outcome would be poor later. In the case of venomous snake bite, it is more rewarding with anti-venom and ICU support. We found five deaths where there was no ICU availability in time. All venomous snake bite patients received ant venom; some had more than one dose to recover. The above findings are also similar to an Indian study.

Conclusion:
There were various poisoning cases, some of which were extremely rare and difficult to treat. Measures to provide immediate treatment at initial encounter may be effective in reducing mortality in fatal poisoning and venomous snake bite.

Limitations:
Small sample size and this single hospital based study did not reflect exact scenario of the whole community. Patients from all socioeconomic status and all parts of the country did not come to seek medical attention in the study place.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee from Sylhet MAG Osmani Medical College.

Acknowledgments:
The authors were grateful to the staffs and management of the Sylhet MAG Osmani Medical College Hospital, Sylhet-31000, Bangladesh.

References:
A CLINICAL UTILITY OF NEUTROPHIL LYMPHOCYTE RATIO AS AN INDEPENDENT PREDICTOR OF SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY

MAHMUDA ABIRA¹, MOHAMMAD SIRAJUL ISLAM², MD. DAHARUL ISLAM³, RAHNUMA AHMAD¹, FARHANA SULTANA¹, TAHMINA AKTER¹, QAZI SHAMIMA AKHTER³

Abstract:

Background: Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease and is associated with considerable morbidity. The neutrophil-to-lymphocyte ratio (NLR) has been chosen as a potential marker of inflammation in SLE. To evaluate the role of NLR as an independent predictor of SLE activity.

Methods: This was a cross-sectional comparative study conducted in the Department of Physiology, Dhaka Medical College, Dhaka, Bangladesh from July 2016 to June 2017. In this study, 30 SLE patients, aged 18 to 55 years, were considered as the study group and 30 aged matched healthy subjects were considered as control group. SLE Disease Activity Index (SLEDAI) score was used to assess disease activity. NLR and ESR was estimated. Independent samples t-test, Chi Square test, Pearson’s correlation co-efficient (r) test, Regression analysis and ROC curve analysis were performed as applicable. 95% confident interval was calculated and p value <0.05 was accepted as level of significance.

Results: In this study, NLR was significantly (p=0.003) higher in SLE patients than control. SLEDAI score was 10 (1-18) and majority (19; 63.33%) of the SLE patients had SLEDAI score >9 (active disease). NLR was significantly (p=0.001) increased more in active SLE than inactive SLE and showed a significant association among NLR and active disease (OR; 6.56, 95% CI; 1.26 to 34.20, p=0.001). NLR was positively correlated with SLEDAI score and ESR in patients with SLE. The optimal NLR cutoff value of 2.2 had 95% sensitivity and 73% specificity \( AUC = 0.957, 95\% CI, 0.892–1.000, p = <0.001 \). Conclusion: This study concludes that NLR is significantly increased in SLE patients and can be served as an independent predictor of SLE activity.

Key words: Neutrophil-lymphocyte ratio (NLR), Systemic lupus erythematosus (SLE), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

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Introduction:
Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune inflammatory disease with a variable severity and duration of flares. Abnormal immune regulation, activation of T cells and B cells, excessive production of autoantibodies and cytokines leads to intense inflammation and multiple organ damage in SLE.

Inflammation and immunity play a critical role in many chronic diseases. Neutrophils and lymphocytes reflect the balance between these two aspects of the immune system. Acute and chronic inflammations are indicated by the circulating neutrophils and adaptive immunity is indicated by lymphocytes. The neutrophil-to-lymphocyte ratio (NLR) is the proportion of absolute neutrophil count to lymphocyte count. NLR has been extensively evaluated and shown to be associated with outcome and predict disease course among patients with a variety of medical conditions including ischemic stroke, cerebral hemorrhage, major cardiac events, sepsis and infectious diseases. Numerous inflammatory indicators such as interleukin 1 (IL1), IL6, IL8, tumor necrosis factor alpha (TNF á) and cytokines (interferon) are used as biomarkers for inflammatory response or disease activity in SLE patient. Lack of availability, expensive and difficult to assay limit their use in routine clinical practice. NLR is a readily available, inexpensive classical inflammatory marker that can be calculated easily and convey reliable information about the patient inflammatory activity. Very few studies have been found to assess the association of NLR with disease activity of SLE previously, but less published data are available in our country. Therefore, present study has been designed to evaluate the role of NLR as an independent predictor of SLE activity.

Methods:
Setting & study participants
This was a cross-sectional study conducted in the Department of Physiology, Dhaka Medical College, Dhaka from July 2016 to June 2017. In this study, 30 diagnosed SLE patients aged 18 to 55 years with duration of disease 5 years were enrolled from SLE clinic of DMCH by purposive sampling. They were diagnosed on the basis of American College of Rheumatology (ACR) Criteria. Similar ageand BMI matched healthy subjects were taken as controls. ACR criteria was consist of 16 points based on clinical and laboratory judgment. The patients with 4 points out of 16 have definite diagnosis of SLE. With 3 points highly suggestive SLE and with 2 points probable SLE. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was used to assess disease activity. According to the SLEDAI score, we categorized the SLE patients into 2 groups such as patients with mild/inactive disease if score was <9 and severe/active disease if score was >9. Sample size was calculated by a statistical formula based on effect size in published results by similar article. The patients having history of liver disease, renal disease (other than SLE), rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriasis and malignant disease, history of taking anticoagulant, chemotherapy and recent history of blood transfusion were excluded from the study.

Procedure
After selection of the subjects, the nature, purpose and benefit of the study were explained to the subject. Informed written consent was taken from the participants. The research work was carried out after obtaining ethical clearance from Ethical Review Committee of Dhaka Medical College Dhaka. All the information was recorded in a prefixed data schedule. With all aseptic precautions, 3.6 ml blood was collected from all subjects. NLR was estimated by Automated Hematology Analyzer (Sysmex XT-2000) and ESR was estimated by Westergren’s method.

Statistical analysis
Data were expressed as frequency, percentage, mean ± SE, median and presented in appropriate tables and figures. Independent samples t-test, Chi Square test and Pearson’s correlation co-efficient (r) test were performed as applicable. Binary logistic regression analysis was performed to observe OR and the association of NLR and ESR with SLEDAI score in SLE patients. The area under the ROC curve (receiver operating characteristic curve) also accessed. Sensitivity and specificity of NLR was calculated from ROC curve. 95% confident interval (CI) was calculated and p value <0.05 was accepted as level of significance. Statistical analyses were performed by using IBM SPSS (statistical package for social sciences) Statistics for Windows version 26.0.

Results:
In this study, the control and the study groups were age, gender and BMI matched and no significant (p>0.05) differences were observed between the groups (Table-I). The mean±SE of NLR and ESR was significantly (p<0.05) higher in SLE patients than control (Table-II). SLEDAI score was 10 (1-18) and majority (19; 63.33%) of the SLE patients had SLEDAI score >9 (active disease) (Table III). NLR and ESR was significantly (p<0.05) increased more in active SLE than inactive SLE and showed a significant association among NLR, ESR and active disease (OR; 6.56, 95% CI; 1.26 to 34.20, p=0.001) and majorit (19; 63.33%) of the SLE patients had SLEDAI score >9 (active disease) (Table III). NLR and ESR was significantly (p<0.05) increased more in active SLE than inactive SLE and showed a significant association among NLR, ESR and active disease (OR; 6.56, 95% CI; 1.26 to 34.20, p=0.001) and majority (19; 63.33%) of the SLE patients had SLEDAI score >9 (active disease) (Table III). Correlation analysis showed, significant (p<0.05) positive correlation among NLR, ESR and SLEDAI score (Figure 1 & 2). Receiver Operating Characteristic curve (ROC) analysis of NLR to predict SLE activity (Figure 3). The optimal NLR cutoff value of 2.2 had 95% sensitivity and73% specificity (AUC = 0.957, 95% confidence interval [CI], 0.892-1.000, p = <0.001).
**Table I: General characteristics of the subjects in both groups (N=60)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SLE patients (n=30)</th>
<th>Control (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Median (range)</td>
<td>35.10 ± 1.93</td>
<td>34.89 ± 2.51</td>
<td>0.929 <strong>ns</strong></td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (6.7%)</td>
<td>4(13.3 %)</td>
<td>0.389 <strong>ns</strong></td>
</tr>
<tr>
<td>Female</td>
<td>28(93.3%)</td>
<td>26(86.7%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.34 ± 1.08</td>
<td>21.91 ± 1.18</td>
<td>0.387 <strong>ns</strong></td>
</tr>
</tbody>
</table>

Data were shown as mean±SE. Statistical analysis was done by Independent samples t-test and Chi Square test (frequency, %). SLE= Systemic lupus erythematosus, Control= Healthy subjects, BMI= Body mass index, **ns**= not significant, N= total number of subjects, n = number of subjects in each group.

**Table II: NLR and ESR of the subjects in both groups (N=60)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SLE patients(n=30)</th>
<th>Control(n=30)</th>
<th>Mean difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>4.74±0.77</td>
<td>2.28±0.14</td>
<td>2.45(0.902 to 4.003)</td>
<td>0.003 ***</td>
</tr>
<tr>
<td>ESR (mm in 1st hour)</td>
<td>47.60±2.91</td>
<td>9.47±0.73</td>
<td>38.13(32.13 to44.14)</td>
<td>&lt;0.001 ***</td>
</tr>
</tbody>
</table>

Data were shown as mean±SE. Statistical analysis was done by Independent samples t-test. NLR= Neutrophil-lymphocyte ratio, ESR= Erythrocyte sedimentation rate, SLEDAI= Systemic lupus erythematosus disease activity index, CI= confident interval***= significant at p<0.001, N= total number of subjects, n = number of subjects in each group.

**Table III: Distribution of the study subjects according to SLEDAI (N=30)**

<table>
<thead>
<tr>
<th>SLEDAI</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>d&quot;9(Inactive SLE)</td>
<td>11</td>
<td>26.70%</td>
</tr>
<tr>
<td>&gt;9 (Active SLE)</td>
<td>19</td>
<td>63.30%</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>10 (1-18)</td>
<td></td>
</tr>
</tbody>
</table>

Data were shown as frequency, percentage and median. SLEDAI= Systemic lupus erythematosus disease activity index, n = total number of SLE patients.

