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EDITORIAL

Transition in Medical Education: Student Support Matters

Zarrin S Siddiqui

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Transition to higher education is a well-researched topic with a focus on first year's experiences. In medical education, each year brings an entirely new experience, and transition never ceases. Additionally, medical education in Pakistan is an undergraduate degree and the entrants are young high school leavers. The learning environment is different from what they have experienced earlier, irrespective of which high school they have attended. This is a huge learning curve and requires adaptation at personal level. The changes that incoming students go through are called transitions and require consistent support. Hussey and Smith (2010) have identified the process of transition in terms of various domains[1]. These include transitions in:

a. Knowledge, understanding, and skills
b. Autonomy
c. Approaches to learning
d. Social and cultural integration
e. Self-concept

On the other hand, Gale and Parker (2012) have identified transition levels based on stages of learning i.e. induction, development, and becoming[2]. Both classifications can be applied to medical students and assist institutions to provide adequate student support.

In 2023, Pakistan Medical and Dental Council (PM&DC) released accreditation standards[3]. This document identifies thirteen standards in the student section including student support.

Reflecting further on the scenario in Pakistan, the following areas also require intense support from institutions.

Language Proficiency

English is not the first language spoken at home in Pakistan. Therefore, many students specially from rural areas struggle as all textbooks are in English. A pretest at the time of induction can identify the level of English with right intervention at right time. This is important if the institution employs small group learning as students with limited English may not participate and their assessment will be affected.

First-generation Students

With the current literacy level in Pakistan, many medical students entering the schools are First-generation students who are change agents in their own areas. There is no published research in Pakistan, but this is an area of discussion and a holistic model from admission to graduation is recommended rather than relying on the individual's grit and resilience[4].

International Students

International students do enter medical schools in Pakistan, but they mainly belong to families of overseas Pakistanis. Their needs are different as they face cultural challenges. Their families are also investing huge amount in their education which places extra pressure to perform well and is a cause of stress.

Special Needs

PM&DC has not included accommodation for students with special needs in the list of essential criteria, but it is crucial to allow for inclusion and accessibility. No educational institution should be licensed if adequate facilities for students with special needs are not available. These facilities should not be restricted only to students with physical needs but learning disabilities should also be accounted for with special accommodation provided as and when required.

Transition to medical school is stressful. A medical education unit can be instrumental in developing longitudinal support, but it requires resource allocation both physical and human. Mentoring has a role to play but it will not work with existing workload for the faculty. Simultaneously, with the changing interests and evolving field of medicine, students cannot be

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expected to stay with one mentor across the years. The needs are different at various stages, for example, a mentor in early years can help in identifying the learning strategies, time management, and integration, while the mentor in clinical years may have a different role. PM&DC has laid down some principles, but it requires more work and input from all stakeholders. A coordinated and structured programme will ensure the success, well-being and professional identity formation of medical students and institutions have an ethical obligation to provide that support. There is also paucity of research in this area in Pakistan and educators may provide evidence-based information as to what exactly works within our setting.

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ORIGINAL ARTICLE

Oral Clefts and Consanguinity: A Report from Karachi, Pakistan

Summera Kanwal[1], Tahera Ayub[2], Fatima Ashraf Ganatra[3], Muhammad Ashraf Ganatra[4], Zara Zahid[5], and Dania Hamid[6]

ABSTRACT

Objective: To evaluate the occurrence of the risk of offspring having cleft lip and palate in consanguineous marriages

Methodology: This is a cross sectional study which was done for a period of six months from March 2022 to November 2022 at Al-Mustafa Hospital, Karachi. All patients without any syndromes and medically fit were included and respondents were interviewed using a questionnaire.

Results: A total of 278 patients with 129 (46.4%) females and 149 (53.6%) males were included. Fifty one (18.3%) patients had isolated cleft lip, 162 (58.3%) patients had complete cleft, and 65 (23.4%) patients had isolated cleft palate. Total 158 (56.8%) parents of children had consanguineous marriages, of which 83 (29.9%) were married to paternal side and 76 (27.3%) were married to the maternal side. History of parental cleft was seen in 9 (3.2%) patients. Among risk factors, 8 (2.9%) mothers had radiation exposure during pregnancy and 8 (2.9%) and 2 (0.7%) had habits of huqqa and smoking respectively. Seven (2.5 %) patients were twins and one was born with cleft either isolated or complete and other without any anomaly.

Conclusion: Nearly half of the study population in this study had consanguineous marriages. Strategies should be developed to educate people about association of orofacial clefts with consanguinity along with risk factors.

Key Words: Consanguinity, cleft lip, cleft palate, non-syndromic

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INTRODUCTION

Non-syndromic cleft lip and palate (NSCLP) are among the commonest craniofacial anomalies, with varying incidence reported across the world. Published reports suggest an incidence rate ranging from 1 in every 500 to 2,000 live births[1].

