pISSN: 2220-7562
eISSN: 2617-9482
CODEN: JBUMB7
Recognized by HEC & PMDC

JBUMDC

Journal of Bahria University Medical & Dental College

Volume 15 Issue 1, January - March 2025

Bahria University Health Sciences Campus Karachi
Adjacent PNS SHIFA, DHA Phase II, Karachi

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
Recognized by HEC & PMDC
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
https://vlibrary.emro.who.int/journals/jbumdc-journal-of-bahria-university-medical-and-detal-college/
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/resource/ISSN/2617-9482
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
Crossref at https://doi.org/10.51985/aluu2996
ICMJE at https://www.icmje.org/journals-following-the-icmje-recommendations/#J
Bahira University DSpace Repository at http://111.68.99.22:8080/xmlui/handle/123456789/6388,
Pakistan Scientific and Technological Information Center (PASTIC) at http://pastic.gov.pk/

Correspondence Address:
Editor, JBUMDC, Bahria University Medical & Dental College, Adjacent PNS SHIFA,
DHA Phase II, Karachi Pakistan
+92-21-35319491-9
https//jbumdc.bahria.edu.pk
editor.bumdc@bahria.edu.pk
https://www.facebook.com/jbumdc/, https://www.facebook.com/journal.bumdc.7
Published by: Bahria University Health Sciences, Campus Karachi

JBUMDC

Journal of Bahria University Medical & Dental College

Recognized by HEC & PMDC

JBUMDC Journal of Bahria University Medical & Dental College
Volume-15, Issue-1. January - March 2025

CONTENTS

Editorial

Noise-Induced Hearing Loss and Tinnitus in the Digital Era: An Alarming Rise in the Younger Generation 01
Iqbal Hussain Udaipurwala

Original Articles

Anticancer Activity of n-Hexane and Acetone Leaf Extracts from *Delonix regia* (Gul Mohar) on HeLa (Cervical) and Prostate Cell Lines 03
Saeed Ahmed Sheikh, Asif Ahmed, Asadullah, Shazia Nawaz

Frequency and Association of Perforated Appendix with Patient's Characteristics in Acute Appendicitis 08
Muhammad Zeb, Rafia Ahmad, Abdul Wadood, Ishtiaq Ahmed, Malak Maaz Hassan, Muhammad Moazzam Farooq

Sensitivity and Specificity of the Neutrophil Lymphocyte Ratio (NLR) in Diagnosing Late Onset Neonatal Sepsis in NICU Patients 15
Zunaira Zulfiqar, Unaiza Syed, Syed Arsalan Hassan, Nabeera Hayat, Hamza Khursheed, Abu Bakar Khan

Analyzing trends in Cesarean Section by Action Oriented Classification (Robson Criteria) at Creek General Hospital, Karachi 21
Saba Pario, Shaista Bashir Anwar, Kaweeta Kumari, Uzair Ahmed, Muhammad Muhib, Ghania Naeem

Mason Radial Head Fractures: Surgical Management 29
Nisar Ahmed, Syed Muhammad Mohtashim Ali, Malik Muhammad Hamdan Tafheem

Prevalence of Hypocalcemia in Infants of Mothers with Gestational Diabetes 34
Nida Sarwar, Khurram Fayyaz, Imrana Ata, Sehar Aslam, Hajra Begum, Khubaib Ahmed

Diagnostic Efficacy of grey-zone Serum Prostate Specific Antigen level in patients with Benign Prostatic Hyperplasia and Prostate Carcinoma 40
Syed Atif Hussain, Rukhsana Tumrani, Afsheen Nigar, Anber Rahim, Mahnoor Chaudhry, Seerat Fatima Tu Zahra

Medical Education - Original Article

Development, Implementation and Initial Evaluation of the Blueprint for MBBS Theory Exams in a Private Medical College of Pakistan 45
Yusra Nasir, Sobia Ali, Muhammad Ahsan Naseer, Sana Farooq Shah

Review Article

Limitations of Artificial Intelligence in Orthodontics. Literature Review 53
Sadia Naureen

Case Report

Aesthetic Management of Coronal Dilacerations with Enamel Hypoplasia of Permanent Maxillary Central Incisors: 60
Nehal Amir, Muqadus Hayat

Commentary

Liraglutide - A Promising Approach Against Obesity 64
Nabila Rafi, Muhammad Sajid Abbas Jaffri, Kamran Yousuf

Letter to Editor

The Evolving Role of Genetic Counseling in Genomic Medicine 67
Ghulam Hassam U Din Tarrar, Nimra Mushtaq, Muhammad Muzamil

"Who am I?" The Hidden Aspects of Dissociative Identity Disorder 68
Alishba Eman

Editorial **Open Access**

Noise-Induced Hearing Loss and Tinnitus in the Digital Era: An Alarming Rise in the Younger Generation

Iqbal Hussain Udaipurwala

How to cite this Article:

Udaipurwala IH. Noise-Induced Hearing Loss and Tinnitus in the Digital Era: An Alarming Rise in Younger Generation. J Bahria Uni Med Dental Coll. 2025;15(1):01-02 DOI: https://doi.org/10.51985/JBUMDC2024451

The digital era has fundamentally transformed how we interact with sound, making music, entertainment, and communication more accessible than ever before. However, with this revolution comes an escalating public health concern: noise-induced hearing loss (NIHL) and tinnitus, particularly among the younger generation.[1] The widespread use of personal listening devices, attendance at loud concerts, and frequent exposure to occupational noise are all contributing factors that subject our ears to harmful sound levels on a near-daily basis. Recent studies have shown that the younger generation is increasingly exposed to recreational noise at hazardous levels, leading to hearing problems that were once considered more common in older populations.[2] NIHL is now recognized as one of the most prevalent causes of hearing impairment globally. It occurs when prolonged exposure to loud sound damages the hair cells within the cochlea. Tinnitus often accompanies NIHL and may persist long after the initial noise exposure. According to the World Health Organization (WHO), over 1.1 billion young adults worldwide are at risk of developing NIHL due to unsafe listening practices.[3] Historically, NIHL was primarily associated with occupational noise exposure among middle-aged or older adults who had spent decades in noisy workplaces.[4] However, recent data indicate that nearly half of teenagers and young adults in middle- and high-income countries are exposed to unsafe sound levels through personal audio devices.[5] This shift in the demographics of NIHL and tinnitus is particularly alarming, as it highlights the growing vulnerability of younger generations to these conditions.

The popularity of personal listening devices, coupled with easy access to downloadable music, has made it convenient for individuals to listen music anywhere, often in noisy environments. The increasing use of earphones and earbuds allows people to listen at high volumes without disturbing those around them, creating a dangerous feedback loop where users inadvertently increase sound to unsafe levels. Studies have shown a strong association between tinnitus in teenagers and young adults who regularly use MP3 players, along with high-frequency hearing loss at 8,000 Hz.[6] One key issue is that MP3 file formats compress original audio files, reducing sound quality particularly in the middle frequency ranges, where damage is more likely to occur.

Research on the sound pressure levels delivered by personal music devices reveals a wide range of potential exposures, from 60 to 120 dB.[7] This variability means that users can easily exceed safe listening levels without realizing the damage being done. Beyond recreational exposure, occupational noise remains a major source of hearing damage. Individuals working in construction, manufacturing, and even the music industry are at heightened risk, as daily exposure to harmful noise levels becomes routine. Compounding the issue is the integration of digital sound into nearly every aspect of life, from loud work environments to constant background noise in urban settings.

The exact mechanisms underlying NIHL are not fully understood, but one prominent theory involves ischemia-reperfusion injury of the cochlea. Loud noise is thought to reduce blood flow to the cochlea, triggering oxidative stress and the production of reactive oxygen species (ROS). This oxidative damage affects hair cells, supporting cells, and spiral ganglion neurons, leading to cell death. Studies have shown that ROS levels increase dramatically within hours of noise exposure and can remain elevated for several days.[8] This suggests that reducing oxidative stress in the cochlea could play a key role in preventing NIHL.

Tinnitus, while often underestimated as a health issue, can severely impact an individual's well-being. It has been linked to sleep disturbances, anxiety, depression, and cognitive difficulties, and in severe cases, may even lead to suicidal tendencies. Social isolation is common among those with chronic tinnitus, as they withdraw from activities that exacerbate their symptoms. Research indicates that between 57% and 76% of tinnitus cases are directly linked to NIHL.[9] The pathophysiology of tinnitus remains poorly understood, but it is believed to result from spontaneous depolarization of auditory nerve fibers in the absence of external stimuli.[10] Another theory suggests that noise exposure can damage synaptic connections between inner hair cells and spiral ganglion cells, leading to a form of "hidden hearing loss." This hidden damage manifests as tinnitus, loudness intolerance, and difficulty hearing in noisy environments.[11,12]

Iqbal Hussain Udaipurwala *(Corresponding Author)*
Senior Professor and HOD Department of ENT
Bahria University Health Sciences, Campus Karachi
Email: iqbal.bumdc@bahria.edu.pk

Received: 03-10-2024
Accepted: 22-11-2024

Currently, there is no definitive treatment for established cases of NIHL or tinnitus, making prevention the most effective strategy. For mild to moderate hearing loss, hearing aids can restore auditory perception, while cochlear implants may be an option for those with severe or profound deafness. Some researchers have experimented with intra-tympanic and oral steroids, but the results remain controversial. Pharmacological approaches that target oxidative stress by scavenging ROS and increasing antioxidant activity within the cochlea are also being explored, but further research is needed to validate these interventions.

Given the preventable nature of NIHL and tinnitus, public health strategies should focus on education, regulation, and early intervention. Key recommendations include:

1. Public Awareness Campaigns: Governmental and health organizations must continue raising awareness about the dangers of excessive noise exposure. Initiatives like the WHO's "Make Listening Safe" campaign aim to educate young people on the risks of high-volume listening and encourage safer habits, such as using volume-limiting features on devices.

2. Regulation of Personal Listening Devices: Manufacturers should be encouraged or even mandated to include volume limits and hearing health warnings on personal audio devices. Smartphone apps that track listening habits and warn users of unsafe noise levels can promote more responsible listening practices.

3. Hearing Conservation Programs: For individuals exposed to occupational noise, mandatory hearing conservation programs should be implemented. These programs typically include regular hearing tests, the use of protective ear equipment, and guidelines to minimize exposure to harmful noise levels.

4. Research and Innovation: Investment in research is critical for understanding the mechanisms of tinnitus and developing effective treatments. Emerging fields such as gene therapy, stem cell research, and neural modulation hold promise for future therapies that could reverse or mitigate the effects of NIHL and tinnitus.

To conclude, the digital world has undeniably transformed the way we interact with sound. However, this transformation has come at a cost, with an increasing number of young individuals at risk for noise-induced hearing loss and tinnitus. Personal listening devices, often delivering dangerously high sound levels directly into the ear, are of particular concern. Without proper education, regulation, and intervention, we may face a growing public health crisis as younger generations continue to expose themselves to hazardous sound levels.

Authors Contribution:
Iqbal Hussain Udaipurwala: Conception, writing, literature search, proof reading

REFERENCES:

1. Loughran MT, Couth S, Plack CJ, Armitage CJ. Identifying targets for interventions to increase earplug use in noisy recreational settings: A qualitative interview study. *Int J Environ Res Public Health*. 2021;18(24):12879. doi:10.3390/ijerph182412879.
2. Armitage CJ, Loughran MT, Munro KJ. Epidemiology of the extent of recreational noise exposure and hearing protection use: Cross-sectional survey in a nationally representative UK adult population sample. *BMC Public Health.* 2020;20(1):1-7. doi:10.1186/s12889-020-09602-8.
3. Xu K, Xu B, Gu J, Wang X, Yu D, Chen Y. Intrinsic mechanism and pharmacologic treatments of noise-induced hearing loss. *Theranostics.* 2023;13(11):3524-3549. doi:10.7150/ thno. 83383.
4. Mirza F, Alam MJ, Hydri AS. Mutiullah S, Udaipurwala IH, Bareeqa B, Nisar A, Samar SS. Assessment of Hearing Status in Rickshaw Drivers of Karachi. J Bahria Uni Med Dental Coll. 2019;9(1):08-12. doi.org/10.51985/JBUMDC2018081
5. Haruna K, Salisu AD, Labaran SA, Fufore MB. Prevalence and pattern of hearing loss among young adults in tertiary institutions with habitual headphone/earphone usage in Kaduna Metropolis. *J West Afr Coll Surg*. 2023;13(4):98-105. doi:10.4103/jwas.jwas_77_23.
6. Figueiredo RR, Azevedo AA, Oliveira PM, Amorim SP, Rios AG, Baptista V. Incidence of tinnitus in MP3 player users. *Braz J Otorhinolaryngol*. 2011;77(3):293-298. doi:10.1590/s1808-86942011000300004.
7. Narahari PG, Bhat J, Nambi A, Arora A. Impact of usage of personal music systems on oto-acoustic emissions among medical students. *Noise Health.* 2017;19(90):222-226. doi:10.4103/nah.NAH_75_16.
8. Honkura Y, Matsuo H, Murakami S, et al. NRF2 is a key target for prevention of noise-induced hearing loss by reducing oxidative damage of cochlea. *Sci Rep.* 2016;6:19329. doi:10.1038/srep19329.
9. Mazurek B, Olze H, Haupt H, Szczepek AJ. The more the worse: The grade of noise-induced hearing loss associates with the severity of tinnitus. *Int J Environ Res Public Health.* 2010;7(8):3071-3079. doi:10.3390/ijerph7083071.
10. Yeh CW, Tseng LH, Yang CH, Hwang CF. Effects of oral zinc supplementation on patients with noise-induced hearing loss-associated tinnitus: A clinical trial. *Biomed J*. 2019;42(1):46-52. doi:10.1016/j.bj.2018.10.009.
11. Song Q, Shen P, Li X, et al. Coding deficits in hidden hearing loss induced by noise: The nature and impacts. *Sci Rep.* 2016;6:25200. doi:10.1038/srep25200.
12. Chen H, Shi L, Liu L, Yin S, Aiken S, Wang J. Noise-induced cochlear synaptopathy and signal processing disorders. *Neuroscience*. 2019;407:41-52. doi:10.1016/j. neuroscience.2018.09.026.

Original Article **Open Access**

Anticancer Activity of n-Hexane and Acetone Leaf Extracts from *Delonix regia* (Gul Mohar) on HeLa (Cervical) and Prostate Cell Lines

Saeed Ahmed Sheikh, Asif Ahmed, Asadullah, Shazia Nawaz

ABSTRACT:

Objective: The purpose of this study was evaluation of the anticancer activity of n-hexane and acetone leaf extracts obtained from *Delonix regia* on BJ (normal fibroblast), cervical (HeLa), and prostate cell lines.

Study Design and Setting: This in vitro study was designed to assess the cytotoxic effects of leaf extracts from *D. regia*. The leaves were harvested, dried, and then subjected to extraction using hexane and acetone. The resulting extracts were concentrated and prepared for analysis. The effects of these extracts were evaluated on HeLa and prostate cell lines under standard laboratory conditions.

Methodology: MTT colorimetric assay was used to evaluate the cytotoxic activity of leaf extracts. Cell cultures were prepared and introduced into the plates. Different concentrations of extracts were added, and reduction of MTT to formazan within cells was measured. The cytotoxicity was monitored as the concentration causing 50% growth inhibition (IC_{50}) for cell lines.

Results: Results show that the acetone extract exhibits moderate inhibition (36.29%) on cervical cell lines, while the n-hexane extract demonstrates higher inhibition (55.84%) on the same cell line. However, both extracts are inactive on prostate cell lines. On BJ cell lines, both extract showing significant inhibition (69.68% & 61.32%) respectively.

Conclusion: In conclusion n-hexane extracts of *D. regia* exhibited more cytotoxic activity than acetone leaf extract. Although, *D. regia* possessed some anticancer activity potential however its efficacy is not comparable to doxorubicin. The study suggests further exploration of acetone and n-hexane extracts from *D. regia* as potential anticancer agents.

Keywords: Acetone, Anticancer, *Delonix regia*, HeLa, Leaf extract, n-Hexane, Prostate cell lines

How to cite this Article:
Sheikh SA, Ahmed A, Ullah A, Nawaz, Anticancer Activity of n-Hexane and Acetone Leaf Extracts from *Delonix regia* (Gul Mohar) on HeLa (Cervical) and Prostate Cell Lines . J Bahria Uni Med Dental Coll. 2025;15(1):03-07 DOI: https://doi.org/10.51985/JBUMDC2024426

INTRODUCTION:

In recent years, natural compounds derived from plants have emerged as highly capable candidates for cancer treatment. These compounds show minimal harm to healthy cells as selectively targeting tumor cells, owing to their minor side effects, inherent biological activity, structural complexity, and chemical diversity.[1] Flavonoids, terpenoids, alkaloids, and phenols are among the various organic compounds derived from plants that possess anti-tumor properties. These compounds have been shown to impede tumor cell progression, inhibit telomerase activity, regulate apoptosis, halt angiogenesis, boost immunity, modulate resistance-causing signaling pathways, and more.[2,3] Currently, the basis of cancer treatment includes radiotherapy, immunotherapy, locally targeted therapy, and surgical resection. Traditional therapies are effective for early-stage cancer; however, they often entail significant side effects, drug resistance, frequent recurrences, and metastases, rendering them less successful for locally advanced or metastatic cervical cancer.[4]

Prostate cancer ranks among the most prevalent types of cancer globally, particularly affecting Western societies. Around 1.1 million men globally diagnosed with prostate cancer in 2012, constituting nearly 15% of all cancers. The 70% of these cases occurred in more developed nations, due to widespread prostate-specific antigen (PSA) testing and subsequent biopsies. Prostate cancer accounted for 307,000 estimated deaths in 2012, making it the 5th leading cause of cancer-related death in men, comprising 6.6% of total male deaths.[5] Moreover, common medications prescribed for cervical cancer have been associated with various side effects and drug resistance.[6] Cisplatin, one of the most potent

Saeed Ahmed Sheikh *(Corresponding Author)*
Assistant Professor, Department of Pharmacology and Therapeutics
Fazaia Ruth Pfau Medical College, Karachi
Email: sheikhsa63@gmail.com

Asif Ahmed
Head Department of Pharmacology,
Baqai Medical College (BMU), Karachi
Email: drasifahmed@baqai.edu.pk

Asadullah
Lecturer, Department of Pharmacology,
Shaheed Mohtarma Benazir Bhutto Medical College, Karachi
Email: drasadali361@gmail.com

Shazia Nawaz
Senior Lecturer, Department of Pharmacology and Therapeutics,
Fazaia Ruth Pfau Medical College, Karachi
Email: shazianawaz19@gmail.com

Received: 08-08-2024
Accepted: 26-11-2024 **1st Revision: 12-08-2024**

anticancer drugs, can encounter resistance mechanisms.[7] Similarly, 5-fluorouracil, used in cervical cancer treatment, has been linked to side effects and resistance.[8] Thus, there is a pressing need to develop medications for cervical cancer with improved safety profiles and efficacy.

The *Delonix regia* tree, commonly known as Gul mohar, Royal Poinciana, or Flamboyant, is native to Madagascar. It was first identified by botanist Wensel Brojer in its natural habitat during the early 19th century. Since then, *D. regia* has spread widely across subtropical and tropical regions around the world and is extensively cultivated, particularly as a decorative garden and avenue tree in Pakistan. Although originally from Madagascar, this species has adapted to various climates and is renowned for its vivid foliage and striking flowers, enhancing landscapes globally.[9] *Delonix regia* is renowned for its medicinal properties, which are attributed to its active compounds and secondary metabolites with notable biological significance. The entire plant is considered to have medicinal potential, with its various constituents providing diverse therapeutic benefits. The botanical name "Delonix" suggests visibility, while "regia" denotes regal magnificence, reflecting the tree's grandeur and its significance within its ecosystem.

The primary plant constituents include essential nutrients such as common sugars, amino acids, proteins, and chlorophyll. Although these are crucial for plant growth, they typically do not possess significant medicinal properties. In contrast, secondary plant metabolites, which include alkaloids, terpenoids, saponins, phenolic compounds, flavonoids, and tannins, are essential for various biological and pharmacological activities. These secondary metabolites are vital for plant defense and ecological interactions and are often used in both traditional and modern medicine due to their diverse and potent bioactive properties.[10, 11]

Traditionally, its flowers have been used to treat various diseases such as malaria, rheumatoid arthritis, constipation, pneumonia, diabetes and inflammation.[12] Extracts from its leaves exhibit anti-inflammatory, anti-hyperglycemic, anti-microbial, anti-oxidant, hepato-protective and cytotoxic effects, while stem bark extracts possess antioxidant and antimicrobial activities.[9,13,14] Despite its ornamental value, *D. regia* harbors significant medicinal potential, prompting research into its anticancer properties beyond its traditional uses.

Different parts of *D. regia* contains different phytochemicals associated with different pharmacological activity. In leaves the most abundant phytochemical constituents are flavonoids, amino acid, alkaloids, saponins, glycosides, proteins, carbohydrates, diterpenes, and steroids. This study was design to evaluate the anticancer potential of *Delonix regia* leaf extracts using both polar (acetone) and non-polar (n-hexane) solvents. The main goal was to understand how these different solvents affect the extraction of bioactive compounds from the leaves and to assess their impact on inhibiting cancer cell growth. By comparing the anticancer effects of the extracts from these solvents, the research aimed to identify which extract holds the most promise for therapeutic applications. Ultimately, this study seeks to offer valuable insights into the effectiveness of *D. regia* leaf extracts in cancer treatment and contribute to the development of new, plant-based anticancer therapies.

METHODOLOGY:

This research was approved by the Institutional Review and Ethical Board (IREB) of Baqai Medical University, Ref. No. BMU-IREB-03-2023 dated 02-08-2023.

This was an in-vitro study. The experimental investigation was conducted at the Department of Pharmacology and Therapeutics, Baqai Medical College and University of Karachi (HEJ), utilizing in vitro methodologies spanning a period of six months from March 2023 to September 2023.

D. regia leaves were brought from the local garden of Karachi University. Subsequently, the plant underwent identification and authentication processes at the herbarium of the Botany Department of Karachi University, where it was assigned voucher number 97626.

Freshly harvested *D. regia* leaves were collected and carefully sorted. They were cleaned using tap water to remove any dirt, then rinsed with distilled water to eliminate contaminants. Afterward, the leaves were air-dried, sliced on a cutting board, and finely pulverized using a blender. The resulting powder was subjected to extraction using n-Hexane and Ethanol solvents in a Soxhlet apparatus. The extracted solution was concentrated using a rotary vacuum evaporator and then stored in a desiccator to maintain its integrity and prolong its shelf life, ensuring its suitability for potential applications. [15,16,17,18]

For determination of anticancer activity MTT (3-[4, 5-dimethylthiazole-2-yl]-2, 5-diphenyl-tetrazolium bromide) colorimetric assay was performed according to previously described protocol.[19] Cytotoxic activity of extracts was assessed in 96-well micro-plates. Cells including BJ (fibroblast), HeLa (cervical cancer), and prostate cell lines were cultured in minimum essential medium eagle supplemented with 5% fetal bovine serum (FBS), 100 IU/ml of penicillin, and 100 µg/ml of streptomycin in 75 cm^2 flasks, and maintained in a 5% CO_2 incubator at 37°C. Exponentially growing cells were harvested, counted with a haemocytometer, and diluted to a concentration of $6x10^4$ cells/ml in a specific medium. Cell suspensions were then introduced into 96-well plates (100 µL/well).

Following overnight incubation, the medium was replaced with 200 µL of fresh medium containing various concentrations of compounds (1-30 µM). After 48 hours, 200 µL of MTT solution (0.5 mg/ml) was added to each well and further incubated for 4 hours. Subsequently, 100

µL of DMSO was added to each well to dissolve the formazan granules formed by MTT reduction. The extent of MTT reduction within cells was quantified by measuring the absorbance at 570 nm using a microplate reader (Spectra Max plus, Molecular Devices, CA, USA). The cytotoxicity of the compounds was assessed by determining the concentration causing 50% growth inhibition (IC_{50}) for HeLa cells. The percent inhibition was calculated using the following formula:

Percent inhibition = 100-((mean of O.D of test compound – mean of O.D of negative control)/ (mean of O.D of positive control – mean of O.D of negative control)*100).

The results (Percent inhibition) were processed by using Soft- Max Pro software (Molecular Device, USA).[19]

RESULTS:

The table presents the anticancer activity of leaf extracts from *D. regia* on HeLa and prostate cell lines, along with BJ cell lines, in comparison with the standard drug doxorubicin. The results are outlined below: The cutoff value for significant inhibition is set at 50%. Results show that the acetone extract exhibits moderate inhibition (36.29%) on HeLa cell lines, while the n-hexane extract demonstrates higher inhibition (55.84%) on the same cell line (Table 1). However, both extracts are inactive on prostate cell lines, with the acetone extract showing some activity (5.24%) and n-hexane extract exhibiting (18.29%) activity (Table 2). On BJ cell lines, both extract showing significant inhibition (69.68% and 61.32%) respectively (Table 1). In contrast, doxorubicin displays significant inhibition on all cell lines tested, surpassing the 50% cutoff value, with notable potency observed in both inhibition percentages and IC_{50} values.

DISCUSSION:

This study demonstrates the anticancer properties of n-hexane and acetone leaf extracts from *Delonix regia* (Gul Mohar) across HeLa, prostate, and BJ (normal fibroblast) cell lines, offering important insights into their possible therapeutic uses and limitations.

This study showed that leaf extracts of n-Hexane of *D. regia* demonstrated higher inhibition ((55.84%) on cervical cancer cells compared to the acetone extract (36.29%). This suggested that the n-hexane extract may contain more potent and bioactive anticancer components which were effective in targeting cervical cancer cells. However it lacked significant activity against prostate cancer cells which suggested that active compounds are not effective this type of cancer cell line. Interestingly, n-hexane extracts exhibited significant inhibition on BJ normal fibroblast cell lines, showing 69.68% inhibition. The significant inhibition on normal cells is less desirable from a therapeutic perspective, so this need careful monitoring. In our previous study, GC-MS (Gas Chromatography-Mass Spectrometry) analysis showed that n-hexane extracts of leaf of *D. regia* contained phytol, di-iso-octyl ester, lupeol, Squalene, 2,6,10,15-tetramethyl-, Pentadecan, nonacosane, 1, 30-triacontanediol, Hexadecane, 2,6,11,15-tetramethyl, Heptadecane 2,6,10,15-tetramethyl-, Tetra- and tri- acontane, Phthalic acid, butyl tetradecyl ester, Vitamin E, Heneicosane, Triacontane and á-Amyrin. In which Heptadecane 2, 6, 10, 15-tetramethyl, Phytol, Heneicosane, squalene, Triacontane, lupeol reported to had anticancer and antineoplastic activities.[20, 21]

The acetone extract exhibited moderate inhibition on HeLa cell lines, however, it lacked considerable activity against prostate cancer cells. Especially, it showed some inhibition on BJ cell lines, indicating a potential impact on non-cancerous cells, possibly through cytostatic effects. In our previous study through GC-MS examination we determined that the *D. regia* leaf extract with acetone contains many phyto-constituents which included phytol, squalene, á-amyrin, lupeol, Vitamin E, Stigmasterol and â Sitosterol. In which phytol, squalene and lupeol are associated with anticancer/anti-tumor activities.[20, 21]

Table 1: Anticancer activity of leaf extracts from *Delonix regia* on cervical (HeLa) cell lines compared with BJ and standard drug (Doxorubicin)

Sample Code	Conc. (µM)	HeLa cell lines		BJ cell lines	
		% Inhibition	IC_{50}±SD	% Inhibition	IC_{50}±SD
Acetone extract	30	36.29	Inactive	69.68	14.51±0.18
n-Hexane extract	30	55.84	26.32±0.48	61.32	19.62±0.21
Doxorubicin (Standard)	30	98.7	1.13±0.16	93.68	0.16±0.19

Table 2**:** Anticancer activity of leaf extracts from *Delonix regia* on prostate cell lines compared with BJ and standard drug (Doxorubicin)

Sample Code	Conc. (µM)	HeLa cell lines		BJ cell lines	
		% Inhibition	IC_{50}±SD	% Inhibition	IC_{50}±SD
Acetone extract	30	05.24	Inactive	69.68	14.51±0.18
n-Hexane extract	30	18.29	Inactive	61.32	19.62±0.21
Doxorubicin (Standard)	30	80.8	1.18±0.21	93.68	0.16±0.19

The differences in activity may stem from variations in the composition and their concentration of bioactive compounds and their mechanisms of action in acetone and n-hexane extracts. n-Hexane contained more anti-cancer components than acetone extracts.

In contrast, doxorubicin which is well established anticancer drug, displayed potent anticancer activity across all cell lines tested. Its efficacy against cervical, prostate as well as BJ cell lines, highlighted its broad-spectrum cytotoxicity, further supported by low IC_{50} values.

The comparison between the leaf extracts and doxorubicin emphasized the superior efficacy of the standard drug in inhibiting cancer cell growth across all cell lines. Whereas the leaf extracts illustrated some level of inhibition on cervical cancer cells, they displayed limited activity against prostate cancer cells and BJ cell lines compared to doxorubicin.

A previous study demonstrated that the methanol extract of *D. regia* leaves exhibited cytotoxic activity against the HepG2 (human liver carcinoma) cell line, which was due to presence of different flavonoid glycosides. These flavonoids had potential anticancer as well as anti-oxidant activities.[22] Additionally, research conducted by El-Sayed et al., (2011) showed that the ethanolic extract of *D. regia* flower also possessed cytotoxic activities against the HepG2 cell line and linked it due to rich contents of flavonoids.[23] Ursolic acid, quercetin and its 3-o-rhamnoside compounds, â-sitosterol and its glucoside present in ethanolic extract of *D. regia* flower possessed significant cytotoxicity when anticancer activity was checked alone. Methanol extract, aqueous and chloroform fractions of stem bar of *D. regia* also possessed cytotoxicity monitored in tadpole model. The order of cytotoxic activity was chloroform fraction, methanol extract and aqueous fraction respectively.[24]

This study aligns with previous findings and supports the cytotoxic potential of *Delonix regia*, likely due to its diverse flavonoid content. The link between antioxidant activity and anticancer effects is crucial here. Oxidative stress, caused by an imbalance of reactive oxygen species (ROS) and antioxidants, can lead to DNA damage, mutations, and cancer progression. The antioxidant compounds in *Delonix regia* help mitigate this oxidative stress by neutralizing ROS, thus protecting healthy cells from damage and potentially preventing their transformation into cancerous cells. By reducing oxidative stress, these compounds contribute to maintaining cellular health and reducing cancer risk, reinforcing the anticancer activity observed in various extracts of *Delonix regia*. Therefore, compounds or treatments that reduce oxidative stress can also help to inhibit tumor promotion.[23, 25]

This research had few limitations. Study was carried out entirely in vitro using cell cultures to evaluate the anticancer properties of acetone and n-hexane extracts from *Delonix regia* leaves. As a result, the study may not necessarily reflect their effectiveness or safety in animal models or humans. Further exploration of acetone and n-hexane extracts from *D. regia* as potential anticancer agents in animals is needed. Comparative study can also be performed using other solvents like aqueous and methanolic solvents using other cell lines of cancer. Specific bioactive compounds within the leaf extracts and their interactions with cancer cells could provide valuable insights for the development of novel anticancer therapies. Combining leaf extracts with conventional chemotherapeutic agents could enhance treatment outcomes.

CONCLUSION:

In conclusion, acetone and n-hexane extracts showed moderate inhibition on cervical cell lines, however no activity observed on prostate cell lines. Doxorubicin, however, illustrated significant inhibition on all tested cell lines. Although, *D. regia* possesses some anticancer activity potential however its efficacy is not comparable to doxorubicin. The study suggests further exploration of acetone and n-hexane extracts from *D. regia* as potential anticancer agents in animals.

Authors Contribution:
Saeed Ahmed Sheikh: Study conception and design, performed all experiments, writing
Asif Ahmed: Study conception and design, supervisor
Asadullah: Helped in experimenting and data collection
Shazia Nawaz: Manuscript writing, review and proof reading of article

REFERENCES:

1. Andreani T, Cheng R, Elbadri K, Ferro C, Menezes T, Dos Santos MR, Pereira CM, Santos HA. Natural compounds-based nanomedicines for cancer treatment: future directions and challenges. Drug Deliv Transl Res. 2024; 1-72. DOI: https://doi.org/10.1007/s13346-024-01649-z
2. Huang M, Lu JJ, Ding J. Natural products in cancer therapy: past, present and future. Nat Prod Bioprospect. 2021; 11(1):5-13. DOI: https://doi.org/10.1007/s13659-020-00293-7
3. Kikuchi H, Yuan B, Hu X, Okazaki M. Chemopreventive and anticancer activity of flavonoids and its possibility for clinical use by combining with conventional chemotherapeutic agents. Am J Cancer Res. 2019; 9(8):1517. PMID: 31497340
4. He M, Xia L, Li J. Potential mechanisms of plant-derived natural products in the treatment of cervical cancer. Biomolecules. 2021; 11(10):1539. DOI: https://doi.org/10.3390/biom11101539
5. Ferlay JS, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1. 0. Cancer incidence and mortality worldwide: IARC Cancer Base. 2013; 11.
6. Federico C, Sun J, Muz B, Alhallak K, Cosper PF, Muhammad N, Jeske A, Hinger A, Markovina S, Grigsby P, Schwarz JK. Localized delivery of cisplatin to cervical cancer improves its therapeutic efficacy and minimizes its side effect profile. Int J Radiat Oncol Biol Phys. 2021; 109(5):1483-94. DOI: https://doi.org/10.1016/j.ijrobp.2020.11.052

7. Park SH, Kim M, Lee S, Jung W, Kim B. Therapeutic potential of natural products in treatment of cervical cancer: A review. Nutrients. 2021; 13(1):154. https://doi.org/10.3390/nu13010154
8. Sethy C, Kundu CN. 5-Fluorouracil (5-FU) resistance and the new strategy to enhance the sensitivity against cancer: implication of DNA repair inhibition. Biomed Pharmacother. 2021; 137:111285. DOI: https://doi.org/10.1016/j. biopha. 2021.111285
9. Shabir G, Anwar F, Sultana B, Khalid ZM, Afzal M, Khan QM, Ashrafuzzaman M. Antioxidant and antimicrobial attributes and phenolics of different solvent extracts from leaves, flowers and bark of Gold Mohar [Delonix regia (Bojer ex Hook.) Raf.]. Molecules. 2011; 16(9):7302-19. DOI: https://doi.org/10.3390/molecules16097302
10. Rungsung W, Ratha KK, Dutta S, Dixit AK, Hazra J. Secondary metabolites of plants in drugs discovery. World J Pharm Res. 2015; 6;4(7):604-13. DOI: http://www.wjpr.net/dashboard/abstract_id/3114
11. Vala M, Maitreya B. Phytochemical analysis and total tannin content (TTC) of Delonix regia (Bojer ex. hook) Raf. bark by using different solvents collected from Saurashtra region. Int Assoc Biol Comput Dig. 2022; 1(2): 144-148.
12. Wang LS, Lee CT, Su WL, Huang SC, Wang SC. Delonix regia leaf extract (DRLE): a potential therapeutic agent for cardioprotection. PloS one. 2016; 11(12):e0167768. DOI: https://doi.org/10.1371/journal.pone.0167768
13. Bhaskar A, Sekhar S. Delonix regia bark alleviated inflammation by stimulating defense responses in rats. J Herbs Spices Med Plants. 2021; 27(4):411-25. DOI:https://doi.org/10.1080/10496475.2021.1943591
14. Salem MZ, Abdel-Megeed A, Ali HM. Stem wood and bark extracts of Delonix regia (Boj. Ex. Hook): Chemical analysis and antibacterial, antifungal, and antioxidant properties. Bio Resources. 2014; 9(2):2382-95. DOI: https://doi.org/10.15376/biores.9.2.2382-2395
15. Ingle KP, Deshmukh AG, Padole DA, Dudhare MS, Moharil MP, Khelurkar VC. Phytochemicals: Extraction methods, identification and detection of bioactive compounds from plant extracts. J Pharmacogn Phytochem. 2017; 6(1):32-6.
16. Azwanida NN. A review on the extraction methods use in medicinal plants, principle, strength and limitation. Med aromat plants. 2015; 4(196):2167-0412.
17. Pandey A, Tripathi S. Concept of standardization, extraction and pre phytochemical screening strategies for herbal drug. J Pharmacogn Phytochem. 2014; 2(5):115-9.
18. Boulfia M, Lamchouri F, Toufik H. Chemical analysis, phenolic content, and antioxidant activities of aqueous and organic Moroccan Juglans regia L. bark extracts. Curr Bioact Compd. 2020; 16(9):1328-39. DOI: https://doi.org/10.2174/1573407216666200203103354
19. Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods. 1983; 65(1-2):55-63. DOI: https://doi.org/10.1016/0022-1759(83)90303-4
20. Fagbemi KO, Aina DA, Coopoosamy RM, Olajuyigbe OO. Gas chromatography-mass spectrometry chemical profile investigation and biological activities of ethylacetate fraction of Baobab (Adansonia digitata L.) pulp used in the treatment of urinary tract infections. J Med Plants Econ Dev. 2022; 6(1):117.
21. Sheikh SA, Asadullah, Ahmed A, Ahmed SN, Jahan F, Nawaz S, Dawood S. Phytocomponents analysis of Delonix regia (Gulmohar) leaves extracts: exploring bioactive compounds and potential health benefits. J Popul Ther Clin Pharmacol. 2024;31(6):07–17.
22. Azab SS, Abdel-Daim M, Eldahshan OA. Phytochemical, cytotoxic, hepatoprotective and antioxidant properties of Delonix regia leaves extract. Med Chem Res. 2013; 22:4269-77.
23. El-Sayed AM, Ezzat SM, Salama MM, Sleem AA. Hepatoprotective and cytotoxic activities of Delonix regia flower extracts. Pharmacogn J. 2011; 3(19):49-56. DOI: https://doi.org/10.5530/pj.2011.19.10
24. Gbolade A, Muazu I, Haruna A. Comparative antioxidant, anti-proliferative and cytotoxic potentials of Piliostigma thonningii (Schum.) Milne-Redh. and Delonix regia (Boj. ex Hook) Raf.(Fabaceae) stem bark. Ethiop Pharm J. 2018; 34(1):51-60. DOI: 10.4314/epj.v34i1.5
25. Gu X, Mu C, Zheng R, Zhang Z, Zhang Q, Liang T. The Cancer Antioxidant Regulation System in Therapeutic Resistance. Antioxidants. 2024 Jun 27;13(7):778. DOI: 10.3390/antiox13070778

Original Article **Open Access**

Frequency and Association of Perforated Appendix with Patient's Characteristics in Acute Appendicitis

Muhammad Zeb, Rafia Ahmad, Abdul Wadood, Ishtiaq Ahmed, Malak Maaz Hassan, Muhammad Moazzam Farooq

ABSTRACT

Objective: To determine the frequency of perforated acute appendicitis in patients with acute appendicitis and its association with patients clinic demographic characteristics.

Study design and setting: This cross sectional study was conducted in general surgery unit from 1st January 2022 to 31st December 2022.

Methodology: 171 patients were included. Patients who were provisionally diagnosed as acute appendicitis were included in the study. Sampling technique was nonprobability consecutive sampling. Statistical analysis was done through SPSS Version 23.

Results: The study included 171 patients, with 58.5% male and 41.5% female. The majority of patients were aged between 25-35 years and had a normal weight. Grossly inflamed appendix was the most common finding (69.6%), followed by perforated appendix (19.3%), normal appendix (8.2%), and gangrenous appendicitis (2.9%). There was no statistically significant difference between gender and intraoperative findings. Age categories and duration of symptoms were significantly associated with intraoperative findings.

Conclusion: In conclusion, 19.3% of patients with acute appendicitis presented with perforation. Age and duration of symptoms were found to be significantly associated with intraoperative findings, highlighting the importance of early diagnosis and timely surgical intervention.

