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# EDITORIAL

## Artificial Intelligence in Dentistry: Hype or Hope?

Ulfat Bashir, Kanwal Zulfiqar

Artificial intelligence is one of the most significant contributions to the fourth industrial revolution, which ushers in a new digital era. It is defined as “the study of intelligent agents, which includes any machine that can comprehend its environment and respond to increase its chances of success.”[1] The term "AI" is used informally when a machine imitates cognitive processes that people often connect with other human minds, such as "learning and problem-solving."[1] Mathematician John McCarthy created the concept of "artificial intelligence" in 1955. McCarthy is widely considered the founder of the field. To explain how machines might be able to perform what can be referred to as "intelligent" activities, he introduced this phrase.[2] Numerous industrial sectors, including robotics, transportation, smart cities, financial analysis, etc., have incorporated AI. As an example, medical and dental imaging diagnostics, decision support, precision and digital medicine, drug discovery, wearable technologies, hospital monitoring, robotic and virtual assistants have all been employed in medicine and dentistry. In many instances, artificial intelligence (AI) can be seen as a helpful tool for physicians and dentists to lessen their labor. AI may learn from various information sources (multi-modal data) to diagnose diseases beyond the capability of humans, in addition to identifying diseases by means of a single information source that is focused on a particular illness.[3]

The introduction of AI platforms such as CHAT GPT has completely revolutionized the dynamics of information being available within seconds. Similarly, health professionals are eagerly contemplating its effects in the Medical and Dental Health profession.[3] The dentists all over the world are also rapidly embracing the advancements in AI and machine learning.[4] One of the biggest advantages of AI in dentistry is its ability to diagnose oral diseases with high accuracy and precision. AI algorithms can analyze dental images and detect early signs of oral cancer, periodontitis, and other oral diseases, allowing for early treatment and prevention of further complications.[5]

AI has been heavily utilized in periodontology to investigate, comprehend, and build periodontal applications, such as detecting periodontal bone loss, identifying gingivitis inflammation, and evaluating connective tissues and other periodontal cavities.[4] Endodontic treatment planning has been greatly aided by AI in recent years. Different types of AI can aid dentists in the diagnosis and management of endodontic issues while fostering performance and assuring improved and precise patient care. The review's main objectives are to extract and evaluate AI-based methods for disease diagnosis and therapy planning.[4]

When teeth exhibit periapical lesions and/or associated symptoms, it may be challenging for doctors to make a diagnosis and formulate a treatment plan.[6] The common disease known as apical periodontitis is responsible for about 75% of cases with radiolucent jaw lesions.[7] Early detection could improve the effectiveness of care, stop it from spreading to other tissues, and lessen potential difficulties.[8] Another benefit of AI in dentistry is its ability to improve the planning and execution of dental procedures.[5] AI algorithms can help dentists plan complex procedures such as implants, orthodontics, and restorations with high accuracy, reducing the risk of complications and ensuring the best possible outcome for the patient.[4]

Due to its capacity to improve the efficiency and accuracy of the diagnostic process, artificial intelligence (AI) has become extremely popular in orthodontics in recent years. Since orthodontic treatments are frequently drawn-out processes, more effective planning calls for more effective and efficient solutions. Dentists can make judgments more precisely and quickly in a time-constrained context by using AI-based knowledge to automate disease diagnosis and treatment prognosis processes. Through their capacity to learn and make

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automobile decisions, AI solutions can further aid in the prevention of human errors. Numerous studies have looked into using AI to diagnose and design treatments for orthodontic diseases.[9,10]

In the area of dental education, AI is extensively used. The preclinical virtual patient input to the students has been much enhanced. The interactive interphase develops top-notch learning environments by letting pupils assess their own work and contrast it with the ideal. Numerous studies on the efficiency of these systems have revealed that, in comparison to conventional simulator units, these systems enable students to reach a competency-based skill level more quickly.[11] Artificial intelligence-powered virtual dental assistants can perform a variety of tasks in dental offices with greater accuracy and fewer errors. It is very helpful when discussing the patient's medical history and any habits they may have, such as smoking and drinking, with the dentist. The patient can choose to receive urgent teleassistance in dental crises, particularly if the practitioner is not readily available.[12]

In recent years, there has been a noticeable increase in the number of research investigating the application of AI in restorative dentistry.[13,14] Various studies investigated the application of AI in helping caries detection, vertical tooth fracture prediction, and treatment planning. To accurately plan therapy utilizing clinical examples, Lee et al. suggested a machine learning method based on a decision tree to evaluate the tooth prognosis. The model's precision was 84.1%.[13]

However, despite the rapid progress made in AI research in dentistry, there are still many challenges that need to be addressed. One of the biggest challenges is the lack of data standardization and interoperability between AI systems and existing dental systems. Also there is lack of understanding and adoption by dental professionals. While some dentists have embraced AI and its benefits, others are still skeptical about the technology and its ability to replace human expertise. Additionally, the high cost of AI technology can also limit its widespread adoption, particularly in resource-limited settings like Pakistan. This can lead to the inability to share data and collaborate on research thus limiting the advancement of the field. Additionally, there is a need for further research on the ethical and legal implications of AI in dentistry, such as data privacy and patient consent.

It is still necessary to use appropriate external data gathered from freshly enrolled patients or gathered from other dental facilities to confirm the generalizability and dependability of the offered AI models, even though their results have been encouraging.[15] Administration and exchange of clinical data are two major barriers to the use of AI systems in the healthcare sector. Patients' personal data is needed for both the initial training of AI algorithms as well as for ongoing training, validation, and improvement. The development of AI will also promote data sharing across multiple institutions and, in some circumstances, across international borders. AI must be integrated into healthcare operations while modifying systems that protect patient confidentiality and privacy.[16] Personal data must therefore be anonymized before considering a wider distribution.[17] Even if these protections are technically possible, the medical community has doubts about secure data sharing.

Despite these limitations, the future of AI in dentistry looks bright. As AI technology continues to advance and become more accessible, we can expect to see an increased adoption of the technology by dental professionals and patients alike. Furthermore, the development of AI-powered devices and tools will revolutionize the way dentists diagnose and treat oral diseases, leading to improved patient outcomes and a more efficient and effective delivery of dental care. computer learning Researchers will be better able to comprehend some multifactorial diseases with the aid of deep learning, and it will be feasible to increase our collective understanding of oral diseases and conditions that are not yet fully known. Artificial intelligence can undoubtedly be a tool for delivering improved healthcare to patients, but it cannot in any way take the place of human knowledge, skills, and capacity of judgment.[18]

Despite the difficulties, there is a good probability that AI will be used in dentistry in the future, and as we adopt these exciting innovations, patient care will only improve. However, for this to happen in the dental sector, new finance resources are required, along with debt and an understanding that open systems lead to innovations that are good for the sector. The possibilities are endless if these problems can be fixed. In conclusion, AI is the next paradigm shift in the healthcare. We as healthcare


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professionals need to carefully evaluate the challenges we face when moving towards this new age of transformation.AI is not absolute and cannot replace human judgement. It is imperative that we adapt to AI to improve patient care but also be watchful of its limitations.

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**CONFLICT OF INTEREST**

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Factors Affecting Early Childhood Caries Among Special Children in Local Population of Peshawar, KPK

Ifra Sana Khattak[1], Madeeha Bangash[2], Laila Mustafa[3], Khadija Sajid[4], Aamir Mehmood Khan[5]

**ABSTRACT**

**Objective:** To access the prevalence and associated causes of early childhood caries among the special children of local population.

**Study Design:** Descriptive Cross-sectional study.

**Place and Duration of Study:** This study was conducted at different special schools of Peshawar over a period of 3 months (10th October 2020- 28th December 2020).

**Materials and Methods:** Sample size was calculated using G-Power (3.1.9.2) using convenience sampling technique.153 children below 6 years of age with unerupted permanent molars were accessed for caries severity using Decayed, Missing, and filled teeth surfaces (dmfs) index using daylight/ artificial torch light.

**Results:** Prevalence of ECC in our study model was found to be 77%. Child's dietary habits and oral hygiene habits were found to be ominously allied with Early Childhood Caries (P value = 0.000). While age, gender and parental education did not show any remarkable role in the widespread presence of ECC.

**Conclusion:** This study accentuates high prevalence of ECC (77%) among special children in Peshawar.

**Key Words:** *Dietary Habits, Early Childhood Caries (ECC), Oral Hygiene habits, Prevalence, Special Children.*

## Introduction

Early Childhood Caries (ECC) has been on expansion in numerous nations and has become a huge and significant health issue particularly in publicly distraught populations. The American Academy of Paediatric dentistry (AAPD)[1] has defined ECC as presence of one or more decayed (cavitated or non cavitated), missing (due to caries) or filled tooth surfaces in any primary tooth in child of 71 months of age or younger.

Different studies have been reported to determine prevalence of nursing caries worldwide. An audit nature of one literature proposes that in most established nations the prevalence of ECC is somewhere in the range of 1-12%.

In less developed nations and among distraught factions in the developing nations the prevalence has been accounted for to be as high as 70%.[3,4] Literature shows ECC has been found more frequent in low socioeconomic groups. In contrast to this, various studies in Pakistan expressed the Prevalence of ECC from 27.9% to 51%[5'6] and even 88.6%[7]. Few social and socioeconomic components have all the earmarks of being elements of ECC which incorporate restricted access to caution, assets, and oral health learning[7,8]. However, not much literature is available regarding prevalence of ECC in special children.

The information on the prevalence and related elements of ECC is important to create embattled intercessions for the anticipation of consequent tooth decay and to diminish the number of children that requires emergency treatments.

This study was meant to access the prevalence and associated causes of early childhood caries among the special children of local population of Peshawar, KPK.

## Materials and Methods

A descriptive cross-sectional study was conducted over a period of 3 months from 10th September 2020 to 28th December 2020 in different special schools of Peshawar. Sample size was calculated using G-Power (3.1.9.2) with effect size 0.3, α error 0.01 and power 0.95 using convenience sampling technique. 153 children of age less than 6 years were included in the study whereas those with erupted first permanent

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molars were omitted from the study. Before the collection of data, ethical approval was obtained from Ethical Review Board at Rehman College of dentistry Peshawar (EC Ref No.: 2020-10-053) and written informed assent was also attained from the parents/Guardians of kids residing there. The data was collected with the help of self-administered questionnaires. The validation of these questionnaire was done by piloting study. These questionnaires were sent to the parents of special children by email who also returned them via email. One questionnaire consisted of sociodemographic characteristics such as age, gender, parental education, oral hygiene habits and dietary habits. The second questionnaire consisted of decayed, missing filled surface (dmfs) score that was filled by the dentist.

Every child was examined by a single Paediatric dentist, on a standard upstanding seat or in knee-to-knee position with the help of wooden spatula in a satisfactory natural daylight or artificial light using torch. Caries severity was accessed by decayed, missing filled surface (dmfs) index for deciduous teeth given by WHO.

Using an evaluator administered questionnaire parents and children were asked about their age, literateness level of their parents, oral hygiene measures comprising teeth cleaning aids. They were also inquired about dietary habits including frequency of sugar consumption, fibrous diet and diet high in carbohydrates.

Data analysis was performed using SPSS version 22.

## Results

The study populace included 153 special children in the range of 3-5 years. Out of 153 children 124 (77%) were found to have ECC which included 50 (40.32%) female and 74 (59.67%) male.

**Table I: Distribution of Early Childhood Caries in Special Children (n= 153)**

| | ECC Present (n%) | ECC Absent (n%) | Mean dmfs Score ± S.D |
|---|---|---|---|
| **Age (Years)** | | | |
| 3 or above | 43 (34.6%) | 7 (24.1%) | 44.52 ± 22.45 |
| 4 or above | 40 (32.25%) | 11 (37.9%) | 36.16 ± 24.625 |
| 5 or above | 41 (33.06%) | 11 (37.9%) | 38.60 ± 25.292 |

ECC: Early Childhood Caries

dmfs: decayed, missing, filled surface.

The females with ECC showed a mean dmfs of 42.38 ± 24.245 SD, whereas males showed a mean dmfs of 38.00 ± 24.247 SD. P value was statistically not significant. (Table II).

When parental education was evaluated 11 (8.87%) of parents had higher level of education and knowledge with mean dmfs score of 33.58. 35(28.22%) had middle education level with mean dmfs of 33.70, while majority 78 (62.9%) had poor education level and knowledge with mean dmfs score of 43.84. Thus, the occurrence of ECC was comparatively greater in children having parents with poor education level. P value was found slightly significant (P=0.000). (Table II).

Regarding dietary habits of special children majority of children consumed high carbohydrate and sugary snacks in between the suppers. About 73 (58.87%) children were habitual consumers of sugary snacks with mean dmfs score 44.09. About 42 (33.87%) children consumed frizzy drinks with mean dmfs score of 48.11 while very minor population 9 (7.25%) consumed fibrous diet with mean dmfs score 7.30. The occurrence of ECC was found less in children who consumed fibrous diet. P value was statistically highly significant (P= 0.000) (Table II).

With respect to oral hygiene only 9 (7.25%) children used brush their teeth twice with mean dmfs score 11.431. 38 (30.64%) accustomed to brush their teeth only once a day with mean dmfs score of 25.44. While majority of the children 77 (62.09%) did not clean their teeth at all with mean dmfs score of 58.79. (Table II).

**Table II: Association of Early Childhood Caries with Age, Gender, Parental Education, Dietary habits, and Oral Hygiene habits**

| | n (%) ECC present | n (%) ECC Absent | dmfs score Mean ± S.D | P value |
|---|---|---|---|---|
| **Age** | | | | |
| 3 or above | 43 (34.6%) | 7 (24.1%) | 44.52 ± 22.405 | 0.325 |
| 4 or above | 40 (32.25%) | 11 (37.9%) | 36.16 ± 24.625 | |
| 5 or above | 41 (33.06%) | 11 (37.9%) | 38.60 ± 25.292 | |
| **Gender** | | | | |
| Female | 50 (40.32%) | 10 (34.48%) | 42.38 ± 24.245 | 0.277 |
| Male | 74 (59.67%) | 19 (65.51%) | 38.00 ± 24.247 | |

| | | | | |
|---|---|---|---|---|
| **Parental Education** | | | | |
| Low | 78 (62.9%) | 13 (44.82%) | 43.84 ± 22.768 | 0.046* |
| Middle | 35 (28.22%) | 15 (51.72%) | 33.70 ± 26.923 | |
| High | 11 (8.87%) | 1 (3.44%) | 33.58 ± 17.835 | |
| **Dietary Habits** | | | | |
| High Carbohydrates | 73 (58.87%) | 13 (44.82%) | 44.09 ± 22.618 | 0.000** |
| Frizzy drinks | 42 (33.87%) | 2 (6.89%) | 48.11 ± 18.173 | |
| Fibrous diet | 9 (7.25%) | 14 (48.27%) | 7.30 ± 11.431 | |
| **Oral hygiene habits** | | | | |
| Once a day | 38 (30.64%) | 14 (48.27%) | 25.44 ± 16.702 | 0.000** |
| Twice a day | 9 (7.25%) | 14 (48.27%) | 7.30 ± 11.431 | |
| Never | 77 (62.09%) | 1 (3.448%) | 58.79 ± 10.944 | |

P< 0.05 = Significant **

## Discussion

ECC is a pervasive and common disease of childhood. The American Academy of Paediatric Dentistry (AAPD) has defined ECC as presence of one or more decayed (cavitated or non cavitated), missing (due to caries) or filled tooth surfaces in any primary tooth in child of 71 months of age or younger[1]. The oral health of special children is disregarded part of child health and wellbeing, particularly in instances of ECC. These children comprise a populace that is at higher risk to caries considering their reliance and inability to communicate with their parents. The current study was thus planned to be directed among special children of Peshawar. The principal purpose behind the enlistment of special children in the study was that there is no such research yet led in Pakistan. Different preventive techniques have been implemented to decrease the burden of ECC in various nations[8]. The World Dental Federation, WHO and international association of Dental Research have set out on setting up the global oral health objectives for the year 2020[8]. Shockingly most of included epidemiological studies demonstrates that ECC stays predominant among pre-school children around the globe[8].

Deciding the pervasiveness pace of caries in special children is a troublesome cycle as the offspring of this age bunch are not easily reachable and are truculent.[9]

In our study, caries prevalence apparently increased with age, which is as per past studies.[10]Current study additionally indicated that caries frequency did not expand fundamentally with age. One possible reason for this could be that many special children with handicapped conditions and increased age are not even admitted to such schools because of their medical conditions[11]. In contrast other studies shows that as kids grow older, the number of erupted primary teeth increases which are then exposed to the oral environment and change in their dietary propensities and oral hygiene measures represent a more noteworthy cariogenic challenge[11,12,13].

This study also showed that male children (60.8%) were more affected than female (39.2%) children. This can likewise be related with increased physical activity that prompts the increase in demand for more food when contrasted with females. This corroborates with the previous study.[14]But in contrast some studies reported increase occurrence of ECC in female children.[15]

This study like past studies did not show any strong correlation of parental education with prevalence of ECC.[16] However in contrast many other studies have shown strong associations between mother education and occurrence of caries.[17,18]

In the current study 56.2% children consumed high carbohydrate snacks amid meals and it supports earlier studies which stated that consumption of sugary snacks in between the meals was a significant risk factor for ECC. The outcome likewise substantiates the previous finding study environment that utilization of sweet snacks multiple times each day was a remarkable risk factor for ECC [19,20]. Frequent intake of sugary snacks, frizzy drinks upsurge the threat for caries. Consequently, dietary proposals of restricting the snacking time amongst children and reassuring standard suppers is basic.

We also found a significant correlation between oral hygiene and dental caries. Special children neither comprehend nor have the physical expertise to keep up good oral hygiene. Hence forth, parental help and direction is fundamental to lessen the menace of increasing caries. Most children in this study either brushed never (51%) or once a day (32%). Tooth brushing by the guardians or parental figures have the capability of eliminating the dental plaque more



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adequately ideally immersing the oral habitat with fluorides thus diminishing the risk of caries among their children.[21]

The pervasiveness of ECC in our study was 77%. The likelihood of ECC was essentially higher in kids with poor oral hygiene and individuals who devoured high carbohydrate snacks in the middle of suppers multiple times a day. One of the objectives was to limit the effect of dental caries on individuals and society and figure out methodologies for early findings, counteraction, viable administration of dental caries.

However, this prevalence rate had some limitations as there's a variety of syndromes associated with special children, each being of different characteristics and medical condition and dental findings, while this study dealt with them in general. Therefore, a detailed study is required in future considering the various medical conditions in specific.

## Conclusion

This study accentuates high prevalence of ECC among special children in Peshawar and is correlated with poor oral hygiene and high carbohydrate snacks. Our study alarms the call for a rapid need to carry out preventative and therapeutic health care programs for special children in our society. Aggressive preventive measures should be implemented as these children are at very higher risk for dental caries. Furthermore, clinicians should mark the predisposing factors resulting from the distinctive characteristics of these individual's underlying condition and treatment.

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**CONFLICT OF INTEREST**

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# An In Vitro Study of Sealing Ability of Commercially Available Root Canal Sealers

Wajahat Hussain, Amjad Hanif

**ABSTRACT**

**Objective:** The current study aimed to explore the sealing ability of commercially available root canal sealers after obturation by using stereomicroscope.

**Study Design:** Experimental laboratory-based study.

**Place and Duration of Study:** The study was conducted at Zoology Department, National Centre of Excellence in Geology and Department of Pathology at College from 10th January 2021 to 31st March 2022.

**Materials and Methods:** Teeth used in this study were divided randomly into four experimental (four commercially available sealers) and one control group (only gutta percha without using sealer) (n=10) denoted by EG1, EG2, EG3, EG4 and CG5 respectively. After obturation, specimens were coated with varnish except for 1-2mm of apical area and immersed in 2% methylene blue for 1 week. Specimens were analyzed using Stereomicroscopy, Scanning electron microscopy and Energy Dispersive X-ray Analysis (SEM, EDX). Kruskal Wallis and Mann-Whitney U-tests were employed to measure statistical significance.

**Results:** Fifty percent samples of Endomethasone sealer had a score of 2 and the rest score 3. Sixty percent of Sealapex sealer had score of 2 and Forty (40) percent had score of 3. Fifty percent of Adseal sealer had score of 2 and remaining fifty (50) percent of Adseal sealer had score of 3. Fifty percent of AH Plus sealer had score of 2. Forty (40) percent had a score of 1 and remaining ten percent had score of 3 (Table. I).

**Conclusion:** AH Plus proves to have better sealing ability with minimal dye penetration when compared to other endodontic sealers.

**Key Words:** *Apical Microleakage, Dye Penetration, Gutta Percha, Root Canal Sealer.*

## Introduction

The endodontic treatment comprises of eradication of bacterial load in the root canal and filling of the entire root canal system three dimensionally.[1] The anticipated outcomes of endodontic treatment rest on mechanical instrumentation, root canal disinfection, eradication of pathogens, absolute debridement of pulp remnants as well as filling the entire root canal. Root canal filling should adequately seal the root canal and hinder the oozing of fluid into the root canal. Thus, it stimulates the resolution of pathologies in the periapical area and ensures the cementum deposition to achieve the biological seal.[1]

Ideally root canal sealer should provide satisfactory adhesion between itself, root canal walls and the core filling materials. It should be radiopaque, act as lubricant, possess antibacterial properties, able to flow easily into surface irregularities.[2,1] An endodontic sealer is applied in conjunction with core filling material (GP), because the root canal system cannot be obturated completely by gutta-percha itself and avoid the infection of root canal by providing seal both apically and laterally.[1] Sealers enhance the possibility of achieving an impermeable seal and aids to act as fillers for canal irregularities.[4] The leakage through a filled root canal occurs between the sealer and dentine interface, or the sealer and the gutta percha interface or through voids within the sealer.[5] Although hermetic seal is not always possible with today's sealers, a fluid-tight seal is at the very least preferable.[1]

The sealers used in root canal treatment are usually divided into groups depending on their constituents, for example sealers based on zinc oxide, sealers based on calcium hydroxide, glass ionomer cement sealers, formaldehyde containing sealers as well as resin-based sealers.[8] Despite the tremendous progress, until today no material meets all requirements and desirable properties to

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hermetically seal the root canal system. Apical leakage is still a common experience in root-filled teeth, which raises concern about the quality of obturation obtained with the presently available root canal filling materials.[7]

Literature search showed that many studies have been conducted in the past to determine the sealing ability of various commercially available sealers by using different techniques due to established concept that improper obturation can lead to reinfection, but the comparison of the efficacy of the sealing ability of various root canal sealers currently available in the local market was not carried out in the past therefore the aim of the present study was to evaluate the ability of different commercially available endodontic sealers to seal the root canal.

## Materials and Methods

This was an in-vitro, study conducted from 10th January 2021 to 31st March 2022, in Department of Dental Materials Peshawar Dental College, after approval by the Institutional Review Board (Prime/IRB/2021-359). The materials used in the study are given in (Table. I). Sample size was determined based on ISO standard (# 11405). A total of fifty (50) intact non-carious human permanent mandibular premolar teeth were selected. Teeth were divided randomly into four experimental and one control group (n=10) denoted by EG1, EG2, EG3, EG4 and CG5 respectively (Table I). Mandibular premolar intact non-carious human extracted permanent teeth were included while carious, fractured teeth, teeth with open apices, root resorptions and teeth with bifurcating canals were excluded from the study.

All the teeth were placed in 5.25% sodium hypochlorite solution[6] for 48 hours to clean the surface of teeth. Coronectomy of all selected teeth was done by fissure bur (1.59 – 1.6mm shank diameter) at the cemento-enamel junction in Ultra Push Type high-speed hand piece. ProTaper universal rotary system (Foshan, Guangdong, China, ISO Specification CEO197) was used to prepare root canals 1mm short of the length, until reaching to a size F2 (master apical file). Barbed broaches were used to extirpate the pulp tissue from. Sodium hypochlorite (5.25%) and 5ml of EDTA was used to irrigate the canals, prior to final irrigation by 5ml distilled water. Canals were dried with paper points.

Each of the sealer was manipulated according to manufacturer's directions and was introduced into the canal using the lentulo-spiral fitted. Hand spreader was used, and entire canal was obturated. Then the teeth in all the groups were placed in an incubator (Intelligent Laboratory Incubator, China) at 37 °C and 100% relative humidity for one week.

Two to three layers of clear nail varnish was applied on the root surface. Apical area (1-2mm) covered with sticky wax was left uncoated. Roots were completely immersed into the 2% methylene blue aqueous solution for 1 week. Then sticky wax and coating was removed from the surface while rinsing under a tap water. The roots were vertically sectioned by using teeth cutting saw. Stereomicroscope was used to determine apical dye leakage. The specimens were scored as follows[1]. 1: (1-3 mm); 2: (3-5 mm); and 3: (>5 mm).

The bond between the sealer and the dentin was examined using scanning electron microscopy. Using a diamond disc on teeth cutting saw machine, the roots were sectioned perpendicular to the longitudinal axis to get 2mm thick samples. The samples were polished with sand discs and washed with distilled water. Then, the samples were dried and fixed on aluminium stubs. Sputter coating of the samples was performed with a gold–palladium alloy before being scanned with SEM (JAPAN, JSM-IT 100).

Statistical analysis was done by using software version 23 of SPSS. Mean and standard deviation values were determined. Kruskal Wallis and Mann Whitney test was applied to determine significant values. P value less than 0.05 was considered as significant.