**Table IV: Association of NLR and ESR with SLE activity (n=30)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Inactive SLE (n₁=11)</th>
<th>Active SLE (n₂=19)</th>
<th>Mean difference (95% CI)</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>1.58±0.30</td>
<td>6.56±0.99</td>
<td>-4.98</td>
<td>6.563</td>
<td>0.001 ***</td>
</tr>
<tr>
<td></td>
<td>(-7.71 to 2.26)</td>
<td>(1.26 to 34.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm in 1st hour)</td>
<td>39.82±2.93</td>
<td>52.11±3.96</td>
<td>-12.29</td>
<td>5.66</td>
<td>&lt;0.001 ***</td>
</tr>
<tr>
<td></td>
<td>(-0.63 to -23.94)</td>
<td>(0.75 to 42.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data were shown as mean±SE. Statistical analysis was done by Independent samples t-test and Binary logistic regression analysis. NLR= Neutrophil-lymphocyte ratio, ESR= Erythrocyte sedimentation rate, OR= Odd ratio, ***= significant at p<0.001, n = number of SLE patients.
Discussion:
Now a day, there has been a growing emphasis on early diagnosis of SLE exacerbation and monitoring of disease activity. Concurrently, concentrated efforts have been made to assess hematological indicators that are capable for prognosing SLE exacerbation in the preclinical period, furthermore, indicates signs of exacerbation in a given organ. The neutrophil-to-lymphocyte ratio (NLR) has been chosen as a potential marker of inflammation in SLE. Neutrophils are the first inflammatory cells that are present at the site of inflammation and second, the pathway that is related to lymphocytes, which have a regulatory function. The present study was undertaken to evaluate the role of NLR as an independent predictor of SLE activity.

In current study, NLR and ESR were significantly higher in SLE patients than healthy control. These findings are parallel to the observation of some groups of authors. Binary logistic regression analysis showed a significant association among NLR, ESR and active disease (SLEDAI score >9). Like other inflammatory marker (i.e., ESR) increased NLR was 6.6 times more risk of developing active disease in SLE patients. Some researchers of different countries found similar association but different methodology was used in those studies.

In Pearson’s correlation coefficient analysis, NLR and ESR showed positive correlation with active disease and NLR also showed positive correlation with inflammatory marker like ESR in patients with SLE. These findings are consistent to the observation of some other researchers. It has been demonstrated that NLR is an index of systemic inflammation. NLR is an easy, cheap and readily available marker that can convey important information about the patient inflammatory activity and prognostic prediction of diseases.

An interesting notice in present study was that NLR could predict SLE activity. The area of NLR under the ROC curve also considered as excellent for separating active from inactive SLE patients. These findings are parallel with other studies.

Though the explanation of these changes in NLR and ESR of SLE patients is not known but literature review suggests that increased ESR may be due to chronic inflammatory response with polyclonal increase in immunoglobulins.

An increase in NLR is determined by an increase of neutrophils and/or reduction in lymphocytes. An increase in circulating neutrophils is suggestive of
an acute or chronic inflammatory response. Lymphocytes generate adaptive immune responses to eliminate specific pathogens, infected cells etc\(^3\). Both innate and adaptive immune pathways become activated in SLE. So, immunosuppressive drugs (steroid, cyclophosphamide etc.) are used to suppress antibody production. They are bio-transformed in the liver. Their active metabolites inhibit purine synthesis and block the proliferation of activated T and B lymphocytes\(^17\).

Systemic lupus erythematous (SLE) is an autoimmune disease of unknown etiology virtually affecting all organs of the body\(^18\). Beyond genetic and environmental factors, cytokine imbalances contribute to immune dysfunction, trigger inflammation and induce organ damage in SLE\(^9\). The key cytokine that is involved in SLE pathogenesis is interferon alpha. Neutrophils are important producers of type I interferon (IFN) via stimulation of plasmatic dendritic cells (pDC) by chromatin\(^19\).Type I IFNs have potent ability to enhance lymphocyte recruitment to tissues, causing lymphopaenia\(^19\). Therefore, the increased neutrophil count was associated with the presence of markers of their activity and a decrease in the number of lymphocytes with activity and a high number of NLR in SLE. Han et al.\(^19\) reported that Neutrophil-lymphocyte ratio (NLR) was more predictive than neutrophil and lymphocyte counts alone.

This increased NLR might be consequence of increased inflammation process in SLE patients which is evident from its relation to disease activity.

**Conclusion:**
Existing study revealed NLR is increased in systemic lupus erythematous (SLE) patients and can be served as an independent predictor of SLE activity. NLR is inexpensive, widely available and easily measurable even in the simplest health care units. Therefore, NLR can be recommended to perceive disease activity in SLE. However, further prospective and multicenter studies with larger sample size are needed to corroborate the clinical value of NLR in patients with SLE and to determine a cut-off level for assessing disease activity with a high sensitivity and specificity.

**Limitations:**
Small sample size and this single hospital based study did not reflect exact scenario of the whole community.

**Data Availability:**
The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

**Conflict of Interest:**
The authors stated that there is no conflict of interest in this study

**Funding:**
Funding from research grant from Bangladesh Medical Research Council (BMRC) was received for this study.

**Ethical consideration:**
The study was conducted after approval from the ethical review committee of Dhaka Medical College. The confidentiality and anonymity of the study participants were maintained.

**Acknowledgement:**
The authors acknowledge the Department of Medicine Dhaka Medical College, Dhaka for their kind co-operation during sample collections and all the study subjects for their active participation.

**References:**
6. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, Hu Z, Liang Y, Yang Z, Zhong R. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod


A CASE REPORT OF TAKAYASU’S ARTERITIS WITH STROKE AS INITIAL PRESENTATION

MOHAMMAD SIRAJUL ISLAM1, AHMED HOSSAIN2, MD. DAHARUL ISLAM3, CHANDRA SHEKHAR BALA4, AMINUR RAHMAN5, MAHMUDA ABIRA6, MD. RANAUL ISLAM7, KHALED MAHMUD7, PARTHA SAROTHI SARKER8

Abstract:
Takayasu’s arteritis a rare, idiopathic, chronic granulomatous vasculitis that affects aorta and its major branches. Stroke is a common complication; however, this is hardly the initial presentation. Here we reported one such case of a 39-year-old man presented with sudden onset right sided hemiparesis, facial deviation towards the left and motor aphasia for last 21 days. He was diagnosed as ischemic stroke with right sided hemiparesis with motor aphasia due to Takayasu’s arteritis.

Key words: Takayasu’s arteritis, Cerebral Infarction, Ischemic stroke, pulseless disease.

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DOI: https://doi.org/10.3329/bjm.v34i2.65618


Introduction:
Takayasu’s arteritis (TA) is a systemic granulomatous inflammation affecting aorta, its main branches, pulmonary, renal and coronary arteries, wherein inflammatory mononuclear cell and giant cells infiltrates leads to intimal proliferation and fibrosis, vascularization of the media, degeneration of the elastic lamina, narrowing of the lumen occurs with or without thrombosis. It is also known as “pulseless disease” or nonspecific aortoarteritis.1,2,3 The disease is primarily confined to the young female, but now males are also affected with variable disease manifestations4. It is most prevalent in Japan, South East Asia, India and Mexico.1

It is considered as an early or pre-pulseless phase presenting as non-specific constitutional symptoms followed by a late, pulseless phase. The most common clinical presentation is diminished or absent pulses, associated with limb claudication and blood pressure discrepancies4. Other manifestations include vascular bruits in the carotids and subclavian arteries, hypertension, aortic regurgitation, neurological features secondary to hypertension and/or ischemia, including seizures, stroke, visual impairment, retinopathy and pulmonary hypertension4. Nevertheless, stroke as the initial manifestation is infrequent and only a few cases are reported5. We report such a case, where stroke in young men heralded the onset of the disease.

Case Report:
A 39-year-old man, non-diabetic, normotensive and smoker, presented with sudden right sided
hemiparesis, facial deviation towards left, and motor aphasia for last 21 days. He had occasional muscle cramps, mild to moderate pain in small and large joints of upper limbs, without joints welling and morning stiffness. There was no history of unconsciousness, convulsion, headache, blurred vision, nausea, vomiting, abdominal pain, claudication in the lower limbs and Raynaud’s phenomenon. There was history of similar attack two years back.

On examination, the patient was ill looking, mildly anemic, pulseless undetectable blood pressure, while pulse and blood pressure on the lower limbs were detectable and normal, motoraphasia with intact comprehension, right facial nerve palsy, increased muscle tone, exaggerated all tendon jerks with planter extensor on right and flexor on left with normal fundoscopy. His ESR was 77 mm/hour, CRP was 15.4 mg/L. In Figure: A CT Scan of brain A which demonstrated cerebral infraction in evidenced by a large hypodense area in the left frontotemporal parietal region, mass effect and perifocal edema. Duplex study revealed vasculitis with thromboembolic disease involving both carotid and vertebral arteries (Figure-B).

Figure-A Cerebral infract: A large hypodense area in the left frontotemporal parietal region, mass effect and perifocal edema

Figure B: Duplex study of neck vessels and vertebral arteries showing heterogeneous thrombus in right common carotid art

Figure C: CT-angiogram showing narrowing of three great vessels near origin and multiple collaterals.
CT angiogram showed short and long segment narrowing in left and right subclavian artery, brachiocephalic trunk and left common carotid artery and established flow by multiple collaterals (Figure-C). He was diagnosed as ischemic stroke with right sided hemiparesis with motor aphasia due to TA and treated with oral prednisone 40 mg daily, aspirin 75 mg, methotrexate 10 mg, calcium and vitamin D supplementation after which he displayed marked clinical improvement and normalization of inflammatory markers by the time of discharge.

**Discussion:**
Evaluation of the inflammatory status and pattern of arterial damage in TAs is still a major challenge. Clinical presentation was ranging from asymptomatic, constitutional features to symptoms of end-organ damage. Stroke as the initial presentation in 5%-8% of the patients occurs due to acute ischemia by thrombosis or embolism of vessels. Our patient was presented with sudden ischemic stroke, along with Takayasu arteritis with thromboembolic disease involving both carotid and vertebral arteries. Kameyama et al. reported that the source of thrombus is stenosed common carotid or internal carotid artery, dislodged by the turbulent blood flow.

Patients characteristically present with diminished or absent pulses, blood pressure discrepancies and vascular bruits over carotid and subclavian vessels. Chen et al. informed that most of the patients had abnormal characteristics of four limbs blood pressure that helped them to diagnose the disease by primary screening and complete assessment. Similarly, in our patient, pulse and blood pressure were undetectable in upper limbs and detectable in lower limbs, which raised the suspicion of TA.