Key Words: Appendicitis, Complications, Perforated, Ruptured

How to cite this Article:
Zeb M, Ahmad R, Wadood A, Ahmed I, Hassan MM, Farooq MM. Frequency and Association of Perforated Appendix with Patient's Characteristics in Acute Appendicitis. J Bahria Uni Med Dental Coll. 2024;15(1):08-14 DOI: https://doi.org/10.51985/JBUMDC2024403

INTRODUCTION

Acute appendicitis is recognized as the most common abdominal surgical emergency, with a lifetime risk of occurrence estimated to be between 7% and 8%. This condition is most frequently observed during the second decade of life, making it a significant health concern, particularly among adolescents and young adults.[1] The history of acute appendicitis dates back several centuries, with the earliest references in medical literature appearing in the 1500s. Originally termed parasyphilitic, acute appendicitis was a condition that puzzled early physicians. The first recorded appendectomy, the surgical removal of the appendix, was documented in 1736, marking a milestone in the surgical treatment of this condition.[1,2]

It wasn't until 1886 that Reginald Fitz, a prominent pathologist, emphasized the importance of appendectomy in managing acute appendicitis. [2] Fitz's work laid the foundation for the surgical approach to this condition, which remains the standard treatment today. Shortly after Fitz's contributions, Charles McBurney, a pioneering surgeon, described the clinical features of acute appendicitis, including the characteristic point of maximum tenderness in the right iliac fossa. This area, now known as McBurney's point, is a key diagnostic indicator in assessing patients suspected of having acute appendicitis.[2,3]

While the diagnosis of acute appendicitis is primarily clinical, advancements in imaging techniques have provided additional support for clinicians. Ultrasound and contrast-enhanced computed tomography (CT) scanning are now commonly used to confirm the diagnosis, particularly in cases where

Muhammad Zeb
Resident, Department of General Surgeon
Hayatabad Medical Complex, Peshawar
Email: drmzeb@gmail.com

Rafia Ahmad *(Corresponding Author)*
Resident, Department of General Surgeon
Hayatabad Medical Complex, Peshawar
Email: Aifar907@gmail.com

Abdul Wadood
Resident, Department of General Surgeon
Hayatabad Medical Complex, Peshawar
Email: housewadood@gmail.com

Ishtiaq Ahmed
Resident, Department of General Surgeon
Hayatabad Medical Complex, Peshawar
Email: ishtiaqahmedkhan77@gmail.com

Malak Maaz Hassan
Resident, Department of General Surgeon
Hayatabad Medical Complex, Peshawar
Email: malakmaazhassan@gmail.com

Muhammad Moazzam Farooq
Resident, Department of General Surgeon
Hayatabad Medical Complex, Peshawar
Email: Moazzamwazir490@gmail.com

Received: 08-07-2024
Accepted: 26-11-2024
1st Revision: 19-08-2024
2nd Revision: 30-10-2024

the clinical presentation is ambiguous.[3] These imaging modalities help to reduce the risk of misdiagnosis and ensure that patients receive timely and appropriate treatment. However, despite these advances, the diagnosis and treatment of acute appendicitis remain time-sensitive. Failure to promptly identify and treat the condition can lead to severe complications, such as gangrene and perforation. [3,4]

Perforation of the appendix is a particularly dangerous complication of acute appendicitis, leading to significant morbidity and mortality. The risk of perforation varies depending on several factors, including the patient's age, immune status, and the underlying cause of the appendicitis.[4] In general, perforation is associated with increased rates of hospitalization, longer recovery times, and greater financial costs for patients. Mortality rates in cases of perforated appendicitis can reach 5% or higher, especially among patients with multiple comorbidities or those at the extremes of age. [5] Both pediatric and geriatric patients are more susceptible to delayed presentations, which increases their risk of perforation. In adults, the risk of perforation begins to rise after 36 hours from the onset of symptoms, increasing by approximately 5% every 12 hours if the condition is left untreated. [6]

Despite technological advancements, the diagnosis of appendicitis continues to rely primarily on the patient's history and physical examination . [7]To assist in diagnosing acute appendicitis, various scoring systems have been developed .[8] These systems are designed to aid clinicians in evaluating patients with suspected appendicitis. Among them, the Alvarado score is the most widely recognized and has performed well in validation studies. However, it has certain limitations. For instance, the Alvarado score was initially created based on a review of patients who had already undergone surgery due to suspected appendicitis, yet it is intended to be applied to all patients with suspected appendicitis. Additionally, the score does not include C-reactive protein (CRP) as a variable, despite numerous studies highlighting the importance of CRP in assessing patients with appendicitis.[9] CRP is a key differential factor in the Appendicitis Inflammatory Response Score (AIRS). Utilizing AIRS can help reduce unnecessary radiological and surgical procedures. [10] The development of the AIR score enhances diagnostic accuracy by combining easily applicable clinical criteria with two simple laboratory tests—CRP and complete blood count (CBC)—to classify patients according to the likelihood of an appendicitis diagnosis .[11]

Several studies have reported varying rates of perforation in patients with acute appendicitis. For example, Omari AH reported a perforation rate of 25.8%, [1] while Imad et al. documented a rate of 20%.[12]

Despite the wealth of research on acute appendicitis, there is a notable gap in the literature regarding the rate of perforation in patients with acute appendicitis in certain regions, including ours. Understanding the frequency of perforation and its association with patient clinicodemographic characteristics in our region is crucial for improving patient outcomes. To address this gap, we have planned a study to determine the frequency of perforation in patients with acute appendicitis and to explore its association with various clinicodemographic factors. By identifying the factors that contribute to the risk of perforation, we aim to enhance early diagnosis and treatment strategies, ultimately reducing the morbidity and mortality associated with this common surgical emergency.

METHODOLOGY:

After obtaining approval from the ethical review board of the institution (ERC No: 904/ HMC/QAD-00), a comprehensive cross-sectional study was meticulously designed and conducted. The study focused on 171 patients who presented with a diagnosis of acute appendicitis, ranging in age from 15 to 50 years. Perforated appendicitis was defined as the presence of a visible perforation in the appendix wall identified during surgery, accompanied by one or more of the following findings:

- Visible hole/breach in the appendicular wall
- Presence of free pus in the peritoneal cavity
- Presence of fecalith in the peritoneal cavity
- Gross contamination of the peritoneal cavity with purulent material

These patients were admitted to the General Surgery department of Hayatabad Medical Complex, located in Peshawar, Pakistan. The study period spanned a full calendar year, commencing on 1st January 2022 and concluding on 31st December 2022, allowing for a thorough examination of seasonal variations and potential trends in appendicitis cases.

The sampling technique employed in this study was nonprobability consecutive sampling, a method chosen for its practicality and ability to capture all eligible patients within the specified timeframe. This approach ensured that every patient meeting the inclusion criteria during the study period was considered for participation, thereby minimizing selection bias and enhancing the representativeness of the sample.

Sample size calculation was performed using the World Health Organization (WHO) sample size calculator, a widely recognized tool in epidemiological research. The calculation was based on several key parameters: the expected frequency of perforated appendicitis was set at 20%, as informed by previous literature and regional data. A confidence interval of 95% was selected to ensure a high level of statistical reliability, and a margin of error of 6% was deemed acceptable for the study's objectives. These parameters were carefully chosen to balance statistical power with feasibility considerations.

To maintain the integrity and specificity of the study, several exclusion criteria were established. Patients presenting with enteric perforation, a condition that can mimic appendicitis symptoms, were excluded to prevent confounding results. Similarly, cases of mesenteric ischemia and intestinal obstruction were omitted due to their potential to complicate the diagnosis and management of acute appendicitis. Pregnant patients were also excluded from the study cohort, considering the unique physiological changes and diagnostic challenges associated with pregnancy. Additionally, patients with known malignancies were not included, as cancer could potentially alter the presentation and progression of appendicitis. Through the rigorous application of these exclusion criteria, a total of twenty patients were deemed ineligible and subsequently excluded from the study population.

Ethical considerations were paramount in the conduct of this research. Written informed consent was diligently obtained from all participating patients or their legal guardians in cases where patients were unable to provide consent themselves. This process ensured that all participants were fully aware of the study's objectives, procedures, potential risks, and benefits, thereby upholding the principles of autonomy and informed decision-making in medical research.

Prior to surgical intervention, all patients underwent a standardized preoperative assessment and investigation protocol, adhering strictly to the institutional guidelines of Hayatabad Medical Complex. This comprehensive evaluation typically included a detailed medical history, physical examination, laboratory tests (such as complete blood count, C-reactive protein levels, and liver function tests), and imaging studies (which may have included abdominal ultrasound or computed tomography scans, depending on clinical indications). The uniformity of this preoperative protocol across all study participants ensured consistency in patient evaluation and decision-making.

The critical decision to proceed with surgery for acute appendicitis was made exclusively by a specialist consultant general surgeon. This approach leveraged the expertise and clinical judgment of experienced professionals, ensuring that surgical interventions were warranted and appropriate for each case. The involvement of senior surgeons in this decision-making process added a layer of quality assurance to the study methodology.

Intraoperative findings were meticulously documented, with particular attention paid to the gross pathology of the appendix. In cases where perforation was suspected or confirmed, the surgical team conducted a thorough inspection of the appendicular wall during the appendectomy procedure. This detailed examination focused on identifying any breach in the continuity of the appendix wall, which is a hallmark of perforation. Furthermore, the peritoneal cavity was carefully explored for the presence of any collections, such as pus or inflammatory exudates, which could indicate advanced disease or complications.

Data regarding perforated appendicitis were recorded with precision, adhering strictly to the operational definition established for the study. This definition likely included specific criteria for classifying an appendix as perforated, such as visible holes in the appendix wall, presence of fecaliths in the peritoneal cavity, or extensive peritoneal contamination. The primary focus of data collection was on determining the frequency of perforated acute appendicitis within the study population.

To ensure consistency and minimize variability in surgical technique and assessment, all surgeries were performed by the same surgical team. This team was led by a highly qualified consultant surgeon with a minimum of 5 years of post-fellowship experience in general surgery. The researcher, who was also involved in the study design and data collection, assisted in these surgeries, providing an additional layer of observation and data verification. This approach not only standardized the surgical procedures but also allowed for real-time documentation of intraoperative findings.

Data was analysed using statistical analysis program IBM SPSS version 23. Frequencies and percentages were recorded for categorical variables including gender and presence of perforated acute appendicitis. Mean standard deviation was computed for numerical variables including age, BMI and duration of pain. Effect modifiers like age, gender, BMI and pain duration was controlled by rough stratification. Post-stratification chi square test/Fischer exact test was be applied. P value =0.05 was considered statistically significant.

RESULTS:

The study encompassed a total of 171 patients, providing a substantial sample size for robust statistical analysis. The mean age of the study participants was calculated to be 26.4 years, with a standard deviation of 10.0263 years. This relatively young average age, coupled with a considerable standard deviation, suggests a wide age range within the study population, potentially capturing diverse presentations of acute appendicitis across different life stages.

Gender distribution within the study cohort revealed a slight male predominance. Males constituted the majority, comprising 100 patients, which represented 58.5% of the total sample. Females, on the other hand, accounted for 71 patients, making up 41.5% of the study population. This gender disparity, while notable, is consistent with some epidemiological studies suggesting a higher incidence of acute appendicitis in males.

Age categorization of the participants yielded interesting insights. The largest age category by far was the 25-35 year group, which included 134 participants, representing a substantial 78.4% of the total sample. This predominance of young adults in the study population could have significant implications for understanding the peak incidence age for

acute appendicitis in this particular geographic and demographic context.

Body Mass Index (BMI) classification of the participants revealed that the majority fell within the normal weight range. Specifically, 118 patients, constituting 69% of the total sample, were classified as having a normal BMI. This was followed by the overweight category, which included 29 patients or 17% of the sample. Interestingly, 14 patients (8.2%) were categorized as underweight. The remaining 5.8% of patients, though not explicitly stated, can be inferred to fall into the obese category. These BMI distributions provide valuable information about the potential relationship between body weight and the incidence or presentation of acute appendicitis. These demographic and BMI data are presented in Table 1.

Intraoperative findings offered crucial insights into the pathological states of the appendix at the time of surgery. The most prevalent finding was a grossly inflamed appendix, observed in 119 cases, which accounted for a significant 69.6% of all surgeries. This high percentage of inflamed appendices underscores the importance of timely diagnosis and intervention in preventing more severe complications.

The second most common intraoperative finding was a perforated appendix, encountered in 33 cases, representing 19.3% of the total. This substantial proportion of perforated cases highlights the potential for rapid progression of appendicitis and the critical nature of early diagnosis and treatment. Perforated appendicitis is associated with increased morbidity and can lead to more complex postoperative courses, emphasizing the need for strategies to reduce the incidence of this complication.

Surprisingly, 14 cases (8.2%) revealed a normal appendix upon intraoperative examination. This finding is particularly noteworthy as it points to the challenges in preoperative diagnosis of acute appendicitis and the potential for false-positive clinical assessments. These cases of negative appendectomies warrant further investigation into improving diagnostic accuracy to minimize unnecessary surgeries.

The least common but potentially most severe presentation was gangrenous appendicitis, observed in 5 cases (2.9%). Although relatively rare, gangrenous appendicitis represents a critical stage of the disease with potentially serious complications, further emphasizing the importance of prompt diagnosis and treatment. The distribution of these intraoperative findings is illustrated in Figure 1.

Stratification of intraoperative findings by various factors provided additional depth to the analysis. Gender stratification, while showing a slight male predominance, did not yield statistically significant differences in appendicitis types between males and females ($p = 0.174$). This suggests that gender may not be a strong predictor of the type or severity of appendicitis in this population.

Age stratification revealed a striking concentration of cases in the 26-35 year age bracket, with 134 patients (78.4%) falling into this category. The 36-45 year category included 27 patients (15.8%), while 9 patients (5.3%) were aged 46-50 years. Notably, only 1 patient (0.6%) was in the 15-25 year category. The distribution of appendicitis types across these age categories demonstrated high statistical significance ($p = 0.00$), indicating a strong relationship between age and the presentation or progression of appendicitis.

BMI classification analysis showed that the majority of patients (118, 69.0%) were of normal weight, followed by 29 overweight patients (17.0%), 14 underweight patients (8.2%), and 9 obese patients (5.3%). The variation in appendicitis types across these BMI categories reached statistical significance ($p = 0.020$), suggesting that body mass index may play a role in the development or presentation of different types of appendicitis.

Analysis of symptom duration revealed that a majority of patients (117, 68.4%) experienced symptoms for more than 24 hours before seeking medical attention, while 54 patients (31.6%) reported symptoms lasting less than 24 hours. The difference in appendicitis types based on symptom duration was highly statistically significant ($p = 0.00$). This finding underscores the critical importance of timely medical intervention and suggests that longer symptom duration may be associated with more advanced stages of appendicitis. The stratification of intraoperative findings by age, gender, BMI, and symptom duration is detailed in Table 2.

DISCUSSION:

Acute appendicitis stands as one of the prevalent surgical emergencies confronted by surgical residents during their residency tenure. Diagnosis of acute appendicitis heavily relies on clinical assessment, making it a notably challenging task. In cases where diagnostic ambiguity persists, CT scan of the abdomen and pelvis with contrast emerges as a commonly employed diagnostic tool, given its impressive sensitivity (94%) and specificity (95%) compared to alternative investigative modalities.[12,13] However, in peripheral healthcare settings where CT scan availability may be limited,

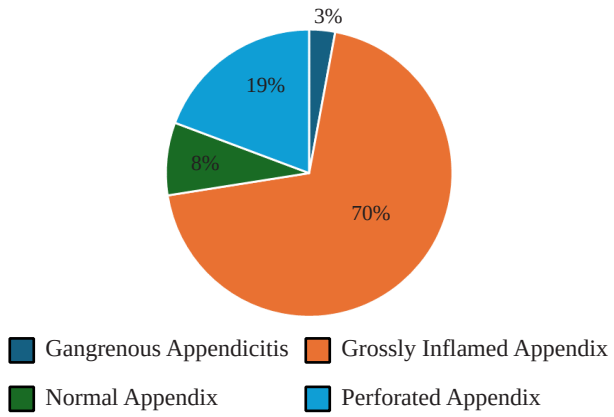
Table 1: Descriptive statistics of preoperative and intraoperative variables

Variables	Categories	Frequency	Percentage
Gender	**Female**	71	41.5
	Male	100	58.5
Age Categories	**15-25yrs**	1	0.5
	25-35yrs	134	63.5
	35-45yrs	27	12.8
	45-50yrs	9	4.3
BMI Categories	**Underweight**	14	8.2
	Normal Weight	118	69
	Overweight	29	17
	Obese	10	5.8

Table 2: Comparison of Intraoperative findings with Gender, Age, BMI and Durations of Symptoms

Variables	Categories	Gangrenous n (%)	Gross Inflamed n (%)	Perforated n (%)	Normal n (%)	Total	P value
Gender	Female	0 (0%)	46 (64.8%)	16 (22.5%)	9 (12.7%)	71	0.174
	Male	5 (5%)	73 (73%)	17 (17%)	5 (5%)	100	
Age Category	15-25 yrs	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1	0.00
	26-35 yrs	1 (0.7%)	101 (75.4%)	22 (16.4%)	10 (7.5%)	134	
	36-45 yrs	3 (11.1%)	14 (51.9%)	9 (33.3%)	1 (3.7%)	27	
	46-50 yrs	0 (0%)	4 (44.4%)	3 (33.3%)	2 (22.2%)	9	
BMI	Underweight	1 (7.1%)	6 (42.9%)	6 (42.9%)	1 (7.1%)	14	0.020
	Normal Weight	1 (0.8%)	87 (73.7%)	17 (14.4%)	13 (11%)	118	
	Overweight	1 (3.4%)	21 (72.4%)	7 (24.1%)	0 (0%)	29	
	Obese	1 (11.1%)	5 (55.6%)	4 (44.4%)	0 (0%)	9	
Duration of Symptoms	Less than 24 hours	1 (1.9%)	40 (74.1%)	2 (3.7%)	11 (20.4%)	54	0.00
	More than 24 hrs	3 (2.6%)	79 (67.5%)	32 (27.4%)	3 (2.6%)	117	

Figure 1: Intraopertative Findings



reliance on clinical examination remains prominent. Consequently, there exists a heightened risk of missing the diagnosis and delay in diagnosis lead to significant morbidity and mortality due to perforation.[14,15]

The distribution of intraoperative findings in the present study is consistent with the current literature on appendicitis. Grossly inflamed appendix was the most common finding, which is in line with previous studies reporting an incidence of inflamed appendix ranging from 65% to 85% .[16,17] Perforated appendix was the second most common finding, which is consistent with the literature indicating that approximately 20-30% of appendicitis cases result in perforation.[1,18] In our study the incidence of perforated appendicitis was 19.3% while study by Nighat G et al in Pakistan reported 11.3% in her study.[19] Finally, the incidence of normal appendix was 8.2%, which is consistent with the reported incidence of negative appendectomy ranging from 5% to 25%.[1,20]

Several studies have examined the association between gender and appendicitis, with mixed results. Some studies have found no significant difference in the incidence of appendicitis between males and females, while others have reported higher incidence rates in males.[21,22] One study conducted in a large hospital in Turkey found no significant difference in the frequency of appendicitis or other intraoperative findings between males and females .[23] Our study results are consistent with this finding, as we found no statistically significant difference in intraoperative findings between male and female patients undergoing appendectomy.

The finding that the highest proportion of patients with grossly inflamed appendix was in the age group of 25-35 years is consistent with previous studies. A study conducted by Bolandparvaz et al. reported that the majority of their study population with acute appendicitis belonged to the age group of 20-40 years.[24] Another study by Al-Qahtani et al. also found that the highest incidence of acute appendicitis was in the age group of 20-30 years.[25]

Moreover, the absence of gangrenous appendicitis in the 15-25 age group in the current study is in line with previous reports. A study by Karaman et al. (2018) also reported no cases of gangrenous appendicitis in the age group of 10-19 years.[26]

One study conducted by Tsai et al. found that patients with acute appendicitis who had symptoms for more than 24 hours had a higher risk of perforation and abscess formation.[27] Similarly, a study by Zhao et al. also found that the duration of symptoms was significantly associated with the severity of appendicitis and the risk of complications.[28]

The association between BMI and intraoperative findings in patients undergoing appendectomy has been investigated in several studies. A systematic review and meta-analysis of 11 studies with a total of 7,163 patients found that higher BMI was associated with increased risk of complicated appendicitis, such as perforation and abscess formation (24).[29] Another study of 1,253 patients showed that overweight and obese patients were more likely to have a complicated appendicitis compared to normal weight patients.[30]

However, there are also studies that have reported no significant association between BMI and appendicitis severity. For example, a study of 399 patients found that BMI was not a significant predictor of appendiceal perforation.[31]

The study highlights the increasing age and late intervention to be the significant factors leading to perforation.

Despite these findings, there are certain limitations of this study worth mentioning. Firstly, it was a cross sectional study. Secondly, it was a single centre study. Thirdly, the sample size can be increased to enhance the power of findings. Lastly, we didn't gather the follow up data.

CONCLUSIONS:

The perforation of the appendix remains a significant complication of acute appendicitis, with implications for both clinical outcomes and patient morbidity. Timely detection of risk factors, such as patient age and the duration of symptoms, plays a critical role in expediting appropriate intervention and potentially preventing perforation.

Authors Contribution:
Muhammad Zeb: Literature Search, Manuscript Drafting, Statistical Analysis, Study Concept and design.
Rafia Ahmad: Manuscript Writing,Proof Reading, Statistical Analysis, Data Interpretation, Drafting.
Abdul Wadood: Data Collection, Proof Reading, Critical Analysis, Final Drafting
Ishtiaq Ahmed: Data Collection, Proof Reading, Critical Analysis, Drafting.
Malak Maaz Hassan: Data Collection, Proof Reading, Critical Analysis ,Drafting.
Muhammad Moazzam Farooq: Data Collection, Proof Reading, Critical Analysis, Drafting

REFERENCES:

1. Calis H. Morbidity and Mortality in Appendicitis in the Elderly. J Coll Physicians Surg Pak. 2018;28(11):875-8.
2. Sajjad MN, Naumeri F, Hina S. Non-operative treatment versus appendectomy for acute uncomplicated appendicitis: A randomized controlled trial. Pak J Med Sci [Internet]. 2021Jul.15 [cited 2024Oct.29];37(5).
3. Imad HS. Risk factors for perforation in acute appendicitis. Al-Qadisiya Med J. 2015;11(19):35-40.
4. Mustafa K, Azmatullah U, Zafar S. Diagnostic Precision of Computed Tomography (CT) Scan in Discriminating Perforated Appendicitis from Non-Perforated Cases. Pakistan Journal of Medicine and Dentistry. 2021;10(4):51-6. Doi: 10.36283/PJMD10-4/009
5. Lastunen K, Leppäniemi A, Mentula P. Perforation rate after a diagnosis of uncomplicated appendicitis on CT. Br J Surg. 2021;108(1):70-75. doi: 10.1093/bjs/znab018.
6. Sammalkorpi HE, Mentula P, Leppäniemi A. The introduction of adult appendicitis score reduced negative appendectomy rate. Scand J Surg. 2017;106(3):196-201. doi: 10.1177/ 145749 6916683091.
7. Shahid MH, Khan FI, Askri ZA, Asad A, Saeed R, Talib TB, Khan AZ, Fatima T, Afzal MF. Two-Year Experiences of 500 Appendectomies in Lahore General Hospital, Lahore. Cureus. 2022;14(1):e21303. doi: 10.7759/cureus.21303
8. Karami MY, Niakan H, Zadebagheri N, Mardani P, Shayan Z, Deilami I. Which One is Better? Comparison of the Acute Inflammatory Response, Raja Isteri Pengiran Anak Saleha Appendicitis, and Alvarado Scoring Systems. Ann Coloproctol. 2017;33(6):227–31. doi: 10.3393/ac.2017.33.6.227.
9. Andersson RE. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. Br J Surg. 2004;91(1):28-37. doi: 10.1002/bjs.4461.
10. Yeþiltaþ M, Karakaþ DÖ, Gökçek B, Hot S, Eðin S. Can Alvarado and Appendicitis Inflammatory Response scores evaluate the severity of acute appendicitis? Ulus Travma Acil Cerrahi Derg. 2018;24(6):557-562. doi: 10.5505/tjtes. 2018. 72318.
11. Husssin M, Kumar D, Ahmed R, Kazim E, Zubair M. Comparison of appendicits inflammaroty response (AIR) score with alvarado score in the diagnosis of acute appendicitis. Pak J Surg. 2019;35(4):284-86.
12. Walia DSW, Shankar N, Singla A, Najmi H, Kaur M. A Comparative Study of Alvarado, Ripasa and AIRS Scoring Systems in the Diagnosis of Acute Appendicitis. Eur J Mol Clin Med. 2022;9(3):369-79.
13. Chan I, Bicknell SG, Graham M. Utility and diagnostic accuracy of sonography in detecting appendicitis in a community hospital. AJR Am J Roentgenol. 2005;184(6):1809-12. doi: 10.2214/ajr.184.6.01841809.
14. Flum DR, McClure TD, Morris A, Koepsell T. Misdiagnosis of appendicitis and the use of diagnostic imaging. J Am Coll Surg. 2005;201(6):933-9. doi: 10.1016/j.jamcollsurg. 2005.04. 039.
15. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, Boermeester M, Sartelli M, Coccolini F, Tarasconi A, de' Angelis N. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15:1-42. https://doi.org/10.1186/s13017-020-00306-3
16. Sartelli M, Baiocchi GL, Di Saverio S, et al. Prospective Observational Study on Acute Appendicitis Worldwide (POSAW). World J Emerg Surg. 2018;13:19. doi: 10.1186/s13017-018-0182-5.
17. Andersson RE. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. Br J Surg. 2004;91(1):28-37. doi: 10.1002/bjs.4461.
18. Mao BP, Collins G, Ayeni FE, Vagg DJ. Risk factors for developing intra-abdominal abscess following appendicectomy for acute appendicitis: a retrospective cohort study. Langenbecks Arch Surg. 2024;409(1):246.
19. Nighat Ghias, Aisha Tasneem, Lekhraj Mal, Abdul Salam Memon, Muhammad Abid Owais, Bushrsa Tasneem. Prevalence of Appendix Perforation in Patients Presenting with Acute Appendicitis: A Cross-Sectional Study. Pak J Med Health Sci. 2022;16(02):986.
20. Dölling M, Andric M, Rahimli M, Klös M, Pachmann J, Stockheim J, Al-Madhi S, Wex C, Kahlert UD, Herrmann M, Perrakis A, Croner RS. Inflammatory Signals Across the Spectrum: A Detailed Exploration of Acute Appendicitis Stages According to EAES 2015 Guidelines. Diagnos (Basel). 2024;14(20):2335.
21. Chong CF, Adi MI, Thien A, et al. Development of the RIPASA score: a new appendicitis scoring system for the diagnosis of acute appendicitis. Singapore Med J. 2010;51(3):220-225.

22. Kýlýç E, Gülcü B, Keskin M, et al. Comparison of clinical and laboratory features between acute appendicitis in male and female patients: is there any gender difference? Ulus Travma Acil Cerrahi Derg. 2017;23(1):9-12. doi: 10.5505/tjtes.2016.76216.

23. Bolandparvaz S, Mollajafari M, Mohebbi HA, Rezaianzadeh A, Asghari-Jafarabadi M. Epidemiology, clinical manifestation, and outcomes of appendicitis in elderly patients: a systematic review and meta-analysis. BMC Geriatr. 2020;20(1):1-11. doi: 10.1186/s12877-020-01519-x.

24. Qahtani MS, Al-Kahtani MS, Al-Qahtani AM. Acute appendicitis in Al-Madinah Al-Munawarah: Epidemiology, histopathology, and influence of lunar calendar on incidence. J Taibah Univ Med Sci. 2017;12(6):511-516. doi: 10.1016/j.jtumed.2017.04.004.

25. Karaman K, Ezer SS, Altuntas B, Aslaner A. Pediatric appendectomy: A retrospective analysis of 692 children. J Pediatr Res. 2018;5(1):1-5. doi: 10.4274/jpr.69176.

26. Tsai MS, Lin CK, Chang KC, et al. Risk factors and outcomes for delayed appendectomy for acute appendicitis: a retrospective analysis. BMC Surg. 2019;19(1):12-16. doi: 10.1186/s12893-019-0484-2.

27. Zhao L, Li S, Wang G, Liang J, Cheng S. Association between duration of symptoms and perforation in pediatric appendicitis. Pediatr Surg Int. 2017;33(8):867-870. doi: 10.1007/s00383-017-4094-9.

28. Becker T, Kharbanda A, Bachur R. Atypical clinical features of pediatric appendicitis. Acad Emerg Med. 2017;24(1):63-68. doi: 10.1111/acem.13074.

29. Gorter RR, Eker HH, Gorter-Stam MAW, et al. Meta-analysis of randomized controlled trials comparing antibiotic therapy with appendectomy for acute uncomplicated (and complicated) appendicitis. Surg Endosc. 2018;32(5):1392-1417. doi: 10.1007/s00464-017-5834-1.

30. Lee HJ, Park YS, Cho YA, et al. Overweight and obesity are not predictors of the severity of acute appendicitis in Korean patients. World J Emerg Surg. 2017;12(1):7-10. doi: 10.1186/s13017-017-0121-0.

Original Article **Open Access**

Sensitivity and Specificity of the Neutrophil Lymphocyte Ratio (NLR) in Diagnosing Late Onset Neonatal Sepsis in NICU Patients

Zunaira Zulfiqar, Unaiza Syed, Syed Arsalan Hassan, Nabeera Hayat, Hamza Khursheed, Abu Bakar Khan

ABSTRACT

Objective: To compare the sensitivity and specificity of the neutrophil lymphocyte ratio in diagnosing late onset neonatal sepsis in NICU patients at a tertiary care center

Study Design and Setting: Prospective observational study at Department of Pediatrics, Combined Military Hospital, Lahore from February 2024-July 2024

Methodology: After admission into the NICU for suspected late onset neonatal sepsis, complete blood count, C-reactive protein and blood cultures were sent before changing or starting broad spectrum anti-biotic therapy for 350 patients included in the study. Primary variables observed were sensitivity and specificity of the neutrophil lymphocyte ratio in diagnosing late onset sepsis once co-related with the culture results.

Results: Blood panel parameters showed mean absolute neutrophil count to be 5928.19796.05/mm^3 versus 7032.80166.02/mm^3 between the suspected and confirmed patients' groups ($p<0.001$). Similarly, mean absolute lymphocyte count was 2745.32394.53/mm^3 versus 3223.60278.90/mm^3 between both groups ($p<0.001$). Median value for NLR was 1.70 (1.00) versus 2.20 (1.00) between the suspected and confirmed culture groups ($p<0.001$). Assessment of receiver operating characteristics (ROC) for NLR when compared with suspected and confirmed sepsis showed area under the curve being 0.644 (CI=95%) with sensitivity of 74.6%, specificity of 55.6%, positive predictive value being 57.3% and negative predictive value being 73.3% with a cut-off value for NLR being 2.05.

Conclusion: We conclude that neutrophil lymphocyte ratio with a cut-off value of 2.05 is a reliable method to diagnose late onset neonatal sepsis with good sensitivity.

Key Words: Lymphocyte ratio, neonatal, neutrophil, sepsis

How to cite this Article:
Zulfiqar Z, Syed U, Hassan SA, Hayat N, Khursheed H, Khan AB. Sensitivity and Specificity of the Neutrophil Lymphocyte Ratio (NLR) in Diagnosing Late Onset Neonatal Sepsis in NICU Patients. J Bahria Uni Med Dental Coll. 2024;15(1):15-20 DOI: https://doi.org/10.51985/JBUMDC2024408

Zunaira Zulfiqar *(Corresponding Author)*
Resident, Department of Paediatrics
Combined Military Hospital Lahore
Email: zunizulfiqar@yahoo.com

Unaiza Syed
Senior Resident, Department of Paediatrics
Combined Military Hospital Lahore
Email: Unaizasyed2506@gmail.com

Syed Arsalan Hassan
Senior Resident, Department of Paediatrics
Combined Military Hospital Lahore
Email: drsyedarsalanhassan@gmail.com

Nabeera Hayat
Resident, Department of Paediatrics
Combined Military Hospital Lahore
Email: Nabeerahayat26@gmail.com

Hamza Khursheed
Resident, Department of Paediatrics
Combined Military Hospital Lahore
Email: Hamzadar2006@gmail.com

Abu Bakar Khan
Resident, Department of Paediatrics
Combined Military Hospital Lahore
Email: Abkhan1221@gmail.com

Received: 08-07-2024
Accepted: 24-10-2024
1st Revision: 20-08-2024
2nd Revision: 03-10-2024

INTRODUCTION

Neonatal sepsis is the leading cause of neonatal morbidity and mortality worldwide.[1] The estimated prevalence for neonatal sepsis is 1-10 per 1000 live births worldwide.[2] The prevalence is considerably higher in the developing world with around 45-50 per 1000 live births in South-East Asia.[3] Neonatal sepsis refers to bacteremia or infection in the bloodstream in neonates less than 28 days post-birth. It constitutes a varied clinical presentation with majority of the neonates affected in the first and second week of life.[4] Various factors contribute as causative and risk factors for the development of neonatal sepsis. The causes increasing susceptibility after birth include neonatal factors including low birth weight, birth asphyxia, prematurity and maternal factors include poor maternal health, smoking, mode of delivery, delivery environment, ante-natal care given and maternal infection especially in the last trimester.[5]

Early onset neonatal sepsis refers to infections during the first week of life and late onset neonatal sepsis are infection from the first week to the 90 days post-birth.[6] Developing countries face a dilemma in the diagnosis of neonatal sepsis due to lack of resources and paucity of diagnostic panels

except for a few large centers of excellence already constrained with the patient load. Various investigations have been proposed to reliably diagnose the condition, but their sensitivity and specificity as sole markers have been questionable. Total leucocyte count, C-reactive protein (CRP), absolute neutrophil count have all been used as panel markers for diagnostic purposes, but their use remains questioned in neonates.[7] The use of blood culture for the diagnoses poses the limitation of delayed time required for results and early intervention required in neonates suspected of infection.[6] Procalcitonin as a sepsis marker has gained widespread acceptance but its high cost and limited availability in our demographic area restricts its use in each case under suspicion.[8]

The **neutrophil-to-lymphocyte ratio (NLR)** plays a crucial role in diagnosing neonatal sepsis. This inflammatory biomarker measures the balance between the innate and adaptive immune systems. Recent literature revealed that NLR is significantly higher in neonates with sepsis compared to healthy controls. Additionally, NLR was higher in septic neonates than in those suspected of sepsis but with negative blood cultures. Integrating NLR into clinical practice can aid in early diagnosis, potentially improving outcomes.

Restoring immune system balance may serve as an attractive therapeutic target. While certain markers including CRP can aid and augment the diagnosis. The sole credibility of the score need to be assessed for its recommendation. The association is also strong with bacterial infections than viral pathogens. It has also been linked to balance between the integrity of the immune system and is very sensitive to changes in normal homeostasis. High NLR values are thought to signify a systemic inflammatory response and poor immune competence, both of which are critical in the pathophysiology of sepsis. Studies have demonstrated that NLR can be a valuable predictive marker for sepsis severity and mortality risk. For instance, research has shown that an elevated NLR is linked to higher mortality rates and prolonged hospital stays, suggesting that it may serve as an adjunctive tool in clinical settings for assessing patient prognosis.

Moreover, NLR's utility in sepsis extends to its potential role in guiding therapeutic interventions and monitoring disease progression, offering a cost-effective and readily accessible parameter for clinicians. However, while NLR is a promising biomarker, it is essential to consider its limitations, such as variability due to pre-existing conditions or other inflammatory diseases, which can affect neutrophil, and lymphocyte counts independently of sepsis. Furthermore, the interpretation of NLR should be integrated with other clinical parameters and diagnostic tools to enhance its accuracy and reliability.

Neutrophil lymphocyte ratio (NLR) has been advocated to be increased in neonates in cases of inflammation and infection.[9] It is simple, cost effective and literature has shown reliable results in diagnosing late onset sepsis when co-related with culture specimen results retrieved later. We aim to incorporate this useful parameter in our diagnostic protocol by assessing its sensitivity and specificity in diagnosing late onset neonatal sepsis in our NICUs.

METHODOLOGY:

This prospective observational study was carried out at the Department of Pediatrics, Combined Military Hospital Lahore from Feb 2024-July 2024 after approval from the ethical review board vide letter no. 501/2024. The sample size was calculated keeping the confidence interval at 95%, margin of error at 5% with the population prevalence of suspected neonatal sepsis in our demographic setup to be 29.5%. Minimum sample size according to WHO calculator came out to be 320 patients. We included 320 patients in the final study protocol.

Inclusion criteria included all in-hospital born neonates presenting to the NICU from the ward or high dependency unit suspected of late onset neonatal sepsis after 7 days of birth

Exclusion criteria included all out of hospital born neonates, those with congenital abnormalities, those suspected of sepsis <7 days after birth, neonates already on broad spectrum antibiotics and non-consent of parents or next of kins to be included in the study.

The study method included all patients as per the inclusion criteria furnished. After admission into the NICU for suspected late neonatal sepsis, complete blood count, C-reactive protein and blood cultures were sent before changing or starting broad spectrum anti-biotic therapy. Neonates were added into the protocol for suspicion of late onset neonatal sepsis using the fetal inflammatory response syndrome criteria (FIRS) standardized and proposed by Haque1.[11] This included clinical variables (Heart rate >180 or <100, resp rate >60, altered mental status, lethargy, glucose intolerance with BSR >10 mmol/l and feeding intolerance), hemodynamic variables of low blood pressure and systolic pressure less than 65 mmHg, tissue perfusion variables (capillary refill time >3 sec, plasma lactate >3 mmol/l) and inflammatory variables (leukocytosis TLC >34, CRP>10, low platelet count <100,000 and immature neutrophils in the peripheral blood film). Presence of two or more of the criteria were regarded as suspected neonatal sepsis as per the study protocol. The differential leucocyte count, absolute lymphocyte count (ALC) and absolute neutrophil count (ANC) were obtained and NLR was calculated and recorded at the time of admission in all subjects. The diagnostic criteria and blood panel was endorsed by the resident pediatrics on duty on a non-descript proforma unaware of the study protocol and submitted at the end shift to the consultant on duty. The patients were divided in the final analysis into the suspected and confirmed neonatal sepsis groups if the cultures were negative or positive respectively.

The type of organism isolated was also recorded and respective NLR recorded at the time of admission was then co-related with the culture results and analyzed for sensitivity and specificity in diagnosing late onset neonatal sepsis with the cut-off value.

Primary variables observed were sensitivity and specificity of the neutrophil lymphocyte ratio in diagnosing late onset sepsis once co-related with the culture results. Maternal and neonatal demographic variables were also recorded including mode of delivery, fetal weight on admission and gestational age at delivery. Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Independent samples t-test was used to compare statistically significant means. Median values were compared using the Mann-Whitney U test. Chi-square test was used to compare frequency variables. Cut-off value for NLR was done using AUC (area under curve) using ROC (receiver operating characteristics). A p value of 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0

RESULTS:

A total of 320 were analyzed in the study protocol for diagnosis of late neonatal sepsis. Once the report of culture was received, they were assigned into the suspected culture negative group (n=142) and confirmed culture positive group (n=178). Mean age of patients in both groups was 14.862.46 days versus 14.962.46 days (p=0.704). Gender distribution was 139 (78.1%) males and 39 (21.9%) females in the suspected versus 96 (67.6%) males and 46 (32.4%) females in the confirmed neonatal sepsis group (p=0.035). Gestational age showed 151 (84.4%) patients as pre-term in the suspected versus 127 (89.4%) in the confirmed group (p=0.225). Weight at birth revealed normal birth weight in 54 (30.3%) versus 07 (4.9%) patients, low birth weight in 81 (45.5%) versus 85 (59.9%) patients, very low birth weight in 36 (20.2%) versus 40 (28.2%) patients and extremely low birth weight in 07 (3.9%) and 10 (7.0%) patients in the suspected versus confirmed neonatal sepsis group respectively (p<0.001). Maternal parameters showed mode of delivery to be vaginal in 15 (8.4%) patients versus 09 (6.3%) patients and caesarian section in 163 (91.6%) versus 133 (93.7%) patients (p=0.481) (Table-I).