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Pathologically, cleft lip and palate result from the failed fusion of nasal and maxillary prominences during the first 6-8 weeks. Although the reasons for this failed fusion remain unknown, several genetic and environmental factors have been associated with the pathogenesis of cleft lip and palate[2]. Environmental factors include advanced maternal age, as well as the use of teratogenic drugs (eg. phenytoin, retinoid, diazepam, and steroids). Other factors include alcohol consumption and smoking during pregnancy[3]. Genetic factors linked to NSCLP include aberrations in various genes, including TGF-β-3 (Transforming Growth Factor beta 3), MSX-1 (Msh home box 1), IRF-6 (Interferon regulatory factor 6), FGF (Fibroblast growth factor), and PVRL-1 (Poliovirus receptor related-1)[4,5].

A significant risk factor for recessive diseases is consanguinity, with higher frequency of congenital conditions observed in children born to first degree consanguineous parents compared to those of non-consanguineous parents[6,7]. Similarly, studies from some countries have observed an association between consanguinity and cleft lip and palate[8].

The primary objective of our study was to explore the history of first-degree consanguinity in a cohort of

children with non-syndromic cleft lip and palate presenting at an established cleft surgery center in Karachi, Pakistan. Furthermore, we describe the patterns of NSCLP, gender distribution, and familial prevalence of CLP observed among this cohort.

METHODOLOGY

We conducted a descriptive cross sectional study from March 2022 through November 2022 at the Cleft Center at Al-Mustafa Hospital in Karachi, Pakistan after approval from IRB (ref: AWS/2023/210). All the patients presenting with cleft lip and palate were included in the study. Patients with self-reported syndromes, or physical exam findings consistent with clearly defined syndromes were excluded. A detailed questionnaire was developed as our data collection tool, and included variables such as age, gender, presence or absence of consanguinity, type of NSCLP, paternal and maternal age at time of birth, history of maternal tobacco consumption, and radiation exposure during pregnancy.

For the purpose of our study, history of consanguinity was considered positive only if the parents were first degree cousins. Due to the low literacy rate in Pakistan, and the medical knowledge necessary to identify type of NSCLP, we opted against a self-administered questionnaire, and a physician in the outpatient clinic setting administered it.

The non-probability convenience sampling method was adopted in the study. Data collected via the questionnaires was archived and analyzed for descriptive statistics using Statistical Package for Social Sciences version 20. Mean was calculated for quantitative variable e.g. age while frequency and percentages was calculated for qualitative variables e.g. gender, type of cleft, paternal / maternal consanguinity and risk factors associated with cleft. The association of cleft lip and palate with consanguineous marriage was calculated with application of Chi-Square Test. P-value of <0.05 was considered significant.

A total of 278 patients who fulfilled the inclusion criteria were included in the study. Mean age of patients was 9.74 months ± SD 7.7, minimum of 3 months and maximum of 36 months (Table 1).

Consanguinity was reported in (n=158, 56.8%) with a slight predominance of paternal consanguinity (n=83, 52.5%) vs maternal consanguinity (n=76, 47.5%). The association of consanguinity and oro-facial cleft was assessed using Chi-Square test which showed a significant association of cousin marriage and presence of cleft lip and palate, p-value <0.05 (Table 2).

Table 1: Gender and Type of Cleft Distribution

		Frequency	Percentage
Gender	Male	149	53.6
	Female	129	46.4
Type of Cleft	Cleft lip	51	18.3
	Cleft palate	65	23.4
	Complete cleft	162	58.3

Table 2: Association of Consanguinity and Cleft

		Type of Cleft				
		Cleft Lip	**Cleft Palate**	**Complete Cleft**	**Total**	**p-Value**
First Degree Consanguinity	**Present**	45 (28.4%)	28 (17.7%)	85 (53.7%)	158 (100%)	0.012
	Absent	6 (5%)	37 (30.8%)	77 (64.1%)	120 (100%)	
Total		51 (18.3%)	65 (23.4%)	162 (58.3%)	278 (100%)	

We found a low prevalence of cleft lip and palate among parents of patients with NSCLP (n=9, 3.2%), but overall family history of cleft lip and palate was high (n=41, 14.7%) after including other relatives such as siblings, aunts, uncles, cousins, etc. A small number of patients with NSCLP reported history of maternal radiation exposure (n=8, 2.9%) and tobacco consumption during pregnancy (n=10, 3.6%) (Table 3).

Table 3: Characteristics of Patient Cohort (n=278)

Other Factors	Frequency	Percentage
Parental Consanguinity		
Present	158	56.8
Absent	120	43.2
Type of Consanguinity		
Maternal	76	27.3
Paternal	83	29.9
Parental History of Facial Clefts		
Present	9	3.2
Absent	269	96.8
Family Members with Facial Clefts		
Present	41	14.7
Absent	237	85.3
Risk Factors of Facial clefts		
Radiation Exposure	8	2.9
Tobacco Exposure	10	3.6

We also identified seven twin siblings in our cohort (2.5%). An interesting finding in all the twin pairs was that only one child out of the twins was born with cleft lip or palate.