The commonly adopted approach for judging TA activity includes acute-phase reactants, new bruits and angiographic features. Wang et al. stated that high resolution sonography was able to provide precise images for evaluation of TA. The first line of management is systemic steroids. Methotrexate and cyclophosphamide is required for long-term disease control. We also used methotrexate along with steroid, aspirin and atorvastatin. Therefore, our patient's clinical and laboratory parameters were improving rapidly.

Takayasu's arteritis can be debilitating to patients physical and mental health, becoming dependent during their most productive years, which can have a greater impact on their socioeconomic status. So early diagnosis, treatment and monitoring are extremely important to control the disease activity and prevent life-threatening complications.

**Conclusion:**
Young patients, who present with stroke, should be evaluated meticulously for Takayasu's arteritis. Initial identification is important for management. It will halt the inflammation and its progression thereby, leading to better clinical outcomes.

**Conflict of Interest:**
The authors stated that there is no conflict of interest in this study

**Funding:**
This research received no external funding.

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

**Acknowledgments:**
The authors were grateful to the staffs of the Department of Medicine in Sir Salimullah Medical College Mitford Hospital, Bangladesh

**References:**


CASE REPORT

A GIRL PRESENTED WITH LEARNING DIFFICULTY AND POOR SCHOOL PERFORMANCE: A CASE REPORT

AMINUR RAHMAN¹, MD. DAHARUL ISLAM², MD. EKHLASUR RAHMAN³, ZAHED ALI⁴, FIROZ AHMED QURAISHI⁵

Abstract:

DiGeorge Syndrome (DGS) which is also known as chromosome 22q11.2 deletion syndrome is a primary immunodeficiency caused by the deletion of chromosome 22. Its main features include dysmorphia, hypoparathyroidism, hypocalcemia, hypoplasia or aplasia of the thymus, cardiac anomalies, renal anomalies, and behavioral/psychiatric issues. This incurable syndrome could be treated for its complications to increase the quality of life. With the advancement of technology, DGS can now be identified in childhood itself where FISH is the main diagnostic method used. A case report of a 7 year-old girl who visited the learning difficulty, poor memorization, poor school performance and socialization problems is presented here. On the evaluation of his case, DiGeorge Syndrome was confirmed.

Keywords: Learning difficulty; Chromosome 22q11.2 deletion; DiGeorge syndrome; Dysmorphia; Hypocalcemia; Hypoparathyroidism; Microdeletion

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Introduction:

DiGeorge syndrome (DGS) is one of the most common chromosomal disorders with an estimated incidence of 1 in 4,000-6,000 live births.¹,² It is usually sporadic; however, autosomal dominant inheritance has been reported in 10-20% of the patients. The phenotypic expression shows wide variability.²,³ Congenital heart defect, typical facial appearance, immune deficiency due to thymic hypoplasia, palatal cleft, velofacial dysfunction, hypocalcemia associated with hypoparathyroidism, developmental and behavioral problems are the main features associated with the syndrome.

Case report:

So we report a 7 years old girl with 22q11.2 DS who presented with Learning Difficulty and socialization Problems, a condition which is unusual for this age and usually is in the differential diagnosis in early childhood.

References:

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patient was referred endocrinology department at the pediatric hospital for evaluation of possible hypoparathyroidism. The patient’s mother reported that she was inattentive, poor school performance and asocial. The girl had a medical history of mild recurrent numbness in his hands in the past 2 years. There is no history of recurrent infection.

During the physical examination, mild facial dysmorphism was seen prominent nose prominent nose, antimongoloid slant, telecanthus, ocular hypertelorism, and long face (Figure: 1). The voice was hypernasal. Chvostek and Trousseau signs were positive. Systemic findings were otherwise normal.

The laboratory investigations revealed a serum calcium level of 6.6 mg/dL (Normal 9-10.5 mg/dL), phosphorus 8 mg/dL (Normal: 2.4 to 4.1 mg/dL) parathormone level of 8 pg/mL (normal: 10-65), 25-hydroxyvitamin D level of 25 ìg/L, and urine calcium/creatinine ratio of 0.01. His thyroid hormone levels were within the reference range (Table: 1). The thymus was not visualized at scintigraphic evaluation but her immunologic studies revealed normal. The echocardiography of the patient revealed normal. Ultrasonography of the left kidney has demonstrated a cortical cyst which is again a feature of DGS.

The diagnosis, suggested by the clinical and biochemical findings, was found to be associated with 22q11.2 DS, which was shown by FISH as a heterozygote deletion. Calcium replacement therapy, combined with active vitamin D was started.

**Laboratory Findings and Analysis:**

**Table-I : Interpretation of laboratory findings**

<table>
<thead>
<tr>
<th>Laboratory Investigation</th>
<th>Result</th>
<th>Normal Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium</td>
<td>6.6 mg/dL</td>
<td>9 – 10.5 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>8 mg/dL</td>
<td>2.4 – 4.1 mg/dL</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>244</td>
<td>145-420</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>1.9</td>
<td>1.5-2.3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.8</td>
<td>4.0-5.3</td>
</tr>
<tr>
<td>Parathormone (PTH)</td>
<td>8 pg/mL</td>
<td>10 – 65 pg/mL</td>
</tr>
<tr>
<td>25-hydroxyvitamin D</td>
<td>25 ìg/L</td>
<td>&gt;30 ìg/L</td>
</tr>
<tr>
<td>Urine Calcium/creatinine ratio</td>
<td>0.01</td>
<td>&lt;0.14</td>
</tr>
<tr>
<td>CD3+ (CD16+56+)</td>
<td>60-68%</td>
<td>58-82%</td>
</tr>
<tr>
<td>Thyroid Hormones</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

**Table-II : Findings of the patient**

<table>
<thead>
<tr>
<th>Features of DiGeorge syndrome</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmorphic findings</td>
<td>Subtle Hypoplasia</td>
</tr>
<tr>
<td>Thymic hypoplasia/aplasia</td>
<td>Absent</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Absent</td>
</tr>
<tr>
<td>Heart defect</td>
<td>No</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>Cortical cyst</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)  
_A girl with DGS - prominent nose, antimongoloid slant, telecanthus, ocular hypertelorism, and long face_

![Figure 2](image2.png)  
_FISH analysis with the Zygolight SPEC HIRA probe specific to DiGeorge region, arrow shows a deletion of chromosome 22q11.2_
Discussion:
Hypoparathyroidism and the resulting hypocalcemia are among the main features of 22q11.2 DS, and are observed in 70 of individuals with this deletion. The hypocalcemia may be of variable inflexibility. In the severest cases, the hypocalcemia is natural. Still, latent hypoparathyroidism is more common than patient cases with characteristic hypocalcemia. In the most cases, hypocalcemia resolves around one time of age, but recurs in in childhood or in adolescence. In latent hypoparathyroidism, PTH is secreted in sufficient amounts in in basal states, and serum calcium (Ca) and phosphorus (P) situations are normal. However, when Ca intake is not sufficient, especially when Ca requirements are high such as the case in infancy, adolescence or pregnancy, PTH secretion becomes inadequate and hypocalcemia becomes evident as recurrent numbness. Mild recurrent numbness in his hands in the past 2 years in our case were presumably related to latent hypoparathyroidism, which came decompensated during puberty, due to increased calcium demand that wasn’t met by an acceptable PTH response.

DGS can be associated with generalized anxiety, phobias, attention deficit hyperactivity disorder; autism, social isolation in children severe psychopathology, in adults including bipolar disorder and schizophrenia in adults. Cognitive disabilities are seen in 40 to 46% of individuals with 22q11.2 deletion and the majority of them are mild to moderate. For this reason, it is possible for patients with undiagnosed DGS to first be admitted to a psychiatry department. So our patient had cognitive disabilities and social isolation. Another manifestation of our case was velopharyngeal dysfunction, which redounded in hypernasal voice and deceleration in speech development.

Congenital heart defects and immune deficiency, which are among other findings reported for cases with 22q11 DS, weren’t encountered in our case. natural asymmetric crying facies, caused by the absence or hypoplasia of the depressor anguillorisor muscle on one side of the mouth, has also been reported in 22q11 DS. This finding wasn’t seen in our case.

There isno phenotype- genotype correlation in 22q11 DS. Wide phenotypic variabilities are seen indeed among family members with the same mutations. Thus early diagnoses may be difficult. A thorough clinical observation is necessary not to over diagnose the cases with atypical findings. It’s easy to make the opinion of 22q11 DS in the presence of natural heart blights, palatal disfigurement and characteristic early onset hypocalcemia. Therefore, in the absence of these major findings, as was the case in our case, 22q11 DS must be considered in differential diagnosis of developmental delay, velopharangeal dysfunction, intermittent attacks of croup, and mild dysmorphic features. Beforehand opinion may prompt early operation of learning difficulties.

Conclusion:
Hypocalcemia due to latent hypoparathyroidism in late childhood and in puberty should be considered in the differential diagnosis of 22q11 DS.

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

Funding:
This research received no external funding.

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

Acknowledgments:
The authors were grateful to the staffs of the Department of Neurology in Sir Salimullah Medical College Mitford Hospital, Bangladesh.

References:


A YOUNG GIRL WITH GRANULOMATOSIS WITH POLYANGIITIS: A RARE CASE REPORT

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Abstract
Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis is a necrotizing vasculitides that primarily affects small-sized arteries and manifests differently depending on the organ involved and the severity of the disease. Here we are reporting a case of a 15-year-old girl presented with purulent nasal discharge with epistaxis, cough, reduced hearing, fever & rash. Tissue biopsy report, positive C-ANCA, imaging and clinical features were consistent with the diagnosis of GPA. After counseling the patient & her parents and taking consent, she has been treated with intravenous methylprednisolone and cyclophosphamide. Despite being a rare disease with a typical age of onset around 40 years, it should be suspected in any aged patient exhibiting constitutional symptoms and other evidence of upper or lower respiratory tract involvement or glomerulonephritis.

Key words: Granulomatosis with polyangiitis (GPA), Wegener's Granulomatosis, necrotizing vasculitides

Introduction:
Granulomatosis with polyangiitis (GPA) is a clinicopathologic condition characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. The German pathologist Friedrich Wegener described it in 1936 leading to the eponymous name “Wegener's granulomatosis”.1 It has a prevalence of 2.3 to 146.0 cases per million people and an incidence of 0.4 to 11.9 cases per million people.2 A positive ANCA test strongly supports but does not confirm the diagnosis as around 10% with patients GPA may be ANCA negative.3 Immunosuppressive therapy is warranted in almost all patients with active GPA. Treatment consists of an initial induction phase followed by a maintenance phase. Despite the ability to successfully induce remission, 50–70% of remissions are later associated with one or more relapses. Here, we reported a case of ANCA positive GPA which predominantly presented with respiratory tract involvement.