Blood panel parameters showed mean absolute neutrophil count to be 5928.19796.05/mm^3 versus 7032.80166.02/mm^3 between the suspected and confirmed patients' groups (p<0.001). Similarly, mean absolute lymphocyte count was 2745.32394.53/mm^3 versus 3223.60278.90/mm^3 between both groups (p<0.001). Median value for NLR was 1.70 (1.00) versus 2.20 (1.00) between the suspected and confirmed culture groups (p<0.001) (Table-II).

Assessment of receiver operating characteristics (ROC) for NLR when compared with suspected and confirmed sepsis showed area under the curve being 0.644 (CI=95%) with sensitivity of 74.6%, specificity of 55.6%, positive predictive value being 57.3% and negative predictive value being 73.3% (Table-III and IV).

DISCUSSION:

We aimed to carry out this study to find an easy, convenient, and cost effective solution for diagnosing late neonatal sepsis. Any blood marker or panel that is easily available and helps to identify possible patients at the risk of developing the condition would be helpful in our resource constrained setup since it would allow only the patients at risk to undergoing advanced blood panel and investigations.

Neonatal sepsis is characterized by a systemic inflammatory response syndrome resulting from the introduction of specific or suspected pathogens into the bloodstream and the continuous generation of toxins, leading to pathological inflammation and dysfunction of organ systems. Neutrophils play a vital role in the innate immune response in sepsis by releasing inflammatory cytokines, chemokines, and regulatory cytokines, as well as by phagocytosing invading pathogens and eliminating them through various antimicrobial peptides, proteases, and oxidants.

The identification of neutrophil extracellular traps (NETs) in recent times has revealed a novel mechanism in the immune system's defense against pathogen invasion. Nevertheless, the excessive production of inflammatory cytokines and the formation of NETs contribute to heightened inflammation and tissue injury. Our study found that the second week of life was the time where majority of the neonates were admitted with clinical suspicion of neonatal sepsis. This is in line with studies carried out by Mukopadhyay et al who also concluded the median age of presentation to be the second week of life.[12] There was a pre-dominantly male pre-disposition in our study and needs further studies to see whether gender is associated with an increased risk of late onset neonatal sepsis. Our study found that even though pre-term infants were more prone to develop the disease, there was no statistically significant co-relation once both groups of suspected and the confirmed neonatal sepsis were compared. There was a significant co-relation between the birth weight at presentation to develop neonatal sepsis. Studies done by Kostlin et al and Pan et al concluded very low birth weight to be associated with the highest incidence of late onset neonatal sepsis,[6,13] Similar findings were concluded in our study with the age group being the most severely affected. The higher incidence is attributed to the increased chance of infection due to insertion of central venous lines, arterial lines and lumbar punctures done for diagnostic and therapeutic purposes. These chances are especially increased in low resources centers where disinfection and NICU care is hampered. Total and differential leukocyte counts are commonly utilized as cost-effective and readily accessible markers of the inflammatory response. The Neutrophil-to-Lymphocyte Ratio (NLR) is indicative

Table-1: Demographic Characteristics (n=320)

Variable	Suspected Neonatal Sepsis (n=142)	Confirmed After Culture (n=178)	P Value
Mean Age (Days)	14.86+2.46	14.96+2.46	0.704
Gender			
Male	139 (78.1%)	96 (67.6%)	0.035
Female	39 (21.9%)	46 (32.4%)	
Gestational Age			
Pre-Term	151 (84.4%)	127 (89.4%)	0.225
Term	27 (15.2%)	15 (10.6%)	
Weight At Birth			
Extremely Low Birth Weight (<1000 Gram)	07 (3.9%)	10 (7.0%)	<0.001
Very Low Birth Weight (<1500 Grams)	36 (20.2%)	40 (28.2%)	
Low Birth Weight (<2500 Grams)	81 (45.5%)	85 (59.9%)	
Normal Birth Weight	54 (30.3%)	07 (4.9%)	
Mode Of Delivery			
Vaginal	15 (8.4%)	09 (6.3%)	0.481
Caesarian	163 (91.6%)	133 (93.7%)	

Table-2 Blood Panel Parameters between Both Groups (n=320)

Variable	Suspected Neonatal Sepsis (n=142)	Confirmed After Culture (n=178)	P Value
Mean Absolute Neutrophil Count (/MM3)	5928.19+796.05	7032.80+166.02	**<0.001**
Mean Absolute Lymphocyte Count (/MM3)	2745.32+394.53	3223.60+278.90	**<0.001**
Median NLR	1.70 (1.00)	2.20 (1.00)	**<0.001**

Table-3 AUC and ROC Characteristics (n=320)

Area	STD Error	Asymptotic Sig	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.664	0.030	0.000	0.604	0.724

Table-4 Sensitivity, Specificity, PPV and NPV of NLR for Late Onset Neonatal Sepsis (n=320)

Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
74.6%	**55.6%**	**57.3%**	**73.3%**

of fluctuations in neutrophil and lymphocyte levels.

Numerous research endeavors have established the NLR as a dependable tool for assessing inflammation and as a prognostic indicator across various medical conditions such as ischemic stroke, cerebral hemorrhage, major adverse cardiac events, and solid tumors. In recent times, the NLR has garnered significant interest as a novel risk factor that holds promise for aiding in the diagnosis of sepsis. Sepsis, characterized by heightened neutrophil counts and reduced lymphocyte counts due to pathogenic microbial invasion, is associated with elevated NLR levels in affected individuals. Extensive epidemiological inquiries and meta-analyses have provided evidence suggesting that NLR could serve as a valuable predictive marker for sepsis, with patients exhibiting elevated NLR levels facing an increased likelihood of an unfavorable prognosis.

When talking about the co-relation of neutrophil lymphocyte ratio (NLR) and diagnosing late onset neonatal sepsis, we found a sensitivity of 74.6% and a specificity of 55.6%. When assessing for a suitable cut-off value, we found that a value of 2.05 was associated with the most suitable sensitivity and minimum false positives. This was in-line with findings in studies done by Sumitro et al and Bai et al. Varal et al also concluded a cut-off value of 2.12 which was in line with our findings as well.[14-16] They concluded that

neonates above the cut-off has twice the chance of being diagnosed with the disease than the ones below it. Local studies done by Naseer et al and Al Nady et al also found NLR to be a good screening tool in resource constrained setups to be utilized for suspicion in patients with specific cut-off values in conjunction with the CRP values.[17,18]

The Neutrophil-to-Lymphocyte Ratio (NLR) is a prominent biomarker in sepsis management, valued for its simplicity and cost-effectiveness, but its utility is often compared to other key biomarkers such as C-Reactive Protein (CRP), Procalcitonin (PCT), and Lactate. NLR, reflecting the ratio of neutrophils to lymphocytes in the blood, provides insight into the balance between systemic inflammation and immune response, with elevated levels indicating heightened inflammatory activity and potentially worse outcomes. However, CRP, an acute-phase protein produced in response to inflammation, offers a more direct measure of systemic inflammatory activity. Although CRP levels rise significantly in sepsis and correlate with disease severity, it lacks specificity as it can be elevated in various inflammatory conditions beyond sepsis. Procalcitonin, a peptide precursor of calcitonin, offers a more specific marker of bacterial infection, distinguishing sepsis from non-bacterial inflammatory processes. Elevated PCT levels are associated with more severe infections and poorer outcomes, making it a valuable tool for identifying bacterial sepsis, though it is typically more expensive and less accessible compared to NLR. Lactate, a marker of tissue hypoperfusion and metabolic distress, is crucial in assessing the severity of sepsis and the need for resuscitation. High lactate levels are closely linked to increased mortality risk and provide direct insight into the physiological impact of sepsis, unlike NLR which primarily reflects inflammatory response rather than tissue perfusion. In clinical practice, the combined use of NLR with CRP, PCT, and lactate can offer a comprehensive evaluation of sepsis, with each biomarker contributing unique and complementary information. While NLR provides an accessible and cost-effective measure of systemic inflammation, CRP and PCT enhance diagnostic specificity, and lactate offers critical insights into tissue perfusion and severity. Integrating these biomarkers can improve diagnostic accuracy and guide more effective management strategies for sepsis.

The neutrophil-to-lymphocyte ratio (NLR) is emerging as a valuable biomarker for diagnosing neonatal sepsis, often outperforming traditional markers like C-reactive protein (CRP) and neutrophil counts alone. NLR offers a pooled sensitivity of 79% and specificity of 91% for sepsis diagnosis, indicating its reliability. While CRP has been shown to have a maximum sensitivity and specificity of 84.3% and 46.1% for sepsis, its takes longer to elevate, while NLR can rise rapidly following infection, allowing for earlier detection. Combining NLR with CRP enhances diagnostic accuracy, making it a promising tool in clinical settings. The neutrophil-to-lymphocyte ratio (NLR) is increasingly recognized as a potential biomarker for neonatal sepsis due to its ability to reflect the balance between the innate and adaptive immune responses. Despite its promise, the use of NLR in clinical settings is hindered by several drawbacks. One significant limitation is that NLR is often measured at a single time point, which may not capture the dynamic nature of sepsis progression.[19] This static assessment can lead to misinterpretation of a patient's condition, particularly in cases where the clinical status may change rapidly. Additionally, many studies investigating NLR are cross-sectional, which restricts their ability to predict future outcomes and may introduce biases that affect the reliability of the findings.[20] Furthermore, the diagnostic accuracy of NLR can be questioned since its association with sepsis is frequently based on clinical features rather than confirmed blood cultures. This reliance on clinical diagnosis can lead to overdiagnosis or underdiagnosis of sepsis, especially in neonates where symptoms may be subtle. Another challenge is the variability in the cut-off values for NLR across different studies, which complicates the standardization of its use in clinical practice. This inconsistency can lead to confusion among healthcare providers regarding what constitutes a clinically significant NLR, ultimately affecting decision-making in the management of neonatal sepsis.

CONCLUSION:

Authors Contribution:
Zunaira Zulfiqar: Conception, design, analysis and interpretation of data and drafting of article
Unaiza Syed: Conception, design, analysis and interpretation of data and drafting of article
Syed Arsalan Hassan: Conception, design, analysis and interpretation of data and drafting of article
Nabeera Hayat: Conception, design, analysis and interpretation of data and drafting of article
Hamza Khursheed: Conception, design, analysis and interpretation of data and drafting of article
Abu Bakar Khan: Conception, design, analysis and interpretation of data and drafting of article

REFERENCES:

1. Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Archives of Disease in Childhood. 2021;106(8):745-52. https://doi.org/10.1136/archdischild-2020-320217
2. Odabasi IO, Bulbul A. Neonatal sepsis. ªiºli Etfal Hastanesi Tip Bülteni. 2020;54(2):142-58. DOI: 10.14744/ SEMB.2020.00236
3. Wen SC, Ezure Y, Rolley L, Spurling G, Lau CL, Riaz S, et al. Gram-negative neonatal sepsis in low-and lower-middle-income countries and WHO empirical antibiotic recommendations: A systematic review and meta-analysis. PLoS medicine. 2021;18(9):e1003787.
4. Hayes R, Hartnett J, Semova G, Murray C, Murphy K, Carroll L, et al. Neonatal sepsis definitions from randomised clinical trials. Pediatric Research. 2023;93(5):1141-8. https://doi.org/10.1038/s41390-021-01749-3

5. Rafi MA, Miah MMZ, Wadood MA, Hossain MG. Risk factors and etiology of neonatal sepsis after hospital delivery: a case-control study in a tertiary care hospital of Rajshahi, Bangladesh. PloS one. 2020;15(11):e0242275. https://doi.org/10.1371/journal.pone.0242275
6. Köstlin-Gille N, Härtel C, Haug C, Göpel W, Zemlin M, Müller A, et al. Epidemiology of early and late onset neonatal sepsis in very low birthweight infants: data from the German Neonatal Network. The Pediatric infectious disease journal. 2021;40(3):255-9. DOI: 10.1097/INF.0000000000002976
7. Glaser MA, Hughes LM, Jnah A, Newberry D, Harris-Haman PA. Neonatal sepsis: a review of pathophysiology and current management strategies. Advances in neonatal care. 2021;21(1):49-60. DOI: 10.1097/ANC.0000000000000769
8. Srinivasan L, Balasubramanian H, Stewart MT, Weiss EM, Kirpalani H, Cooper C, et al. Procalcitonin for the diagnosis of sepsis in neonates: a diagnostic test accuracy review. The Cochrane Database of Systematic Reviews. 2023;2023(4). https://doi.org/10.1002%2F14651858.CD014196
9. Li T, Dong G, Zhang M, Xu Z, Hu Y, Xie B, et al. Association of neutrophil–lymphocyte ratio and the presence of neonatal sepsis. Journal of immunology research. 2020;2020. https://doi.org/10.1155/2020/7650713
10. Ahmed M, Yasrab M, Khushdil A, Qamar K, Ahmed Z. Neonatal sepsis in a tertiary care hospital: bacteriological profile and its antibicrobial sensitivity. Pakistan armed forces medical journal. 2018;68(6):1654-58.
11. Haque KN. Definitions of bloodstream infection in the newborn. Pediatric Critical care medicine. 2005;6(3):S45-S9. DOI: 10.1097/01.PCC.0000161946.73305.0A
12. Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, et al. Neurodevelopmental outcomes following neonatal late-onset sepsis and blood culture-negative conditions. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2021;106(5):467-73. https://doi.org/10.1136/archdischild-2020-320664
13. Pan T, Zhu Q, Li P, Hua J, Feng X. Late-onset neonatal sepsis in Suzhou, China. BMC pediatrics. 2020;20:1-7. https://doi.org/10.1186/s12887-020-02103-y
14. Sumitro KR, Utomo MT, Widodo ADW. Neutrophil-to-lymphocyte ratio as an alternative marker of neonatal sepsis in developing countries. Oman Medical Journal. 2021;36(1):e214. https://doi.org/10.5001%2Fomj.2021.05
15. Bai L, Gong P, Jia X, Zhang X, Li X, Zhang Y, et al. Comparison of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for the diagnosis of neonatal sepsis: A systematic review and meta-analysis. BMC pediatrics. 2023;23(1):334. https://doi.org/10.1186/s12887-023-04094-y
16. Varal IG, Dogan P. Can neutrophil-lymphocyte ratio be a predictor of late-onset sepsis in preterm infants? 2020.
17. Naseer N, Sheikh TK, Zulfiqar S, Bashir H, Haroon S, Jahangir J. Neutrophil Lymphocyte Ratio as Screening Tool for Neonatal Sepsis in Developing Countries. Pakistan Armed Forces Medical Journal. 2023;73(2):583-86. https://doi.org/10.51253/pafmj.v73i2.8450
18. AL Nady N, Ismaiel Y, Assar E, Saleh M. Diagnostic Value of Neutrophil to Lymphocyte Ratio on Neonatal Sepsis in Full Term and Preterm Neonates. Benha Journal of Applied Sciences. 2021;6(6):169-77.
19. Zhao G, Chen J, Wang J, Wang S, Xia J, Wei Y, et al. Predictive values of the postoperative neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio for the diagnosis of early periprosthetic joint infections: a preliminary study. Journal of Orthopaedic Surgery and Research. 2020;15:1-7. https://doi.org/10.1186/s13018-020-02107-5
20. Chen C, Yang H, Cai D, Xiang L, Fang W, Wang R. Preoperative peripheral blood neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratio (PLR) related nomograms predict the survival of patients with limited-stage small-cell lung cancer. Translational lung cancer research. 2021;10(2):866. https://doi.org/10.21037%2Ftlcr-20-997

Original Article **Open Access**

Analyzing trends in Cesarean Section by Action Oriented Classification (Robson Criteria) at Creek General Hospital, Karachi

Saba Pario, Shaista Bashir Anwar, Kaweeta Kumari, Uzair Ahmed, Muhammad Muhib, Ghania Naeem

ABSTRACT

Objectives: The objective of this study is to analyze Cesarean section trends using the Robson classification system and identify the cause of cesarean section in each group, in a tertiary care hospital located in Karachi, Pakistan.

Study Design and Settings: This cross-sectional study was conducted in the obstetric department of Creek General Hospital Karachi, from 1 Jan 2021 to 31 Dec 2022.

Methodology: Data collection utilized a non-probability consecutive sampling method. This study examined the sociodemographic characteristics, indications for cesarean section, and the Robson classification system in the women who underwent cesarean section in the hospital during specified duration. Inclusion criteria of study were all women who underwent for C-section procedure during the study timeline. Data was analyzed using IBM SPSS Statistics version 26. The study adhered to the Helsinki Declaration and ethical approval.

Results: The Robson classification system was analyzed in this study, and group 5 was shown to be the primary contributor followed by group 2 and then group 1. Most frequently noted indication was previous CS (43.2%), followed by non-progress of labor (15.1%), and fetal distress (11.6%).

Conclusion: Cesarean section rate can be reduced by encouraging vaginal birth after cesarean section in multiparous women who had one cesarean section, under supervision of senior obstetrician. Meanwhile, the Non-progress of labor can be targeted by improving antenatal and intrapartum care, birth preparation classes and presence of companion during labor.

Through CTG interpretation and their standardized management protocols will be effective in preventing and curbing the rising cesarean rate due to fetal distress

Keywords: Cesarean Section, Delivery, Pregnancy, Robson.

How to cite this Article:
Pario S, Anwar SB, Kumari K, Ahmed U, Muhib M, Naeem G. Analyzing trends in Cesarean Section by Action Oriented Classification (Robson Criteria) at Creek General Hospital, Karachi. J Bahria Uni Med Dental Coll. 2025;15(1):21-28 DOI: https://doi.org/ 10.51985/JBUMDC2024420

Saba Pario *(Corresponding Author)*
Associate Professor, Department of Gynae/OBS
United Medical & Dental College
Email: drsabapario@gmail.com

Shaista Bashir Anwar
Assistant Professor, Department of Gynae/OBS
United Medical & Dental College
Email: drshaistaanwar@yahoo.com

Kawaeeta Kumari
Professor, Department of Gynae/OBS
United Medical & Dental College
Email: kaweetadhomeja@gmail.com

Uzair Ahmed
House Surgeon, Department of Gynae/OBS
United Medical & Dental College
Email: uzairahmeda1@gmail.com

Muhammad Muhib
House Surgeon, Department of Gynae/OBS
United Medical & Dental College
Email: muhibshah19@gmail.com

Ghania Naeem
Medical Officer, Department of Gynae/OBS
United Medical & Dental College
Email: ghanianaeem2@gmail.com

Received: 31-07-2024
Accepted: 16-10-2024
1st Revision: 13-08-2024
2nd Revision: 21-08-2024

INTRODUCTION:

A Cesarean section (C-section/CS) is a surgical obstetric procedure employed to assist delivery of the baby, an incision is made on the mother's abdomen and uterus, this procedure is usually recommended in pregnancies where vaginal deliver (VD) can pose a significant threat to the mother, fetus or both. VD may be complicated by prolonged or obstructed labor, fetal distress, elevated blood pressure or glucose, multiple pregnancies, or abnormal position/presentation of the fetus. [1]

C-section has been a mode of delivery for decades (i.e. dating back to 1500, when the first successful C-section was performed in Switzerland) in either emergency or planned setting. This procedure significantly reduces maternal and neonatal morbidity and mortality, although C-section has profound benefits it may be detrimental if practiced unreasonably. [2]

In recent times, there has been an escalating trend in the unnecessary pratice of C-sections, with an alarming annual increase of 4% globally.[3] This trend is particularly pronounced in South Asia, where a significant upsurge in deliveries via

C-section has been observed, rising from a rate of 3.2% in 1990 to a 20% in 2018. Similarly, Pakistan ranks third in the South Asian nation for the high incidence of cesarean section rate, which stood at 19.9% during the period from 2017 to 2018. [3,4]

Numerous non-medical indications of unnecessary C-section have been outlined in previous literature, which include: maternal request due to presumed anxiety and pain from VD, wanting to deliver the baby on a specific day, physician's bias or ease and associated financial incentives. [5] Furthermore, recent studies have also found that C-section rates were generally higher in private institutes as compared to public institutes. [6] The rate of cesarean section are also influenced by sociocultural background, as the practice of C-section is discouraged in some societies. [5]

According to the World Health Organization (WHO), a nationwide C-section rate exceeding 10% does not effectively reduce perinatal and maternal morbidity and mortality. Undue reliance on C-sections can lead to adverse outcomes for the mother and the fetus, including prolonged maternal recovery periods, the need for blood transfusions, hysterectomies, neonatal intensive care admissions, and, tragically, maternal and neonatal mortality. [2,7,8] This trend has a significant impact on healthcare systems and economies, with an estimated 6.2 billion unnecessary C-sections performed globally each year, totaling to US$ 2.3 billion spent annually. [9]

In-order to establish an effective regulatory system and reduce the rate of unnecessary C-sections, it is imperative to identify and distinguish the group of women who are undergoing these procedures unnecessarily. To address this concern, the Robson classification tool was introduced in 2001. This tool stratifies and monitors rates of unnecessary C-sections based on easily obtainable obstetric parameters including: parity, previous C-sections, gestational age, onset of labor, fetal presentation, and the number of fetuses, hence, the Robson classifications was adopted by the World Health Organization (WHO) in 2015 as a global standard for effectively monitoring unnecessary C-section rates in hospital settings. [6,10]

Robson's Ten-Group Classification allows detailed analysis, based on individual characteristics. That includes factors such as; single/multiple pregnancies, nulliparous/multiparous status, presentation of the fetus, type of labor, and term/preterm status. The Robson classification, divides women into 10 groups accordingly. [11] Studies report cesarean section frequencies of 30% in primigravidas and 70% in multigravidas, with specific distribution percentages across the Robson groups. Group 5 and Group 2 contribute most to the total cesarean section rate. While smaller groups have higher cesarean rates, their overall impact is minimal. [12]

C-section performed without any medical indication exposes the mother and the baby to short-term and long-term risks. Hence, the Robson classification is a standardized method to analyze C-section rate. This study aims to determine cesarean section rates at a tertiary care hospital in Karachi using the Robson classification. Allowing us to analyze the distribution of C-sections across different Robson groups, to identify high-risk populations, and detect the primary reason for cesarean section within each group.

This research will compare local cesarean section rates with national and international benchmarks, exploring the association between maternal, sociodemographic factors and cesarean section rates. Enabling us to assess the impact of maternal and fetal complications on cesarean section rates, and ultimately identify potential areas for intervention to reduce unnecessary C-sections.

METHODOLOGY:

This was cross-sectional study conducted in the Gynecology and Obstetrics department of Creek General Hospital, Karachi from 1st Jan 2021 to 31st Dec 2022. The samplig technique used in this study was non-probability consecutive sampling method. The sample size of the study calculated was 500, calculated through Rao software. The Inclusion criterion of the study was all women who underwent for Ceaserian section procedure in between the study timeline. Exclusion criteria include all those women who went under normal labour. All women who were involved in the study were taken informed consent to maintain the ethical grounds. The data was collected through well-structured questionnaire that was design and critically evaluated by the help of team of researchers, statisticians and OBGYN doctors. This study got ethical approval from the Institutional Review Board (IRB) of United Medical and Dental College, (UMDC/Ethics/2019/28/10/262) and the study was conducted in accordance with the Helsinki Declaration24.

Every woman enrolled in the hospital, her maternal history, socio-demographic data, symptomatology, clinical examination, management, outcomes, pregnancy-related information (gestational age, fetal presentation, number of fetus and onset of labor) and maternal and fetal outcomes (complications, APGAR score at five minutes, birth weight) were recorded on a predesigned proforma. The Robson tool incorporated six predefined obstetric variables in pregnant women: parity (categorized as nulliparous or multiparous), cesarean section history, type of onset of labor (spontaneous, induced, or pre-labor cesarean section), fetal count (singleton or multiple gestations), gestational age (stratified into preterm and term), and fetal presentation and lie (comprising cephalic, breech, or transverse positions). It classified pregnancies admitted for labor into one of ten distinctive categories.

Data analysis was conducted using IBM SPSS Statistics version 26, Continuous variables were presented as means with the confidence interval of 95%, while categorical variables were reported as frequencies and percentages through figures and tables. Statistical analysis included the

utilization of the chi-square test, to show the relation between independent and dependent variables with the p-value of less than 0.005 was considered significant.

RESULTS:

During the study interval, a total of 500 cesarean deliveries occurred. Overall, mean age was 26.6±4.4 years while most of the women, 53.6% were between 18-26 years of age. Majority of the women were nulliparous or with one parity, 66.3% women were delivered between gestational age 37-42 weeks.

The Robson classification showed that group 5 (Previous cesarean section, singleton, cephalic, =37 weeks' gestation)

Table 1: Distribution of C-section according to Robson's Ten group classification system

Robson Classification	Description of Robson's Ten group classification	Frequency	Percentage
1	Nulliparous, single cephalic, =37 weeks, in spontaneous labour.	88	17.6
2	Nulliparous, single cephalic, =37 weeks, induced or caesarean section (CS) before labour.	90	18
3	Multiparous (excluding previous CS), single cephalic, =37 weeks, in spontaneous labour.	23	4.6
4	Multiparous (excluding previous CS), single cephalic, >37 weeks, induced or CS before labour.	9	1.8
5	Previous CS, single cephalic, = 37 weeks	191	38.2
6	All nulliparous breeches	34	6.8
7	All multiparous breeches	12	2.4
8	All multiple pregnancies (including previous CS).	7	1.4
9	All abnormal lies (including previous CS).	1	0.2
10	All single cephalic, <37 weeks(including previous CS)	45	9
Total		500	100

Table2 : Count and persentages according to indications of robsons ten group classification system.

Indication	Robson										P-Value
	1 (n=88)	2 (n=90)	3 (n=23)	4 (n=9)	5 (n=191)	6 (n=34)	7 (n=12)	8 (n=7)	9 (n=1)	10 (n=45)	
Anhydroamnios	0	50	0	0	0	0	0	0	0	50	
APH	50	10	10	0	0	0	0	0	0	30	
CPD	33.3	66.7	0	0	0	0	0	0	0	0	
Failed IoL	0	88.9	0	8.3	0	0	0	0	0	2.8	
Fetal Distress	64.3	14.3	12.5	0	1.8	0	0	0	0	7.1	
Fetal Mal-presentation	2.1	2.1	0	0	0	72.3	19.1	0	0	4.3	
Hypertensive Disorder of Pregnancy	0	66.7	0	0	0	0	0	0	0	33.3	
IUGR	5.6	38.9	11.1	16.7	0	0	0	0	0	27.8	0.001
Maternal Wish	0	82.4	0	5.9	0	0	0	0	0	11.8	
NPOL	57.9	22.4	15.8	0	2.6	0	0	0	0	1.3	
Placenta Previa	0	25	25	50	0	0	0	0	0	0	
Precious pregnancy	0	100	0	0	0	0	0	0	0	0	
Previous Caesarean Section	0	0	0	0	86.2	0	1.4	0.9	0.5	11.1	
Twins	0	0	0	0	16.7	0	0	83.3	0	0	
Total	17.6	18	4.6	1.8	38.2	6.8	2.4	1.4	0.2	9	

Table 3: frequency of confounders according to indications of robsons ten group classification system

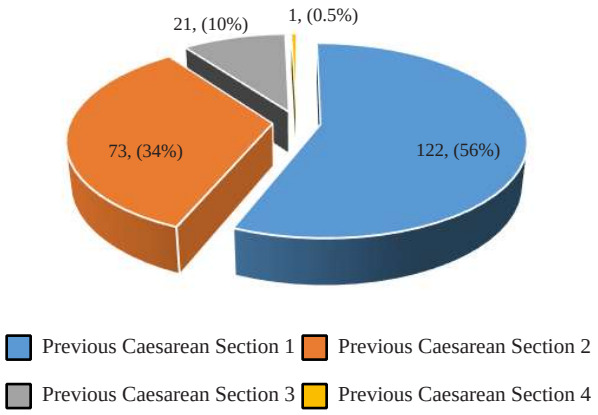
Confounder		Robson										P-Value
		1 (n=88)	2 (n=90)	3 (n=23)	4 (n=9)	5 (n=191)	6 (n=34)	7 (n=12)	8 (n=7)	9 (n=1)	10 (n=45)	
Age Group	18-26 (n= 269)	24.5	23.4	2.2	0.7	27.1	9.3	1.5	1.5	0	9.7	0.001
	> 26 (n= 232)	9.5	12.1	7.3	3	50.9	3.9	3.4	1.3	0.4	8.2	
Parity Group	0-1 (n= 367)	22.9	24.8	3.8	1.4	28.1	9	1.6	0.8	0	7.6	0.001
	2 - 4 (n= 125)	1.6	0	6.4	2.4	69.6	0	3.2	3.2	0.8	12.8	
	> 4 (n= 6)	0	0	16.7	16.7	16.7	0	33.3	0	0	16.7	
Presenting Complaints Group	26-37 (n= 168)	7.1	11.3	4.2	2.4	38.1	4.8	3	2.4	0	26.8	0.001
	> 37 (n= 333)	22.8	21.6	4.8	1.5	38.1	7.8	2.1	0.9	0.3	0	
Baby Gender	Boy (n= 277)	17.7	17.3	5.1	1.8	38.6	7.9	2.2	0.7	0	8.7	0.001
	Girl (n= 218)	17.9	19.7	4.1	1.8	38.1	5.5	2.8	0	0.5	9.6	
	Twins (n= 6)	0	0	0	0	16.7	0	0	83.3	0	0	
Baby Weight Group	1-2.5 (n= 110)	11.8	19.1	3.6	2.7	31.8	4.5	2.7	3.6	0.9	19.1	0.001
	2.6-4 (n= 387)	19.4	18.1	4.7	1.6	40.1	7.5	1.8	0.8	0	6.2	
	> 4 (n= 4)	0	0	25	0	25	0	50	0	0	0	

Table 4: Sub Groups of C-section with previous scar and grand total

Sub Groups of C-section with previous scar	Previous Caesarean Section 1		Previous Caesarean Section 2		Previous Caesarean Section 3		Previous Caesarean Section 4		Grand Total	
	Count	%	Count	%	Count	%	Count	%	Count	%
Breech	5	4.10							5	2.30
CPD	2	1.64							2	0.92
Failed IOL	3	2.46							3	1.38
Fetal Distress	7	5.74	2	2.74					9	4.15
GDM	1	0.82							1	0.46
Impending scar dehiscence	40	32.79	37	50.68	7	33.33			84	38.71
IUGR	1	0.82	2	2.74					3	1.38
Maternal Wish	8	6.56							8	3.69
NPOL	13	10.66							13	5.99
PIH	1	0.82							1	0.46
Placenta Previa	2	1.64							2	0.92
Poor Bishop	2	1.64							2	0.92
Post Dates	5	4.10							5	2.30
Post Term	3	2.46							3	1.38
Precious Pregnancy	2	1.64							2	0.92
Prom	3	2.46			1	4.76			4	1.84
Rupture Uterus	1	0.82							1	0.46
Severe Preeclampsia		0.00			1	4.76			1	0.46
Short inter pregnancy interval	1	0.82							1	0.46
Twins	1	0.82	1	1.37					2	0.92
Grand Total	101	82.79	42	57.53	9	42.86			152	70.05
(blank)	21	17.21	31	42.47	12	57.14	1	100	65	29.95
Total	122	100	73	100	21	100	1	100	217	100

was the highest contributor to the overall CS rate, contributing 43.2% of all CS. Group 2 (Nulliparous, single cephalic, =37 weeks, induced or CS before labor) was the second highest contributor, contributing 15.1% to the overall CS. The third highest contributors were group 1 (Nulliparous, single cephalic, =37 weeks, spontaneous labor) contributing 11.6% to the overall CS rate. The least contributor to the overall CS rate was group 9 (All women with a single pregnancy

Figure 1: Sub Groups of C-section with previous scar and grand total



in transverse or oblique lie (including those with previous cesarean section)), contributing 0.2 % of all CS.

The most frequent indication for C-section was previous C-section followed by non-progress of labor and fetal distress.

The pie graph shows that 56% of patients were with previous one C-section among scarred uterus, 34% were with previous two C-section, 10 % were made through previous three C-section and 0.5 % was from previous four caesarean section showing the distribution of births among women who had varied numbers of C-section prior.

The table shows that the p-value of confounder age, parity, presenting complaints, baby gender and baby weight with respect to Robson classification are less than 0.05 indicating significant relationship between the mentioned confounding variables and the Robson classification. This could imply that these confounding variables influence or are linked to the result that the Robson categorization represents.

The P-value of Robson classification with respect to indication is less than 0.05, indicating significant relation and conclude that indications are associated with or has an impact on the Robson classification.

DISCUSSION:

Cesarean section rates have been increasing gradually. This escalating prevalence of cesarean section (CS) in Pakistan and worldwide has emerged as a critical focus in contemporary maternal healthcare research. The upward trajectory of CS deliveries raises critical questions regarding its drivers and potential consequences, since, unnecessary C-section can lead to negative health consequences for mothers; these include hemorrhage, infection, shock, and uterine rupture. As for Children born via CS have a higher incidence of developing obesity, asthma, allergies, and non-communicable diseases (NCDs).

Our study aimed to implement the Robson classification system in-order to identify major contributing groups to the overall CS rates at our institute. Along with identifying the prevalence of CS rates in each group, we also assessed the primary indications for CS within these groups and proposed potential strategies for optimizing CS rates.

During the study period, a total of 500 cesarean deliveries were recorded. According to the data we collected, the Robson group 1, group 2, and group 5 accounted for the majority of the C-section conducted at the institute, together representing approximately 70% of the total C-section rate. With group 5 being the predominant contributor, followed by group 2 and group 1.

These groups are characterized by; nulliparous women with spontaneous or induced labor, and multiparous women with previous C-sections. These groups have consistently been identified as high-risk populations, hence, the results we obtained were in accordance with the studies conducted by Roberge S et al. in Quebec, Canada, and Robson M et al. in Ireland. [13,14] Similarly, Tahir N et al. reported that group 5 was the most frequently noted indication for CS, followed by groups 2 and 1, in a tertiary care hospital in Abbottabad, Pakistan. [15] In an audit conducted in a tertiary care hospital in Rawalpindi by Ansari et al., group 5 made the maximum contribution to the overall CS rate, followed by group 2. [16]

In contrast to our findings, Fatima S.S. et al. observed Group 1 to be the second most common group following group 5 in a cross-sectional study conducted at a tertiary care hospital in the capital city of KPK Province, Pakistan. [17] H. O. Tontus, in his report, conducted in Turkey also found Group 1 to be the second most common group contributing to overall CS rates. [18] Gilani S, in a retrospective study conducted at the Pakistan Institute of Medical Sciences, Islamabad, Pakistan, reported group 5 to be the major contributor to the overall CS rate followed by groups 1 and 2 with almost equal contributions. However, according to her report, group 9 made the least contribution to the overall CS rate, which is in agreement with our results. [19]

Since our study found that Robson group 1, group 2, and group 5 were the primary contributors, it was crucial to investigate the underlying factors contributing to the rates of cesarean section at our institute. Hence, our analysis revealed that previous cesarean delivery, non-progression of labor, and fetal distress were the most commonly mentioned causes for surgical intervention in these groups. These findings align with previous literature, for instance, Abdo et al. found that Group 1 and Group 5 were major contributors towards CS rates, the reasons behind their contributions were; fetal compromise and previous cesarean delivery. [20] Similarly, Khan et al. concluded that majority of CS rates are driven by the role of previous cesarean delivery and poor labor progress in driving cesarean section rates, further validating our findings. [21] These studies collectively highlight the complex interplay of factors that often necessitate cesarean section in these specific patient

populations.

Through this study we have determined that, all multiparous women with previous CS must be encouraged to have vaginal birth after cesarean section (VBAC) and should undergo a trial of labor (TOL) in the presence of a senior obstetrician. Robson, M. et al state that a higher percentage of women in Group 5 reflects a high CS rate in past years, specifically in Groups 1 and 2 (both containing nulliparous women). Therefore, to reduce the percentage of multiparous women requiring CS due to previous CS (Group 5), the rate of CS must be reduced in nulliparous women (i.e., Groups 1 and 2). [22]

This highlights that the key to lowering overall CS rates is to decrease the number of primary CS procedures. In addition to previous CS, our study reported non-progress of labor (NPOL) as the second most common indication contributing to the overall CS rate and as the most common indication for CS in nulliparous women. Antenatal consultations regarding weight gain during pregnancy and smoking may also be helpful. Birth preparation classes and guidelines should be provided to reduce anxiety and fear of delivery and childcare. At the time of labor, the presence of a birthing companion should be facilitated, and the environment should be arranged according to the mother's request to make labor more comfortable for her. However, if interventions are needed, they should be performed according to the guidelines to facilitate vaginal delivery, ensuring the safety of both the mother and the fetus. [23] The right to vaginal delivery should be discussed, and an agenda should be created. Mothers are the only person to decide the mode of delivery. However, they should be counseled about the pros and cons of CS and encouraged for vaginal delivery, as a maternal wish for CS is also an indication for CS, especially in group 2.

Induction of labor (IOL) should only be performed if necessary, and decisions and procedures should be made by an experienced obstetrician, as failed inductions also lead to unwanted CS. Despite clear protocols and instructions for external cephalic version (ECV), offering ECV is often met with hesitation. Meanwhile, the surgical alternative remains readily available for cases involving breech presentation during labor. This reluctance could be due to insufficient training and experience in managing vaginal breech deliveries. [24] Residents should be trained to perform vaginal breech deliveries and ECV to successfully deliver breech babies vaginally. Almost four-fifths of women who underwent successful ECV gave birth vaginally. [25]

This study was conducted at Creek General Hospital in Karachi, Pakistan, which is a tertiary care hospital. The study was aimed to identify factors contributing to increasing cesarean section rates in Pakistan, while providing valuable insights, our study had several limitations. It was a single-center designed study which restricted the generalizability of findings among other healthcare settings and institutes nationally. Secondly, the time period during which the study was conducted could not be used to capture long-term trends or variations in cesarean section rates. Lastly, determining the practice of "unnecessary" C-sections can be subjective and may vary among healthcare providers. Confounding factors, such as maternal age, parity, socioeconomic status, and underlying medical conditions, were not adequately controlled for, potentially influencing the observed cesarean section rates.

Therefore, in-order to enhance the robustness of future studies on similar subject, following recommendations are made; employing a larger sample size by incorporating a multicenter design, and utilizing standardized criteria for determining "unnecessary" C-sections. The future studies must explore the relation between the C-section rates among private and public institutes in Pakistan in-order to determine whether the rate of C-sections among these institutes is variable or not.

By including these changes into the study the authors can help improve the generalizability and reliability of the findings. Additionally, to avoid two of the most profound biases; observer's bias and socioeconomic bias, the researchers must employ blind data collection and must obtain detailed socioeconomic history of all the patients. They must also use of statistical techniques to control for confounding variables and prolonging the study period to capture long-term trends, this would contribute to a more comprehensive understanding of cesarean section rates and their underlying factors.

CONCLUSION:

The rising prevalence of CS rates is a major public health concern, and interventions should be devised and implemented to counter this phenomenon. Hence, the healthcare workers can play a significant role in optimizing CS rates i.e. by influencing the decision to undergo the CS. Even though financial incentives can create conflict of interest and may hinder the details disclosed by the healthcare provider, to prevent this, public health education must be employed to provide detailed information about the short-term risks and long-term risks and benefits of CS to delivering mothers in-order to promote rational decision making.

Furthermore, to reduce cesarean section rates, interventions should be targeted at the groups identified as high contributors. Consistent use of the Robson classification for CS audit in Ob/Gyn departments throughout Pakistan can help identify these groups and guide targeted interventions such as: improving the management of spontaneous and induced labor, strengthening clinical practice around encouraging vaginal birth after cesarean, and promoting active management of labor. These interventions can potentially reduce the need for cesarean section.