DISCUSSION

Orofacial clefts are among the commonest congenital defects in the world, with incidence rates as high as 1 in 2000 live born children[9]. Moreover, in developing countries such as Pakistan, the incidence is significantly higher, reaching up to 1 in 500 live born children[10]. There are significant resources in the developed world to promptly diagnose and manage children with the congenital defect of cleft lip and palate, and multidisciplinary team approach is adopted for surgical repair, speech, hearing, and nutritional optimization. Unfortunately, similar resources are usually lacking in most developing countries, and identification and prevention of risk factors associated with orofacial clefts offer a more pragmatic strategy in these settings.

Previously published literature from Karachi, Pakistan has found the prevalence of first-degree consanguineous marriages to be around 25%[11]. However, our cohort of children with NSCLP had a significantly higher background of first-degree parental consanguinity at approximately 57%. Although we did not design our study as a case-control, which is a limitation of our study, but comparing our data with published data on consanguinity from the same geographical area in Pakistan[11] suggests that first-degree consanguineous marriages are associated with a higher risk of NSCLP.

Various studies across the world have demonstrated a strong association between NSCLP and consanguinity. Interestingly, a study from Saudi Arabia in 2012, found the background of consanguinity among patients with NSCLP to be equal to ours: 56.8%[12]. However, their estimate included parents with first and second-degree consanguinity, whereas we only assessed for first-degree consanguinity. This suggests that the prevalence of parental consanguinity in our cohort might have been higher if we had included second-degree consanguinity.

The only population-based epidemiological study on CLP in Pakistan was conducted in the Northern Areas of Pakistan, and utilized a provincial birth registry from documented health facilities[10]. Compared to our data, this large-scale study found a relatively lower prevalence of first or second-degree parental consanguinity among children with CLP, approximately 32%. Our study from Karachi, Pakistan found the prevalence to be as high as 57%, whereas another hospital-based study conducted in Lahore, Pakistan found 63% of children with CLP had parents with consanguineous marriage[13]. We feel that the lower prevalence recorded by Elahi et al is likely due to limitations of birth registries in Pakistan, as up to 74% of births may take place outside of health facilities, and are therefore not documented in birth registries[14].

Consistent with previous studies, our study found males were predominantly afflicted with complete cleft of lip and palate and also isolated cleft lip, while females were predominantly afflicted with isolated cleft of palate[9]. We also identified that 2.5% of our patients were twins, and this is the first study, to the best of our knowledge, from Pakistan to identify twinning among patients with NSCLP.

Tobacco consumption among females in Pakistan is relatively high, and most pregnancies are unplanned due to the low rates of family planning[15]. However, when evaluating risk factors for NSCLP, we found only 2.9% of patients had a history of maternal radiation exposure during pregnancy, and only 3.6% had a history of maternal tobacco use during pregnancy. Tobacco use among women is associated with significant social stigma in Pakistan, and the low rates in our study are likely a limitation of the self-reported nature of our project, thereby leading to under-reporting[15].

In summary, we demonstrate a high prevalence of parental consanguinity leading to NSCLP in Pakistan. Although several national and international organizations are devoting significant resources to provide medical and surgical services for children afflicted with NSCLP, there is virtually no effort to prevent NSCLP.

In our opinion, a dire need for educational efforts exists at the population level to highlight the negative outcomes associated with consanguineous marriages. We propose that the government implement a mandatory premarital screening programme to detect carrier couples with recessive diseases, and counsel all couples against consanguineous marriages. Although there is mixed data regarding the utility of these measures in conservative societies where consanguineous marriages are a deep rooted tradition, similar programmes have been implemented successfully in many Arab countries that are identical to Pakistan from a cultural and religious standpoint[16,17]. We feel these measures would be a reasonable first step to reduce the burden of NSCLP in Pakistan and would also produce the added benefit of decreasing other recessive disorders.

CONCLUSION

From this study, it can be concluded that consanguineous marriages can be considered as one of the risk factors that can result in the occurrence of non-syndromic congenital cleft lip and palate. This study also enables us to design strategies for counselling regarding the most common craniofacial anomaly.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contributions: SK is the principal author who conceived the idea and penned the manuscript; TA provided valuable assistance in drafting the manuscript; FAG contributed to data collection efforts; MAG, ZZ, and DH conducted thorough final reviews of the manuscript and provided critical feedback on the final version.