Case Report:
A 15-year-old girl was admitted to the medicine department of Rangpur Medical College & Hospital with a three-year history of purulent nasal discharge with a three-year history of purulent nasal discharge and multiple episodes of epistaxis in the previous two months. She also complained of rash in lower...
limbs, ear & palm of both hands for ten days, as well as fever for same duration. There was history of recurrent sinusitis, occasional dry cough, reduced hearing in both ear & pain over multiple joints. She had no history of hemoptysis, chest pain, and redness of eye, visual loss, weight loss, tingling or numbness, high colored frothy urine. Her past medical history and family history were unremarkable. There was no history of tuberculosis or exposure to any known tuberculosis patient.

On examination the patient was anemic. She had crusting over nasal septum & nasal bridge was depressed [Fig 1(A)] & there was an ulcer in soft palate [Figure 1(B)]. Maculopapular rash was present in both lower limbs up to the knee which were erythematous, non-tender & some were palpable [Figure 1(C)]. Jaundice, lymphadenopathy, bony tenderness, or organomegaly were absent. Bed side urine for heat coagulation test for protein was negative & Fundoscopy reveals no abnormality.

Laboratory studies showed normocytic normochromic anemia (Hb- 8.5 gm/dl), raised WBC (total count - 17.5k/ìL, eosinophil - 01%), ESR & CRP. Proteinuria, hematuria & urinary sediment were absent. S creatinine, ACR, S electrolytes, SGPT, C3 & C4 level were normal. HBsAg, Anti HCV, RA test, ANA, Anti-ds-DNA all were negative. C-ANCA was positive [182.0 U/ml (Normal <12)] whereas P-ANCA was negative [0.60 U/ml (Normal <12)]. Pure Tone Audiometry (PTA) revealed severe sensory neural type hearing loss in the left ear and moderate conductive type hearing loss in the right ear. Chest X-ray showed nodular opacity [Figure 2(A)]. X-ray PNS showed Hazy right maxillary sinus & mucosal thickening of left maxillary sinus [Figure 2(B)]. Biopsy from nasal tissue revealed infiltration of inflammatory cells along with granulomas made of epithelioid cells.

**Figure 1(A)** Depressed nasal bridge

**Figure 1(B)** Ulcer in soft palate

**Figure 1(C)** Maculopapular rashes in both lower limb

**Figure 2(A)** Chest X-ray showed nodular opacity
After excluding illnesses resembling vasculitis, patients may be classified as having GPA under the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology diagnostic criteria. A score of 5 is required to classify as GPA. In our patient, the total score was 16 [for nasal involvement +3, cartilaginous involvement +2, hearing loss +1, positive cANCA +5, pulmonary nodule +2, and inflammation of paranasal sinus +1, granuloma on biopsy +2]. This criterion has sensitivity of 93% and specificity of 94%.

**Discussion:**

Granulomatosis with polyangiitis (GPA) is an ANCA-associated vasculitis which predominantly affects small size arteries. Males and females are equally affected. Though GPA most commonly affects the respiratory tracts and the kidneys, it can affect small blood vessels in almost any organ or tissue. Its presentation varies from less severe nonspecific clinical symptoms to severe organ-threatening or life-threatening disease. Nonspecific symptoms include fever, weight loss, myalgias, and arthralgias and without showing any specific organ involvement, these symptoms may persist for weeks to months. ENT manifestations are nasal crusting, discharge or epistaxis, recurrent sinusitis, oral and/or nasal ulcers, saddle nose deformity. Patients frequently develop conductive and/or sensorineural hearing loss, which can impair hearing permanently.

Coughing, dyspnea, hemoptysis are symptoms of pulmonary involvement. In studies from the National Institutes of Health (NIH) in the United States, evident glomerulonephritis was present in only 18% of patients at presentation, although glomerulonephritis later occurred in 77–85% of patients, usually within the first two years of disease onset. In case of our patient, there was no renal involvement. The most typical skin condition is purpura, which typically affects the lower limbs. Neurologic involvement includes mononeuritis multiplex, cranial nerve abnormalities. The presence of mononeuritis multiplex associated with a worse prognosis compared with those without this feature.

Initial investigations include CBC which may show anemia, leukocytosis or thrombocytosis, ESR & CRP may be raised. Kidney involvement may be detected with a serum creatinine test and a urinalysis with urine sediment. Anti-GBM Ab, C3 and C4 levels, ANA, cryoglobulins, tests for HIV, hepatitis B & C, liver function tests, tuberculosis screen, blood cultures should also be done to rule out other possible diagnoses. Chest X-ray may show nodules, patchy or diffuse opacities and fleeting pulmonary infiltrates & hilar lymphadenopathy. GPA is primarily associated with C-ANCA (65–75% cases). However, 20–30% is associated with P-ANCA, and at least 10% are ANCA negative. Whenever possible, the diagnosis of should be confirmed by biopsy of a site of suspected active disease.

Therapy for GPA has two main components: induction of remission with immunosuppressive therapy and maintenance of remission with immunosuppressive therapy to prevent relapse. Glucocorticoids in combination with either rituximab or cyclophosphamide should be used in patients with GPA who have organ- or life-threatening illness. Observational studies revealed that the induction therapy regimen of cyclophosphamide plus glucocorticoids was linked to a greater than fivefold increase in survival and a decreased incidence of relapse. Complement C5a receptor inhibitor avacopan can be used as an adjunctive agent with standard induction therapy. For maintenance of remission after induction immunosuppressive therapy, rituximab, azathioprine, methotrexate, and mycophenolate may be used.

Our patient got pulse cyclophosphamide with methylprednisolone & with this treatment though hearing impairment hasn’t been improved significantly, there was no history of epistaxis, sinusitis, fever in last 4 months & chest x-ray was also normal.
Without treatment survival in GPA is 10% in 2 years. Therefore, it’s crucial to take this diagnosis into consideration in patients for early treatment to reduce mortality and morbidity.

**Conclusion:**

GPA is a complex multifactorial pathology, with various clinical manifestations, and specific criteria have not been unified to be able to issue an early diagnosis and timely start of treatment. Pediatric GPA is a rare systemic vasculitis with life-threatening and severe complications. Our case shows the importance of considering the GPA as one of the differential diagnosis amid adolescent presenting with recurrent sinusitis and multiple episodes of epistaxis and joint pain. The early diagnosis of this type of cases leads to early management of the disease and achieve a significant impact on survival and thus improve its prognosis.

**Conflict of Interest:**

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

**Funding:**

This research received no external funding.

**Consent:**

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

**Acknowledgments:**

The authors were grateful to the staffs of the Department of Medicine in Rangpur Medical College & Hospital, Bangladesh.

**References:**


CASE REPORT

POST-COVID-19 INFECTION TIEZTE’S SYNDROME IN A YOUNG ADULT PATIENT

SAYEEF HOSSAIN KHAN MARK1, RASIF HOSSAIN KHAN2, SHAIMA RAHMAN MISHU3, KHAN ABUL KALAM AZAD4

Abstract:
Tietze syndrome is a benign inflammation of one or more of the costal cartilages. The condition is characterized by tenderness and painful swelling of the anterior (front) chest wall at the costochondral (rib to cartilage), sternocostal (cartilage to sternum), or sternoclavicular (clavicle to sternum) junctions. We describe a previously healthy 35 years old gentleman with repeated presentations to the emergency department (ED) with left-sided chest and sternoclavicular pain on a background of recent asymptomatic COVID-19 infection. Labs and imaging subsequently confirmed the diagnosis of Tietze’s syndrome. Anti-inflammatory medications and colchicine eventually led to uneventful recovery. This case highlights how Tietze’s syndrome — a disorder that is potentially self-limiting, can cause recurrent hospital admission and should be a differential diagnosis of chest pain related to COVID-19.

Keywords: Tietze’s syndrome, Costochondritis, COVID-19, nonsteroidal anti-inflammatory drugs, Colchicine, SARS-CoV-2

Received: 28.02.2023 Accepted: 10.04.2023 DOI: https://doi.org/10.3329/bjm.v34i2.63511

Citation: Mark SHK, Khan RH, Mishu SR, Azad KAK. Post-COVID-19 Infection Tietze’s Syndrome in a Young Adult Patient. Bangladesh J Medicine 2023; 34: 155-159.

Introduction:
Tietze’s syndrome; a rare inflammatory disorder distinguished by additional chest wall swelling. These benign conditions are often reproducible on palpation1. Tietze syndrome affects the true ribs and has a predilection for the 2nd and 3rd ribs, commonly affecting only a single joint. The exact cause is often unknown, although it has been associated with few respiratory infections particularly viral. After excluding the other possible serious causes of chest pain, early diagnosis is essential, otherwise it can be stressful for the patient which can lead to recurrent hospital admission. We report a case of a man who presented with left-sided chest and sternoclavicular pain and had confirmed radiologic features of Tietze’s syndrome. This is on the background of full COVID-19 vaccination including booster shot and recent asymptomatic infection.

Case report:
A 35-year-old male, businessman presented to the emergency department (ED) in a tertiary care hospital with symptoms of sudden onset of the left-sided chest pain radiating to his neck at home. Chest pain was sharp in nature and was not associated with cough, shortness of breath, palpitation, leg swelling.

He had no significant past medical history except he was tested positive for COVID-19 three weeks ago with uneventful recovery. He was not on any long-term medications, had no history of any other cardiovascular disease or no significant family history.

Initial investigations including routine blood tests, troponin-T, electrocardiogram, and chest radiograph were unremarkable. He was prescribed analgesia (paracetamol and tramadol) and was sent home with a diagnosis of musculoskeletal pain. He came back

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to emergency department after 3 days as the symptoms persisted with same severity and again was discharged with additional analgesia etoricoxib after a few tests. The initial impression of musculoskeletal pain remained unchanged after the second emergency department presentation. After 4 more days, pain increased in severity to a pain score of 9/10 in comparison to previous presentations which was 7/10 over the next two days and this time, required hospital admission.

On clinical examination, his vitals were normal. The lateral range of movement of his left shoulder was limited due to the pain. Point tenderness was maximal over the left sternoclavicular joint with soft tissue swelling noted. The other systemic examination was otherwise unremarkable.

Investigations revealed normal hemoglobin, platelet, kidney, electrolyte, liver panel, serum uric acid, and creatine kinase including repeated troponin-T levels and d-dimer. Inflammatory markers were elevated with C-reactive protein 95 mg/L (range 0.2-9.1 mg/L), leucocyte count 10.09 (range 4.0-10 x 10^9/L), and erythrocyte sedimentation rate 71 mm/h (range 1-10 mm/h). Laboratory findings are shown in Table 1.

