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Editorial

Original Article

Case Report

Editorial

Safe Fasting for Diabetic Patients

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Fasting in the holy month of Ramadan is one of the five pillars of Islam. Fasting for patients with diabetes can become a serious problem if proper precautions are not taken. Navigating Ramadan with diabetes requires careful planning and close monitoring. The changes in eating and sleeping patterns can significantly impact blood sugar levels, making it crucial for individuals with diabetes to understand the potential risks and how to address them.[1] I will try to summarize the risks and challenges of diabetic patients in Ramadan and will suggest evidence-based solutions to these problems. Ramadan involves fasting from dawn to sunset, meaning prolonged periods without eating and drinking[1,2,3]. This can lead to the following complications:

Hypoglycemia is a significant risk, especially during the later hours of the fast. Symptoms include lethargy, dizziness, sweating, confusion and even coma.

Hyperglycemia (high blood sugar): Eating sugary or carbohydrate-rich foods during Iftar (the evening meal) can cause very high blood sugar spikes. Symptoms may include dry mouth, thirst, increased urination, weakness, nausea and vomiting, restlessness etc.

Lack of water and other fluids during fasting can lead to dehydration, low blood pressure and further complications

Increased risk of diabetic ketoacidosis (DKA) is a serious complication that can occur when high levels of blood acids called ketones are produced in the body. It is mainly seen in type 1 diabetes but can also present in patients with type 2 diabetes.

Effective diabetes management during Ramadan involves a combination of pre-Ramadan counselling, dietary and medications' adjustments and regular glucose monitoring.[1,2] All this should start 6-8 weeks before Ramadan when patient should visit his/her physician for proper guidance about fasting.

It is important that diabetic patients should consult their physician well before Ramadan, ideally 6-8 weeks for proper advice and adjustment of medications' dosages. [1,2,5] Risk stratification is important. The attending physician will assess each individual's risk for fasting. It is a simple calculation based on age of patient, type of diabetes, previous experiences of fasting, chronic complications of diabetes, type of medications etc., and stratifies the individuals in low, moderate and high risk categories. Low risk patients can fast safely, moderate risk can fast but with precautions and high risk individuals are advised against fasting. Suhur (pre-dawn meal): should be balanced and should include complex carbohydrates, fiber, and protein to provide sustained energy. [1,3,4] Patients should take in plenty of water to keep them hydrated. Iftar (evening meal) Break the fast with 1-2 dates and water, followed by a balanced meal. Avoid excessive consumption of sugary drinks and fried foods. Fruit juices are generally avoided and if taken the quantity should not exceed 180 ml. Rather, taking fresh fruits is recommended. Portion control is key to healthy fasting in Ramadan. Proper drinking of water is very important to maintain hydration. Medication dosages and timings must be adjusted and individualized during Ramadan under the guidance of a certified healthcare

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professional.[1,4] Individuals taking insulin or certain oral medications are at higher risk of hypoglycemia and must see their physician for their adjustment. [1,3]

Frequent blood sugar monitoring is essential during fasting to avoid hypo or hyperglycemia. Research has proven that there are timings when chances of hypo or hyperglycemia are maximum. These include suhoor time, 2 hours after suhoor, at mid-day, at afternoon, pre-iftar and 2 hours after iftar. Patient should monitor their sugar levels at these times or at any other time when they experience symptoms of hypo or hyperglycemia. It is important to know that it does not break the fast.

It is advisable to break the fast if: Blood sugar levels drop below 70 mg/dL (3.9 mmol/L), blood sugar levels rise above 300 mg/dL (16.7 mmol/L), [1,2,3] patient experiences symptoms of hypo or hyperglycemia. Moderate exercise is generally safe. Patients can continue their usual exercise schedule after iftar. [1,2,3] No additional exercise is advised for those who pray 'Tarawih'. In summary, safe fasting in Ramadan is quite possible for diabetic patients if they follow timely pre-Ramadan counselling with their physician, risk stratification, dietary and medications adjustments and proper exercise as advised in the guidelines.

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Original Article

CORRELATION BETWEEN BMI AND CARRYING ANGLE AMONG YOUNG ADULTS OF MEDICAL COLLEGE IN LAHORE

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ABSTRACT

Background: The carrying angle refers to the angle formed between the arm's long axis and the forearm at elbow joint, also referred to as cubital angle. Body Mass Index (BMI) is a metric used to evaluate a person's weight in proportion to their height. Carrying angle and other anthropometric measurements have been studied to explore differences in CA. The objective of the study was to analyze the correlation between BMI and Carrying angle among young adults in Lahore.

Materials and Methods: It was a cross-sectional study design. One-hundred & forty-six healthy young adults (18-25 years of age) were taken by non-probability convenience sampling, out of which 81 were females and 65 were males. Carrying Angle was measured using Goniometer. Weight was measured with a scale, height with a measuring tape, and pelvic circumference with a measuring tape. Correlation of BMI and Carrying Angle among young adult population was determined by using Pearson's Correlation Coefficient and shown with scatter diagram

Results: The carrying angle showed no correlation with BMI, pelvic circumference, or weight. There was significantly. The correlation between height and carrying angle of left side was -0.184 with p-value of 0.026 and at right side it was -0.189 with p- value of 0.023.

Conclusion: No significant correlation was identified between the carrying angle and BMI, pelvic circumference or weight. BMI correlated negatively with Height.

Key Words: Carrying angle, Body Mass Index, Young Adults, Goniometer

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INTRODUCTION

Body Mass Index is a parameter that interprets fitness through a wide range varying from being underweight to obese in various age groups which is further marked by different biological and psychological changes.[1,2] There are various anatomical variations that exists with respect to BMI. These changes bring about biomechanical differences in execution of function. Some studies have found that the ranges of motion for elbow flexion, supination, hip extension, knee flexion, and ankle plantar flexion were notably smaller in the overweight and obese groups than in the normal-weight group.[3,4] Elbow is a complex hinge joint between the humerus and forearm bones (radius and ulna), allowing flexion, extension, and limited rotation, which is stabilized by ligaments and tendons, and protected by articular cartilage to reduce friction.[5, 6] The CA is the angle between the arm and forearm in the anatomical position, also known as Cubital Angle. It can be measured using a goniometer or X-ray images. The universal goniometer

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shows high intra- and inter-rater reliability for measuring the elbow joint.[7] Studies show that the carrying angle is greater in women (13.6°) compared to men (6.7°), and it correlates with forearm length.[8] Variation in CA has been heeded with respect to gender and other anthropometric measures.[9] An increase or decrease in carrying angle is referred to as valgus and varus deformity, respectively. These deformities can lead to elbow instability, pain and other associated symptoms leading to disability.[10] BMI has been widely studied in various populations to study the variations of carrying angle. In most studies higher BMI is found to be associated with a greater carrying angle.[11] Tantawy SA et al., has explained a positive correlation between musculoskeletal disorders (MSDs), academic stress, and BMI.[12] Assessment of the elbow carrying angle in healthy individuals showed significant correlations with height ($r = 0.366$, $p < 0.001$) and arm length ($r = -0.273$, $p < 0.001$).[13] Patel MR et al., study, conducted on 200 young adults, investigated how changes in the carrying angle affect grip strength. A significant negative correlation between the carrying angle and grip strength of both hands was found, suggestion that smaller carrying angle leads to more grip strength, or vice versa.[14] There is a vast literature available that examines the relationship between carrying angle and various anthropometric factors in diverse populations of different age groups. The objective of this study was to assess the relationship between body mass index and carrying angle among young adults at a medical college in Lahore.

MATERIALS AND METHODS

The study was conducted at Akhtar Saeed Medical and Dental College in Lahore, with approval granted by the Institutional Review Board (IRB) under approval number M23/135/ - DPT, dated 29-08-2023. Using a cross-sectional study design, 146 medical students, both male and female, were selected through a non-probability convenience sampling method. The sample size was calculated using Taro Yamane formula having 95% confidence interval.[15] The study was completed in 6 months from June 2024 to November 2024. The main variables under study were BMI and carrying Angle of elbow joint. To calculate BMI was a composite variable which comprised of weight and height. Weight was measured by weight scale (in kg) and height was measured by measuring tape (in meters). The carrying angle of the elbow was assessed using a goniometer (measured in degrees). The person was positioned on their back, with the elbow straightened and rotated outward. The goniometer's hinge was aligned with the cubital area, with the ulna at the distal and the humerus at the proximal end, placed along the front of the upper limb. Equipment used were Goniometer, Weight Scale and Measuring Tape. The inclusion criteria were students of Akhtar Saeed medical & dental college, both males and females, within age group of 18-26 years. The individuals with congenital deformities of upper extremities, fractures or surgeries around the elbow joint & Paget's disease were excluded from the study. The data was analyzed using SPSS version 27. BMI, Carrying Angle and Pelvic circumference were presented using mean, standard deviation. Demographic variables of gender and hand dominancy were presented through frequency tables. Correlation of BMI and Carrying Angle among young adult population was obtained by using Pearson's Correlation Coefficient. The p-value of 0.05 or less was considered significant.

RESULTS

The results of this study showed that mean age of participants was 21.92 years, mean pelvic circumference of participants was 88.38cm and mean BMI of participants was 22.18 kg/m^2. It is depicted in table 1.

Majority of participants had right dominant hand. Out of 146, only 10 participants had

left dominant hand out of the sample taken from medical students, 81 were females and 65 were males as shown in table 2.

No significant correlation was found between the carrying angle of either elbow and the BMI or weight of the participants. A significant negative correlation, however, was noted between the carrying angles of the right and left elbows and the height of the participants, with a p-value of 0.05 or below indicating statistical significance. (Table no:3)

Table no. 1: Mean Age, Pelvic Circumference and BMI of Participants:

	N	Min	Max	Mean	Std. Deviation
Age (in years)	**146**	**18.00**	**26.00**	**21.92**	**1.57**
Pelvic Circumference (in cm)	**146**	**72.00**	**112.00**	**88.38**	**8.15**
BMI (kg/cm^2)	**146**	**15.20**	**33.50**	**22.18**	**3.64**
Carrying angle left (in degrees)	**146**	**3.00**	**21.00**	**12.67**	**3.96**
Carrying angle right (in degrees)	**146**	**4.00**	**23.00**	**14.69**	**3.87**

Table no. 2: Frequency of Dominant Hand and Gender of the Participants:

Dominant Hand		
	Frequency	**Percent (%)**
Left	**10**	**6.8**
Right	**136**	**93.2**
Total	**146**	**100.0**
Gender of the Participants		
	Frequency	**Percent (%)**
Male	**65**	**44.5**
Female	**81**	**55.5**
Total	**146**	**100.0**

Table no. 3: Correlation between Carrying Angle of Both Hands and Weight of Participants:

variables	Mean	Standard Deviation	N	r	p
BMI	22.18	3.64	146	0.002	.981
Carrying Angle (right)	14.69	3.87			
BMI	22.18	3.64	146	0.04	.633
Carrying Angle (left)	12.67	3.96			
Weight (kg)	62.02	12.66	146	-0.12	0.14
Carrying Angle (right)	14.69	3.87			
Weight (kg)	62.02	12.66	146	-0.07	0.43
Carrying Angle (left)	12.67	3.96			
Height	166.97	9.34	146	-0.184	0.026
Carrying Angle (right)	14.69	3.87			
Height (cm)	166.97	9.34	146	-0.189	0.023
Carrying Angle (left)	12.67	3.96			
Pelvic Circumference	88.37	8.15	146	-0.03	0.75
Carrying Angle (left)	12.67	3.96			
Pelvic Circumference	88.38	8.15	146	-0.07	0.41
Carrying Angle (right)	**14.69**	**3.87**			

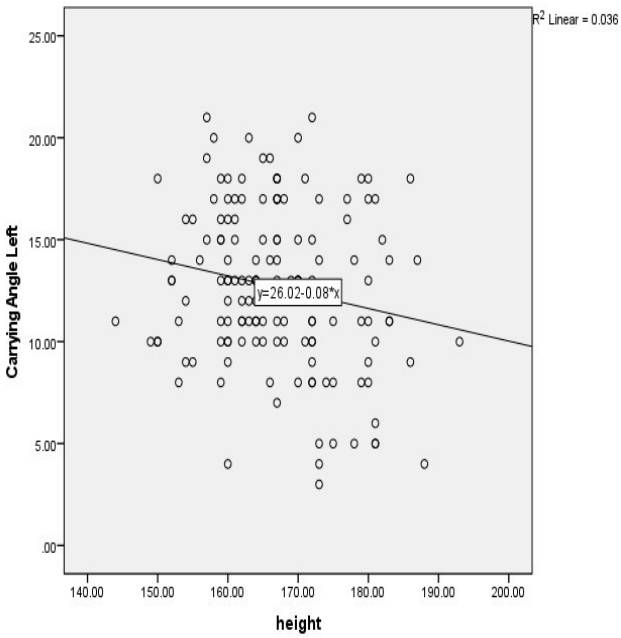

Figure no. 1: Correlation between Carrying Angle of Right Elbow and Height.