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ORIGINAL ARTICLE

Ethnicity Based Anatomical Variations in Malleus on Computerized Tomographic Scan

Mariya Azam Khattak[1], Ambreen Usmani[2], Ayesha Mehwish[3], Rida Rubab Ahmad[4], Maryam Faiz Qureshi[5] and Noman Ullah Wazir[1]

ABSTRACT

Objective: To determine the anatomical variations in malleus among different ethnic groups
Methodology: An observational investigation was conducted within the Otorhinolaryngology and Radiology department of a public hospital in Karachi, (PNS) Shifa. In this study, 100 participants were included from January-July 2021 with ages ranging from 10-51 years. After obtaining consent and complete history from each participant, a detailed examination of ear was done. Subjects were arranged for petrous temporal bone (PTB) computed tomographic scans based on the inclusion criteria of no deformity concerning ear ossicles. The parameters considered for potential anatomical differences were width of malleus head, manubrium length, and complete malleus length.
Results: In 100 subjects, the mean ±S.D (mm) for width of malleus head was 3.02±0.31, for manubrium length 4.39±0.46 and complete malleus length was found to be 7.59±0.57. The value for length of manubrium among ethnic groups was found to be significant (p= 0.05).
Conclusion: Identification of these variations in such small bones is difficult but it is not impossible to comprehend, considering the availability of advance technologies. As, morphological variants can disrupt the prosthesis procedures, therefore, CT-PTB are suggested to acknowledge these modifications in size and shape. This study showed variations among groups.

Key Words: Ear ossicles, ethnicity, malleus, morphological variations, petrous temporal bone

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INTRODUCTION

Hearing is an essential sense because it influences the mental, physical, and social well-being of an individual. It is one of the dominant senses and similar to vision, it is also used for cautioning and communication[1]. Like a headset, the ear is animated by vibration. In the earpiece, the vibration changes into an electrical signal and then into an anxious motion in the ear in the form of sound which is then handled by the focal audible conduits of the mind, in which ear ossicles play a major role. This kind of mechanism is very complex[2].

The ear comprises outer, middle, and inner sections. Within the air filled space of the middle ear, located in petrous temporal bone, the auditory ossicles can be appreciated, named malleus, incus, and stapes. They create a chain that delivers vibration of sound from middle to inner section cochlea, facilitating auditory reception[3]. Malleus bone sits in the middle ear between incus and tympanic membrane, which has two processes (anterior and lateral), a head, neck, and handle (manubrium). Incus also has two processes (short and long) and a body[4]. A synovial type of joint is present between the body of incus and malleus articulating surface and an 'incudostapedial joint'is present between stapes head and incus lenticular process[5]. The tiniest bones in human skeleton are the ossicles found in the middle section. Malleus being the largest amongst three, measures 8–9 mm in average length[6].

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Some scientists think that these ossicles reach a definite morphological form during the fetal period in human beings, and therefore, there are no noticeable variations, however, other studies contradict this idea[7]. These two different remarkable assertions motivated us to attempt to discover the variations found in the malleus of absolute adult size in different ethnic groups. One article reports that the ossification of malleus completes in intrauterine life (IUL)[8]. Another study also mentioned that how neonatal-ear dynamics changes with chronological age may be important in furthering hearing research and development of hearing devices and diagnostic tools suitable for neonates[9]. A study found that growth of ear ossicles in humans continues beyond the prenatal stage. The morphological parameters in the fetal periods vary noticeably in the post-natal life and that could be due to the bone remodeling phenomenon[10].

These changes need to be added to anatomical information for future procedures for ear ossicles which must be planned carefully to avoid complications in prosthesis. Apart from cadaveric studies, no evident data was available which could help otorhinolaryngologists in appreciating these variations for making immediate decisions when planning any surgical procedure like prosthesis relating to this structure to maintain its functional reliability. Complete comprehension of the anatomy of a subject is crucial for gaining a deeper insight into how it functions and interacts within its context[11].

Many studies mention anatomical variations in these structures but the information is insufficient to record these changes as these studies are mostly cadaveric. Due to the minute structure of these ossicles, they are extracted from cadavers and stored once in a while[12]. The varieties among people are fascinating organically, and are significant for procedures like ossiculoplasty and portable hearing assistants inserts after the birth[13].

Many studies have been carried out worldwide on morphological variations of ear ossicles on cadavers but in Pakistan up to this point, no research paper in literature has explored this specific aspect and its significance in the field of surgery. Given the variations seen in different ethnic groups globally, it was crucial to undertake such a study in Pakistan. This formed an underlying rationale to conduct this study.

The objective of this study was to determine anatomical variations in malleus among different ethnic groups and see which morphological feature had significant variation in malleus bone.

METHODOLOGY

An observational investigation was conducted within Otorhinolaryngology and Radiology department of a public hospital in Karachi (PNS) Shifa, between Jan and July 2021. Before starting this research, ethical approval was secured from the Ethical Review Committee of Bahria University of Health Sciences (ERC 62/2021). A software was used (open epi version 3 calculator) for sample size calculation indicating 100 participants. The study lasted for a total of six months, with each participant spending two hours for their individual study period. The quota sampling technique was used for 20 participants of each ethnicity. Participants from different ethnic groups, fulfilling the inclusion criteria with undamaged ear ossicles, were recruited. The participants had one ear with damaged ossicles (excluded from the study) and the other ear with undamaged ossicles, to fulfil the ethical criteria for avoiding unnecessary scans.