Table-I: Laboratory values of investigations performed

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>15.3 (14-18)</td>
<td>4-10</td>
</tr>
<tr>
<td>WBC (x10^9/L)</td>
<td>10.9 (4-10)</td>
<td>40-75</td>
</tr>
<tr>
<td>Neutrophil (%)</td>
<td>85.9 (40-75)</td>
<td>15-41</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>8.0 (15-41)</td>
<td>14-18</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>88.4 (78-98)</td>
<td>78-98</td>
</tr>
<tr>
<td>Platelet count (x10^9/L)</td>
<td>384 (140-440)</td>
<td>140-440</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>71 (1-10)</td>
<td>1-10</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38 (40-51)</td>
<td>40-51</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>3.2 (2.7-6.9)</td>
<td>2.7-6.9</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>63 (54-101)</td>
<td>54-101</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138 (136-146)</td>
<td>136-146</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.8 (3.6-5.0)</td>
<td>3.6-5.0</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>102 (100-107)</td>
<td>100-107</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>24.8 (19-29)</td>
<td>19-29</td>
</tr>
<tr>
<td>Total calcium (mmol/L)</td>
<td>2.26 (2.09-2.46)</td>
<td>2.09-2.46</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.50 (0.94-1.5)</td>
<td>0.94-1.5</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>95 (0.2-9.1)</td>
<td>0.2-9.1</td>
</tr>
<tr>
<td>D-dimer (microgram/mL FEU)</td>
<td>0.13 (0.19-0.55)</td>
<td>0.19-0.55</td>
</tr>
<tr>
<td>Troponin (ng/L)</td>
<td>11 (&lt;30)</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Uric acid (umol/L)</td>
<td>459 (218-578)</td>
<td>218-578</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>69 (56-336)</td>
<td>56-336</td>
</tr>
<tr>
<td>Bilirubin (umol/L)</td>
<td>15 (7-32)</td>
<td>7-32</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>87 (39-99)</td>
<td>39-99</td>
</tr>
<tr>
<td>Alkaline transaminase (U/L)</td>
<td>19 (6-66)</td>
<td>6-66</td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>30 (12-42)</td>
<td>12-42</td>
</tr>
</tbody>
</table>
Chest X-ray P/A view and X-ray shoulder joint was unremarkable and there was no evidence of fractures or destructive lesions. Electrocardiogram was unremarkable and was in sinus rhythm.

However, an MRI of the sternoclavicular joint was performed to rule out other pathologies as pain was still increasing. There was edema of the left sternocostal joint and also showed edema of his distal left first rib involving the costochondral junction. This was likely due to the close proximity between these locations. There was neither effusion nor significant marrow edema in the sternum (Figures 1-2). There was also enhancing edema in the slightly thickened left pectoralis major muscle and no abscess or fractures were seen. On the basis of the MRI findings, diagnosis of Tietze’s syndrome post-COVID-19 infection was made.

The patient was initially started on nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen 400 mg three times a day. But he was still complaining pain with same intensity after 3 days. Then, he was started with colchicine 500 mcg three times a day. The patient reported a reduction in pain, as well as an improvement in left shoulder range of movement. He was discharged with both regular doses of colchicine and ibuprofen for another one week and was asked to come for follow-up after two weeks. The patient reported a further improvement in his pain of about 80% after two weeks and ibuprofen was given as needed. There was complete resolution of pain after six weeks in the next follow-up.

Discussion:
Tietze’s syndrome occurs due to inflammation of the costal cartilage which connects the ribs to the sternum. Patients frequently present with chest pain that is exacerbated with movement and/or positional changes. The pain tends to be exacerbated by movement and can be both dull and sharp in nature. Often, there is tenderness on palpation of the involved sternocostal joints of the chest wall. Tietze’s syndrome normally affects single joints and is unilateral in 70% of the cases while costochondritis typically affects multiple joints and is bilateral in 90% of cases. Painful swelling of the affected area such as in this case helps to differentiate Tietze’s syndrome from costochondritis.

The exact cause is often unknown, although it has been associated with chronic excessive coughing, vomiting, trauma to the chest as well as respiratory infections particularly post viral. The etiology of chest pain determination in COVID-19 is crucial as lethal causes such as acute myocardial infarction and pulmonary embolism need to be excluded before committing to the diagnosis of Tietze’s syndrome or costochondritis. The treatment generally involves the use of anti-inflammatory medications such as...
NSAIDs. Heat compression over the affected areas can also help to relieve pain. Colchicine was also successfully administered as an alternative to the standard therapy of NSAIDs to help resolve the pain associated with post-COVID-19 costochondritis. In our case report, colchicine helped in addition to conventional analgesia such as NSAIDs and tramadol with good outcomes. Colchicine, a drug traditionally used for gout prophylaxis and treatment, has been used off-label to treat several other conditions such as pericarditis due to its anti-inflammatory properties. Colchicine’s ability to reduce pain and inflammation involves disrupting the cellular cytoskeleton, thereby preventing activation, degranulation, and migration of neutrophils associated with gouty inflammation. Many suggest that colchicine can be used to help fight COVID-19 due to its anti-inflammatory and antiviral properties and that it could help to spare the morbidity and mortality associated with the disease. In the search for drugs that can be repurposed, colchicine has been shown to reduce the risk and severity of cardiovascular events while demonstrating rare risks of myopathies, cytopenia, and transaminitis. Although rarely needed, local administration of combined lidocaine/corticosteroid into costochondral areas can also be done in refractory cases in costochondritis and Tietze’s syndrome. Physiotherapy is crucial in improving symptoms and function caused by costochondritis.

Previously, there has been case reports of post-COVID-19 costochondritis was reported adults who was immunosuppressed. To our best knowledge, this is a first case of post COVID-19 Tietze’s syndrome who was immunocompetent with no past medical history.

We recommend considering post-COVID-19 Tietze’s syndrome and costochondritis as differential diagnoses, especially if other causes have been ruled out in an individual with a recent COVID-19 infection. Early diagnosis and appropriate treatment can prevent repeated emergency department visits and improve patient care.

Conclusion:
This case report demonstrates a case of Tietze’s syndrome in a patient post-COVID-19 infection. The diagnoses of Tietze’s syndrome and costochondritis post-COVID-19 infection should be considered, after ruling out other sinister causes of chest pain. With increased awareness of post-COVID-19 complications, non-life-threatening conditions such as these may have a great impact on a patient’s quality of life. With appropriate diagnosis and prompt targeted treatment, repeated ED visits can be prevented with improved patient experience and reduced financial costs.

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

Funding:
This research received no external funding.

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

References:


A DEADLY TUNNEL: A CASE REPORT OF ATRIAL-ESOPHAGEAL FISTULA AFTER ATRIAL FIBRILLATION ABLATION

FARZANA HOQUE

Abstract:
The left atrial-esophageal fistula is an exceedingly rare but lethal iatrogenic complication after atrial fibrillation ablation. Variability in timing of clinical presentation may lead to delayed diagnosis of this fatal complication. It is crucial to have high clinical suspicion when patients present with new neurologic symptoms, chest discomfort or sepsis after ablation. This is a unique case of a 78-year-old white man who presented with fever, hematemesis & confusion attributed to left atrial-esophageal fistula after ablation for medically refractory atrial fibrillation.

Key words: Atrial-esophageal fistula, atrial fibrillation ablation, atrial fibrillation, cerebral air emboli.

Introduction:
The left atrial-esophageal fistula is an extremely rare iatrogenic complication that happen in between 0.03% to 0.08% of patients undergoing catheter ablation for atrial fibrillation.1,2 The mortality rate is remarkably high, ranging from 67% to 100%.1,2 A major reason for high mortality is failure to have rapid diagnosis.3,4 It often occurs one to six weeks following the atrial ablation.3,4 However, patients can present years after the ablation procedure that may lead to late diagnosis.1,4 An initial presentation to the emergency room (ER) with nonspecific symptoms may not lead to timely correct diagnosis. For this reason, awareness about clinical presentation of this potential life-threatening complication can prompt timely management which could save our patient’s life.

Case Report:
A 78-year-old white man with a past medical history of paroxysmal atrial fibrillation status post 3 radiofrequency catheter ablations presented with fever, hematemesis, and confusion. One month prior to this admission, he underwent radiofrequency catheter ablation to treat refractory atrial fibrillation. The patient was stable after the procedure. Vitals on this admission are remarkable for the temperature of 102.1°F. Labs were significant for WBC of 13.4 × 10^3/µl, lactic acid 3.7 mg/dl. CT head without contrast showed no acute abnormalities. Then, emergency esophagastroduodenoscopy (EGD) was done which revealed a 1 cm superficial ulcer in the mid-esophagus. He developed left hemiparesis two hours after the upper endoscopy. Brain magnetic resonance imaging (MRI) demonstrated multiple bilateral embolic infarcts both in cerebral and cerebellar hemispheres (Figure 1).

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Blood culture grew Streptococcus viridians. Because of multiple bilateral embolic infarcts in MRI brain and positive blood culture, infective endocarditis was high in differential diagnosis. Therefore, a transesophageal echocardiography (TEE) was done which was unremarkable for vegetations and valve regurgitation. Of note, it revealed multiple air bubbles inside the left atrium, an unusual finding highly suggestive of left atrial-esophageal fistula (Figure 2).

This devastating complication can easily be misdiagnosed as infective endocarditis, which can lead to the performance of transesophageal echocardiography (TEE). However, if left atrial-esophageal fistula is suspected, esophageal manipulation with esophagogastroduodenoscopy (EGD), TEE, and nasogastric tube placement is absolutely contraindicated. These procedures can insufflate air through fistula resulting air embolization or increasing the fistula size. In this case, EGD was done due to hematemesis before the diagnosis of atrial-esophageal fistula. Chest MRI or CT with intravenous contrast is the preferred diagnostic test demonstrating extraluminal air, pneumomediastinum, presence of intravenous contrast in the esophagus. Brain MRI should also be done to diagnose cerebral emboli if patient presents with neurologic symptoms.

The prognosis strongly depends on the patient’s clinical status during the diagnosis, time interval between the onset of symptoms and definitive surgical management. The mainstay management is urgent cardiothoracic surgical repair. Recent evidence suggests that surgical intervention leads to better outcomes.
patient survival compared to endoscopic intervention. Of note, both procedures have high operative and mortality risks. Prompt diagnosis and management of this life-threatening condition is paramount to prevent catastrophic complications.\(^3\)

**Conclusion:** Atrial-esophageal fistula is invariably deadly without prompt treatment. Clinicians’ awareness of this rare but highly fatal complication is imperative as delay in diagnosis and definitive management can cause devastating neurological injury or death. Multidisciplinary approach and early cardiothoracic surgical intervention are pivotal for better patient outcomes.