## Results

The mean and standard deviation values for Endomethasone, Sealapex, Adseal, AH Plus, and control are 4.48±0.99, 5.06±0.98, 5.02±0.89, 3.75±1.21, 6.54±0.47 mm respectively (Table I), while the Table II shows the distribution of samples for dye leakage based on scoring criteria. Kruskal Wallis test specified statistically significant difference among the various experimental groups *(p=0.039).* Dye penetration was highest (5.06mm) in Sealapex (EG2) and lowest (3.75mm) in AH Plus (EG4). Adseal (EG3) showed less dye penetration than Sealapex (EG2) *(p=0.970)*. AH-Plus (EG4) showed lower amount of dye penetration when



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compared to Endomethasone (EG1), Sealapex and Adseal (EG3*) (p<0.05)*. When Endomethasone sealer was compared with Sealapex, Adseal and AH Plus, no statistically significant difference was found *(p>0.05).* Similarly, comparing Sealapex (EG2) to Adseal (EG3), no statistically significant difference was observed *(p > 0.05)*. While comparing Sealapex sealer with AH Plus sealer, statistically significant difference *(p < 0.05)* was found. Similarly, when Adseal (EG3) was compared with AH Plus (EG4), a statistically significant difference *(p < 0.05)* was noted.

In SEM analysis, Endomethasone showed no gap (good adaptation) between the sealer and dentin at the interface. Sealapex, showed gap (poor adaptation) between the dentin and sealer. Epoxy resin based endodontic sealer (Adseal) displayed no gap (reasonable adaptation) between dentin and sealer. Also, AH- Plus displayed no gap (good adaptation) between the sealer and the dentin.

**Table I: Descriptive Analysis of Experimental Groups Showing Mean, Standard Deviation, Minimum and Maximum Values**

| Sealer | Mean(mm) | Std. Deviation | Minimum | Maximum |
|---|---|---|---|---|
| Endomethasone | 4.48 | ±0.99 | 3.16 | 5.93 |
| Sealapex | 5.06 | ±0.98 | 3.16 | 6.47 |
| Adseal | 5.02 | ±0.89 | 3.12 | 6.12 |
| AH Plus | 3.75 | ±1.21 | 1.83 | 5.66 |
| Control Group | 6.54 | ±0.47 | 5.75 | 7.00 |

**Table II: Distribution of Samples as per the Dye Leakage Scoring Criteria**

| Groups | Score 1 | Score 2 | Score 3 |
|---|---|---|---|
| **Endomethasone Sealer** | 0 | 5 | 5 |
| **Sealapex Sealer** | 0 | 6 | 4 |
| **Adseal Sealer** | 0 | 5 | 5 |
| **AH Plus Sealer** | 4 | 5 | 1 |

## Discussion

In experimental groups, mean dye penetration values for each group revealed that dye penetration was highest in Sealapex sealer (60% of Sealapex sealer had score of 2 and 40% percent had score of 3) and lowest in AH Plus. Afterwards, Adseal sealer showed dye penetration less than Sealapex (50% of Adseal sealer had score of 2 and remaining 50% of Adseal sealer had score of 3). AH Plus shows lowest amount of dye penetration (50% of AH Plus sealer had score of 2, 40% had a score of 1 and remaining 10% had score of 3) as compared to Endomethasone

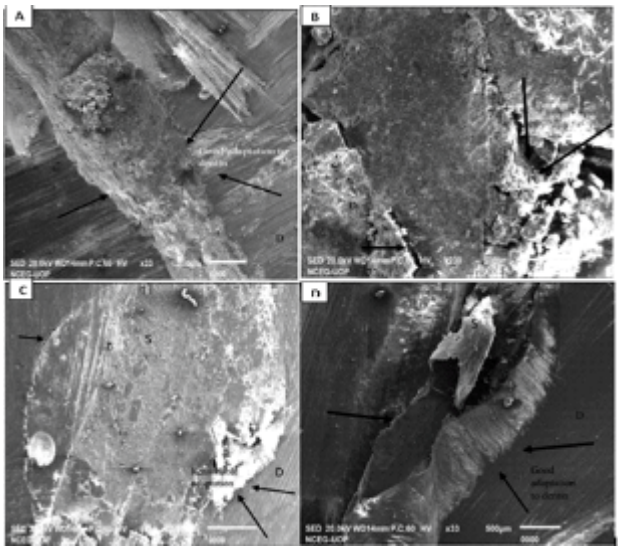

**Figure 1: (A). Endomethasone, SEM with 33X magnification. 'Arrow' indicates no gap (good adaptation) between the dentin and sealer at the interfaces. (B) Sealapex, SEM with 230X magnification. 'Arrow' indicates gap (poor adaptation) between the dentin and sealer (C) Adseal, SEM with 43X magnification. 'Arrow' indicates no gap (reasonable adaptation) between the dentin and sealer. (D) AH Plus, SEM with 33X magnification. 'Arrow' indicates no gap (good adaptation) between the dentin and sealer. S: Sealer D: Dentine**

sealer (50% had a score of 2 and the rest scored 3).

The results of this study demonstrated that leakage was present in the apical area, between root canal walls and the sealers, between the sealer and gutta percha, and through the sealer. The dye penetration inside the sealers also indicated leakage in the sealer's body, opening up another avenue for leaking. The results of this study were also supported by previous studies that all root canal fillings leak.[15,16]

The results of apical micro leakage are influenced by numerous factors. Besides the sealing ability and properties of root-end materials, the technique of assessment, root canal morphology and the diameter of the root canal may influence the results of sealing ability.[17] Several approaches of microleakage assessment have been employed, such as fluid filtration, dye penetration, bacterial leakage, radioactive isotopes and others. It is essential to highlight that no standard method of microleakage assessments exists, and there is a lack of technical standardization even when the same methodology is employed. The lack of standardization is possibly the

main reason why there are so many different methods to investigate the same phenomenon.[17]

In this study, Sealapex demonstrated significantly higher leakage than AH Plus sealer. Sealer's porous nature allows for significant water intrusion, promoting the powder-binder reaction to continue. Other study reported insignificant difference between the Sealapex and AH Plus in apical leakage.[1] Because of water sorption due to the presence of calcium oxide, Sealapex expands in volume during the setting process. This property may increase the solubility of the substance, increasing the danger of leaking over time.[19]

ZOE-based sealer (Endomethasone) displayed the highest dye penetration when compared to sealer based on epoxy resin (AH Plus), which is in agreement with the previous findings.[1,20] Earlier studies have reported that sealers based on ZOE have not good dentin adhesion and sealing qualities and is highly permeable.[21,22]

The findings of the current study demonstrated that AH Plus had a better sealing ability than the other types of sealers. These results are similar with the findings of the Patni et al[6] which revealed that AH-Plus has a superior capability to seal than traditional zinc oxide eugenol and calcium hydroxide-based sealers. Superior adaptation of AH Plus is due to its ability to bond to root dentine chemically by reacting with exposed amino groups in collagen.[10]

Resin-based endodontic sealers (Adseal) did not provide a superior seal than ZOE-based sealers in the current study. This is since the specimens were kept at temperature and humidity level similar to the human body[23]. In the current study, AH Plus was found to give low dye absorption values, implying less dye leakage, and impacting sealer's strategic advantage over the other sealers. Finally, dye was seen in all sealers, regardless of kind, implying that a full airtight seal is impossible to achieve with contemporary sealers.

Linear dye penetration measurement is the most frequent, simple, and quick approach for determining sealant microleakage.[1,18] For obturation, lateral compaction technique was utilized in this work as it has been used as standard for comparison[10]. Methylene blue (MB) is a commonly used dye with concentrations of 0.25, 1 and 2%. We selected 2% MB in our study, because it was the most prevalent concentration and a reliable method.[13] It was reported that MB penetrates more deeply along the root canal filling and exhibits greater penetration than India ink due to low molecular.[12,14]

The SEM of the Endomethasone sealer demonstrated uneven surface and a uniform distribution of components (Fig. 1). The surface was entirely covered by huge granules. SEM image of Adseal sealer display rough surface and a homogenous distribution of components. It contains particles of variable morphology as shown in (Fig. 1). Cakici and his coworkers[24] stated, that for an epoxy resin sealer (Adseal & AH Plus), the apical area exhibits the highest bond strength when compared to other areas. AH Plus, an epoxy resin-based sealer, displayed smooth surface and a consistent distribution of elements, with particles having spherical shape and similar size. Balaguerie et al[25] reported deeper flow of AH Plus sealer in tubules on SEM examination. In this study, humidity and heat factor were not investigated; however, they are known to alter sealer flow and penetration. Because of their creep capability and extended polymerization duration, epoxy-based sealers penetrate easier into micro irregularities.

One of the limitations of this study was that it used the traditional dye-penetration approach. Dye penetration approach is an invasive approach since the specimens were split vertically and during the splitting, there was a possibility that core material would be extruded from the specimens, influencing the outcome of this study. Also, the linear dye penetration technique does not provide information about the volumetric data of the tracer penetrating the interface between the root filling and the root canal wall. Additionally, due to lack of a simulated periodontal ligament and other clinical characteristics, data obtained in in-vitro studies may not be applicable and instantly extrapolated to clinical conditions.

Furthermore, there is still a need for future work to compare different canal preparation methods, sealers and obturation skills since all of these factors may influence the seal of the root canal. It is also essential not to overlook the biocompatibility and cytotoxicity. Other causes of leakage in this study might be linked to the presence of entrapped air or atypical anatomy which was not investigated in our



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work and may be topic of research in future studies.

## Conclusion

Within the limitation of this study, it can be concluded that among all the commercially available root canal sealers tested, epoxy resin-based sealer (AH Plus) proves to have better sealing ability and good adaptation between the dentin and sealer at the interfaces with least amount of dye infiltration, implying minimal dye penetration and microleakage.

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**DATA SHARING STATMENT**

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ORIGINAL ARTICLE

# Non-Caseating Granulomas in Skin Biopsies of Leishmania Cases

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**ABSTRACT**

**Objective:** To determine the frequencies of different types of granulomas in patients suffering from cutaneous leishmaniasis.

**Study Design:** Descriptive cross-sectional study.

**Place and Duration of Study:** Armed Forces Institute of Pathology, Combined Military Hospital, Rawalpindi, Dec 2021 to Oct 2022.

**Materials and Methods:** This study was conducted on 290 patients suffering from cutaneous leishmaniasis. Patients aged between 18 and 70 years of both genders were included, while those who had already received treatment for leishmaniasis, or suffered from mucocutaneous or visceral leishmaniasis were excluded. All patients underwent a punch biopsy, tissue which was stained with hematoxylin and eosin, and then studied for the presence of granulomas and Parasitic Index. PCR was done to confirm species of Leishmania causing disease. Data was analyzed using SPSS 26.0.

**Results:** Our study population had a median age of 38.00 (16 - 63) years, with a male majority: 185 (63.8%). Granuloma formation was seen in 185 (63.8%) patients: 121 (41.7%) had a tuberculoid granuloma and 13 (4.5%) had suppurative granulomas, while 51 (17.6%) had caseating ones. L. Tropica was the most seen organism accounting for 255 (87.9%) cases, L. Major was the infective organism in 26 (9.0%) patients, while L. Infantum was found in 9 (3.1%) cases. Factors such as gender ($p$=0.273), age of the patient ($p$=0.901), disease duration ($p$=0.366), site of lesion ($p$=0.669), type of skin lesion ($p$=0.490), parasite index ($p$=0.297) and species of Leishmania ($p$=0.870) did not have any significant association with the development of non-caseating granulomas.

**Conclusion:** Chronic granulomatous inflammation is a common finding on histopathology in cutaneous leishmaniasis and vigilance is required to avoid confusion with other endemic granulomatous skin conditions.

**Key Words:** *Cutaneous Leishmaniasis, Mycobacterium Tuberculosis, Non Caseating Granulomas, Polymerase Chain Reaction, Ridley Modified Parasitic Index.*

## Introduction

Leishmaniasis is a common tropical disorder attributed to an obligate intracellular protozoan which is transmitted to humans by the bite of the Phlebotomus or Lutzomyia sand-fly and causes manifestations by which it is classified into the cutaneous, mucocutaneous, and visceral disease, with just the cutaneous form having an estimated incidence of one million new cases per annum.[1,2] Pakistan accounts for approximately 10% of the global disease burden for all forms of leishmaniasis which amounts to an estimated half a million cases.[3] Leishmania is diagnosed using a wide variety of tests such as direct visualization of the parasite in a tissue specimen, skin hypersensitivity testing, antibody detection and molecular methods such as polymerase chain reaction, however, such definitive but expensive methods are not readily available in resource-poor countries, and diagnosis is based on clinical and tissue examination.[4,5]

However, this diagnostic approach is not without risk: Leishmania is known for its ability to imitate different skin conditions not only macroscopically, but microscopically as well.[6] Histologically, the disease may present in wide variety of ways including

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parasitized macrophages with lymphocytic infiltration or non-specific chronic inflammation.[7] It is also associated with the formation of granulomas: these can vary from non-specific ill-defined granulomas to epithelioid granulomas.[7,8] Cases of cutaneous leishmaniasis have been demonstrated to show caseous necrosis as well, and have the potential to be misdiagnosed as tuberculosis,[9] or may be mischaracterized as a non-infectious disease such as pyoderma gangrenosum.[10] We conducted this study with the aim of determining frequencies of different types of granulomatous inflammation in patients suffering from cutaneous leishmaniasis. Understanding the nature of the myriad types of histological pictures that leishmaniasis can present with is an important concept to understand, the lack of which can result in the misdiagnosis of the disease, and the institution of inappropriate management, with potentially dire consequences for the patient and the treating team. Recognition that leishmaniasis can mimic the histological picture of other diseases and remaining sentient to the possibility of the presence of this endemic parasite will go a long way towards reducing the morbidity associated with it.

## Materials and Methods

We conducted this descriptive cross-sectional study between 1st Dec 2021 and 31st Oct 2022 in Armed Forces Institute of Pathology, Combined Military Hospital, Rawalpindi, on 290 patients suffering from cutaneous leishmaniasis, after obtaining informed consent. Approval from the institutional review board of the hospital was obtained. Sample selection was carried out via non-probability, consecutive sampling. The WHO sample size calculator was used to calculate the sample size keeping a confidence level of (1-α) of 95%, an absolute precision (d) of 0.05 and an anticipated population proportion (P) of 0.748, which was the percentage of patients with cutaneous leishmaniasis suffering from non-caseating granulomas, from Aoun et al.[11]. For convenient sampling patients aged between 15 and 70 years of both genders were included in the study. Patients who had received previous treatment for leishmaniasis, or suffered from mucocutaneous or visceral leishmaniasis, or those who were suffering from malignancies, immunosuppressed states, drugs that caused immunosuppression, or patients who had a positive PCR for Mycobacterium Tuberculosis were excluded.

All patients' details were documented for demographic data such as age and gender on enrollment, as well as for duration of disease, site of lesion and type of skin eruption. Each patient underwent a punch biopsy of about 5 mm, which was processed and preserved as tissue blocks. Subsequent slides were prepared using hematoxylin and eosin stain. At this point, patients were documented for type of granuloma, if any. Diagnosis of leishmaniasis as well as confirmation of species was done by Polymerase Chain Reaction (PCR) targeting kinetoplast DNA.

In a brief, the formalin-fixed, paraffin-embedded tissue blocks were used to extract DNA. Leishmania ribosomal internal transcribed spacer 1 (ITS1) was amplified using primers. This was done in a 50 mL amplification reaction. The following stages and conditions were employed for amplification on the Px2 thermal cycler: 95 C for 2 min, 35 cycles of (95 C for 20 sec, 53 C for 30 sec, 72 C for 1 min), and 72 C for 6 min.[11]

Furthermore, Ridley modified parasitic index quantifies the parasitic load of amastigotes in cutaneous lesions and has a numerical score from 1 to 6 as displayed in table I.[11]

**Table I : Ridley Modified Parasitic Index**

| Parasitic Index | Number of Amastigotes Per Standard Section |
|---|---|
| 6+ | ≥100, 000 |
| 5+ | ≥100, 00 |
| 4+ | ≥100, 0 |
| 3+ | ≥100 |
| 2+ | ≥10 |
| 1+ | ≥1 |

Data was analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA). Mean and standard deviation was calculated for quantitative variables specifically patient age and duration of disease. Qualitative variables like gender, site of skin lesion, type of eruption, Parasitic Index, species of Leishmania, presence and type of granuloma were recorded in terms of frequency and percentage. Patients were divided into three groups: one with caseating granulomas, one without and one with no


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granuloma formation. Quantitative variables were compared across groups using the independent samples *t*-test / One-Way ANOVA test while the Chi square test / Fischer exact test was used for qualitative variables and a *p*-value of ≤ 0.05 was considered significant.

## Results

This study was conducted on a total of 290 patients with a median age of 38.00 (16 - 63) years. Most of the patients were male i.e., 185 (63.8%), while the median duration from onset of skin lesion to presentation was 27.00 (6 - 49) weeks. A total of 112 (38.6%) had a lesion present on the upper limbs, the lower limbs were affected in 89 (30.7%), while the head and neck region and the trunk were involved in 80 (27.6%) and 9 (3.1%) cases, respectively. Nodules were seen in 159 (54.8%) i.e., most of our cases, followed by ulcers: 97 (33.4%) and 34 (11.7%) had papular lesions at presentation.

Table-II shows the patient characteristics distributed according to gender at the time of presentation.

**Table II: Patients Characteristics According to Gender**

| Variable | Male (n=185) | Female (n=105) |
|---|---|---|
| **Gender** | 185 (63.8%) | 105 (36.2%) |
| **Age (years)** | 37.75 ± 13.87 | 39.21 ± 13.51 |
| **Duration of Disease (weeks)** | 27.74 ± 11.84 | 26.51 ± 10.92 |
| **Site of Lesion** | | |
| **Upper Limbs** | 67 (36.2%) | 45 (42.9%) |
| **Lower Limbs** | 62 (33.5%) | 27 (25.7%) |
| **Head and Neck** | 51 (27.6%) | 29 (27.6%) |
| **Trunk** | 5 (2.7%) | 4 (3.8%) |
| **Type of Skin Lesion** | | |
| **Nodule** | 103 (55.7%) | 56 (53.3%) |
| **Ulcer** | 62 (33.5%) | 35 (33.3%) |
| **Papule** | 20 (10.8%) | 14 (13.4%) |

Table-III displays the histological characteristics of the leishmaniasis for the sample according to gender. A Parasite Index of One was seen in 27 (9.3%) patients, cases with an index of Two were 45 (15.5%), those with a Parasite Index of Three accounted for 59 (20.3%) cases, while an index of Four, Five and Six were seen in 67 (23.1%), 63 (21.7%), and 29 (10.0%) cases, respectively. Leishmania Tropica (L. Tropica) was the most seen organism accounting for 255 (87.9%) cases, while Leishmania Major (L. Major) was the infective organism in 26 (9.0%) patients, while Leishmania Infantum (L. Infantum) were found in the least number of patients i.e., 9 (3.1%). Granuloma formation was seen in 185 (63.8%) patients: 121 (41.7%) had a tuberculoid granuloma while 51 (17.6%) and 13 (4.5%) had caseating and suppurative granulomas, respectively. Thus, a total of 134 (46.2%) patients had non-caseating granulomas while and 105 (36.2%) had no evidence of any granuloma on histology.

**Table III: Histological Characteristics According to Gender**

| Variable | Male (n=185) | Female (n=105) |
|---|---|---|
| **Parasite Index** | | |
| **One** | 15 (8.1%) | 12 (11.4%) |
| **Two** | 24 (12.9%) | 21 (20.0%) |
| **Three** | 35 (18.9%) | 24 (22.9%) |
| **Four** | 48 (25.9%) | 19 (18.1%) |
| **Five** | 47 (25.4%) | 16 (15.2%) |
| **Six** | 16 (8.6%) | 13 (12.4%) |
| **Species of Leishmania** | | |
| **L. Tropica** | 161 (87.0%) | 94 (90.5%) |
| **L. Major** | 19 (10.3%) | 7 (6.7%) |
| **L. Infantum** | 5 (2.7%) | 4 (3.8%) |
| **Granuloma Formation** | 123 (66.5%) | 62 (59.0%) |
| **Granuloma Type** | | |
| **Tuberculoid** | 85 (45.9%) | 36 (34.4%) |
| **Caseating** | 31 (16.8%) | 20 (19.0%) |
| **Suppurative** | 7 (3.8%) | 6 (5.7%) |
| **None** | 62 (33.5%) | 43 (40.9%) |

Table-IV shows the comparison between patients with non-caseating granulomas, those without and those patients who did not have granulomas. Factors such as gender, age of the patient, disease duration, site of lesion, type of skin lesion, parasite index and species of Leishmania were not associated with the development of non-caseating granulomas.

## Discussion

Granuloma formation occurs in response to persistent inflammatory stimulation which results in the aggregation of inflammatory cells (primarily macrophages): an immune protective mechanism which neutralizes foreign/pathogenic matter by encapsulation and neutralization.[12] Cutaneous leishmaniasis, in its limited form, is usually cleared spontaneously by the immune system without

**Table IV: Comparison of Different Variables with and Without Chronic Granulomatous Inflammation**

| Variable | Non-Caseating (n=134) | Caseating (n=51) | None (n=105) | *p* value |
|---|---|---|---|---|
| **Gender** | | | | |
| **Male** | 92 (68.7%) | 31 (60.8%) | 62 (59.0%) | 0.273 |
| **Female** | 42 (31.3%) | 20 (39.2%) | 43 (41.0%) | |
| **Age (years)** | 38.62 ± 14.19 | 37.61 ± 12.42 | 38.14 ± 13.86 | 0.901 |
| **Duration of Illness (weeks)** | 28.33 ± 11.51 | 26.49 ± 11.87 | 26.36 ± 11.33 | 0.366 |
| **Site of Lesion** | | | | |
| **Upper Limbs** | 48 (35.8%) | 24 (47.1%) | 40 (38.1%) | 0.669 |
| **Lower Limbs** | 47 (35.1%) | 13 (25.5%) | 29 (27.6%) | |
| **Head and Neck** | 34 (25.4%) | 13 (25.5%) | 33 (31.4%) | |
| **Trunk** | 5 (3.7%) | 1 (1.9%) | 3 (2.9%) | |
| **Type of Skin Lesion** | | | | |
| **Nodule** | 76 (56.8%) | 31 (60.8%) | 52 (49.5%) | 0.490 |
| **Ulcer** | 42 (31.3%) | 17 (33.3%) | 38 (36.2%) | |
| **Papule** | 16 (11.9%) | 3 (5.9%) | 15 (14.3%) | |
| **Parasite Index** | | | | |
| **One** | 11 (8.2%) | 7 (13.7%) | 9 (8.6%) | 0.297 |
| **Two** | 21 (15.7%) | 6 (11.8%) | 18 (17.1%) | |
| **Three** | 22 (16.4%) | 16 (31.4%) | 21 (20.0%) | |
| **Four** | 30 (22.4%) | 8 (15.7%) | 29 (27.6%) | |
| **Five** | 37 (27.6%) | 8 (15.7%) | 18 (17.1%) | |
| **Six** | 13 (9.7%) | 6 (11.7%) | 10 (9.6%) | |
| **Species of Leishmania** | | | | |
| **L. Tropica** | 119 (88.8%) | 44 (86.3%) | 92 (87.6%) | 0.870 |
| **L. Major** | 10 (7.5%) | 6 (11.8%) | 10 (9.5%) | |
| **L. Infantum** | 5 (3.7%) | 1 (1.9%) | 3 (2.9%) | |

intervention in about a month, however, that is not always necessarily the case and the disease may take as long as six years to clear, necessitating confirmation of diagnosis and institution of appropriate treatment.[13] However, the process of diagnosis may be difficult in areas without molecular methods of disease confirmation i.e., reliant on histology for establishing presence of the disease: cutaneous leishmaniasis is known as the great imitator and it has the ability to mimic almost any dermatosis, hence the requirement for this study.[14]

Granulomas were seen in 63.8% (46.2% non-caseating, 17.6% caseating), while 36.2% did not appear to have any granulomas on histological examination in our study. Most of the non-caseating granulomas were tuberculoid, while a minority were suppurative. Cardozo et al reported that 84.0% of their cases had granuloma formation, with the majority of these having non-caseating granulomas, while less than 1.0% had caseating ones.[15] Most of their patients had ill-defined histiocytic aggregates rather than the well-formed granulomas seen in our study.[15] Aoun et al reported granuloma formation in 61.5% of their study, of which 46.1% were non-caseating, while 15.4% demonstrated caseation,[11] while Andrade-Narvaez et reported that 43.8% had granulomas in their study, none of whom demonstrated caseation.[16] The variability in results may be attributable to a number of reasons: granuloma formation may be dependent on a number of host and disease factors which were not homogenous across the studies mentioned above, which may account for the differences in histological patterns seen.