After obtaining written informed consent, participants from otorhinolaryngology were referred to the Radiology department. A Toshiba Prime CT scanner (Aquilion-160 slice) was used to perform a CT scan of petrous temporal bone. The individual was positioned fully supine and motionless on the 47 cm wide couch, following a comprehensive ear examination of each participant[14]. A software (Vitrea1.5.2265.3045) was used for measuring the anatomical variations in three distinct planes (coronal, sagittal, and axial). The malleus head width, manubrium length, and complete malleus length were the parameters taken into consideration. For accuracy, measurements were taken by making the landmarks. For malleus width, reference points were made on its upper part (Mup), a center point on its head (Mhead), and (Mneck) on its neck. For manubrium length, the points were marked from its neck (Mneck) till handle (Mhandle), and for complete length of malleus, a point on its upper point (Mup) and on its handle (Mhandle) were made[15].

Data analysis was conducted using SPSS (version 23.0). Post Hoc Test was done with Anova for comparison of ethnic groups. Continuous data was written in mean ± SD. The results with p-value = 0.05 were considered statistically significant.

RESULTS

The study involved 100 participants who were evenly divided into subgroups of 20 each, irrespective of gender. The ethnic groups included Sindhi, Punjabi, Balochi, Pushto, and Urdu speaking people. The parameters included were malleus head width, its

Malleus on HRCT in Three Planes

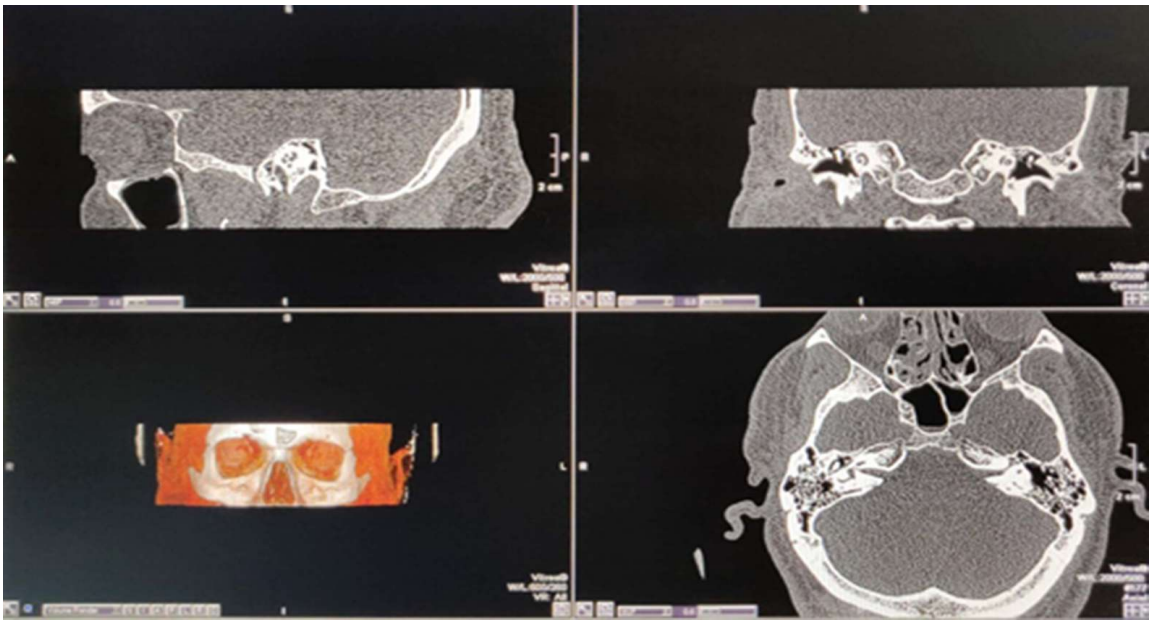

Table 1: Mean and Standard Deviation Observed in Ethnic Groups

		N	Mean± SD (mm)	Confidence Interval 95% for Mean		Lowest	Highest
				Lower Limit	Upper Limit		
Malleus (Width of Head)	Sindhi	20	2.97±0.25	2.85	3.08	2.4	3.4
	Punjabi	20	3.03±0.37	2.86	3.21	2.3	3.4
	Balochi	20	3.03±0.31	2.89	3.17	2.5	3.5
	Pushto	20	3.17±0.28	3.04	3.30	2.7	3.6
	Urdu	20	2.89±0.27	2.76	3.01	2.5	3.3
	Total	100	3.02±0.31	2.96	3.08	2.3	3.6
Length of Manubrium	Sindhi	20	4.43±0.34	4.27	4.59	3.7	5.0
	Punjabi	20	4.12±0.31	3.98	4.27	3.5	4.6
	Balochi	20	4.52±0.59	4.24	4.80	3.5	5.5
	Pushto	20	4.43±0.35	4.27	4.59	3.9	5.1
	Urdu	20	4.45±0.58	4.18	4.72	3.8	5.6
	Total	100	4.39±0.46	4.30	4.48	3.5	5.6
Total Length of Malleus	Sindhi	20	7.55±0.40	7.36	7.73	6.7	7.9
	Punjabi	20	7.39±0.54	7.14	7.64	6.3	8.4
	Balochi	20	7.67±0.61	7.38	7.96	6.4	8.7
	Pushto	20	7.71±0.53	7.46	7.96	6.8	8.9
	Urdu	20	7.61±0.74	7.27	7.96	6.7	8.8
	Total	100	7.59±0.57	7.47	7.70	6.3	8.9