**Financial support and sponsorship:** None

**Conflicts of interest:** None

**References:**
A CASE REPORT OF RESISTANT HYPERTENSION DUE TO RENAL ARTERY STENOSIS: LONG TERM SUFFERINGS OF A MIDDLE-AGED GENTLEMAN

HOMAYRA TAHESEN HOSSAIN1, NAWSABAH NOOR2, SHARMIN AKHTER3, ISHRAT BINTE REZA4, MAHBUB MAYUKH RISHAD2, QUZI TARIKUL ISLAM5

Abstract:
Atherosclerotic renal artery stenosis is the leading cause of reno-vascular hypertension and is prevalent in elderly patients (over 65 years) and those with resistant hypertension. This article presents a case report of a 60-year-old gentleman who presented with resistant hypertension resulting in heart failure and significant morbidity. The patient’s medical history included frequent hospitalizations with uncontrolled hypertension, flash pulmonary edema and heart failure. Despite multiple hospitalizations, the underlying cause of his condition remained unrecognized until further investigation revealed left sided renal artery stenosis as the culprit lesion. Successful renal artery angioplasty resulted in the resolution of the patient’s high blood pressure and improvement of general well-being. This case highlights the potential for resistant hypertension due to renal artery stenosis to be overlooked, particularly in patients with multiple comorbidity. It is important to consider the possibility of renal artery stenosis in patients with uncontrolled blood pressure with recurrent pulmonary oedema, not responding to multiple anti-hypertensive drugs in the highest possible dose.

Key words: Resistant hypertension, Renal artery stenosis, Flash pulmonary edema, Renal angioplasty

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Introduction:
Renal Artery Stenosis (RAS) is a pathological condition that results in restricted blood flow to the kidneys due to the narrowing of the renal artery. Atherosclerotic renal artery stenosis (ARAS) is the most common type of RAS, caused by the buildup of plaque in the renal artery, resulting in a decrease of more than 60% in luminal diameter. ARAS is the leading cause of renovascular hypertension and is prevalent in elderly patients (over 65 years) about 6.8%; more than 14% in patients with another atherosclerotic lesion, and 24% in patients with resistant hypertension (RHTN)1. RAS is found in patients with high blood pressure, chronic kidney disease, congestive heart failure, myocardial infarction, and stroke. RAS can lead to Reno-vascular hypertension, resulting in activation of the Renin-Angiotensin-Aldosterone (RAAS) system, which leads to sodium retention, vascular contraction, and secondary hyperaldosteronism.

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Bilateral or unilateral RAS can cause renal and cardiac failure due to sodium and liquid retention in the kidneys. Ischemic nephropathy is a potential cause of irreversible renal failure that may lead to high blood pressure and chronic kidney disease. RAS may destabilize patients with heart failure or acute coronary syndromes due to uncontrolled blood pressure and volume retention.

Here, we have reported a case of 60-year-old gentleman presented with recurrent severe breathlessness due to acute pulmonary oedema with uncontrolled hypertension. All groups of anti-hypertensive drugs in highest possible dosage along with diuretics failed to control his blood pressure below 140/90 mmHg. Detailed investigations were done to find out any secondary cause of hypertension and later revealed the presence of left sided renal artery stenosis. Successful renal artery angioplasty with the implantation of a drug-eluting stent resulted in the resolution of the patient’s high blood pressure and improvement of general well-being. This case highlights the potential for resistant hypertension due to renal artery stenosis to be overlooked.

Case Report:

A 60-year-old gentleman came to the emergency department in a wheelchair with severe breathlessness. He was unable to walk or lie down due to dyspnoea. There was no fever or cough. Examination revealed he was conscious, oriented, dyspnoeic, and anemic, and his blood pressure was 260/140 mm Hg, pulse 84/min, temperature normal, respiratory rate 30 breaths/minute, SpO2 95% in room air. Auscultation of the chest revealed bilateral fine basal crepitations up to midzone with widespread rhonchi. Fundoscopy revealed grade 4 hypertensive retinopathy. He was immediately hospitalized as a patient of hypertensive emergency. He was managed with intravenous furosemide, other anti-hypertensive medications & other supportive treatments for acute left ventricular failure in the ICU setting.

After some improvement, he mentioned his long story of sufferings. He has suffered from hypertension for the last 20 years with regular medications & follow-ups. However, his BP has remained high for the last 1 year despite regular anti-hypertensive medication intake. Different combinations of anti-hypertensive drugs were prescribed by internists & cardiologists with the highest possible dosage along with diuretics and centrally acting anti-hypertensive drug, but most of the time, his BP was uncontrolled; average BP was > 160/100 mmHg. He used to suffer from exertional breathlessness, unable to perform his daily activities. There was sleep disturbance due to orthopnoea. He was non-smoker, non alcoholic, and used to lead a healthy lifestyle. On routine check-ups, his renal function was found to be deteriorating; serum creatinine became > 2mg/dl. He was gradually becoming anemic.

About 6 months back, he was admitted to CCU with severe breathlessness & was diagnosed with NSTEMI with acute left ventricular failure. His echocardiogram revealed ischemic heart disease with regional wall motion abnormality of the left ventricle (LV), dilated LV with mild LV systolic dysfunction (LVEF =43%), and concentric left ventricular hypertrophy. He was non diabetic. His serum creatinine was 2.8 mg/dl, eGFR 26. HRCT chest revealed healed lesion with fibrotic streaking in the left posterior segment. Coronary angiogram was done, which revealed non-critical coronary artery disease (30-40% stenosis in the proximal segment of the right coronary artery). He was discharged with optimum medical management.

Unfortunately, he needed hospitalization 3 more times with similar complaints within a short period of time. Each time, his blood pressure was very high with features of pulmonary oedema, which used to improve with intravenous furosemide in high doses.

When he was admitted for the fifth time within less than 6 months period, he requested his treating physician team earnestly to come to a solution to his recurrent problem. He & his family were drained physically, mentally & also financially. He was evaluated thoroughly again with the supervision of an internist, cardiologist, and nephrologist. His current anti-hypertensive regime included: Tab Atenolol 50 mg OD, Tab Nifedipine 20mg TDS, Tab Prazosin ER 5mg 2tab TDS, Tab Clonidine 0.1 mg TDS, Tab Furosemide 40 mg 5 tab daily in divided doses. ARB was avoided due to rising serum creatinine. With these 5 antihypertensive drugs in high doses, his blood pressure was still > 160/100 mmHg, pulse was 55-60/ min. He could not lie down or sleep; his life was miserable.

His investigations profile during this setting is shown in Table -01.
Table-I: Investigations

<table>
<thead>
<tr>
<th>Name of Investigation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Blood Count</td>
<td>Haemoglobin- 8.7 mg/dl (MCV, MCH was low); total &amp; differential count was normal, ESR 82 mm in 1st hour,</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>2.14 mg/dl</td>
</tr>
<tr>
<td>Serum electrolytes</td>
<td>Na 134, K 4.73, Cl 104, HCO3 20 mmol/L</td>
</tr>
<tr>
<td>Cardiac Troponin I</td>
<td>Normal</td>
</tr>
<tr>
<td>Name of Investigation</td>
<td>Findings</td>
</tr>
<tr>
<td>NT-pro BNP</td>
<td>&gt;35,000.00 pg/ml (normal &lt; 125.00)</td>
</tr>
<tr>
<td>ECG</td>
<td>Sinus bradycardia with features of left ventricular hypertrophy</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Cardiomegaly with features of pulmonary oedema</td>
</tr>
<tr>
<td>Echocardigram</td>
<td>Concentric LVH with moderate LV systolic dysfunction (LVEF 37%), moderate pulmonary hypertension (PASP 67 mmHg)</td>
</tr>
<tr>
<td>Urin RE</td>
<td>Albumin Trace, otherwise normal</td>
</tr>
<tr>
<td>Liver function, serum calcium, inorganic phosphate, Blood sugar</td>
<td>Within Normal Limit</td>
</tr>
<tr>
<td>USG of KUB</td>
<td>Bilateral chronic renal parenchymal disease (right&gt;left), prominent inferior venacava (2.2cm), mild enlargement of prostate, right sided mild pleural effusion</td>
</tr>
<tr>
<td>ABG</td>
<td>Metabolic acidosis</td>
</tr>
</tbody>
</table>

We were searching for any secondary cause of his resistant hypertension. This time, a meticulous examination of the abdomen revealed the presence of renal bruit. Renal angiogram was performed, which revealed the left renal artery was visualized, which has got 90-95% stenosis at its origin (Fig-1). Stenting of the left renal artery was done by an experienced vascular surgeon in the proper setting (Fig-2), which finally brought the end of the long-term sufferings of this gentleman.

Figure-1: Renal Angiogram showing the stenosis and post stenotic dilatation

Figure-2: Renal Angioplasty with Stenting, showing the Nephrogram

In the follow-up visit after stenting, he came with a happy face without any features of dyspnoea. He does not have any physical complaints now. He can sleep now without an additional pillow. His blood pressure is maintained at 130/80 mm Hg with Tab Bisoprolol 10 mg, Tab Prazosin 5 mg BD, Tab Nifedipine 20 mg TDS, and Tab Clonidine 0.1 mg BD. His lung bases are clear.
Discussion:
Renal artery stenosis (RAS) is a condition characterized by the narrowing of one or both renal arteries and is a major cause of hypertension. The etiology of RAS can be attributed to atherosclerosis or fibromuscular dysplasia, with potential complications including chronic kidney disease and end-stage renal disease.

Detecting RAS is challenging because it is usually asymptomatic, and most cases occur with other diseases such as chronic kidney disease and diabetes. Screening for RAS can be done using Doppler ultrasound, computed tomography angiography, and magnetic resonance angiography. The gold standard for diagnosis is renal angiogram. In this case, imaging modalities help us to make the diagnosis of left sided renal artery stenosis.