Our study had a median age of 38.00 (16 - 63) years, age did not appear to have any association with the visualization of non-caseating granulomas, (*p*=0.901). This figure is in keeping with existing studies on the subject such as Debash et al who reported that the maximum number of cases of cutaneous leishmaniasis were seen in the range of 15 to 49 years in their study, while Bisetegn et al reported a mean age of 31.9 ± 14.29 years for their sample.[17,18] Moreover, Aoun et al also reported that there was no association between the development of different types of granulomas and age.[11]

The most of our study sample was male i.e., 185 (63.8%). Gender did not appear to have an association with the formation of non-caseating granulomas, (*p*=0.273). Wijesinghe et al and Solomon et al both noted that cutaneous leishmaniasis was more likely to be present in males, which is likely due to increase outdoor activities and differences in clothing when compared to females.[19,20] In addition, Aoun et al also concluded that gender did not appear to be associated with the development and type of granuloma.[11]

Most patients i.e., 38.6% had a lesion on the upper limbs, while the lower limbs had lesions in 30.7% cases. The head and neck region were affected in



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27.6% patients while the trunk was least affected: 3.1% cases, in our study. Anatomical location of the lesion did not appear to have an association with the development of non-caseating granulomas, ($p$=0.669). Rather et al noted in their study that lesions tended to occur on exposed areas, while Aoun et al also confirmed that the bites were most commonly found on the extremities and the head and neck region as in our study, and that location did not have any effect on the development of non-caseating granulomas, a fact that was also concurred with by Aguado et al.[11,22]

The principle macroscopic skin manifestation of disease were nodules in our study which accounted for 54.8% cases. Ulcers were seen in 33.4% patients while papular lesions were the least common and occurred in 11.7%. The type of macroscopic skin lesion did not appear to have a significant association with the development of non-caseating granulomas, ($p$=0.490). Our results were in contrast to Wijesinghe et al who noted that the occurrence of papules, nodules and ulcers occurred at the roughly same frequencies of 34.7%, 32.7% and 30.6%, respectively,[19] while Aoun et al reported that the majority of patients had nodular lesions (49.2%), while ulcerative lesions were also common (49.2%), which was in agreement with our results.[11]Variability in results between our study and Wijesinghe may be due to the delayed presentation seen in the latter study which may lead to worsening of the skin lesion. Aoun et al, like our study, also noted that the type of macroscopic lesion was not associated with the development of non-caseating granulomas.[11]

The Parasitic Index did not appear to have a relationship with the development of non-caseating granulomas, ($p$=0.297), in our study, which was concurred with by Aoun et al ($p$=0.09),[11] however, Wijesinghe et al reported that having a higher Parasitic Index was associated with a higher risk of developing granulomas, ($p$=0.027), which was at odds with our study.[19] This aspect of research requires further study before concrete conclusions can be drawn, but studies have shown that the number of organisms reduce as the cutaneous leishmaniasis becomes chronic but the granulomas form regardless.[23]

Lastly, L. Tropica was the most seen species in our study, accounting for 87.9% of our sample, followed by L. Major, which affected 9.0% patients, while L. Infantum was isolated in 3.1% cases. None of the species had any propensity towards the development of non-caseating granulomas, ($p$=0.870). Previous studies have shown the most common organism in Pakistan is L.Tropica in patients with cutaneous leishmaniasis which forms the bulk of cases, while L. Major accounts for a minor percentage, and L. Infantum is rarely seen.[24] Studies have also previously demonstrated that no species is associated with the development of non-caseating granulomas.[11]

## Study Limitations

This research protocol was conducted as a single-center study and was limited by its small sample size. Secondly, this study was performed on military personnel and their wards which has robust screening programs which may have resulted in early detection of disease which may or may not have affected the frequency of granuloma formation. Lastly, a case-control study would give a better idea of the association of different disease and patient factors with the formation of different types of granulomas and should be the subject of future research.

## Conclusion

Cutaneous Leishmaniasis is a commonly encountered disease that may present as a diagnostic dilemma in our part of the world due to its ability to mimic other common skin conditions such as tuberculosis and leprosy in terms of histological features. Recognition that the disease can commonly cause manifestations such as non-caseating and caseating granulomas, the pathologist must remain vigilant in making the correct diagnosis and institute appropriate and timely management. Future research should focus on the effect of granuloma formation on response to treatment and prognosis in terms of scarring.

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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Prognostic Value of Cyclin-D1 Expression in Head-a nd-Neck Squamous Cell Carcinoma: A Half-Decade Follow-Up

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**ABSTRACT**

**Objective:** To check the expression pattern of cyclin-D1 in stage I head and neck squamous cell carcinoma (H.N.S.C.C.) cases (evaluated based on history, clinical, medical, and radiological records) in our setting and evaluate the role of cyclin-D1 as a prognostic marker of H.N.S.C.C. (considering recurrence within five years and metastasis).

**Study Design:** Retrospective cohort study.

**Place and Duration of Study:** The study was carried out at Armed Forces Institute of Pathology (A.F.I.P.) Rawalpindi working in conjunction with the Department of Radiation Oncology, Rawalpindi. The duration of study was from 7th March 2022-14th October 2022.

**Materials and Methods:** The study comprised 92 patients from year 2015-16 of stage I diagnosed with squamous cell carcinoma of head and neck with complete five-year follow-up after fulfilling the inclusion and exclusion criteria. After collecting and matching the data on follow-up with record of the patients from Department of Radiation Oncology, C.M.H., Rawalpindi; paraffin-embedded blocks of these patients from year 2015/2016 were retrieved. Fresh *Hematoxylin and Eosin (*H&E) slides were prepared, and diagnosis was reconfirmed, vimentin stain was applied to check the antigenicity of the tissue followed by application of cyclin-D1 immuno-histochemical marker (I.H.C.) marker with controls to check the expression pattern.

**Results:** In our study we included a total of 92 diagnosed cases of stage I H.N.S.C.C. with a complete 5-year follow-up. Out of 92 cases male to female ratio was almost 3:1 with males comprising a total of 68 (73.9%) and females comprising 24 (26.1%). Mean age of patients was 62.48± 11.439 years. Larynx was the most frequently involved site 34.8% (n=32), followed by tongue 23.9% (n=22) and buccal mucosa 13.0% (n=12). Cyclin-D1 expression and tumor grade were revealed to have a statistically significant clinicopathological relationship (p value 0.001). A statistically significant association between the expression of cyclin-D1 and tumor recurrence (p value < 0.001) and duration of tumor recurrence (p value 0.003) was seen. The cyclin-D1 expression was also compared with metastasis which was also statistically significant (p value 0.003).

**Conclusion:** An increased risk of metastasis and recurrence is linked to increased levels of cyclin-D1 expression in the early years. Hence it is valuable to include cyclin-D1 expression in the initial diagnostic work up of H.N.S.C.C. for an early prognostic assessment. Further use of these results could be made for targeted treatment of head and neck malignancies.

**Key Words***: Cyclin-D1, Five-Year Follow-Up, Head-and-Neck Squamous Cell Carcinoma, Immuno-Histochemical Expression, Prognosis*.

## Introduction

Among the top ten types of human cancer, head and neck malignancies are a diverse category of tumors with distinct clinical and biological characteristics, causing an estimated 17,960 deaths worldwide each year.[1] H.N.S.C.C. has a substantial risk of both metastases and local recurrence, so aggressive treatments are typically performed to maximize the likelihood of long-term control.[2] These treatments may include surgery, radiotherapy, and/or chemotherapy. The high prevalence of this cancer requires special concern to devise authentic treatment protocols that are least invasive and show better outcomes.[3] Despite advancements in cancer prevention and treatment, the five-year survival rate of a patient with head and neck squamous cell

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carcinoma remains lower than that of other malignancies, such as colorectal, breast and cervical.[4] In conventional T.N.M. classification systems, the molecular heterogeneity of squamous cell carcinoma of the head and neck (H.N.S.C.C.) is not taken into account.[5] Hence, it is imperative to understand how recent molecular markers that have been identified correlate with prognosis for H.N.S.C.C., as they may offer new methods for early diagnosis, evaluation of prognosis and treatment. Cyclin-D1 a gene found on chromosome 11q13 plays a major role in activation of cell-cycle progression.[6]

Cyclin-D1 overexpression has been proposed by various international studies as a good marker for predicting poor prognosis in diagnosed cases of H.N.S.C.C.,[6,7,8,9] but these studies show the lack of proper follow-up, the uncertainty of such results in oral squamous cell carcinoma (O.S.C.C.), and smaller overall sample size.[10] This study's objective was to assess the expression of cyclin-D1 on a larger sample of stage I H.N.S.C.C. cases with a documented complete five-year follow-up to determine its prognostic significance. So that if the association is proved then cyclin-D1 marker should be made part of the diagnostic protocol. Patients with strong expression of cyclin-D1 on premier biopsy should be kept at close follow-up and treatment should be planned accordingly (targeted therapy can be given to patients such as cyclin-D inhibitors). If on the contrary this association is disapproved then we should stop investing time and money on this marker and evaluate better prognostic markers for the improvement in the treatment of patients with H.N.S.C.C. Information in regard to this study was collected on data collection questionnaire in the form of variables, statistical analysis was performed using S.P.S.S. version 26.0, Microsoft Excel 2013 was used for diagrammatic representations, qualitative / categorical variables were presented as frequency and percentages, to compare various parameters Chi-square test was performed and p-value of 0.05 was considered to be the essential level of significance.

## Materials and Methods

A retrospective cohort study was carried out at Armed Forces Institute of Pathology (A.F.I.P.). This study had 92 patients in total. The approach of non-probability convenient sampling was applied. The study was conducted after the approval of Ethical Review Committee (Letter number: MP-OMP20-1/READ-IRB/21/781, dated: 30th-December-2021). Contact details of all cases diagnosed from Armed Forces Institute of Pathology (A.F.I.P.) of squamous cell carcinoma of head and neck region from January 1, 2015, to December 31, 2016 were taken from archives of Histopathology Department at Armed Forces Institute of Pathology (A.F.I.P.), Rawalpindi, Pakistan. The diagnosed patients of stage 1 H.N.S.C.C. were contacted for consent to participate in the research and five-year follow-up i.e., till December 31, 2021, and onwards. The data was matched with the record of these patients kept in the Department of Radiation Oncology, C.M.H. Rawalpindi. After collecting the data on follow-up of these patients, paraffin-embedded blocks of these patients from year 2015 to 2016 were retrieved. Confounding factors were excluded by firmly following the exclusion criteria [patients lost to follow-up or could not be contacted, poorly fixed specimens, very scanty tissue specimens, extensive necrosis or the retrieved blocks failed to take vimentin stain to check the antigenicity of tissue, patients dying within the study period, patients who had irretrievably taken away paraffin sections, cases diagnosed with H.N.S.C.C. of conjunctiva or skin or cases diagnosed with any immuno-morphological subtype of squamous cell carcinoma or mixed forms (with more than one component) i.e. adeno-squamous carcinoma ] and inclusion criterion [all stage I H.N.S.C.C. cases with a documented complete five-year follow-up (evaluated on the basis of history, clinical, medical and radiological records) in our setting at A.F.I.P. during the calendar year January 1, 2015- December 31, 2016 (irrespective of age, gender or ethnicity)].H&E slides were prepared freshly for already diagnosed cases, but to eliminate bias the slides were viewed by three investigators separately. After confirmation of diagnosis on freshly prepared H&E slides, vimentin stain was applied to check the antigenicity of the tissue, followed by the application of cyclin-D1 immunohistochemical marker by Leica Microsystem (Germany). Lymph node tissue (mantle cell lymphoma) was used as positive control and appendix tissue was used as negative controls for cyclin-D1. When distinct brown nuclear staining was observed in ≥1% of the cells, the

tissue samples was considered positive for cyclin-D1. Cytoplasmic staining was not considered. The quantification criteria by *Dhingra et al.,* was used to quantify cyclin-D1 expression.[9] The sections with an inter-observer difference of more than 10% were re-examined by means of a multi-headed light microscope to reach consensus. Information was collected on data collection questionnaire in the form of variables, statistical analysis was performed using S.P.S.S. version 26.0, Microsoft Excel 2013 was used for diagrammatic representations, qualitative / categorical variables were presented as frequency and percentages, to compare various parameters chi-square test was performed and p-value of 0.05 was the essential level of significance.

## Results

A total of 92 diagnosed cases of stage I H.N.S.C.C. with a complete 5-year follow-up were included in the study. Out of 92 cases male to female ratio was almost 3:1 with males comprising a total of 68 (73.9%) and females comprising 24 (26.1%). Mean age of patients was 62.48± 11.439 years. Larynx was the most frequently involved site 34.8% (n=32), followed by tongue 23.9% (n=22) and buccal mucosa 13.0% (n=12). The chi-square test revealed a statistically significant clinico-pathological relationship between cyclin-D1 expression and tumor grade (p value 0.001) Table I.

The cyclin-D1 expression was also compared with recurrence within five years by using chi-square test which was statistically significant (p value < 0.001) Table II and a statistically significant association was also seen between cyclin-D1 expression and duration of tumor recurrence (p value 0.003) Table III.

The cyclin-D1 expression was also compared with metastasis within five years by using chi-square test which was also statistically significant (p value = 0.003) Table IV

**Table I: Case Distribution Based on Overall Cyclin-D1 Expression Score and Tumor Grade (n=92)**

| Expression of cyclin D1 | Diagnostic Grade | | | Total |
|---|---|---|---|---|
| | Well differentiated. (%) | Moderately differentiated (%) | Poorly differentiated (%) | |
| Weak + (1-4) | 10 (33) | 28 (50) | 2 (33) | 40 |
| Moderate ++ (5-8) | 18 (60) | 16 (29) | 0 (0) | 34 |
| Strong +++ (9-12) | 2 (7) | 12 (21) | 4 (67) | 18 |
| **Total** | **30** | **56** | **6** | **92** |

***p*-value = 0.001**

**Table II: Case Distribution Based on Overall Cyclin-D1 Expression Score with Recurrence (n=92)**

| Recurrence | Expression of Cyclin D1 | | | Total |
|---|---|---|---|---|
| | Weak + (1-4) | Moderate ++ (5-8) | Strong +++ (9-12) | |
| Absent | 40 | 32 | 4 | 76 |
| Present | 0 | 2 | 14 | 16 |
| **Total** | **40** | **34** | **18** | **92** |

***p*-value = 0.001**

**Table III: Case Distribution Based on Overall Cyclin-D1 Expression Score With Recurrence as Per Follow up Duration (N=92)**

| Recurrence | Cyclin-D1 Expression | | | Total |
|---|---|---|---|---|
| | Weak + (1-4) | Moderate ++ (5-8) | Strong +++ (9-12) | |
| First year | 0 | 0 | 4 | 4 |
| Second year | 0 | 0 | 6 | 6 |
| Third year | 0 | 0 | 2 | 2 |
| Fourth year | 0 | 2 | 0 | 2 |
| Fifth year | 0 | 0 | 2 | 2 |
| **Total** | 0 | 2 | 14 | 16 |

***p*-value = 0.003**

**Table IV: Case Distribution Based on Overall Cyclin-D1 Expression Score with Metastasis (n=92)**

| Metastasis | Cyclin-D1 Expression | | | Total |
|---|---|---|---|---|
| | Weak + (1-4) | Moderate ++ (9-12) | Strong +++ (9-12) | |
| Absent | 38 | 32 | 12 | 82 |
| Present | 2 | 2 | 6 | 10 |
| **Total** | 40 | 34 | 18 | 92 |

***p*-value = 0.003**

## Discussion

Cyclin-D1 is a gene located on chromosome 11q13 and plays a major role in activation of cell-cycle progression. Cyclin-D is a cyclin-dependent kinase (C.D.K.) 4 and C.D.K. 6-binding cell cycle regulator. The stimulation of D.N.A. synthesis and the transition of cells between the G1/S phases are both significantly influenced by this cyclin-CDK complex, [11] rendering it a genuine target during carcinogenesis.[12] As a result, it has been determined that 30% of head and neck S.C.C. have cyclin-D1 amplification.[13]

In our investigation, it was discovered that cyclin-D1 expression positively associated with tumor grade. When the histopathological grade increased, from well differentiated to poorly differentiated



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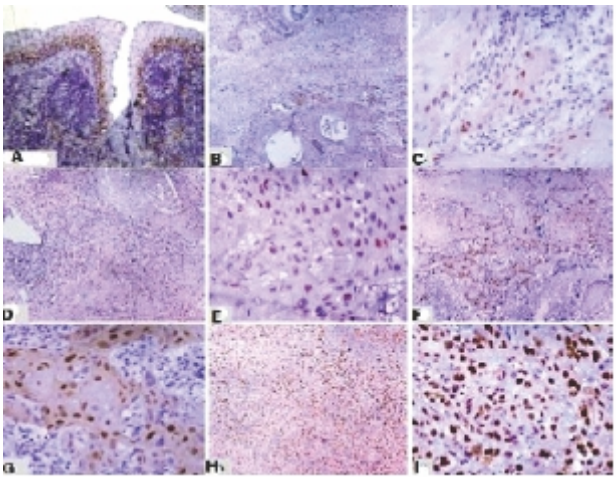
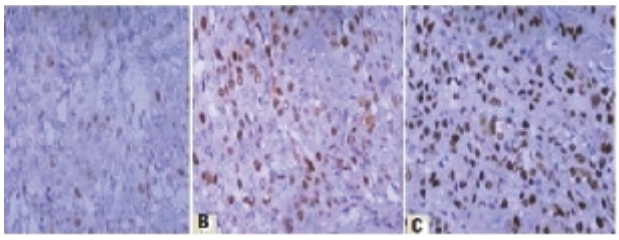


This figure is showing expression score as per quantification criteria.



This figure is showing intensity score as per quantification criteria

**Figure 1: Figure Showing Total Score of Cyclin-D1 Expression (Product of Expression Score and Intensity Score)**

H.N.S.C.C., the percentage of cyclin-D1 expression increased as well. In various studies, higher cyclin-D1 expression has been linked to poor histological grade.[8] According to Chinnathambi et al., in year 2021cyclin-D1 immuno-expression was discovered in all patients, and it was substantially correlated with deteriorating tumor grade and positive lymph node disease. Nevertheless, several authors discovered no clinical correlation. Batool et al. in 2020 in her study described similar findings that the histological grade of H.N.S.C.C. was not substantially correlated with cyclin-D reactivity.[14] Zand et al. in 2020 and Nazar et al. in year 2020 also described that the results of their study demonstrated no link between expression of cyclin-D1 and grade of the disease.[15,16]

The main finding of our research was that the stage I diagnosed cases of H.N.S.C.C. showing an elevated expression of cyclin-D1 at the time of diagnosis were at a greater risk of developing recurrence in the earlier years of five-year period of follow-up as compared to those cases showing a weak or no expression of cyclin-D1 immuno-histochemical stain. Another important finding of this study was that cyclin-D1 expression was found to positively correlate with tumor metastasis. An increase in cyclin-D1 expression at the time of diagnosis of stage I cases of H.N.S.C.C. was found to show an increased risk of developing tumor metastasis within the five year of diagnosis of tumor.

Various studies have been conducted on this molecular marker suggesting that strong positivity of cyclin-D1 expression in H.N.S.C.C. is related to metastasis and recurrence in operable cases of H.N.S.C.C.[9] Sharada et al., in year 2018 and Patel et al., in year 2017 described similar results in their studies that overexpression of cyclin-D1 has been seen to associate with an increased risk of metastasis of lymph nodes and increased risk of recurrence.[17,18]

Our research had this limitation that five year survival of the cases could not be included in the study to determine prognostic value of cyclin-D1 as it was a retrospective study and confounders could not be removed for those who died within five years; as exact cause of death could not be determined for those dying within study period (five years of diagnosis of H.N.S.C.C.).Hence, prospective follow-up study is recommended including five year survival of cases as a variable to determine prognostic value of cyclin-D1 thus minimizing confounders by notifying exact cause of death of participants within the study period.

## Conclusion

This study showed a statistically strong association between recurrence, duration of developing recurrence and metastasis with increasing cyclin-D1 expression. Therefore, an increased risk of metastasis and recurrence is linked to increased levels of cyclin-D1 expression in the early years. Hence it is valuable to include cyclin-D1 expression in the initial diagnostic work up of H.N.S.C.C. for an early prognostic assessment. . Further use of these results could be made for targeted treatment of head and neck malignancies.

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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

**GRANT SUPPORT AND FINANCIAL DISCLOSURE**

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Effectiveness of HIV Pre-Exposure Prophylaxis (PrEP) in Pakistan

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## ABSTRACT

**Objective:** To evaluate the effectiveness of HIV Pre-Exposure Prophylaxis (PrEP) in HIV Clinic of a tertiary care hospital in Pakistan.

**Study Design:** A descriptive study covering the data of clients who were offered PrEP.

**Place and Duration of Study:** HIV treatment center Pakistan Institute of Medical Sciences (PIMS) Islamabad, Pakistan, from October 2019 to September 2022.

**Materials and Methods:** Total of 118 people without HIV from various high-risk population groups were reported in HIV treatment center PIMS during a period of 3 years including 39 females from serodiscordant couples, 16 transgender females, and 63 men having sex with men (MSM). All of them were given oral PrEP after necessary screening, investigations, and evaluation. These clients were prescribed a fixed drug combination of Tenofovir/Lamivudine (TDF/3TC) one tablet daily as PrEP. The alternate regimen used was Event-driven PrEP (EDP) for MSM. Monthly follow-up was performed, and all patients were found to be HIV negative.

**Results:** All 118 clients receiving PrEP remained seronegative on regular monthly follow-ups after a sufficiently long period of unsafe sexual practices that frequently exposed them to HIV-positive sex partners. Based on their age mean age of the clients in young group below 35 years was 27 $\pm$ 6, all 62 young clients had 100% protection. Similarly, 41 middle aged (mean age 43 $\pm$ 6) and 15 old clients (mean age 56 $\pm$ 5) had 100% protection with PrEP. Six women from serodiscordant couples while receiving PrEP became pregnant with partners who had completely suppressed viral load (<50 copies).

**Conclusion:** Oral PrEP has offered complete protection to all seronegative individuals belonging to high-risk population groups despite their frequent exposure to HIV-positive partners. All 118 individuals who received PrEP remained seronegative.

**Key Words:** *HIV, Pre-exposure prophylaxis, Serodiscordant Couples, Event-driven PrEP. HIV Prevention, MS.*

## Introduction

HIV/AIDS is a global public health problem. There is no cure for the disease and once the HIV infection is acquired by an individual, he needs life-long treatment with ARVs to keep the viral load suppressed.[1-6] Most common ways for HIV transmission are unsafe sex practices and injection drug use with shared syringes. Despite a global awareness campaign, many people tend to ignore the risks involved and indulge in unsafe sex practices or share syringes with other injection drug users**.** A systematic review of published and unpublished data from randomized trials found no significant differences in the efficacy of lamivudine and emtricitabine, consistent with very similar chemical structures of these two nucleoside analogues.[13] There has been a growing need to find effective methods to stop spread of HIV infection to healthy individuals. PrEP is an effective and safe method of prevention of HIV transmission in high-risk population groups. While the incidence of HIV has declined worldwide over the past decade, many new HIV infections occur globally highlighting the ongoing need for new and effective HIV prevention initiatives. Oral pre-exposure prophylaxis of HIV (PrEP) is the use of antiretroviral drugs (ARVs) by HIV seronegative individuals from high-risk population groups to block the acquisition of HIV[1]. The US Food and Drug Administration approved TDF with emtricitabine (FTC) for oral PrEP in 2012. In 2015, WHO recommended once-daily oral PrEP to population susceptible of HIV. However, for MSM,

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the 2019 WHO guidance include options for event driven dosing (on demand PrEP).[14] Oral PrEP trials have shown evidence of effectiveness in certain high-risk population groups in society including serodiscordant couples, MSM, transgender females, and injection drug users (IDUs)[5]. In Pakistan, the PrEP regimen consists of a fixed-dose combination of Tenofovir with Lamivudine in place of Emtricitabine. Oral PrEP containing TDF co-formulated with FTC[3] or 3TC is recommended as an additional prevention option for persons at substantial risk of HIV infection by both WHO and the US President's Emergency Plan for AIDS Relief (PEPFAR).[21]Clinically 3TC is interchangeable with FTC for PrEP given comparable pharmacologic equivalence, resistance, and toxicity patterns[2], and indirect clinical trial evidence from TDF-containing studies.[12] PrEP has provided significant protection to these high-risk population groups[4]. Daily oral PrEP with tenofovir/emtricitabine is highly efficacious in preventing HIV infection with high adherence and safe to use during pregnancy and breast-feeding.[9] Therefore we design our study to evaluate the effectiveness of HIV Pre-Exposure Prophylaxis (PrEP) in HIV Clinic of a tertiary care hospital in Pakistan.

## Materials and Methods

This descriptive study was carried out in a tertiary care hospital in the Federal Capital of Pakistan after obtaining approval from Institutional Ethical Committee Ref no 6/9/22 (1). This study covers a period of 3 years from October 2019 to September 2022. Behavioral therapy was conducted by experienced counselors of the HIV Clinic before initiating the PrEP therapy, and biomedical interventions[8] were explained to the clients. As per WHO guidelines, seronegative males, females, and transgender women of all ages from key population groups and those with unsafe sex practices were offered PrEP. During the last 3 years, 118 individuals from high-risk population groups were given PrEP including 63 MSM, 39 female members of serodiscordant couples, and 16 transgender females.[15] Selection criteria were strictly followed as per the WHO guidelines for offering PrEP. After initiation of ARVs, regular follow-up of individuals was ensured and compliance/adverse effects as well as the HIV-negative status of clients monitored. The following three eligibility criteria were necessary for offering PrEP: Confirmed HIV-negative status, no signs, and symptoms of acute HIV infection, and acknowledged being at substantial risk for HIV. Exclusion criteria for PrEP include HIV infection, Adolescents less than 35 kg, impaired renal function, Allergy, or contraindication to any drug in the PrEP regimen, Refusal to follow up, and Pregnancy.