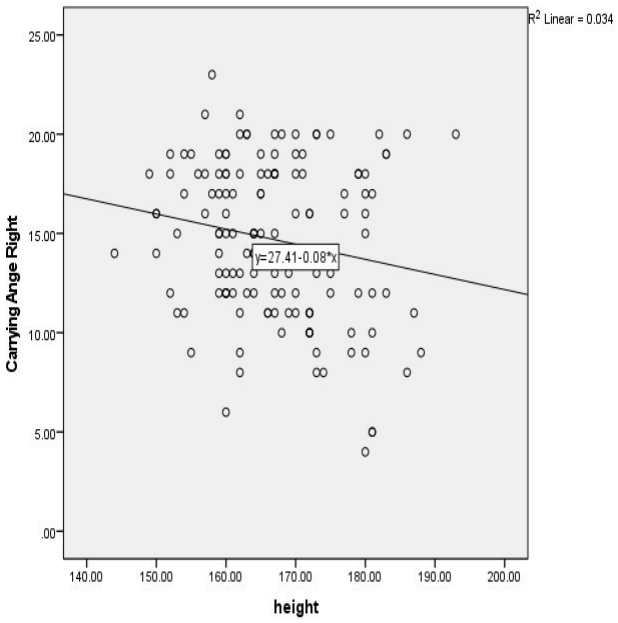

Figure no. 2: Correlation between Carrying Angle of Left Elbow and Height

DISCUSSION

A study conducted by Rajesh B et al., on evaluation of the CA of the elbow joint in the juvenile concluded that an average carrying angle of 13.6° in females and 6.7° in males. However, our study observed a mean carrying angle of 15.4° in females and 13.7° in males. The slight discrepancy warrants further exploration, particularly in terms of demographic differences between the two studies.[8] A similar study was conducted by Ahmed SK et al., on Determination of Carrying Angle of Elbow Among Adult Pakistani Population. The study with 500 participants from Indus Hospital, Karachi, found a mean carrying angle in females (14.4°) similar to this research. However, the mean carrying angle in males (9.5°) differed from this research.[16]

Another study performed by Sadacharan CM et al., on Carrying angle of the elbow joint in young Caucasian and Indian American population. A descriptive cross-sectional study performed on 200 students, concluded that females had larger CA than males similar to this research as shown in table 7.4. Both the studies have similar age groups consisting of young adults.[17]

An Anthropometric Study of Carrying Angle and other Parameters in Young Adults of Kathmandu, Nepal by Yadav SK et al., also showed that females had greater carrying angle values than in males. Both the method of measurement of carrying angle and age group of participants were same in both researches.[18]

Hypothesizing a gender-related carrying angle difference linked to pelvis width, our study found no correlation between carrying angle and pelvic circumference. In contrast, a study conducted by Chinweife KC et al., on Correlation of Carrying Angle of the Elbow in Full Extension and Hip-Circumference in Adolescents of Nnewi People in Anambra State reported a significant correlation between elbow CA and waist circumference in both genders. Both studies used the same measurement methods for CA and pelvic circumference.[19] In the present research height and carrying angle were negatively correlated similar to the study conducted by Nayak S et al., on relationship of carrying angle with grip strength and anthropometric measurements in young adults.[20]

Another study conducted by Verma V et al., on Correlation between morphometric measurements and carrying angle of human elbow showed a positive association between carrying angle and height, weight and other

morphometric measurements. No weight-carrying angle correlation was found in this study, in contrast to a negative height-carrying angle correlation. Unlike the previous research showing a negative correlation between carrying angle and BMI, this study found no such correlation. The data difference may be attributed to the age gap, as the previous research focused on children up to 15 years old.[21]

A study conducted by Nejat DR et al., on Kyphosis and Carrying Angle: Prevalence and correlation between anthropometric features showed carrying angle was positively associated with height and weight but in this research there was no correlation of CA with weight and an Inverse relationship between carrying angle and height. Both the studies were performed on young adults.[22]

A study conducted by Chakrabarti S et al., on Carrying angle and its correlation to height in young adult males and females showed that carrying angle was inversely proportional to height. The results were significant with this research that is carrying angle was negatively correlated to height. The only difference in both the studies is the age group, the former study was performed on age group 17 to 19 years.[23]

Existing literature on BMI and carrying angle shows inconclusive evidence-some studies report positive correlation, while others find no significant relationship. In our study, no correlation existed, in contrast to study conducted by Efe OJ et al., on Correlation between BMI and CA among adolescents in Abraka Nigeria, which showed a weak positive correlation. The studies differ in correlation results, sample size, and age group.[11]

Similar study performed on adolescents by Ansari MA et al., on Evaluation of the CA of the elbow joint in adolescents and its correlation with BMI, gender and dominant side showed significant positive correlation between BMI and CA of both sides. The findings are not consistent with present study, which found no correlation between CA and BMI.[24] In one of the study performed by Kabir MA et al., on Correlation Between BMI and CA Among Bangladeshi Adult Population concluded a negative association between BMI and carrying angle.

CONCLUSION

The findings of this study revealed no significant relationship between the carrying angle and BMI. However, a notable negative correlation was observed between the carrying angle and height. No significant correlation was found between the carrying angle and either weight or pelvic circumference.

LIMITATIONS

1. Hormonal factors might contribute to shaping the correlation between the carrying angle and the variables under study.
2. The impact of hand dominance on the carrying angle has not been explored in our investigations.

SOURCE OF FUNDING

None

CONFLICT OF INTEREST

None

AUTHOR'S CONTRIBUTION

DJ: Research Proposal, Manuscript, Data Collection, Result Writing

SP: Supervision of project, Guidance, Data Analysis and Result Writing

MMA: Review of Article, Guidance

RT: Guidance (Project)

LJ: Data Collection, Discussion Writing

FZ: Data Collection, Discussion Writing

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Original Article

NEUTROPHIL LYMPHOCYTE RATIO AND PLATELETS LYMPHOCYTES RATIO WITH GLYCEMIC CONTROL IN PATIENTS WITH DIABETES MELLITUS

Saira Gul[1], Ismat Ullah[2], Tooba Fateen[3], Noareen Tufail,[4] Hassan Abdal[5]

ABSTRACT

Background: Diabetes mellitus (DM) is a long-term health problem, which causes swelling of atissue. The Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are promising biomarkers of the blood sugar level in the type 2 diabetes mellitus (T2DM) Patients**.** The purpose of the study was to evaluate the relationship between NLR, PLR, and glycemic control in T2DM patients.

Material and Methods: The inclusion of 102 T2DM patients who had HbA1c levels <7% and >7% was based on a cross-sectional study carried out at Allama Iqbal Medical College/Jinnah Hospital Lahore from May to December 2024. Thereafter, the NLR and PLR were calculated through the blood counts. The most important results were the change in the blood sugar levels and HbA1c.

Results: Type 2 diabetes mellitus (HbA1c>7%) was noted in 63% of the patients, and it was correlated with decrease in NLR and PLR (p<0.001. NLR showed a positive correlation with HbA1c (r=0.45) and PLR a figure of 0.48.

Conclusion: A higher number of NLR and PLR in the body could lead to the development of poor glycemic regulation in T2DM patients, identifying them as valuable diagnostic tools for disease management and their benefits.

Keywords: NLR and PLR Biomarkers, Hyperglycemia Indicators, Immune-Inflammatory Markers, HbA1C Correlation, Diabetic Risk Stratification, Cost-Effective Biomarkers, Chronic Inflammation in Diabetes.

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INTRODUCTION

Diabetes mellitus is a multifaceted metabolic disorder that has developed into an epidemic. The International Diabetes Federation estimated that more than 463 million adults lived with DM in 2019, while projections indicate that this number will climb to 700 million by 2045.[1] Diabetes affects the individual, community, families, and healthcare systems all around the world. It is a major source of illness and death due to its associated complications such as cardiovascular disease, chronic kidney disease, and neuropathy.[2] The economic impact is also huge with billions of dollars spent every year on diabetes-related healthcare and lost productivity.[3] More than 90% of all diabetes cases are of the type 2 diabetes mellitus (T2DM) type.

It is rather a complicated interplay of genetic predisposition and environmental factors, like diet, physical inactivity, and overweight.[4] The important thing of T2DM is insulin resistance, mostly leading to beta-cell dysfunction over the

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time.[5] Chronic hyperglycemia, the basic element of DM, is a major cause of long-term damage and dysfunction in the different parts of the body.[6] In the past, people became more and more interested in finding the connection between inflammation of the whole body and diabetes.[7] Persistent low-grade inflammation is now recognized as a key driver of insulin resistance and a major contributor to the development of microvascular and macrovascular complications.[8]

The NLR is defined as the number of neutrophils, which are members of the innate immune response, divided by the number of lymphocytes, which are the main cells of adaptive immunity.[9] An NLR that is elevated is a marker for a pro-inflammatory state and is one of the factors that are already associated with poor outcomes in various conditions, e.g. cardiovascular difficulties, cancer, and autoimmune disorders.[10] On the same note, PLR is the ratio of platelets to the lymphocytes which lead to inflammation and thrombosis, respectively. High levels of PLR have been associated with the loss of people in some inflammatory and metabolic diseases.[11] Emerging evidence indicates that NLR and PLR are also relevant when it comes to diabetes. Studies have identified that the higher levels of the NLR and PLR markers are associated with poor glycemic control, increased risk of complications, and higher mortality rates.[12] However, markers of these controls in diabetes management are still in the dark. In this context, the study aimed to address the gap and provide answers by evaluating the relationship among the NLR, PLR, and glycemic control in persons with T2DM.[13] The study was conducted to investigate the association of NLR and PLR with glycemic control in T2DM patients, examining whether these markers could be used as predictors for glycemic status and management in this patient population.

MATERIALS AND MATHODS

This descriptive cross-sectional study was conducted in the Department of Medicine at Allama Iqbal Medical College/Jinnah Hospital Lahore, spanning from May 2024 to December 2024, after obtaining ethical approval (REF No. ERB168/4/15-07-2024/S1 ERB).

The study included 102 patients with T2DM, selected using non-probability consecutive sampling. The sample size was calculated using the World Health Organization's (WHO) formula for health studies, $n = Z^2 \times P(1 - P) / d^2$, where Z represents the confidence level (1.96 for 95%), P is the anticipated proportion (3%), and d is the margin of error (5%).

Participants were divided into two groups based on glycemic control: patients with HbA1c ≤ 7% were categorized as good glycemic control (Group 1), while those with HbA1c > 7% were categorized as poor glycemic control (Group 2).

The study aimed to measure the relationship between neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with glycemic control. Patients were primarily recruited from the general medicine and surgical wards, where individuals frequently visit for routine follow-ups or management of glycemic complications. Eligible participants were aged 25–70 years and had undergone complete blood count (CBC) and HbA1c testing. Patients with idiopathic thrombocytopenic purpura, cardiac or stroke conditions, liver cell failure, myeloproliferative neoplasms, acute or chronic infections, or those on anticoagulant or antiplatelet drugs, immunosuppressive therapy, or active inflammation in the past two weeks were excluded to avoid confounding results.

Pregnant or lactating females were also excluded. Informed consent was obtained from all participants, and data collection included detailed medical histories, clinical examinations, and laboratory investigations.

Blood samples (5 ml) were collected in EDTA tubes under aseptic conditions, and HbA1c, NLR, and PLR were calculated using standard methods. NLR was determined by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was calculated by

dividing the platelet count by the absolute lymphocyte count. The laboratory analyses were conducted using a Sysmex XN-1000 hematology analyzer for CBC and the high-performance liquid chromatography (HPLC) method with an Abbott Architect Analyzer for HbA1c measurement.

Baseline characteristics such as age, gender, HbA1c levels, and hematological parameters were summarized using descriptive statistics. Mean ± standard deviation or median with the range of interquartiles were employed to represent continuous variables, with frequencies and percentages being the mode of presentation of the categorical variables.

Gender distribution revealed higher proportion males (~60%), and this imbalance was accounted for during analysis. Independent samples t-tests were used to compare continuous variables between low and high NLR/PLR groups, and stratification for age, BMI, and duration of diabetes was performed to control effect modifiers. Pearson's correlation coefficients were calculated to assess the relationships among the NLR, PLR, HbA1c, and other clinical parameters such as hemoglobin, white blood cell counts, and platelet counts. Statistical analyses were performed based on The SPSS version 25.0 for windows with the p-value ≤ 0.05 level of the significance adopted.

RESULTS

The mean age of the 102 participant's was 50 yeas. The cohort consisted of 55% males and 45% females. The mean HbA1C level was 7.8% ± 1.5%, with 63% of patients having poor glycemic control (HbA1C ≥7%). Hematological parameters showed hemoglobin levels of 13.2 g/dL, white blood cell counts of 7,500 cells/µL on average, and platelet counts of 200,000 cells/µL on average. The median NLR was 2.5 (interquartile range: 1.8–3.2), and the median PLR was 120 (interquartile range: 95–150). (Table 1)

Table 1: Baseline Characteristics of the Study Population

Characteristic	Value (Median [Range])
Age (years)	50 (13–95)
Hemoglobin (Hb, g/dL)	13.2 (11–25)
Platelet Count (x10⁹/L)	200,000 (115000–465000)
Neutrophil-to-Lymphocyte Ratio (NLR)	1.82 (0.92–2.32)
Platelet-to-Lymphocyte Ratio (PLR)	6000 (2577.78–0628.57)
Hematocrit (HCT, %)	43.6 (36–86)
Mean Corpuscular Volume (MCV, fL)	90.6 (56–100)
Mean Corpuscular Hemoglobin (MCH, pg)	27.3 (6–36)
Mean Corpuscular Hemoglobin Concentration (MCHC, g/dL)	31.05 (28–35)
HbA1C (%)	7.8 (5–14)
Neutrophils (%)	60 (43–65)
Lymphocytes (%)	33 (28–48)
Monocytes (%)	5.0 (3–9)
Eosinophils (%)	2.0 (1–2)

Using a 3.0 cut-off point, the patients were divided into low and high NLR groups, whereas PLR groups were also divided by the use of a cut-off value of 150. These groups showed significant differences in several clinical parameters when compared with one another. Patients with high NLR had markedly higher percentages of neutrophils 63.8% ± 6.5% vs. 55.2% ± 5.0%, $p < 0.001$) and lymphocyte percentages (28.5% ± 4.2% vs. 38.8% ± 5.5%, $p < 0.001$) than those with low NLR. High PLR was connected with an increased number of platelets (260,000 ± 50,000 cells/µL vs. 170,000 ± 25,000 cells/µL, $p < 0.001$) and reduced numbers of lymphocytes (30.5% ± 4.7% vs. 39.1% ± 5.0%, $p = 0.001$).(Table 2)