complete length and manubrium length. The mean and standard deviation of each parameter were noted for each ethnicity that showed the mean total length of malleus to be 7.59±0.57 mm, length of manubrium to be 4.39±0.46 mm, and width of malleus head was noted to be 3.02±0.3 mm (Table: 1). These were then compared between sub-groups and a test was applied which showed that the length of manubrium had a significant value (p= 0.05) shown in (Table: 2).

Table 2: Significant Morphological Reading in Malleus

		Mean Square	F	*p*- value
Malleus (Width of Head)	Between Groups	0.20	2.35	0.06
	Within Groups	0.09		
Length of Manubrium	Between Groups	0.48	2.37	0.05*
	Within Groups	0.20		
Total Length of Malleus	Between Groups	0.31	0.95	0.44
	Within Groups	0.33		

*significant at 0.05

DISCUSSION

Research from the literature indicates that the morphometric data acquired can have valuable applications in reconstructive procedures. It is recommended to perform preoperative radiological assessments for these small bones. It is equally important for both medical research and training to comprehend the typical and uncontrolled inconsistency of anatomical structures in humans (e.g. reconstruction of the middle ear ossicular chain, ossiculoplasty); and anthropological research focused on assessing variations at the population level, like examining diversity[16]. The gold standard for identification of middle ear diseases that cause ossicles erosion and morphological modifications are high-resolution CT scans that are fastest and easiest means of investigation to do so[17].

A comparison of these discrepancies in different populations is a good prospective to know how these ossicles vary among different groups of people around the world. Any environmental factors are insignificant to cause any parametric changes in shape and size of these ossicles postnatally, whereas during skull development, they go through a medio-lateral shift[18]. An analysis was conducted on the morphological characteristics of the ear ossicles of both sides. It summarized that no significant variations were seen in the sides of the ear[19].

A study also revealed that malleus shape had bilateral symmetry concluding negligible dimensional variations between both sides of the ear[20]. In accordance to this, the current study included ear ossicles irrespective of side of the ear. Studies done on different populations showed variability in malleus characteristics. A study on Central Europe, Poland population recovered human ear ossicles, analyzed malleus and documented that the mean total length was found to be significant as compared to this current study that showed variation in length of manubrium to be prominent[21]. In both sides, height range of malleus bone was measured. Statistically, the left malleus bone was longer and heavier than its right counterpart showing the difference in malleus morphology between sides of the ear[22]. For prosthesis fitting, significant variation in all dimensions of each ossicle between individuals were noted to optimize prosthesis fit. From published data, an accurate 3-D model of these ossicles could be created, which can then be further modified for each patient's individual anatomy[23].

Ossicles of ancestors were matched with modern humans, using different techniques, and concluded that size changes in brain with time, resulted in alterations in middle ear cavity, subsequently, modifying the shape and morphology of these bones. However, it had a negligible effect on hearing outcomes, resulting in variations in different ethnic groups as compared to the current study[24]. Mostly variations were observed in its distal portion (manubrium free end) and in lateral and anterior processes. Variations in morphology were observed mainly in free ends of manubrium which curved anteriorly in 29 (55.8%) while straight free ends of manubrium were observed in 23 (44.2%) malleus. Among some mallei, the lateral processes exhibited notable variation, with certain instances having elongated and sharp features, while others appeared blunter. Additionally, the length of the anterior process displayed variability, including one case where the process was extremely tiny and rounded, nearly absent[25].

The current study showed variations in the length of manubrium, due to different shaped ends of manubrium (straight/curved). It was therefore similar to studies in literature that focused on different regions showing dimensional changes. In addition, the current study also showed variations among different ethnic groups in a country as mentioned in Table No. 1.

CONCLUSION

In this study, variations in the morphology of ear ossicles with respect to their sizes were compared in different ethnic groups. The malleus manubrium exhibited the most frequent anatomical variation with significant value, which could be due to its shape (curved/straight manubrium) in different individuals related to bone remodeling phenomena with time. The mean width of malleus head and its complete length was found to be greater in Pushto ethnic group and for the length of manubrium, it was found to be greater in Balochi group as compared to other groups. A radiological technique was first time used to measure and assess these variations.

Limitation of study: Multicenter studies must be done in order to increase the scope of investigation. This research was a part of thesis; therefore, the study was single centered because of limited time.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contributions: MAK worked on methodology and prepared a manuscript draft; AU supervised the research; AM conceptualized and guided; RRA worked on data collection, review and editing; MFQ critically reviewed the final draft; NUW assisted in study and proof reading.