PrEP Regimen:

I. FDC (Fixed Dose Combination; Lamivudine 300 mg + Tenofovir (TDF) 300 mg
II. Daily Dosing PrEP
III. EDP (Event Driven PrEP) or 3-day PrEP[15]

Following lab investigations were performed to determine the eligibility status of the individual for PrEP:-

1. Rapid test: Negative
2. RFTs: Normal
3. Pregnancy test for the female client: Negative

Clients receiving PrEP were divided into three groups based on gender i.e., males, females, and transgender women. Another division was made based on age i.e., clients less than 35 years, 35 to 60 years, and more than 60 years. Another grouping was done according to the high-risk population groups i.e., MSM, HIV-negative members of serodiscordant couples, and heterosexual sex workers. Follow-up was done regularly for an uninterrupted supply of medicines. A rapid test was performed after every 3 months. Serum creatinine was also checked after every 3 months. PrEP was discontinued in 6 females temporarily due to pregnancy and resumed after childbirth with the mother's consent.

## Results

A total of 118 seronegative clients from high-risk population groups were given PrEP[7]. All individuals remained seronegative on regular follow-up tests with rapid test kits. These clients were MSM, female members of serodiscordant couples, and transgender women.

The total number of clients were divided in three groups based on their ages : <35 Y, 35-50 Y, and >50 y. Based on their age (Table-1), mean age of the clients in young group below 35 years was 27 $\pm$ 6, all 62 young clients had 100% protection. Similarly, 41 middle aged (mean age 43 $\pm$ 6) and 15 old clients (mean age 56 $\pm$ 5) had 100% protection with PrEP.

Another comparison based on gender (Table -1)



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**Table I: Age, Gender, and Risk Population-Based Data of Study Participants (n= 118)**

| Age Groups | | | Gender | | | Risk Population group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| <35 Y | 35-50 Y | >50 y | Male | Female | TG | MSM | Serdiscordant | Transgender Women | IDUs | Female sex workers |
| 62 | 41 | 15 | 63 | 39 | 16 | 63 | 39 | 16 | 0 | 0 |

**MSM: Men who have sex with Men**
**IDU: Injection drug use.**

shows all three groups have 100% protection from HIV with PrEP. Another group based on high-risk population groups (Figure-1) shows complete protection for MSM, discordant couples and transgenders. However, there was no client in IDUs group since no one opted to get PrEP from IDUs, those who are registered with HIV Clinic are all HIV positive and do not fulfill criteria to administer PrEP.

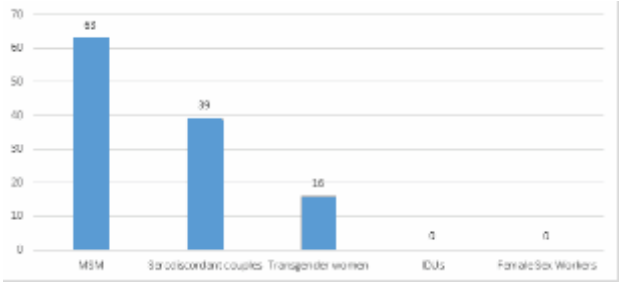


**Figure 1: Comparison of Prep Clients According to High-Risk Population Groups**

## Discussion

The Centers for Disease Control and Prevention (CDC) reports that studies on PrEP effectiveness have shown that consistent use of PrEP reduces the risk of getting HIV from sex by about 99%.[15] Certain HIV seronegative population groups are more at risk of acquiring HIV infection because of their marital relationship with an HIV-positive spouse or due to their adopted unsafe practices. Such individuals need protection against the potential transmission of infection by physical methods like the use of condoms and avoidance of unsafe sex practices.[10,19] However, this approach is seldom adopted either by these vulnerable people themselves or by their sex partners resulting in the transmission of HIV to a previously uninfected individual. To avoid this risk, PrEP was introduced by FDA and WHO. PrEP is offered to people who are HIV-negative but are at risk of getting HIV through sex or injection drug use, they take ARVs daily to prevent HIV infection. The fixed drug combination of TDF (300 mg) with 3TC (300 mg) is used mostly as a daily single dose[12]. In the case of MSM, EDP is offered as it needs less frequent dosing and provides an option to the individual to administer the PrEP as per his sexual practices[11]. This regimen is supposed to provide better compliance by the client.[17]

An uninfected member of a serodiscordant couple is offered PrEP after behavioral therapy and counseling of the HIV-positive partner to use ARVs and ensure compliance to keep the viral load at an undetectable level (<50 copies on PCR). In case the female is on PrEP and the couple meets the above criteria, then pregnancy is permitted, and according to WHO guidelines pregnant female is given a choice to discontinue PrEP to avoid any adverse effects on the fetus. PrEP is restored after the delivery of the baby. In our study 6 females from serodiscordant couples became pregnant, their PrEP was stopped during pregnancy and all 6 delivered healthy babies. Their PrEP was restored after delivery and all of them were advised to breastfeed their babies since it is a safe practice.[9]

Transgender female clients were advised daily PrEP regimen because of their unsafe practice and a lifestyle that makes them vulnerable to acquiring HIV infection from multiple sex partners. These clients are mostly registered with NGOs due to which they remain under continuous surveillance by the dedicated staff. Their compliance is good and regular follow-up is expected.

Most clients from the MSM group were referred by NGOs that deal with HIV/AIDS population. They are reluctant to show up and need a lot of persuasion, encouragement, and a guarantee of complete confidentiality to convince them for starting PrEP. Due to efforts of NGOs, this group constitutes the biggest proportion of clients receiving PrEP from HIV treatment center PIMS.

It was noted with interest while conducting the analysis that no client was registered in PrEP from population groups like IDUs and female sex workers. On further investigation main reason was the fact that IDUs are mostly HIV positive and therefore do not fit into the inclusion criteria for PrEP. Moreover, some MSM may be using injection drugs but there is a possibility that they did not disclose because most of these clients were reluctant to seek PrEP and reported voluntarily only due to motivation by NGOs

to use PrEP. Female sex workers do not agree to document their activities by disclosing their profession or activities.[20]

PrEP has been providing safety to 118 registered clients since 2019. Some of them are using ARVs for 2 to 3 years and are still HIV-negative. The analysis of the study and results obtained show complete safety to the clients on PrEP. Their regular follow-up and investigations provide a pattern of the efficacy of ARVs as well as the safety of the regimen used. It has been a useful tool so far for the prevention of HIV transmission to vulnerable population groups who are frequently exposed to sexual contact with HIV-positive patients.

## Conclusion

Results compiled from this study showed that PrEP therapy is highly effective to prevent HIV in different risk groups of different ages. High-risk population groups are benefiting from this program which is successfully working since October 2019. There were no reports of any serious side effects of ARVs, no therapeutic failure, no case of loss to follow-up, no issue of compliance, and no evidence of resistance to used drugs. There is a need to initiate PrEP in other HIV Clinics in Pakistan after a successful launch in Islamabad.

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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

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Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Protective Effects of Turmeric (Curcuma Longa) Against Methotrexate Induced Liver Toxicity in The Albino Mice

Farah Deeba[1], Ronaq Zaman[2], Shehla Khatoon[3], Fatima Daud[4], Maqbool Illahi[5], Farzana Begum[6]

**ABSTRACT**

**Objective:** To study the protective effects of Turmeric against hepatic damage brought on by Methotrexate.

**Study Design:** Randomized controlled trial.

**Place and Duration of Study:** This experimental research was conducted at Animal House of Institute of Basic Medical Science (IBMS), Khyber Medical University, Peshawar from 10June 2017 to 25 June 2018.

**Materials and Methods:** A total of 28 adult albino mice were divided into four groups. Group A was control group. Control group received no medication. Group B received a daily dose of Turmeric extract (400 mg/kg) for 14 days. Group C received an intraperitoneally (I.P) injection of Methotrexate (40 mg/kg) on day 7. Group D received oral administration of Turmeric extract (400mg/kg) for 14 days and injection Methotrexate (40mg/kg) was administered intraperitoneally (I.P) on day 7. All mice were sacrificed on day 14. Weight of liver of all the animal was recorded. For data analysis Statistical package for social sciences (SPSS) version 21 was used. Quantitative variables were expressed as mean ±standard deviation and the significant difference was assessed using ANOVA test. The Chi square test was used to determine statistical significance based on the categorical variables. P value <.05 was significant statistically.

**Results:** On microscopic examination of liver tissue, abundant inflammatory cells were observed around the portal area in all mice (100%) of Methotrexate group (Group C) with increase in liver weight. In Methotrexate + Turmeric group (Group D) few inflammatory cells were observed with slight decrease in liver weight as compared to Group C in all mice (100%).

**Conclusion**: The results of this study revealed that Turmeric (*Curcuma Longa*) treatment protects liver tissue against Methotrexate-induced damage.

**Key Words:** *Curcuma Longa, Hepatotoxicity, Inflammatory cells, Methotrexate, Reactive oxygen species*

## Introduction

Methotrexate is one of folic acid antagonists. It was initially used for acute leukemia in children. The effective use in treating other cancers followed thereafter.[1] Methotrexate has been commonly used in the treatment of a rheumatoid arthritis, psoriasis and other autoimmune disorders such as juvenile idiopathic arthritis for more than 40 years.[2] Methotrexate is effective in the treatment of systemic lupus erythematosus, vasculitis, inflammatory bowel syndrome and several other diseases of connective tissue.[3] It is also used for the treatment of leukemia and malignancies of different organs such as breast and lung.[4]

The most frequent side effects of Methotrexate are nausea, vomiting, loss of appetite, ulcers of mucosa, when taken in low doses.[5] After used as a continuous therapy, its other side effects are alopecia, low white cell count, increased risk of infection, GI bleeding, bone marrow suppression, hepatotoxicity and renal failure.[6,7,8]

Methotrexate and its metabolite-polyglutamated inhibit the dihydrofolate reductase enzyme, which converts dihydrofolate into tetrahydrofolate (The folic acid's active form). The nucleoside thymidine denovo can only be produced with folic acid. Methotrexate thus has an indirect effect on the thymidylate synthesis, which is required for synthesis of DNA[9]. Hepatocytes are damaged by

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reactive oxygen molecules such as hydrogen peroxide, hydroxyl radicals, and superoxide. Methotrexate inhibits NADP, which is needed by the glutathione reductase enzyme to neutralize reactive oxygen species.[10]

Herbs have a key part in the treatment of many liver illnesses because there are no effective pharmaceuticals that can protect the liver in allopathic medical procedures.[11] Numerous studies have demonstrated the significance of plant extracts in liver diseases .[12]

The use of Turmeric in Chinese and Indian medicine has a long history. [13] There are more than 300 ingredients in Turmeric, diarylheptanoids, monoterpenes, diterpenes, sesquiterpenes, phenyl propene, alkaloids, and curcuminoids are some of these ingredients.[14] It is used to treat inflammatory disorders, cancer, hepatitis and other hepatic disorders, Alzheimer's disease, skin diseases and rheumatoid arthritis[15].

The generation of reactive oxygen species (ROS), such as hydroxyl radicals and hydrogen peroxide, is inhibited by Turmeric. Turmeric's antioxidant properties thereby prevent the liver damage caused by free radicals.[16,17] Limited studies have been conducted to know the role of Turmeric in protection against Methotrexate hepatic damage. Therefore, this study was planned to–assess the defensive effects of Turmeric on Methotrexate induced hepatic toxicity in mice.

## Materials and Methods

This randomized controlled study was conducted at the animal house of Institute of Basic Medical Sciences, KMU, and Peshawar from 10 June 2017 to 25 June 2018. Sampling technique was convenient sampling. Ethical clearance was taken from the ethical review board of Postgraduate Medical Department, Khyber Girls Medical College with reference number.3325/PGMED/KGMC. Male albino mice were included in study. Female albino mice were excluded. Adult male albino mice weighing 25 to 45 grams (5 to 7 weeks) were acclimated for two weeks in a 12-hour cycle of darkness and light at temperature of $22^0$C. Mice were split between the control group (Group A) and the experimental groups B, C, and D. There were four mice in the control group (A) and eight mice each in groups B, C, and D. Group A received no medication. Group B was given Turmeric extract orally (400mg /kg) for 14 days. Group C received Injection Methotrexate (40mg/kg) intraperitoneally on day 7. Both Turmeric and Methotrexate given to Group D. Turmeric extract (400mg /kg) daily for 14 days was given to Group D. On day 7, injection of Methotrexate (40mg/kg) was administered intraperitoneally to Group D [17]. All mice were sacrificed on day 14. Weight of the livers of all the animal was recorded. Analytic balance was used to measure liver organ weight. The liver was preserved in formalin. By tissue processing, various liver sections were made. Eosin and hematoxylin were used to stain the slides. To observe the histological parameters, tissues were seen under a light microscope. Slides were examined by histopathologist. (Assistant Professor, MPhil histopathology).

For data analysis Statistical package for social sciences (SPSS) version 21 was used in this study. Quantitative variables were expressed as mean ±standard deviation and the significant difference was assessed using ANOVA test. The Chi square test was used to determine statistical significance based on the categorical variables and results. P value <.05 was significant statistically.

## Results

The mean value of liver weight was significantly increased in Methotrexate Group i.e. 1.650 ± 0.17gm as compared to control group i.e. 1.352 ± 0.20gm. Whereas mean value of liver weight of mice treated with Methotrexate and Turmeric was significantly reduced i.e. 1.464 ± .016gm as compared to Group receiving Methotrexate ($p< 0.00$). The weight of liver of different groups is shown in figure 1.

On gross examination of mice liver in Methotrexate and Methotrexate + Turmeric group, there was no change in color, texture and consistency as compared to control group.

On histological examination of liver tissue, no periportal inflammation was present in all animals of control as well Group B (Turmeric). Abundant inflammatory cells were present around portal area in all eight animals receiving Methotrexate Group C (figure 2) with p value < 0.00 (table 1) which is statistically significant, where as in the Group D (Methotrexate plus Turmeric) few inflammatory cells were seen as compared to Group C with $p< 0.00$ (figure 3).

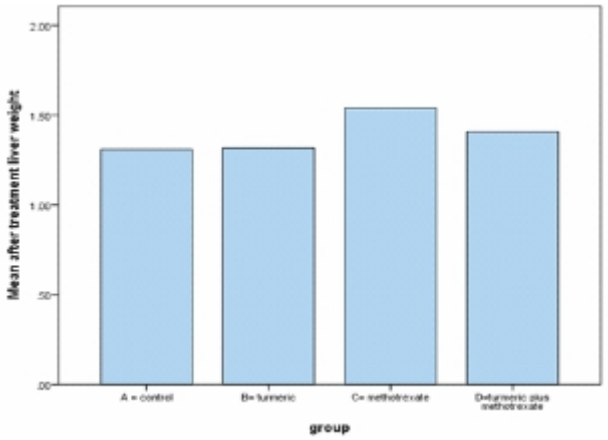


**Figure 1: Increase in Weight of Liver of Methotrexate Group**

**Table I: The Effect of Methotrexate and Turmeric on Periportal Inflammation**

| Parameter | Control group A *n*=4 | Turmeric group B *n*=8 | Methotrexate group C *n*=8 | Methotrexate plus Turmeric group D *n*=8 | p value |
|---|---|---|---|---|---|
| Periportal inflammation | Absent n=4 | Absent n=8 | marked n=8 | Mild n=8 | 0.00 |

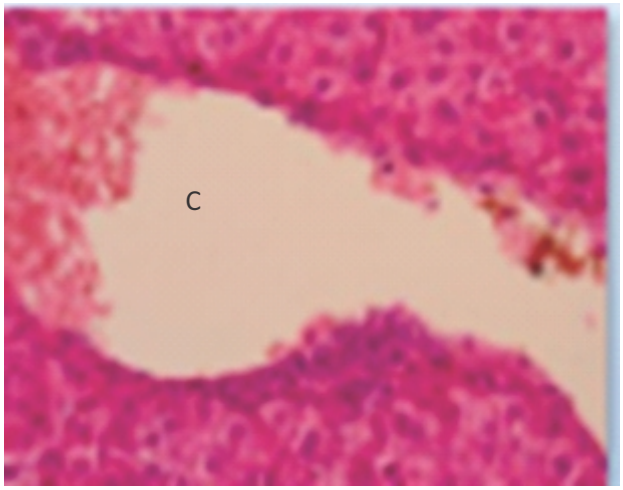


**Figure 2: Photomicrograph of Liver Tissue of (MTX Group) Where " C" Shows Abundant Inflammatory Cells Around Portal Area At 40x**

## Discussion

Methotrexate has been highly criticized for its hepatotoxicity. If a medicine is used with a good ameliorative agent, the liver may be protected. Several researchers scientifically demonstrated that Curcuma longa (Turmeric) has anti-inflammatory, antimicrobial, anti-cancer and antioxidant properties[18,19]. Thus, Curcuma Longa (Turmeric) have capability to provide protection against oxidative stress induced by Methotrexate[20,21]

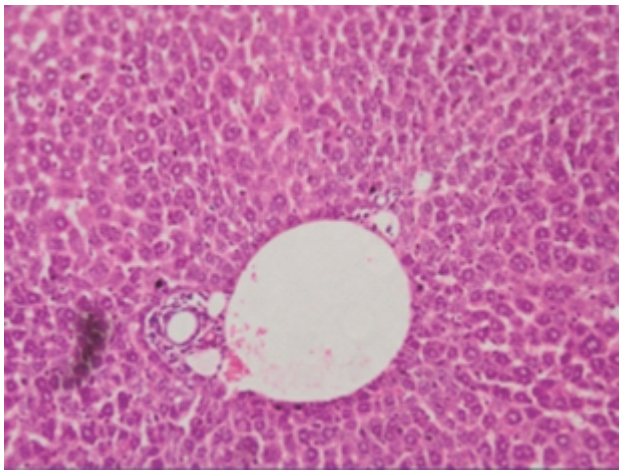

**Figure 3: Photomicrograph of Liver Tissue of (MTX+ Turmeric Group) Where Few Inflammatory Cells Round Portal Area At 40x**

Liver weight was significantly increased in Methotrexate group. Whereas in Methotrexate Turmeric group administration of Turmeric causes significant reduction in liver weight as compared to Methotrexate group. Liver weight increased because of diffuse inflammatory cellular infiltration, collagen deposition, mild hepatic edema and fatty infiltration.[22,23] Our findings concur with those made by Tag et al, who observed that administration of mulberry leaves extract causes significant reduction in liver weight of mice as compared to Methotrexate group.[24]

Significant periportal inflammation was observed in all eight animals in Methotrexate group. Few inflammatory cells are observed in Methotrexate Turmeric group. Our results correlate with the result of Adel Rezaei et al. In his study he also observed that periportal inflammation induced by Methotrexate is significant reduced by ethanolic extract of Turmeric (*Curcuma Longa*) [19]. The protecting effects of curcumin against liver damage were also observed by a study conducted by Erenoğlu etal.[25]

## Conclusion

In conclusion, turmeric (*Curcuma Longa*) treatment protects liver tissue against Methotrexate-induced damage.

## Recommendations

It is feasible to use Turmeric as a potential addition to a Methotrexate therapy regimen by conducting clinical trials to examine the herb's effects on human.



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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.




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ORIGINAL ARTICLE

# Loud Noise; Wound Angiogenic Stimulator or Inhibitor?

Khalida Moeed[1], Jamshed Khan[2], Anum Usman[3], Fauzia Siraj[4], Waseem Kausar[5]

**ABSTRACT**

**Objective** : To observe how loud noise affects the growth of new blood vessels in rat skin wounds.

**Study Design :**QUASI experimental study.

**Place and Duration of Study:** The study was conducted at National Institute of Health Islamabad from 28th June 2017 to 28thFebruary 2018.

**Materials and Methods:** Thirty male Sprague Dawley rats were split into control and experimental groups by convenient sampling, with 15 animals belonging to each leading group. On the dorsum of each rat, a 2 cm incision was created. While experimental subgroups endured 4h/d intermittent noise exposure of 85-95db five days a week for two consecutive weeks, control subgroup rats were left to heal with routine background noise exposure. On days 3, 7, and 14, five rats from each group were slaughtered. Wounds were excised, repaired, and prepared for H&E stain before being able to see and count the freshly grown blood vessels**.**

**Results:** Although difference in mean number of newly formed blood vessels among both control and experimental group was found with more numbers in control group but it was not statistically significant.

**Conclusion**: Intermittent noise exposure has tendency to impair the process of angiogenesis thus delaying wound healing.

**Key Words:** *Angiogenesis, Noise, Skin Wound, Stimulator, Inhibitor.*

## Introduction

Restoration of skin integrity following injury is dependent on cell and ECM interaction and it can be hindered at any point during the process of wound healing.[1] Multiple research models concluded that psychological stress may affect wound healing. It is evident from experimental work done in the past that aircraft noise is linked to stress-induced vascular damage, which is mediated by inflammatory cells infiltrating the blood vessels, endothelial nitric oxide synthetase being uncoupled, and NADPH oxidase being oxidized.[2] Transcriptome research has also revealed alterations in the expression of genes involved in controlling vascular function, re modelling, and cell death in the aortic tissues of animals exposed to noise. This explains how noise-induced vascular damage works. White noise exposure between 70 and 100 dB is believed to cause structural alterations in the vasculature as well as morphological changes due to an increase in stress hormone and lipid peroxidation.[3] The sympathetic nervous system is activated as a result of elevated levels of epinephrine and norepinephrine, angiotensin II.[4] Angiotensin ii in turn activates NADPH oxidase, which is responsible for oxidation stress in vasculature. Angiogenesis is integral to successful wound repair involves, budding from capillaries of wound edge.[5] Soon after the invasion into damaged site newly formed vessels appear as a network to nourish the tissue and helps in formation of granulation tissue.[6] Formation of granulation tissue from the wound edge involves immigration of local fibroblast and lying down of fibrin network.[7] Sprouting of capillaries initiates neovascularization and angiogenesis.[8] Previously noise exposed subjects showed more pronounced association between noise and endothelial functions.[9] Although significant efforts have been made in the past to address the issue of delayed wound healing[10], further research on the angiogenesis process is still required to identify all the factors that contribute to the delay. Present study by demonstrating all stressors that harm the physical environment will aid in effective wound healing and, more specifically, by shedding light on noise-induced poor vascular regeneration.

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The objective of my study was to know how noise affects the growth of new blood vessels in rat skin wound.

## Materials and Methods

Study period of this Quasi experiment was from 28th June 2017 to 28th February 2018. Institutional Ethical Review Committee approved the research proposal via registration no,F.2/IUIC-ANMC /EC 64/2025 on June 23,2015. 30 Sprague dawley male rats purchased from NIH Islamabad were included in the study aged between three and five months, they weighed between 250 and 300 grams, and rats with any skin conditions discovered during or after the trial were eliminated. The control and experimental groups of rats were housed in separate cages. Each cage had five rats. The normal settings for temperature, light, and humidity were given to both groups. The animals were kept in 12-hour cycles of light and darkness, with lights on at 8 a.m. and off at 8 p.m, at a temperature of 23–27 °C, 30–40% humidity, and a normal pelleted feed with unlimited access to tap water. The animals were acclimatized to the surroundings for a week prior to the experiment to reduce handling and habitat-like stressors. Two groups of thirty rats were created: control A (incised but not exposed to loud noise) .H&E stain was used to see the newly formed blood vessels.They were counted three times in incisional space in control A(incised but not exposed to white noise) and experimental B (incised and exposed to white noise). There were fifteen rats in each group (Table i). The control and experimental groups were then separated into three subgroups, each with five rats (A1, A2, A3, and B1, B2, and B3). Their days of exposure to noise (3, 7 and 14)—which consisted of white noise for the experimental groups and routine noise for the control groups—formed the basis for the grouping (Table-i). The rats were put to sleep using intramuscular injections of Xylazine and ketamine. The predicted dose for rats was 0.1ml/100g body weight and was created by mixing 5ml of ketamine and 0.5ml of xylazine. After shaving the back to produce a single 2 cm wound parallel to the right side of the vertebral column, a full-thickness incision was created. Metallic clips were used to close wounds with a disposable skin stapler. Five rats were housed in each cage, they were kept in a quiet environment, and they were only exposed to typical background noise at a volume of 40 to 50 dB. After three days of exposure to noise, seven days for group A2 and fourteen days for group A3, rats were slaughtered. All rats in the test groups were subjected to white noise (85-95db). The exposure period began in the morning and lasted from 8 am until 4 am. The noise exposure was 4 hours per day with hourly breaks, followed by 5 days per week for two weeks straight (sub-acute stress) occasionally to prevent adaption. A sound player amplified and recorded the sound of pressure horns by an amplifier that was mounted 30 cm from the cages and connected to two 15 w loudspeakers. B1for three days, B2 seven days, and B3 fourteen days, the subgroup was exposed to loud noise. Rats from group B1 were sacrificed on day 3, group B2 on day 7, and group B3 on day 14 after being exposed to noise (table - i). Wounds were repaired, histologically examined,in pre calibrated unit area at x100magnification.Mean value of these readings was calculated. Unit area was calculated by calibrating the stage and ocular micrometers. Statistical analysis was performed according to standard methods (SPSS version 20). Result was expressed as mean standard deviation (mean ± SD). Mean of the two groups was compared using independent student's t test. p-value of ≤ 0.05 was considered statistically significant.