Table 2: Patient Characteristics by Neutrophil-to-Lymphocyte Ratio Groups

Characteristics	Low NLR (n=71, Mean ± SD)	High NLR (n=31, Mean ± SD)	p-value
Age (years)	50.10 ± 11.50	54.70 ± 12.80	0.11
Hb (g/dL)	14.10 ± 1.80	12.80 ± 1.10	0.030*
WBC (cells/µL)	7500.50 ± 1600.00	9100.00 ± 1900.50	0.002*
RBC (millions/µL)	5.20 ± 0.40	4.80 ± 0.35	0.012*
HCT (%)	44.90 ± 4.50	41.70 ± 3.30	0.050*
MCV (fL)	87.50 ± 8.00	92.00 ± 10.50	0.030*
Platelet count (cells/µL)	200500 ± 30000	210400 ± 45000	0.4
MCH (pg)	27.50 ± 3.00	26.90 ± 2.60	0.28
MCHC (g/dL)	31.30 ± 1.10	30.00 ± 1.00	0.010*
Neutrophils (%)	55.20 ± 5.00	63.80 ± 6.50	0.001*
Lymphocytes (%)	38.80 ± 5.50	28.50 ± 4.20	0.001*
Monocytes (%)	5.10 ± 0.70	5.20 ± 0.60	0.25
Eosinophils (%)	1.70 ± 0.40	2.00 ± 0.00	0.001*
HbA1C (%)	6.80 ± 1.20	8.10 ± 1.30	0.020*

Table 3: Patient Characteristics by Platelet-to-Lymphocyte Ratio (PLR) Groups

Characteristic	Low PLR (n=52, Mean ± SD)	High PLR (n=50, Mean ± SD)	p-value
Age (years)	49.80 ± 10.20	55.10 ± 13.70	0.08
Hb (g/dL)	14.20 ± 1.70	12.60 ± 1.20	0.015*
WBC (cells/µL)	7600.00 ± 1500.00	8900.50 ± 2000.00	0.010*
RBC (millions/µL)	5.10 ± 0.35	4.75 ± 0.45	0.010*
HCT (%)	45.00 ± 3.90	40.90 ± 4.20	0.004*
MCV (fL)	89.00 ± 7.50	92.50 ± 8.20	0.06
Platelet count (cells/µL)	170000 ± 25000	260000 ± 50000	0.001*
MCH (pg)	28.00 ± 2.80	26.50 ± 2.40	0.09
MCHC (g/dL)	31.20 ± 1.00	30.10 ± 1.10	0.015*
Neutrophils (%)	56.10 ± 4.90	62.50 ± 5.80	0.004*
Lymphocytes (%)	39.10 ± 5.00	30.50 ± 4.70	0.001*
Monocytes (%)	4.80 ± 0.70	5.40 ± 0.80	0.030*
Eosinophils (%)	1.60 ± 0.40	2.00 ± 0.00	0.001*
HbA1C (%)	6.70 ± 1.30	8.20 ± 1.10	0.005*

Correlation analysis was undertaken, which reported a moderate positive correlation between HbA1C and both NLR ($r = 0.45$, $p < 0.001$) and PLR ($r = 0.48$, $p < 0.001$). These observations point on raising glycemic index that follows the progression of NLR and PLR (Table 3). Analysis of logistic regression demonstrates that NLR as well as PLR play key roles in poor glycemic control. The other factors are age and gender that are independent as well

DISCUSSION

In the current study, we investigated the relationship between the Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and glycemic control in patients with Type 2 Diabetes Mellitus (T2DM). Our results suggest that elevated NLR and PLR were associated with poor glycemic control, as indicated by higher HbA1c levels in patients with increased values of these ratios. A study by Ahmed et al. (2021) explored the relationship between NLR, PLR, and blood glucose regulation in T2DM patients. They found that patients with poor glycemic control had elevated NLR and PLR levels, indicating a potential link between these markers.[14] The mean NLR in patients with poor glycemic control was significantly higher compared to those with good glycemic control, aligning with the findings of previous studies.[15] Our study found a mean NLR of 3.2 (±1.1) in patients with poor glycemic control and 1.8 (±0.6) in those with good control shows that results are consistent with the study by Li et al. (2023), who reported that elevated NLR was significantly correlated with poor glycemic control in T2DM patients, with patients having higher HbA1c levels associated with higher NLR values.[16] The association between elevated PLR and poor glycemic control could reflect underlying metabolic dysfunction and platelet activation are consistent with the work of Rahman et al. (2021), who found that elevated PLR was linked to poor glycemic control and an increased risk of complications in T2DM patients.[17] Such results also indicated that PLR might become a pivotal sign of the presence of patients who are at a higher risk of having a permanent diabetes-related issue.[18] Given the simplicity and availability of complete blood count tests, NLR and PLR could be useful markers for early detection of patients at risk for complications related to poorly controlled diabetes.[19] Monitoring these markers may help identify patients who require more intensive management to prevent the progression of diabetes-related complications. In our study, we also observed significant correlations between other clinical parameters, such as age and hemoglobin levels, with NLR and PLR.[20] The results of our study have significant implications for clinical practice, especially in resource-constrained settings. By incorporating simple, accessible biomarkers such as NLR and PLR into routine clinical assessments, healthcare providers can better identify high-risk patients and intervene early to prevent complications. Given that NLR and PLR are derived from routine blood tests, they are both cost-effective and easily accessible, making them suitable for widespread use in various healthcare settings.

LIMITATIONS:

Despite the promising findings, this study has several limitations. The cross-sectional design limits our ability to establish causal relationships between NLR, PLR, and glycemic control. Future research needs to include long-term research to identify the possibility of predicting diabetes-related complications and long-term results by these markers. Additionally, we did not assess factors such as medication adherence, lifestyle habits, or comorbidities, all of which could influence the results. Future studies should take these factors into account to provide a more comprehensive understanding of the role of NLR and PLR in diabetes management.

CONCLUSION:

In conclusion, this study supports the growing body of evidence indicating that NLR and PLR are valuable markers for assessing glycemic control in T2DM patients. These markers were associated with poor glycemic control and may help identify patients at higher risk for complications. Given their ease of measurement and clinical relevance, NLR and PLR have the potential to be integrated into routine diabetes care to improve patient outcomes

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CONFLICT OF INTEREST

None.

AUTHOR'S CONTRIBUTION

SG: Research Proposal,
IU: Review of Article,
TF: Review of Article, Supervision of project
NT: Data Analysis and Result Writing
HA: Data Analysis and Result Writing

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Original Article

ANALYSIS OF DIFFERENTIAL EXPRESSION OF CLAUDIN-1 IN RELATION TO VEGF IN HEPG2 AND CACO-2 CELLS USING FLOW CYTOMETRY

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ABSTRACT

Background: The sustained polarity of epithelial cells, differentiation, and cell signaling are underpinned by Claudins, which are the principal proteins of tight junctions, essential for vital cell-to-cell adherence. Claudins play a significant role in both physiology and pathogenesis, as numerous studies have depicted their involvement in these processes. These proteins have an impact on normal body functions and disease development, including tumors. Due to their cell-specific expression, Claudins have been associated with the development of various tumors, suggesting their potential use as diagnostic or prognostic markers. It can be suggested that could serve to predict or diagnose the development of possible cancers. The objective of this study was to investigate the expression of Claudin-1 associated with VEGF in the liver and colon cancer cell lines namely HepG2 and Caco-2 respectively.

Materials and Methods: In-vitro study of Claudin-1 expression linked to VEGF in HepG2 and Caco-2 cell lines This study incorporates HepG2 and Caco-2 cell lines. Expression of Claudin-1 in HepG2 and Caco-2 cells was determined after flow cytometry analysis.

Results: Claudin-1 showed different expression patterns in HepG2 and Caco-2 cells underscoring its significant involvement in tumorigenesis and tumor progression.

Conclusion: The study evaluates the relationship between Claudin-1 and VEGF in cancer. It highlights Claudin-1 as a key indicator to identify and predict cancer. This might open doors to new treatment approaches.

Keywords: Biomarkers, Tumors, Claudins, Diagnosis, Cell lines, Epithelial Cells

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INTRODUCTION

Different types of claudin proteins make up tight junctions between cells where some members form closure into intercellular spaces and others create paracellular channels. Ions move through the pore pathway located at these channels. Among both tight junction development factors and structural elements, Claudin proteins create the paracellular channels that act as ion-selective pores, hence are required for barrier functionality. The leak route gets regulated by both Zonula occludens proteins (ZO) family members and essential membrane proteins with the MARVEL protein family (TAMP) controlling the leakage mechanism. The tight junction leak route is under stringent control through the ZO-1 actin-binding domain which operates through the peri-junctional actomyosin ring.[1]

The main claudin that creates the paracellular barrier at tight junctions in the epidermis is encoded by Claudin-1 (CLDN1), a gene that is believed to be a major contributor to human skin disorders.[2] The cellular entry of HCV depends primarily on four host determinants known as

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occludin (OCLN), claudin-1 (CLDN1), scavenger receptor class B type I (SR-BI) and cluster of differentiation 81 (CD81). Multiple host factors which confer cell susceptibility to HCV infection exist because their expression leads to infection readiness. CD81 and OCLN independently determine HCV tissue tropism in humans but the viral factors do not confer tissue tropism alone. The process of HCV attachment (attachment/binding factors) together with internalization/fusion (co-variables) depends on various host elements that go beyond these four fundamental entry components.[3]

All areas of study maintain a focus on creating protein-free media as a purification method and to secure biologically secure raw materials. The manufacturing costs and material production need continuous optimization especially during the development of viral vectors for gene therapy and recombinant proteins and antibodies synthesis. Cell culture methods for recombinant protein production must adapt to competing technology advances including those based on transgenic animal systems. All mammalian cells end up producing viruses as a natural result of gene therapy and vaccination development. The field of cultured mammalian cells has recently started using re-transplantation methods and investigators widely employ cultured cells for toxicity assessment.[4] The development of efficient mAb-based assays and diagnostic imaging techniques used to detect antigens and small chemicals from malignant cells will produce big improvements in modern cancer diagnostic medicine. The development of recombinant antigen synthesis combined with antibody creation methods has expanded mAb technology beyond its current state as an immature scientific field. Precise quantitative geographical and temporal measurements exist for disease diagnosis in mAb-based assays when compared to other alternative procedures.[5]

The defective tight junctions cause patients to experience volume loss and hypercalciuria leading to polyuria with polydipsia from excess sodium (Na^+) together with hypomagnesemia and its related symptoms and infantile nephrocalcinosis. Patients who have CLDN19 mutations show additional eye-related defects apart from their kidney symptoms. The poor renal projection affects both versions since chronic kidney disease typically requires renal replacement treatment during the patient's second or third life decade. Medical experts recognize nephrocalcinosis as a potential contributor to CKD (chronic kidney disease) development yet they have not identified its fundamental cause.[6]

Healthcare professionals identify major differences between malignant tumor blood vessel characteristics and those of regular blood arteries. Angiogenesis gets its main control from vascular endothelial growth factors also known as VEGFs. VEGFs use binding with vascular endothelial growth factor receptors (VEGFRs) to improve vascular permeability as well as vascular endothelial cell survival, migration, proliferation, tube formation and angiogenesis. The manifestation of VEGFs occurs because of three pathologic events including poor blood supply along with oxygen deprivation and malignant tumor growth. Secreted VEGFs enhance vascular permeability thus enabling plasma proteins to easily reach the extracellular matrix for aiding vasculogenesis while providing temporary support to entering endothelial cells.[7]

Cell analysis in solution becomes possible quickly through flow cytometry because of its multi-parametric abilities. The main function of lasers in flow cytometers involves the generation of scattered and fluorescence signals that photomultiplier tubes or photodiodes convert into readouts. A computer records the electrical signals derived from light impulses into data files. Flow cytometers use cell population testing by fluorescence and light scattering properties to conduct both evaluations and purification processes. Various fluorescent reagents serve purposes in flow cytometry systems. The system employs fluorescent antibodies as well as expression proteins and nucleic acid dyes as well as viability indicators and ion sensory agents.[8]

The basic flow cytometer contains four major components which include a fluid control

system that manages particle movements, an optical laser source, several capture components such as filters and detectors along with electronic data acquisition systems to analyze the results. The identification of cellular functions through fluorochrome-labeled probes along with natural cell detection has served as the primary basis for flow cytometry traditionally.[9]

MATERIALS AND METHODS

As it is done on cells study IRB is not required. Caco-2 and HepG2 cells were cultured in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% fetal bovine serum (FBS), 1% penicillin-streptomycin, and maintained at 37°C in a humidified atmosphere with 5% CO_2. The cells were incubated for three days before further processing. Three cell treatment conditions were defined: untreated cells (control group), VEGF-treated cells, which received VEGF treatment for 48 hours at a concentration of 30 ng/ml, and VEGF + anti-VEGF antibody-treated cells, which received VEGF treatment (30 ng/ml) for 48 hours while also receiving an anti-VEGF monoclonal antibody (120 ng/ml for 48 hours). After adding 0.25%trypsin-EDTA (ethylenediaminetetraacetic acid) to the culture flasks, the cells were trypsinized and incubated at 37°C until they separated. The cell suspension was collected, and trypsin was neutralized with complete media. The cells were then centrifuged at 300 x g for 5 minutes, and the supernatant was discarded. The cell pellet was resuspended in 1 ml of PBS (Phosphate Buffered Saline). Cells were counted using a hemocytometer. An aliquot of 10 µl of the cell suspension was mixed with an equal volume of trypan blue solution (0.4%), and 10 µl of the mixture was loaded onto a hemocytometer. Viable cells were counted under a light microscope, and the cell concentration was calculated. The counting was done by laboratory personnel prior to staining. Cells were prepared for staining using an indirect staining technique to identify protein expression.[10,11]

Aliquots of 1 x 10^6 cells were taken for each condition. Cells were labeled as untreated cells, VEGF-treated cells, and VEGF + anti-VEGF antibody-treated cells. Negative and positive control samples were also prepared. Cells were fixed with 4% paraformaldehyde for 10 minutes at room temperature, then washed twice with PBS. Cells were permeabilized with 0.1% Triton X-100 for 5 minutes and washed again. Primary antibodies against Claudin-1 (rabbit anti-Claudin-1) and VEGF (mouse anti-VEGF) were added to the experimental samples and incubated for 1 hour at 4°C. Cells were washed three times with PBS and incubated with fluorophore-conjugated secondary antibodies for 30 minutes at 4°C in the dark: Anti-rabbit IgG Alexa Fluor 488 (green channel) for Claudin-1, Anti-mouse IgG Alexa Fluor 594 (red channel) for VEGF. Following staining, cells were washed, resuspended in 500 µl of PBS, and stored at 4°C until analysis.[12] Cells were analyzed using fluorescence-activated cell sorting by BD FACS Canto II (Becton, Dickinson and Company - BD Biosciences). The samples were run on a flow cytometer with appropriate settings for detecting Alexa Fluor 488 (green) and Alexa Fluor 594 (red). Data acquisition and analysis were conducted using BD FACS Diva Software.