Although the practice of VBAC and ECV is considered to be outdated, the obstetricians and midwives should be

thoroughly trained to perform these procedures to successfully manage fetus malpresentation to successfully deliver breech babies vaginally. Through this approach the CS rates in Robson group 5, 6, 7, and 8. Induction of labor should only be decided after accurate calculation of gestational age and indication where delivering the fetus will be more beneficial than continuation of pregnancy. Standardized fetal heart rate interpretations on CTG and their standardized management protocols will be effective in preventing and curbing the rising cesarean rate due to fetal distress in groups 1, 2,3 and 4. For groups 9 and 10, the effective fetal monitoring and specialized care by experienced obstetrician can lead to a decline in CS rate

Non-progress of labor (NPOL) is also a common indication for CS in nulliparous women. Hence, to improve CS rates in this group antenatal care should be improved, birth preparation classes to be arranged, implementing midwife-led care, and involving spouse during labor can contribute to better outcomes and potentially lower cesarean section rates.

Regular audits and external reviews can help monitor CS rates. By assessing CS rates and identifying areas of improvement, healthcare facilities can work to reduce unnecessary CS procedures and ensure that surgeries are performed only when medically necessary.

Authors Contribution:
Saba Pario: Conception of study, data collection, drafting.
Shaista Bashir Anwar: Data collection and analysis of results
Kaweeta Kumari: Design of study, supervision of work
Uzair Ahmed: Data collections and drafting
Muhammad Muhib: Data collections and drafting
Ghania Naeem: Data collections and drafting

REFERENCES:

1. Keag OE, Norman JE, Stock SJ. Long-term risks and benefitsassociated with cesarean delivery for mother, baby, and subsequentpregnancies: systematic review and meta-analysis. PLoS Med.2018;15(1):e1002494. DOI: 10.1371/journal.pmed.1002494
2. Blustein J, Liu J. Time to consider the risks of caesarean delivery for long term child health. Bmj. 2015;350. doi: https://doi.org/10.1136/bmj.h2410
3. Verma V, Vishwakarma RK, Nath DC, et al. Prevalence and determinants of caesarean section in South and South-East Asian women. PLoS One. 2020;15(3):e0229906. DOI:https: //doi.org/10.1371/journal.pone.0229906
4. Amjad A, Imran A, Shahram N, et al. Trends of caesarean section deliveries in Pakistan: secondary data analysis from Demographic and Health Surveys, 1990-2018. BMC Pregnancy Childbirth. 2020;20(1):753. DOI: https://doi.org/10.1186/s12884-020-03457-y
5. Akadri AA, Odelola OI. A Six Year Review of Caesarean Sections at Olabisi Onabanjo University Teaching Hospital Sagamu, South West Nigeria. Nigerian Medical Practitioner. 2017 Jun 5;71(3-4):53-7.
6. Betrán AP, Ye J, Moller A-B, Zhang J, Gülmezoglu AM, Torloni MR. The increasing Trend in caesarean section rates: Global, Regional and National estimates: 1990–2014. PLoS ONE. 2016;11(2):e0148343. https://doi.org/10.1371/journal.pone.0148343.
7. Vogel JP, Betrán AP, Vindevoghel N, Souza JP, Torloni MR, Zhang J, et al. Use of the Robson classification to assess caesarean section trends in 21 countries: a secondary analysis of two WHO multi-country surveys. Lancet Glob Health. 2015;3:e260–70. https://doi.org/10.1016/S2214-109X(15)70094-X.
8. Villar J, Carroli G, Zavaleta N, et al. Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. BMJ. 2007 Nov 17;335(7628) :1025DOI: 10.1136/bmj.39363.706956.55
9. Souza JP, Gülmezoglu A, Lumbiganon P, et al. Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health. BMC Med. 2010;8:71 DOI: https://doi.org/10.1186/1741-7015-8-71
10. World Health Organization. WHO statement on caesarean section rates. 2015. Accessed 20 September 2023. DOI:http://apps.who.int/iris/bitstream/10665/161442/1/WHO_RHR_15.02_eng.pdf?ua=1
11. Robson MS. Classification of caesarean sections. Fetal Matern Med Rev. 2001; 12: 23–39. DOI: https://doi.org/10.1017/S0965539501000122
12. Shinwari L, Bukhari B, Irfan S, Faisal R. Comparison of the rate and indications of caesarean section in primigravida and multigravida in a maternity hospital of Pakistan. q. The Professional Medical Journal. 2024; 31(07): 1100-5. doi: 10.29309/TPMJ/2024.3 1.07.7653.
13. Roberge S, Dubé E, Blouin S, Chaillet N. Reporting Caesarean Delivery in Quebec Using the Robson Classification System. J Obstet Gynaecol Can. 2017;39(3):152-156. DOI: https://doi.org/10.1016/j.jogc.2016.10.010
14. Robson M, Murphy M, Byrne F. Quality assurance: The 10-Group Classification System (Robson classification), induction of labor, and cesarean delivery. Int J Gynaecol Obstet. 2015 Oct;131 Suppl 1:S23-7. DOI:https://doi.org/10.1016/ j.ijgo. 2015.04.026 2
15. Tahir N, Adil, M, Fatima S, Khan S. Caesarian sections: frequency and indications at peripheral tertiary care hospital: Caesarian Sections: Frequency And Indications. Pak Armed Forces Med J [Internet]. 2018 Apr. 30 [cited 2024 Aug. 21];68(2):273-79. Available from: https://pafmj.org/PAFMJ/article/view/493
16. Ansari A, Baqai S, Imran R. An Audit of Caesarean Section Rate Using Modified Robson Criteria at a Tertiary Care Hospital. J Coll Physicians Surg Pak. 2019;29(8):768-770.DOI: https://doi.org/10.29271/jcpsp.2019.08.768
17. Fatima SS, Zeb L, Shafqat T, Qazi Q. Analysis of caesarean section rate according to robson classification criteria: a cross sectional study in a tertiary care hospital. American Journal of Health, Medicine and Nursing Practice. 2022;7(5):18-27. DOI: https://doi.org/10.47672/ajhmn.1009
18. Tontus HO, Nebioglu S. Improving the Caesarean Decision by Robson Classification: A Population-Based Study by 5,323,500 Livebirth Data. Ann Glob Health. 2020;86(1):10. DOI: https://doi.org/10.5334/aogh.2615

19. Gilani S, Mazhar SB, Zafar M, Mazhar T. The modified Robson criteria for Caesarean Section audit at Mother and Child Health Center Pakistan Institute of Medical Sciences Islamabad. J Pak Med Assoc. 2020;70(2):299-303. DOI: 10.5455/JPMA.293708

20. Abdo AA, Hinderaker SG, Tekle AG, et alCaesarean section rates analysed using Robsonâ€™s 10-Group Classification System: a cross-sectional study at a tertiary hospital in EthiopiaBMJ Open 2020;10:e039098. doi:10.1136/bmjopen-2020-039098

21. Khan A, Hanif K, Uzma Q, Thome E, Ezra Reza T, et al. (2023) Analysis of C-section Rates Using Robson's Ten Group Classification System (RTGCS) in Pakistan: A Review. ARCH Women Health Care Volume 6(3): 1–7. DOI: 10.31038/AWHC .2023634

22. Robson M, Hartigan L, Murphy M. Methods of achieving and maintaining an appropriate caesarean section rate. Best Pract Res Clin Obstet Gynaecol. 2013;27(2):297-308. DOI: https://doi.org/10.1016/j.bpobgyn.2012.09.004

23. O'Riordan N, Robson M, McAuliffe FM. Management of poor progress in labour. Obstetrics, Gynaecology & Reproductive Medicine. 2021;31(12):342-50. https://doi.org/10.1016/j.ogrm.2021.10.003

24. Chinnock M, Robson S. Obstetric trainees' experience in vaginal breech delivery: implications for future practice. Obstet Gynecol. 2007 Oct;110(4):900-3 DOI: 10.1097/01.AOG.0000267199.32847.c4

25. Melo P, Georgiou EX, Hedditch A, Ellaway P, Impey L. External cephalic version at term: a cohort study of 18 years' experience. BJOG: An International Journal of Obstetrics & Gynaecology. 2019;126(4):493-9. https://doi.org/10. 1111/1471-0528.15475

Original Article **Open Access**

Mason Radial Head Fractures: Surgical Management

Nisar Ahmed, Syed Muhammad Mohtashim Ali, Malik Muhammad Hamdan Tafheem

ABSTRACT:

Objective: To evaluate the efficacy of radial head replacement in Mason Type III and IV radial head fracture. To evaluate the clinical outcomes of patients who received radial head replacement implant.

Study design & setting: This is a cross-sectional, analytical study, conducted in the Orthopedic Department of Doctor's Hospital Kharian.

Methodology: Study was conducted from 15th April 2023 to 15th February 2024, Stability was assessed, radial head replacement was performed, and bone fragments were extracted during surgery. Radiographic evaluations were carried out to confirm the diagnosis at presentation, to determine the surgical outcome post-procedure, and during follow-up. SPSS-22 was used for data entry and statistical analysis, Cross-tabulation and chi-square test was performed, P-value of < 0.05 was considered significant.

Results: The research comprised 70 patients, whose average age was 38.5 ± 9.4 years. Upon presentation, their mean hemoglobin level was 12.1 ± 1.5 mg/d. The mean time of the operation was recorded as 68.5 ± 18.9 minutes, with a minimum of 45 minutes and a maximum of 100 minutes. The frequency of the Mayo elbow performance score was determined using pre-validated categories: >90 for outstanding performance, 89–75 for good performance, 74–60 for fair performance, and <60 for bad performance, the study participants were divided into 38 (54.2%), 18 (25.7%), 10 (14.2%), and 4 (5.7%) groups, respectively.

Conclusion: Redo surgery and rate of infection are greater in patients who underwent surgery after 24 hours of injury as compared to patients who were operated within 24 hours.

Keywords: Implant of radial head, Mason III, Mason IV, Orthopedic surgery, Radial Head fracture

How to cite this Article:
Ahmed N, Ali SMM, Tafheem MMH. Mason Radial Head Fractures: Surgical Management. J Bahria Uni Med Dental Coll. 2025;15(1):29-33 DOI: https://doi.org/10.51985/JBUMDC2024411

INTRODUCTION:

Radial head fractures constitute 4% of all reported fractures while a whopping 33% of elbow fractures are reported worldwide.[1] They most commonly present with pain of the affected side, elbow swelling, mild restriction of mobility, tenderness, and stiffness. This benign-looking presentation is deceptive to the surgeon who can render this fracture as a simple or uncomplicated elbow fracture, leading to inadequate management and/or joint dysfunction.[2] Elbow dislocation is associated with 10% of radial head fractures and makes it more challenging to deal with,[3] and is also a poor prognostic factor in terms of patient outcome.

In 1954, Mason established a predictive tool for the classification of radial head fractures that has been used as a gold standard for many years.[4] In 1962, Johnston rephrased four forms of radial head fractures,[5] namely, Type I - <2mm displacement, Type II ->2 mm displacement, Type III – Comminuted, and Type IV -Associated proximal radial dislocation, and now the classification is also known as Mason-Johnston Classification.

Mason Types I and II are likely to be dealt with conservative management or ORIF (screws) respectively.[6] Type II with bigger displacement may require radial head replacement, while types III and IV are complex and more challenging to deal with owing to the communited fragments causing collateral soft tissue damage and ligamentous loss that sways the limb toward instability. Literature states proximal migration of radius and longitudinal instability, decline grip strength, and ulnar neuropathy. The management of these two types is a thought for debate and causes a battle between two schools of thought, one favoring ORIF while others

Nisar Ahmed *(Corresponding Author)*
Associate Professor, Department of Orthopedics
CMH Kharian Medical College
Email: nisarr2005@yahoo.com

Syed Muhammad Mohtashim Ali
Registrar, Department of Orthopedics
Childre's Health Ireland
Ireland
Email: smmohtashimali@gmail.com

Malik Muhammad Hamdan Tafheem
Resident, Department of Orthopedics
Ghurki Trust Teaching Hospital, Lahore
Email: hamdantafheem007@gmail.com

Received: 10-07-2024
Accepted: 13-12-2024
1st Revision: 24-08-2024

incline toward reconstruction of the native radial head. Both these procedures pose a risk of complications postoperatively in terms of limb deformity.[7] The primary aim is to preserve the integrity of the Medial Collateral Ligament (MCL) as it is the prime contributor to joint stability.

In surgically difficult radial head fractures, radial head replacement serves as an option for acute management. Different prostheses have been developed to perform this surgery, which is diverse in geometry, design, and options for fixation. Loosening of this radial head can cause paresthesia, pain, stiffness, or expansion of the radial neck. [8] The radial head is an important adjunct for the provision of the valgus.

Auxiliary arthroplasty can provide further stability in case of radial head fractures associated with other lacerations. Non-union, osteoarthritis, and other situations also warrant the need for an auxiliary prosthesis. Prosthesis failure and rejection are documented in numerous literature, but the cause of failure and prognosis of redo surgery are not identified to date.[9] The incidence of radial head fractures is highest in the younger population with a mean age of 43 at the time of injury which is heavily dependent on the mobility of the elbow. The rate of redo surgery has been documented up to 15% at 2 years. Lack of evidence limits our understanding regarding common causes of adjustment following radial head fractures and relevant management options. When radial head fractures are the result of high-energy traumatic processes, they may be linked to other injuries that are clinically significant. When assessing radial head fractures, ligament disruption and related elbow fractures—particularly coronoid fractures—must be taken into account. The degree of soft tissue damage, related fractures, and bone involvement all play a role in determining how best to treat these complicated injuries.[10]

Our study aims to evaluate the efficacy of radial head replacement in Mason Type III and IV radial head fracture, clinical outcomes of patients who received this implant, by MAYO scoring scale, causes of failure and need and type of redo surgery at tertiary care hospital of Pakistan.

METHODOLOGY:

This is a cross-sectional, analytical study, conducted in the orthopedic department of the Doctor's Hospital Kharian, data was collected after getting prior approval from the Institutional Review Board (IRB# 09-24). Data collection was started from 15th April 2023 till 15th February 2024, Radial head fractures were classified as per the Mason classification system modified by Johnston, and only Mason type III and IV fractures were included. Informed consent in the language of understanding was obtained before enrollment.

Upon radiological assessment, patients with minimally displaced fractures (Mason type I) and >2mm fractures (Mason type II) were excluded from the study. Only severely comminuted fractures (Mason Type III and IV) were included along with associated injuries.

Sample size was calculated with the help of another published study conducted on Pakistani population, reporting results of 105 patients from tertiary care hospital, Hayatabad, Peshawar. The population quantity was kept same (n=105) in WHO sample size calculator, keeping confidence level of 95%, margin of error as 5%. the estimated minimum smaple size was 70.

Demographic details, site of the fracture, and presence of any additional injury. Pre-operative hemoglobin, date of surgery, duration of surgery, and intra-operative complications, post-operative pain VAS score, complications, hospital stay, reported success or failure of surgery and, post-operative hemoglobin levels were documented.

The main useful score for assessing elbow function, including elbow stiffness, is the Mayo Elbow Performance Index (MEPI). For patients, the most frequent challenge is a variety of movements (ROM, flexion-extension). Numerous research has supported the Mayo score, which is among the best for identifying the physiological activities of the elbow.[12] This score falls under one of the four main categories of elbow performance: function, motion, stability, and pain. The distribution of points is dependent on the degree of pain, motion in the arc degree, stability points, and day-to-day functioning. For instance, the pain function has 45 points, the motion function has 20, the stability function has 10, and the function has 25 points for flawless performance.

After finishing, the total number of points represents elbow performance. The outcomes are divided into four categories: Achieving a score of >90 indicates excellent performance, 89-75 indicates good performance, 74-60 indicates acceptable performance, and <60 indicates bad performance overall.

For this process, the Kochers technique was employed. Stability was assessed, radial head replacement was performed, and bone fragments were extracted during surgery. Soft tissue was rebuilt or healed as needed, and the incision was bandaged in layers. An aggressive rehabilitation regimen was undertaken when the patient was pain-free or under excellent analgesia.

Patients were asked to attend a medical facility every 30 days for four months after being released from the hospital. Patients were questioned about their generalized daily activities, issues they were having with the afflicted arm, any discomfort they were experiencing, and any other clinical signs they had noticed. Re-do the procedure if the first attempt failed.

Radiographic evaluations were carried out to confirm the diagnosis at presentation, to determine the surgical outcome post-procedure, and during follow-up. X-rays were employed as a radiological method. Statistical package of social science version 22 was used for data entry and statistical analysis,

for independent variables frequencies and percentages were analyzed. Mean ± standard deviation was used to report descriptive data such as age, hemoglobin values, hospital stay in days, and duration of surgery in minutes. Cross-tabulation was performed to assess the correlation between the two variables, chi-square test was performed to check the significance of the data. The P-value of < 0.05 was considered significant.

RESULTS:

The research comprised 70 patients, whose average age was 38.5 ± 9.4 years. Upon presentation, their mean hemoglobin level was 12.1 ± 1.5 mg/d. The mean time of the operation was recorded as 68.5 ± 18.9 minutes, with a minimum of 45 minutes and a maximum of 100 minutes. A hospital stay of 2.7 ± 1.3 days was average. The post-operative hemoglobin (HB) value was 10.4 ± 1.3, and the mean hemoglobin decline was 1.2 ± 0.8. After calculating the mean time between injury-related presentations and surgical procedures, the result showed 2.1 ± 1.0 days, with a minimum of 1 day and a high of 4 days between breaches. To evaluate the impact of treatment, the time interval between the diagnosis and radial head replacement was analyzed. The results showed that 59 (84.2%) had surgery within 2 days of presentation, 7 (10%) had to wait 3 days before surgery, and only 4 (5.7%) had to wait 4 days, redo surgery was needed in 7 (10%) patients with delayed presentation. The p-value was reported as significant and 0.004. (Table 1)

The frequency of the Mayo elbow performance score was determined using pre-validated categories: >90 for outstanding performance, 89–75 for good performance, 74–60 for fair performance, and <60 for bad performance. Within the aforementioned categories, the study participants were divided into 38 (54.2%), 18 (25.7%), 10 (14.2%), and 4 (5.7%) groups, respectively.

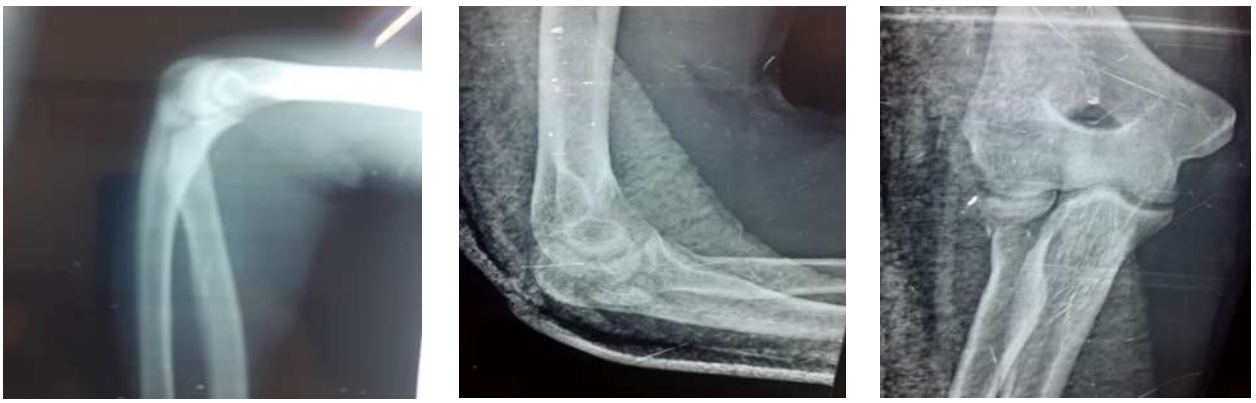
DISCUSSION:

Management of radial head fractures has advanced in the past decade. A rise in reported cases and late diagnosis are extra challenges of radial head fracture. As most of the time the RHF is supplemented with collateral elbow injuries, restoration of mobility, strength, and function of the arm is a prime priority. Mason type I fracture comprises minimally displaced fractures of less than 2 mm of displacement and no mechanical block to forearm rotation and can be managed conservatively. Mason II poses some mechanical block to forearm rotation with intra-articular displacement > 2 mm and needs Open Reduction and Internal Fixation (ORIF) for optimum results, but with displacement > 3 fragments and marked communication, radial head replacement provides the ideal management option. Mason III and IV are surgically managed by Radial Head Replacement, with the main target to achieve practical elbow mobility along with stability with minimal complications, and since these targets cannot be achieved by ORIF alone, radial head replacement becomes

Table 1: Association of time from injury to surgery with the success of procedure

Variables		Surgery after 1 day	Surgery after 2 days	Surgery after 3 days	Surgery after 4 days
Redo Procedure	**Yes**	0	0	3 (4.2%)	4 (5.7%)
Pain VAS Score	**Mild**	6 (8.5%)	5 (7.1%)	1 (1.4%)	0
	Moderate	5 (7.1%)	4 (5.7%)	5 (7.1%)	10 (14.2%)
	Severe	2 (2.8%)	1 (1.4%)	11 (15.7%)	20 (28.5%)
Complications	**Infection**	0	0	5 (7.1%)	8 (11.4%)
Hospital Stay (Days)	**2 days**	34 (48.5%)	22 (31.4%)	3 (4.2%)	0
	3 days	0	2 (2.8%)	2 (2.8%)	3 (4.2%)
	4 days	0	1 (1.4%)	1 (1.4%)	2 (2.8%)

Figure 1: Radiological presentation of pre-operative and post-operative elbow adjustment



the ideal choice. Press-fit of anatomical reimplants showed complications in literature thereby supporting the use of metallic or amooth implants. Bipolar implants have longer-lasting results.[17,18]

The goal of our study is to evaluate the efficacy of radial head replacement after MASON type IV radial head fracture. The allotment of study participants in our study was similar to most of the studies conducted to evaluate the efficacy of radial head replacement, although a few studies had smaller sample sizes, our study had a larger number of included patients as no loss to follow-up was reported. [19,20 The] Age of study participants was reportedly lower than in another study where the maximum age was 74 years,[21] the age plays a significant role in healing mechanism and pain tolerance and threshold of patients. Our study participants were comparatively younger as it has been recognized that RHF has a higher incidence in younger populations due to traumatic etiology. Our results showed a lower pain VAS score in the post-operative period, with good to excellent MAYO elbow performance score. the outcomes from the published case series indicate that radial head replacement yielded favorable results. Only four patients exhibited poor performance, while the majority reported excellent self-reported outcomes. This suggests that radial head replacement could be an effective treatment option for radial head fractures. Such findings underscore the potential benefits of this procedure in clinical practice.[22] Lower Pain VAS score has been reported in many retrospective analyses of radial head replacement studies, Mayo elbow performance scores have been used for quantification and results showed good results post-operatively. [23] Reported complications such as post-operative pain, reduced strength, stiffness, post-traumatic arthritis, unsteadiness, valgus, and rotation issues like the functional range of movement of the elbow are from 301 to 1301 degree flexion.[24] The importance of time of presentation and its relation with the outcome of surgery has been proved as crucial in other studies too, our study participants had only 4 patients with a waiting time of 48 hours that showed poor elbow performance scores and led to surgical failure.[25] Success rates of radial head replacement outcomes after recent injury range from 60%-80%, while our study indicated 26/30 (86.7%) success after radial head fractures, similar to other published studies indicating > 85% success rate overall.[26-27] The need for revision or redo surgery, classified with Mason type of fracture indicated that in Mason type I and type II injuries, the chief reasons for revision are stiffness and symptomatic osteoarthritis. Mason type III specifically displayed nonunion, deranged reduction, or necrosis. In Mason type IV fractures also known as fracture-dislocations, numerous complications were described including instability and stiffness further leading to revision.[28] Other complications such as aseptic loosening, Elbow instability, and osteoarthritis were not reported in our study participants.

Another study highlights that the need for radial head arthroplasty is indicated when open reduction and internal fixation are surgically not possible for comminuted radial head fractures, and it offers grander outcomes when compared to radial head excision. Arthroplasty shows superiority in elbow stability, improved range of motion, postoperative pain, and fewer complications. However, radial head resection might still be amenable for isolated fractures without any collateral ligament damage or in elderly patients with lower functional needs. This outlines the significance of bearing in mind patient-related factors in determining the optimal treatment approach.[29]

However, another contrasting study undermines the role of radial head prosthesis in Mason IV fracture-dislocation, done by Nestorson J et al. They retrospectively reviewed and compared two surgical options on a smaller sample size of patients: radial head excision and radial head arthroplasty, both combined with lateral ligament repair. 18 patients underwent arthroplasty while 14 patients underwent resection. After a follow-up of at least 2 years, functional outcomes showed no noteworthy differences between the groups in terms of functional scores, range of motion, or patient-reported outcomes. However, the arthroplasty group had a higher rate of auxiliary surgeries while the group with radial head resection displayed more marked ulno-humeral osteoarthritis. Overall, functional outcomes were consistent with previous findings for similar injuries. Secondary osteoarthritis after radial head resection did not influence functional outcomes.[30]

The limitation of our study is the small sample size and short follow-up duration. A multicenter study with a larger sample size from all age groups and a longer follow-up time is vital to remove all confusing factors related to study results. A larger randomized control trial will help determine the accuracy of different techniques and procedures of radial head fracture as well. Degenerative arthritis was not assessed as follow-up was only limited.

CONCLUSION:

In our study, the results specified that the likelihood of revision surgery and rate of infection is greater in patients who underwent surgery after 24 hours of injury as compared to patients who were operated on within 24 hours. The success rates are comparable with many available studies, Mayo elbow performance score results were decent and elbow stability and motion were restored in almost all patients after surgery.

Authors Contribution:
Nisar Ahmed: Objective, data Collection
Syed Muhammad Mohtashim Ali: Data analysis, Interpretation
Malik Muhammad Hamdan Tafheem: Manuscript write-up

REFERENCES:

1. Gruszka D, Nowak TE, Tkacz T, Wagner D, Rommens PM. Complex radial head and neck fractures treated with modern locking plate fixation. Journal of shoulder and elbow surgery. 2019;28(6):1130-8. doi.org/10.1016/j.jse.2018.11.056
2. Karimijashni M, Yoo S, Barnes K, Poitras S. Pre-and Post-Operative Rehabilitation Interventions in Patients at Risk of Poor Outcomes Following Knee or Hip Arthroplasty: Protocol for Two Systematic Reviews. Advances in Rehabilitation Science and Practice. 2023 doi.org/10.1177/27536351231170
3. Kovar FM, Jaindl M, Thalhammer G, Rupert S, Platzer P, Endler G, Vielgut I, Kutscha-Lissberg F. Incidence and analysis of radial head and neck fractures. World journal of orthopedics. 2013;4(2):80. doi: 10.5312/wjo.v4.i2.80
4. Burkhart KJ, Wegmann K, Müller LP, Gohlke FE. Fractures of the radial head. Hand clinics. 2015;31(4):533-46. DOI: 10.1016/j.hcl.2015.06.003
5. Grazette AJ, Aquilina A. Suppl-8, M5: The Assessment and Management of Simple Elbow Dislocations. The Open Orthopaedics Journal. 2017;11:1373. doi: 10.2174/1874325001711011373
6. Midtgaard KS, Ruzbarsky JJ, Hackett TR, Viola RW. Elbow fractures. Clinics in sports medicine. 2020;39(3):623-36. DOI: 10.1016/j.csm.2020.03.002
7. Hamoodi Z, Singh J, Elvey MH, Watts AC. Reliability and validity of the Wrightington classification of elbow fracture-dislocation. The Bone & Joint Journal. 2020;102(8):1041-7. doi.org/10.1302/0301-620X.102B8.BJJ.2020.0013.R1
8. Santos CC, García BE, González EM, Campoverde MP, Espinoza JM, Maldonado LX, Barba MC, Banegas ES. radial head fractures, epidemiology, anatomy, mechanism of injury, classification, imaging presentation, clinical presentation, management and complications. epra International Journal of Multidisciplinary Research (IJMR). 2023;9(5):125-32.
9. Hildebrand AH, Zhang B, Horner NS, King G, Khan M, Alolabi B. Indications and outcomes of radial head excision: a systematic review. Shoulder & elbow. 2020;12(3):193-202. doi.org/10.1177/17585732198643
10. van der Windt AE, Langenberg LC, Colaris JW, Eygendaal D. Which radial head fractures are best treated surgically?. EFORT Open Reviews. 2024;9(5):413-21. doi.org/10.1530/EOR-24-0035
11. Rahman N, Ahmad I, Anwar W, Khan JZ, Niaz QZ. Radiological outcome of distal radius fractures undergoing closed reduction and cast splint. KJMS. 2021;14(2):71. doi.org/10.70520/kjms.v14i2.76
12. Hackl M, Wegmann K, Hollinger B, El-Zayat BF, Seybold D, Gühring T, Schnetzke M, Schmidt-Horlohé K, Greiner S, Lill H, Ellwein A. Surgical revision of radial head fractures: a multicenter retrospective analysis of 466 cases. Journal of Shoulder and Elbow Surgery. 2019;28(8):1457-67. doi.org/10.1016/j.jse.2018.11.047
13. Le Mapihan M, Amsallem L, Ing D, Masméjean EH. Midterm outcomes of a short-cemented bipolar radial head arthroplasty, in a cohort of 56 cases with minimum 2-years follow-up. Orthopaedics & Traumatology: Surgery & Research. 2023:103716. doi.org/10.1016/j.otsr.2023.103716
14. Delclaux S, Lebon J, Faraud A, Toulemonde J, Bonnevialle N, Coulet B, Mansat P. Complications of radial head prostheses. International orthopaedics. 2015;39:907-13. doi.org/10.1007/s00264-015-2689-7
15. Van Riet RP, Van den Bekerom MP, Van Tongel A, Spross C, Barco R, Watts AC. Radial head fractures. Shoulder & elbow. 2020;12(3):212-23.
16. Klug A, Gramlich Y, Wincheringer D, Hoffmann R, Schmidt-Horlohé K. Epidemiology and treatment of radial head fractures: a database analysis of over 70,000 inpatient cases. The Journal of Hand Surgery. 2021;46(1):27-35. doi.org/10.1016/j.jhsa.2020.05.029
17. Sun H, Duan J, Li F. Comparison between radial head arthroplasty and open reduction and internal fixation in patients with radial head fractures (modified Mason type III and IV): a meta-analysis. European Journal of Orthopaedic Surgery & Traumatology. 2016;26:283-91. doi.org/10.1007/s00590-016-1739-1
18. Swensen SJ, Tyagi V, Uquillas C, Shakked RJ, Yoon RS, Liporace FA. Maximizing outcomes in the treatment of radial head fractures. Journal of Orthopaedics and Traumatology. 2019;20:1-9. doi.org/10.1186/s10195-019-0523-5
19. Nosenzo A, Galavotti C, Menozzi M, Garzia A, Pogliacomi F, Calderazzi F. Acute radial head replacement with bipolar prostheses: midterm results. European Journal of Orthopaedic Surgery & Traumatology. 2021;31(2):309-18.
20. Viveen J, Kodde IF, Heijink A, Koenraadt KL, van den Bekerom MP, Eygendaal D. Why does radial head arthroplasty fail today? A systematic review of recent literature. EFORT open reviews. 2019;4(12):659-67. doi.org/10.1302/2058-5241.4.180099
21. Sun H, Duan J, Li F. Comparison between radial head arthroplasty and open reduction and internal fixation in patients with radial head fractures (modified Mason type III and IV): a meta-analysis. European Journal of Orthopaedic Surgery & Traumatology. 2016;26:283-91. doi.org/10.1007/s00590-016-1739-1
22. Harrison JW, Chitre A, Lammin K, Warner JG, Hodgson SP. Radial head fractures in adults. Current Orthopaedics. 2007;21(1):59-64. doi.org/10.1016/j.cuor.2006.10.003
23. Somerson JS, Matsen III FA. Timely recognition of total elbow and radial head arthroplasty adverse events: an analysis of reports to the US Food and Drug Administration. Journal of shoulder and elbow surgery. 2019;28(3):510-9. doi.org/10.1016/j.jse.2018.08.043
24. Swensen SJ, Tyagi V, Uquillas C, Shakked RJ, Yoon RS, Liporace FA. Maximizing outcomes in the treatment of radial head fractures. Journal of Orthopaedics and Traumatology. 2019;20:1-9. doi.org/10.1186/s10195-019-0523-5
25. Levy JC, Formaini NT, Kurowicki J. Outcomes and radiographic findings of anatomic press-fit radial head arthroplasty. Journal of Shoulder and Elbow Surgery. 2016;25(5):802-9. doi.org/10.1016/j.jse.2015.11.014
26. Lott A, Broder K, Goch A, Konda SR, Egol KA. Results after radial head arthroplasty in unstable fractures. Journal of Shoulder and Elbow Surgery. 2018;27(2):270-5.
27. Catellani F, De Caro F, De Biase CF, Perrino VR, Usai L, Triolo V, Ziveri G, Fiorentino G. Radial head resection versus arthroplasty in unrepairable comminuted fractures Mason type III and type IV: a systematic review. BioMed research international. 2018 Jul 16;2018. doi.org/10.1155/2018/4020625
28. Nestorson J, Josefsson PO, Adolfsson L. A radial head prosthesis appears to be unnecessary in Mason-IV fracture dislocation. Acta Orthopaedica. 2017;88(3):315-9. doi.org/10.1080/17453674.2017.1293440

Original Article **Open Access**

Prevalence of Hypocalcemia in Infants of Mothers with Gestational Diabetes

Nida Sarwar, Khurram Fayyaz, Imrana Ata, Sehar Aslam, Hajra Begum, Khubaib Ahmed

ABSTRACT

Objective: To evaluate the prevalence of newborn hypocalcemia among infants of mothers with gestational diabetes.

Study Design & Setting: This cross-sectional study was conducted at PNS Shifa Hospital, Karachi, from November 2023 to March 2024

Methodology: Each mother's fasting blood sugar level was evaluated by drawing 5 ml of blood. At 24 hours after delivery, sterile blood samples (2 cc) were taken to determine the neonate's calcium level; a serum calcium level below 7 mg/dl was regarded as hypocalcemia. All information was gathered using a research template that was created in-house. Serum calcium was measured using the Arsenazo III method, and serum albumin was assessed using the bromocresol green (BCG) method.

Results: The mean ± S.D. of the maternal age of the study participants was 26.83 ± 3.87 years. The mean ± S.D. of the gestational age of the study participants was 37.35 ± 0.86 weeks. The mean ± S.D. of fasting glucose levels of the study participants was 104.5 ± 15.1 mg/dl. A total of 27.5% of infants born to mothers with gestational diabetes had hypocalcemia. Infants' median Apgar scores at 1 and 5 minutes were 6 and 9, respectively. The prevalence of hypocalcemia in newborns was highest among mothers aged 21–30, though this difference was not statistically significant (p = 0.139).

Conclusion: The results showed that 27.5% of infants born to mothers with gestational diabetes had hypocalcemia. Maternal age did not have a statistically significant association with hypocalcemia in newborns.

Keywords: Hypocalcemia, Infants, Gestational Diabetes, Maternal Hyperglycemia

How to cite this Article:
Sarwar N, Fayyaz K, Ata I, Aslam S, Begum H, Ahmed K. Prevalence of Hypocalcemia in Infants of Mothers with Gestational Diabetes. J Bahria Uni Med Dental Coll. 2025;15(1):34-39 DOI: https://doi.org/10.51985/JBUMDC2024419

INTRODUCTION:

Pregnancy-related mortality and morbidity have long been associated with diabetes in mothers.[1] The impact of maternal diabetes extends beyond pregnancy itself, influencing both prenatal and postnatal health outcomes for the infant. A significant concern in this context is the exposure of the developing fetus to maternal hyperglycemia, which is a critical factor contributing to a range of prenatal, natal, and postnatal complications. Insufficient metabolic control in the mother exacerbates these issues, leading to various disorders that can affect the child's development and health outcomes.[1,2,3]

The spectrum of complications arising from maternal diabetes is broad, and among these, metabolic and hematological complications are particularly concerning. Infants born to mothers with diabetes are at an increased risk of developing conditions such as hyperbilirubinemia and polycythemia.[4] These conditions can have serious consequences for the newborn, necessitating careful monitoring and management from birth. Moreover, infants with a familial history of hypomagnesemia are particularly vulnerable to developing hypocalcemia, a condition that is closely linked to birth asphyxia.[5]

Hypocalcemia, characterized by abnormally low levels of calcium in the blood, is a frequent issue in newborns, especially those born to diabetic mothers. Normal blood calcium levels naturally decline in the first 48 hours after birth in healthy term infants. Typically, this drop in calcium levels reaches its lowest point, or trough, between 7.5 to 8.5 mg/dl within the first two days of life.[5] However, in certain

Nida Sarwar
PG Trainee, Department of Pediatrics
PNS Shifa Hosital, Karachi
Email: nida106584@gmail.com

Khurram Fayyaz
Assistant Professor, Department of Paediatrics
PNS Shifa Hosital, Karachi
Email: Kfc113@hotmail.com

Imrana Ata
Consultant, Department of Pediatrics
PNS Shifa Hosital, Karachi
Email: Imranaata.dr@gmail.com

Sehar Aslam
PG Trainee, Department of Pediatrics
PNS Shifa Hosital, Karachi
Email: seharaslam126@gmail.com

Hajra Begum
PG Trainee, Department of Pediatrics
PNS Shifa Hosital, Karachi
Email: hajrakhan70@gmail.com

Khubaib Ahmad *(Corresponding Author)*
House Officer
PNS Shifa Hospital, Karachi
Email: khubaibahmadsiddiqui@gmail.com

Received: 31-07-2024
Accepted: 21-11-2024
1st Revision: 15-08-2024
2nd Revision: 12-11-2024

cases, this decline can lead to significant health concerns. The most severe form of hypocalcemia can cause symptoms such as seizures, which are particularly common in premature newborns, babies born to mothers with diabetes, and infants who have experienced perinatal asphyxia.[6]

The incidence of hypocalcemia in infants born to diabetic mothers varies widely, with studies reporting rates ranging from 4% to as high as 50%, and an average incidence of around 22.7%. This wide variation highlights the need for further research to understand the factors contributing to this condition better. Hypocalcemia in these infants can be attributed to several factors, including premature delivery, birth asphyxia, low maternal calcium intake, high maternal calcium excretion rates, low neonatal parathyroid hormone (PTH) production, inadequate calcium intake, and poor calcium absorption. Among these, hypomagnesemia in both the mother and the child, resulting from increased maternal urinary excretion of magnesium during pregnancy, has been identified as a prevalent cause.[7,8]

One of the mechanisms by which maternal diabetes influences neonatal calcium levels involves the transfer of maternal calcium to the fetus through the placenta. In cases where the mother has hyperparathyroidism, this increased maternal calcium can inhibit fetal PTH synthesis, leading to a decreased PTH response after birth, which in turn contributes to hypocalcemia.[7] Furthermore, hypomagnesemia in the newborn can induce functional hypoparathyroidism, further exacerbating the hypocalcemia.[8]

Hypocalcemia is a common metabolic disorder in infants and young children, and its management remains a topic of ongoing debate in the medical community. While there is general agreement on the need to treat symptomatic hypocalcemia promptly, the appropriate calcium levels at which to initiate treatment and the best approach to managing asymptomatic cases are still under discussion.[8] The symptoms of neonatal hypocalcemia and hypomagnesemia often resemble those of hypoglycemia and can include jitteriness, tachypnea, sweating, convulsions, and irritability.[9]

The increasing recognition of the long-term effects of maternal diabetes on offspring has led to a growing awareness among obstetricians and neonatologists of the need to understand these complications better. Gestational diabetes mellitus (GDM) has been linked not only to impaired glucose tolerance during pregnancy but also to a higher incidence of perinatal complications, including neonatal hypocalcemia.[10] Despite the acknowledgment of these associations, there is a critical gap in the medical literature concerning the precise prevalence and mechanisms underlying neonatal hypocalcemia in the context of maternal diabetes, particularly on a regional basis.