**Table I: Group Distribution of Rats**

| Groups | Sub Groups | Exposed to | Days of Excision |
|---|---|---|---|
| **A** n=15 Control | A1 n=5 | Routine background noise | 3 |
| | A2 n=5 | | 7 |
| | A3 n=5 | | 14 |
| **B** n=15 Experimental | B1 n=5 | 85- 95 db of noise | 3 |
| s | B2 n=5 | | 7 |
| | B3 n=5 | | 14 |

## Results

New blood vessels were counted at wound site for all three days of noise exposure.



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Blood vessels count per unit area in incisional space in control group. Three days of white noise exposure to A1 resulted in (12%,1.20 ±0.44). (Table ii ). In the experimental sub-group B1 exposed to white noise for three days, blood vessels were discovered to be present with a mean number (08%,0.80 ± 0.83). (Table ii). Process of angiogenesis was slower in noise exposed group than routine noise exposed group. Comparison of mean number of blood vessels present per unit area showed insignificant p value (p=0.37) (Table ii) on day three. Mean number of newly formed blood vessels counted in group A2 on day seven was (16%,1.60 ± 0.89) and blood vessels in experimental group B2 were seen in number (14%,1.40 ± 0.89) (Table ii). Difference in mean number of newly formed blood vessels among both groups on day seven was not significant (p value= 0.73) (Table ii). Newly formed blood vessels were counted in control group (A3) on fourteenth day showed mean number (20%,2.00 ± 0.00) (Table ii) while Mean number of blood vessel in experimental group B3 was counted as (16%,0.70 ±.18) (Table ii) per unit area, difference in mean number of blood vessels was not significant (p value= 0.14) (Table ii).

**Table II: Number of Blood Vessels/Unit Area at Different Days of Sacrifice**

| Groups | Days | Blood vessels Mean± SD | % age | p-value |
|---|---|---|---|---|
| A1 | 3 | 1.20 ± 0.44 | 12 | 0.37 |
| B1 | 3 | 0.80 ± 0.83 | 08 | |
| A2 | 7 | 1.60 ± 0.99 | 16 | 0.73 |
| B2 | 7 | 1.40 ± 0.89 | 14 | |
| A3 | 14 | 2.00 ± 0.00 | 20 | 0.14 |
| B3 | 14 | 1.60 ± 0.54 | 16 | |

## Discussion

Non-healing of wounds drives patient morbidity and increases healthcare cost, became a major medical problem.[11] Reduced vascular growth by the process of angiogenesis is found to be one among the key factors of chronic non healing wounds.[12] We observed and counted newly formed blood vessels at wound site in both control and experimental groups and found the fact mentioned previously, to be true

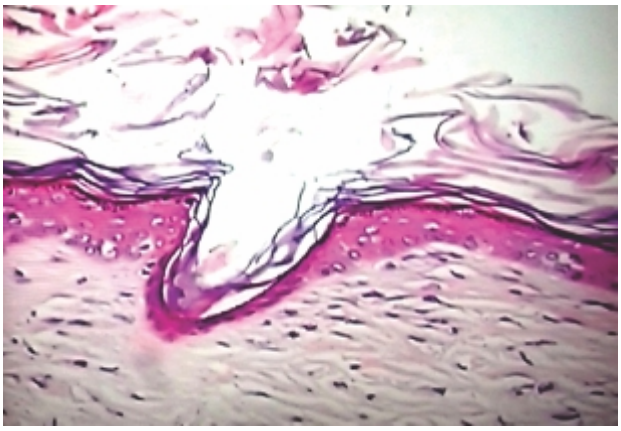

**Figure 1: Photomicrograph of Specimen Number 1's Third Day Skin Wound(Group experiment B1). The arrow indicates how granulation tissue is growing and bridging the wound space. the H&E stain 10X10.**

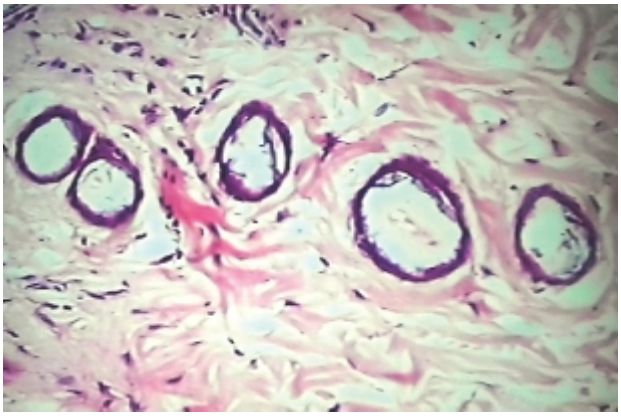

**Figure 2: Photomicrograph showing newly formed blood vessels at base of wound in specimen number 5 (control group A2). H&E stain.40X10**

that as a normal phenomenon in intact tissue delivery of oxygen and nutrients equalizes the removal of waste products , hence maintaining the vascular homeostasis.[13] While in injured tissue disrupted microvasculature leads to inflammation and hypoxia which in turn activates endothelial cells.[14,15]Thereafter; the new vessels differentiate into arteries and venules. The difference between capillaries and arterioles was made by the presence or absence of smooth muscles in their walls. When all control groups A1, A2 & A3 were compared with experimental groups B1, B2 & B3, on days three, seven, and fourteen. The difference was found to be insignificant (p >0.05) . These findings don't match with previous studies which said that most probable factor responsible for process of angiogenesis, were a protein called hypoxia inducible factor I (HIF-1),

thought to be inhibited by noise stress.[16] This has been shown by another researcher that ''HIF'' has a key role in wound healing.[17] Another study done in past has also supported the above-mentioned conclusion that at the site of wound, pro-inflammatory cytokines were affected by stress, that might be a possible mechanism of inadequately formed blood vessels, resulted in delayed wound healing in noise exposed group.[18] Another study showed not only difference in inflammatory cell count but significant inhibition of epidermal regeneration in experimental rats too.[19] In addition to count the proliferation and migration 0f fibroblast and number of new vessels was also decelerated.[20] Underlying mechanism is explained by another author in terms of correlation of reduced number of inflammatory cytokines and enzymes involved in tissue repair with inhibition of regeneration of endothelial cells consequent on delayed wound healing.[21] Any study in favor of our conclusion regarding formation of new blood vessels in experimental groups subjected to noise stress for fourteen days doesn't exist as per my knowledge. The matter of conflict might be the alternative exposure of noise, with (one hour exposure followed by one hour rest) as mentioned in ''subject and method'' in our study was quite different from previous above-mentioned studies. Present study adopted the said pattern of noise exposure based upon the fact that prolonged repeated stress can be extremely harmful to auditory apparatus of rats as they are more sensitive to auditory stimuli than humans.[22] It is also a fact that harmfulness of noise to hearing or even healing depends not only on the sound level only, but there are some other factors like sensitivity of the exposed person or experimental animal and the duration of exposure.[23]

## Conclusion

Intermittent noise exposure has tendency to impair the process of angiogenesis thus delaying wound healing.

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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

**GRANT SUPPORT AND FINANCIAL DISCLOSURE**

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Perceptions of Pakistani Orthodontists in Covid-19: An Assessment of Knowledge, Attitude and Practices

Hafsa Khalid Mahida[1], Sarwat Memon[2], Farheen Naz[3]

**ABSTRACT**

**Objective:** The purpose of this study was to assess the knowledge of Pakistani orthodontists regarding Covid-19 pandemic, their attitude towards the situation and their practices in this duration.

**Study Design:** The study design was cross-sectional.

**Place and Duration of Study:** The study spanned over a course of one month from the 10th of March to the 10th April 2021 with the data collected at the Department of Orthodontics, Ziauddin University, Karachi, Pakistan.

**Materials and Methods:** Online questionnaire was sent to all qualified orthodontists registered with the Pakistan Association of Orthodontists practicing in Pakistan. The question-themes were divided into three segments for knowledge, attitude and practice directed towards exploring the approach of the orthodontists. Data were analyzed using IBM SPSS version 20. Percentages and frequencies were generated for all qualitative variables.

**Results:** Majority of the orthodontists were aware of the mode of transmission (91.8%) and up to date. 58.3% were treating only urgent cases and emergencies. 57.4% remotely provided care based on images sent by the patients. All of them had reduced the number of patients in the clinical area at a time. In the event of staff having symptoms, their attendance was mandated based on test results. SOP-compliance increased in response to new variants. Willingness for vaccination, if the process started, was by almost two thirds of the orthodontists (86.7%).

**Conclusion:** The Orthodontic community of Pakistan has overall shown good standing in knowledge, practice, and attitudes to meet with the challenges of the Covid-19 pandemic. They are aware of and follow the latest research and guidelines of regulatory authorities.

**Key Words:** *Orthodontists, COVID-19, Pandemic, Clinical Approaches, Practice Management, Delivery of Dental Care.*

## Introduction

COVID-19 emerged in Pakistan possibly through air-travel in the middle of February 2020. By the middle of March, each province of the country was found afflicted with the disease. A national lockdown was put into place April onwards and from May a gradual, phasic ease in lockdown commenced. A peak was observed by mid of June as every district in Pakistan had reported cases and then onwards there was a downward trend in new cases reported. The second wave was declared in November adding to the total number of deaths of around 7300[1].

COVID-19 had put the health community in Pakistan into both a state of alertness and chaos[2]. The lockdown did not extend to the provision of healthcare services and a majority of even non-emergency, elective treatments were continued [3]. This met with great absenteeism from several members of the healthcare community and came in with a mix of responses ranging from holding a sense of duty, holding onto a job, to complete absenteeism or in some cases even quitting jobs.

By and large, most of the procedures in Orthodontics involve elective procedures but span over a course of two to four years or beyond. The follow-ups are scheduled nearly every month and the only dental emergencies are sharp wires that need to be cut, broken brackets that can potentially become an

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ingested/inhaled foreign body, and dislodged, lose or broken appliances [8]. As with everyone in the health community, providing care during COVID-19 has been overwhelming for orthodontists. Globally, deaths of orthodontists were reported as well [4]. Guidelines from CDC, NHS, American Association of Orthodontists, and the British Orthodontic Society had been issued to ease the process but there was fear amongst them as well [5,6,7,8].

Due to the span of orthodontic treatments, regular follow-ups are needed, and guidelines have been created on virtual consultations in order to limit the spread of the disease and to cope with the public fear of visiting health practices [7]. Organizations such as the British Orthodontic society and American Association of Orthodontists comprehensively elaborated the protocols orthodontists could adopt in prioritizing cases that could be managed virtually via social-media communication and in deciding the need to schedule live-visits in OPDs [8].

The situation in Pakistan was different from countries such the USA and UK where these guidelines could be followed to the letter, due to the differences in systems of healthcare delivery. The advent of COVID-19 is a novel situation and demands evidence on the scenario of knowledge, attitudes, and practices of Orthodontists amidst the pandemic in Pakistan. Our study aimed to gather this evidence.

## Materials and Methods

This cross-sectional study was conducted on a total population of 71 registered orthodontists of Pakistan with the data gathered at Ziauddin University and spanned over a course of one month from the 10th March to the 10th April 2021. Ethical approval for this study was taken from the Ethics Review Committee of Ziauddin University [3080121HMOM]. Confidentiality was maintained by individual administration of the questionnaire which was sent with an informed consent stating that the published data would keep their details confidential and anonymous. To meet inclusion criteria the participant had to be a qualified orthodontist, registered with the Pakistan Association of Orthodontists, and practicing in Pakistan. Pakistani orthodontists not practicing in Pakistan were not included in this survey.

A google-questionnaire designed to assess the knowledge, attitude, and practices of Orthodontists in Pakistan during COVID-19, was created and validated by review of three orthodontic experts and a pilot.

run amongst 10 % of the total number of participants planned for the major study. After this it was distributed amongst the 71 study participants. Out of 30 close-ended questions, 3 were for epidemiological data (age, gender, and practice set), 5 questions were based on the participants, 19 were based on their practices and 6 were based on their attitude.

The knowledge component included questions regarding mode of transmission; keeping up to date with the latest guidelines and the frequency of doing so; the sources they found reliable and the medium of awareness (online or on-job training).

The questions regarding practice were based on patient appointments and screening; modifications in the duration; number and approach of treatments; changes in the seating arrangements of clinical and waiting areas; usage of protective gear amongst personnel and the workplace policies in case of infection amongst staff.

The participants' attitude was assessed based on the participants' response times (whether self-endorsed or in response to national policies), the variation in attitude during each wave in the country, the role of orthodontists in the spread of disease and finally, the willingness to receive vaccination and endorse compulsory vaccination at practice. The data was analyzed using IBM SPSS version 20. Percentages and frequencies were generated for all variables.

## Results

The study included 60 orthodontists comprising of 22(36.7%) females and 38(63.3%) males, aged 32- 65 years with mean age 44.50±11.96 as shown in figure 1. The percentage of the type of practice setup of Pakistani orthodontists is shown in figure 2.

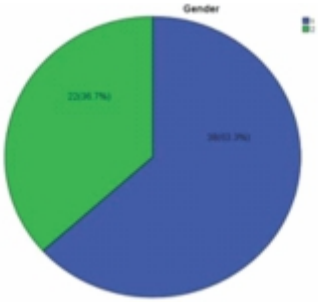


**Figure 1: Gender Distribution of Pakistani Orthodontists [1: Male 2: Female]**

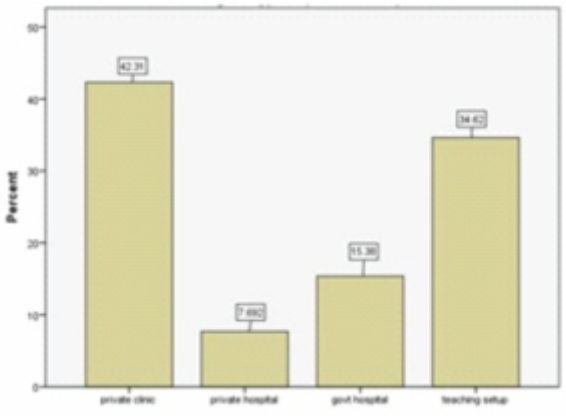


**Figure 2: Percentage of the type of practice setup of Pakistani Orthodontists**

Majority of the orthodontists (91.8%) were aware of the mode of transmission of the SARS-Cov2 virus. Most of the orthodontists (75.4%) were updated with the latest guidelines on COVID-19 prevention and 52.5% of them kept themselves updated monthly. Majority relied on W.H.O guidelines to update themselves (68.9%) followed by NHS guidelines (21.3%) and ADA (8.2%). Most of the orthodontists reported that they used internet articles for their awareness (55.7%) Table I.

Practices of Pakistani orthodontists in COVID-19 are depicted in Table II. Majority of orthodontists (58.3%) were treating only urgent cases and orthodontic emergencies. Almost sixty percent of Orthodontists (57.4%) were delivering orthodontic care to their patients by looking at the images sent by them. Patients were advised to use home gadgets such as nail cutters, after disinfecting them, to cut off poking wires, or in the case of any dislodged brackets they were given demonstrative videos on how to remove and keep them. If the patients were unable to attend to these themselves, these were classified as emergencies and appointed and treated. Cases of aligners were treated as non-emergency and deferred initially during the first wave. All had limited the number of patients they treated per day. In addition to this they had reduced the number of patients seated in the clinical area at a time. Majority of orthodontists (93.3%) asked their auxiliary and other support staff to get tested if they reported symptoms, with 96.7% asking their staff to quarantine for two weeks and 90% permitting them to resume work if testing negative. Majority of them (68.3)% had increased their compliance with SOPS in response to news regarding new variants of SARS-Cov 2 virus and (48.3%) followed the Government's policy to keep OPDs open during the pandemic.

Table III depicts attitude of Pakistani Orthodontists towards Covid 19. Regarding spreading awareness to the public about COVID-19-Prevention, 68.9% orthodontists believed that they had a role. However 16.4% replied they do not play any role and 13.1% said that they were not sure regarding their role in spreading awareness to the public regarding COVID-19-Prevention. Nearly sixty percent (59%) provided their patients with information regarding COVID-19 prevention. Nearly 90 % of them (86.7%) expressed willingness to get vaccinated when a COVID-19 vaccine was made available in their region, however (13.3%) said they were not sure. Majority of the orthodontists (88.5%) replied that they will ask their patients to get vaccination done before resuming their treatment when a COVID-19 vaccine is made available in their region.

**Table I: Knowledge of Pakistani Orthodontists Towards Covid-19**

| Question | | Responses | Frequency | Percentage |
|---|---|---|---|---|
| 1 | Knowledge about mode of transmission of the SARS-Cov2 virus | Yes | 56 | 91.8 |
| | | No | 4 | 6.6 |
| | | Not sure | 0 | 0 |
| 2 | Are you updated with the latest guidelines on COVID-19 prevention | Yes | 46 | 75.4 |
| | | No | 2 | 3.3 |
| | | Not sure | 12 | 19.7 |
| 3 | Knowledge update frequency | Daily | 12 | 19.7 |
| | | Weekly | 16 | 26.2 |
| | | Monthly | 32 | 52.5 |
| | | Bimonthly | 0 | 0 |
| 4 | Knowledge sources used by orthodontists | WHO | 42 | 68.9 |
| | | N.H.S | 13 | 21.3 |
| | | ADA | 5 | 8.2 |
| | | CDC | 0 | 0 |
| | | Others | 0 | 0 |
| 5 | Modes of knowledge source access | Internet articles | 34 | 55.7 |
| | | Online courses | 12 | 19.7 |
| | | On job training | 14 | 23.0 |



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**Table II: Practices of Pakistani Orthodontists in Covid-19**

| | Question | Responses | Frequency | Percentage |
|---|---|---|---|---|
| 1 | Clinical approaches by the doctors during the pandemic | Regularly appointing and treating patients | 19 | 31.7 |
| | | Treating only urgent cases and orthodontic emergencies | 35 | 58.3 |
| | | Deferring practice throughout the pandemic | 1 | 1.7 |
| | | Deferring the practice until vaccination processes begin in the region | 5 | 8.3 |
| 2 | Method used by the orthodontics for clinical consultation | Online consultation by video calls | 7 | 11.5 |
| | | Live messaging and guiding by looking at the images sent by patients. | 35 | 57.4 |
| | | Via email by sending guidelines for at-home care | 1 | 1.6 |
| | | Treatment at the clinical sites | 17 | 11.5 |
| 3 | For treatments of the patient inside clinical site, which of the following measures do you/your team take | Triage and/or Telescreen | 12 | 20 |
| | | Check the Patient's temperature | 43 | 71.7 |
| | | Request the patient to not have electronic devices/ bags/ jewelry on them inside. | 5 | 8.3 |
| | | Take a brief travel-history. | 41 | 59.4 |
| | | Disinfect the dental unit after the patient leaves | 19 | 31.7 |
| | | Have the patient rinse their mouth with hydrogen peroxide | 10 | 14.5 |
| 4 | Do you ask them if they experienced the common symptoms associated with COVID-19? | Yes | 42 | 68.9 |
| | | No | 5 | 8.2 |
| | | Not always | 13 | 21.3 |
| 5 | Which of the following symptoms do you ask them about? (You can mark more than one) | Cough | 55 | 91.7 |
| | | Flu | 45 | 75 |
| | | Runny Nose | 5 | 8.3 |
| | | Body Ache | 15 | 25 |
| | | Fever | 53 | 88.3 |
| | | Shortness of Breath | 7 | 11.7 |
| 6 | Do you require your patients to get tested for COVID-19 before any treatment or appointment | Yes | 1 | 1.6 |
| | | No | 33 | 54.1 |
| | | Only when they will undergo procedures of longer duration | 14 | 23 |
| 7 | Lab test used for the screening of patients | Serology for COVID-19 | 6 | 10 |
| | | PCR | 45 | 75 |
| | | Rapid Antigen Test | 9 | 15 |
| 8 | Do you modify the treatment duration? | Yes | 33 | 55 |
| | | No | 2 | 3.3 |
| | | Not always | 21 | 34.4 |
| 9 | If yes, what is the usual treatment duration during one visit? | Up to 5 min | 7 | 11.5 |
| | | 5- 10 min | 26 | 42.6 |
| | | 10-20 min | 27 | 44.3 |
| | | Above 20 min | 1 | 1.6 |
| 10 | Have you limited/reduced the number the number of patients you treat per day? | Yes | 60 | 100 |
| | | No | - | - |
| 11 | | Yes | 60 | 100 |

| | | | | |
|---|---|---|---|---|
| | Have you limited/reduced the number of patients seated in the clinical area at a time? | No | - | - |
| 12 | Have you made any of the following changes in the waiting area arrangement? | Allowing only one attendant per patient to be in the waiting area | 6 | 10 |
| | | Making people sit at 6ft from each other | - | - |
| | | Place patient awareness posters or wall mountings regarding COVID-19 | 4 | 6.7 |
| | | Appoint a fixed number of patients at a time to ensure limited number of people sitting inside the waiting area | 50 | 83.3 |
| 13 | How are the appointment schedules for regular, ongoing treatment patients spanned? | Frequent short visits every two weeks/shorter duration | 3 | 5 |
| | | Regular visit with patient recalled after a month | 47 | 78.3 |
| | | Regular visit with patient recalled after two months or more | 10 | 16.7 |
| 14 | Which of the following personal protection gear do you use? (You can mark more than one) | Surgical Three-ply Masks | 47 | 78.3 |
| | | N95 Masks | 57 | 95 |
| | | Face shield | 55 | 91.7 |
| | | Disposal drapes | 53 | 88.3 |
| | | Washable Drapes | 9 | 15.0 |
| | | Safety goggles | 33 | 54.1 |
| | | Hazmat suit | 2 | 3.3 |
| 15 | Which of the following approaches do you adopt if your auxiliary and other support staff reports symptoms? You may mark more than one) | Ask them to get tested | 56 | 93.3 |
| | | Ask them to go in quarantine for one week | 1 | 1.7 |
| | | Ask them to quarantine for two weeks | 58 | 96.7 |
| | | Ask them to resume work if tested negative | 54 | 90 |
| | | Ask them to stay at home if symptomatic even if tested negative | 51 | 85 |
| | | Ask them to quarantine only if positive | 5 | 8.3 |
| | | Ask them to resume work after symptoms subside | 9 | 15 |
| | | Ask them to resume work after symptoms subside and they test negative | 4 | 6.7 |
| 16 | If you follow any of the above-mentioned measures, when do you tend to do so? | When I hear more cases reported | 4 | 6.7 |
| | | Only during the first wave | 1 | 1.7 |
| | | Only during the second wave | 55 | 91.7 |
| | | Throughout the pandemic so far | | |
| 17 | In response to news regarding new variants of SARS-Cov 2 virus how do you modify your practice? | Continue to use the same measures as above | 7 | 11.7 |
| | | Increase compliance with SOPS | 41 | 68.3 |
| | | Create clinical audits to assure the preventive measures are being strictly followed | 12 | 20.0 |
| | | Consider closing practice for an indefinite period | - | - |
| 18 | What is your decision to deliver care at the clinical site is based on? | Government policy to keep OPDs open | 29 | 48.3 |
| | | Workplace policy to keep elective procedures open | 8 | 13.3 |
| | | Both above | 23 | 38.3 |



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**Table III: Attitude of Pakistani Orthodontists towards Covid-19**

| | Questions | Responses | Frequency | Percentage |
|---|---|---|---|---|
| 1 | Do you believe that orthodontists have a role in spreading awareness to the public regarding COVID-19 Prevention? | Yes | 42 | 68.9 |
| | | No | 10 | 16.4 |
| | | Not sure | 8 | 13.1 |
| 2 | Do you provide your patients with information regarding COVID-19 prevention? | Yes | 36 | 59.0 |
| | | No | 8 | 13.1 |
| | | Not always | 16 | 25.2 |
| 3 | Would you be willing to get vaccinated when a COVID-19 vaccine is made available in your region? | Yes | 52 | 86.7 |
| | | No | 0 | 0 |
| | | Not sure | 8 | 13.3 |
| 4 | Would you ask your patients to get vaccinated before resuming their treatment when a COVID-19 vaccine is made available in your region? | Yes | 54 | 88.5 |
| | | No | 3 | 4.9 |
| | | Not sure | 3 | 4.9 |

## Discussion

During the pandemic of COVID-19 dental practices were affected worldwide with dentists exhibiting different responses to the situation. This included and affected orthodontists as well. Our study is the first to have assessed the knowledge, attitude and practices of all registered Orthodontists in Pakistan.

According to our study, majority of the orthodontists in Pakistan (91.8%) were aware of the mode of transmission of the virus, were regularly updating themselves with newer findings(75.4%). Most of them kept up through the information provided by internet articles (55.7%) which is comparable to the findings of a study conducted on orthodontists in China by Hua et al [9] where 92.8 % were using the internet as the main source of receiving knowledge. In another study conducted in the United States by Motavasel et al [10], internet articles were the second main source of information for orthodontists after the information provided by professional associations especially the state dental associations and the American Association of Orthodontists. In our study the participants relied mostly on the guidelines of the World Health Organization (WHO) (68.9%) whereas in that of Motavasel et al WHO was the least common accessed source (less than 10%).