Treatment of RAS involves various medical measures, such as blood pressure control, lipid-reducing therapy, and antiplatelet agents. Lifestyle modifications such as dietary counseling, smoking cessation, and physical activity are also recommended. Accurately correcting dyslipidemia, using drugs that block platelet aggregation, may require three or more different drugs to control blood pressure. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are preferably used for this purpose. Unfortunately, these two classes of drugs can also lead to an increase in serum creatinine and hyperkalemia and limit their use. In such a case, calcium channel blockers are a potential alternative. Fat reduction therapy is widely accepted as an important treatment for all atherosclerotic vascular diseases. A statin is recommended to achieve LDL ≤ 70 mg/dL. In a retrospective study, statin treatment was associated with a lower progression rate for renal failure (7.4% vs. 38.9%) and lower overall mortality (5.9% vs. 36.1%), P<0.001 for both. The use of antiplatelet agents and smoking cessation in patients with ARAS has the same benefits as the other forms of atherosclerotic disease, including coronary and peripheral vascular disease.

Invasive procedures, such as renal artery stenting (PTRAS), are the preferred choice in most patients with high-grade RAS and cardiac instability symptoms. Stenting has been associated with improved kidney function and overall survival. Revascularization can also enable treatment with renin-angiotensin blockers, which may confer mortality benefits in patients with RAS who tolerate these medications. Our patient had improvement in his blood pressure control within days after his procedure, and it has remained controlled in follow-up. He has had no further admissions with heart failure or pulmonary edema. Similar improvement of heart failure has been described by Alyamani M et al. after renal angioplasty in a patient with renal artery stenosis. Also, Milewski et al. analyzed the clinical improvement of hypertension in 265 consecutive patients with ARAS treated with stenting.

In summary, here we presented a case study of a patient with unilateral RAS who experienced rapid improvement in blood pressure control within days of renal artery stenting, with sustained good results at follow-up visits. No adverse events were observed, and the patient's general condition remained good. These findings highlight the potential benefits of renal artery stenting in managing RAS and associated complications.

Conclusion:
Renal artery stenosis (RAS) leading to resistant hypertension can result in significant morbidity, which can be prevented with appropriate management. However, diagnosing and treating RAS can be challenging. A high level of suspicion is necessary for timely diagnosis. Revascularizations of the affected vessel are beneficial, particularly in sicker patients with recurrent hospitalizations due to hypertensive emergency and flash pulmonary edema.

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

Funding:
This research received no external funding.

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

Acknowledgments:
The authors were grateful to the staffs of the Department of Medicine in Popular Medical College & Hospital, Bangladesh.

References:
A Case Report of Resistant Hypertension due to Renal Artery Stenosis


CASE REPORT

IF THE MIND DOESN’T KNOW, THE EYES CANNOT SEE: A CASE REPORT OF LOCALIZED TETANUS

NAWSABAH NOOR1, HOMAYRA TAHSEEN HOSSAIN2, MOHAMMAD MOHSIN3, MAHBUB MAYUKH RISHAD1, MOHAMMAD ZAHIRUDDIN4

Abstract:
Tetanus is a vaccine-preventable disease caused by a potent neurotoxin released by an obligate anaerobic bacterium, Clostridium tetani infection. Presentations of tetanus include generalized tetanus, neonatal tetanus, cephalic tetanus, and localized tetanus, the latter two being much rarer. This is a case report of localized tetanus involving the facial muscle in the form of lock jaw in 63-year inadequately immunized gentleman following an unhygienic tooth extraction from rural area. The condition deteriorated further, and the patient was under ventilatory support for 3 days. The patient had antibiotics, antitetanus serum, sedatives, and wound care. The case is reported because of the rarity of localized tetanus, the diagnostic dilemma presented by the case, and the cultural interplay and understanding of the disease process by the patient/caregivers. It is also reported to highlight the gap in routine immunization and the need for booster doses in this age group. Successful management includes prompt diagnosis, neutralization of circulating toxin and elimination of C. tetani infection, control of spasms, maintenance of the airway, and management of respiratory failure and autonomic dysfunction.

Key words: neurotoxin, tetanus, lock jaw, Trismus, Local tetanus

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Citation: Noor N, Hossain MT, Mohsin M, Rishad MM, Zahiruddin M, Islam QT. If the Mind Doesn’t Know, the Eyes cannot See: A Case Report of Localized Tetanus. Bangladesh J Medicine 2023; 34: 168-170.

Introduction:
Tetanus is a severe and potentially fatal infectious disease caused by the bacterium Clostridium tetani, which produces the neurotoxin tetanospasmin1. While the classical generalized form of the disease is more common and often requires ventilator support, atypical forms such as neonatal, cephalic, and localized tetanus are infrequently reported in clinical practice2. Looking into the journals and scientific literature, we can find very few publications on localized tetanus in humans. Despite their rarity, it is essential to recognize these subtypes early for timely diagnosis and treatment.

We present a case of localized tetanus in a 63-year-old male with inadequate immunization status who underwent an unhygienic tooth extraction in a rural area. The patient presented with lockjaw involving the facial muscles, and the diagnosis was initially challenging to establish. However, careful examination and evaluation ultimately confirmed the presence of localized tetanus.

This case report serves as an important reminder to healthcare providers in intensive care units to be aware of the unique features of localized tetanus and consider it a potential diagnosis in patients presenting with clinical manifestations. Early recognition and appropriate management are critical in achieving...
favorable outcomes in patients with this rare subtype of tetanus.

**Case Report:**
A 63-year-old hypertensive, non-diabetic Bangladeshi gentleman came to a tertiary care hospital with a sore throat for 10 days associated with odynophagia. After a few days, he started facing difficulties opening his mouth and chewing food. He also complained of non-productive cough for ten days. He had no complaints of excessive salivation, anorexia, nausea, fever, nasal regurgitation of food or nasal voice. Suddenly he developed severe shortness of breath, and oxygen saturation was falling, for which he got hospitalized. As a child, the patient had received a complete immunization program but had no further boosters. Furthermore, he did not give any history of ingestion of poisonous substances or any alternative medications.

On admission, the patient was ill-looking, dyspnoeic with average build, pulse was 78 beats/minute, blood pressure 160/90 mm Hg; respiratory rate was 26 breaths/minute, SPO2 was 80% in room atmosphere; GCS score was 15/15. He had widespread coarse crepitations on chest auscultation. He was then given 4–5L oxygen, after which his saturation increased to 96%. On complete neurological examination, no abnormality was detected, including intact cranial nerves.

The complete blood count result showed slight leukocytosis (14.42 K/μL), and CRP and CPK were slightly raised. CPK was 836 g/dL and CRP was 184 mg/L. The Blood culture and sensitivity yielded no growth; cerebrospinal fluid analysis was not suggestive of bacterial meningitis; serum electrolytes, urea, and creatinine, as well as serum calcium, magnesium, and phosphate, were normal.

To manage the patient, a multidisciplinary admission team was formed involving a Medicine specialist, Otolaryngologist, oral and maxillofacial surgeon, psychiatrist, and critical care medicine specialist. One day later, his saturation had drastically dropped to 35%, and he had to be intubated. He was on life support for three days. After extubation, he was hemodynamically stable with minimum oxygen support (99% with 2L oxygen), but the patient had difficulty in speech, and the previous complaints of difficulty in opening his mouth and sore throat were still persistent. Again, the multidisciplinary team reviewed the patient once again, and then on a query, we found that the patient had a history of tooth extraction 2.5 months back from a local non-registered dentist in a rural village. On further examination, it was found that he had trismus and rigidity of the muscles of the face and neck, which was initially missed. There were no apparent spasms in other parts of the body.

Given spasmodic contractions localized mainly on the face, a diagnosis of localized tetanus was made, and immediately human tetanus immunoglobulins, 3000 IU IM, were given to the patient to neutralize the circulating toxins along with the administration of tetanus toxoid (TT). For muscle spasms, a diazepam infusion of 1 mg/kg/day was given, with which his spasm subsided and was tapered within three days and switched to the oral form. He did not have any further worsening.

Here, localized tetanus was diagnosed in this patient based on repeated clinical examination and the retrograde method of exclusion. After ruling out other possible causes of the patient’s symptoms and finding of normal results from previous investigations, the diagnosis of localized tetanus was being considered by finding the trismus and the supportive history. The diagnosis was indirectly confirmed by administering tetanus immunoglobulin and tetanus toxoid to which the patient responded well. He was discharged after a week in good health and no residual deficits were detected during follow-up. Prompt diagnosis and treatment of tetanus are crucial to prevent severe complications and ensure a positive outcome for the patient.

**Discussion:**
Clostridium tetani is an anaerobic bacterium commonly found in soil and the gastrointestinal tracts of mammals, and it produces the potent neurotoxin tetanospasmin. The incubation period for tetanus typically ranges from 3 to 21 days, with an average of 10 days. Tetanospasmin exerts its effects by blocking the release of the inhibitory neurotransmitter α-aminobutyric acid, resulting in violent spastic paralysis.

Although national immunization programs have successfully reduced the incidence of tetanus in developed countries, there are still cases with non-specific prodromal symptoms that can progress to generalized tetanus. Localized tetanus is a rare subtype, with only a few cases reported in the literature over the past decade. Diagnosing tetanus is primarily clinical, but distinguishing between localized and other forms of the disease can be challenging, especially when the presentation is atypical. The former involves muscle spasms limited to specific body areas with generally good outcomes. However, rare cases go on to involve vital structures.
such as the cranial nerves leading to cephalic tetanus and increasing the risk of developing generalized tetanus with high mortality rates.\(^5\)

However, a case of localized or cephalic tetanus has a varied presentation and may be difficult to distinguish from a local disorder involving the joints or a hysterical disorder. Cephalic tetanus commonly follows craniofacial injuries, as with our patients. Dong Hyuk Seo et al. reported a case report of cephalic tetanus in 64 years old lady who presented to the hospital with ptosis, facial nerve palsy, and trismus after a forehead abrasion injury after a road traffic accident. Similarly, our patient had a history of facial and dental injury following unhygienic tooth extraction in a rural area and developed localized tetanus. The patient presented with lockjaw involving the facial muscles, which made the diagnosis challenging initially. However, careful evaluation ultimately confirmed the presence of localized tetanus. Likewise, Bassey GO et al.\(^8\) and Ajayi EA\(^9\) reported different case reports of localized tetanus after tooth extraction.

Localized tetanus has a generally good prognosis, but aggressive management is required to prevent progression to generalized tetanus. About two-thirds of cephalic tetanus cases progress to generalized tetanus with bad prognosis.\(^10\) The prognosis is good for those who do not progress to generalized tetanus. However, our patient did not progress to generalized tetanus, with a good outcome, probably, due to prompt intervention.