This study is motivated by the need to address this gap by providing a comprehensive analysis of the prevalence, causes, and potential implications of hypocalcemia in newborns of diabetic mothers. Understanding the scope and nature of this issue is essential for developing targeted interventions and clinical guidelines that can improve neonatal outcomes and reduce the burden of hypocalcemia in this vulnerable population. Consequently, this research aims not only to quantify the prevalence of neonatal hypocalcemia in the context of maternal hyperglycemia but also to explore the contributing factors and possible preventive measures that could mitigate this significant health challenge. By doing so, this study seeks to contribute valuable insights that could enhance clinical practices and ultimately improve the health and well-being of infants born to mothers with diabetes.[8]

METHODOLOGY:

After receiving ethical approval from the institutional review board, this cross-sectional study was conducted at PNS Shifa Hospital, Karachi (ERC/2023/PED/57) over a five-month period from November 2023 to March 2024. The primary aim of the study was to evaluate the prevalence of neonatal hypocalcemia in infants born to mothers with gestational diabetes. Given the importance of this research and the need for robust data, the sample size calculation was a crucial step in the study design. The sample size was determined using the OpenEpi calculator, which is widely used in epidemiological studies for accurate sample size estimations.

The calculation was based on an anticipated prevalence rate of neonatal hypocalcemia in infants born to mothers with gestational diabetes, derived from previous studies. With a confidence level of 95%, a margin of error of 5%, and the estimated prevalence rate, the minimum required sample size was determined to be 70 subjects. However, to enhance the reliability of the findings and considering the available resources and time frame, the sample size was increased to 80 subjects. This slight increase was deemed sufficient to ensure that the study would have adequate statistical power to detect significant differences or associations.

The study employed a non-probability consecutive sampling technique, selecting all eligible patients who met the inclusion criteria during the study period. The inclusion criteria were specifically designed to focus on mothers aged 18 years and older diagnosed with gestational diabetes who had undergone any mode of delivery. Patients under the age of 18 or those with additional complications, such as autoimmune diseases, hypertension, or multiple pregnancies, were excluded from the study. This careful selection process ensured that the sample was as homogeneous as possible, minimizing confounding variables and increasing the study's internal validity.

Upon delivery, detailed records were made of each infant's Apgar scores at 1 minute, 5 minutes, and, if necessary, at later intervals. These scores provided a quick assessment of the newborn's health and helped identify infants who required further medical attention. Simultaneously, each mother's

diabetes status and treatment compliance were documented to establish any correlations between maternal diabetes control and neonatal outcomes. Information regarding the mothers' HbA1c levels and fasting blood glucose was also recorded as part of the evaluation of maternal hyperglycemia.

Immediately after the umbilical cord was clamped and cut, 2 mL of blood was collected from the newborn in a sterile container for calcium and albumin analysis. This step was crucial in diagnosing hypocalcemia and understanding its prevalence in the study population. All newborns underwent a thorough examination for major congenital defects at birth, and those with significant anomalies were excluded from further analysis to avoid skewing the results.

The gestational age of each infant was carefully estimated using the mother's reported due date, with further verification using the New Ballard Scoring System within a two-week margin of error. Birth weights were measured using an electronic scale and recorded to the nearest 10 grams. These weights were then plotted on percentile charts according to gestational age to assess growth standards.

Infants requiring admission to the neonatal intensive care unit (NICU) based on specific criteria, such as a birth weight under 2000 grams, an Apgar score of less than 7 at 5 minutes, or signs of respiratory distress, were immediately transferred to the NICU. These infants were started on intravenous fluids with calcium supplementation at the standard rate of 4 ml/kg/day. Healthy infants, on the other hand, were placed with their mothers and breastfed on demand, supporting natural feeding practices and promoting maternal-infant bonding.

During the first two to four days of life, each newborn's length was measured using an infant meter and compared to percentile charts for gestational age. At 48 hours of life, another 2 mL blood sample was collected from each newborn in a sterile container for repeat calcium and albumin testing. This allowed for the monitoring of changes in serum calcium levels and the early detection of hypocalcemia. Serum calcium was measured using the Arsenazo III method, known for its precision, and serum albumin was assessed using the bromocresol green (BCG) method, which is a standard procedure in clinical chemistry.

All data collected were meticulously entered into a custom-designed research template to ensure consistency and accuracy. Statistical analysis was performed using SPSS version 26, enabling a comprehensive examination of the data to identify significant trends and associations related to neonatal hypocalcemia in infants born to mothers with gestational diabetes. This methodological rigor ensured that the study's findings would be both reliable and valuable for guiding future research and clinical practice.

RESULTS

A total of 80 pregnant women who fulfilled the inclusion criteria were included in the present study. Table 1 shows the clinical and demographic parameters of the study participants. Mean±S. D of the maternal age of the study participants was 26.83±3.87 years. Mean±S. D of the gestational age of the study participants was 37.35±0.86 weeks. Mean±S. D of fasting glucose level of the study participants was 104.5±15.1 mg/dl. 73.7% of the participants in the present study had Primiparous parity and majority of the participant's mode of delivery was normal vaginal delivery (66.3%). 27.5% infants had hypocalcemia to all the diabetic mothers enrolled in the study (Figure 1). Infants' median Apgar scores at 1 and 5 minutes were 6 and 9, respectively (Figure 2). The prevalence of hypocalcemia in newborns was highest among mothers aged 21–30, although this difference was not statistically significant (p=01.39). The prevalence of hypocalcemia in newborns was highest among gestational age 37-39, although this difference was not statistically significant (p=0.991) (Table 2).

DISCUSSION:

Gestational diabetes mellitus (GDM) is a form of glucose intolerance that occurs during pregnancy, posing significant risks to both mother and infant. The impact of GDM on neonatal outcomes has been a topic of growing concern, particularly as the global prevalence of diabetes continues to rise. This study aimed to evaluate the prevalence of newborn hypocalcemia among 80 diabetic mothers, with

Table 1: Cinical and demographic parameters of the study participants

Parameters		Statistics
Mother age		26.83±3.87
Gestational Age		37.35±0.86
Fasting glucose		104.5±15.1
Parity	Primiparous	59 (73.7%)
	Multiparous	21 (26.3%)
Mode of delivery	Normal	53 (66.3%)
	C-section	27 (33.7%)
Infant gender	Male	35 (43.7%)
	Female	45 (56.3%)

Figure 1: Frequency of Hypcalecemia in infants born to diabetic mother

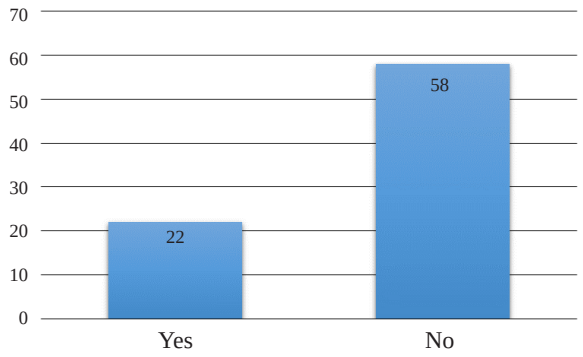


Figure 2: Apgar score of the newborns

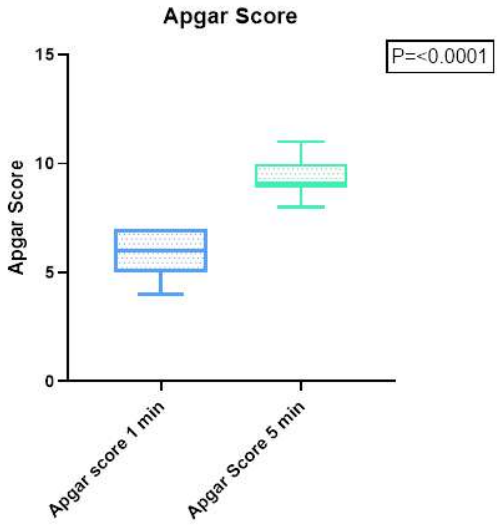


Table 2: Neonatal hypocalcemia as per maternal age and

Parameters		Hypocalcemia		P Value
		Yes	No	
Maternal age	<20	2	1	1.39
	21-30	13	51	
	<30	7	6	
Gestational Age	<36 weeks	4	9	0.991
	37-39 weeks	14	43	
	>40 weeks	4	6	

the goal of shedding light on the potential risks associated with maternal diabetes and informing clinical practices aimed at mitigating these risks.

The mothers in this study had an average gestational age of 37.35±0.86 weeks and were on average 26.83±3.87 years old. These demographic characteristics are consistent with those reported in similar studies, though there are some variations. For instance, previous studies have reported an average gestational age of 37.58±1.35 weeks, with 81.25% of births occurring between 37 and 39 weeks.[11] The slight difference in gestational age between studies could be attributed to differences in study populations, healthcare practices, and the criteria used to diagnose and manage GDM.

The age of the mothers in this study was slightly younger on average compared to some other studies. For example, one study found the average age of women with diabetes in the untreated IGT group to be 32.5±5.0 years, which is higher than the average age in the present study.[12] This discrepancy might be due to differences in the populations being studied or variations in the age distribution of diabetic pregnancies in different regions. Additionally, other studies have found that the majority of diabetic mothers were between 31 and 35 years of age.[13] These variations in maternal age could potentially influence the outcomes of pregnancies complicated by diabetes, as age is a known risk factor for both GDM and adverse neonatal outcomes.

The mode of delivery and neonatal outcomes also showed variation across studies. In this study, 26.3% of mothers had multiple pregnancies, 33.7% of births involved cesarean sections, and 56.3% of the neonates were female. These findings are somewhat consistent with other research, though differences in cesarean section rates and gender distribution are noted. For instance, one study found that 52.5% of infants born to diabetic mothers were male, while another study reported a gender distribution of 64% male and 36% female.[11,14] These differences could be attributed to variations in population demographics, the criteria used for diagnosing GDM, and the management practices during pregnancy, which differ across different healthcare settings.[14]

The variation in cesarean section rates is particularly interesting, as the decision for cesarean delivery in diabetic pregnancies can be influenced by several factors, including fetal macrosomia, poor glycemic control, and the presence of obstetric complications. The higher rate of cesarean sections in some studies may reflect more aggressive management strategies aimed at preventing complications associated with difficult vaginal deliveries in diabetic women. However, cesarean sections themselves carry risks for both mother and infant, including the potential for respiratory distress in the newborn, which underscores the need for careful decision-making in these cases.[14,15]

In terms of hypocalcemia, 27.5% of the infants in this study were affected, a prevalence that aligns with some previous studies.[15] However, other research reported lower incidences, while still others have shown higher frequencies of neonatal hypocalcemia, especially among infants of mothers with pregestational diabetes.[16,17] The relatively high prevalence observed in this study highlights the potential vulnerability of infants born to diabetic mothers to calcium metabolism disorders. This finding is particularly concerning given the critical role of calcium in various physiological processes, including neuromuscular function and bone development.[17]

The inconsistencies in the reported prevalence of neonatal hypocalcemia across studies could be due to several factors, including differences in sample sizes, study designs, or selection criteria. Additionally, variations in the management of GDM, such as differences in glucose control strategies and the timing of delivery, might also contribute to these discrepancies. For instance, stricter glycemic control during pregnancy might reduce the risk of neonatal hypocalcemia, whereas poorly controlled diabetes could exacerbate the condition. Some studies suggest that maternal and fetal hypomagnesemia contribute to transient neonatal hypocalcemia, particularly in infants born to women with pregestational, insulin-dependent diabetes.[16,17] This link

between hypomagnesemia and hypocalcemia is supported by the fact that magnesium plays a crucial role in the regulation of parathyroid hormone (PTH) secretion, which in turn regulates calcium homeostasis.

The severity of maternal diabetes has been linked to the degree of neonatal hypocalcemia, with a noted inverse relationship between neonatal calcium levels and maternal HbA1c concentrations.[18] This suggests that poor glycemic control during pregnancy may exacerbate the risk of hypocalcemia in newborns. Elevated HbA1c levels in mothers indicate chronic hyperglycemia, which could lead to various metabolic disturbances in the fetus, including impaired calcium metabolism.[19] Furthermore, maternal hyperglycemia can lead to fetal hyperinsulinemia, which has been associated with decreased calcium levels in the neonate.[20]

This study's findings emphasize the need for heightened clinical awareness and proactive management strategies to address the risk of hypocalcemia in infants born to mothers with GDM. The identification of risk factors such as maternal hypomagnesemia and poor glycemic control could allow for targeted interventions, such as magnesium supplementation or more rigorous monitoring of blood glucose levels during pregnancy. Additionally, early identification and treatment of hypocalcemia in newborns could prevent complications such as seizures, cardiac arrhythmias, and long-term developmental issues.

The strengths of this study include its focused examination of the prevalence of newborn hypocalcemia in diabetic mothers, providing crucial insights into a relatively underexplored area of neonatal health. The comparison with other studies and the use of a well-defined diabetic mother cohort add value to the findings. However, limitations exist, such as the relatively small sample size and the study's cross-sectional design, which may limit the generalizability of the results. The cross-sectional nature of the study precludes any conclusions about the long-term outcomes of hypocalcemia in these infants. Additionally, the study did not account for the potential influence of other factors, such as maternal nutritional status or genetic predispositions, which could also affect calcium levels in the newborn. These limitations underscore the need for further research in this area.

The scope for future research is vast. Future studies could expand on this work by including larger and more diverse populations to enhance the generalizability of the findings. Longitudinal studies could provide more definitive information on the progression of hypocalcemia in newborns of diabetic mothers and its long-term effects. For example, tracking these infants over time could help determine whether early hypocalcemia leads to developmental delays or other health issues later in life. Additionally, exploring the impact of various factors, such as different types and severities of maternal diabetes, dietary influences, and genetic predispositions, could provide deeper insights into the mechanisms behind neonatal hypocalcemia.

Further research could also explore the effectiveness of different prevention and treatment strategies. For instance, studies could examine whether early calcium supplementation or tighter glycemic control during pregnancy can reduce the incidence of neonatal hypocalcemia. Additionally, the role of magnesium supplementation in preventing hypocalcemia in infants of diabetic mothers warrants further investigation, given the potential link between maternal hypomagnesemia and neonatal hypocalcemia.

In conclusion, while this study provides important insights into the prevalence of hypocalcemia among newborns of diabetic mothers, it also highlights the complexity of this condition and the need for further research to fully understand its causes and consequences. Addressing this knowledge gap is crucial for developing effective interventions that can improve the health and well-being of infants born to mothers with diabetes. The findings underscore the importance of comprehensive prenatal care that includes close monitoring and management of maternal diabetes to prevent adverse neonatal outcomes, including hypocalcemia.

CONCLUSION:

In conclusion, this study indicates that a significant proportion, 27.5%, of infants born to diabetic mothers are affected by hypocalcemia, highlighting a clear association with maternal diabetes. While the study offers valuable insights, it underscores the necessity for broader research to fully understand and address this health issue. Future investigations should aim for larger sample sizes and a wider range of demographic settings to validate these findings and explore comprehensive preventive and treatment strategies for hypocalcemia in newborns of diabetic mothers.

Authors Contribution:
Nida Sarwar: Conception of Study, Data Collection, Drafting
Khurram Fayyaz: Design of Study Supervision of work
Imrana Ata: Data Collection, Drafting, Analysis of results
Sehar Aslam: Data Collection. Drafting
Hajra Begum: Data Collection, Drafting
Khubaib Ahmed: Data Collection, Drafting

REFERENCES:

1. Sabzehei MK, Otogara M, Ahmadi S, Daneshvar F, Shabani M, Samavati S, et al. Prevalence of hypoglycemia and hypocalcemia among high-risk infants in the neonatal ward of Fatemieh Hospital of Hamadan in 2016-2017. Hormozgan Med J. 2020;24(1).DOI: 10.5812/hmj.94453.
2. Awan NN, Abbas S, Naz M, Jameel M, Iftikhar S. Frequency of Hypocalcemia in Infants of Diabetic Mothers within 24 Hours of Life. Pak J Med Health Sci. 2023;17(02):586. DOI: 10.53350/pjmhs2023172586.
3. Shah SB, Bawar S, Farooq N. Common Complications in Infants Born to Diabetic Mothers: Complications in Infants Born to Diabetic Mothers. Pak J Health Sci. 2024:84-9. DOI: 10.54393/pjhs.v5i1.973.

4. Islam MM, Ahmmad BN, Karim MR, Islam MR, Uddin MB, Hoque MS. Glucose and Calcium Profile in Infants of Diabetic and Nondiabetic Mothers-A Comparative Study. TAJ: Journal of Teachers Association. 2022;35(2):93-102. DOI: 10.3329/taj.v35i2.58600.
5. Kavitha R, Vanitha R. A Study of Incidence of Hypoglycaemia and Hypocalcaemia in Infants Born to Diabetic Mothers and a Correlation with Maternal Third Trimester Glycaemic Control. J Clin Diagn Res. 2020;14(3). DOI: 10.7860/JCDR /2020/42574.13589.
6. Suda-Ca³us M, D¹browska K, Gulczyñska E. Infant of a diabetic mother: clinical presentation, diagnosis and treatment. Pediatr Endocrinol Diabetes Metab. 2024;30(1):36-41. DOI: 10.5114/pedm.2024.127360.
7. Raghuveer G, BhanuPrakash BP, Reddy GC, Mahati M. Morbidity Profile of Neonates Born to Diabetic Mothers in a Rural Tertiary Care Hospital. Int J Acad Med Pharm. 2023;5(3):465-72. DOI: 10.46939/ijamp.v5i3.130.
8. Vuralli D. Clinical approach to hypocalcemia in newborn period and infancy: who should be treated? Int J Pediatr. 2019;2019. DOI: 10.1155/2019/4318075.
9. Patra D, Jena PK, Murmu MC, Swain B, Bhat S. Outcome of Infants Born to Diabetic Mother in a Tertiary Care Hospital. DOI: (DOI not available).
10. Stewart A, Malhotra A. Gestational diabetes and the neonate: challenges and solutions. Res Rep Neonatol. 2015;5:31-9. DOI: 10.2147/RRN.S61559.
11. Toor KM, Wahid S, Azeem K. Frequency of Metabolic Complications in Infants Born to Diabetic Mothers at KRL Hospital, Islamabad. J Islamabad Med Dent Coll. 2015;4(1):23-6. DOI: 10.35787/jimdc.v4i1.73.
12. Ostlund I, Hanson U, Bjorklund A, Hjertberg R, Eva N, Nordlander E, et al. Maternal and fetal outcomes if gestational impaired glucose tolerance is not treated. Diabetes Care. 2003; 26(7):2107-11. DOI: 10.2337/diacare.26.7.2107.
13. Peters S, Andrews C, Sen S. Care of infants born to women with diabetes. Curr Diab Rep. 2020;20:1-4. DOI: 10.1007/ s11892-020-01321-5.
14. Bhavya SO, Ranitha R. Early predictors of early onset neonatal hypocalcaemia in infants of diabetic mother. Int J Contemp Pediatr. 2019;6:1325-9. DOI: 10.18203/2349-3291.ijcp2019 2739.
15. Ashokkumar H, Natesh S, Mohammed S. Cord blood HbA1c and neonatal outcomes in infants of diabetic mothers in a tertiary care hospital. Rom J Diabetes Nutr Metab Dis. 2024;31(1):928-41. DOI: 10.46389/rjd-2024-1389.
16. Sonia SF, Haque MF, Parvin R, Sultana A, Afroze S, Hassan MS. Metabolic and haematological profile of infants born to gestational and pregestational diabetic mothers. Bangladesh J Child Health. 2020;44(2):82-6. DOI: 10.3329/bjch.v44i2. 52908.
17. Almhanna MG, Easa ZO, Alatwani SH. Morbidity and mortality among infants of diabetic mothers admitted to a neonatal care unit in Karbala pediatric teaching hospital. J Med Life. 2022;15(8):994. DOI: 10.25122/jml-2022-0014.
18. Radwan MA, El Mansori NA, Elfergani MA, Halies FR, Lawgali MA. Neonatal Morbidity Pattern among Infants Born to Diabetic Mothers at Jamhouria Hospital, Benghazi-Libya. Asian J Pediatr Res. 2021;7(4):38-55. DOI: 10.9734/ajpr/ 2021/v7i430258.
19. Bhatta M, Aneja V. Morbidities and its Immediate Outcome in Newborns Born Through Mothers with Gestational Diabetes Mellitus. Nepal J Health Sci. 2022;2(1):72-9. DOI: 10.3126/ njhs.v2i1.47169.
20. Đukiæ E, Milas D, Prutki A, Nað T, Arambašiæ M, Milas V. Comparison of the Neonatal Outcome in Mothers with Gestational Diabetes (GD) in Two Periods. Coll Antropol. 2020;44(1):29-36. DOI: 10.5671/ca.44.1.5.

Original Article **Open Access**

Diagnostic Efficacy of grey-zone Serum Prostate Specific Antigen level in patients with Benign Prostatic Hyperplasia and Prostate Carcinoma

Syed Atif Hussain, Rukhsana Tumrani, Afsheen Nigar, Anber Rahim, Mahnoor Chaudhry, Seerat Fatima Tu Zahra

ABSTRACT:

Objective: Evaluation of diagnostic role of grey zone serum prostate specific antigen level(4-10ng/ml) in patients with benign prostatic hyperplasia (BPH) and prostate carcinoma keeping histopathology as gold standard.

Study design and setting: Cross-sectional study conducted in Department of Urology and Chemical Pathology, Sheikh Zayed Hospital Rahim Yar Khan.

Methodology: Patients with grey zone serum prostate specific antigen level (4-10ng/ml), lower urinary tract symptoms or abnormal DRE (digital rectal examination) were included and diagnosis was confirmed on the basis of histopathology. Chi square test used to see the statistically significant difference between subgroups. P value <0.05 was deemed as significant. Diagnostic role evaluated by ROC curve analysis.

Results: Mean age of study subjects was 60.21±10.046 years and 155 (81.2%) subjects were having serum prostate specific antigen level in grey zone (4-10ng/ml). Of the total 191 study subjects, 59(30.9%) were histopathologically confirmed cases of benign prostatic hyperplasia and 34(17.8%) were confirmed cases of prostate carcinoma. 41 (26.45%) cases of benign prostatic hyperplasia were having serum PSA level in grey zone (4-10ng/ml) and 16(10.32%) cases with prostate carcinoma were having PSA level in grey zone (4-10ng /ml). ROC curve analysis shows AUC=0.584 in case of BPH and AUC=0.707 in case of CA prostate.

Conclusion: On the basis of our study, it is concluded that grey zone serum PSA level in symptomatic individuals should be used in conjunction with other non-invasive diagnostic and clinical parameters to improve diagnosis and to avoid unnecessary biopsy in every symptomatic individual.

Key words: Benign Prostatic Hyperplasia; BPH; Grey zone PSA; Prostate specific antigen; Prostate carcinoma; Serum PSA

How to cite this Article:
Hussain SA, Tumrani R, Nigar A, Rahim A, Chaudhry M, Zahra SFT. Diagnostic Efficacy of grey-zone Serum Prostate Specific Antigen level in patients with Benign Prostatic Hyperplasia and Prostate Carcinoma. J Bahria Uni Med Dental Coll. 2025;15(1):40-44 DOI: https://doi.org/ 10.51985/JBUMDC2024431

Syed Atif Hussain
Associate Professor and HOD, Department of Urology
Sheikh Zayed Hospital, Rahim Yar khan
Email: dratifqmc@gmail.com

Rukhsana Tumrani *(Corresponding Author)*
Assistant Professor, Department of Chemical Pathology
Shalamar Medical and Dental College, Lahore
Email: r.tumrani333@gmail.com

Afsheen Nigar
Senior Demonstrator, Department of Pathology
Shalamar Medical and Dental College, Lahore
Email: afsheen.nigar@gmail.com

Anber Rahim
PGR, Department of Chemical Pathology
Sheikh Zayed Hospital, Rahim Yar Khan
Email: anber.reem@gmail.com

Mahnoor Chaudhry
Senior Demonstrator, Department of Pathology
Shalamar Medical and Dental College, Lahore
Email: mahnoorchaudhry474@gmail.com

Seerat Fatima Tu Zahra
Senior Demonstrator, Department of Pathology
Shalamar Medical and Dental College, Lahore
Email: drsfzahra@gmail.com

Received: 12-08-2024
Accepted: 24-10-2024 **1st Revision: 20-08-2024**

INTRODUCTION:

Both cancerous and normal prostate epithelial cells release PSA, a serine protease linked to kallikrein. [1] Serum Prostate specific antigen level is non-invasive marker for the management of patients with prostate enlargement. By using PSA as a noninvasive screening biomarker, the number of patients with metastatic cancer can be decreased by improving the early detection of the disease. [2, 3] PSA is specific to the prostate but not to prostate carcinoma; therefore, its use as a diagnostic tool for prostate adenocarcinoma is debatable because of its increased presence in other lesions and procedures like ejaculation, digital rectal examination, benign prostatic hyperplasia, urinary tract infections, acute and chronic prostatitis, and urethral instrumentation.[4] To lower death rates from prostate cancer, early diagnosis is crucial. One of the finest diagnostics for prostate cancer early detection is the serum prostate-specific antigen (PSA) test. As a result, many people today utilize this noninvasive test to screen for prostate cancer, especially among older men. However, even while PSA levels have a high sensitivity for detecting prostate cancer, they lack sufficient specificity

when PSA levels are relatively low, as they do in the 4–10 ng/mL "gray zone." Elevated PSA levels in progressing carcinoma can be utilized as a prognostic tool; the values are adjusted for age and race. [5]

Urgent attention is needed to increase the detection rates of prostate cancer and to prevent unnecessary prostate biopsies in men whose PSA levels are in the gray zone. [6, 7]When the PSA level is in the gray area, it's critical to research the associated factors that lead to a positive biopsy result for Prostate carcinoma. The two related parameters that are currently most frequently employed to determine the positive rate of prostate biopsies are PSA density (PSAD) and the ratio of free to total PSA (f/tPSA). Still, there are issues with clinical prediction. It is widely acknowledged that prostate cancer typically develops in the prostate's peripheral zone, whereas lesions associated with benign prostatic hyperplasia (BPH) are primarily found in the core gland. [8, 9]

It is vital to assess the clinical importance of different PSAs and PSA density (PSAD) connected to peripheral zones in patients with gray zone PSA level (4–10 ng/mL) because the limited specificity of PSA leads to needless and invasive prostate biopsies. [10, 11]

An increasing percentage of prostate cancers, primarily indolent disease, have been identified early because to the widespread use of prostate specific antigen (PSA) in screening techniques. The availability of several treatment approaches, each of which has a distinctly different effect on the patient's quality of life, indicated that there was a clear need for instruments capable of identifying clinically significant malignancy at diagnosis. When it came to pre-biopsy diagnosis, multiparametric magnetic resonance performed incredibly well. It does, however, require an experienced radiologist and is a costly technology. It is worthwhile to look into a straightforward blood test in this situation. Under these circumstances, scientists concentrated on creating a lab test that may reduce overdiagnosis without compromising the ability to identify malignant tumors. [12]

The study aims to evaluate grey zone serum prostate specific antigen level in patients with lower urinary tract symptoms and abnormal digital rectal examination and to evaluate the diagnostic efficacy of grey zone serum prostate specific antigen (PSA) level in patients diagnosed with benign prostatic hyperplasia (BPH) and prostate carcinoma. The implication will be that by evaluating the diagnostic role of non-invasive screening biomarker serum prostate specific antigen (PSA) level help to prevent unnecessary invasive biopsies in patients with abnormal digital rectal examination and it will help in early detection and management of patients with metastatic disease.

METHODOLOGY:

Cross-sectional study conducted in Department of Urology and Chemical Pathology, Sheikh Zayed Hospital Rahim Yar Khan from January 2022 to December 2023. After taking ethical approval from institutional review board (Ref no. 239/IRB/SZMC/SZH Dated 25-11-2021), data was collected by using non-probability consecutive sampling technique. Patients with grey zone serum prostate specific antigen level (4-10ng/ml), lower urinary tract symptoms or abnormal DRE (digital rectal examination) were included and informed consent was taken. Histopathology was taken as gold standard to confirm the diagnosis of prostate carcinoma and benign prostatic hyperplasia. Patients with history of prostate surgery, hormonal manipulation, history of taking 5 alpha reductase inhibitor, urinary tract infection, indwelling urinary catheter and acute or chronic bacterial prostatitis were excluded. Sample size calculated by using formula ($n=z^2x\ p\ (1-p)/E^2$) where z is z score, p is proportion of population having PSA level in grey zone and E is margin of error. Confidence interval is taken as 95% and z score value is 1.96 for 95% confidence interval. Margin of error is calculated as 7% by using the sample size 197 and proportion as 41%. So, the sample size(n) calculated as 190 by using p (the proportion of subjects having PSA level in grey zone taken as 41%).[24] Data was analyzed by using SPSS version 29. Mean and SD calculated for quantitative variables (Age, Serum PSA level) while frequency and percentages calculated for qualitative variables (Prostate carcinoma, Benign prostatic hyperplasia). Effect modifier (age) controlled through stratification. Post stratification chi square test is applied to see the statistically significant difference. Statistically significant difference of grey zone serum PSA level with respect to benign prostatic hyperplasia and prostate carcinoma is evaluated by applying chi square test. P value <0.05 was taken as statistically significant. Diagnostic role is evaluated by ROC curve analysis. Sensitivity and specificity of grey zone PSA level (4-10ng/ml) calculated in benign prostatic hyperplasia and prostate carcinoma by using formulas;

Sensitivity= True positive/True positive+ False negative

Specificity= True negative/ True negative+ False positive[14]

- True positive= Number of cases correctly identified as diseased (Histopathologically confirmed cases with total serum PSA level in grey zone)
- True negative= Number of cases correctly identified as non-diseased (Histopathologically not confirmed serum total PSA level not in grey zone)
- False positive= Number of cases incorrectly identified as diseased (Histopathologically not confirmed with PSA level in grey zone)
- False negative= Number of cases incorrectly identified as non-diseased (Histopathologically confirmed with PSA level not in grey zone)

RESULTS:

Mean age of the study subjects was 60.21±10.046 years and 93(48.7%) were =60years age and 98 (51.3%) were above 60 years with age range 39 to 82 years (Table 1). Of the total 191 study subjects, 155 (81.2%) subjects were having serum PSA level in grey zone (4-10ng/ml) while 36 (18.8%)

were not having PSA level in grey zone (Table 1). 59 (30.9%) were histopathologically confirmed cases of benign prostatic hyperplasia and 34(17.8%) were confirmed cases of prostate carcinoma. 80 (51.61%) subjects =60years of age were having serum PSA level in grey zone while 13 (36.11%) were not having serum PSA level in grey zone (Table 1). 75 (48.38%) subjects >60years age were having PSA level in grey zone while 23 (63.88%) subjects were having PSA level not in grey zone (Table 2). The difference of grey zone PSA level with respect to age subgroups was not statistically significant with p value 0.094 (Table 2). Of the total 59 study subjects with benign prostatic hyperplasia, 41 (69.49%) were having serum PSA level in grey zone while 18(30.50%) were not having serum PSA level in grey zone (Table 2). Of the total 34 study subjects with Prostate carcinoma, 16 (47.05%) were having serum PSA level in grey zone while 18 (52.94%) were not having serum PSA level in grey zone (Table 2). ROC curve for grey zone serum PSA level in Benign Prostatic Hyperplasia shows Area under the curve (AUC=0.584) (Fig 1) while ROC curve for grey zone serum PSA level in Prostate carcinoma shows Area under the curve (AUC=0.707) (Fig 2). Sensitivity of grey zone serum PSA level in case of benign prostatic hyperplasia calculated as 26.45% while specificity calculated as 50%. Sensitivity in case of prostate carcinoma for grey zone serum PSA level calculated as 10.32% while specificity calculated as 50%.

Table 1: Distribution of study subjects with respect to age, serum PSA level (Grey zone PSA), Benign Prostatic Hyperplasia and Prostate Carcinoma (n=191)

Variable	Subgroups	Frequency	Percentage
Age (Years) 60.21±10.046	=60years	93	48.7
	>60years	98	51.3
Serum PSA level (ng/ml) 9.1067±8.457	Gray zone	155	81.2
	No Gray zone	36	18.8
Benign Prostatic Hyperplasia (BPH)	Present*	59	30.9
	Absent	132	69.1
CA Prostate	Present*	34	17.8
	Absent	157	82.2

Figure 1: ROC Curve for Grey Zone PSA level in BPH (AUC=0.584)

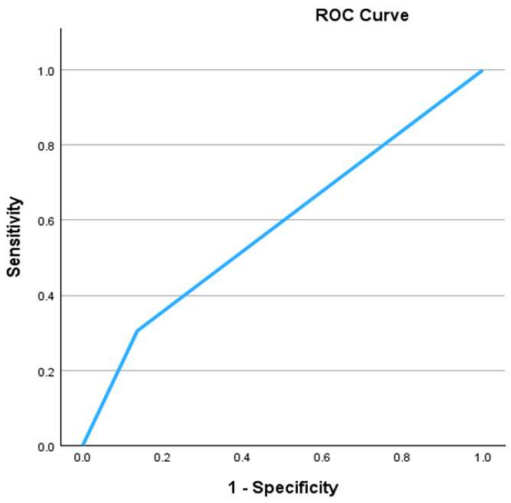


Figure 2: ROC curve for Grey Zone PSA level in CA Prostate (AUC=0.707)

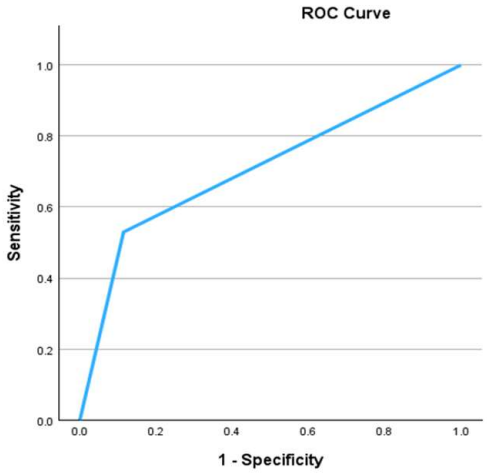


Table 2: Cross tabulation of Age, Benign Prostatic Hyperplasia and CA Prostate with respect to Grey Zone PSA level (n=191)

Variable	Subgroups	PSA level		Chi square value	*P* value
		In Gray zone	Not in Grey zone		
Age	=60 years	80 (51.61%)	13 (36.11%)	2.810	0.094
	>60years	75 (48.38%)	23 (63.88%)		
	Total	155(100%)	36 (100%)		
Benign Prostatic Hyperplasia	Present	41 (26.45%)	18(50%)	7.589	0.006*
	Absent	114 (73.54%)	18(50%)		
	Total	155 (100%)	36(100%)		
CA Prostate	Present	16(10.32%)	18(50%)	31.43	<0.001*
	Absent	139(89.67%)	18(50%)		
	Total	155(100%)	36(100%)		

**p value <0.05 taken as statistically significant*

Sensitivity (BPH) = 41/41+114 =26.45%

Specificity (BPH) =18/18+18=50%

Sensitivity (CA prostate) =16/16+139=10.32%

Specificity (CA Prostate) =18/18+18=50%

DISCUSSION:

Serum prostate specific antigen is valuable, non-invasive marker for screening prostate carcinoma but the intermediate PSA level make it difficult to discriminate between benign and malignant prostate conditions. In these conditions, many patients are subjected to unnecessary biopsies to make a definitive diagnosis. [13, 15] So, the grey zone level of serum total PSA evaluated in our study with mean PSA level 9.1067±8.457ng/ml. Of the total 191 study subjects, 155(81.2%) were having serum PSA level in grey zone while 36 (18.8%) were having serum PSA level not in grey zone. Diagnostic efficacy of serum PSA level in grey zone established for prostate carcinoma with AUC (0.707), sensitivity 10.32%, specificity 50%. Distribution of prostate carcinoma patients with respect to grey zone serum PSA level was statistically significant with p value <0.001. Diagnostic efficacy of serum PSA level established for benign prostatic hyperplasia with AUC (0.584), sensitivity 26.45% and specificity 50%. Distribution of benign prostatic hyperplasia patients with respect to grey zone serum PSA level was found statistically significant with p value 0.006.

Diagnostic efficacy of total serum PSA evaluated by Wu B et al in their study and AUC by ROC analysis was 0.508 for grey zone PSA level (p value <0.001) and for total PSA overall AUC 0.699 (P value 0.012). Mean age of study subjects in their study was 67.5±7.9 years with median total PSA level 7.94ng/ml with statistically significant difference of median total PSA level in prostate carcinoma and non-carcinoma patients (p value 0.001). [16] Screening of prostate carcinoma has important role in the management of carcinoma and clinically significant prostate cancer with PSA level in grey zone (4-10ng/ml) should have proper screening by other diagnostic tools such as prostate health index density, prostate health index and % of free prostate specific antigen to avoid unnecessary biopsies.[16, 17]On the basis of previous literature, it has been shown that many of the patients undergoing unnecessary biopsies based on serum total PSA results.[18, 19]

A single centered study conducted by Castro et al at PSA cut off 3ng/ml established the sensitivity 1.000 and specificity 0.017 with mean PSA level in cancer patients 7.50±1.70ng/ml and mean PSA in benign prostatic hyperplasia was 6.29±1.81ng/ml. [20] Another study conducted by Vukovic et al established the sensitivity of serum PSA level at cut off 3ng/ml as 0.923 and specificity as 0.063 with mean serum PSA level in cancer patients 5.81±1.98ng/ml and mean PSA level in benign prostatic hyperplasia as 6.24±1.96ng/ml. [21]

On the basis of previous literature search, it is recommended that in asymptomatic individuals with PSA level in grey zone (3-10ng/ml) and normal digital rectal examination should be evaluated further by non-invasive tools for indication of biopsy such as risk calculation, magnetic resonance imaging and if PSA doubling time is less than 3 years then it is strongly recommended that MRI should be repeated and biopsy should be performed.[22] Liu J. et al In their study evaluated the use of clinical parameters to predict prostate carcinoma in patients with total PSA level in grey zone (4-10ng/ml). On the basis of their study, the total serum PSA level didn't show significant difference in carcinoma and non-carcinoma patients with p value 0.824. Other parameters such as age, free PSA, f/t PSA also show no significant difference between carcinoma and non-carcinoma patients, however, prostate volume and PSA derivatives show significant difference with p value <0.05. It was concluded that in patients with grey zone serum PSA level, prostate volume, PSA derivatives and MRI should have been used to predict prostate carcinoma and to prevent unnecessary prostate biopsies. [23]

Our study had certain limitations. It was a single centered study. Different prostate specific reference ranges (cut-off) should have been evaluated with respect to age as age specific reference ranges are being used for interpretation of total PSA results and diagnostic efficacy should be established for each cut-off value with respect to age.

Further larger studies should be performed to further evaluate the patients with PSA results in grey zone (4-10ng/ml) by using different non-invasive investigations and clinical parameters to improve the diagnostic value and preventing the unnecessary biopsies.

CONCLUSION:

On the basis of our study, it is concluded that grey zone serum PSA level (4-10ng/ml) in symptomatic individuals with lower urinary tract symptoms and abnormal digital rectal examination should be used in conjunction with other non-invasive diagnostic and clinical parameters to improve diagnosis and to avoid unnecessary biopsy in every symptomatic individual.

Authors Contribution:
Syed Atif Hussain: Concept, design, final approval
Rukhsana Tumrani: Data analysis, manuscript writing
Afsheen Nigar: Data analysis, discussion
Anber Rahim: Data collection
Mahnoor Chaudhry: Discussion, Data interpretation
Seerat Fatima Tu Zahra: Proof reading, data analysis

REFERENCES:

1. Antony T, Talwar R, Thomas T, Trehan V, Manwatkar S, Mohan H, et al. Correlation of serum prostate specific antigen with clinical, radiological and pathological variables in patients with prostate enlargement. Int Surg J 2019; 6:4408-14. DOI: https://doi.org/10.18203/2349-2902.isj20195403
2. Cary K. C, & Cooperberg M. R. Biomarkers in prostate cancer surveillance and screening: past, present, and future. Therapeutic advances in urology, 2013;5(6): 318-329. doi: 10.1177/1756287213495915.