The fear and anxiety of the pandemic was experienced by both the orthodontists and the patients. Majority of the participants of our study were treating mostly emergencies (58.3%), had reduced the number of patients they were treating per day (60%), and had modified the treatment duration (55%) making visits shorter (44%). This corresponds with the findings of several studies. In one study conducted by Chaudhary et al [11] on oral healthcare workers, only 26% were willing to work during the pandemic. Another study, by Almas et al [12] showed that dentists in general were reluctant about directly treating patients in the COVID-19 pandemic.

Despite the above findings, majority did not alter patient appointment scheduling which is often once a month. This could be because of patients' concerns regarding delay in treatment according to a study done by Cotrin et al [13], or due to financial concerns.

According to our findings, majority of the participants' practices did include some screening measures taken before commencing with treatment. Most common practices were checking the temperature (71.7%) and obtaining a brief travel history (59.4%). This is similar to the findings of Thakur et al [14] where screening for temperature was done in 88% of the orthodontic set ups in Hyderabad, India. However compared to Thakur et al 's study where only 32% of the orthodontic practices were enquiring COVID-19 symptoms from their patients , majority of our participants followed this practice (68.9%).

Majority of the orthodontists (68.9%) in our study

believe that they do have a role in spreading awareness and that they do play the role relaying information on prevention of COVID-19 to their patients. 59% of the participants did convey information to their patients. According to Seneviratne et al the role of the dental fraternity goes beyond dentistry in COVID-19 and that community dentistry drills can upscale the needed work to stop the transmission of communicable diseases such as COVID-19[15].

Vaccine-hesitancy is a complicated issue globally[16]. Our study findings were collected during the time public vaccination was about to commence. Our results regarding vaccination showed an overall willingness of orthodontists to get vaccinated (86.7%) and a similar percentage (88.5%) would advise their patients to do so as well. A few were unsure (13.3%) but none of them refused the possibility of getting vaccinated. This concurs with the findings of a study by Kaur et al in India, where majority of the medical and dental practitioners showed willingness to getting vaccinated and had full confidence in its efficacy[17].

Future studies could be conducted on a detailed comparison in retrospect of the common practice-patterns throughout the course of the pandemic. In addition, holding evidence-based practice shall go a long way in preparedness for future such events.

## Conclusion

The Orthodontic community of Pakistan has largely shown a good standing in knowledge, practice and attitudes. Their knowledge is updated regularly, put into practice diligently and they have a positive attitude to meet with emerging COVID-19 challenges. The practices chosen are all compliant and function considering the latest research and guidelines of regulatory authorities.

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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Socio Demographic Risk Factors of Bullying and Victimization in Adolescents: Prevalence Based Study

Sameera Shafiq, Sidra Batool

**ABSTRACT**

**Objective:** To investigate the prevalence of bullying-victimization in adolescents and to subsequently explore impact of socio-demographic variables.

**Study Design**: This cross-sectional research design.

**Place and Duration of Study**: The study was conducted in Department of Psychology, University of Gujrat and data was collected from February to May 2019.

**Materials and Methods**: Stratified sampling technique was applied to select 608 students, with age range between 16 to 19 years, from the private-public colleges of Sarai Alamgir with the permission of principals and teachers. Urdu version of Adolescent Peer Relationship Inventory (APRI) along with demographic form was administered on the students with their informed consent.

**Results:** In 608 college students, 246(59.3%) were males and 169(40.8%) females. The prevalence for bullying in low, moderate and high categories was 57.2%, 21.1% and 21.7% respectively. Whereas 47.7%, 28%, and 24.3% of victimization in adolescents was prevalent in low, moderate and high categories. Hierarchical regression analysis found that gender, family system, and institution type are significant risk factors for predicting bullying-victimization syndrome and contributed to 19% of variance explained. Significant differences existed between gender, in which male students suffered more by bullying-victimization syndrome as compared to female students ($\chi^2$=103.50, p<0.001). However, adolescents living in joint family system were significantly victimized more than the one living in nuclear family systems ($\chi^2$ =5.55, p<0.05). There were significant differences in bullying behaviours of the students studying in public and private colleges ($\chi^2$=4.20, p<0.05). Students studying in public colleges expressed more bullying behaviour than students studying in private colleges.

**Conclusion:** The phenomenon of bullying and victimization is prevalent in the adolescents studying at college level. Demographic variables of gender, family system, and institute type served as risk factors for bullying and victimization syndrome**.**

**Key Words:** *Adolescent, Adolescent Health, Bullying, Peer Influence, Victims.*

## Introduction

A recent survey with 17.2% depression and 21.4% anxiety in adolescents between eleven to eighteen years in Pakistan[1], set an alarm for investigation of possible factors playing role in contributing to emotional distress in Pakistani youth. In early adolescence, peer group influences played a significant role in the mental health, inclusion of the phenomenon of bullying and victimization in the present study is necessitated. Empirical research has posited the point that emotional distress, depression, and even suicidal ideation are linked with bullying-victimization syndrome in adolescents.[2-3] In addition, frequent fights and harassment has been found to shrink academic achievements of the adolescents[4], effect their future careers indirectly and making concerned issue worth studying.

Internationally, the phenomenon of bullying-victimization syndrome is widespread. The peak prevalence rate of bullying and victimization in 11 to 15 years old children across 40 Baltic and European countries was found to be 45.2% in boys, and 35.8% in girls.[5] In 1,529 Chinese adolescents with fifteen years mean age, 6% showed high traditional bullying-victims prevalence and 2% showed high *cyber bully-victims* prevalence rate in males with high

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interparental problems[6], thus acme the importance of gender, and family support. A systematic list of identified risk factors for bullying and victimization in the review of literature, relevant to the present study were found to be age[7], urban/rural setting[8], family system[9-10], socio-economic status[9-11], and gender.[7-8] Thus, literature review has highlighted the importance of various socio-demographic variables as playing role in bullying and victimization of the adolescents. In Pakistan, research based on study of prevalence and demographic correlates of bullying were based on the sample of either school children or university early adult students. Negligence is observed in identifying crucial factors of peer violence in early adolescents studying in colleges. These college students comprised part of youth and are approximately 29% of the general population. Therefore, sample of college students cannot be ignored for investigation of bullying and victimization that might affect their prognosis for mental health in adulthood. Thus, implications of the findings of the present study would point out towards conducting effective intervention plans in college students, screened for risk factors, identified in the present study. The objectives of the present study included investigation of the prevalence of occurrence of bullying and victimization in college adolescents. Moreover, socio-demographic risk factors have also been explored to understand the phenomenon in detail in Pakistani youth.

## Materials and Methods

The present cross-section research was conducted at the Department of Psychology, University of Gujrat, Gujrat. The data was collected from February to May 2019. Stratified random sampling technique was used and two strata were identified as private and public college domains. A list of institutions (both public and private) in Sarai Alamgir was taken from District Office, Gujrat. Randomly two public and two private colleges were selected from the provide list. Taro Yamane Formula[14] was used to calculate the sample and 608 students were contacted randomly in their classes. Moreover, the students exhibiting any mental or physical disorder were excluded. Ethical approval was taken from Advanced Studies and Research Board with reference no: UOG/ASRB/Psychology/15177. Inclusion criteria focused on the students who were more than 16 and less than 19 years of age. The students with age below 15 and above 20 were excluded from the study. Demographic sheet along with Urdu version[12] of Adolescent Peer Relations Instrument (APRI)[13] with 36 items and two subscales of bullying and victimization, each having three components verbal, social, and physical aspects was used in the present study. It is Likert type scale with six categories of responses having scored one to six. The Cronbach Alpha Reliability Coefficient of APRI on the present sample was 0.88, showing strong index of acceptance. Prior to taking informed consent from the students, formal permission was taken from the principals and concerned teachers. The students were approached in the classrooms. Written informed consent with introduction to the research study was taken. Confidentiality was maintained and they were informed of their right to withdraw at time from the study. Any queries and concerns were addressed appropriately, and satisfactory answers were given.

The parametric data obtained was analysed in SPSS-21. Frequencies and percentages were calculated for low, moderate, and high levels of bullying and victimization. Inferential statistics was used to calculate the significant results with p value less than 0.05 level. A hierarchical regression analysis, conducted in two steps to analyse the effects of socio-demographic variables along with self-regulation on bullying and victimization of adolescents. Before conducting hierarchical regression analysis, the categorical variables such as gender, class, profession, residential area, family system and intuition type were dummy coded where boys, 1st year, arts group, rural area, joint family, and public served as a reference point and the remaining served as a dependent category. Chi-square was calculated to investigate the association of predicting variables such as gender, family system, and institution type with three levels (low, moderate, and high) of bullying and victimization syndrome in adolescents.

## Results

The high prevalence rate of bullying is 21.7% and victimization is 24.3% in 608 college students, selected by stratified sampling technique in private-public colleges of Sarai Alamgir (Table-I). In Step-I of hierarchical regression analysis, socio-demographic

variables such as age, class, line of professional studies (such as arts, science), residential area, and family monthly income with ambivalent research findings were entered. In Step-II, empirically significant socio-demographic variables such as gender, family system, and institution type were entered. Consequently, two models emerged. The first model showed that age, class, profession, residential area, and monthly income did not significantly predict peer relationship of adolescents. The second model showed that gender (β= -.427, p<.001), family system (β= -.090, p<.001), and institution type (β= -.127, p<.001) significantly predicted the relationships of adolescents with their friends, explaining 19% variance in the scores of bullying and victimization (F=17.90; p<.001). The negative signs in gender, family system, and institution type showed that girls, nuclear family, and private colleges have less impact on bullying and victimization as compared to boys, joint family, and public colleges (Table- II). Chi-square analysis showed significant gender differences in bullying ($\chi^2$ = 103.50, p<0.001) and victimization ($\chi^2$ = 82.49, p<0.001) as boys suffered more than girls. Similarly, significant victimization occurred in adolescents living in joint families ($\chi^2$ =5.50, p<0.001) as compared to nuclear counterpart. Public colleges ($\chi^2$ = 4.20, p<0.001) exhibited significant bullying than private colleges in adolescents (Table-III).

**Table I: Levels, Frequencies, and Percentages of bullying and Victimization in Adolescents (n=608)**

| Levels | Bullying | | Victimization | |
|---|---|---|---|---|
| | F | % | F | % |
| **Low** | 348 | 57.2 | 290 | 47.7 |
| **Moderate** | 128 | 21.1 | 170 | 28.0 |
| **High** | 132 | 21.7 | 148 | 24.3 |

f=frequencies, %=percentages

**Table II: Hierarchical Regression Analysis for Socio-Demographic Variables in Peer Relationship in Adolescents (n=608)**

| Variables | Model 1 | | Model 2 | | 95% CI | |
|---|---|---|---|---|---|---|
| | B | β | B | β | Model 1 Lower-upper | Model 2 Lower-upper |
| Constant | 44.562 | | 46.616 | | 24.559, 64.565 | 28.559, 64.673 |
| Age | .418 | .034 | .553 | .045 | -.732, 1.568 | -.486, 1.593 |
| Class | -.361 | -.018 | -.490 | -.024 | -2.288, 1.565 | -2.230, 1.251 |
| Profession | .570 | .026 | .654 | .030 | -1.208, 2.349 | -.955, 2.263 |
| Residential area | -.056 | -.002 | .578 | .026 | -1.850, 1.738 | -1.050, 2.207 |
| Monthly income | -1.735 | -.022 | 1.817 | .023 | .000, .000 | .000, .000 |
| Gender | | | -8.745*** | -.427 | | -10.239, -7.251 |
| Family system | | | -1.941*** | -.090 | | -3.504, -.378 |
| Institution type | | | -2.601*** | -.127 | | -4.112, -1.090 |
| R | 0.04 | | 0.44 | | | |
| $\Delta R^2$ | 0.002 | | 0.19 | | | |
| F | 0.235 | | 17.90*** | | | |
| ΔF | 0.235 | | 47.28*** | | | |

***p<0.001

**Table III: Association of Predicting Socio-Demographic Risk-Factors for Bullying and Victimization in Adolescents (n=608)**

| Socio-Demographic Variables | Categories | Bullying | | | $\chi^2$ | Victimization | | | $\chi^2$ |
|---|---|---|---|---|---|---|---|---|---|
| | | Low | Moderate | High | | Low | Moderate | High | |
| Gender | Boys | 130 | 86 | 114 | 103.50*** | 123 | 79 | 128 | 82.49*** |
| | Girls | 218 | 42 | 18 | | 167 | 91 | 20 | |
| Family System | Joint Family System | 218 | 88 | 94 | 3.75 | 178 | 115 | 107 | 5.55* |
| | Nuclear Family System | 130 | 40 | 38 | | 112 | 55 | 41 | |
| Institution Type | Public Colleges | 180 | 71 | 82 | 4.20* | 150 | 94 | 89 | 2.82 |
| | Private Colleges | 168 | 57 | 50 | | 140 | 76 | 59 | |

***p<0.001, *p<0.05

## Discussion

The findings of the present research showed that the average percentage of bullying is 22.25% and victimization is 17.45% which implied that the high bullying prevalence rate (21.7%) in college students of Sarai Alamgir and this result is relatively like findings from other districts. A cross-sectional study conducted (2020) in five districts of Punjab namely Lodhran, Rahim Yar Khan, Bahawalpur, Faisalabad, Multan; and two districts of Sindh namely Thatta, and Nawabshah showed that 26.6% children were bullied at school and 17.9% were bullied away from school. 18.6% children were victimized at school and 16.3% away from school[15]. However, 24.3% victimization prevalence is high in college students of Sarai Alamgir as compared to other provinces of Pakistan. Still this frequency of occurrence of bullying-victimization problem in our study is relatively low as compared to prevalence rate of Faisalabad (2021) which was reported to be 49% bullying and 36% victims in adolescents with mean age fifteen years.[16] Yet a controlled randomized trial (2017) of school children in Hyderabad showed relatively high bullying-victimization percentage in boys and girls, reported as 72.6% and 46.4% respectively.[17] Similarly, in district Gujrat, 42.6% school children reported victimization and 50.5% reported being bullied.[18] The findings implied that



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high prevalence of violence against children and adolescents in Pakistani schools and colleges, contributed to poor emotional-behavioural physical and mental health in youth.[19,20] Thus, alarming condition of increasing incidences of bullying and victimization implied for the introduction of counselling services at college level to handle and manage the affected cases with proper psychotherapeutic intervention. Though in comparison to the other cities of Pakistan, District Gujrat has showed relatively low prevalence of bullying and victimization yet has set an alarm to take notice of the situation by screening youth for possible mental issues on one hand, and introduce coping strategy based interventions on other hand. Socio-demographic variables such as age, class, line of professional studies (such as arts or science), residential area, and monthly in-come were found to be insignificant predictors of bullying-victimization syndrome in early adolescents. The results are consistent with the findings of the previous studies. No significant differences were found with respect to age, and urban or rural area in cyber bullying across Sindh, Pakistan in adolescent[21]. Age has been found to be non-significant predictor of bully-victim cases in the students studying under Pakistani universities.[21]

In present study, socio-demographic variables such gender (girls versus boys), family system (joint versus nuclear family) and institutional type (private college versus public college) are found to be significant predictors of bullying-victimization syndrome in early adolescents. Findings of past research revealed that 950 university adolescents in Pakistan show significant gender differences with reference to traditional bullying-victimization phenomenon in which boys are high in bullying and low in victimization as compared to girls.[9,22] The patriarchal pattern of Pakistani society would serve as plausible explanation for such a discrepancy of aggression expression in the form of fights and harassments in adolescents. Female students also exhibited victimization, yet the prevalence is low than male students.

In addition to gender, family context and values are found to be associated with the bullying phenomenon in adolescents[23-24]. The research findings of the present study show that adolescents experienced significant victimization while living in joint family system as compared to nuclear family system. Perhaps family's over intrusion or negligence has caused sufferings for the adolescents as they would have become more dependent on the circle of the friends for their secondary need satisfaction and might have become prone to their victimization. Moreover, earlier research indicated that students studying in public schools are more victim of bullying as compared to private counterparts in Pakistan[25-26]. These findings are consistent with the results of the present study with implications to launch strategic changes in the environmental elements of the government schools that foster reduction of fights and victimization issues in the adolescents.

## Conclusion

There is 21.7% bullying and 23.4% victimization prevalence among adolescents studying in various colleges of Sarai Alamgir. Being male, living in joint family system and studying in public colleges serve as risk factors for high experiencing of peer related violence in the form of bullying and victimization. Male students face significantly more incidences of bullying and victimization as compared to female students. Victimization is significantly high in joint family systems as compared to nuclear family systems of the adolescents. The students of public colleges show significant high incidences of bullying as compared to private colleges. Therefore, policy makers should initiate steps for recruitment of psychologists and school psychologists in public colleges of Punjab and enforce laws for better handling issues of grievances.

## Limitations and Suggestions

The present quantitative research has not explored the perceptions of the students regarding the concepts of bullying and victimization. In future, qualitative study could be designed to gauge the issue in-depth and enrich narration could be published for devising intervention strategies to sooth traumatic experiences of youth as a result of bullying and victimization. The current study has only focused on Sarai Alamgir. Further, study might use multistage cluster sampling technique to collect data from various cities of Punjab and get a better picture of the study variables in detail. Some important factors effecting the bullying and victimization are missing. Personality variables long with parental

interaction could be studied to understand the bullying-victimization syndrome in detail in future.

## Disclaimer

This article along with its abstract has not been published in any conference. The data for the article was taken from MPhil thesis of Sidra Batool, conducted under supervision of Ms. Sameera Shafiq, Lecturer, department of Psychology, university of Gujrat, Gujrat.

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**CONFLICT OF INTEREST**

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

# Future Health Professionals Readiness and Awareness Towards Interprofessional Education in a Health Care Institution of Lahore

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**ABSTRACT**

**Objectives:** To measure the level of readiness and awareness of future health professionals about interprofessional education and to evaluate the differences in the readiness towards interprofessional education amongst different disciplines.

**Study Design:** This was a cross-sectional study in which a questionnaire "Readiness for Interprofessional Learning Scale" (RIPLS) was used.

**Place and Duration of Study:** The study, was conducted in June and July 2021 at CMH Lahore medical college, Lahore, Pakistan.

**Materials and Methods** Using Google forms, a web-based questionnaire "Readiness for Interprofessional Learning Scale" inventory was emailed to students through their email ID and WhatsApp group. The itemized and total mean scores of all nineteen items of the questionnaire covering the five health professions were compared. SPSS 22 was used for statistical analysis and all responses were analyzed upon 5-point Likert scale.

**Results:** Of the 924 future health professionals 582 completed the questionnaire with a response rate of 63%. The undergraduate students showed positive attitude towards IPE with a global mean score of 74.54±1.139. The overall RIPL mean was above the midpoint score (47.5). Students' ratings were low for two subscales, namely: Roles and Responsibilities and Professional identity, Whereas Teamwork & collaboration subscale showed high ratings. Nursing students showed highly significant mean = 79.4±1.16, whereas dentistry students showed lowest significant mean= 71.4±1.13.

**Conclusion:** Future health Professionals at CMH had a positive attitude towards IPE. Results of present study revealed that nursing undergraduate students appreciated interprofessional education more than the undergraduates of other disciplines. However, dental and medicine undergraduate students indicated minimum readiness and awareness. Result of current study suggests that curriculum developers could consider basic awareness of future health professionals for development of interprofessional education curricula.

**Key Words:** *Competencies, Curriculum, Disciplines, Interprofessional Education, Undergraduate.*

## Introduction

The basic goal of every current and future health professional is to provide comprehensive and effective healthcare to all patients.[1] The process of learning and teaching between health care providers from two or more health or social professions promotes collaboration to produce better health outcomes.[2] IPE is progressively recognized as a basic component of medical education. IPE targets to educate and train future health care professionals involved in providing team-based safe care to patients for their wellbeing.

At the student level, it is revealed that learners involved in Interprofessional education (IPE) have a better understanding of health professions and show mutual respect towards their coworkers.[3] IPE also promotes the acquisition of competencies through interprofessional experiences which assist them to learn the skills required to be a member of the collaborative team.[4]

IPE is essential for augmenting patient safety as well as ensuring an effective system for the delivery of safe care to patients globally.[5,6] The World Health Organization (WHO) also recognized IPE's importance and published a framework in 2010 for Action on IPE & Collaborative Practice for producing healthcare professionals as a member of the collaborative practice team [1].To deliver holistic and optimal care to patients, the sharing and

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contribution of every health care provider from various fields play a major role.[7] IPE has been associated with the promotion of effective care, enhancement of patient's safety, and management of patients.[8] It is also a vital component for the training of future health professionals to acquire the generic skills for working as a team member.

In medical curriculum of Pakistan IPE is not given due importance. Most of the health professions' education focuses on practice and does not emphasize on the importance of interprofessional training for their learners. On the other hand, differences in future health professionals awareness of IPE may be a vital challenge for all health professions.[9]

Globally nowadays, IPE has been integrated into the medical education curriculum of many health care educational institutions.[10] The main challenge of this issue is how and when it is appropriate to teach and train undergraduates regarding IPE.A valid and reliable Readiness for Interprofessional Learning Scale(RIPL) questionnaire provides the baseline data and information to instructional designers for designing appropriate IPE educational programs for the medical curriculum.[11]The current study was conducted with the overall aim to explore the readiness and awareness of undergraduate health professional students towards IPE and to find the difference with respect to various disciplines.

## Materials and Methods

Cross-sectional questionnaire-based study was carried out at CMH Lahore Medical College & institute of dentistry, CMH Institute of Nursing, and School of Allied Health Sciences Lahore, Pakistan. Targeted study population included all fourth and final year students of medicine, third and final year students of dentistry, final year students of Allied and nursing school of CMH Lahore Medical College., sample size, was calculated by Open Epi which is a valid and reliable tool for the mentioned purpose. The confidence limit was set at ± 5% which gave a sample size of 249 students with 95% confidence interval (CI).

Institutional Review Board Committee of CMH Lahore Medical College &, CMH, Lahore IOD, Institute of Nursing and School of Allied Health Sciences approved the study protocol, case# 542/ERC/CMH/LMC. The study was conducted following the Declaration and all the students provided electronic consent was taken prior to participation. All these participants had started clinical training and exposed to the patients in hospitals during the 2020-2021 academic years. Students who refused to take part in the study were not included in the study. Purposive sampling was used and the Readiness for Interprofessional Learning Scale (RIPLS) questionnaire, a free online, valid, reliable, and pretested instrument was used to measure the readiness of undergraduate students towards IPE. Reliability of questionnaire calculated by the developer was 0.83.[12]

The tool used was having 19 items which were further divided into three subscales: Labelling of the three subscales, items numbers and scoring for the subscales of this questionnaire are shown in the below table:

| Subscales | Item numbers | Scoring of items |
|---|---|---|
| Teamwork and collaboration | 1-9 | 9×5= 45 |
| Professional Identity | 10-16 | 7×5=35 |
| Roles and Responsibilities | 17-19 | 3×5=15 |

The questionnaire was distributed to 924 undergraduate students. Using Google Forms. The link was disseminated using students' institutional mailing list. The link to the questionnaire was also shared with cohort groups of eligible students on WhatsApp Messenger. Data was collected within a period of one week from June 29 to July5, 2021. Daily reminders were given to the students during the study period to increase the response rate. All were informed regarding the anonymity of the study. The first part of the survey composed of the demography of participants: undergraduate's gender and 'discipline of participants while the second part of questionnaire consisted of 19 items. Questions were measured on a Likert scale of five points (5= strongly agree, 1 = strongly disagree). Items 10, 11 and 12 were reverse coded according to the instructions of developer. The scale was reversed for these three items so that for the other 16 items: the greater the marks the greater the indication of positivity towards readiness. This implies that the best possible points of RIPL was 95 and minimum points was19.Overallscore of 57 out of 95 would indicate a

neutral readiness, score>57 would indicate a more positive towards readiness, while score<57 would indicate a less than satisfactory towards readiness. The scores of the subscales were utilized to recognize the positive and negative areas of participants regarding awareness and readiness towards IPE.

The data collected was analyzed by using statistical software SPSS-22. Mean and standard deviation were calculated for the score of questionnaires. ANOVA test was used to find the difference of attitudes among five groups based on different disciplines. The statistical significance was set at a value ≤0.05. Cronbach's Alpha test was applied to check the reliability of questionnaire.

## Results

Inventories were completed and returned by 582 students out of 924 students registered in medical, dentistry, nursing, physiotherapy, and medical imaging at CMH, yielding a response rate of 63%.Distribution of the future health professionals by academic year is illustrated in Table-I

(Table II) The best score (4.2) was given by most students for two items # 2 and 7: "Patients would ultimately benefit if health care students / professionals worked together" and "For small group learning to work, students / professionals need to respect and trust each other". Students gave low scores to last three items (17,18,19) of sub scale "Roles and Responsibilities" and lowest score 3.0 for item # 12: Clinical problem solving can only be learnt effectively with students / professionals from my own program highlighted the area for improvement.

Overall participants of all five disciplines were positive towards IPE. Cronbach alpha calculated for the complete questionnaire was 0.91. It was an excellent value. The total mean score of the inventory was 74.54 out of 95 for the 19 items. RIPL questionnaire scored >57 so the participants showed more satisfactory awareness and readiness regarding IPE.