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ORIGINAL ARTICLE

Periodontal Health and its Impact on Oral Health-Related Quality of Life Among Diabetes Mellitus Patients

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ABSTRACT

Objectives: This study aimed to investigate the relationship between periodontal health and oral health-related quality of life (OHRQoL) in people with diabetes mellitus. The secondary objective was to compare the OHRQoL between diabetic and non-diabetic individuals.

Methodology: This study was performed at the Department of Operative Dentistry, Pakistan Institute of Medical Sciences (PIMS), Islamabad from April 2023 to June 2023. The study comprised 80 participants: 40 individuals with diabetes in case group and 40 individuals without the condition taken as control. Clinical periodontal disease examination was performed at six sites per tooth, to determine clinical attachment loss. After the examination, the patient was asked to complete self-administered questionnaires covering the OHIP-14 domains. To compare the clinical attachment loss between the two cohorts, a chi-square test was employed. An independent t-test was used to evaluate disparities in OHIP-14 domain scores between the diabetes and non-diabetes groups.

Results: There were 80 patients, with a mean age of 39.07± 5.96. Among those, 40 had diabetes and the remaining 40 did not. The majority of participants were women. In contrast to individuals without diabetes, a significantly higher proportion of those with diabetes exhibited a CAL (Clinical Attachment Loss) of =3mm. Significant associations between the two groups were observed in OHIP-14 domains such as Impaired functionality, physical impairment, psychological disability, and social disability, while the remaining domains showed no significant associations (p>0.001).

Conclusion: This research provided valuable insights into the intricate correlation among diabetes mellitus, periodontal health, and oral health-related quality of life, underscoring the multifaceted nature of their interrelation.

Key Words: Clinical attachment, diabetes mellitus, OHIP -14 domain, OHRQoL, periodontal disease

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INTRODUCTION

Periodontitis is a prevalent long-term inflammatory condition that influences the tooth's supporting structures. The subgingival bacterial biofilm initiates periodontal inflammatory conditions, however, tissue damage results primarily from the host's immune-inflammatory response to the microorganisms. Certain systemic conditions, such as Diabetes Mellitus (DM), have been connected to an increased risk of developing periodontitis. It is associated with a two-to three-fold elevated risk, particularly in cases where it is improperly managed[1]. Diabetes mellitus represents a chronic metabolic disorder with hyperglycemia, that results from a lack of insulin production or a resistance to insulin, or both[2,3]. Extensive research has been carried out on the correlation between diabetes and periodontitis; in individuals with diabetes as well as, surprisingly, in those without the disease, elevated levels of glycated hemoglobin (HbA1c) were linked to increased periodontal inflammation. In addition, severe periodontal breakdown was linked to metabolic syndrome and increased oxidative stress in patients with type 2 diabetes[4].

Diabetes mellitus not only affects the periodontal tissues but also increases the risk of several oral and dental diseases, such as tooth decay, gingival inflammation, decreased salivary flow, candida infection, taste

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disturbance, and delayed wound healing[5]. Oral complications/ manifestations of diabetes may be associated with various mechanisms, such as compromised neutrophil function, elevated collagenase action, decreased production of collagen, neuropathy, and microangiopathy[6].

Diabetes and periodontitis have complex relationships because of their multifactorial etiology and chronic inflammatory nature[7]. Research findings suggest that both diabetes and periodontitis exert an adverse influence on certain aspects of daily life and health-related quality of life[8]. Furthermore, certain original studies identified diabetes as a factor that may affect the quality of life related to oral health (OHRQoL)[9-11].

Oral health-related quality of life (OHRQoL) denotes an individual's assessment of the factors affecting their general health and overall quality of life. It encompasses components like discomfort and pain, in addition to elements of function like speech and mastication, psychological elements like appearance and self-esteem, and social elements like interpersonal interaction[12]. The most frequently used tool for measuring oral health related quality of life is OHRQoL. It is a questionnaire that assesses seven different domains of quality of life including: handicap, limitation in social activities, impairment in physical function, discomfort of psychological nature, physical pain, and functional limitations[13].

At both the patient and population levels, OHRQoL should be taken into account when making decisions about diagnosis, options for treatment, and treatment results. It should also be taken into account when allocating resources and keeping an eye on oral health trends and policies[14]. In light of the rising importance of OHRQoL and the ever-increasing burden of diabetes mellitus, the objective of this study was to evaluate and contrast the oral health-related quality of life in individuals with and without diabetes. Furthermore, it aimed to investigate how periodontal health influences the oral health-related quality of life specifically among diabetic patients.