RESULTS

Three distinct samples—untreated, VEGF-treated, and VEGF in the presence of monoclonal anti-VEGF-treated cells—were subjected to flow cytometric analysis of HepG2 and Caco-2 cells. The degree of Claudin-1 expression in connection to VEGF varied, according to the data. Relative Fluorescent Units (RFU) were used to express the values. The FACS machine was used to get all of the values, including those for the positive and negative controls. Both HepG2 and Caco-2 cells exhibit elevated Claudin-1 expression when used as positive controls. Green fluorescence, as detected by the FACS machine, revealed this (refer to table 1). Comparatively less fluorescence was seen in negative controls. The outcomes of untreated HepG2 and Caco-2 cell

samples were nearly identical. The values were essentially the same when VEGF was administered to both cells. In contrast to VEGF in the presence of monoclonal anti-VEGF antibody-treated HepG2 cells, VEGF in the presence of monoclonal anti-VEGF antibody-treated Caco-2 cells exhibited a higher fluorescence value and, consequently, higher manifestation of Claudin-1.

Table 1: Shows the average of value of fluorescence and therefore the average Claudin-1 expression in the HepG2 and Caco-2 Cells

Samples	Relative Fluorescent Unit (RFU)	Average
Positive HepG2 Cells	1029, 1004, 963	998.7
Positive Caco-2 Cells	1006,1017,1073	1032
Negative HepG2 Cells	244.1, 264, 198	235.4
Negative Caco-2 Cells	104,101,123	109.3
Untreated HepG2 Cells	507.4,511,578, 446,478,564	514.1
Untreated Caco-2 Cells	514.6,532.2,567, 553,499,561	537.8
VEGF HepG2 Cells	732,741,766,843,900.3, 774,737,812,754	784.4
VEGF Caco-2 Cells	831,813,821.5,881,772, 668,737,699,772	777.2
VEGF+AB HepG2 Cells	307,312,344,216, 294.2,319	298.7
VEGF+AB Caco-2 Cells	416.9,400,338.8, 418.9,373,330	379.6

Relative fluorescence averages for each of the samples are displayed. From each sample's three experimental readings, the average value has been determined (refer to table 1).

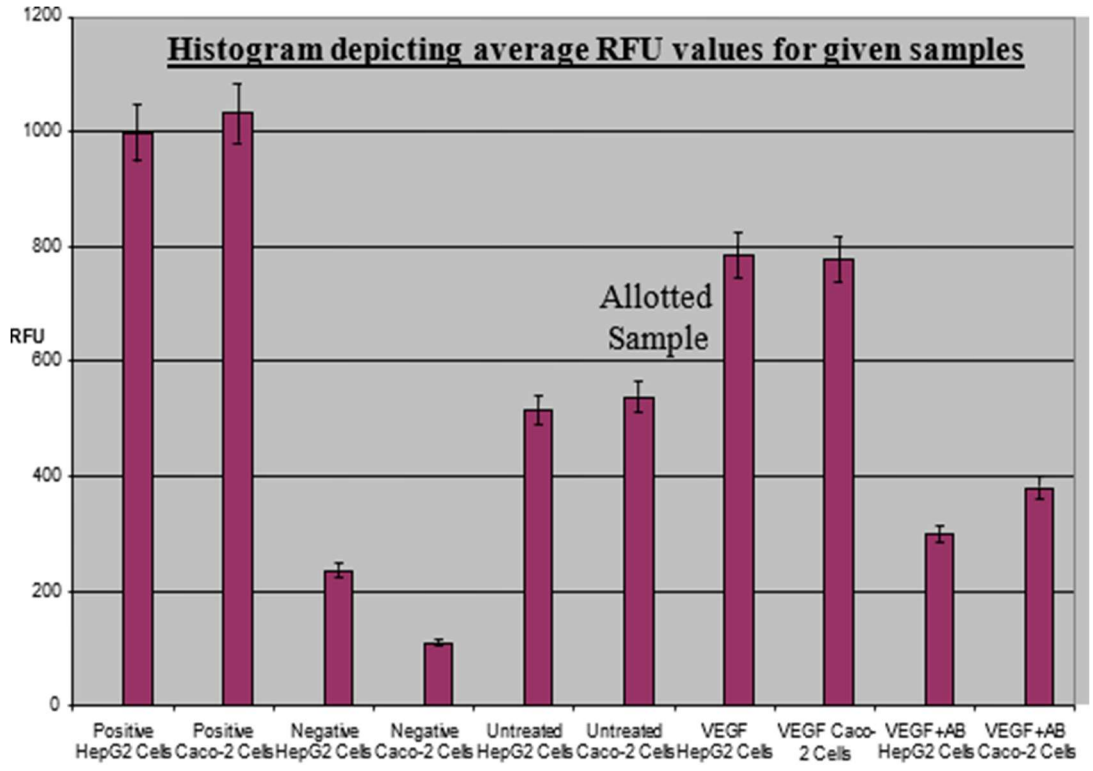
Table 2: Comparison of fluorescence values in Untreated Caco-2 Cells against Positive and Negative Control

Samples	Relative Fluorescent Unit (RFU)	Average
Negative Control (Caco-2 Cells)	104,101,123	109.3
Positive Control (Caco-2 Cells)	1006,1017,1073	1032
Untreated Caco-2 Cells	**553,499,561**	**537.7**

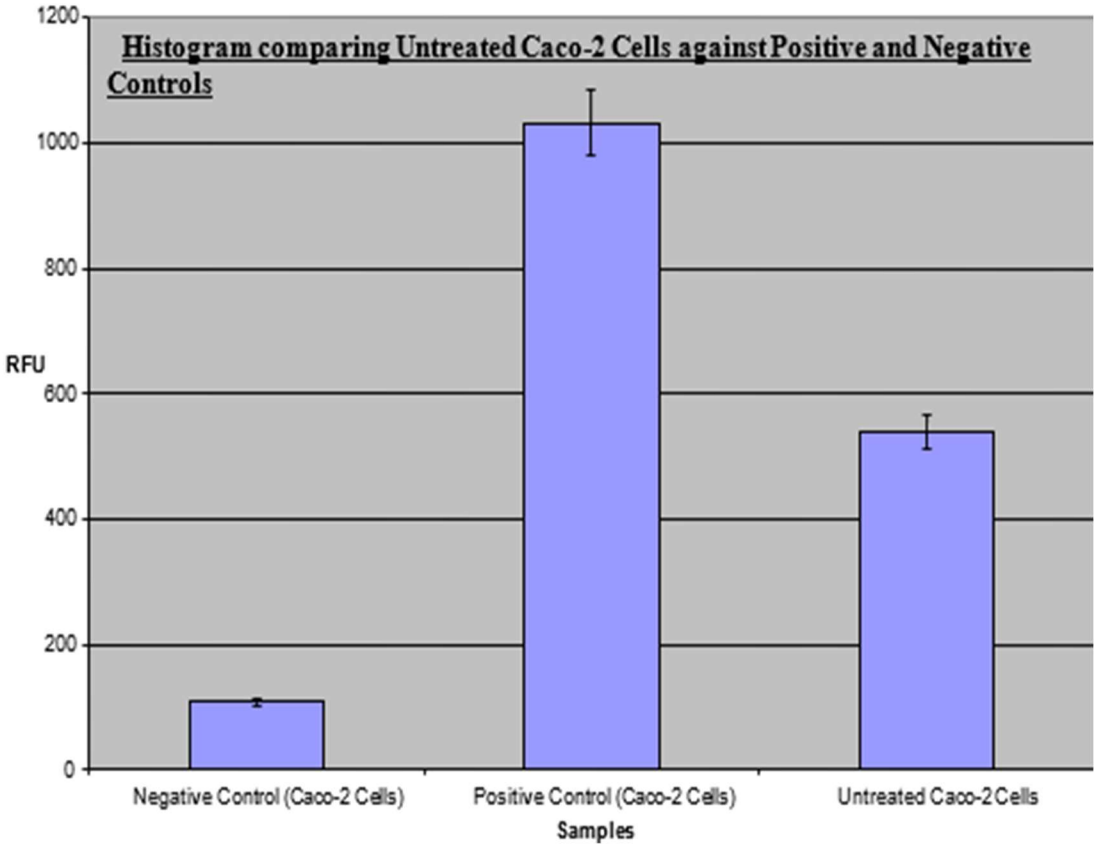
Fluorescence levels of the designated experimental sample, which includes both positive and negative controls and untreated Caco-2 cells. Untreated Caco-2 cells exhibit optimal claudin-1 protein expression when their average relative fluorescence value is lower than that of the positive control (refer to table 2).

The RFU value of VEGF-treated cells (both HepG2 and Caco-2 cells) significantly increases, suggesting that Vascular Endothelial Growth Factor is up-regulated. HepG2 and Caco-2 untreated cells exhibit respectable fluorescence levels (although lower than those of VEGF-treated samples), indicating claudin-1 expression (Graph 1).

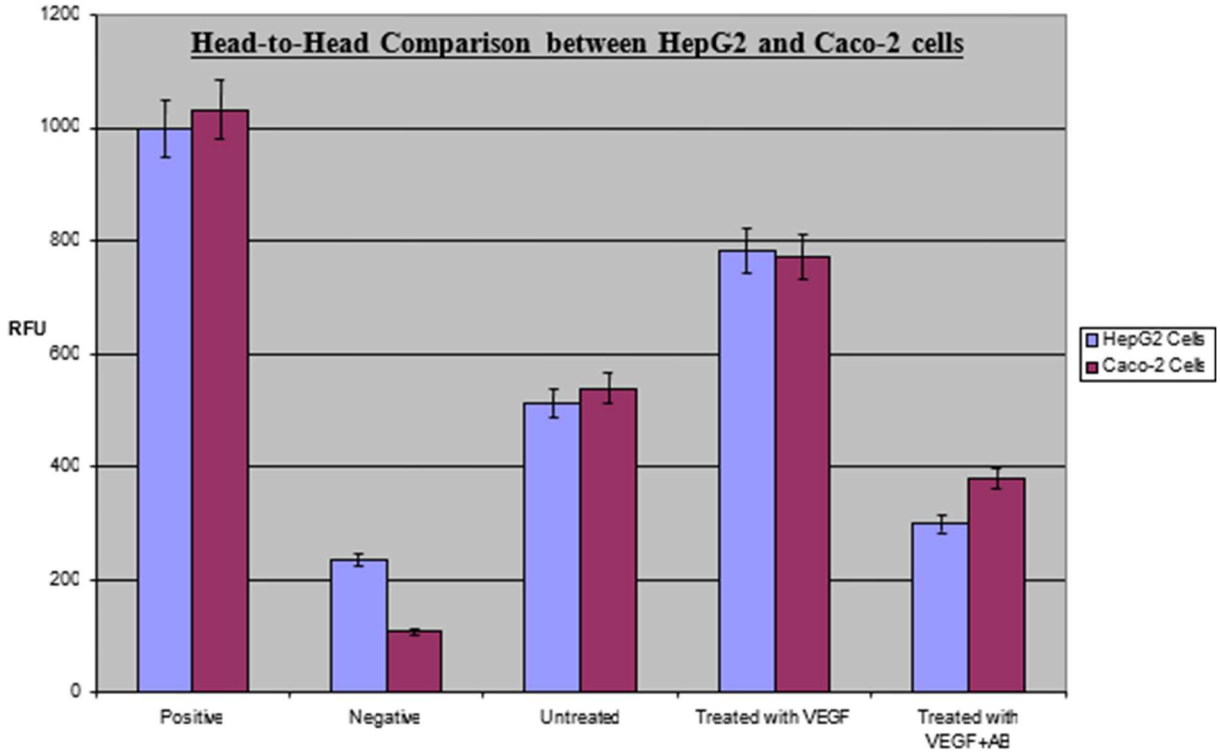
Untreated Caco-2 cells have demonstrated a significant fluorescence value when compared to both positive and negative controls.(Graph 2). HepG2 and Caco-2 cells, along with their corresponding positive and negative controls, have been directly compared (Graph 3). The RFU value for Caco-2 cells under positive control is somewhat higher than that of HepG2 cells. In the negative control, HepG2 cells exhibit greater fluorescence than Caco-2 cells, indicating higher claudin-1 expression. Compared to HepG2 cells, untreated Caco-2 cells express claudin-1 at a comparatively higher level. Both cell types exhibit nearly comparable fluorescence levels in untreated, VEGF-treated, and VEGF + Anti-VEGF monoclonal antibody-treated samples, with only minor differences in claudin-1 expression and VEGF regulation.