(Table III) The highest percentage score of 81.7% was given to the "Teamwork and collaboration" subscale, followed by the "Professional Identity" subscale which gained 75.4 %, whereas "Roles and Responsibilities" obtained a minimum percentage of 68.60%. The mean overall score of the whole group was 78.4%.Analysis of Variance (ANOVA) was used to calculate the differences among groups of five disciplines given in Table IV in the form of items' mean, standard deviation, and p-values. Statistical analysis by utilizing ANOVA showed that nursing students scored higher points than students of other health professions (P values between 0.00 and 0.05)Table IV.

**Table I: Demographic Characteristics of Participants in The Study n= 582**

| Variables | | n= No. of Students | % Percentage of Students |
|---|---|---|---|
| Gender | | | |
| | Male | 168 | 28.9% |
| | Female | 409 | 70.3 % |
| Discipline | | | |
| | MBBS | 233 | 40% |
| | BDS | 106 | 18.2% |
| | DPT | 108 | 18.6% |
| | MIT/MID | 64 | 11% |
| | Nursing | 64 | 11% |

**Table II**

| RIPLS Items | Description: Using a 5-point Likert scale (5-strongly agree to 1-strongly disagree) | Mean | Std. Deviation |
|---|---|---|---|
| 1. | Learning with other health professional students will make me a more effective member of a health care team. | 4.092 | 1.078 |
| 2. | Patients would ultimately benefit if health care students / professionals worked together. | 4.209 | 1.066 |
| 3. | Shared learning with other health care students / professionals will increase my ability to understand clinical problems. | 4.168 | 1.050 |
| 4. | Learning with other health care students before qualification would improve working relationships after qualification. | 4.104 | 1.054 |
| 5. | Communications skills should be learned with other health care students /professionals. | 4.190 | 1.012 |
| 6. | Shared learning will help me think positively about other health care professionals. | 4.132 | 1.037 |
| 7. | For small group learning to work, students / professionals need to respect and trust each other. | 4.231 | 1.042 |
| 8. | Shared learning will help me to understand my own professional limitations. | 4.094 | 1.010 |
| 9. | Team-working skills are vital for all health and social care students / professionals to learn | 4.011 | 1.0 |
| 10 | I don't want to waste time learning with other health care students / professionals. | 3.890 | 1.141 |
| 11 | It is not necessary for undergraduate / postgraduate health care students /professionals to learn together. | 3.658 | 1.153 |


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| | | | |
|---|---|---|---|
| 12 | Clinical problem solving can only be learnt effectively with students / professionals from my own program. | 3.072 | 1.177 |
| 13 | Shared learning with other health care professionals will help me to communicate better with patients and other professionals. | 4.032 | 1.044 |
| 14 | I would welcome the opportunity to work on small group projects with other health care students / professionals. | 4.061 | 1.039 |
| 15 | Shared learning and practice will help me clarify the nature of patients' or clients' problems. | 4.042 | 1.027 |
| 16 | Shared learning before and after qualification will help me become a better team worker. | 4.075 | 1.026 |
| 17 | The function of nurses and therapists is mainly to provide support for doctors. | 3.283 | 1.274 |
| 18 | I am not sure what my professional role will be / is | 3.554 | 1.229 |
| 19 | I have to acquire much more knowledge and skill than other students /professionals in my own faculty / organization. | 3.611 | 1.122 |

**Table III: Three Subscales Measuring Future Health Professionals' Readiness and Awareness Towards Interprofessional Education**

| Sub scales | Item numbers | Total score of sub scales | Obtained Score of sub scales in current study | Mean | % age |
|---|---|---|---|---|---|
| Teamwork and collaboration | 1-9 | 45 | 36.8 | 36.8 | 81.7 |
| Professional Identity | 10-16 | 35 | 26.4 | 26.4 | 75.4 |
| Roles and Responsibilities | 17-19 | 15 | 10.3 | 10.3 | 68.6 |

## Discussion

This study revealed positive attitudes of participants from five different disciplines at CMH towards IPE. This is evident from a score of 78.4% in the

**Table IV**

| RIPLS Questions | All Students N= Mean(SD) | Medicine N= Mean(SD) | Dentistry N= Mean(SD) | Nursing N= Mean(SD) | Physiotherapy N= Mean(SD) | MIT N= Mean(SD) | P- value |
|---|---|---|---|---|---|---|---|
| Q1 | 4.092(1.078) | 4.004(1.081) | 3.764(1.167) | 4.375(1) | 4.296(1.016) | 4.324(0.953) | 0.000 |
| Q2 | 4.209(1.066) | 4.185(1.053) | 3.972(1.191) | 4.578(1.005) | 4.259(0.999) | 4.25(1.013) | 0.009 |
| Q3 | 4.168(1.050) | 4.107(1.059) | 3.896(1.121) | 4.516(1.008) | 4.324(0.984) | 4.25(0.952) | 0.001 |
| Q4 | 4.104(1.054) | 4.064(1.051) | 3.962(1.086) | 4.219(1.091) | 4.204(1.083) | 4.206(0.939) | 0.341 |
| Q5 | 4.190(1.012) | 4.197(1.015) | 4.019(1.042) | 4.453(0.975) | 4.204(1.030) | 4.162(0.956) | 0.115 |
| Q6 | 4.132(1.037) | 4.060(1.053) | 4.019(1.033) | 4.359(1.060) | 4.240(1.031) | 4.162(0.971) | 0.150 |
| Q7 | 4.231(1.042) | 4.210(1.023) | 4.047(1.124) | 4.531(0.975) | 4.315(1.038) | 4.176(1.021) | 0.048 |
| Q8 | 4.094(1.010) | 4.082(0.977) | 3.934(1.017) | 4.25(1.054) | 4.120(1.030) | 4.176(1.050) | 0.285 |
| Q9 | 3.890(1.141) | 3.708(1.218) | 3.660(1.170) | 4.484(0.690) | 4.111(0.998) | 4(1.146) | 0.000 |
| Q10 | 3.658(1.153) | 3.481(1.156) | 3.519(1.213) | 4.219(0.826) | 3.787(1.120) | 3.764(1.211) | 0.000 |
| Q11 | 3.072(1.177) | 2.948(1.155) | 3.123(1.127) | 3.344(1.263) | 3.130(1.208) | 3.103(1.186) | 0.169 |
| Q12 | 4.032(1.044) | 3.957(1.054) | 3.934(1.035) | 4.266(1.043) | 4.093(1.081) | 4.132(0.976) | 0.179 |
| Q13 | 4.061(1.039) | 4.004(0.989) | 3.849(1.094) | 4.281(1.119) | 4.194(1.054) | 4.176(0.992) | 0.032 |
| Q14 | 4.042(1.027) | 4.009(0.996) | 3.858(1.099) | 4.188(1.111) | 4.185(0.978) | 4.074(1.012) | 0.129 |
| Q15 | 4.042(1.027) | 4.009(0.996) | 3.858(1.099) | 4.188(1.111) | 4.185(0.978) | 4.074(1.012) | 0.129 |
| Q16 | 4.075(1.026) | 4.060(1.020) | 3.830(1.055) | 4.281(1.076) | 4.139(1.009) | 4.206(0.955) | 0.035 |
| Q17 | 3.283(1.274) | 3.506(1.130) | 3.377(1.082) | 2.734(1.576) | 2.824(1.426) | 3.588(1.149) | 0.000 |
| Q18 | 3.554(1.229) | 3.339(1.229) | 3.472(1.156) | 4.25(1.069) | 3.657(1.305) | 3.618(1.120) | 0.000 |
| Q19 | 3.611(1.122) | 3.687(1.103) | 3.321(1.029) | 3.891(1.236) | 3.6021.168) | 3.515(1.072) | 0.015 |
| Total | 74.54(1.139) | 73.61(1.128) | 71.41(1.131) | 79.40(1.160) | 75.86 (1.164) | 75.95(1.084 | 0.001 |

questionnaire, a good value that supports IPE. Our findings are similar to the findings from Riaz et al. study conducted in Pakistan[13]and international studies conducted by Talwalkar at Yale University which is located in the northeastern United States[9], Coster et al. in the UK[14] and a study conducted by University of Central Arkansas 'College of Health and Behavioral Sciences.[15] However, our study revealed a few significant differences. Nursing students appreciated (83.5%) IPE more than other health professions in the present study. They believe more in collaboration as compared to dentistry and medical students who believe in individualism.[13] Nurses usually perform their duties along with other health professionals. and support working of systems for optimum health care while due to the privileged position of doctors, MBBS students think that doctor as an individual is responsible for working in health care settings. This is similar to the findings from countries like Sweden[16] and Canada[17] but studies from UK[14], and Iran[18] contradict this finding. A study in KSA conducted by Hind Ibrahim Fallatah et al. revealed that MBBS students considered IPE important as compared to nursing students for improving patient safety and thought that IPE should be a part of their academic program.[4]
Our study revealed that dentistry students scored lowest among all groups. This finding is in accordance with another multicentered study conducted by Amna et.al in Pakistan.[13] Curriculum in most dental colleges of Pakistan is based on traditional model. The teamwork and collaboration with other health professions are negligible and focused more on specific dental field. This could be the probable reason of demonstrating less positive attitude towards IPE. Medical students scored second last (77%). This finding may be due to the privileged position of doctors in our health system. The reason of highest mean of Nurses, physiotherapists and MIT undergraduates may be that these professions are not satisfied with their professional relationship with doctors and thought about the lack of their role in providing suggestions to doctors[19].A study conducted in Pakistan by Raisa Gul et al, highlighted lack of respect for nurses by doctors and not valuing the role of nurses in decision making, which is a point of concern for our health system.[20]
Generally, all students showed high readiness for IPE. However, compared to the nursing, physiotherapy and MIT students, a noticeable low readiness was found in the dentistry and medical students. Our study supports the necessity to improve the dentistry and medical students' awareness of their professional role in collaborative practice and the advantages of IPE in their clinical practice.
Majority of students in the present study reported attitudes supportive to statements regarding Teamwork and Collaboration. The highest scored item (4.23) was about respect and trust each other. This is in line with the study conducted by Talwalkar et al. in USA, Qadeer et al. and Riaz et al. in Pakistan.[13,21]
The low mean scores of last three items in subscale "'Roles and Responsibilities" provided us the opportunity to investigate the weakness of health professionals in terms of their role in IPE. This finding was in accordance with findings from other studies of Pakistan, Amna etal. (2020) conducted for undergraduates and Qadeer et.al (2020) conducted for postgraduate reported that the lowest scored item was regarding the role of participants toward IPE.[13,21] The lowest mean score item of current study is "Clinical problem solving can only be learnt effectively with students / professionals from my own program". This finding also supports the need for integrating IPE, as the students showed lack of awareness about the roles of health care team. Majority of students needed comprehensive understanding of IPE, Lama et al. (2018) conducted at Beirut Arab University mentioned that IPE was found to provide the defined roles of each of the health professions and augment the participants' views on the importance of the roles of other providers. The point of IPE is to develop an environment where each health provider recognizes his strengths and limitations and performs his/her duties competently for the safe care of the patient[22]
Education regarding the various roles of health professions would assist to improve the knowledge needed for collaboration with other coworkers which has been associated with effective clinical practice.[22] Due to this fact, it was suggested that the training of future health professional should give the type of IPE that allows them to get deep understanding regarding the roles, and practices of


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other health professionals, as well as their own.[23] Romanow et al. noted that it is imperative for all health care workers to identify and understand their role for collaboration and mutual respect which improve working environment, health care and patient safety. Currently, lack of training is noticed in academic programs for healthcare settings among health professions.[24] This issue could be solved by providing early IPE and training to our future health professionals for patient centered practice. The advantage of incorporating IPE in early years of education may discourage the stereotyping and prejudices and encourage mutual respect and trust among students.[25]

The results of local and foreign studies can give a broad picture regarding readiness of future health professionals for IPE. Moreover, the findings can assist the curriculum developers and instructional designers to integrate IPE in the curriculum of Pakistani health professions.

**Implications**

Carefully designed IPE courses and workshops regarding the basic knowledge and holistic view of IPE could be developed for students of all health professions based on their baseline data. To strengthen IPE in workplace settings, the roles and responsibilities of all stakeholders should be clearly defined.

**Strengths and Limitations**

A validated and reliable survey RIPL was utilized. The limitation of this study is that it is done in only one private institution of Pakistan. Future research is also needed for the replication of the current study in other private and public medical, nursing, dental and allied schools for the generalization of results.

## Conclusion

A clear positive attitude of future health care professionals of our institution (undergraduate students of medical, dental, nursing, DPT & MIT)is shown towards IPE analyzed through this questionnaire. However, noticeable differences have emerged among students of health professions. The results encourage pilot projects and provide baseline information with the goals to incorporate IPE into health professions curriculum all over Pakistan, take initiatives and develop strategies for the promotion of patient safety among future health professionals. This will bring change in professional personalities of our future doctors according to the global needs and standards.

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**CONFLICT OF INTEREST**

Authors declared no conflicts of Interest.

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

REVIEW ARTICLE

# Efficacy of Paracetamol or Ibuprofen in The Management of COVID-19 Fever: A Systematic Review

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**ABSTRACT**

The Global outbreak of COVID-19 pandemic affected almost all countries and territories worldwide. The outbreak was first identified from Wuhan, China, in December 2019 and was declared a pandemic in March 2020. Virus incubation time is usually 7 days and initial symptoms includes fever, cough, flu, muscle fatigue and difficulty in breathing. Ibuprofen and paracetamol are the two most commonly used over the counter (OTC) drugs to treat fever due to COVID-19. Some researchers discouraged the use of ibuprofen initially due to possible adverse effects related with longevity of infection, increased morbidity, and mortality rate. This study aimed to compare the effectiveness of paracetamol and ibuprofen as anti-pyretic drugs to treat fever caused in COVID-19 infection. A systematic review of major databases i.e., PubMed, Cochrane library, Web of Science, Google scholar and ClinicalTrials.gov was performed, to screen the studies conducted on managing fever using paracetamol and ibuprofen. Review of the selected articles based on the inclusion/exclusion criteria was performed by two independent researchers. The titles of selected publications were screened for relevance to the preset criteria followed by review of the abstracts. Finally, the full-length articles were evaluated for the final selection of studies to be included. Outcomes of use of ibuprofen and paracetamol were estimated by analyzing selected case control and cohort studies. Overall, eleven observational studies were selected for the compilation of systematic review, based upon the preset inclusion/ exclusion criteria. All studies included adult COVID-19 patients both male and female from different age groups. Paracetamol users were compared with ibuprofen users and no adverse effects of ibuprofen were found related to longevity of infection, complications, increased mortality rate and ventilation support requirement, when treating fever or pain caused by COVID-19. However, further studies and randomized control trials need to be conducted to assess and compare the effectiveness of these drugs to manage fever caused by coronavirus disease.

**Key Words:** *COVID-19, COVID-19 Management, Ibuprofen, Paracetamol, Systematic Review.*

## Introduction

Around the globe the emergence of new viral diseases has been a burden to the economy and health. The cases of unknown upper respiratory tract infection flooded the hospitals of Wuhan, China in December 2019.[1] The causative agent for this disease was identified as a novel coronavirus, later named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the disease was known as coronavirus disease or COVID-19[1]. Later, several cases of COVID-19 were reported throughout the world and was declared a global pandemic by the World Health Organization (WHO) in March, 2020.[2] Virus usually takes about seven days to incubate and initial symptoms include fever, sore throat, cough, headache, fatigue, diarrhea and loss of smell/taste.[3,4] In fact, as many as 45–89% of adult patients suffering from COVID-19 report fever, even with mild to moderate disease.[5,6] There are few antipyretics over the counter available, among those ibuprofen and paracetamol are most commonly used. Ibuprofen belongs to NSAIDs, a class of drugs which includes anti-inflammatory properties. Although, paracetamol has anti-pyretic characteristics, but it has no antiplatelet and anti-inflammatory properties like NSAIDS.[7] NSAIDs/ibuprofen could lead to high expression of angiotensin-converting enzyme 2 (ACE-2) receptors and hence they can result in a

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superior infection, that is why paracetamol was also recommended in place of NSAIDs/ibuprofen.[8]

The debate around the usage of ibuprofen for patients of COVID-19 was ignited by the reporting of adverse effects among four young patients, without any previous morbidity, who had used ibuprofen to relieve COVID-19 fever.[9] The French health minister also cautioned the public against ibuprofen use as an antipyretic during COVID-19.[9] This led to an eighty percent decrease in ibuprofen use for COVID-19 fever in France. In addition, Randomized Controlled Trials (RCTs) conducted showed that the use of ibuprofen for the treatment of respiratory infection related symptoms could possibly be a factor in prolonging the duration of symptoms and therefore, the recommendation for ibuprofen use for such infections should be withdrawn.[10] As a result, paracetamol was preferred for treating COVID-19 fever, rather than ibuprofen and other NSAIDs.[8] However not only the WHO, but also the Healthcare Products Regulatory Agency UK and the Italian Society for Pharmacology later reversed the statements against ibuprofen prescription to COVID-19 patients, owing to absence of any conclusive evidence against the use of ibuprofen.

This study aims to compare the effectiveness of paracetamol and ibuprofen for managing fever caused by COVID-19.

## Methodology

The current Systematic Review has employed the criteria included in the Preferred Reporting Items for Systematic Review (PRISMA; Figure 1). The protocol for this review was published in the International Prospective Register of Systematic Reviews, PROSPERO (Registration number CRD42020198538) (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020198538).

**Inclusion Criteria**

1. Studies on hospitalized COVID-19 patients
2. Studies on infected individuals aged 18 years and above
3. Clinical studies published in English only
4. Studies published between December 2020 and June 08, 2022
5. Observational studies

**Exclusion Criteria**

1. Studies on pregnant women and children
2. Studies published in languages other than English or studies on animals.

**Databases used and Strategy for Data Synthesis**

The review was based on search results obtained from the databases of the Google Scholar, ClinicalTrials.gov, Web of Science, Cochrane Library and MEDLINE and using the search strategy previously published in the protocol. Each database was systematically searched for the three main concepts of COVID-19, ibuprofen, and paracetamol, using synonyms of the three terms. Explicit search strategy has already been published on PROSPERO (Registration no: CRD42020198538).

The studies thus retrieved were all exported to Microsoft Office 365 Excel (Microsoft Corporation, USA) file. After the process of removing the duplicates, screening the titles, abstracts, and full text articles was completed by two reviewers, by using the inclusion/exclusion criteria as mentioned above. The full text articles were assessed for the quality of evidence according to the Quality assessment criteria (Table 1). Results shared by the two independent reviewers were compared and disagreements were resolved by seeking advice of the third reviewer.

**Study selection process**

The search of the Google scholar, ClinicalTrials.gov, MEDLINE, Web of Science databases and Cochrane Library yielded a total of 1,069 publications. Seventy-one, duplicate records were removed to yield a total of 998 publications. The titles of the remaining 998 publications were screened for relevance to research topic by the two independent reviewers and 926 were excluded. Remaining 72 publications were reviewed for abstracts and 40 studies were excluded due to non-relevance to the subject, only being commentaries or summaries of available treatments with just a passing reference to the treatment of fever and pain in COVID-19. Thirty-two full text articles were assessed for inclusion in the final stage of the review; of which only eleven studies were found eligible to be included in the final review. Reasons for non-inclusion are as follows: some of the publications explained the underlying mechanism of action of ibuprofen and paracetamol describing how they produce their effects in COVID-19. Only those studies were selected which investigated the effectiveness of either NSAIDs/ibuprofen or paracetamol or compared the effectiveness of these



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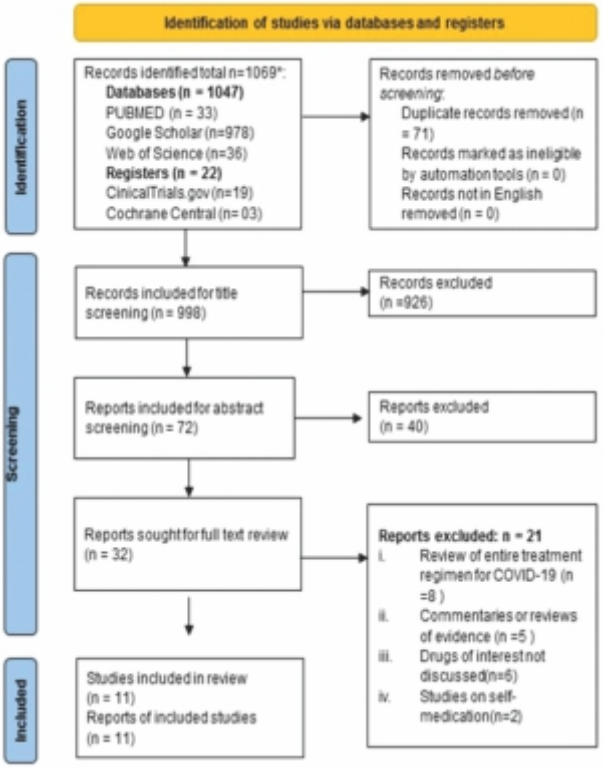
two drugs.

**Risk of bias assessment**

The criteria of risk bias assessment for observational studies, was used (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Participation rate was 50%, research question and population were clearly defined, and inclusion/exclusion criteria were explicitly described in all of studies. In all of the studies, sample size calculation was not clearly defined along with power description (Table I).

**Figure 1: Flowchart Diagram for Systematic Review on Efficacy of Paracetamol or Ibuprofen in the Management of COVID-19 Fever**




## Results

Results of all selected/screened studies are given in table 2. In the Danish Cohort, NSAID user were identified by being prescribed with NSAID/ibuprofen from 30 days before being diagnosed with COVID-19 infection.[11] The filling of the prescription did not imply that the patients had taken the medicine as well. However, it is outweighed by the large sample size of 9,236 individuals in the study. In the study conducted by Bruce *et al.*, 2020,[12] sample information was extracted from the COPE (COVID-19 in geriatric population) study, and it analyzed the intake of NSAIDs/ibuprofen in patients among 65, 65-79 and 80 years or more in age. Despite their dissimilarities all the included studies report that the practice/intake of NSAIDs/ibuprofen does not have a significant effect on the death rate and stay in hospital.

In the South Korean cohort, the association of NSAIDs/ibuprofen and adverse clinical outcomes was analyzed in 1,824 hospitalized COVID-19 patients.[13] NSAID/ibuprofen users had a higher proportion of adverse outcomes including in hospital deaths, ICU admissions, use of mechanical ventilation and sepsis compared to the non NSAID users. In another study conducted on Danish cohort of 4,002 individuals, 264 patients were identified as ibuprofen users. Based on the time of diagnosis of COVID-19 infection, the patients were divided into higher than fourteen days vs less than or equal to fourteen days before diagnosis.[14] No significant association was found between ibuprofen use and 30-day severe COVID-19 infection complications defined as severe respiratory complications, ICU admission or death.

Another study conducted on two cohorts consisting of current NSAID users and nonusers, found no evidence for COVID-19 related deaths in both cohorts.[15] To characterize the demographics, clinical symptoms, the course of treatment, and stay in hospital, patients (n=307) were followed after being discharged from hospital.[16] Estimated length of stay in hospital due to COVID-19 infection was found to be 5.59 days longer for patients receiving supportive care (NSAIDs/ibuprofen & Paracetamol) than for those receiving azithromycin + hydroxychloroquine or hydroxychloroquine alone.