3. Atif Hussain, S.., & Tumrani, R. (2022). Correlation between Pre-Biopsy Serum Prostate Specific Antigen Level and Gleason Score in Patients Diagnosed with Prostate Adenocarcinoma: A Hospital Based Study: Pakistan Journal of Health Sciences, 2022; 3(07): https://doi.org/10.54393/pjhs.v3i07.404
4. O'Shaughnessy M, Konety B, Warlick C. Prostate cancer screening: issues and controversies. Minnesota medicine, 2010; 93(8):39-44
5. Elshahmi E, Emaetig F, Elgaraboli F, Abushnaf A, Alqawi O. The Evaluation of PSA levels in Libya Prostate Cancer Patients. Clinical Oncology Research and Reports. 2022; 3(1): DOI: 10.31579/2693-4787/029
6. Li, X., Li, C. and Chen, M. (2023), Patients With "Gray Zone" PSA Levels: Application of Prostate MRI and MRS in the Diagnosis of Prostate Cancer. J Magn Reson Imaging, 57: 992-1010. https://doi.org/10.1002/jmri.28505
7. Lu YF, Zhang Q, Chen HY, Chen JY, Pan Y, Xu CC, Xu JX, Yu RS. Improving the detection rate of prostate cancer in the gray zone of PI-RADS v2 and serum tPSA by using prostate-specific antigen-age volume. Medicine (Baltimore). 2019;98(26): e16289. doi: 10.1097/MD.0000000000016289.
8. Guo Z-F, Yang F, Lu X-W, Wu J-W, He C, Han C-H. Significance of the prostate central gland and total gland volume ratio in the diagnosis of prostate cancer patients in the prostate specific antigen grey zone. Journal of International Medical Research. 2021;49(7): doi:10.1177 /0300060521 1019879
9. Falagario UG, Martini A, Wajswol E, et al. Avoiding Unnecessary Magnetic Resonance Imaging (MRI) and Biopsies: Negative and Positive Predictive Value of MRI According to Prostate-specific Antigen Density, 4Kscore and Risk Calculators. Eur Urol Oncol 2020; 3: 700–704.
10. Lee, J., Yang, S.W., Jin, L. et al. Is PSA density of the peripheral zone as a useful predictor for prostate cancer in patients with gray zone PSA levels? BMC Cancer 21, 472 (2021). https://doi .org/10.1186/s12885-021-08216-6
11. Falagario UG, Jambor I, Lantz A, et al. Combined Use of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy Decision Planning: A Retrospective Multi-Institutional Study Using the Prostate Magnetic Resonance Imaging Outcome Database (PROMOD). Eur Urol Oncol 2020: S2588-9311(20):30142-5.
12. Ferro M, De Cobelli O, Lucarelli G, et al. Beyond PSA: The Role of Prostate Health Index (phi). Int J Mol Sci 2020; 21: 1184.
13. Guo ZF, Lu XW, Yang F, et al. Significance of prostate central gland/total gland volume ratio combined with PSA in the diagnosis of prostate cancer patients. Zhonghua Yi Xue Za Zhi 2019; 99: 2836–2839
14. Baratloo A, Hosseini M, Negida A, El Ashal G. Part 1: Simple Definition and Calculation of Accuracy, Sensitivity and Specificity. Emerg (Tehran). 2015;3(2):48-9
15. Castro HAS, Iared W, Santos JEM, Solha RS, Shigueoka DC, Ajzen SA. Impact of PSA density of transition zone as a potential parameter in reducing the number of unnecessary prostate biopsies in patients with psa levels between 2.6 and 10.0 ng/mL. Int Braz J Urol. 2018;44(4):709-716. doi: 10.1590/S1677-5538.IBJU.2017.0506.
16. Wu B, Shao Y, Lin X, Hasi C, Jia W, Wang D, Cao X. Comparisons of the diagnostic accuracy across prostate health index, prostate health index density, and percentage free prostate-specific antigen for clinically significant prostate cancer: a prospective diagnostic study. Transl Androl Urol. 2023;12(3):425-432. doi: 10.21037/tau-23-80. Epub 2023 Mar 28.
17. Chen H, Qian Y, Wu Y, et al. Modified Prostate Health Index Density Significantly Improves Clinically Significant Prostate Cancer (csPCa) Detection. Front Oncol 2022; 12:864111. 10.3389/fonc.2022.864111
18. Zhang L, Zhang J, Tang M, et al. MRI-Based Radiomics Nomogram for Predicting Prostate Cancer with Gray-Zone Prostate-Specific Antigen Levels to Reduce Unnecessary Biopsies. Diagnostics (Basel) 2022; 12:3005. 10.3390/ diagnostics12123005
19. Alijaj N, Pavlovic B, Martel P, et al. Identification of Urine Biomarkers to Improve Eligibility for Prostate Biopsy and Detect High-Grade Prostate Cancer. Cancers (Basel) 2022; 14:1135. 10.3390/cancers14051135
20. Castro HAS, Iared W, Santos JEM, Solha RS, Shigueoka DC, Ajzen SA. Impact of PSA density of transition zone as a potential parameter in reducing the number of unnecessary prostate biopsies in patients with PSA levels between 2.6 and 10.0 ng/mL. Int Braz J Urol. 2018; 44:709–716.
21. Vukovic I, Djordjevic D, Bojanic N, Babic U, Soldatovic I. Predictive value of [-2] propsa (p2psa) and its derivatives for the prostate cancer detection in the 2.0 to 10.0ng/mL PSA range. Int Braz J Urol. 2017; 43:48–56.
22. European Association of Urology. EAU guidelines on prostate cancer, https://uroweb.org/guideline/prostate-cancer/ (2019)
23. Liu, J., Dong, B., Qu, W. et al. Using clinical parameters to predict prostate cancer and reduce the unnecessary biopsy among patients with PSA in the gray zone. Sci Rep 10, 5157 (2020). https://doi.org/10.1038/s41598-020-62015-w
24. Ding Z, Wu H, Song D, Tian H, Ye X, Liang W, Jiao Y, Hu J, Xu J, Dong F. Development and validation of a nomogram for predicting prostate cancer in men with prostate-specific antigen grey zone based on retrospective analysis of clinical and multi-parameter magnetic resonance imaging/transrectal ultrasound fusion-derived data. Transl Androl Urol. 2020;9(5):2179-2191. doi: 10.21037/tau-20-1154.

Medical Education - Original Article **Open Access**

Development, Implementation and Initial Evaluation of the Blueprint for MBBS Theory Exams in a Private Medical College of Pakistan

Yusra Nasir, Sobia Ali, Muhammad Ahsan Naseer, Sana Farooq Shah

ABSTRACT

Objective: This study aimed to enhance the validity of the exam bank at Liaquat National Medical College (LNMC), Karachi, through the development and evaluation of the exam blueprinting process as part of an ongoing quality assurance initiative.

Study design and setting: This study was conducted at Liaquat National Medical College (LNMC), Karachi. Participants included key stakeholders i. faculty members, ii-officials from the examination department (involved in the development of the fourth-year MBBS neuroscience exam blueprint), and iii-students.

Methodology: Ethical approval for this study was taken by the LNMC Ethics Review Committee. For the ease of understanding, this article was divided into two sections: In first section, the stepwise approach of blueprint development was discussed whereas the second section dealt with feedback from 105 4th Year MBBS students, feedback from faculty involved in this process and the experiences of examination unit personnel.

Results: Following the Calgary model by Coderre et al., a blueprint for undergraduate MBBS theory exam was developed. Students (85%) agreed that the exam accurately assessed the taught content. Faculty expressed satisfaction with the blueprinting process, noting improvements in exam quality, topic representation, and the elimination of redundant questions. Examination unit personnel reported better time management and improved alignment with curricular objectives. Initial challenges, such as faculty's lack of training and resistance were also identified.

Conclusion: The blueprinting process significantly enhanced alignment of theory exam with educational objectives thereby ensuring the content validity. Continued training and institutional support are vital in overcoming initial challenges and ensuring the long-term success of blueprinting.

Keywords: Blueprinting, Exam Quality, Faculty Satisfaction, MCQs, Quality Assurance, Validity Written theory exam.

How to cite this Article:
Nasir Y, Ali S, Naseer MA, Shah SF. Development, Implementation and Initial Evaluation of the Blueprint for MBBS Theory Exams in a Private Medical College of Pakistan. J Bahria Uni Med Dental Coll. 2025;15(1):45-52 DOI: https://doi.org/10.51985/JBUMDC2024433

INTRODUCTION

At the core of medical education lies the principle "assessment drives learning." To fully leverage the potential of this principle, it is essential that the assessments themselves are valid, offering a true reflection of a student's competence and understanding. Without such validity, assessments fail to achieve their primary purpose, which is to guide and shape meaningful learning.[1] Traditional assessment designs have their pitfalls, including the subjectivity of the paper setter and frequent complaints from students about the representation of topics.[1] Conversely, blueprint development in medical education offers a systematic multistep approach to assessment, defining purpose (formative/summative and written/practical) and scope (undergraduate or postgraduate students) of the test to subsequently determine the content and method of assessment.[2] It assists in developing assessment more congruent with the objectives, content area, and curriculum, and can be implemented to improve the reliability and content validity of the assessment. This in turn helps in distribution of appropriate weightage and questions across the topics.[3]

The study conducted on undergraduate traditional assessments have identified several shortcomings. Among these deficiencies, a prominent concern is the subjectivity inherent in the formulation of examination papers.[4] Undergraduate medical students have reported dissatisfaction

Yusra Nasir *(Corresponding Author)*
Lecturer, Department of Health Professions Education
Liaquat National Hospital & Medical College
Email: yusra.nasir@lnh.edu.pk

Sobia Ali
Professor, Department of Health Professions Education
Liaquat National Hospital & Medical College
Email: sobia.a@lnh.edu,pk

Muhammad Ahsan Naseer
Lecturer, Department of Health Professions Education
Liaquat National Hospital & Medical College
Email: nahsan26@gmail.com

Sana Farooq Shah
Assistant Professor, Department of Health Professions Education
Liaquat National Hospital & Medical College
Email: sana-fshah@hotmail.com

Received: 20-08-2024
Accepted: 24-10-2024
1st Revision: 30-08-2024
2nd Revision: 23-10-2024

with the underrepresentation of themes covered in assessment[5]. Moreover, frequent challenges impacting the content and construct validity of a test may arise from its creation with inadequate coverage of essential learning outcomes or the use of inappropriate assessment tools, leading to irrelevant variability[5].This brings to light the issues of subjectivity, lack of uniformity, and potential threats to the content and construct validity of an exam. These challenges undermine the very purpose of assessments: to accurately measure students' knowledge, skills, and attitudes. Exam Blueprinting address these challenges by reducing construct under-representation (CU) and construct irrelevant variance (CIV) .[5]

A test blueprint defines as:

"*The key elements of a test, including the content to be covered, the amount of emphasis allocated to each content area, and other important features."*[7]

An exam blueprint in medical education serves as a crucial tool for mitigating major threats to validity in assessments. The alignment offered by blueprint connects the three foundational pillars of education: structured learning objectives, teaching and learning activities, and assessment tasks.[6] By utilizing a blueprint, educators can ensure that these pillars are harmoniously aligned, leading to more effective and valid assessments. They also provide valuable metadata for managing Multiple Choice Questions (MCQs) bank. Once test items are coded according to a blueprint, it becomes easier to retrieve them from a larger pool of items and assemble them into various test forms for different purposes.[7]

One of the study investigated the impact of implementing an exam blueprint on student performance and satisfaction in a basic imaging module showed that students who were assessed in an exam using blueprints outperformed those who were not, with statistically higher scores, greater satisfaction, and improved achievement of learning outcomes.[8]

The literature describes the blueprinting development process in several key stages: (1) clearly defining the purpose and scope of the assessment; (2) identifying the primary domains of knowledge and skills to be evaluated; (3) outlining the objectives or learning outcomes to be assessed within each domain for each topic; (4) selecting the appropriate assessment format; and (5) assigning specific weights to each content category, such as knowledge and skills domains.[9] Despite the clear advantages of using a test blueprint in assessment, certain challenges persist. These include the lack of a standardized approach to blueprint design, and incomplete awareness among test developers about the importance and effectiveness of test blueprints.[10]

The Examination Unit (EU) at Liaquat National Hospital & Medical College (LNMC), Karachi, involved in exam development since its inception in 2012. It was highlighted through frequent exam feedback that the theory exam faced the issues of content distribution. As a result EU undertook a continuous quality assurance process. This process prioritizes exam validity by incorporating recent evidence-based recommendations while considering the contextual challenges and enablers. A one-year revision focused on the creation of new blueprints for the multiple-choice question assessments was done as part of this continuous quality assurance process.

Objectives: This article aims to:

1. Outline a methodical approach towards blueprint development for a written examination.

2. Explore the experiences and satisfaction of faculty and examination department officials involved in the blueprinting process.

The article will conclude with a discussion proposing a way forward for further advancing the exam blueprint development process in other domains of assessment.

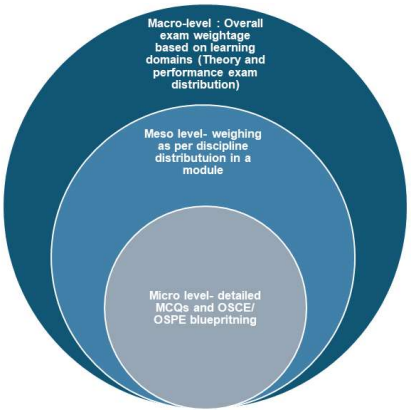
METHODOLOGY

To conduct this research, we gathered data from multiple sources that includes stepwise blueprint development process, surveys, and interviews. For the ease of understanding, this quality assurance process will be delineated in two sections; the first section will deal with the process that we follow for blueprint development and second section will deal with the experiences and satisfaction with the process of major stakeholders of this endeavor.

1) *Blueprint development process*

Blueprints were formulated through a three-tiered approach; at first theory and performance exam distribution was decided for each module (Macro level; figure 1) after that weightage of each discipline in the module was identified (Meso level; figure 1) and finally the third layer was developed in which the detailed distribution of MCQs and OSCE was made along with the specification of their topics and subtopics (Micro level; figure 1).

Figure-1: Blueprinting Process across Macro, Meso and Micro Levels



To explain the blueprint development process at our institution, we will use the example of Year 4 MBBS Neuroscience module. This process took six month from Blueprint development to its evaluation by stakeholders. The following steps were employed to construct the blueprints.

The process started with the repetitive training sessions for faculty (basic and clinical sciences) involved in the exam development at college. The sessions targeted specifically hands-on practice on the various models of blueprints. With the collaborative effort of exam unit, and module committee (included the faculty involved in the module development and implementation), blueprints were developed at three levels as follows:

Step 1: Weightage according to learning domains (Macro-level)

The first step in this process was to map the curriculum to identify the content coverage of knowledge & skill components in the module. A detailed review of learning objectives was done to identify their domains, and levels that will help target the path toward assessment validity claim.[8] The process started when faculty were working together for module development. This first layer of the blueprint consisted of a broad division of content in terms of knowledge and skills domains. The weightage (table 1) was calculated based on hours allocation and importance of objectives (as prescribed by the faculty) to be covered for that module.

Step 2: Discipline-based weightage of exam content in a module (Meso-level)

This layer of blueprint was developed for ensuring the adequate weightage for individual discipline in a module. Before this stage, the weighting of a content area has already been established through consensus (based on its importance) during module development meetings. The weightage of this layer is simply based on hour allocation as described by Abdellatif and Al-Shahrani.[11] Discipline wise weightage distribution in the theory exam of Neuroscience module is presented in Table 2.

Step 4: Detailed description of MCQs with objective alignment

The third layer encompasses the detailed attributes of multiple-choice questions (MCQs) for each identified topic or disease within each discipline. The blueprint model employed the development of this layer using the impact x frequency model (Table 3.1) outlined by the University of Calgary in the literature.[12,13] Through a consensus-building process involving subject specialists, impact and frequency were calculated, which subsequently determined the weight of each item. Further item descriptions were finalized by revisiting the objectives to ensure alignment. For instance, five questions were determined for headache, with diagnosis, investigation, treatment, complications and prognosis options identified as the essential knowledge areas to be assessed as shown in Table 3

Table 1: Learning domain division in neuroscience 4th year MBBS module

Neuroscience Module	
Knowledge	**Skills**
62%	38%

Table 2: Discipline wise weightage distribution of Neuroscience module Theory exam

Subjects	Teaching Hours	Weightage	No. of MCQs
Neurology	25	28%	42
Pediatrics	5	6%	8
Pathology	20	22%	34
Pharmacology	20	22%	33
Psychiatry	10	11%	17
Neurosurgery	8	9%	13
Radiology	2	2%	3
Total=T	T= 90	T=100%	T=150

2) Experiences & Satisfaction with the process: The satisfaction with the process was done by using three evidences:

i. Taking feedback from students about the content validity of the exam

ii. Taking feedback from faculty involved in the process by doing a survey

iii. In depth interview from exam unit personnel

Ethical approval for this study was granted by the Liaquat National Hospital Ethics Review Committee (1020-2024-LNH-ERC). Feedback was collected from students regarding the content validity of the exam. A total 105, 4th year MBBS students were asked the question in post exam survey taken after the module exam. The question been asked was, "Did the module examination accurately assess the taught content?"

Faculty feedback was taken in the form of questionnaire from those involved in blueprinting process of the module and these included Professors, Associate & Assistant Professors from both clinical and basic sciences, all with backgrounds in medical education training. The sample size was calculated using the Online OpenEpi Version 3 tool. For a population size (N) of 33, it was hypothesized that the outcome frequency in the population would be approximately 50%, with a margin of error of ±5% and a confidence level of 95%. Based on these parameters, a sample size of 31 individuals was calculated. A Likert scale-based survey was developed by a medical educationist and reviewed by three medical education experts. The survey was administered via Google Forms to 33 faculty members involved in the exam blueprint development for the year 2023.

Table 3: Distribution of multiple-choice questions (MCQs) for each disease within Neurology

Theme	I	F	I*F	IxF/T	Weightage (Tx42)	No of items	Patho-physio	Diagnosis	Investigations	Treatment / Management	Complications	Prognosis
CNS Infections / Meningitis	3	2	6	0.11	4.9	5	✓	✓	✓	✓ ✓		
Coma	2	2	4	0.07	3.2	3		✓	✓	✓		
Cranial nerve lesions	2	1	2	0.03	1.6	2		✓	✓			
Dementia	1	1	1	0.01	0.8	1		✓				
Epilepsy/Seizures	3	2	6	0.11	4.9	5	✓	✓	✓	✓	✓	
Guillain-Barre syndrome	2	3	6	0.11	4.9	5		✓	✓	✓	✓	✓
Headaches	3	2	6	0.11	4.9	5		✓	✓	✓	✓	✓
Movement disorder	1	1	1	0.01	0.8	1	✓					
Lesion localization	1	1	1	0.01	0.8	1	✓					
Parkinson's Disease	3	1	3	0.05	2.47	1		✓				
Muscular dystrophies	1	1	1	0.01	0.8	1			✓			
Multiple Sclerosis	2	1	2	0.03	1.6	2		✓	✓			
Myasthenia Gravis	3	2	6	0.11	4.9	5			✓	✓	✓✓	✓
Stroke	3	3	9	0.17	7.4	7		✓	✓	✓	✓	✓
			51		42.7	42						

Table 3.1: Impact and frequency descriptors

Score	Impact Description	Frequency Description
1	Non-urgent, little prevention potential	Rarely seen
2	Serious, but not immediately life threatening	Relatively common
3	Life threatening emergency and/or high potential for prevention impact	Very common

At the end, three in-depth interviews (IDIs) of 30-40 minute duration were conducted with exam officers and the examination in-charge using a pre-developed interview guide. In-depth interviews were conducted until we achieve the theoretical saturation, following the recommendations of Corbin.J, Strauss A.[14] Interviews were audio-recorded and transcribed verbatim using Microsoft Office 365, ensuring confidentiality and anonymity. Transcripts were anonymized before data analysis. Credibility of responses was ensured by summarizing the responses at the end of interview as well as by member checking after transcription. Privacy and confidentiality of all the participants and their responses was maintained throughout the data collection and analysis process.

Data Analysis

I. A descriptive analysis using SPSS version 23 was done to gauge the percent of agreement from feedback from both students and faculty.

II. In-depth interviews (IDIs) with personnel from the examination unit were analyzed using manual thematic analysis.[15] Braun & Clarke's thematic analysis methods were used to identify, organize, describe, and report themes found within the data set.[16] After multiple readings of interview transcripts, the researchers assigned codes based on the interview questions and responses. Through an iterative process of examining and re-examining the coded excerpts, themes were identified along with key quotes to develop evidence-based narratives and recommendations.[17]

RESULTS:

After development and implementation of the theory exam blueprint as described above, the students' and faculty feedback survey was conducted and exam officers' experiences were measured through interviews.

I. Students feedback:

With a response rate of approximately 96.2%, eighty five

Table 4: Faculty level of agreement on the Blueprinting Process for Exam Development

Statement	Strongly disagree (%)	Disagree (%)	Neutral (%)	Agree (%)	Strongly Agree (%)
I was provided clear guidelines for the blueprinting process	0	0	10	50	40
I was provided with sufficient resources & tools (study guide & time tables) for blueprint development	0	0	13.3	36.7	50
I understood the Blueprint template/model easily.	0	0	23.3	43.3	33.3
I was given full opportunity to develop my subject's blueprint	0	3.3	6.7	43.3	46.7
I believe that blueprint has significantly enhanced the quality of MCQs.	0	0	6.7	50	43.3
I feel confident while utilizing formulated blueprints for my subject's exam preparation.	0	0	0	53.3	46.7
I believe that blueprinting ensured well balanced distribution of MCQs across topics.	0	0	10	53.3	36.7
I believe that Blueprinting has improved alignment of the MCQs with course objectives	0	0	3.3	70	26.7
I believe that overall process of paper setting has become simplified after blueprint development.	0	0	6.7	53.3	40
I acquired a comprehensive understanding of exam development through my active involvement in the blueprinting process.	0	0	6.7	46.7	46.7

percent of the students showed agreement to the question being asked about the content validity of the exam (N=101)

II. Faculty feedback: Feedback survey was filled by the 31 faculty members with a 100% response rate. The departmental representation for blueprinting included a mix of clinical and basic sciences faculty members, with designations ranging from Assistant Professor to senior positions.

Table 4 summarizes the levels of agreement for ten statements related to the blueprinting process for the development of theory examination. Overall, the survey results indicated a highly positive response to the blueprinting process across various specialties.

In-Depth Interviews: In-depth interviews were conducted from in-charge of the examination unit (IEU) and two senior exam officers (SEO) to explore their experiences, challenges, and the impact of blueprinting on exam development which are highlighted in Table 5.

DISCUSSION:

This study offered insights into the extent to which blueprinting can markedly enhance the quality and alignment of exams with course objectives, ensuring that assessments are both comprehensive and closely tied to the curriculum. The student's survey revealed a high level of agreement (85%) regarding the content validity of the exam, indicating that students perceived the exams as closely aligned with the taught material. This is consistent with findings from previous studies where MBBS students expressed satisfaction with exam blueprints that ensured appropriate question distribution and alignment with learning objectives.[2,18] In a study conducted in 2023 by Dutta & Goswami, MBBS students demonstrated satisfaction with the biochemistry exam blueprint, which was praised for ensuring content validity, construct reliability, and fairness over two academic years.[18]

The faculty survey results from this study showed that most faculty members were satisfied with the blueprinting process, particularly regarding the clarity of guidelines and the availability of resources. This positive feedback suggested that blueprinting simplifies the exam development process and making it more efficient and aligned with educational objectives. These findings are consistent with existing research, which indicated that faculty members value clear and structured exam blueprints as they enhance the alignment between teaching and assessment, ultimately improving educational outcomes.[2] Additionally, in 2022, Chrisyarani et.al. found that faculty satisfaction is significantly influenced by their involvement in the blueprinting process, highlighting that participatory approaches can improve perceptions of fairness and relevance in assessments.[19]

The in-depth interviews with examination officers and in-charge revealed several key benefits of blueprinting, including improvements in time management, ease of question selection, and better alignment of exams with curriculum objectives. These findings are supported by Bhardwaj's study that emphasizes blueprints are essential for aligning content with curriculum objectives and ensuring comprehensive assessments.[20] The interviewees highlighted the elimination of redundant questions and improved

Table 5: Examination Officers' and In-Charge's Perspectives on the Blueprinting Process

Theme	Sub-Theme	Verbatim Quotes
Shifts in Exam Development Approach	Time Management Improvements	"Benefit of time management for exam development was evident"??... *(IEU)*
	Ease of Question Selection	"The exam development has become easier. Faculty (Content experts) used to visit DHPE and select questions randomly from taught topics"?? *(SEO_1)* "Previously the practice was... the question were being selected by the faculty randomly from the subtopics and topics"??.. *(IEU)*
	Balanced Representation of Topics	"The risk of out of course exam was reduced significantly after Blueprinting" *(SEO_2)* "After BP the exam is reflecting timetables and study guides... previously the exam was under or over represented and some areas were entirely skipped"??*(IEU)*
	Appropriate Weightage Assignment	"Now what we have seen is that the proper weightage has been given to all the topics as we wanted from the start of the process"?? *(SEO_2)* "Previously the proper weightage was not given in the blueprint….. It was not there before"?*(SEO_1)*
	Objective Alignment & Curriculum Reflection	"This time we know the objectives and their weightage in assessment"? *(SEO_1)* "The topics in the exam paper are exactly what the reflection of the study guide"?
	Elimination of Redundant Questions	"Duplications of questions has been reduced" *(SEO_1)*?? "The overlapping was there, the duplication was there in the exam... these weaknesses which used to be there previously are rectified this time after developing of the blueprint""*(IEU)*
	Faculty Satisfaction	"This time faculty didn't complain"?? *(SEO_1)* "Faculty has mentioned numerous time in the meetings that significant difference in the exam results has been seen, as a result of proper exam development"*(IEU)*
Needs and Challenges	Initial Lack of Training	"Faculty needs proper training for that. Up till now the faculty has been trained pretty much but still there is a need of some kind of proper training"??*(SEO_2)*
	Resistance from Faculty	"As far as my department is concerned my department faculty is already trained. I just had to guide... But if you talk about college faculty. There was some resistance"?? *(IEU)*
Provision of Support & Resources	Departmental Support	"I collected the timetable and study guide, which were essential for preparing the Blueprint, with full support from the DHPE faculty and administrative staff." (*SEO_2)*
	Faculty Support	"There was strong teamwork throughout the process, with valuable support from both the medical college faculty and DHPE staff." *(SEO_1)*
	Institutional Support	"I received full institutional support and all the necessary resources right from the very beginning, and that support continues to this day." *(IEU)*
Suggestions for Future Improvement	Increasing Question Bank Size	"Adequate no of questions should be there in future against the developed BP at least three questions against one sub-theme"?? (*SEO_2)*
	Clarifying Study Guide Objectives	"Next time what we can do is... the objectives are still in the study guide needs to be clearly mentioned so that we can exactly identify the content*"??(SEO_1*

reflection of the curriculum, which aligns with the work that emphasize the role of blueprinting in enhancing the coherence and relevance of assessments.[21] Furthermore, the interview identified key challenges in the implementation of blueprinting, primarily due to the initial lack of support from faculty. This resistance was largely due to unfamiliarity with the blueprinting process and concerns about the perceived additional workload. These findings align with existing

literature which highlighted that exam officers often face challenges due to resource limitations, including insufficient training of faculty.[22] Such limitations can significantly hinder the creation of effective blueprints and the smooth implementation of the process. Overcoming this resistance required targeted efforts to familiarize faculty with the benefits and procedures of blueprinting.

Limitations of the study: As the data is derived from a single site, this limit this study. Additionally, our feedback data, consisting solely of faculty self-ratings, may not accurately reflect actual practices. Despite these limitations, we believe this study warrants publication as it offers valuable guidance and a framework for developing a valid exam bank, particularly within the curricular structure in Pakistan. Ongoing research by the authors on the blueprinting of assessment of skills and attitudes and its impact on students' learning will provide further elaboration.

CONCLUSION:

This study outlined a methodical approach to the quality assurance process of written examinations within an undergraduate medical curriculum, guiding the development of a reliable bank of multiple-choice questions (MCQs). The experiences and satisfaction of the faculty and examination department officials highlighted the notion that exam blueprints are instrumental in aligning exams with educational objectives, thereby improving the quality and effectiveness of assessments. Additionally, the importance of clear guidelines, adequate resources, and strong institutional support are critical in the successful implementation of such an endeavor. While initial challenges were present, the overall positive outcomes indicated that blueprinting was a valuable tool in educational assessment, contributing to the validity and fairness of exams.

Moreover, it is recommended that providing continued training, coupled with institutional support, is essential for establishing and sustaining initiatives to build validity evidence of exams through the blueprinting process. In addition, there is a need to investigate the long-term effects of blueprinting on student outcomes and faculty satisfaction.

Authors Contribution:
Yusra Nasir: Data acquisition, analysis and interpretation, Drafting, revising & Final review of Manuscript
Sobia Ali: Substantial contributions to conception and design, analysis and interpretation of data, Drafting, revising & Final review of Manuscript
Muhammad Ahsan Naseer: Data acquisition, analysis and interpretation, Drafting of manuscript
Sana Farooq Shah: Conception of study, data acquisition, analysis and interpretation

REFERENCES:

1. Pawade YR, Chalak AS, Pawade DY. Blueprints in biochemistry: Systematic assessment in undergraduate medical education. Res Dev Med Educ 2022;11:22. DOI :http://dx.doi.org/10.34172/rdme.2022.022
2. Patil SY, Gosavi M, Bannur HB, Ratnakar A. Blueprinting in assessment: A tool to increase the validity of undergraduate written examinations in pathology. Int J Appl Basic Med Res 2015;5:S76-9. DOI : http://dx.doi.org/10.4103/2229-516X.162286
3. Kundoor N, Hussain F, Lingam S, Reddy VN, Arcot R, Bondugula H, et al. Developing and Validating an Assessment Blueprint for Clinical Skill Competencies in General Surgery for the Medical Undergraduates. SDME. 2023;20(1):8–15.DOI: https://doi.org/10.22062/sdme.2023.198234.1156
4. de Montbrun S, Louridas M, Szasz P, Harris KA, Grantcharov TP. Developing the blueprint for a general surgery technical skills certification examination: A validation study. J Surg Educ. 2018;75(2):344–50. DOI: http://dx.doi.org/ 10.1016 /j.jsurg.2017.08.007
5. Abdellatif H, Alsemeh AE, Khamis T, Boulassel M-R. Exam blueprinting as a tool to overcome principal validity threats: A scoping review. Educ médica. 2024;25(3):100906. DOI: http://dx.doi.org/10.1016/j.edumed.2024.100906
6. Mohajan HK. Two criteria for good measurements in research: Validity and reliability. Annals of Spiru Haret University. Annals of Spiru Haret University Economic Series. 2017;17(4):59–82.
7. Raymond MR, Grande JP. A practical guide to test blueprinting. Med Teach. 2019;41(8):854–61. DOI: http://dx.doi.org/ 10.1080/0142159X.2019.1595556
8. Ahmad RG, Hamed OAE. Impact of adopting a newly developed blueprinting method and relating it to item analysis on students' performance. Med Teach [Internet]. 2014;36 Suppl 1(sup1):S55-61. DOI : http://dx.doi.org/ 10.3109/ 0142159X.2014.886014
9. Banerjee Y, Tambi R, Gholami M, Alsheikh-Ali A, Bayoumi R, Lansberg P. Augmenting Flexnerism via Twitterism: Need for integrating social media application in blueprinting pedagogical strategies for undergraduate medical education. JMIR Med Educ [Internet]. 2019;5(1):e12403.DOI : http://dx.doi.org/10.2196/12403
10. Gottlieb M, Bailitz J, Fix M, Shappell E, Wagner MJ. Educator's blueprint: A how-to guide for developing high-quality multiple-choice questions. AEM Educ Train. 2023;7:e10836. DOI: https://doi.org/10.1002/aet2.10836
11. Abdellatif H, Al-Shahrani AM. Effect of blueprinting methods on test difficulty, discrimination, and reliability indices: cross-sectional study in an integrated learning program. Adv Med Educ Pract. 2019;10:23–30. DOI: http://dx.doi.org/ 10.2147/ amep.s190827
12. Coderre S, Woloschuk W, McLaughlin K. Twelve tips for blueprinting. Med Teach. 2009;31(4):322–4. DOI: https://doi.org/10.1080/ 01421590802225770
13. Ismail MA-A, Mat Pa MN, Mohammad JAM, Yusoff MSB. Seven steps to construct an assessment blueprint: a practical guide. EIMJ. 2020;12(1): 71– 80. DOI : https://doi.org/ 10.21315/eimj2020.12.1.8
14. Corbin J, Strauss A. Basics of qualitative research: Techniques and procedures for developing grounded theory. Sage publications. 2015
15. Fona C. Qualitative data analysis: Using thematic analysis. In Researching and Analysing Business 2024 (pp. 130-145). Routledge.

16. V, Clarke V. To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. Qual Res Sport Exerc Health 2021;13(2):201–16.DOI : http://dx.doi.org/ 10.1080/ 2159676x.2019.1704846

17. Maietta R, Mihas P, Swartout K, Petruzzelli J, Hamilton AB. Sort and sift, think and shift: let the data be your guide an applied approach to working with, learning from, and privileging qualitative data. Qualitative Report. 2021;26(6). DOI: http://dx.doi.org/ 10.46743/2160-3715/2021.5013

18. Dutta AK, Goswami K. Developing a blueprint for theoretical assessment of biochemistry of phase I MBBS students. Med Sci Educ 2023;33(2):339–42. http://dx.doi.org/10.1007/s40670-023-01757-4

19. Chrisyarani DD, Rahayu S, Yulianti Y, Meviana I, Asmah A, Ladamay I. Analysis of the impact of curriculum development and implementation of MBKM on student satisfaction at FIP UNIKAMA. J. Bs. Edu. R 2022 18;6(1):47-55. DOI: https://doi.org/10.21067/jbpd.v6i1.6617

20. Bhardwaj N, Krishna H, Ghatak S, Singh K. Blueprinting of assessment for the lower limb in undergraduate anatomy curriculum. Cureus 2023;15(11):e49357. DOI : http://dx.doi.org/10.7759/cureus.49357

21. Gujarathi AP, Dhakne-Palwe S, Patil RN, Borade-Gedam P, Mahale MS, Gosavi SV, et al. Preparation of blue prints for formative theory assessment of undergraduate medical students in Community Medicine. MVP J Med Sci 2015;2(2):100. DOI : http://dx.doi.org/10.18311/mvpjms/2015/v2/i2/782

22. Er, H.M., Nadarajah, V.D., Hays, R.B. et al. Lessons Learnt from the Development and Implementation of an Online Assessment System for Medical Science Programmes. Med Sci Educ 2019;29:1103–1108. DOI : https://doi.org/10.1007/s40670-01900802-5

Review Article **Open Access**

Limitations of Artificial Intelligence in Orthodontics. Literature Review

Sadia Naureen

ABSTRACT

In the 21st century, advances in computer technology and data science have brought significant innovation to orthodontics, especially through Artificial Intelligence (AI) and Machine Learning (ML). This study, conducted from July 2 to August 15, 2024, in the Orthodontic Department at Rawal Institute of Health Sciences Islamabad, reviews AI's transformative role in dentistry, focusing on its applications, benefits, and challenges. A comprehensive literature search across PubMed and Google Scholar yielded 260 peer-reviewed articles from 2001 to 2024. After applying stringent selection criteria, the review focused on AI's historical development, applications, and limitations in orthodontics. While AI enhances diagnostic imaging and patient care, it cannot replace clinical expertise. Key challenges include patient privacy, data security, and ethical considerations. AI systems rely heavily on high-quality data, necessitating rigorous training. Therefore, AI should be viewed as an adjunct in orthodontics, providing a "second opinion" to support clinical decisions.

Key words: Artificial Intelligence, Hazards, Machine learning, Orthodontics.

How to cite this Article:
Naureen S. Limitations of Artificial Intelligence in Orthodontics. Literature Review. J Bahria Uni Med Dental Coll. 2025;15(1):53-59
DOI: https://doi.org/10.51985/JBUMDC2024452

INTRODUCTION:

In the 21st century, we are witnessing unprecedented advancements in computer technologies and data science, which hold significant potential for applications in orthodontics. One such innovation is Artificial Intelligence (AI), defined as the replication of human cognitive abilities within a machine that is designed to simulate human thought processes.[1] Arthur Samuel coined the term "Machine Learning" (ML), a branch of AI focused on developing algorithms and statistical models that enables computer to learn from historical data and predict conclusions, or decisions without requiring explicit human intervention.[2]

A major leap in this domain occurred with the rise of hypercomputers and the shift from central processing units (CPUs) to graphic processing units (GPUs), which facilitated the handling of vast data—commonly named as "Big Data." The concept of Big Data gained prominence in the early 2000s following Laney's publication that introduced volume, velocity, and variety. Since then, the continuous collection of data has resulted in an ever-growing dataset that fuels innovation.[3,4]

In past few years, deep learning has revolutionized machine learning, marking a major advancement in the field.[5] Both AI and deep learning have gained immense traction in dentistry, where they rely extensively on the availability of large-scale data.[6] Until recently, artificial intelligence (AI) primarily operated within the realm of narrow intelligence and supervised learning, such as automated cephalometric point recognition, tooth segmentation from 3D files, and orthodontic treatment staging. The next advancement involves developing neural networks emulating general intelligence akin to human cognition. Utilizing powerful computers and sophisticated algorithms, these networks will learn to diagnose orthodontic issues and plan treatments, ultimately suggesting optimal strategies for enhanced outcomes and greater predictability.[7] AI is mainly based on electronic data,which is not biological in nature.[8] Integrating patient autonomy, informed consent, ethics, and morality into AI remains challenging, as these are inherently human attributes. While AI serves as a tool within electronic systems, it lacks the ability to recognize patient autonomy, personal identity, or well-being. Additionally, the collection and sharing of vast amounts of data raise significant concerns regarding safety, privacy, and ethics.[9] (Medical healthcare data is among at the most sensitive and confidential). Incorporating AI into routine medical and dental care necessitates careful consideration of issues related to the public sector, patient privacy, and the autonomy rights of patients. A thorough understanding of the possible adverse impacts of AI in dentistry could potentially reshape the current trajectory of its adoption. Furthermore, the future of dental healthcare may increasingly prioritize human-centered AI, focusing on patient well-being, ethical transparency, and respect for patient autonomy.[10] Such an approach would encourage responsible AI development, aligning technology more closely with the specific needs and rights of patients within the field of dental care.

Sadia Naureen *(Corresponding Author)*
Associate Professor, Department of Orthodontics
Rawal Institute of Health Sciences, Islamabad
Email:drsaadis12@gmail.com

Received: 04-10-2024
Accepted: 19-12-2024
1st Revision: 28-10-2024

METHODOLOGY:

A comprehensive search was conducted using the PubMed and Google Scholar databases, targeting peer-reviewed articles published between 1st July 2001 and 30th June 2024. The search employed keywords such as “Hazards of Artificial Intelligence,” “Hazards of Artificial Intelligence in Dentistry,” “Artificial Intelligence in Orthodontics: Pros and Cons,” “Application and Challenges of Artificial Intelligence in Orthodontics,” and “Limitations of Artificial Intelligence in Dentistry,” yielding 88, 78, 15, 12, and 67 papers, respectively.

This review article is organized following a meticulous analysis and examination of the pertinent literature available in the English language. Duplicates, studies involving animals, in vitro experiments, case reports, pilot studies, and redundant or irrelevant data were excluded. The remaining material was carefully reviewed and incorporated into this article. The final selection of articles included those covering the historical development, applications, challenges, and limitations of AI, with a focus on systematic reviews, meta-analyses, and original research articles.