Graph 1: Indicating average values of fluorescence in untreated, VEGF treated and VEGF + antibody treated HepG2 and Caco-2 cells



Graph 2: Comparing the fluorescence value of untreated Caco-2 cells against positive and negative control



Graph 3: Direct Comparison between all samples of HepG2 and Caco-2 along with Controls

DISCUSSION

The human body protects itself from chemical entry through the protective function of the gut barrier. The proper functioning of this barrier preserves organisms at equilibrium state. The proteins known as claudins enable strong cellular bond formations between epithelial cells. The failure of the intestinal barrier worsens both celiac disease and inflammatory bowel disease along with other gastrointestinal disorders. Physiological disruptions of epithelial connectivity along with permeability reakdown from these pathogens cause numerous pathological diseases which potentially lead to cancer development. Tight junctions that connect cells together are formed through the proteins which belong to the claudin family.[13] Scientific studies have extensively researched CLDN-1 as the primary claudin protein because researchers have observed links between cancer cell initiation and spread through this protein. Scientific research shows that this particular protein suppresses cancer development in select cancer types. CLDN-1 produces tumor-promoting or tumor-suppressive activities as an individual factor or in combination with multiple molecules. Cancer progression is determined by CLDN-1 transport between cell membranes and cytoplasm as well as the nucleus. CLDN-1 engages many signaling pathways which represent an essential component in its overall significance.[14] Every HepG2 and Caco-2 cell sample that was sent to each group, together with the positive and negative controls for both cancer cell types, had its fluorescence levels measured using a FACS machine, yielding three readings for each sample. All of the readings were fairly close to each other within the experimental error range. Cancer invasion and metastasis require claudins to perform the functions of ion exchange and cell motility alongside epithelial-to-mesenchymal transition Scientists have started using claudins as

therapeutic targets to improve the outcomes of cancer patients. Scientists have proven that CLDN expression modifications occur with NA methylation DNA changes. DNA hypermethylation causes CLDN1 and CLDN7 downregulation in breast cancer cells as well as CLDN11 downregulation in gastric cancer cells. Colon cancer cells were shown to use histone-deacetylase enzymes for modifying mRNA stability which affects CLDN1 expression.[15] Mucosal tissue preservation requires the presence of Claudin-1 for proper physiological operations. Various research links claudin-1 to colorectal cancer yet the predictive significance remains questionable. This meta-analysis assessed the clinical significance along with predictive value of claudin-1 in CRC evaluation.[16] There is a remarkable boost in the proliferation of colon cancer cells caused by upregulation and desensitization of claudin-1 following EGFR/PKC/CLDN1 signaling pathway.[17] It has been reported that signaling pathways resulting in the invasion and migration of cells involve claudin-1.[18] The untreated samples displayed some fluorescence in the green channel. Auto-fluorescence can be assumed because there was no antibody present. Using the FACS apparatus, particular fluorescence patterns were seen following the samples' probing with fluorescent antibodies. Compared to Caco-2 stomach cancer cells, HepG2 liver cancer cells exhibited more auto-fluorescence. Green positive control cells at the time showed undeniable amounts of Claudin-1 articulation. Auto-fluorescence was unquestionably present in the fluorescence of the negative control cells. HepG2 and Caco-2 cells treated with VEGF exhibit remarkable fluorescence, according to earlier research (graph 1). Hepatocellular polarity and tight junction integrity are regulated by VEGF. The concept that cytokine or growth factor-induced alterations in hepatocyte permeability will promote HCV entry is supported by the fact that hepatoma polarization restricts the availability of basolaterally expressed tight junction protein viral receptors. Without a doubt, the VEGF-treated HepG2 significantly raised the HCV level.[19] In cancer, a proangiogenic state arises from an imbalance of stimulatory and inhibitory elements that seem to be driving the move to angiogenesis. The result of somewhat insufficiently blood supplied hyperplasia turning into an uncontrolled new vascular development is the advance of malignant tumors. When this balance is perturbed, angiogenesis increases and tumor growth gets out of control. Angiogenesis is strongly controlled by vascular endothelial growth factor A (VEGFA) whether one is healthy or suffering. Proangiogenic imbalance often develops at the gene level from the activation of oncogenes or the inactivation of tumor suppressor genes to cell environmental variables like hypoxia, hypoglycemia, cellular nutritional deficiencies, and metabolic acidosis.[20] The average fluorescence value and, thus, the average Claudin-1 expression in each cell sample showed fairly similar results. The auto-fluorescence phenomenon was illustrated by comparison with the positive and negative controls. Compared to Caco-2 cells, HepG2 cells showed a significantly higher level of autofluorescence.

CONCLUSION

This study discussed the distinct expression patterns of claudins in HepG2 and Caco-2 cells, in relation to VEGF, affirm their potential as diagnostic and prognostic markers for various tumors. This study has paved the way for future investigations into targeted therapies and precision medicine approaches that leverage claudins as biomarkers.

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ETHICAL APPROVAL

The conducted research is not related to either human or animal use.

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None

CONFLICT OF INTEREST

We declare that there is no conflict of interest regarding the publication of this paper.

AUTHOR's CONTRIBUTION

SA: Study Design, Analysis and Results Interpretation, Manuscript Writing
MR: Data Collection, Manuscript Writing
AH: Conceptualization, Critical Review
CM: Critical Review

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Original Article

TRAUMATIC DUODENAL INJURY: A DIAGNOSTIC AND MANAGEMENT DILEMMA

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Muhammad Usama Aziz[5], Aziz Ahmad Chattha[6]

ABSTRACT

Background: Duodenal injuries are challenging and can lead to significant morbidity and mortality in pediatric patients. The management of these injuries has evolved over the years, and understanding the nuances of pediatric duodenal injury is crucial for optimizing patient care. The objective of this study is to understand the nuances of pediatric duodenal injury by evaluating our record of previous years in our department.

Materials & Methods: A retrospective study was conducted at The Children's Hospital, University of Child Health Sciences, Lahore, analyzing patient records of traumatic duodenal injuries from April 2017 to November 2019. Data on patient demographics, mode of injury, clinical presentation, diagnosis, management, complications, and outcomes were collected and reviewed.

Results: Seventeen pediatric patients with traumatic duodenal injuries were included in the study, with the majority being males presenting with blunt trauma abdomen. Most common presenting complaints included abdominal discomfort, bilious vomiting, and abdominal distension. Surgical intervention was pursued for all patients, and associated injuries were observed in 23.5% of patients. The classification of duodenal injuries varied, with Grade III injuries being the most prevalent. Postoperative complications and mortality were also noted.

Conclusion: Blunt abdominal trauma, mainly from falls and road traffic accidents, was the most common cause of pediatric duodenal injuries. Limited access to contrast-enhanced CT highlighted the importance of clinical assessment and basic imaging in guiding timely intervention, while a multidisciplinary approach remained crucial for managing severe cases.

Keyword: Pediatric, Traumatic Duodenal Injury, Case Series

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INTRODUCTION

Duodenal injuries are one of the most notorious injuries and pose a serious morbidity and mortality risk in all patients regardless of their age groups. The mortality associated with these injuries rise up to 25%.[1] The duodenum lies in a relatively protected area of the abdomen i.e., in the retroperitoneum, and thus only a small percentage of blunt trauma injuries will result in its damage. A similar fact may render its early diagnosis and ultimate management a tough task. Its relative position to the surrounding structures makes it a high likelihood to be associated with other injuries.[2] The most common mechanism of injury in the pediatric age group leading to duodenal injury is the direct hit to the epigastrium and that may

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be due to road traffic accidents, fall directly on the abdomen, or handle bar injuries in the playground.[3] Blunt abdominal trauma induces duodenal injury through mechanisms such as crushing, compression, and traction. The duodenum may be crushed between a rigid external object and the spine during such trauma. Additionally, sudden acceleration or deceleration forces at the duodenal attachment point, specifically the ligament of Treitz, can elevate intraluminal pressure and cause traction on the duodenum resulting in tearing of the lumen.[4]

The ever-evolving medical profession has seen the management recommendation for duodenal injuries change a lot over the years, especially in the pediatric age groups. The doctrines of operative management involving duodenal trauma revolve around these decisions, damage control, non-viable tissue resection, restoration of the gastrointestinal continuity, along with possibility of a diversion of the contents of the gastrointestinal tract including bile and pancreatic enzymes, ultimately allowing the repair to heal alongside a feeding access during this time.[5] The management options have evolved from tube duodenostomies and duodenal diverticulization to the primary repair with an option of pyloric exclusion depending upon the complexity of the injury.[2] Understanding the nuances of pediatric duodenal injury is essential for healthcare professionals to provide optimal care for these vulnerable patients.

MATERIALS & METHODS

This is a retrospective study focusing on the analysis of series of cases involving patients who were diagnosed with duodenal injuries due to trauma, at The Children's Hospital, University of Child Health Sciences, Lahore, Pakistan. The study period spans from April 2017 to November 2019, during which the team meticulously collected and reviewed data related to patient demographics, mode of injury, clinical presentation, diagnosis, management, complications, and the final outcomes of the patients. Study approval was obtained by the Institutional Review Board of University of Child Health Sciences, The Children's Hospital, Lahore. No: 919/CH-UCHS dated 24-05-2024

RESULTS

During the period of this study, we had 17 patients with traumatic duodenal injury of which 12 were male and 5 were female. The mean age of presentation was 7.16 years. The majority of the patients in the study had the mechanism of injury as blunt trauma abdomen either with a history of fall, road traffic accident, or trauma to the abdomen via something falling on the patient's abdomen. Only 1 patient had a firearm injury. None of the cases in this study were identified as non-accidental injuries. All injuries had a clear traumatic mechanism consistent with accidental causes, and there were no concerns regarding inflicted trauma based on history, clinical assessment, or imaging findings. The prevalent presenting complaints included abdominal discomfort, vomiting with bile, and abdominal swelling. We observed that the patients presenting with altered consciousness had a 100% mortality rate and also patients with relatively milder symptoms had a higher mortality rate compared to other groups as they may have misled the surgeon in making a timely decision.

Preoperative imaging was done in all of the patients, but CT scan of the abdomen and pelvis was not available in the emergency department at our hospital during the study period. As a result, imaging was limited to X-ray and ultrasound, which were used as the primary diagnostic modalities to guide clinical decision-making. The erect X-ray of the abdomen and pelvis was non-specific in 11 cases. Among the remaining cases, three demonstrated air-fluid levels, one showed pneumoperitoneum, and two exhibited haziness. Additionally, ultrasound was performed in all patients,

Table 1

Grade	Type of Injury	Description of Injury
I	Hematoma	Involving single portion of duodenum
	Laceration	Partial thickness, no perforation
II	Hematoma	Involving more than one portion
	Laceration	Disruption <50% of circumference
III	Laceration	Disruption 50%-75% of circumference of D2
		Disruption 50%-100% of circumference of D1,D3,D4
IV	Laceration	Disruption >75% of circumference of D2
		Involving ampulla or distal common bile duct
V	Laceration	Massive disruption of duodeno-pancreatic complex
	Vascular	Devascularization of duodenum

revealing bowel dilatation with mild ascites, mild to moderate free fluid in the pelvis, and, in some cases, gross debris-laden ascitic fluid. These imaging findings played a role in the overall clinical assessment and decision-making for surgical intervention.

Following optimization in accordance with the ATLS protocol, surgical intervention was pursued for all patients. Surgical exploration was indicated based on clinical and imaging findings. Patients with peritonitis, hemodynamic instability, or persistent abdominal distension underwent immediate laparotomy. Additionally, pneumoperitoneum, debris-laden ascitic fluid, or significant bowel dilatation with free fluid on imaging warranted exploration. In cases with non-specific findings, worsening clinical status or failure to improve with conservative management guided the decision for surgery. Based on the American Association for the Surgery of Trauma's classification system for duodenal injuries, the traumatic rupture of the duodenum was categorized as Grade II in 3 patients, Grade III in 9 patients, 4 patients categorized as Grade IV and only one patient was having a Grade V injury. (Table 2) (Figure 1)

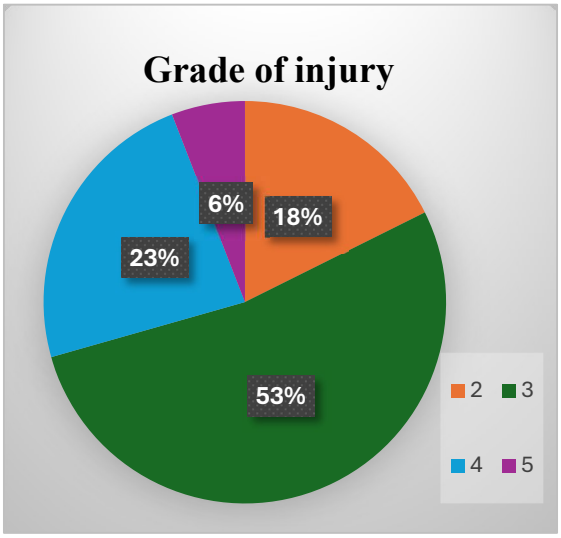

Figure 1

Table 2

Additional supportive procedure & Procedure performed Cross-Tabulation				
		Procedure Performed		Total
		End to end duodenoduodenal anastomosis	Repair of perforation with/ without omental coverage of anastomosis	
Additional supportive procedure	Duodenostomy, cholecystostomy & feeding jejunostomy	2	3	5
	Duodenostomy & feeding jejunostomy	0	1	1
	Duodenostomy, cholecystostom, gastrojejunostomy & pyloric exclusion	1	2	3
	Tripple drainage & pyloric exclusion	1	1	2
	Feeding jejunostomy	0	1	1
	Cholecystostomy & Feeding jejunostomy	1	0	1
Total		5	8	13

About 23.5 percent of patients had associated injuries which included liver laceration, pancreatic injury, and jejunal and colonic perforations. Among these patients we saw that there was a 100 percent mortality in the patients with an associated pancreatic injury. In our study, we observed that 5 patients underwent end-to-end anastomosis while 12 patients underwent repair of the perforation with or without omental coverage. Additional supportive procedures were performed in 13 of these patients and included tube duodenostomy, cholecystostomy, feeding jejunostomy, and pyloric exclusion. (Table 3)

Table 3

Clinical features * Final outcome Crosstabulation				
		Final outcome		Total
		Survived	Died	
Clinical Features	Pain abdomen, vomiting	8	3	11
	Pain abdomen, distension	1	0	1
	Pain abdomen, vomiting, altered consciousness	0	1	1
	Pain abdomen, vomiting, distension	2	1	3
	Pain abdomen, hematemesis	1	0	1
Total		12	5	17

Three patients were re-explored for anastomotic leakage (2) and retroperitoneal collection (1). Five patients (29.4%) succumbed in the postoperative period in our study. An association between the grade of injury and the final outcome is shown in the table above.