Treatment principles include neutralizing the toxin with tetanus immunoglobulin and wound debridement, with metronidazole being the antibiotic of choice. However, caution is advised when using penicillin, as it may exacerbate spasms. Complete primary immunization is recommended for all patients with tetanus to ensure adequate immunity.\(^11\) Our patient responded well after administering tetanus immunoglobulin, tetanus toxoid and diazepam. A retrospective analysis done in 2001 by Kakou et al. showed a cure rate of 82% with 16% mortality in 37 cases reported of tetanus in the last 22 years.\(^2\)

**Conclusion:**

In conclusion, this case highlights the significance of maintaining a broad perspective while managing patients in today’s interconnected world. Obtaining a detailed medical history, including information on prior treatments, occupation, recent travel, and exposure to materials, can provide valuable insights in situations where clinical manifestations are atypical. As such, clinicians must remain vigilant and consider all possibilities to make an accurate diagnosis and provide appropriate care.

**Conflict of Interest:**

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

**References:**

I was a bit late in my daily round in the hospital that day. Senior Medical Officer Dr. Asif rushed towards me with anxious face and asked me to move to the High Care ward for a 65-year-old female patient who was in collapse with profuse hematemesis. Ringer’s lactate was on running IV. It took me less than a minute to understand the situation. Emergency blood requisition was already sent. After having a quick short history from her daughter, I was at a loss, “Possibly the patient is on the edge.”

After 2 units of blood transfusion her vitals were stable and the lady could communicate but still drowsy. Total 4 units of blood had been transfused. Initially my thoughts were oesophageal variceal bleeding or bleeding peptic ulcer.

Next day the patient was fully conscious and well oriented, vitals were good. She smiled at means thanked me for the care of the doctor. I thanked the Almighty that my patient is stable now and started talking with her. I requested the attending nurse to expose the patient’s abdomen so that I could examine her. A moderate sized tender lump was felt in my hand in the right hypochondrium. Tender epigastrium and mild ascites were also appreciated. In the next 24 hours, Endoscopy of upper GI tract, Ultrasound of abdomen, and CECT abdomen had been done and those reports were a slap on my face. There was a mass in the gall bladder which invaded almost all of the stomach with peritoneal seedling, also multiple intra-abdominal lymph nodes and ascites. Liquid diet was advised with parenteral nutritional support.

Her past histories were more tragic. Back in 2015, she suffered from endometrial carcinoma. Total hysterectomy with bilateral salpingo-oophorectomy was done followed by chemotherapy and brachytherapy. She was doing well with the treatment given to her.

In 2018, she had been diagnosed as a case of papillary carcinoma of the Thyroid gland. After radical thyroidectomy she was on thyroxin replacement.

In the doctor’s room, the daughter of the patient was crying and asking for the present diagnosis of her mother, “Is this cancer again?” All the doctors around me and myself were out of words for a few minute. I could not answer to her. The environment of the room was gloomy. Dr. Raka suddenly rushed in to the room who was with the patient and told that the patient was having another episode of massive haematemesis and was critical. The patient was gasping.

Immediately shifted to the ICU she was intubated quickly. Urgent chest x-ray showed both lungs is opaque up to mid zone suggestive of huge aspiration of blood as evidenced by the blood-stained fluid through endotracheal tube. Patient survived for next 2 days with supportive treatment.

We all went numb with the whole story. What are the odds for a patient to face three different malignancies in three different years. She stood every one of them with a great courage and a warm smile till the last one. It was the Stage 4 carcinoma of gallbladder with metastasis that took her life on 10th March 2023.

To me, in my 4 decades of clinical practice I had never encounter such type of case that distinct malignancies took its toll in one organ after another. God must be crazy.

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A 35-year-old lady presented with progressive breathlessness, dysphagia for 3 months, and hoarseness of voice for 1 month. She was on anti-tubercular drugs for the presumptive diagnosis of pulmonary tuberculosis, but there was no response. Physical examination revealed irregularly irregular pulse, tapping apex beat, variable intensity of S1, and a localized mid-diastolic murmur in apical area. Endoscopy of upper gastrointestinal tract found no organic lesion. She underwent barium (Ba) swallow X-ray of oesophagus (A), echocardiography (B), and fibreoptic laryngoscopy (FOL) (C).

Questions:
A. What are the findings in Ba-swallow x-ray of oesophagus?
B. What is the single-most important observation in echocardiography?
C. Mention the relevant finding(s) in fibreoptic laryngoscopy.
D. What is the clinical diagnosis?
E. Outline the pathophysiology of the condition.
A 28-year-old woman with no past medical history presents to the general physician with a 4-month history of waxing and waning unilateral visual impairment and facial numbness back. Then she was referred to a neurologist. She gave the history as follows. She was reasonably well 4 months back when she noticed the onset of right-sided facial numbness and blurred vision lasting several weeks and tingling sensation to the right upper limb. She states that three episodes have occurred during the past 6-month time period. There was no associated muscle weakness of the facial muscles. Earlier today, upon waking up, the patient noted a sudden onset of blurry vision in her right eye and numbness on the right side of her face. She states she has not observed any muscle weakness, gait disturbance, fever, or urinary incontinence. Physical examination reveals a well appearing, anxious woman. Vital signs are temperature: 98.6 °F, heart rate:76 beats per minute, blood pressure: 110/70 mmHg, respiratory rate: 16 breaths per minute. Neurologic exam reveals fundoscopy including visual acuity normal in the right eye. Muscle strength is 5/5 in all extremities. There is unilateral loss of sensation on the entire right half of the face; otherwise, all other cranial nerves are intact. Romberg sign is negative, and no gait disturbances are noted. Cardiac, pulmonary, and abdominal examinations are unremarkable.

A MRI of brain and spine had done and T2WI were given below. Answers the following questions.

A. What is the imaging finding?
B. What is the most likely diagnosis?
C. What are the common differential diagnoses?
D. Which biochemical test is done to confirm the diagnosis?
E. What are the main modalities of acute treatment?

Figure: 1 Axial magnetic resonance imaging (MRI) of brain (A-C) and MRI of the cervical spine (D)

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**Answer to Medical Quiz - 1**

AKM MONWARUL ISLAM, HUMAIRA JESMIN

**Answers:**

A. Ba-swallow X-ray of oesophagus oblique view reveals posterior displacement of the oesophagus with smooth indentation on the anterior border presumably by the dilated left atrium.

B. Two-dimensional echocardiography apical 4-chamber view shows hugely dilated left atrium.

C. Fibreoptic laryngoscopy shows unilateral (left) vocal cord palsy.

D. Ortner’s syndrome due to mitral valvular disease with left recurrent laryngeal nerve palsy.

E. Mitral valvular disease causes huge dilatation of left atrium, the result of which is dysphagia. The dilated left atrium compresses the left recurrent laryngeal nerve leading to left vocal cord palsy. The vocal cord palsy results in hoarseness of voice, recurrent aspiration, and respiratory tract infection. Hoarseness of voice due to recurrent laryngeal nerve palsy secondary to nerve impingement, stretching, or compression at the mediastinum classically due to mitral stenosis in called Ortner’s syndrome or cardiovocal syndrome.

**Review:**

Ortner syndrome, also called cardiovocal syndrome, refers to left recurrent laryngeal nerve palsy due to cardiovascular disease. Mitral stenosis is a well-recognized cause; however, other conditions like mitral valve prolapse, aortic aneurysm, pericardial effusion and primary pulmonary hypertension may cause Ortner syndrome.¹⁻³ Left recurrent laryngeal nerve palsy causes the hoarseness in Ortner syndrome. The nerve injury is commonly caused by the pressure effect on the nerve by the dilated left atrium or other structures like dilated pulmonary artery, aortic aneurysm, or even pericardial effusion.

Hoarseness of voice, recurrent aspiration pneumonia, dysphagia and features of underlying cause are the common manifestations.

High degree of clinical suspicion is needed for diagnosis. Besides chest X-ray, echocardiography, computed tomographic scanning of chest and fibre-optic laryngoscopy are the first-line investigations.₁

Treatment is mainly directed to the correction of underlying pathology. Early management of underlying condition and advanced treatment of vocal cord palsy might improve hoarseness of voice.

**References:**

Answer to Medical Quiz - 2

AMINUR RAHMAN

Answers:
A. Right cerebellar hemisphere, in the left pons & superior colliculus and adjacent to the lateral ventricles and cervical cord lesion with marked swelling.
B. Neuromyelitis optica spectrum disorder (NMSOD)
C. Multiple sclerosis (MS)/Acute disseminated encephalomyelitis (ADEM)/ Sarcoidosis,/CNS vasculitis/ Leber hereditary optic neuropathy,
D. Serum Anti-AQP4 antibody
E. Intravenous methylprednisolone/ Plasmapheresis

Review:
Neuromyelitis optica spectrum disorder (NMOSD) is a rare and chronic autoimmune disorder of the central nervous system (CNS) that typically presents with inflammation to the optic nerves (optic neuritis) and the spinal cord (acute transverse myelitis) caused by an autoantibody to the aquaporin-4 water channel. The classic presentation of NMO is with the triad of optic neuritis, longitudinally extensive myelitis, and positive anti-AQP4 antibody, although a far wider range of manifestations are now recognized as part of NMOSD.

Neuromyelitis optica is typically found in patients somewhat older than those with multiple sclerosis (MS), with an average age of presentation of 41 years, and there is an even stronger female predilection (F:M 6.5:1). It is found more frequently in patients of Asian, Indian, and African descent. NMO is characterized by bilateral optic neuritis and myelitis resulting in blindness and paraplegia. Although the two usually present concurrently, it is not uncommon for one to precede the other by up to several weeks. Additionally, it is now recognized that some patients present with unilateral optic nerve involvement.

Although NMO was initially thought of as a monophasic illness, it is now evident that, as with MS, it is usually a relapsing-remitting disease with symptomatic events separated by many years.

Furthermore, NMOSD also encompasses non-neurological manifestations in anti-AQP4 antibody seropositive patients including systemic lupus erythematosus (SLE) and Sjogren's In approximately 70% (sensitivity of 70-90%; specificity of 90%) of patients with established NMO, a specific immunoglobulin can be isolated (AQP4-IgG) which targets a transmembrane water channel (aquaporin 4) present on astrocyte foot processes abutting the limiting membrane.

The most common diagnostic test used for diagnosing NMOSD is MRI of the brain, orbits, and spinal cord. Imaging of the CNS is typically performed with gadolinium, and follow-up examinations are obligatory.

A curative treatment for NMOSD does not currently exist. Intravenous methylprednisolone is the first-line therapy for treatment of acute NMOSD. Plasma exchange is used as a second-line therapy. Treatment in the acute or early stages aims to improve relapse symptoms and restore neurological function.

References:
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