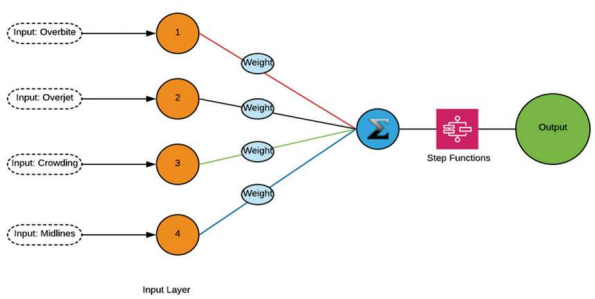
DISCUSSION:

Functioning of Artificial Neural Networks

An Artificial Neural Network (ANN) is a machine learning technique inspired by biological neurons, processing input data through multiple layers to produce output. Variants include Deep Neural Networks (DNNs), which have many hidden layers for complex feature extraction, and Convolutional Neural Networks (CNNs), which use filters to capture spatial information. Generative Adversarial Networks (GANs) generate new data that closely resembles the input data.[10]

Neural networks consist of nodes, or neurons, connected by links that represent the "weights," indicating their influence (figure 1). Each node corresponds to a variable, mirroring the columns in a data table. Inputs such as overbite, overjet, and crowding start with random weights (0 to 1%) and are linked to input nodes that compute correlations.To improve learning, extra "hidden layers" are added, forming deep learning neural networks that enhance prediction accuracy. These networks detect patterns and calculate the probability of correct outcomes, with the final diagnosis determined by input data volume and assigned weights.For neural networks to function effectively, large datasets must be properly labeled and weighted.[11]

Figure 1: Simple neural network showing the input layer, the hidden layer, and the output layer.[11]



Data safety

AI relies heavily on comprehensive computer knowledge, with data protection, extraction quality, and reliability being pivotal concerns. Storing such vast amounts of data necessitates significant investment in large-scale solutions such as cloud storage or data-sharing systems. To ensure consistency and improve accuracy, data collection formats must be standardized from the outset. Unfortunately, existing healthcare databases are not yet sufficiently advanced. Due to the limited availability of high-quality digital data, less than 20% of global medical data has been accessible for use in AI machine learning algorithms.[12] For instance, common limitations in databank analysis, such as unverified diagnosis codes, incomplete information on disease severity, lifestyle factors, habits, and unmeasured confounders, are notable challenges when utilizing Taiwan’s National Health Insurance Research Database.[13]

Patient handling:

Orthodontic treatment typically extends over 3-4 years, making patient management a critical concern. While AI models present impressive potential, they still require ongoing human oversight, as errors can occur during patient care.In orthodontics, the adoption of AI has led to the creation of various AI-based programs, such as WeDoCeph (Audax, Ljubljana, Slovenia), WebCeph (Assemble Circle, Seoul, Republic of Korea), and CephX (ORCA Dental AI, Las Vegas, NV, USA). These systems can automatically identify cephalometric landmarks, compute angles and distances, and generate cephalometric reports with significant findings.However, this accessibility has also sparked concerns about patient safety, especially when AI is used for diagnosis and treatment.[14]Being inherently machine- and software-based, AI lacks the capacity for interpersonal relationships, such as empathy and compassion toward patients. This introduces ethical and security risks, as patient confidentiality becomes more challenging to uphold when sensitive information is stored within systems.[15]

AI models without robust quality control are prone to data errors, outliers, and sudden trend shifts. Additionally, poor integration with clinical workflows limits their ability to adapt to changing data. Concerns also arise over AI reinforcing racial or socioeconomic disparities in healthcare. To address these challenges, AI systems must be built for continuous learning and adaptation.[16] As with any medical technology, the establishment of a robust AI governance framework is essential to maintain result accuracy and ensure patient safety.[17] Continuous evaluation of algorithm performance is crucial to prevent degradation and to enable timely intervention when necessary.One of the most troubling facets of the unpredictable behavior exhibited by AI-driven

diagnostic algorithms within clinical settings is their failure to identify and address issues as they occur. In the absence of robust internal monitoring systems, these algorithms may yield inaccurate outputs alongside valid ones. This unpredictability poses a significant risk of patient harm, often occurring without the awareness of the clinical staff, local system administrators, or the manufacturers involved.[18]

Orthodontic treatment need

The need for orthodontic treatment is determined using standardized indices that assess various diagnostic factors, mainly focusing on the positioning of teeth. Recently, a new multicentric benchmarking dataset was created to compare AI-based tooth segmentation and labeling models, following the "3DTeethSeg'22 challenge." This dataset includes 1,800 labeled intraoral scans from three different commercially available scanners to improve generalization. The leading model achieved an impressive segmentation accuracy of 0.99. However, even with these advancements in automated tooth evaluation, deciding on the necessity for orthodontic treatment is still challenging, particularly in borderline cases. This complexity is exacerbated by significant interexaminer variability, with kappa values ranging from 0.16 to 0.37 for remote evaluations and 0.22 to 0.38 for on-site assessments. Such variability creates challenges for training models and affects the integration of AI into orthodontic evaluations.[19]

Growth analysis

A crucial aspect of designing an orthodontic treatment plan involves analyzing growth patterns and estimating biological age. Several methods can be employed to determine a patient's developmental stage, with one of the most widely used being the evaluation of cervical vertebrae stages (CVS) through lateral cephalometric radiographs.[20] In a study by Kök et al.[21] seven AI algorithms commonly used for classification were compared: k-nearest neighbors (k-NN), Naive Bayes (NB), decision tree (Tree), artificial neural networks (ANN), support vector machine (SVM), random forest (RF), and logistic regression (Log.Regr.). Logistic regression performed the worst in identifying stages CVS1, CVS4, CVS5, and CVS6, often misclassifying CVS4 as CVS3 and CVS5 as CVS4. All algorithms, except for ANN, had difficulties consistently and accurately classifying the stages. However, ANN struggled specifically with correctly identifying CVS5. The confusion matrices revealed ANN's classification accuracy for each stage as follows: CVS1 (93%), CVS2 (89.7%), CVS6 (78%), CVS3 (68.8%), CVS4 (55.6%), and CVS5 (47.4%).

Cephalometric analysis

AI tools have the capability to analyze images obtained from a wide range of imaging modalities, including X-rays and MRIs. Cephalometric analysis and pretreatment imaging are vital in orthodontics, making the field ideal for AI integration. Various AI programs, like WeDoCeph, WebCeph, and CephX, can automatically identify cephalometric landmarks, calculate angles and distances, and produce detailed reports. Additionally, these AI tools are now available on mobile platforms, enhancing accessibility and ensuring global users have equal access.However, it is essential to acknowledge the limitations of AI in cephalometric analysis. Currently, these systems still fall within the scope of supervised machine learning. Common errors in AI-assisted cephalometric analysis include tracing inaccuracies, errors in landmark identification, and miscalculations in measurements.[22] With respect to automated landmark identification, challenges persist, such as variations in individual skeletal structures, image blurring caused by device-specific projection magnifications, and image complexity due to overlapping contralateral structures.[23] Even minor errors in these processes can lead to misclassification, ultimately resulting in potential misdiagnoses.

Radiographic errors are significantly high for several hard tissue landmarks, such as the posterior nasal spine, lower incisor, articular, pterygomaxillary fissure, and upper incisor, even with advanced techniques.[24] Identifying these points is difficult due to the complexities caused by varying X-ray projections on the left and right sides of the craniofacial structure. In cases of malocclusion, the presence of open root apices and dental crowding further reduces the accuracy of AI detection for both upper and lower incisors.[25]

Research conducted by Duran et al. using automatic cephalometric analysis software, including OrthoDx™ and WebCeph, supports these observations.[26] Landmarks such as the basion and orbitale are typically regarded as challenging to identify and are often considered unreliable in cephalometric assessments. Additionally, finding the porion is difficult due to various radiolucencies in the area that can mimic the internal auditory meatus.[27] Regarding soft tissue landmarks, points such as pronasale, subnasale, and pogonion exhibit lower accuracy, often due to increased darkness or reduced brightness in these areas compared to others.[28]

Diagnosis and Treatment Planning

Extraction Decision Making

One of the most intricate challenges in orthodontic treatment is deciding whether extractions are needed for a particular case. This decision is influenced by several factors, including the specific orthodontic issue, patient preferences, expected results, sociocultural factors, and the orthodontist's professional viewpoint. These elements all play a role in shaping the patient's perspective on the recommended extraction therapy.[29,30] Additionally, the orthodontist's decision-making is influenced by their experience, training, and clinical philosophy.[31]These variables make the extraction decision particularly difficult, even for seasoned practitioners. Moreover, treatment recommendations can significantly differ among experts, particularly in borderline cases, further complicating the extraction decision process.[32]

In recent years, various AI tools have emerged to aid in orthodontic treatment decisions.[33,34] Initial research on AI-assisted extraction decision-making has shown promising results, with AI systems aligning with expert evaluations over 80% of the time.[35] For example, a study by Xie et al.[36] found an 80% agreement between AI predictions and expert opinions on extraction decisions, although it was based on just 20 cases. Similarly, Jung and King[37] assessed an artificial neural network (ANN) that achieved 93% accuracy in distinguishing between extraction and non-extraction cases using 12 cephalometric variables, along with an 84% success rate in identifying specific extraction patterns.Semerci et al.[38] reported comparable outcomes, with 94% accuracy in differentiating extraction scenarios, 84.2% for extraction patterns, and 92.8% for anchorage patterns. These studies emphasized key factors for predicting treatment outcomes, including upper arch crowding, positioning of anterior teeth, lower incisor inclination, overjet, overbite, and lip closure ability.

However, it's important to recognize significant limitations in these studies that could introduce bias. For example, the AI systems were trained on data from a small group of experts, which may only represent their individual treatment philosophies without proper validation. Additionally, critical dental factors like extensive fillings, periapical lesions, periodontal issues, previous root canal treatments, and tooth loss were not considered.

Given these limitations, reaching a conclusive decision on orthodontic extractions can be difficult, particularly in borderline cases. Various factors, such as systemic diseases, ongoing growth, and patients' primary concerns, can influence the extraction decision. Therefore, the Arch Length Discrepancy (ALD) value should not be the sole criterion for determining extractions but rather one of several considerations when addressing overcrowding.[39,40] In cases of bimaxillary protrusion, midline discrepancies, profile improvements, orthognathic surgery, and other aesthetic factors, extraction may be necessary despite the normal ALD value.[41] Orthodontists develop treatment plans not only based on clinical data but also on their accumulated experiences, which may include biases from past outcomes. This indicates that treatment strategies can be shaped by a clinician's personal experiences, background, philosophy, aesthetic preferences, and educational influences.[43] Considering these limitations, it's crucial to recognize that reaching a conclusive decision about orthodontic extraction therapy can be complex, particularly in borderline situations. Numerous factors influence the extraction decision in orthodontic treatment planning, including systemic health conditions, ongoing growth, and patients' primary concerns. As such, the Arch Length Discrepancy value alone cannot serve as the sole criterion for extraction but should be considered a primary factor when addressing crowding issues[39,40] Even with a normal ALD value, tooth extraction may be required for cases like bimaxillary protrusion, correcting midline discrepancies, improving facial profiles, orthognathic surgery, or other aesthetic factors. Orthodontists create treatment plans that consider clinical data as well as their own experiences and possible biases from prior cases. As a result, these plans can be shaped by the clinician's personal history, educational background, treatment philosophy, aesthetic preferences, and the institutions they are associated with.[41]To effectively address specific malocclusions with numerous variables, software must gather and learn from extensive data. This is necessary for determining and implementing the most suitable treatment approach. Typical AI models, developed using narrow and specific datasets, often struggle to perform adequately across a broad spectrum of information.[42] Currently, the entire dental field, encompassing orthodontics, is deficient in curated "benchmarking" datasets that facilitate the testing of AI software on standardized, representative data, thereby enabling meaningful comparisons among various applications. Additionally, the absence of uniform reporting metrics further complicates the evaluation and comparison of orthodontic AI technologies.[43] Validation of the AI models for orthodontic treatment planning remains crucial and is currently lacking. Data sets are constructed using unicentric data; in some studies, only 1 expert provided the treatment decisions.[30,35] Moreover, the excessive use of AI in orthodontic diagnosis and treatment planning may hinder the development of critical thinking and learning skills in young, inexperienced practitioners. Another concern is the lack of transparency and accountability. The decision-making processes of AI systems can be opaque, making it challenging to provide explanations or hold them responsible for their outcomes.[44-46]

Orthognathic surgery

Research on AI in orthognathic surgery treatment planning is limited but promising.[47] Knoops et al.[48] utilized a 3D morphable model (3DMM) to automatically diagnose patients, evaluate their risk levels, and generate simulations for treatment plans, achieving 95.5% sensitivity and 95.2% specificity, with an average accuracy of 1.1 ± 0.3 mm. Meanwhile, Chung et al.[49] developed a method using a DeepPose regression neural network to align CBCT images with optically scanned models, improving accuracy by 33.09% over previous leading techniques. Additionally, Choi et al.[35] demonstrated a model that effectively predicted the need for surgery and outlined extraction plans for surgical patients, with accuracy rates between 88% and 97%.

A systematic review conducted by Salazar et al.[50] highlights that current research findings are challenging to generalize because of considerable heterogeneity. For example, profile preferences vary among different ethnic groups, including Asians, Europeans, and Black individuals. The authors noted that although AI has the potential to be a useful tool in orthognathic surgery planning, human judgment remains

essential for making final decisions.

Miscellanious Hazards

Artificial intelligence (AI) presents ethical challenges, particularly in healthcare, where concerns arise about autonomy and decision-making, exemplified by the use of autonomous surgical robots.[51,52] The automation of tasks like image analysis and patient data processing by AI can result in job losses and unemployment.[53]

A major challenge in current orthodontic AI research is its limited generalizability. Due to significant variations in outcomes, metrics, and the lack of standardized datasets, comparing AI across different studies and tasks is extremely difficult. Only a few AI applications in orthodontics have reached full clinical maturity and received regulatory approval.[54] Pianykh[55] highlights several key unresolved issues, starting with reproducibility; AI models are often trained on specific, narrow datasets, limiting their effectiveness across diverse data. Additionally, there are concerns about privacy, safety, and health disparities, particularly regarding AI algorithms that may exacerbate racial or income inequalities. Furthermore, these models can perpetuate biases from their training data, leading to inaccurate diagnoses or treatment for certain demographic groups.[56]

The lack of transparency and accountability in AI systems makes it challenging to understand their decision-making processes, complicating efforts to explain or hold them accountable.[57]There is also a risk of over-reliance on technology, where healthcare professionals may become too dependent on AI, potentially losing the ability to complete tasks without its assistance.[58] Furthermore, AI systems may struggle to grasp context and have difficulty understanding the nuances and subtleties of human health and disease.

Future Implications

Unsupervised learning is a more complex approach where the data lacks labels or classifications. In this method, algorithms are trained to recognize patterns and suggest possible outcomes from the data provided. In orthodontics, unsupervised learning is being increasingly applied to analyze large datasets of malocclusion cases, enabling computers to predict the most effective treatment options.[59] In today's digital era, the phrase "data is power" highlights the importance of ensuring that orthodontic data is protected with the same rigor as medical information, which cannot be shared without prior consent regarding its use. When shared responsibly, the extensive data collected in orthodontic practices, combined with deep neural networks, has great potential to advance the field.Moreover, robotic systems have emerged as invaluable assets, assisting clinicians during surgeries and intricate procedures. Driven by artificial intelligence, these robotic technologies can perform delicate tasks with remarkable precision, leading to improved patient outcomes. The integration of AI with robotics significantly reduces the risk of human error in dentistry, enhancing the accuracy of procedures beyond what traditional methods can achieve.[60]

CONCLUSION:

Undoubtedly, AI has the potential to revolutionize medicine, particularly in the field of diagnostic imaging, including orthodontics. However, AI cannot replace clinical acumen or input of a dentist or radiologist. It is an aid and will always be. Also, every AI tool in dentistry is trained based on annotations by calibrated dental professionals (especially in the deep learning space). If we can trust the reading from electronic sphygmomanometer then there is no reason why similar tools if created in dentistry should not be trusted and accepted to be accurate especially if it has gone through rigorous reliability and validity checks. Errors and Bias in prediction from AI is often introduced by humans during the training process. It still follows the idea of "garbage in , garbage out". If it is fed with faulty data, the output is going to be faulty. Finally, it is important not to be over reliant on AI as a diagnostic tool. It should only be used as

Authors Contribution:
Sadia Naureen: Conception, design, Introduction and discussion

REFERENCES

1. M'hamed J, Dallel I, Tobji S, Ben Amor A. The Impact of Artificial Intelligence on Contemporary Orthodontic Treatment Planning - A Systematic Review and Meta-Analysis. Sch J Dent Sci. 2022 ;(5): 70-87. Doi:10.36347/sjds. 2022.v09i05 .001.
2. Agrawal P, Nikhade P. Artificial Intelligence in Dentistry: Past, Present, and Future. Cureus. 2022 ;14(7):e27405. doi: 10.7759/cureus.27405.
3. Nayak S ,Patgiri R, Doren Singh T. Big Computing: Where are we heading? TD.EAI Endorsed Transactions on Scalable Information Systems.2020;7(27):e9. https://doi.org/10. 4108/eai.13-7-2018.163972.
4. Ng Kam. (2024). Big Data: Understanding and Implementation in the Data-Driven Era. https://www.researchgate. net/ publication/377359928.
5. Soori M, Arezoo B,Dastres R.Artificial intelligence, machine learning and deep learning in advanced robotics, a review.Cognitive Robotics.2023;3:54-70.https://doi.org/ 10.1016/j.cogr.2023.04.001.
6. Fatima A, Shafi I, Afzal H, Díez IT, Lourdes DRM, Breñosa J, Espinosa JCM, Ashraf I. Advancements in Dentistry with Artificial Intelligence: Current Clinical Applications and Future Perspectives. Healthcare (Basel). 2022;10(11):2188. doi: 10.3390/healthcare10112188.
7. Nordblom NF, Büttner M, Schwendicke F. Artificial Intelligence in Orthodontics: Critical Review. J Dent Res. 2024;103(6):577-84. doi: 10.1177/00220345241235606.
8. Bhardwaj A, Kishore S, Pandey DK. Artificial Intelligence in Biological Sciences. Life (Basel). 2022;12(9):1430. doi: 10.3390/life12091430.

9. Arbelaez Ossa L, Lorenzini G, Milford SR, Shaw D, Elger BS, Rost M. Integrating ethics in AI development: a qualitative study. BMC Med Ethics. 2024 Jan 23;25(1):10. doi: 10.1186/s12910-023-01000-0.
10. Huang YK, Hsu LP, Chang YC. Artificial intelligence in clinical dentistry: The potentially negative impacts and future actions. J Dent Sci. 2022;17(4):1817-1818. doi: 10.1016/j.jds.2022.07.013.
11. Retrouvey JM. The role of AI and machine learning in contemporary orthodontics. APOS Trends Orthod. 2021;11(1):74-80. DOI:10.25259/APOS_148_2020.
12. Khalid N, Qayyum A, Bilal M, Al-Fuqaha A, Qadir J.Privacy-preserving artificial intelligence in healthcare: Techniques and applications,Computers in Biology andMedicine. 2023;158:106848.
13. Yu HC, Chen TP, Chang YC. Inflammatory bowel disease as a risk factor for periodontitis under Taiwanese National Health Insurance Research database. J Dent Sci. 2018;13(3):242-47. doi: 10.1016/j.jds.2018.03.004.
14. Kazimierczak N, Kazimierczak W, Serafin Z, Nowicki P, No¿ewski J, Janiszewska-Olszowska J. AI in Orthodontics: Revolutionizing Diagnostics and Treatment Planning-A Comprehensive Review. J Clin Med. 2024 ;13(2):344. doi: 10.3390/jcm13020344.
15. Hung K, Montalvao C, Tanaka R, Kawai T, Bornstein MM. The use and performance of artificial intelligence applications in dental and maxillofacial radiology: A systematic review. Dentomaxillofac Radiol. 2020 ;49(1):20190107. doi: 10.1259/dmfr.20190107.
16. Aldoseri A, Al-Khalifa KN, Hamouda AM. Re-Thinking Data Strategy and Integration for Artificial Intelligence: Concepts, Opportunities, and Challenges. Applied Sciences. 2023; 13(12):7082. https://doi.org/10.3390/app13127082
17. Baelum V, Borchorst E, Buch H, Dømgaard P, Hartig LE. Inter-examiner variability in orthodontic treatment decisions for Danish children with 'borderline' treatment need. Eur J Orthod. 2012 ;34(2):250-6. doi: 10.1093/ejo/cjq195.
18. Larson DB, Harvey H, Rubin DL, Irani N, Tse JR, Langlotz CP. Regulatory Frameworks for Development and Evaluation of Artificial Intelligence-Based Diagnostic Imaging Algorithms: Summary and Recommendations. J Am Coll Radiol. 2021 Mar;18(3 Pt A):413-424. doi: 10.1016/j.jacr.2020.09.060.
19. Ben-Hamadou A, Smaoui O, Rekik A, Pujades S, Boyer E, Lim H, Kim M, Lee M, Chung M, Shin Y-G, et al. 2023. 3DTeethSeg'22: 3D teeth scan segmentation and labeling challenge [accessed 2023 Jul 26]. doi:10.48550/ arXiv.2305.18277.
20. Amasya H, Cesur E, Yýldýrým D, Orhan K. Validation of cervical vertebral maturation stages: Artificial intelligence vs human observer visual analysis. Am J Orthod Dentofacial Orthop. 2020;158(6):e173-e179. doi: 10.1016/j.ajodo. 2020.08.014.
21. Kök H, Acilar AM, Ýzgi MS. Usage and comparison of artificial intelligence algorithms for determination of growth and development by cervical vertebrae stages in orthodontics. Prog Orthod. 2019 ;20(1):41. doi:10.1186/s40510-019-0295-8.
22. Shahidi S, Oshagh M, Gozin F, Salehi P, Danaei SM. Accuracy of computerized automatic identifcation of cephalometric landmarks by a designed software. Dentomaxillofac Radiol. 2013;42:20110187. https://doi.org/10. 1259/dmfr.20110187.
23. Forsyth DB, Shaw WC, Richmond S, Roberts CT. Digital imaging of cephalometric radiographs, Part 2: Image quality. Angle Orthod. 1996;66(1):43-50. doi: 10.1043/0003-3219(1996)066<0043:DIOCRP>2.3.CO;2.
24. Patel KS, Kulkarni N, Singh VP, Parikh K. Identifcation of an alternate maxillary apical base landmark from pre-existing substitutions. Acta Inform Med. 2014;22:347–9. https://doi.org/10.5455/aim.2014.22.347-349.
25. Oh K, Oh IS, Le VNT, Lee DW. Deep anatomical context feature learning for cephalometric landmark detection. IEEE J Biomed Health Inform.2021;25:806–17. https://doi.org/10.1109/JBHI.2020.3002582.
25. Ye, H., Cheng, Z., Ungvijanpunya, N. et al. Is automatic cephalometric software using artificial intelligence better than orthodontist experts in landmark identification?. BMC Oral Health. 2023; 23 : 467. https://doi.org/10.1186/s12903-023-03188-4.
27. Wang CW, Huang CT, Lee JH, Li CH, Chang SW, Siao MJ, Lai TM, Ibragimov B, Vrtovec T, Ronneberger O, Fischer P, Cootes TF, Lindner C. A benchmark for comparison of dental radiography analysis algorithms. Med Image Anal. 2016;31:63–76. https://doi.org/10.1016/j.media.2016.02.004.
28. Ploder O, Kohnke R, Winsauer H, Gotz C, Bissinger O, Haller B, Kolk A. Skeletal-versus soft-tissue-based cephalometric analyses: Is the correlation reproducible? Acta Odontol Scand. 2019;77:135–41. https://doi.org/ 10.1080/00016357. 2018.1515443.
29. Al-Ani MH, Mageet AO. Extraction Planning in Orthodontics. J Contemp Dent Pract. 2018 May 1;19(5):619-23. PMID: 29807975.
30. Real AD, Real OD, Sardina S, Oyonarte R. Use of automated artificial intelligence to predict the need for orthodontic extractions. Korean J Orthod. 2022 ;52(2):102-111. doi: 10.4041/kjod.2022.52.2.102.
31. Evrard A, Tepedino M, Cattaneo PM, Cornelis MA. Which factors influence orthodontists in their decision to extract? A questionnaire survey. J Clin Exp Dent. 2019 ;11(5):e432-e438. doi: 10.4317/jced.55709.
32. Chambers DW, Thakkar D. Consistency of orthodontists' clinical decisions: A systematic review, meta-analysis, and theory development. Am J Orthod Dentofacial Orthop. 2022 ;161(4):497-509.e4. doi: 10.1016/j.ajodo.2021.05.009.
33. Evangelista K, de Freitas Silva BS, Yamamoto-Silva FP, Valladares-Neto J, Silva MAG, Cevidanes LHS, de Luca Canto G, Massignan C. Accuracy of artificial intelligence for tooth extraction decision-making in orthodontics: a systematic review and meta-analysis. Clin Oral Investig. 2022;26(12):6893-6905. doi: 10.1007/s00784-022-04742-0.
34. Liu J, Chen Y, Li S, Zhao Z, Wu Z. Machine learning in orthodontics: Challenges and perspectives. Adv Clin Exp Med. 2021;30(10):1065-74. doi: 10.17219/acem/138702.
35. Choi HI, Jung SK, Baek SH, Lim WH, Ahn SJ, Yang IH, Kim TW. Artificial Intelligent Model With Neural Network Machine Learning for the Diagnosis of Orthognathic Surgery. J Craniofac Surg. 2019;30(7):1986-1989. doi: 10.1097/SCS.0000000000005650. Erratum in: J Craniofac Surg. 2020;31(4):1156. doi: 10.1097/SCS.0000000000006531.
36. Xie X, Wang L, Wang A. Artificial neural network modeling for deciding if extractions are necessary prior to orthodontic treatment. Angle Orthod. 2010 ;80(2):262-6. doi: 10.2319/111608-588.1.

37. Jung SK, Kim TW. New approach for the diagnosis of extractions with neural network machine learning. Am J Orthod Dentofacial Orthop. 2016;149(1):127-33. doi: 10.1016/j.ajodo.2015.07.030.

38. Semerci ZM, Yardýmcý S. Empowering Modern Dentistry: The Impact of Artificial Intelligence on Patient Care and Clinical Decision Making. Diagnostics (Basel). 2024 Jun 14;14(12):1260. doi: 10.3390/diagnostics14121260.

39. Carey CW. Linear arch dimension and tooth size; an evaluation of the bone and dental structures in cases involving the possible reduction of dental units in treatment. Am J Orthod. 1949 ;35(10):762-75. doi: 10.1016/0002-9416(49)90148-7.

40. Saghafi N, Heaton LJ, Bayirli B, Turpin DL, Khosravi R, Bollen AM. Influence of clinicians' experience and gender on extraction decision in orthodontics. Angle Orthod. 2017 ;87(5):641-50. doi: 10.2319/020117-80.1.

41. Chikankar T, Kaiser J, Gupta K, Kamble R. Non-extraction Approach in a Borderline Case of a Growing Patient: A Case Report. Cureus. 2024 Jun 11;16(6):e62195. doi: 10.7759/cureus.62195.

42. Rauf AM, Mahmood TMA, Mohammed MH, Omer ZQ, Kareem FA. Orthodontic Implementation of Machine Learning Algorithms for Predicting Some Linear Dental Arch Measurements and Preventing Anterior Segment Malocclusion: A Prospective Study. Medicina (Kaunas). 2023 Nov 9;59(11):1973. doi: 10.3390/medicina59111973.

43. Arsiwala-Scheppach LT, Chaurasia A, Müller A, Krois J, Schwendicke F. Machine Learning in Dentistry: A Scoping Review. J Clin Med. 2023 Jan 25;12(3):937. doi: 10.3390/jcm12030937.

44. Felzmann H, Fosch-Villaronga E, Lutz C, Tamò-Larrieux A. Towards Transparency by Design for Artificial Intelligence. Sci Eng Ethics. 2020 ;26(6):3333-3361. doi: 10.1007/s11948-020-00276-4.

45. Daneshjou R, Smith MP, Sun MD, Rotemberg V, Zou J. Lack of Transparency and Potential Bias in Artificial Intelligence Data Sets and Algorithms: A Scoping Review. JAMA Dermatol. 2021 ;157(11):1362-1369. doi: 10.1001/ jamadermatol. 2021. 3129.

46. Haibe-Kains B, Adam GA, Hosny A, Khodakarami F; Massive Analysis Quality Control (MAQC) Society Board of Directors; Waldron L, Wang B, McIntosh C, Goldenberg A, Kundaje A, Greene CS, Broderick T, Hoffman MM, Leek JT, Korthauer K, Huber W, Brazma A, Pineau J, Tibshirani R, Hastie T, Ioannidis JPA, Quackenbush J, Aerts HJWL. Transparency and reproducibility in artificial intelligence. Nature. 2020 ;586(7829):E14-E16. doi: 10.1038/s41586-020-2766-y.

47. Sharma, Anju & Kaur, Ginpreet & Tuli, Hardeep Singh & Chhabra, Raunak & Rana, Rashmi. (2024). Advent of artificial intelligence in orthognathic surgery: Advancements and challenges. Scripta Medica.2024;55:231-43. 10.5937/scriptamed55-46960.

48. Knoops PGM, Papaioannou A, Borghi A, Breakey RWF, Wilson AT, Jeelani O, Zafeiriou S, Steinbacher D, Padwa BL, Dunaway DJ, Schievano S. A machine learning framework for automated diagnosis and computer-assisted planning in plastic and reconstructive surgery. Sci Rep. 2019;9(1):13597. doi: 10.1038/s41598-019-49506-1.

49. Chung M, Lee J, Song W, Song Y, Yang IH, Lee J, Shin YG. Automatic Registration Between Dental Cone-Beam CT and Scanned Surface via Deep Pose Regression Neural Networks and Clustered Similarities. IEEE Trans Med Imaging. 2020 ;39(12):3900-3909. doi: 10.1109/TMI.2020.3007520.

50. Salazar D, Rossouw PE, Javed F, Michelogiannakis D. Artificial intelligence for treatment planning and soft tissue outcome prediction of orthognathic treatment: A systematic review. J Orthod. 2024;51(2):107-19. doi: 10.1177/14653125231203743.

51. Naik N, Hameed BMZ, Shetty DK, Swain D, Shah M, Paul R, Aggarwal K, Ibrahim S, Patil V, Smriti K, Shetty S, Rai BP, Chlosta P, Somani BK. Legal and Ethical Consideration in Artificial Intelligence in Healthcare: Who Takes Responsibility? Front Surg. 2022;9:862322. doi: 10.3389/fsurg.2022.862322.

52. Arnold MH. Teasing out Artificial Intelligence in Medicine: An Ethical Critique of Artificial Intelligence and Machine Learning in Medicine. J Bioeth Inq. 2021;18(1):121-139. doi: 10.1007/s11673-020-10080-1.

53. Chen N, Li Z, Tang B. Can digital skill protect against job displacement risk caused by artificial intelligence? Empirical evidence from 701 detailed occupations. PLoS One. 2022 ;17(11):e0277280. doi: 10.1371/journal.pone.0277280.

54. Nordblom NF, Büttner M, Schwendicke F. Artificial Intelligence in Orthodontics: Critical Review. J Dent Res. 2024;103(6):577-584. doi: 10.1177/00220345241235606.

55. Pianykh OS, Langs G, Dewey M, Enzmann DR, Herold CJ, Schoenberg SO, Brink JA. Continuous Learning AI in Radiology: Implementation Principles and Early Applications. Radiology. 2020 ;297(1):6-14. doi: 10.1148/radiol.2020200038.

56. Peters U. Algorithmic Political Bias in Artificial Intelligence Systems. Philos Technol. 2022;35(2):25. doi: 10.1007/s13347-022-00512-8.

57. Ostherr K. Artificial Intelligence and Medical Humanities. J Med Humanit. 2022 ;43(2):211-232. doi: 10.1007/s10912-020-09636-4.

58. Haibe-Kains B, Adam GA, Hosny A, Khodakarami F; Massive Analysis Quality Control (MAQC) Society Board of Directors; Waldron L, Wang B, McIntosh C, Goldenberg A, Kundaje A, Greene CS, Broderick T, Hoffman MM, Leek JT, Korthauer K, Huber W, Brazma A, Pineau J, Tibshirani R, Hastie T, Ioannidis JPA, Quackenbush J, Aerts HJWL. Transparency and reproducibility in artificial intelligence. Nature. 2020;586(7829):E14-E16. doi: 10.1038/s41586-020-2766-y.

59. Wadhwa V, Alagappan M, Gonzalez A, Gupta K, Brown JRG, Cohen J, Sawhney M, Pleskow D, Berzin TM. Physician sentiment toward artificial intelligence (AI) in colonoscopic practice: a survey of US gastroenterologists. Endosc Int Open. 2020 ;8(10):E1379-E1384. doi: 10.1055/a-1223-1926.

60. Zhou C, Pan S, Zhou T, editors. Design and implementation of software simulation system for dental orthodontic robot In: IOP Conference Series: Materials Science and Engineering. Bristol: IOP Publishing; 2019.

Case Report **Open Access**

Aesthetic Management of Coronal Dilacerations with Enamel Hypoplasia of Permanent Maxillary Central Incisors:

Nehal Amir, Muqadus Hayat

ABSTRACT

Dilaceration is a peculiar developmental dental anomaly. It is associated with traumatic events of deciduous teeth affecting the permanent tooth buds. It is chiefly a precipitous change in the axial inclination between the crown and the root of a tooth. Dilacerated crown, a rare clinical presentation, is a result of the non-axial displacement of pre-formed hard tissues of a developing crown at an angle to its longitudinal axis. It conspicuously impacts the appearance of patient. Enamel hypoplasia is primarily due to the trauma or infection of primary predecessor tooth resulting in a quantitative defect in enamel of permanent successors. Occasionally, both conditions; dilacerated crown and enamel hypoplasia can occur concomitantly producing many unpropitious outcomes. This particular case is about a 14-year-old boy presenting to the Department of Operative dentistry and Endodontics for the esthetic management of anomalous maxillary central incisors. These anomalous teeth were conservatively managed using direct composite veneers.

Keywords: Dental anomaly, Dilaceration, Enamel hypoplasia

How to cite this Article:
Amir N, Hayat M. Amir N, Hayat M. Aesthetic Management of Coronal Dilacerations with Enamel Hypoplasia of Permanent Maxillary Central Incisors: J Bahria Uni Med Dental Coll. 2025;15(1):60-63 DOI: https://doi.org/10.51985/JBUMDC2024445

INTRODUCTION:

Dental anomalies are characteristically aberrant morphological or histological alterations in the normal shape, structure, form or number of teeth. They can be developmental or acquired. Developmental anomalies are localized or generalized inherited defects during tooth formation. Dilaceration is a distinctive localized developmental dental anomaly characterized by abnormal deviation in the normal angulation of coronal or radicular portion of the tooth. [1]

Coronal Dilaceration is an abrupt, non-axial derangement in the developing crown in response to a traumatic episode along its longitudinal axis. The etiology of dilaceration can be categorized into traumatic or ectopic tooth bud development. The cause is chiefly accredited to dental trauma in primary predecessors affecting permanent tooth germs but there is a vast array of clinical scenarios in which no traumatic cause could be designated as an etiological factor. A possible explanation could be that majority of pediatric traumatic events remain unrecognized or merely neglected by the guardians. [2]

Subsequently, another commonly encountered localized, inherited dental defect is Enamel hypoplasia. It is primarily linked to trauma or infection of primary predecessor tooth resulting in a quantitative defect in enamel of permanent successors. Occasionally, both coronal dilaceration and hypoplastic enamel defects can occur concomitantly producing many unpropitious outcomes. [3] The management of these developmental defects necessitate a strategic multidisciplinary approach for patient rehabilitation. A tailored treatment plan has to be devised encompassing restorative, endodontic, orthodontic and surgical domains providing high-quality dental care to patients. This not only ameliorate the symptoms but also enhance the quality of life. [4] The aim of this case report is to shed light on the prompt diagnosis and timely intervention of inherited dental defects. Such anomalies, if managed rationally, can drastically upgrade the final treatment outcomes.

Case Report

A 14-year-old male patient, resident of Islamabad, reported to the Outpatient Department of Operative Dentistry and Endodontics, School of Dentistry, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad on 25th July, 2024 with the complaint of deformed upper front teeth and misaligned dentition. A comprehensive medico-dental history was documented scrupulously. The patient, escorted by his father, couldn't recall any significant history of childhood illness or dental trauma. Moreover, they reported that the primary dentition was well-formed but as soon as the permanent front two teeth erupted, they were disfigured. They had also previously consulted many dental practitioners concerning their dental issue. This esthetic concern emanated considerable psycho-social impact on the patient's mental well-being and self-confidence.

Nehal Amir *(Corresponding Author)*
Resident, Department of Operative Dentistry & Endodontics
Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad
Email: dr.nehal511@yahoo.com

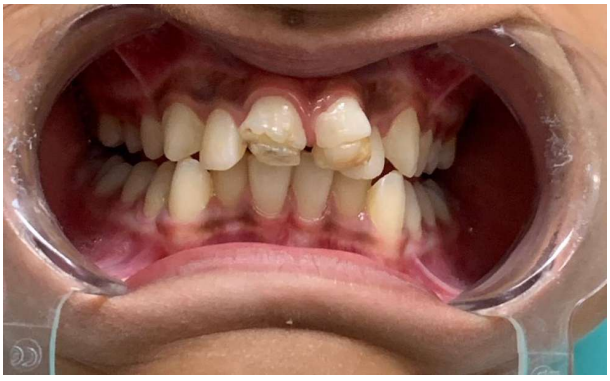
Muqadus Hayat
House Officer, Department of General Dentistry
Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad
Email: muqadushayat2000@gmail.com

Received: 26-09-2024
Accepted: 19-12-2024 **1st Revision: 09-12-2024**

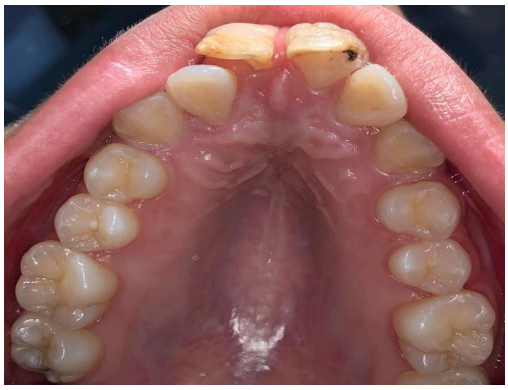
On clinical examination, the extra-oral findings were non-contributory. On intra-oral examination, the maxillary right and left central incisors were affected. The coronal portion of the tooth was displaced palatally. The enamel was hypoplastic in the middle-incisal third region of the crown. On palatal aspect of these anomalous teeth, there was a deep groove depicting carious lesion along the junction of the dilacerated and non-dilacerated coronal part of the tooth. The teeth were in Angle Class II malocclusion. *Figure 1* depicts the clinical presentation of these malformed maxillary central incisors. The examination was supplemented by periapical radiography to investigate for any radicular anomaly (*Figure 2*). After cumulating all significant aspects, the case was diagnosed as Crown Dilaceration with Localized Enamel Hypoplasia. Dental trauma, despite being a very common cause, could not be specified as the etiological factor for this case presentation since, the patient and the guardian didn't recollect any episode of childhood accident.

The treatment plan was devised. The case was primarily managed in three stages. The first stage, *Reassurance and Counselling*, was the pivot of management in this case. The patient and the guardian were meticulously briefed about the dental issue, its possible causative factors, the cos and pros of dental intervention, and the anticipated treatment outcomes. The second stage, *Restorative phase*, was fundamentally an interim esthetic intervention for the two maxillary central incisors till the patient reaches adulthood, after which the case would be subjected to a definitive

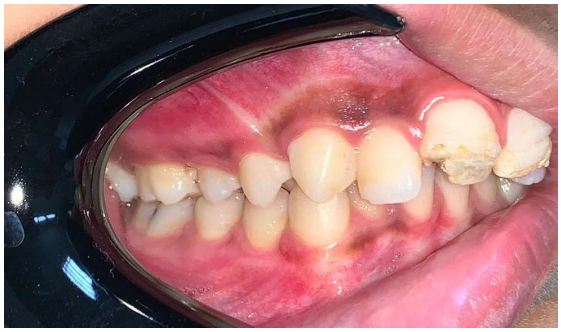
Figure 1. Clinical representation of dilacerated crowns with localized hypoplastic enamel.