In our study, we also observed that 3 patients who underwent re-exploration survived ultimately which may have been due to an early diagnosis of a complication followed by an early intervention.

DISCUSSION

The management of traumatic duodenal injury in pediatric patients poses significant challenges due to the complex anatomy, the potential for delayed presentation, and the risk of associated injuries.[6] The predominant cause of duodenal injury in our study was blunt trauma abdomen and this aligns with findings from other research indicating that blunt mechanisms are the most frequent causes of duodenal injuries. The most common blunt mechanisms in our series were falls and road traffic accidents.[7] Due to their close anatomical location to other organs, these injuries seldom occur in isolation.[8] Morbidity and late mortality in duodenal injuries are generally associated with sepsis and/or other intra-abdominal complications, especially dehiscence of the duodenal suture line. Nonetheless, identifying the most effective method to repair the injured duodenum to avoid leaks at the duodenal suture line has proven challenging.[9] A literature review highlights that in many resource-limited settings, advanced imaging modalities like CT scans are often unavailable in emergency situations. Similar constraints have been highlighted in studies carried out in Africa.[10] Consequently, healthcare providers rely more heavily on clinical assessments, X-rays, and ultrasound for diagnosing abdominal injuries. This reliance underscores the importance of clinical judgment and the need for improved access to advanced imaging technologies in such environments.[11] In a study carried out in Texas, they observed that the majority of duodenal injuries were of Grade I and II (59.3%) and only 53.1% of their patients underwent exploration which was in contrast to our study as our study showed that about 82% of patients had a higher than Grade II injury and 100% of the patients underwent exploration.[12] In another study carried out in Indianapolis,

they observed associated injuries in 67% of patients whereas in our study this was found to be true in 23.5% of patients.[13] In a similar study the grade of injuries was found to be I or II in the majority of the cases. In a more recent study in Virginia that was also a multi-center retrospective study the percentage of associated injuries was significantly higher than our study but the grade of injury was more comparable to our findings.[9]

A case report from New Delhi reported the management of duodenal injury by simple repair along with duodenal decompression achieved by the triple tube technique.[14] Another study from Morocco has advocated for the conservative management of minor duodenal injuries and has shown favorable outcomes in their series.[15] Another case report from New Delhi has advocated for the use of Roux-en-Y duodenojejunostomy for a major duodenal injury leading to a significant defect.[16] In a retrospective analysis carried out in the USA primary repair was carried out in 80% of patients undergoing operative management for duodenal injury.[9] In our study however 5 (29.4%) patients underwent repair of the primary perforation without any additional procedures and the rest of the patients either had triple drainage with or without pyloric exclusion.

The choice of surgical intervention for duodenal injuries varies significantly across different healthcare settings. In high-resource environments, the availability of advanced imaging allows for more tailored surgical approaches based on detailed preoperative assessments. In contrast, resource-limited settings often necessitate a more generalized approach due to constraints in diagnostic capabilities.[17] This variation highlights the ongoing debate between individualized versus standardized surgical protocols and emphasizes the need for context-specific strategies to optimize patient outcomes.[18]

Our study showed that an associated pancreatic injury and a Grade V injury showed a 100% percent mortality rate similarly a presentation with altered consciousness had a worse outcome. This was corroborated by other international studies.[9] A recent study reviewing the medical literature also showed that complex duodenal injuries, defined as Grade III or higher, had significantly higher morbidity and mortality.[19]

The mortality rate in our study was 29.4% which was comparable to 24% in an international multi-center retrospective analysis.[9] In another study treatment of children with blunt duodenal injuries at Pediatric trauma centers certified by the American College of Surgeons was linked to lower odds of complications compared to non-certified centers.[20] This may explain the comparable mortality rates of our study to the international standards.

CONCLUSION

Blunt abdominal trauma, particularly from falls and road traffic accidents, was the leading cause of pediatric duodenal injuries in our study. The absence of contrast-enhanced CT in the emergency setting posed a diagnostic challenge, making clinical assessment and basic imaging essential for timely decision-making. We observed that patients with higher-grade injuries, especially those with pancreatic involvement, had significantly higher mortality. Notably, children presenting with altered consciousness had a universally fatal outcome, while even those with seemingly mild symptoms required careful evaluation to prevent delays in intervention. Early recognition and timely re-exploration for complications played a crucial role in improving survival, underscoring the need for close postoperative monitoring and a proactive surgical approach. The treatment process, particularly for more severe injuries, should consistently implement a multidisciplinary approach.

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CONFLICT OF INTEREST

None

AUTHOR's CONTRIBUTION

CEA: Manuscript Writing Data Analysis
NT: Supervision of the Project manuscript writing Guidance Review
MBM: Curation of the Study Supervision of the Project Manuscript review
ZS: Manuscript Editing
MUA: Date Collection
AAC: Data Collection

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Original Article

TENDENCY AND ASSOCIATION OF DEVELOPING RELATED SYMPTOMS WITH CHRONIC FATIGUE AMONG COVID-19 SURVIVORS FROM LAHORE; CROSS-SECTIONAL STUDY.

Hassan Sarwar[1], Anna Zaheer[2], Sahar Fatima[3].

ABSTRACT

Background: Humanity has suffered a great deal from COVID-19 as it resulted in enormous morbidity and mortality. It was Commonly observed that people felt sluggish post-covid and found it difficult to carry out household chores. In short it impacted the quality of life. The objective of this study was to determine whether anyone in Lahore has experienced fatigue-like symptoms quite similar to chronic fatigue along with its association during or after the fight against COVID-19.

Material and Methods: The initiation of this study required permission from the ethical committee of University Institute of Physical Therapy. Participants from Lahore in a number of 125 calculated through Epitool application took part in this cross-section study that have accompanied and survived COVID19. Study has been carried out across participants who were isolated at home during the pandemic. Hospitalized patients were excluded. Self-administered proforma was used to assess demographic data but also commonly encountered symptoms of chronic fatigue. MFI scale was administered for validating fatigue related responses.

Results: Total of 125 individuals who have undergone COVID19 took part in this study. About 91 (55%) of individuals impacted from chronic fatigue as a symptom after COVID19. Nearly 109 (66%) survivors encountered body aches, and pains while they suffered from COVID19. About 112 (68%) participants felt low at energy while recovering from COVID19, while 71 (43%) got pain in their digits, back or even in head region after getting recovered from corona virus.

Conclusion: Hence it has been concluded the individuals that participated in the study from Lahore majorly developed symptom of fatigue or felt low at energy not only while being tested positive but also suffered from chronic fatigue after recovering from COVID19. Positive correlation has been established between total fatigue of multidimensional fatigue scale and combating feeling of body aches, pain while being covid positive. Similarly, association of gross fatigue developed with lost interest as well as patience after covid.

Key words: Fatigue, COVID19, Cross-sectional study, Survivors.

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INTRODUCTION:

Humanity has suffered a great deal from COVID-19 as it resulted in enormous morbidity and mortality. Covid-19 resemble in many aspects to SARS-CoV-2, MERS (Middle East Respiratory Syndrome) and Spanish flu outburst in 1917's era.[1] On January 24, 2020, SARS-CoV-2 was confirmed as cause of Covid-19 after being found in bronchoalveolar lavage fluid of three patients at Jinyintan hospital.[2] Among the numerous nations severely impacted by Covid-19, the UK has suffered the worst, with over 286,000

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confirmed cases and over 44,000 fatalities.[3] Studies have suggested that the phase of illness continued for a span of 2-3 weeks while its after effects carried for even months.[4] Corona virus has impacted the world in many aspects from creating a wave of horror i.e. anxiety, panic, lung impairment causing trouble in airways also associated with SARS making people lethargic, leading to fatigue, deteriorating sleep awakens cycle persisting for a span of up to 6 months even after getting recovered from disease. Abnormal weariness after typical activity has been referred to as fatigue. GABA deficits (fatigue and weariness) have been caused by direct hematogenic and indirect systemic inflammation (IL-6) as well as hyperinflammatory generated pathways triggered by SARS-CoV-2 infection.[5] Along with above generated adversities pain, irregular sleep patterns, immunological, neurosensory, gastrointestinal and cellular energy metabolism dysfunction has been considered as symptoms of chronic fatigue syndrome along with severe post-exertional exhaustion that would not improve with rest.[6] Generally, it has been seen that after recovering from COVID-19, over 30% of those afflicted with the virus, either symptomatic or asymptomatic during the acute phase, continued to have accompanied symptoms.[7] Prior studies have reported that nausea, headache and sore throat were the most commonly faced symptoms by the individuals who combated COVID-19.[8,9,10] Moreover fatigue, insomnia and dyspnea have been the most reported symptoms lasting over span of 3 weeks revealed by the systematic review of 28 post-COVID-19 symptom studies.[11] After pandemic it has been commonly observed that people felt sluggish and found difficult to carry out household chores, in short quality of life got impacted.[12] From July 10 to July 28, 2020, a research was carried out at Hayat National hospital in Riyadh, Saudi Arabia. They recorded mean fatigue score as 40.81 ±5.75 in post Covid patients.[13] Women have come across chronic fatigue syndrome more often while overall prevalence in general population is about 0.17- 0.89% as referred by same study. This Study also suggested that individuals had to go through a span of 3 months before the actual onset of chronic fatigue syndrome. Another study which was carried out on patients who got discharged from indoor of hospital, about 63% experienced fatigue as the most prominent symptom for a period of 6 months post-covid.[14]

Every 1 out of three individuals reported fatigue as the most encountered one symptom.[15] Rates of similar weariness have been documented as a result of earlier epidemics such as SARS and MERS.[16] Studies have also reported that fatigue, loss of taste and smell continued for span of 3 to 7 months after combating virus like SARS-CoV-2.[17] Some studies suggested that it occurred because of multiple reasons due to which it closely resembled with Epstein Barr virus, influenza and other related forms of coronavirus.

This study has been carried out mainly to detect whether individuals across Lahore region have undergone fatigue like symptoms while recovering from COVID-19. It was determined in the study that whether the association between fatigue related situation while being covid positive was configured (through MFI scale) with feeling low or lack interest after combating virus lacked in previous studies.

Additionally, previous studies did not invite people from all sectors and were limited to hospital setting or had associated fatigue with increasing age.[12]

According to our knowledge, it was a novel study done at that time of pandemic in our region and highlighted the tendency of developing symptoms of chronic fatigue in Covid-19 home setting. It will help clinicians in identifying the fact that fatigue impacted patients not only during the disease but continued to depict its effects after surviving covid-19 and keep it in consideration for their patients in future.[4]

MATERIAL AND METHODS

The initiation of this cross-section study required permission from the ethical committee

of University Institute of Physical Therapy. IRB letter No 837-II dated 02 February 2021. Participants in a number of 125, calculated through Epitool application, took part in the study. They had undergone corona virus but managed to survive it and as a result suffered from tiredness and fatigue-like symptoms not only during, but after the disease. Sample size was attained with help of biostatistician who used parent article to calculate it.[18] Lack of energy and extreme sense of tiredness that could interfere with a person's usual daily activities was termed as chronic fatigue. Mean age of the survivors has been 30.29±11.28. People under the age of 18 were excluded from the study. Individuals of age group 21 to 45 years including males and females, participated in the study. Those individuals were eligible for study who had survived COVID19 confirmed through reverse transcriptase polymerase chain reaction test (RTPCR). Chronic fatigue was assessed through multidimensional fatigue inventory scale containing five domains of fatigue including general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue.[2] Total fatigue in MFI scale was calculated by summing scores of all five domains where greater value indicated greater fatigue encountered by participants. Each item of scale was scored on Likert scale "1" depicted not at all to "5" showing very much. Demographics was recorded through self-administered questionnaire so in total two questionnaires was used. Study was carried out among participants who were isolated at their homes during the time of pandemic. Hospitalized patients were not considered for data collection, specifically those who were critical at the time of pandemic and were admitted in intensive care units as a result of suspected virus. Moreover, individuals who were immunocompromised suffering from diabetes mellitus, hypertension, cancer, asthma etc. or the individuals who had not undergone COVID19 or were admitted in the hospital for any disease during COVID19 pandemic were not considered for the study. Informed consent was taken in an online form prior to recording response from the participants. Non-probability convenient sampling was used to negate any sort of biasness while recording data. Study was done at time of pandemic where it was impossible to collect data physically, therefore online method was applied with non-probability sampling method. Moreover, people who willingly gave their consent by filling the questionnaire made part of study. The study took 6 months for completion after approval from relevant authority of institution. All the data was recorded in the Google form which later got converted into SPSS version 25.0 via Microsoft Excel. Qualitative data was recorded in the form of frequencies, percentages, bar graphs while quantitative data was expressed as mean, standard deviation, histogram etc. Previous literature validated all the questions of proforma being used.[2,19]

RESULTS:

Total of 125 individuals who suffered from COVID19 took part in this study. Mean age of the participant was recorded as 30.29± 11.283. Out of which 61(49%) were males, and 64(51%) were females. Students got more impacted by COVID19 in this study and have outnumbered rest of professions. About 56 (34%) students got affected by this global pandemic. Mostly middle-class individuals, about 115 (70%) become victim of corona virus. Unmarried participants suffered more from the pandemic than the married ones. Mean total fatigue accustomed by participants as per MFI scale was recorded as 58.45±12.76. Minimum value of total fatigue was recorded as 20 while maximum was 96. About 91 (55%) individuals impacted from chronic fatigue as a symptom after COVID19. Nearly 109 (66%) survivors encountered body aches, body pains while they were suffering from COVID19. About 112 (68%) participants felt low at energy while COVID19 affected them while 71 (43%) got pains in their extremities, back or even in head region after recovering from corona virus. Association has been found out between chronic fatigue as a symptom (calculated by

MFI scale) after of covid with facing body pains and aches (p value = 0.00) significance between feeling moody, lack of patience or loss of interest after COVID19 and fatigue was found (p value = 0.00) through application of chi-square test. Pearson correlation was also applied between the variables, where p-value was found to be significant.