Rinott *et al.*,2020 in their retrospective study, specifically classified patients into Paracetamol and Ibuprofen users.[17] In Abu Esba *et al.*, 2021 study, the NSAID users were classified into acute and chronic users of NSAIDs/ibuprofen, to assess the effect of NSAIDs/ibuprofen use. Neither of the NSAID users' group showed any increase in risk of mortality or the hospital admission, increase in length of stay or time to improvement.[18] A study conducted on a large UK cohort, compared the severity and susceptibility of COVID-19, among NSAIDs/ibuprofen using patients and paracetamol users. No association was found

**Table I. Risk of Bias Assessment according to the criteria of US National Institute of Heart, Lung and Respiratory Diseases (Low Risk ✓High risk ✕Unclear (Not reported=NR, cannot determine=CD, Not Available=NA)**

| No. | Criteria | Lars Christian Lund; 2020: Denmark | Eilidh Bruce;2020: UK | Han Eol Jeong;2020: South Korea | Kristian Kragholm;2020: Denmark | Angel YS Wong; 2021:UK | Mary EyramAshinyo;2020: Ghana | Ehud Rinott, 2020: Israel | Laila Carolina Abu Esba;2021: Saudi Arabia | Joht Singh Chandan;2021: UK | Justin T. Reese:2021: USA | Heather M. Campbell;2022: USA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Was the research question or objective in this paper clearly stated? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2. | Was the study population clearly specified and defined? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3. | Was the participation rate of eligible persons at least 50%? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 4. | Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 5. | Was a sample size justification, power description, or variance and effect estimates provided? | Unclear | unclear | unclear | Unclear | unclear | unclear | unclear | unclear | ✓ | unclear | unclear |
| 6. | For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | ✓ | ✓ | ✓ | ✓ | ✓ | ✕ | ✕ | ✓ | ✓ | ✓ | ✓ |
| 7. | Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |



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| 8. | For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| 9. | Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 10. | Was the exposure(s) assessed more than once over time? | NR | NR | ✗ | NR | ✗ | NR | NR | NR | NR | ✗ | ✗ |
| 11. | Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 12. | Were the outcome assessors blinded to the exposure status of participants? | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 13. | Was loss to follow-up after baseline 20% or less? | Less | NA | NA | NA | NA | NA | CD | NA | NA | NA | NA |
| 14. | Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**Table II: Studies Included in The Systematic Review**

| No. | Study Title | First Author; Year: Country | Study Type | Sample size | Age (y) | Subjects | Study groups | Treated patients | Route of Administration | Main findings |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study [11] | Lars Christian Lund;2020: Denmark | Cohort study | 9,236 (NSAID users=248, Non-NSAID users=8,988) | Median age= 50 years | COVID-19 patients | All Danish residents who had a positive PCR test for SARS-CoV-2 during the period 27 February 2020 to 20 April 2020 were included in the study | Users of NSAID users were compared to individuals without NSAID use in the corresponding time window | Not specified | Use of NSAIDs was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in Danish individuals who tested positive for SARS-CoV-2. |
| 2 | Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalized patients with COVID-19 [12] | Eilidh Bruce;2020:UK | Prospective Cohort study | 1222 | 3 groups, 1: under 65 years, 2: 65-79 years, 3: over 80 years | COVID-19 patients | Adults ≥18 years admitted to 10 hospitals in the United Kingdom and one in Italy with the diagnosis of COVID-19 | Hospitalized patients | All types except topical NSAIDS | This study found that the routine use of NSAIDs might confer a modest survival benefit and is not associated with poorer outcomes |
| 3 | Association between non steroidal anti-inflammatory drug use and adverse clinical outcomes among adults hospitalized with coronavirus 2019 in South Korea: A nationwide study [13] | Jeong, Han Eol, 2020, South Korea | Cohort study | 1824 | Mean age (NSAID users= 54 years and non NSAID users=47.8 years) | Hospitalized COVID-19 patients | 1824 adults hospitalized for COVID-19 were divided into two groups; 354 NSAID users and 1470 nonusers | Hospitalized COVID-19 patients | oral and intravenous administration | NSAID use was associated with worse COVID-19–related outcomes compared with nonuse among patients hospitalized with COVID-19 |



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| 4 | Association between prescribed ibuprofen and severe COVID-19 infection: A nationwide register-based cohort study [14] | Kristian Kragholm, 2020, Denmark | Cohort Study | 4,002 | Median age for individuals with Ibuprofen prescription claim=58 years while for No ibuprofen prescription claim=57 years | COVID-19 patients | COVID-19 patients were divided into ibuprofen and non-ibuprofen users | COVID-19 patients | Not specified | In this nationwide study, there was no significant association between ibuprofen drug prescription claims and severe COVID-19 diagnosis. |
| 5 | Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts [15] | Angel YS Wong, 2021, UK | Cohort study | **Cohort 1:** 536,423 current NSAID users and 1,927,284 non-users, **Cohort2:** 175,495 current NSAID users and 1,533,286 non-users | Cohort 1 : Median age=53 years, Non-users=49. Cohort2: Median age=63 years among current users and non-users=68 | NSAID users of COVID-19 patients | The first cohort was all people with ≥1 oral NSAID prescription within the 3 years before study start (1 March 2020), identified from the general population. The second cohort was all people with a diagnosis of rheumatoid arthritis (RA)/osteoarthritis (OA) before study start. | COVID-19 patients | Not specified | No evidence of a harmful effect of routinely prescribed NSAIDs on COVID-19 related death found. |
| 6 | Clinical characteristics, treatment regimen and duration of hospitalization among COVID-19 patients in Ghana: a retrospective cohort study [16] | Mary Eyram Ashinyo, 2020' Ghana | Retrospective Cohort Study | 307 | Mean age=37.9 years | COVID-19 patients | COVID-19 patients discharged from the hospital after treatment | The patients were categorized into five groups based on the type of treatment they received during hospitalization: (1) chloroquine+azithromycin, (2) hydroxychloroquine+azithromycin, (3) azithromycin only, (4) hydroxychloroquine only and (5) Supportive treatment only (vitamin C and analgesics (paracetamol or ibuprofen). | Not specified | Based on the data of 244 fully recovered patients, the use of the azithromycin +chloroquine combination or hydroxychloroquine alone shortened the duration of hospitalization compared to the use of azithromycin only |

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| | | | | | | | | | | or supportive treatment. |
| 7 | Ibuprofen use and clinical outcomes in COVID-19 patients [17] | Ehud Rinott, 2020: Israel | Retrospective Cohort Study | 403 (Cases=179, Controls= 224) COVID-19 patients | Median age=40 year | Confirmed cases of COVID-19 | COVID-19 patients with fever | One hundred and seventy-nine (44%) patients had fever, with 32% using paracetamol and 22% using ibuprofen (Both hospitalized and non-hospitalized) | Not specified | When compared to exclusive paracetamol users, no differences were observed in mortality rates or the need for respiratory support among patients using ibuprofen. |
| 8 | Ibuprofen and NSAID Use in COVID-19 Infected Patients Is Not Associated with Worse Outcomes: A Prospective Cohort Study [18] | Laila Carolina Abu Esba;2021: Saudi Arabia | Prospective Cohort Study | 503 | Group 1: acute ibuprofen users=34.5; group 2: aspirin/NSAID users=38; group 3: aspirin/NSAID chronic users=57; group 4: any NSAID users, acute/ chronic combined=47.5. Non-NSAID users=36 | Adult COVID patients | Group 1: acute ibuprofen users during infection only; group 2: aspirin/NSAID acute use during infection; group 3: aspirin/NSAID chronic users; group 4: any NSAID users, acute/ chronic combined. Non-NSAID users were the control group. | Both hospitalized and non-hospitalized | Not specified | Acute ibuprofen use was not associated with a greater risk of mortality relative to nonusers (adjusted hazard ratio (HR) 0.632 [95% CI 0.073–5.441; P = 0.6758]). NSIAD chronic use was also not associated with greater risk of mortality (adjusted HR, 0.492 [95% CI 0.178–1.362; P = 0.1721]) |
| 9 | Nonsteroidal Anti-inflammatory Drugs and Susceptibility to COVID-19 [19] | Jot Singh Chandan, 2021, UK | Cohort study | 13,202 | Mean age in matched cohort=68 years | Diagnosis of osteoarthritis in COVID-19 patients | Patients prescribed an NSAID were compared to those prescribed either co-codamol (paracetamol and codeine) or co-dydramol (paracetamol and dihydrocodeine). | Osteoarthritis patients already prescribed with NSAIDS | All types except topical NSAIDS | Prescriptions of NSAIDs (excluding topical preparations) in primary care do not increase susceptibility to COVID-19 or all-cause mortality, including in older patients. |
| 10 | NSAID use and clinical outcomes in | Justin T Reese; 2022: USA | Retrospective Cohort Study | 857061 (NSAIDS users:19,746, | Median age of cohort=47.6 years | COVID-19 patients | Individuals diagnosed with COVID-19 were | COVID-19 patients | Not specified | The findings of the study did not show an |

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| | COVID-19 patients: a 38-center retrospective cohort study [20] | | | Non-NSAID users= 19,746) | | | | | association in hospitalized COVID-19 patients between NSAID use and increased COVID-19 severity, or increased risk of invasive ventilation, AKI, ECMO, and all-cause mortality. There is a significant association between NSAID use and decreased risk of these outcomes. |
| 11 | Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen and relationship with mortality among United States Veterans after testing positive for COVID-19 [21] | Campbell HM, 2022, USA | Retrospective Cohort Study | 28,856 patients | Mean age=57.8 years | COVID-19 patients | COVID-19 patients divided into sporadic NSAID users, chronic NSAID monotherapy users, chronic acetaminophen users | Studied NSAIDs included aspirin > 150mg/day, ibuprofen, naproxen, meloxicam, celecoxib, and diclofenac. | Not specified | The results of this study show no association between chronic use of any of the six NSAIDs studied or with acetaminophen and all-cause mortality in Veterans diagnosed with COVID-19 infection. Clinically important association was also not revealed when chronic acetaminophen use was substituted for sporadic NSAID use. |

between increased risk of mortality and ibuprofen/NSAID use, when compared to paracetamol.[19]

In the study conducted by Reese *et al.*, electronic health record data from 38-centers was analyzed for a retrospective cohort analysis. Cases using NSAID were matched with 19,746 COVID-19 inpatients to create a propensity-matched cohort. NSAIDs/ibuprofen use was not associated with increase in severity of COVID-19 outcomes. The prescription of NSAIDs/ibuprofen was also not associated with high rate of mortality.[20] Campbell *et al.*, 2022 studied the impact of continuous usage of specific NSAID/ibuprofen and paracetamol on death/mortality. No significant differences in mortality were established between chronic use of NSAIDs/ibuprofen and paracetamol use.[21]

## Discussion

During the early days of COVID-19 outbreak, speculations based on unpublished data on the NSAIDs/ibuprofen particularly ibuprofen and COVID-19 symptoms worsening, caused quite a stir around the world. Harmful effects of NSAIDs/ibuprofen were attributed to the up regulation of ACE2 receptors which facilitate the viral entry in the different organs such as lungs, heart, kidney, and intestines, hence contributing to worse outcomes of COVID-19 infection.[22] Evidence from *in vitro* as well as cohort studies shows that ibuprofen is not associated with harmful impacts in COVID infection.[21,23,24] Despite the intrinsic limitations of the observational studies, this systematic review has shown that with NSAIDs/ibuprofen, there was no harmful effect observed, either in terms of increased mortality or morbidity. It was suggested that a modest survival benefit for older patients treated with NSAIDs/ibuprofen might exist.[1] We found that no Randomized Controlled Trial (RCT) was done to assess the ibuprofen effects in comparison with paracetamol in people infected with COVID-19.

With regards to the treatment of COVID-19 fever, Rinott *et al.*, concluded that there was no increased death rate or the requirement of ventilator in patients on ibuprofen exclusively compared to those taking paracetamol.[17] Most of the studies included found no association between increased mortality in COVID-19 patients prescribed with ibuprofen or NSAIDs/ibuprofen. However, a study conducted in a South Korean cohort indicated a greater proportion of complication related to COVID-19 and death among NSAID users compared to the nonusers.[25]

There are few studies on the efficacy of paracetamol as an antipyretic agent for COVID-19. We have taken care to include only studies that were conducted on COVID-19 patients since SARS-CoV-2 is a novel virus, has a different behavior as compared to different viruses of the same family such as MERS viruses originated from middle east countries.[26] The studies showed slight variations, with some including both hospitalized as well as non-hospitalized individuals diagnosed with COVID-19,[17,18] while others included only hospitalized COVID-19 patients.[12,25] While Rinott *et al.*, studied the findings on patients receiving NSAIDs/ibuprofen during the treatment period and did not explore the pre-admission use of NSAIDs/ibuprofen,[17] Bruce *et al.*,2020 emphasized the pre-COVID treatment history and clearly documented the prior use of NSAIDs/ibuprofen as well the presence/absence of co-morbidities.[12]

The present study has a few limitations. Firstly, only limited published studies on the efficacy of paracetamol and NSAIDS/Ibuprofen for management of COVID-19 fever were available. While all the eleven included studies were observational, the prospective nature of the studies excludes the possibility of reverse causality. Secondly, despite the limitations of the included studies, their results indicate that the exclusion of NSAIDs/ibuprofen from COVID-19 management plan, is not supported by empirical evidence and RCTs are much needed. Currently we have no results from clinical trials, only cohort studies were included for the compilation of this systematic review. Although we followed all the standard protocols for searching and screening studies, the probability of missing some studies still exist. Moreover, studies on children and pregnant women were excluded, so the results of current study can not be applied to them.

## Conclusion

According to the results of the present systematic review, there is no evidence refuting the efficacy and/or safety of ibuprofen in comparison with paracetamol and that the use of ibuprofen should not be prohibited during the treatment of fever and pain accompanying the COVID-19 infection.



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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.





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ORIGINAL ARTICLE

# A Rare Case: Spontaneous Bilateral Rectus Sheath Hematoma in A Patient with Dengue Fever

Muneeb Ullah, Aqsa Adeel, Adil Shafi, Muhammad Faisal Murad

**ABSTRACT**

Bilateral rectus sheath hematoma secondary to Dengue fever is very rare. Mainstay of treatment is conservative. Surgical intervention is reserved for those who have expanding hematomas, infected hematomas, persistent pain, hemodynamic instability, etc. We present a rare case of spontaneous bilateral rectus sheath hematoma in a patient with dengue fever. Patient was initially managed conservatively, and later drainage of bilateral rectus sheath hematoma was performed.

**Key Words:** *Dengue Fever, Hematoma, Rectus Sheath.*

## Case

A 39-year-old female with no known co-morbidities presented in emergency department with three days history of fever, epistaxis, heavy menstrual bleeding, lower abdominal fullness and pain. At presentation patient was tachycardiac, febrile and tachypneic. Lower abdomen was mildly tender, more on left side as compared to right. Patient had Hemoglobin (Hb) of 11.6 g/dl, white blood cells (WBCs) 2.14 x 103 /ul, Platelets count of 41,000 x $10^3$ /ul, Prothrombin time 11 seconds (Control 10.8 seconds), activated partial thromboplastin time (APTT) 27.3 seconds (Control 27 seconds) and International Normalized Ratio (INR) of 1. Dengue virus Non-Structural protein 1 (NS1) antigen was positive while liver function tests were normal. Ultrasound revealed 10.9ml left rectus sheath hematoma (RSH). After 12 hours of admission patient had platelets count of 42000 x $10^3$ /ul and Hb of 9.7 g/dL while remaining hemodynamically stable. On second day morning platelets increased to 93000 x $10^3$ /ul while Hb decreased to 7.7 g/dl. A CT Scan abdomen and pelvis with intravenous contrast was performed that showed hematoma involving bilateral rectus muscle measuring 9.7 x 6.5 cm on right side and 9.3 x 5.9 cm on left side (Arrows in Figure *1a, 1b and 2*).

There was no active bleeding from epigastric vessels or contrast extravasation, so the patient was continued on conservative management and blood products transfusion. At night Hb was repeated and it came out to be 8.9 g/dL. Follow up ultrasound on day three showed no interval increase in size of hematoma and a platelet count of 180,000 /uL. Patient was discharged on day five after conservative management and followed up on outpatient basis.

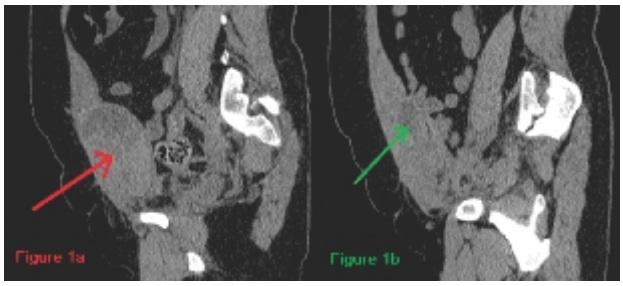


**Figure 1a: CT scan (Sagittal Section) with red arrow showing Right Rectus Sheath Hematoma**

**Figure 1b: CT scan (Sagittal section) with green arrow showing Left Rectus Sheath Hematoma**

**Figure 2: CT scan (Axial Section) Image showing Right (Red Arrow) and Left (Green Arrow) Rectus Sheath Hematoma**

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Patient remained well for four days at home and presented to us on day five with fever and lower abdominal pain for last 24 hours. Patient was tachycardiac and had tenderness in lower abdomen. Hb was 9.8 g/dL with raised WBCs of 13.3 x $10^3$ /uL. C-Reactive proteins test was also raised (70mg/dL). Patient had interval increase in RSH, 440ml on left side (Figure *3*) and 275ml on right side (Figure *4*).

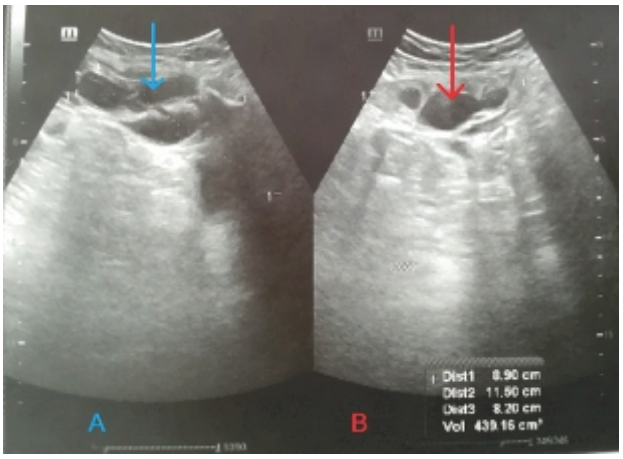


**Figure 3: Ultrasound Image showing Left Rectus Sheath Hematoma (Arrows)**
**A (Blue) - Transverse View**
**B (Red) - Longitudinal View**

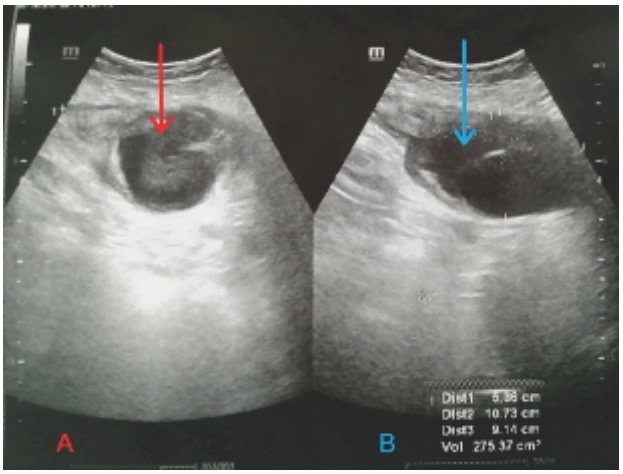


**Figure 4: Ultrasound showing Right Rectus Sheath Hematoma (Arrows)**
**A (Red) - Longitudinal View**
**B (Blue) - Transverse View**

Patient was admitted and bilateral separate incision and drainage of infected expanding hematoma was performed under spinal anesthesia. About 400ml hematoma was drained on the right side and 200ml hematoma was drained on the left side. Specimen for culture sensitivity was sent. After securing hemostasis, wound was kept open and daily dressings were continued. Patient was discharged on day three and injectable antibiotics (tazobactam + piperacillin and metronidazole) were continued for two more days. Patient was then shifted to oral antibiotics for five days according to culture sensitivity report. Patient remained well and was completely settled in further three weeks.

## Introduction

Dengue fever is a viral illness common in tropical and subtropical regions of the world.[1,2] It has four serotypes and it is transmitted to humans by bite of Aedes mosquito.[1,3] The disease ranges from asymptomatic to serious dengue hemorrhagic fever or dengue shock syndrome that may cause bleeding into retroperitoneal tissues or gastrointestinal tract.[4] Bleeding is due to complex pathophysiological pathways involving vasculopathy, thrombopathy and disseminated intravascular coagulopathy.[5,6] In very rare cases it may cause rectus sheath hematoma which is an uncommon disease itself. RSH may occur due to tear in rectus muscle or bleeding from epigastric vessels.[7] Rectus sheath is deficient below arcuate line in abdomen so hematomas below the arcuate line have the tendency to expland.[8] It presents as abdominal pain or palpable abdominal mass or fullness.[7,9] Predisposing factors for RSH include anticoagulation, old age, female gender, pregnancy, trauma, iatrogenic injury, intramuscular injection, hypertension, hematologic disease, coughing or strenuous physical activity.[9,10] The mainstay of treatment is conservative management. Conservative management includes intravenous hydration, blood products transfusion, vitals and input-output monitoring, stoppage of anticoagulation, etc. In case of hemodynamic instability, persistent pain, infective process or neurologic deficit, intervention is required. Intervention can be angioembolization or surgery.[11,13] Rectus sheath hematoma secondary to dengue fever is uncommon and in literature only few cases are reported.[5] Bilateral RSH are even rarer. We discuss a case of spontaneous bilateral rectus sheath hematoma secondary to Dengue Fever requiring surgical intervention.

## Discussion

RSH associated with dengue fever is rare and only a few cases of bilateral rectus sheath hematoma



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complicated by dengue fever are known to date.[5] Bleeding complications in dengue hemorrhagic fever patients result from combination of thrombocytopenia, increased vascular fragility, increased fibrinolysis, immunological disturbance and unbalance between pro-coagulation and anti-coagulation.[5,13] Persistent thrombocytopenia was seen in our patient. Our patient presented with fever, abdominal fullness, leucopenia, and thrombocytopenia which is usual presentation of a dengue fever patient with RSH.[9,10] Literature review shows female predisposition attributed to lesser muscle mass, as was our case.[5,12] Ultrasound abdomen is the initial radiological investigation of choice. CT scan with intravenous contrast is superior to ultrasound since it gives accurate identification of bleeding vessels, contrast extravasation, hematoma, its size, and extent.[7,13] It has the disadvantage of need to transfer to CT room, radiation exposure and contrast induced nephrotoxicity. MRI is superior to CT scan but needs more time. For MRI our patient needed to be transferred to nearby facility due to non-availability at our setup and additionally our patient was claustrophobic. Therefore, CT Scan with intravenous contrast was performed to know the exact details of bilateral RSH, contrast extravasation, hemoperitoneum, hematoma size and extent. Our patient was initially managed for Dengue Fever and RSH conservatively, including intravenous hydration, analgesia, blood transfusion and platelets transfusion. Platelets transfusion is based on individual case, but transfusion is usually considered when levels fall below 50,000 /uL.[5] Later expanding hematoma with fever and pain required surgical intervention in the form of Bilateral Incision and Drainage of Hematoma.[7,12] Angioembolization is reserved for cases where active bleeding epigastric vessels are identified as well as the availability of Interventional Radiology services.

## Conclusion

Dengue fever in complicated cases can present with RSH. These patients should be admitted and kept on strict observation. CT scan is the investigation of choice. RSH can be managed by conservative management. Surgical intervention should be reserved for cases with expanding hematoma, infected hematoma, or hemodynamically unstable patients. Outcomes are usually good with proper management.

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**DATA SHARING STATMENT**

The data that support the findings of this study are available from the corresponding author upon request.

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The manuscript should be typed in MS Word. Each manuscript should include a title page (containing email address, cell numbers, institution, and postal address of the corresponding author), abstract, key words, text, acknowledgements (if any), references, tables (each table, complete with title and footnotes) and legends for illustrations and photographs. Each component should begin on a new page. Sub-headings should not be used in any section of the script except in the abstract.

**TEXT ORGANIZATION**

All manuscripts except Short Communication and Letter to the Editor should be divided into the following sections.

**ABSTRACT**

Abstracts of original article should be in structured with following sub-headings:

- Objective
- Study Design
- Place & Duration of Study
- Materials & Methods
- Results
- Conclusion

Four elements should be addressed: "why did you start?", "what did you do?", "what did you find?" and "what does it mean? “.” Why did you start?" is addressed in the objective. "What did you do?" constitutes the methodology and could include design, setting, patients or other participants, interventions, and outcome measures. "What did you find?" is the 'results', and "what does it mean?" would constitute the conclusions. Please label each section clearly with the appropriate sub-headings. Structured abstract for an original article, should not be more than 250 words. At least 3 key words should be written at the end of the abstract. Review articles, case reports and others require a short, unstructured abstract. Commentaries do not require an abstract.

**INTRODUCTION**

Write this section with references as per following instructions:

1. Give background information about the subject matter and the issues your study intends to address. Only strictly pertinent references should be cited, and the subject should not be extensively reviewed.
2. Describe what is known (in the literature) and what is not clear about the subject with reference to relevant literature thus identifying the literature gap.
3. You write the rationale (justification) of your study.
4. Finally, you mention the objective of your study

**MATERIALS AND METHODS**

Methodology is written in past tense.

Follow this sequence **without headings:**

- Study design
- Place and Duration of Study
- Sample size
- Sampling technique
- Mention about permission of the ethical review board and other ethical issues addressed.
- Inclusion and Exclusion Criteria
- Data collection procedure-
- Type of data: parametric or nonparametric
- Data analysis: including Statistical Software used, and statistical test applied for the

calculation of p value and to determine the statistical significance. Exact p-values and 95% confidence interval (CI) limits must be mentioned instead of only stating greater or less than level of significance. All percentages must be accompanied with actual numbers.

**RESULTS**

These should be presented in logical sequence in the text, tables, and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized. No opinion should be given in this portion of the text.

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This section should include the author's comments on the results. Write in present tense, active voice except for results, which are written in past tense. It should be written in following sequence:

- First, very briefly summarize, Interpret and discuss main results and don't merely repeat the results.
- Discuss key studies relevant to your study.
- Compare your work with other's work.
- Describe limitations of your study.
- Suggest future work if necessary.

**CONCLUSION**

Conclusion should be provided under a separate heading. It should be in congruence with the objective. No recommendations are needed under this heading.

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Tables and illustrations should be merged within the text of the paper, maximum number of tables and illustrations should not exceed four, and legends to illustrations should be typed on the same sheet. Tables should be simple and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 ½" x 11' paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scattergrams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be made with MS Excel and be sent as a separate Excel file even if merged in the manuscript. For scanned photographs the highest resolution should be used.

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System International (SI) Unit measurements should be used. All drugs must be mentioned in their generic form. The commercial name may however be mentioned within brackets, if necessary.

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- Cover Letter

- JIIMC Checklist
- JIIMC Conflict of Interest Performa
- JIIMC CopyRight and Undertaking Agreement
- IRC Certificate
- Bank draft as initial processing fee (Original bank draft send in JIIMC office)

Template of these files is available in the download section.

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