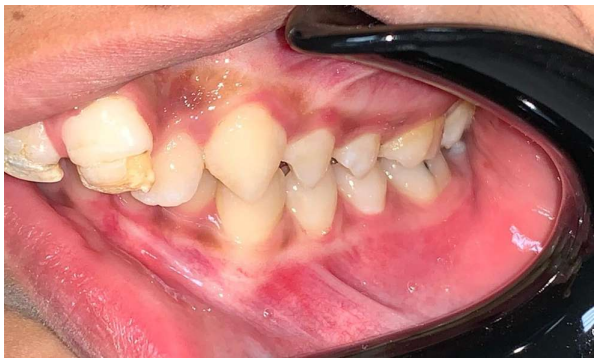
(A) Anterior intra-oral view: The maxillary right and left central incisors are deformed (dilacerated crowns and hypoplastic enamel defect involving middle-incisal region of teeth)



(B) Maxillary Occlusal view: The maxillary central incisors are displaced (bending) palatally. Carious lesions involving the palatal aspect of these teeth.



(C) **Right Buccal view:** Clinical presentation of palatal curvature of the crown of right maxillary central incisor. Hypoplastic enamel defect is involving middle-incisal third region of the tooth.



(D) **Left Buccal view:** The palatally curved coronal portion of left maxillary central incisor along with its hypoplastic enamel surface.

Figure 2. Intra-oral Periapical Radiographic representation of dilacerated crowns of maxillary right and left central incisors

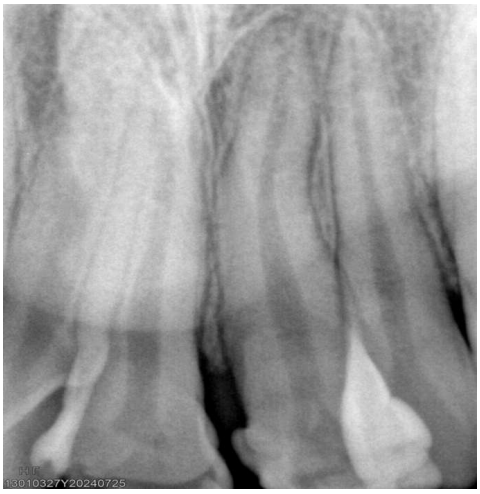
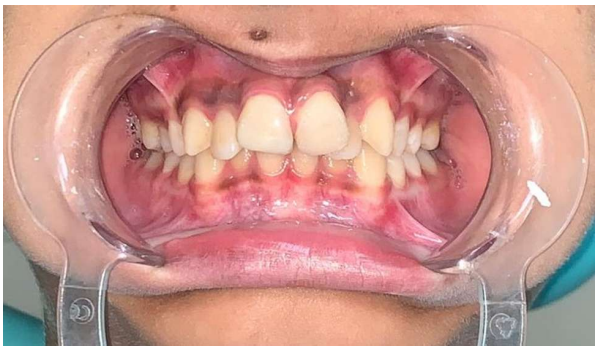


Figure 3. Post-operative clinical depiction of the restored maxillary central incisors. The anomalous maxillary central incisors were conservatively managed using direct composite veneers.



restorative plan. The Light cure direct composite veneers were planned as a preferable treatment option in this case. This was a conservative and practicable option that would address the esthetic complaint appreciably. The third stage, *Fixed Orthodontic treatment phase*, was planned to rectify the malocclusion. Afterwards, an informed consent form was signed by the patient with due permission granted by the guardian.

Succeeding the pre-treatment planning phase, the restorative intervention was performed under rubber dam isolation. After the concerned teeth were prepared, an etch-and-rinse adhesive strategy was accomplished for the esthetic treatment. Acid etching was performed using Phosphoric acid 35% (Etchant gel S Coltene, Switzerland) followed by rinsing and air drying of the affected region of the teeth. Subsequently, the etched surface was vigorously coated with adhesive (One Coat Bond SL Coltene, Switzerland) for 20 seconds. This was followed by another application for 20 seconds. Afterwards, the adhesive coating was light-cured using an LED curing light (Woodpecker DTE LUX E Plus, Woodpecker, China) for 40 seconds. Eventually, the affected teeth were restored with direct composite veneers using light cure composite resin (Brilliant NG Universal Nano Composite Coltene, Switzerland) followed by light curing for 40 seconds. The final restoration was polished using a Jiffy Original Composite System (Ultradent, USA). *Figure 3* represents the post-operative clinical presentation of the restored teeth. The patient was eminently satisfied by the final treatment outcome. Post-restorative instructions were given and the patient was referred to the Department of Orthodontics for the management of maloccluded teeth.

DISCUSSION:

Dental traumatology is an indispensable predicament in oral public health. Being an emergency situation, it mandates expeditious intervention to avoid any inauspicious consequences. Besides medico-dental aspects of traumatic events, it has a noteworthy psychological impact. Owing to the contiguity of permanent tooth bud with the apex of the deciduous tooth, any infection or trauma to the deciduous teeth can have a crucial impact on the eruption of permanent dentition.[5] The developmental malformations in the permanent successors due to dento-alveolar trauma or periapical infection associated with the deciduous predecessor teeth encompasses from yellowish-brown discoloration to hypoplastic enamel defects, coronal dilaceration, radicular duplication or dilaceration, restricted or absolute arrest of root development, odontoma-like deformations, sequestration of the permanent tooth bud, and disruption in the eruption of successor teeth.[6] In this particular case report, the patient presented with localized hypoplastic enamel defect in association with a dilacerated crown. The coronal portion of the teeth were palatally displaced where a plaque stagnation site was established that resulted in the development of a carious lesion palatally. These anomalous defects were conservatively managed in accordance with the fundamentals of minimal intervention adhesive dentistry. T.S. Mellara et al [7] had reported similar cases of dilacerated teeth that were conservatively restored utilizing direct composite resin to reclaim aesthetics and functionality of patients. An analogous case was reported by Sodhi JS. et al [8] where localized enamel hypoplasia was co-existent on a dilacerated crown. However, the coronal displacement was in the labial direction in opposition to the current case where the crown was displaced palatally.

Developmental dental malformations, frequently witnessed in the maxillary arch, have a variable presentation, with hypoplastic enamel defects being the most commonly encountered while coronal or radicular dilaceration being an infrequent clinical finding.[5, 9, 10] Dento-alveolar trauma, despite being a widespread cause of localized dental anomalies, in this specific case, the patient and the guardian could not recollect any history of childhood accidents indicating an idiopathic etiology. However, Topouzelis et al. [2] have significantly highlighted the fact that many episodes of dental trauma are either forgotten or unobserved by parents. Nonetheless, Walia PS. et al.[11] have clearly mentioned in their study that trauma to the predecessor tooth is not the absolute etiological factor for dilaceration and idiopathic dental deformations could be a causative factor in case of unclear evidence of a traumatic event. Regardless of the etiology behind dental anomalies, these malformations necessitate early detection, well-planned intervention, and periodic follow-ups to provide an aesthetic, functional, and psychological benefit to the patients.

CONCLUSION:

Developmental dental malformations are frequently encountered findings in clinical settings. They constitute significant diagnostic, prognostic, and interventional challenges. Coronal dilaceration, despite being a rare finding, can produce massive aesthetic and psychological influence and hence require prompt intervention. These developmental defects, if not managed timely, can result in loss of tooth structure, aesthetic problems, endodontic or periodontal

implications, and functional disability in patients. Henceforth, it is extremely crucial to treat these cases on a priority basis with a multidisciplinary approach to provide prodigious dental care to patients.

Authors Contribution:
Nehal Amir: Conception, Principal Investigator (clinician), Literature Review, Manuscript writing and Critical Revision
Muqadus Hayat: Contributed to assistance during the treatment, contributed to manuscript writing and editing

REFERENCES:

1. Abeer AlHadidi, Pui P, Yazan Hassona. Developmental and Acquired Abnormalities of the Teeth. Dental Clinics of North America. 2024;68(2):227–45.
2. Topouzelis N, Tsaousoglou P, Pisoka V, Zouloumis L. Dilaceration of maxillary central incisor: a literature review. Dent Traumatol. 2010;26(5):427-33.
3. Patel A, Aghababaie S, Parekh S. Hypomineralisation or hypoplasia? Br Dent J. 2019;227(8):683-686.
4. Shekhar MG, Almugla YM, Mohan R, AlNasser BM. Concomitant Crown Dilaceration and Concrescence in Maxillary Incisors following Trauma to their Primary Predecessors: A Case Report. J Pharm Bioallied Sci. 2023;15(Suppl 2):S1341-S1343.
5. Caeiro-Villasenín L, Serna-Muñoz C, Pérez-Silva A, Vicente-Hernández A, Poza-Pascual A, Ortiz-Ruiz AJ. Developmental Dental Defects in Permanent Teeth Resulting from Trauma in Primary Dentition: A Systematic Review. Int J Environ Res Public Health. 2022;19(2):754.
6. Avinash A, Dubey A, Khandelwal V, Nayak PA. 'Mend the bend': a report of two cases of labial dilacerated and palatal dilacerated crown. BMJ Case Rep. 2013;2013:bcr2013200291.
7. Mellara Tde S, Nelson-Filho P, Queiroz AM, Santamaria Júnior M, Silva RA, Silva LA. Crown dilaceration in permanent teeth after trauma to the primary predecessors: report of three cases. Braz Dent J. 2012;23(5):591-6.
8. Sodhi, Jasmeet & Khambete, Neha & Kumar, Rahul & Sodhi, Sonia & Abraham, Reji. (2013). Crown Dilaceration of Maxillary Left Permanent Central Incisor with Localised Enamel Hypoplasia. J Res Adv Dent. 2. 34.
9. Olatosi OO, Oyapero A, Akinwande KO, Ayedun OS, Aladenika ET, Obe OI. Pattern and prevalence of dental anomalies among a paediatric population in Lagos, Nigeria. Niger Postgrad Med J. 2022;29(2):167-172.
10. Jabeen, Nusrat & Rauf, Musarrat & Hussain, Musarrat & Sarwar, Huma & Muhammad Naeem, Meshal & Majeed, Mansoor. (2020). Frequency of Developmental Dental Anomalies in Patients Presented with Dilacerated Teeth. Pakistan Journal of Medical and Health Sciences. 14. 1489.
11. Walia PS, Rohilla AK, Choudhary S, Kaur R. Review of Dilaceration of Maxillary Central Incisor: A Multidisciplinary Challenge. Int J Clin Pediatr Dent 2016;9(1):90-98.

Commentary **Open Access**

Liraglutide - A Promising Approach Against Obesity

Nabila Rafi, Muhammad Sajid Abbas Jaffri, Kamran Yousuf

How to cite this Article:
Rafi N, Jaffri MSA, Yousuf K. Liraglutide - A Promising Approach Against Obesity. J Bahria Uni Med Dental Coll. 2025;15(1):64-66
DOI: https://doi.org/10.51985/JBUMDC2024455

Back ground

Obesity has emerged as a global chronic condition that poses a significant public health issue. The World Health Organisation (WHO) has reported a significant increase in obesity rates, which have nearly quadrupled since 1975.[1] Thus, it is crucial to consider the significant health risks associated with this issue, including the potential for developing type 2 diabetes, cardiovascular diseases, endocrinal malignancies, and musculoskeletal difficulties. Furthermore, obesity incurs substantial expenses for healthcare systems and populations at large.[2]

Traditional weight loss methods such as dieting and exercise, while successful in addressing obesity, have shown limited effectiveness in the long-term.[3] Although lifestyle modifications are the primary strategies in treating obesity, most individuals struggle to achieve and sustain significant weight loss with these treatments alone. Several crucial elements that influence weight reduction include gene predisposition, metabolic adaption, environmental conditions, and psychological state.[4]

Liraglutide; As antidiabetic drug

Liraglutide is a GLP-1 receptor agonist and is derived from diabetes type 2 medication . It was initially developed for this purpose, but its unusual action, namely suppressing hunger and facilitating weight loss, has resulted in its approval by the FDA for the treatment of obesity.[5] Liraglutide functions by mimicking the effects of naturally occurring GLP-1, which plays a role in controlling glucose metabolism, insulin release, and feelings of fullness. Moreover, as Nadkarni et al. claim, it reduces the intake of calories, slows down stomach emptying, and speeds up the passage of food through the intestines, which also results in the activation of the central nervous system and peripheral tissues.[6]

Gastric emptying

Gastric emptying is the process by which food is expelled from the stomach and enters the small intestine.[7] The decrease in the jejunum's functionality is due to the reduced rate of absorption of nutrients from the digestive tract into the bloodstream. Consequently, the duration of the feeling of fullness is extended and the quantity of consumed food is diminished. During this time frame, liraglutide was found to slow down the process of stomach emptying.[8]

Insulin Secretion

Liraglutide exerts various effects on insulin production. Additionally, it helps regulate hunger and accelerates the process of emptying the stomach, while also promoting the secretion of insulin from pancreatic beta cells in response to elevated blood sugar level.[9] Type 2 diabetes mellitus (T2DM) patients will have enhanced regulation of blood sugar levels through the insulinotropic property. Liraglutide affects glucagon release from pancreatic alpha cells by acting as a full agonist of the glucagon-like peptide-1 receptor. Moreover, it exerts a hypoglycemic impact by reducing hepatic glyconeogenesis, hence enhancing glucose tolerance. Liraglutide aids in achieving positive outcomes in situations of overweight and insulin resistance by enhancing metabolism.[10]

Central and Peripheral Mechanisms of Action:

Liraglutide demonstrates a particular action through its overlapping impact on both central and peripheral pathways, which, in combination, facilitates fat loss.[11] It is directed on the hypothalamus and other brain regions related to appetite regulation, which leads to decreasing hunger and increasing the feeling of satiety. Furthermore, it also has an indirect impact on the emptying of stomach, the secretion of insulin and the metabolism of glucose, thereby bringing about reduction of calorie absorption and partaking in the metabolic processes successfully.[12]

Clinical Trial

Previous SCALE study has revealed that subjects assigned to the liraglutide 3.0 mg group for 56 weeks did achieve greater weight loss than those in the placebo group in overweight/obese patients with the prediabetes. Another example is the SCALE Diabetes program released liraglutide

Nabila Rafi *(Corresponding Author)*
M.Phil Student in Pharmacology
Bahria University Health Sciences, Campus Karachi
Email: nabz_27@hotmail.com

Muhammad Sajid Abbas Jaffri
Senior professor, Department of medicine
Bahria University Health Sciences, Campus Karachi
Email: drsajid.jaffry@live.com

Kamran Yousuf
Assistant professor, Department of Pharmacology,
Bahria University Health Sciences, Campus Karachi
Email: kamran.bumdc@bahria.edu.pk

Received: 09-10-2024
Accepted: 18-12-2024

1.8 mg administration superior in weight loss and better blood sugar control in type 2 diabetic patients (T2DM) over 56 weeks compared to placebo.

The SCALE Maintenance trial was conducted to detect the lasting effect of liraglutide 3.0 mg on weight management and to see if liraglutide was as safe for continuous use as it was for weight management. Although 56 weeks of liraglutide medicine had already showed its effectiveness, the benefits of the therapy remained steady, which resulted in longer term weight loss and a lower risk of weight regain than the placebo group.

Dose-Response Relationship:

Studies[13-15] have conclusively demonstrated a clear connection between liraglutide and the reduction of body weight. The amount of weight loss achieved is directly influenced by the dosage administered. Greater doses of liraglutide, namely over 3.0 mg, resulted in more significant weight reduction results in comparison to lesser doses or a placebo. While the precise processes behind this dose-response connection are not fully understood, it is likely that it involves increased feelings of fullness, decreased consumption of food, and better metabolic factors.

Side effects

Commonly seen side effects of liraglutide usage include gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and constipation.[16] Usually, these negative effects appear in the first few weeks after starting treatment and may get better over time as individuals adjust to the medication. Higher doses of medication often lead to an increase in gastrointestinal side effects. In severe circumstances, some persons may stop taking the medication because the adverse effects become intolerable.[17]

The primary adverse effects of liraglutide are pancreatitis and hypoglycaemia.[18] Furthermore, pancreatitis is an infrequent negative outcome observed in people who get this medication. Pancreatitis can be identified by attentively observing symptoms such as prolonged abdominal pain.[19] Immediate discontinuation of medication is necessary for suspected cases of pancreatitis. In addition, liraglutide has the potential to cause hypoglycemia, especially when used in combination with insulin or sulfonylureas in persons diagnosed with type 2 diabetes mellitus.[20]

Cardiovascular Safety:

The cardiovascular safety data for liraglutide is obtained from wide-ranging clinical trials and continuous post-marketing observations. Unlike other medications in the market, liraglutide is not only free of those adverse cardiovascular effects but it also reduces cardiovascular risks of individuals with obesity and type 2 diabetes mellitus.

The LEADER (Liraglutide Effect and Action in Diabetes), which dealt with the cardiovascular consequences in high-risk patients with cardiovascular disease and type 2 diabetes. This trial indeed proved a significantly high occurrence of the major cardiovascular adverse events, including the cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, among the liraglutide participants compared with the placebo group.

Similarly, the SCALE trial demonstrated that liraglutide, as one of the GLP-1 receptor agonists, improves many cardiovascular risk factors like lowering blood pressure, cholesterol, blood sugar, and inflammation markers.

Patient selection:

Liraglutide has received approval as a treatment choice for those with body mass index (BMI) that falls under the 30 kg/m² mark in their adulthood. Besides this, guidelines say it should be suggested for those who have a BMI of over 27 kg/m², provided they have any of the weight-related co-morbid conditions such as hypertension, type 2 diabetes mellitus or abnormal lipid levels. Determining individuals at risk of obesity-related complications should be one goal.

The assessment of patients' conditions should involve the prioritization of and consideration of many issues, such as patients' BMI, their comorbidities already existing, and the treatment history. An individual with a body mass index of 30 kg/m² or higher is considered an appropriate patient for liraglutide therapy because he/she belongs to the group of people vulnerable to obesity-related health problems. Nevertheless, patients with a BMI of 27 kg/m² and suppose that they also suffer from diseases including diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, dyslipidemia, and high blood pressure could also benefit from liraglutide treatment. But in our part of the world it is very costly .The inclusive technique is oriented at working with the problems of weight and metabolic aspects at the same time.

Current scientific research on the GLP-1 associated treatment for obesity centers around creating new formulations and combination treatments in order to enhance weight loss outcomes. Researchers are studying if the long-acting release forms of liraglutide might facilitate patient compliance and the convenience of use. Moreover, the continuous evaluation of the combination of liraglutide with other medications commonly prescribed in weight-loss management is being conducted, for instance, GLP-1 receptor agonists and metabolic modulators. This collaborative approach aims to bring together the two approaches for additive weight loss and potent therapeutic outcomes in obesity treatment.

CONCLUSION:

In conclusion, liraglutide stands out among the group of anti-obesity drugs and there is a possibility that it will fill the gaps in the current treatment of obesity. Meta-analysis of a wide range of clinical studies revealed that it has a significant impact on weight loss, metabolic parameters, as well as reduction of use of medications in the treatment of

obesity-associated comorbidities. The unique feature of its dual-action mechanism that targets both appetite control and metabolism determines it as an innovatively reliable treatment approach. For the future, research should aim at focusing on improving patient selection criteria, examining combo therapies and overcoming the obstacles to the maintenance and success. Additionally, spurring research on new formulations and personalized models is a major step towards extending the clinical utility of liraglutide in dealing with obesity and its related metabolic implications which would in turn improve patient outcomes in this evolving scenario.

Authors Contribution:
Nabila Rafi: Conception of Study
Muhammad Sajid Abbas Jaffri: Critical Review
Kamran Yousuf: Final Proof read

REFERENCES:

1. Boutari, C. and C.S. Mantzoros, A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism, 2022. 133: p. 155217, DOI: 10.1016/j.metabol.2022.155217 .
2. Hecker, J., K. Freijer, M. Hiligsmann, and S.M.A.A. Evers, Burden of disease study of overweight and obesity; the societal impact in terms of cost-of-illness and health-related quality of life. BMC Public Health, 2022. 22(1): p. 46; https://doi.org/10.1186/s12889-021-12449-2.
3. Montesi, L., M. El Ghoch, L. Brodosi, S. Calugi, G. Marchesini, and R. Dalle Grave, Long-term weight loss maintenance for obesity: a multidisciplinary approach. Diabetes Metab Syndr Obes, 2016. 9: p. 37-46 doi: 10.2147/DMSO.S89836.
4. Greenway, F.L., Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes (Lond), 2015. 39(8): p. 1188-96; DOI: 10.1038/ijo.2015.59 .
5. Lin, C.-H., L. Shao, Y.-M. Zhang, Y.-J. Tu, Y. Zhang, B. Tomlinson, P. Chan, and Z. Liu, An evaluation of liraglutide including its efficacy and safety for the treatment of obesity. Expert opinion on pharmacotherapy, 2020. 21(3): p. 275-285; DOI: 10.1080/14656566.2019.1695779 .
6. Nadkarni, P., O.G. Chepurny, and G.G. Holz, Regulation of glucose homeostasis by GLP-1. Prog Mol Biol Transl Sci, 2014. 121: p. 23-65; DOI: 10.1016/B978-0-12-800101-1.00002-8.
7. Maselli, D., J. Atieh, M.M. Clark, D. Eckert, A. Taylor, P. Carlson, D.D. Burton, I. Busciglio, W.S. Harmsen, A. Vella, and A. Acosta, Effects of liraglutide on gastrointestinal functions and weight in obesity: A randomized clinical and pharmacogenomic trial. 2022. 30(8): p. 1608-1620; DOI: 10.1002/oby.23481 .
8. Papaetis, G.S., Liraglutide therapy in a prediabetic state: rethinking the evidence. Current Diabetes Reviews, 2020. 16(7): p. 699-715; DOI: 10.2174/1573399816666191230113446.
9. Wajcberg, E. and A. Amarah, Liraglutide in the management of type 2 diabetes. Drug Des Devel Ther, 2010. 4: p. 279-90; doi: 10.2147/DDDT.S10180 .
10. Babic, I., D. Sellers, P.L. Else, J. Nealon, A.L. Osborne, N. Pai, and K. Weston-Green, Effect of liraglutide on neural and peripheral markers of metabolic function during antipsychotic treatment in rats. Journal of Psychopharmacology, 2021. 35(3): p. 284-302; DOI: 10.1177/0269881120981377.
11. Kumari, P., M. Nakata, B.Y. Zhang, Z. Otgon-Uul, and T. Yada, GLP-1 receptor agonist liraglutide exerts central action to induce â-cell proliferation through medulla to vagal pathway in mice. Biochemical and Biophysical Research Communications, 2018. 499(3): p. 618-625; DOI: 10.1016/j.bbrc.2018.03.199.
12. Trenson, L., S. Trenson, F. van Nes, C. Moyson, M. Lannoo, E. Deleus, A. Meulemans, C. Matthys, A. Mertens, B. Van der Schueren, and R. Vangoitsenhoven, Liraglutide for Weight Management in the Real World: Significant Weight Loss Even if the Maximal Daily Dose Is Not Achieved. Obes Facts, 2022. 15(1): p. 83-89; DOI: 10.1159/000520217.
13. Blackman, A., G.D. Foster, G. Zammit, R. Rosenberg, L. Aronne, T. Wadden, B. Claudius, C.B. Jensen, and E. Mignot, Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond), 2016. 40(8): p. 1310-9; doi: 10.1038/ijo.2016.52.
14. Astrup, A., S. Rössner, L. Van Gaal, A. Rissanen, L. Niskanen, M. Hakim, J. Madsen, M. Rasmussen, and M. Lean, Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet, 2009. 374: p. 1606-16; DOI: 10.1016/S0140-6736(09)61375-1.
15. Gorgojo-Martínez, J.J., P. Mezquita-Raya, J. Carretero-Gómez, A. Castro, A. Cebrián-Cuenca, A. de Torres-Sánchez, M.D. García-de-Lucas, J. Núñez, J.C. Obaya, and M.J. Soler, Clinical recommendations to manage gastrointestinal adverse events in patients treated with Glp-1 receptor agonists: a multidisciplinary expert consensus. Journal of Clinical Medicine, 2022. 12(1): p. 145; DOI: 10.3390/jcm12010145.
16. Seo, Y.-G., Side Effects Associated with Liraglutide Treatment for Obesity as Well as Diabetes. Journal of Obesity & Metabolic Syndrome, 2020. 30; doi: 10.7570/jomes20059.
17. Dimitrios, P., D. Michael, K. Vasilios, S. Konstantinos, I. Konstantinos, P. Konstantinos, B. Spyridon, and K. Asterios, Liraglutide as adjunct to insulin treatment in patients with type 1 diabetes: a systematic review and meta-analysis. Current Diabetes Reviews, 2020. 16(4): p. 313-326; DOI: 10.2174/1573399815666190614141918.
18. Javed, H., G.S. Kogilathota Jagirdhar, R. Kashyap, and P.H. Vekaria, Liraglutide-Induced Pancreatitis: A Case Report and Literature Review. Cureus, 2023. 15(4): p. e38263; DOI: 10.7759/cureus.38263.
19. Nafisah, S.B. and D. Almatrafi, Liraglutide overdose: A case report and an updated review. 2020. 20(1): p. 46-49; DOI: 10.4103/2452-2473.276386.
20. Kalra, S., Follow the LEADER-Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results Trial. Diabetes Ther, 2016. 7(4): p. 601-609; doi: 10.1007/s13300-016-0197-4.

The Evolving Role of Genetic Counseling in Genomic Medicine

Ghulam Hassam U Din Tarrar, Nimra Mushtaq, Muhammad Muzamil

How to cite this Article:
Tarrar GHU, Mushtaq N, Muzammil M. The Evolving Role of Genetic Counseling in Genomic Medicine. J Bahria Uni Med Dental Coll. 2025;15(1):67 DOI: https://doi.org/10.51985/JBUMDC2024435

Genetic counseling involves educating at-risk patients or their close relatives about the occurrence of genetic diseases, their likelihood, and treatment, including ways to prevent or cure them. Counsellors will discuss the genetics and treatment of the disease, as well as the personal, familial, social and insurance implications. Additional diagnostic procedures, such as genetic testing, may be recommended to better understand risks or confirm the diagnosis.[1]

Genetic counselling not only informs the patient about the risks of disease but also helps them to be psychologically prepared to face it. There have been several ongoing researches, one particular in which meta-analysis techniques were employed to evaluate the psychological impacts of genetic counseling on women with a family history of breast cancer shows significant decreases in generalized anxiety and stress.[2]

In the emerging field of Genomic medicine, Genetic counselors play a crucial role throughout the entire patient's experience. They are crucial in the early phases, helping to establish agreement, facilitate decision-making, and aid in the assessment of genetic risk. To facilitate efficient communication between patients, healthcare providers, and the system, they also assist in the administration and interpretation of test results. Furthermore, genetic counselors advise patients on an ongoing basis and assist kids in comprehending and incorporating genetic knowledge into their lives.[3]

Historically, a key ethical ambiguity for genetic counseling has been the idea of patient's autonomy. But as the genomic era approaches, it is necessary to reassess this principle's application in genetic counseling. To enable counselors to provide clarity on the acquisition and use of genetic information, this paper argues for a more balanced strategy that replaces the prioritization of patient autonomy. We start by outlining the historical setting in which the patient's independence was attained in the field and how it changed over time, including the incorporation of abstract, non-existent concepts. Understanding the initial stages of removing injustice, we offer the reasons, considering the significance of patient autonomy and the rising levels of genetic variation, of why it has not been successful.[4]

We believe that some new molecular tests will be developed because of the global endeavor to sequence the human genome in the 21st century. Adoption of these tests will also increase the variety of conversations about genetics. These developments in technology can more effectively gather the information required to interpret genetic results appropriately and create preventive or therapeutic interventions. For instance, before epidemiological and molecular data were available to appropriately interpret the results, clinical trials for BRCA1 and BRCA2 mutations were started in the United States. These days, geneticists, genetic counselors, and geneticists are crucial to the use of novel tests. However, it is envisaged that specialists and primary care doctors will use genetic testing directly to predict the risk of disease and this will completely transform our current practice of medicine.[5]

Ghulam Hassam U Din Tarrar *(Corresponding Author)*
Student, 4th year MBBS
Bahria University Health Sciences
Email: hassamar846@gmail.com

Nimra Mushtaq
Student, 5th year MBBS
Bahria University Health Sciences
Email: Nimra4490@gmail.com

Muhammad Muzamil
Student, 1st year MBBS
Bahria University Health Sciences
Email: Mmuzamilsonu2@gmail.com

Received: 28-08-2024
Accepted: 09-10-2024

Authors Contribution:
Ghulam Hassam U Din Tarrar: Write up and editing
Nimra Mushtaq: Idea Conception, Proof reading
Muhammad Muzamil: Final Approval

REFERENCES:

1. Rehder H. Humangenetische beratung. Wiener Medizinische Wochenschrift 2005;155:249–57. https://doi.org/10.1007/S10354-005-0182-4.
2. Meiser B, Halliday JL. What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Soc Sci Med 2002;54:1463–70. https://doi.org/10.1016/S0277-9536(01)00133-2.
3. Patch C, Middleton A. Genetic counselling in the era of genomic medicine. Br Med Bull 2018;126:27–36. https://doi.org/10.1093/bmb/ldy008.
4. Schupmann W, Jamal L, Berkman BE. Re-examining the Ethics of Genetic Counselling in the Genomic Era. J Bioeth Inq 2020;17:325–35. https://doi.org/10.1007/S11673-020-09983-W.
5. Bowles Biesecker B, Marteau TM. The future of genetic counselling: an international perspective. vol. 22. 1999.

"Who am I?" The Hidden Aspects of Dissociative Identity Disorder

Alishba Eman

How to cite this Article:
Eman A. "Who am I?" The Hidden Aspects of Dissociative Identity Disorder. J Bahria Uni Med Dental Coll. 2025;15(1):68 DOI: https://doi.org/10.51985/JBUMDC2024470

Dissociative identity disorder (DID) is a persistent post-traumatic condition marked by impaired memory and self-identity functions resulting from childhood trauma. It is a severe chronic psychiatric illness characterized by neurobiological, cognitive, and interpersonal disintegration in reaction to intolerable stress. Dissociative Identity Disorder (DID) remains inadequately researched; nevertheless, more investigation may elucidate neurobiological and cognitive characteristics, as well as the interplay between individuals and environmental stressors. Comparing people with Dissociative Identity Disorder to non-dissociative individuals with other psychiatric diseases could further clarify the disorder's characteristics.[1] Research on dissociative identity disorder (DID) from 2011 to 2021 identified 1,354 new cases, predominantly from Western nations, especially the United States. The bulk of instances utilized validated metrics, with 74% of new cases originating from six research organizations.[2] A 49-year-old gentleman with a history of alcohol use disorder and psychosis requests outpatient treatment for medication management. He possesses a familial predisposition to bipolar disease and schizophrenia and has endured considerable physical abuse. The patient delineates 11 distinct personality types, although only two are elaborated upon. Dimensional Identity Disorder (DID) is a psychological illness defined by the presence of two or more distinct personality states and recurrent memory deficits. Symptoms of Dissociative Identity Disorder (DID) result in distress or impairment and are not ascribed to cultural or religious practices, substance use, or other medical problems. The similarities between BPD and DID indicate a possible connection via common traumatic experiences. Dissociative Identity Disorder (DID) is frequently linked to childhood trauma and abuse, and is regarded as the most severe manifestation of childhood-onset Post-Traumatic Stress Disorder (PTSD). Evidence-based treatment for Dissociative Identity Disorder (DID) often employs a tripartite strategy, encompassing trauma-focused therapies and psychopharmacological interventions.[3] Another study on dissociative identity disorder (DID) found that inaccurate media portrayals of DID perpetuate misconceptions and contribute to delays in seeking treatment, accurate diagnosis, and increased shame and self-loathing among individuals with DID. The study involved 377 individuals with DID who completed an anonymous online survey about the impact of media portrayals. The results showed that 309 participants felt these portrayals impacted their treatment, while 153 reported no impact and 151 reported an impact. The study also found that participants self-reported their DID diagnosis, which may be further biased due to their greater awareness of their dissociation.[4] The research examined 28 interviews with 15 patients regarding their Dissociative Identity Disorder (DID) and identified two primary themes: divergent worldviews and conflicts among dissociative identities. Patients possess diverse comprehensions of the origins of their DID, and disagreement is both prevalent and complex. The research underscores the significance of inter-identity awareness in resolving these conflicts.[5]

In conclusion, Dissociative Identity Disorder (DID) is a multifaceted psychiatric disorder associated with childhood trauma, resulting in disturbances in memory, identity, and personality. Notwithstanding advancements, a considerable disparity persists in studies. Treatment modalities frequently emphasise trauma-informed therapies; nevertheless, media portrayal complicates the diagnostic process. Inter-identity awareness is essential for resolving conflicts. Enhanced research and public awareness could elevate the quality of life for individuals with Dissociative Identity Disorder (DID).

Alishba Eman
M.Phil Student
Bahria University Health Sciences Campus Karachi
Email: alishbah015@gmail.com

Received: 14-11-2024
Accepted: 19-12-2024

Authors Contribution:
Alishba Eman: Write up and editing

REFERENCES:

1. Sar V, Dorahy MJ, Krüger C. Revisiting the etiological aspects of dissociative identity disorder: a biopsychosocial perspective. Psychol Res Behav Manag. 2017 May 2;10:137-146. doi: 10.2147/PRBM.S113743.
2. Boysen, Guy A. PhD. Dissociative Identity Disorder: A Review of Research From 2011 to 2021. The Journal of Nervous and Mental Disease 212(3):p 174-186, March 2024. | DOI: 10.1097/NMD.0000000000001764
3. Bistas K, Grewal R. Unraveling the Layers: Dissociative Identity Disorder as a Response to Trauma. Cureus. 2024 May 20;16(5):e60676. doi: 10.7759/cureus.60676.
4. Briana L. Snyder, Stacey Marie Boyer, Jennifer E. Caplan, M. Shae Nester, Bethany Brand, It's not just a movie: Perceived impact of misportrayals of dissociative identity disorder in the media on self and treatment, European Journal of Trauma & Dissociation, Volume 8, Issue 3, 2024,100429
5. Marais L, Bezuidenhout M, Krüger C. How do Patients Diagnosed with Dissociative Identity Disorder Experience Conflict? A Qualitative Study. J Trauma Dissociation. 2023 Jan-Feb;24(1):125-140. doi: 10.1080/15299732.2022.2119630.

Instructions to Author

The Journal of Bahria University Medical and Dental College abbreviated as JBUMDC is a peer reviewed quarterly multidisciplinary biomedical journal of basic and clinical health sciences. It accepts manuscripts prepared in accordance with the "Uniform Requirements for Submission of Manuscripts for Biomedical Journals, updated December 2015", adopted by International Committee of Medical Journal Editors (ICMJE) & PMDC guidelines for Medical & Dental journals. The Journal will encompass manuscripts from all fields of biomedical sciences in the form of Editorial (Invited/Editor), Original Article, Review Article (narrative reviews and systematic reviews), short communication, Commentary, case study, and letter to editor.

Peer Review Policy:

Every paper will be read by the editor and then will be sent to two reviewers, one internal and one external reviewer. If statistical analysis is included assessment by statistician will be carried out.

Plagiarism:

JBUMDC follows the ICMJE, PMDC and HEC guidelines. Each manuscript will be scrutinized. Plagiarism of the manuscript should be less than 18%.

Preparation of Manuscript:

Type the manuscript on ISO A4 (212 × 297 mm), with margins of at least 25 mm (1 inch). Type or print on only one side of the paper. Use double spacing throughout the manuscript. Number pages consecutively, beginning with the title page. Put the page number in the lower right-hand corner of each page.

Contents of Manuscript for submission:

Submission items include a Covering letter, letter of undertaking duly signed by all authors, Ethical Review Committee (ERC) Letter, Author's declaration on JBUMDC template stating authors contribution, Title page and the Manuscript [Abstract, Key words, Introduction, Methodology, Results, Discussion, Conclusion, Acknowledgement, Authorship, Conflict of interest, References, Tables , Figures]**.** Title page should have complete title of the manuscript, along with the short running title, the names of all authors with qualifications, their department, affiliation, telephone number, e-mail, corresponding author, address for correspondence, short running title, source of funding (grant/equipment/drugs), number of figures and tables, total word count, total number of pages. Original manuscript should be of 2500 words excluding abstract and references and the references should be at least 20-25 for original study.

1. Abstract:

It should have no more than 150 words for unstructured abstracts or 250 words for structured abstracts. The structured abstract should include:

1) Objective, 2) Study design and setting, 3) Methodology, 4) Result and 5) Conclusion.

[state the purpose of the study (objective), basic procedures (methodology with study design, subjects/animals, place & duration of study, drug/chemical/equipment, procedure or protocol), main findings (results) and conclusion (It should emphasize new and important aspects of the study.)]

Below the abstract provide, 3-10 key words that will assist indexers in cross-indexing the article. The key words should be in alphabetical order.

2. Introduction:

State the purpose of the article and summarize the rationale for the study. Give only strictly pertinent references and do not include data or conclusions from the work being reported. At least 10 to 12 references should be included in the introduction. International and national literature review indicating the rational and objective of the study.

3. Methodology:

This section should include a statement indicating that the research was approved by independent local or regional or national review body(eg. Ethics committee, institutional review board) with ERC number. Clearly describe the type of study, selection of observational or experimental participants, including eligibility and exclusion criteria and a description of source population. Identify the age, gender and other characteristics of subjects. Mention the sample size and how it is calculated and the sample technique. Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. For randomized clinical trials provide information on all major study elements, including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding). Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract. Describe statistical methods with enough detail to enable a knowledgeable person with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Define statistical terms, abbreviations, and most

symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

4. Results:

Present your results in logical sequence in the text, tables, and illustrations according to the objective of the study. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Describe appropriate indicators of measurement error or uncertainty such as confidence intervals, P values. Report complications of treatment and dropouts from a clinical trial. Specify any general-use computer programs employed for analysis.

5. Discussion and Conclusion:

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies. Link the conclusions with the goals of the study.

6. Acknowledgment:

List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged.

7. Authorship:

Authorship credit is based only on the criteria laid down by International committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilibies/defining-the-role-of-authore-and-contributors. html).1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. 4) Agreement to be Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Conditions must be met. Authors should provide a description of what each contributed.

8. Conflict of interest:

All authors have to disclose and submit any financial /personnel relationship that might bias and inappropriately influence their work.

9. References:

Minimum 50% of the references must be from last five years. Local references must also be included. Vancouver style should be followed. Examples are:

a) Standard journal article:

List the first six authors followed by et al. I) Less than 6 authors:

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreato-biliary disease. Ann Intern Med 1996; 1;124 (11):980-3

II) More than six authors:

Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006-12

b) Organization as author:

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4

c) No author given:

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15

d) Chapter in a book:

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh

JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78

e) Newspaper:

Hasan Mansoor. Excessive use of drugs creating resistance to antibiotics. The Dawn 2013, 24 June; sect. Metropolitan (col.1-4)

10. Tables:

Type or print out each table with double spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes. Explain in footnotes all nonstandard abbreviations that are used in each table. Identify statistical measures of variations, such as standard deviation and standard error of the mean. Do not use internal horizontal and vertical rules.

11. Illustrations (Figures):

Figures should be professionally drawn and photographed. Photographic prints 127 × 173 mm (5 × 7 inches). Photomicro-graphs should have internal scale markers. Symbols, arrows, or letters used in photomicro graphs should contrast with the background. If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source