Table 1: - Descriptive statistics of Demographics (N=125).

Gender	Frequency	Percentage
Male	61	49
Female	64	51
Married	52	42
Unmarried	73	58
Lower Class	02	1.6
Middle Class	115	92
Upper class	8	6.4
Total	125	100%

Table 2: - Descriptive statistics of COVID19 survivors who suffered Chronic fatigue (N=125).

COVID19 survivors who encountered chronic fatigue after virus	Frequency	Percentage
Yes	91	73
No	34	27
COVID19 survivors who felt low at energy or fatigue at time affected by virus.		
Yes	112	90
No	13	10
Total	125	100%

Table 3: - Correlation of symptoms related fatigue during covid-19 period as well as after combating virus or similar to it with total fatigue of MFI scale (N= 125).
Correlation has been significant at 0.05* level (2-tailed).

Domain of MFI Scale	Self-Administered Symptoms	Pearson Correlation (R-value)	P-value
Total Fatigue	You faced body aches or pains while covid positive	.519**	0.00
Total Fatigue	After covid you felt moody, lack patience or lost interest	.364**	0.00
Total Fatigue	Felt pain in digits, back head or body	.229*	0.01

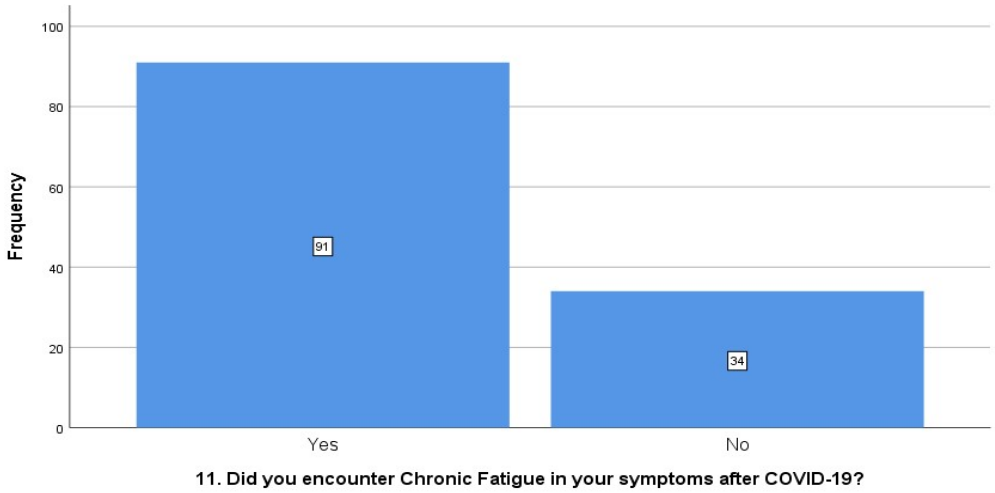

Figure 1: - Graphical representation of COVID19 survivors who encountered Chronic fatigue as a symptom after COVID19 period.

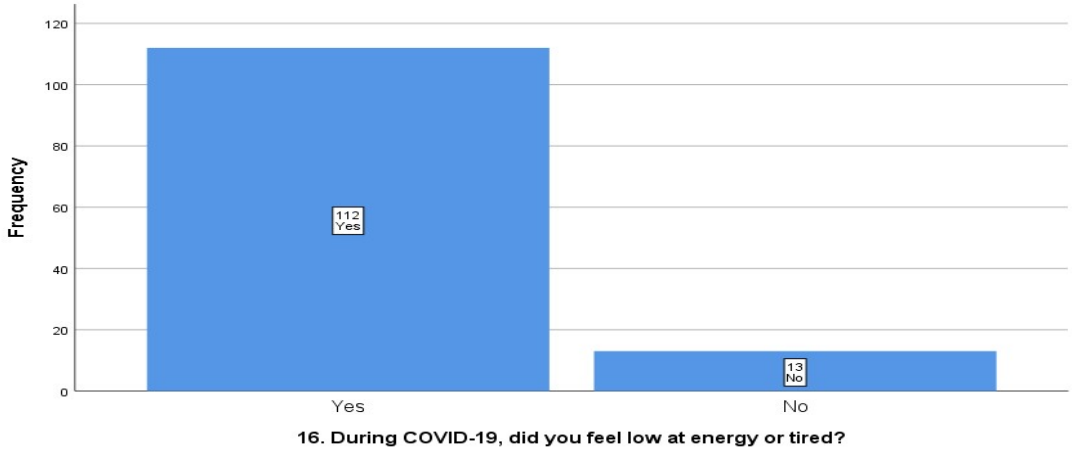

Figure 2: - Graphical representation of COVID19 survivors who felt low at energy or chronic fatigue as symptom after accompanying corona virus.

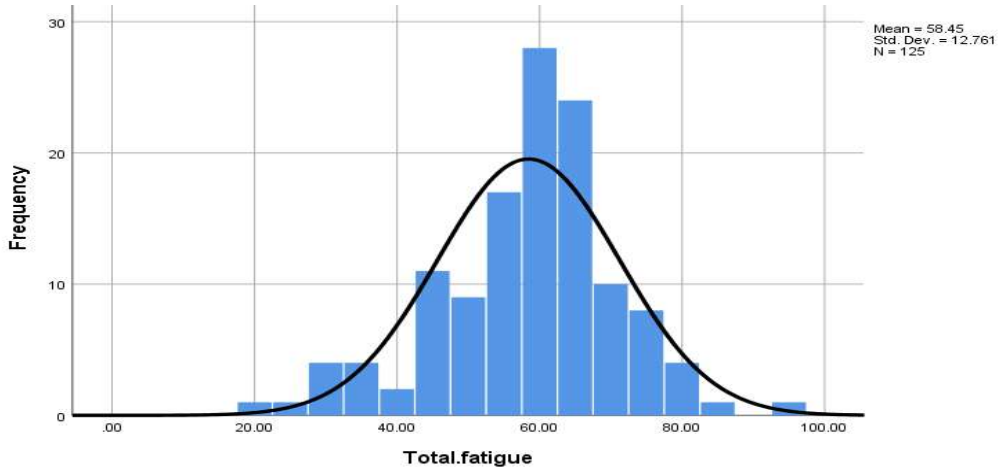

Figure 3: - Graphical representation of total fatigue estimated by MFI (Multidimensional fatigue inventory) scale among COVID19 survivors with mean value of 58.45±12.76.

DISCUSSION:

This study included individuals from almost every sector of the community where students dominantly got affected intensely among all individuals or professionals of society contrary to studies carried among health professionals of hospital as chief target.[12] Chronic tiredness even after being medically cleared of original ailment has an influence on day-to-day functioning and return to work. Majority reported fatigue or felt low at energy even after getting recovered from pandemic. The study has emphasized the point that participants came across fatigue or associated symptoms not only while having the disease but encountered feelings of chronic fatigue after getting recovered.[12] Prior studies suggested the fact that about 70% of individuals Suffered from fatigue post covid, where most of them were doctors by profession. In line with this our study concluded that nearly same number of COVID19 affected individuals had chronic fatigue from all sects after disease while more than half of the participants reported fatigue even during the disease. Similar to it, vast number of participants also reported with the feeling of body aches and pains while sustaining covid-19. Individuals have additionally reported pain in head, back or digits after recovering from the disease which was missed in prior studies.[12]

Past studies have mostly estimated limited domain of fatigue by application of fatigue assessment scale whereas we have administered multidimensional fatigue scale and estimated five domains like general fatigue, physical fatigue, reduced activity motivation and mental fatigue.[2] Total fatigue has also been calculated where greater score indicated higher level of fatigue, calculated by summing all domains lacked by prior literature.[12] We have estimated that the association of fatigue and related symptoms lacked prior to this study in our region.[2] Previous literature has highlighted evidence on fatigue encountered by the individuals while staying at hospital but this study did not cover such individuals who stayed at the hospital during the pandemic period.[20] One of the studies suggested that fatigue continued as a symptom among sufferers for more than a year.[21],[22]

In future, studies should be carried out for longer period to see adversities related to fatigue among COVID19 suffers. A survey by British association carried out online suggested that the population in their study got affected by muscular fatigue while this study lacked evidence of muscular pain.[23] Future studies should also keep this point in mind. Fatigue has been indicated as one of the most common symptoms among two to three symptoms which continued after recovering from COVID19.[24] Prior studies also suggested that single stranded SARS- CoV-2 led to malaise and lack of concentration but this study lacked that,[25] previous studies have not been able to establish association between age and fatigue while we configured association between age group cut-off with fatigue symptoms and feeling of pain, body aches while being covid-19 positive.[26] Future studies should consider factors like obesity, respiratory symptoms and quality of life into consideration to find its association with chronic fatigue. Our study found relation between total fatigue as well as individuals who lost interest, post-covid while it lacked to configure association between among depression and systemic inflammation which have been reported by earlier studies.[27] Future studies should establish more associations keeping malaise, sleep like factors in view while considering our findings. This study has limitations like future studies could incorporate scale where they would not recode items to finalize responses related to fatigue which made it difficult to analyze data specifically items i.e. 2, 5, 9, 10, 13, 14, 16, 17, 18 and 19 which have been reverse scored.[2] Hospitalized individuals who suffered chronic fatigue were not taken into account as the study was completed during pandemic. They should be considered for further studies. Future studies should consider long term effects of chronic fatigue for extended period of time to address chronic fatigue syndrome. Sample size should

be increased along with the refinement of study design as our study has an observational method and limited time.

CONCLUSION:

Individuals participating in the study from the territory of Lahore majorly developed symptom of fatigue or felt low at energy not only while suffering from the disease but also had chronic fatigue after recovering from COVID19. Positive correlation has been established between total fatigue of multidimensional fatigue scale and feeling of body aches and pain while being covid positive. Similarly, association of gross fatigue was found with loss of interest as well as patience after covid.

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CONFLICT OF INTEREST:

None

AUTHOR's CONTRIBUTION

HS: Manuscript Writing, Data Analysis
AZ: Study Concept, Data Analysis
SF: Manuscript Review

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Case Report

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA: A CASE REPORT

Noor Zahid[1], Muhammad Tayyab[2]

ABSTRACT:

Juvenile Nasopharyngeal Angiofibroma is a rare benign neoplasm almost exclusively seen in adolescent males, which proliferates under the influence of steroid hormones at puberty. It arises from the margin of sphenopalatine foramen and spreads widely along the skull base. Histologically, it comprises a hamartomatous tumor of vascular tissue lacking smooth muscle and elastic coats. Its propensity to bleed heavily and extensive spread along the skull base and cranial fossae pose significant risk of hemorrhage during surgical resection. Various techniques are employed before and during surgery to reduce the risk of per-operative hemorrhage. Advances in interventional radiology such as pre-operative embolization of feeder vessels enable safer resection. We present a case of a 15-year old male admitted with triad of nasal obstruction, recurrent spontaneous epistaxis and fleshy mass in right nasal cavity. HRCT paranasal sinuses revealed a large nasopharyngeal mass infiltrating the nasal cavity, the nasopharynx, sphenoid sinus, and bilateral posterior ethmoidal cells, extending up to the infratemporal fossa. Cross-sectional imaging enabled accurate staging and open surgical technique was opted. Pre-operative embolization of internal maxillary artery allowed successful complete surgical resection with minimal bleeding per-operatively. With accurate staging and correct choice of hemostatic technique, angiofibroma can be excised completely with relatively less morbidity

Key Words: Angiofibroma, Interventional Radiology, Epistaxis, Head and Neck Neoplasm

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NTRODUCTION

Juvenile Nasopharyngeal Angiofibroma (JNA) is a rare androgen-dependent locally aggressive benign tumor accounting for less than 1% of head and neck neoplasms. It is almost exclusively seen in males with mean age of onset between 13 and 22 years,[1] hypothesized to arise from the surge in steroid hormone at puberty.[2] JNA tumors have been postulated to originate from the margin of sphenopalatine foramen, spreading submucosally along the skull base and cranial fossae with 4-11% of cases being associated with intracranial invasion.[3] Histologically, it is a lobulated, non-encapsulated tumor arising from hamartomatous nidus of vascular tissue.[4] Over 10 staging systems having been proposed based on cross-sectional imaging. Coronal computed tomography shows extent of bony destruction whereas, magnetic resonance imaging highlights soft tissue involvement pre-operatively and residual or recurrent disease post-operatively. JNA is managed definitively by surgical resection involving endoscopic resection, open surgical resection, or a combination of the two. Radiotherapy is reserved for residual or inoperable cases such as those involving internal carotid artery.[5] Recent advances in interventional radiology have allowed pre-operative embolization of feeder vessels to reduce blood loss during resection. JNA remains a surgical challenge,

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especially in developing countries where embolization facilities are not available ubiquitously. Here we present a case of a 15-year old male having JNA with intracranial extension treated by pre-operative embolization and surgical resection at a tertiary care hospital of Lahore.

CASE DESCRIPTION

A 15-year-old male was admitted in Otorhinolaryngology Department of Jinnah Hospital, Lahore in September 2024 with chief complaint of nasal obstruction and recurrent per nasal bleed for 6 months. Nasal obstruction was gradual in onset, constant, slowly progressing from unilateral (right) to bilateral, not relieved by topical or oral medication. It was associated with occasional serous discharge and no air entry. For the preceding 3 months, it was associated with progressively increasing mouth breathing, snoring and development of nasal speech. The patient also complained of multiple episodes of profuse spontaneous epistaxis comprising fresh blood clots, relieved by topical medication and application of cold water. In the preceding one month, he developed progressive swelling of right cheek and right orbit. Systemic inquiry revealed occasional episodes of ipsilateral hearing loss, otalgia and cough. He also reported progressive post-nasal dripping, anosmia, broadening of nasal bridge and widening of sclera. However, he had no complaints of decreased visual acuity, diplopia or ophthalmoplegia. He had no noteworthy past medical history, family history or drug history. General physical examination revealed pallor and S-shaped external nasal deformity. Anterior rhinoscopy revealed mucoid discharge and a red fleshy mass filling the right nasal cavity. He also had swelling of right cheek with normal overlying skin. There was mild proptosis of right eye. However, visual acuity was 6/6 bilaterally and all eye movements were full in range. Oro-dental and neurological examination was unremarkable, with intact cranial nerve function. Routine hematological investigations were within normal range except decreased hemoglobin level (10.5 g/dl) (Table 1).

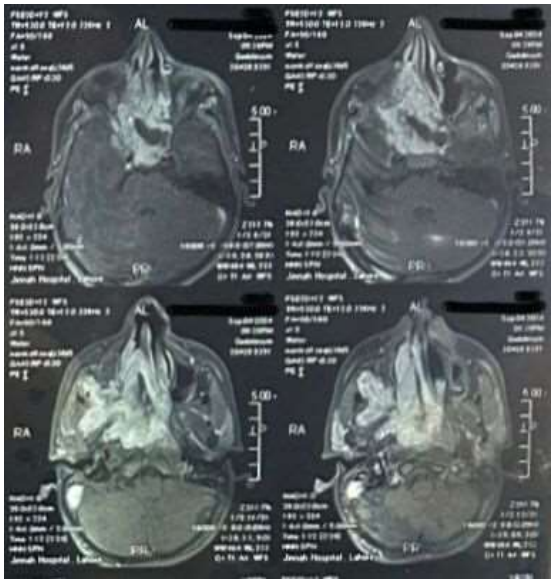
Table 1. Results of baseline investigations performed prior to open surgical resection under general anesthesia

Laboratory Parameter	Value
Hemoglobin (g/dl)	10.5
Total Leukocyte Count (x10^9/L	8.0
Platelet Count (x10^9/L)	303
Hematocrit (%)	33.4
Urea (mg/dl)	13.97
Creatinine (mg/dl)	0.54
Bilirubin total (mg/dl)	0.5
ALT (U/L)	24
AST (U/L)	29
Sodium (mmol/L)	132
Potassium (mmol/L)	4.78

HRCT paranasal sinuses revealed a large sinonasal mass lesion involving posterior portion of both nasal cavities and ethmoidal air cells, expanding the sinuses with a large nasopharyngeal component. There was compression of the right osteomeatal complex with fluid impaction in the right maxillary sinus. Left maxillary sinus and bilateral frontal sinuses were unremarkable. MRI face with contrast showed soft tissue mass lesion measuring 7.5 x 6.5 x 6.5 cm (craniocaudal anteroposterior transverse) centered in the right sphenopalatine foramen, infiltrating right nasal cavity, nasopharynx, sphenoid sinus, bilateral posterior ethmoidal cells, right pterygopalatine fossa and right infratemporal fossa (Figure 1). Right masticator space was also invaded. Mass involved the orbital apex closely abutting the right optic nerve, extending into the middle cranial fossa (intracranial, extra-axial),

contacting the cavernous sinus. Provisional diagnosis of nasopharyngeal angiofibroma (Andrew-Fisch Stage 3B) was made.

Figure 1. Cross-sectional imaging showing extent of sinonasal mass



Patient underwent digital subtraction angiography of feeder vessels and pre-surgical embolization under general anesthesia at Lahore General Hospital (Figure 2). Bilateral feeder vessels from both branches of internal maxillary artery were embolized with spongostan. Recovery was uneventful and patient was prepared for surgical resection within the following 24 hours.

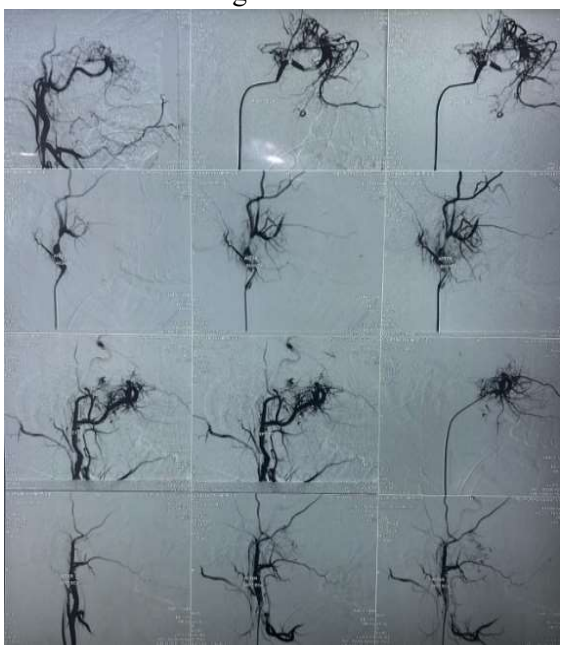


Figure 2. Pre-operative digital subtraction angiography performed at a tertiary care hospital of Lahore to identify feeder vessels for embolization prior to open surgical resection of angiofibroma

Open surgical resection was performed under general anesthesia in reverse Trendelenburg position with 15-degree head elevation and intra-oral delivery of endotracheal tube. Lateral rhinotomy incision was given and right medial maxillectomy was performed. Intra-operatively, the tumor was found to involve nasopharynx and sphenoid sinus, extending up to right infratemporal fossa. Posterior nasal plug was placed followed by anterior nasal packing. On 2nd post-operative day, the nasal pack was removed under general anesthesia.

Pre-operative and immediate post-operative hemoglobin levels were 10.8 and 9.5 g/dl, respectively. Two pints of blood were transfused post-operatively to achieve baseline hemoglobin levels within first two post-operative days. Recovery was unremarkable. Patient developed mild swelling of right cheek and right eye following surgery and was managed successfully on intravenous dexamethasone. Neurological function and visual acuity remained intact post-operatively. Histopathological examination of resected specimen revealed proliferating vessels in a background of fibrous and collagenized stroma, thus confirming the diagnosis of JNA. Patient was discharged on sixth post-operative day and follow-up nasal endoscopic examination revealed no residual disease.

DISCUSSION

Juvenile Nasopharyngeal Angiofibroma (JNA) is a benign locally aggressive tumor of the head and neck seen almost exclusively in adolescent males. It accounts for 0.05 to 0.5% of head and neck neoplasms[6]. Mean age of presentation ranges from 13 to 22 years.[1] Immunohistochemical staining has identified its receptor status as androgen positive thus suggesting androgen influence on the origin of this tumor.[7] Patient usually presents with a triad of nasal obstruction, recurrent spontaneous epistaxis and a mass in the nasal cavity. Erosion

of orbit and intracranial involvement may cause proptosis and cranial nerve palsies. Advanced stages result in anosmia, eye pain and Eustachian tube blockage leading to recurrent otitis media. Our case was a 15-year-old adolescent male who presented with typical signs and symptoms of JNA in accordance with previous literature. Our differential diagnoses included antrochoanal polyp, nasopharyngeal cyst, sinonasal malignancy and granulomatous diseases of nose.

JNA tumors arise from margin of sphenopalatine foramen. Acharya et Al. has identified its precise location of origin as trifurcation of the sphenoidal process of palatine bone, roof of pterygoid process and horizontal process of vomer[4]. It is known to spread along every axis; superiorly into sphenoid and cavernous sinuses, medially pushing the nasal septum, posteriorly invading the basisphenoid and laterally extending into the pterygomaxillary and infratemporal fossae. 10-20% of JNAs possess the potential to extend intracranial and into the orbit through the infraorbital fissure; however, dural invasion is rare.[8]

Cross-sectional imaging has a valuable rule in diagnosis and staging. Coronal computed tomography (CT) shows extent of bony destruction and anatomical location of the tumor. Lateral expansion of the tumor results in bowing of the posterior wall of ipsilateral maxillary sinus, which is known as the Holman Miller sign - pathognomonic for angiofibroma. However, magnetic resonance imaging (MRI) is superior to CT in delineating soft tissue and intracranial involvement. The size of this tumor as seen on cross-sectional imaging may not be an accurate estimate of the actual size. Acharya et al. has described the tumor as "only tip of the iceberg."[4] Over 10 staging systems have been devised based on cross-sectional imaging, of which Radkowski and Andrew-Fisch are commonly used (Table 2).

Table 2. Radkowski and Andrew staging systems in use for Juvenile Nasopharyngeal Angiofibroma

Stage	Radkowski[9]	Andrew[9]
1	**A=Limited to nose or nasopharyngeal vault B=Extension into one or more sinuses**	Limited to nose or nasopharyngeal vault
2	**A=Minimal extension into pterygopalatine fossa B=Involvement of entire pterygopalatine fossa C=Extension into infratemporal fossa or posterior to pterygoid plates**	Invasion of pterygopalatine fossa or any sinus
3	**A=Minimal involvement of middle cranial fossa or pterygoid plates B=Intracranial extension with or without cavernous sinus invasion**	A=Extension in infratemporal fossa or orbital invasion B=Intracranial extradural extension
4	-	Intra-dural extension

In this case, both HRCT paranasal sinuses and MRI face were done and extent of the tumor was delineated. The nasopharyngeal mass was large, infiltrating the nasal cavity, nasopharynx, sphenoid sinus, and bilateral posterior ethmoidal cells, extending up to the infratemporal fossa. Andrew-Fisch staging was used and the tumor was classified as stage 3b.
Treatment options include nasal endoscopic, endoscopic-assisted and open surgical resection. Open surgical approaches based on the anatomical location and extent of tumor include lateral rhinotomy, transpalatal, transmaxillary, mid facial degloving, Le Fort I-

III, Denker, infratemporal and various combinations of approaches. Radiotherapy is reserved for recurrent, residual or inoperable cases such as those having intracranial extension. Open surgical technique was thus preferred over endoscopic technique in our case to allow maximal resection.

Histologically, nasopharyngeal angiofibroma comprises a lobulated non-encapsulated mass of stellate and staghorn blood vessels in loose fibrous stroma[4]. These blood vessels lack elastic or smooth muscle coat, thus accounting for excessive bleeding during surgery. The propensity to bleed heavily and ability to spread along cranial fossae and base of skull make the tumor surgically challenging.[10] Biopsy of the resected specimen confirmed the diagnosis of our case. Network of blood vessels in fibrous stroma was identified on histopathology, in line with previous case report.[4]

Various techniques may be employed pre-operatively and intra-operatively to reduce the risk of hemorrhage during surgical resection, such as ligature of internal maxillary artery and pre-operative embolization of feeder vessels[11]. The tumor is usually supplied by branches of internal maxillary artery and occasionally by other branches of external carotid artery. Feeder vessels can be identified pre operatively via digital subtraction angiography. Pre-operative embolization of feeder vessels from external carotid allows surgical resection with relatively less bleeding. Blood loss in non-embolized patients is reduced to almost half in embolized patients[11]. JNA recurrence in embolized patients has also been reported to be lower than in non-embolized patients.[12] However, surgical resection must be done within 48-72 hours of embolization before revascularization from contralateral vessels occurs.

JNA is a highly vascular tumor. As surgical manipulation carries high risk of severe bleeding intra-operatively, multi-disciplinary approach was undertaken by otorhinolaryngologists and interventional radiologists for optimal management of this case. Pre-operative digital subtraction angiography and embolization of feeder vessels permitted surgical resection with minimal blood loss and patient's hemoglobin was optimized within 2 days following surgery. Nasal packing removed under general anesthesia on 2nd post-operative day revealed minimal bleeding.

Our case had certain limitations. Pre-operatively, the patient had to wait for embolization facilities to be available, which was also only possible at another tertiary care center of Lahore. The patient returned to out-patient department for follow-up only once and could not be followed any further.

CONCLUSION

Juvenile nasopharyngeal angiofibroma is a surgical challenge for otorhinolaryngologists, owing to its intense vascularity and complex anatomical location. However, cross-sectional imaging allows accurate staging of the tumor and hence, the correct choice of surgical technique. It is mandatory to employ techniques to reduce per-operative hemorrhage. Radiological advancements such as digital subtraction angiography and pre-operative embolization allow safer resection with better surgical outcome.

AUTHORS' CONTRIBUTION

NZ: Introduction, Case Description, Discussion, and Abstract
MT: Case Description, Review, and References

CONSENT FOR PUBLICATION

Written informed consent was taken from patient and his guardians regarding data collection and publication.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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