METHODOLOGY

After taking permission from the ethical board of the School of dentistry SZABMU (SOD/ERB/2023/36), this case control study was done at the Pakistan Institute of Medical Sciences' Operative Dentistry department from April 2023 to June 2023. The study was registered at Clinicaltrials.gov under the number (NCT06125561). The sample size was 80, calculated on the WHO calculator, and divided into two equal groups of diabetic and non-diabetic subjects, using a computer-generated randomization method. A convenient sampling technique was used to achieve the required sample. Diabetic patients and healthy participants with age range of 18 to 60 years and willingness to participate were included in case and control group respectively. Exclusion criteria for each group was:

1. Patients suffering from severe systemic illnesses like Papillon-Lefèvre syndrome, severe neutropenia, leukocyte adhesion deficiency syndromes, and Down's syndrome that can impact periodontal health

2. Women who were pregnant

3. Patients who smoked

4. Patients suffering from severe cognitive impairment

5. Patients with mental health conditions such as eating disorders,schizophrenia, depression, and anxiety disorders

A single examiner conducted the clinical examinations after receiving both verbal and written consent from each participant. Using a manual periodontal probe equipped with William's markings and a 0.45mm tip diameter, a comprehensive clinical periodontal disease examination was carried out at six sites per tooth. Importantly, the examiner remained blind to the diabetic status of the participants. The examination encompassed assessments of pocket depth and gingival recession, which were added up to get the CAL.

After completion of clinical examination, patients were asked to answer a brief questionnaire about their demographic data which included age and gender. The next task assigned to them was to finish the OHIP-14, a self-administered questionnaire consisting of 14 items that evaluate seven domains: physical pain, psychological discomfort, disability, social disability, functional limitation, and handicap.

A five-point Likert scale was used to record responses to the items (0, never; 1, hardly ever; 2, occasionally; 3, fairly often; 4, very often). Summing up all of the responses yields the OHIP-14's overall score, which goes from 0 to 56 points.

The study utilized SPSS software version 23 for conducting data analysis. Descriptive statistics, which included mean and standard deviation calculations, were performed for demographic variables like gender. To compare clinical attachment loss between the two groups, a chi-square test was employed. Additionally, an independent t-test was used to evaluate differences in OHIP-14 domain scores between the diabetic and non-diabetic groups.

RESULTS

The study had 40 diabetic patients and 40 non-diabetic patients divided into case and control groups. The mean age of study participants was 39.07 ±5.96. The diabetic group had 65% female and 35 % male participants (Figure 1).

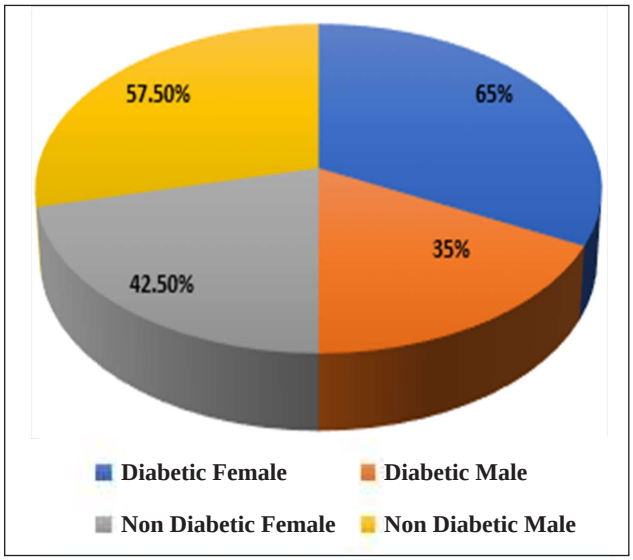

Figure 1: Distribution of Gender in Study

The other important factor is clinical attachment loss. A significantly greater proportion of individuals diagnosed with diabetes demonstrated a CAL (Clinical Attachment Loss) of =3mm compared to those without diabetes (Figure 2).

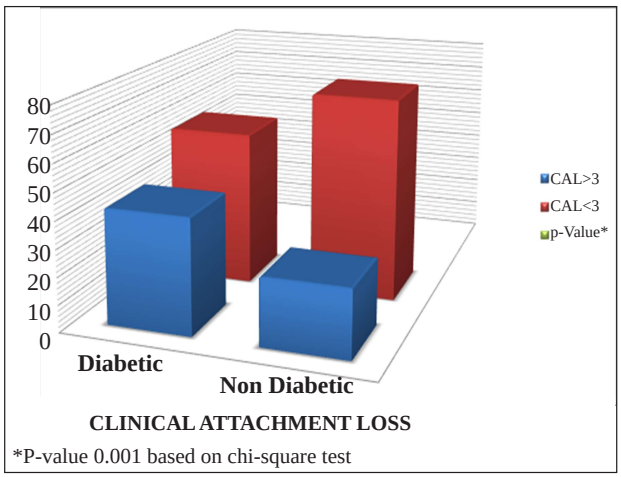

Figure 2: Clinical Attachment Loss in Both Groups

Table 1 shows a notable correlation between the groups in terms of OHIP-14 domains, encompassing functional limitation, psychological discomfort, psychological disability, and social disability (P value <0.001). In both groups, no significant correlation was found between physical handicap, physical disability, or physical pain.

DISCUSSION

In the present case-control study, our objective was to explore the association between periodontal health and the oral health-related quality of life (OHRQoL) in individuals diagnosed with diabetes mellitus. A robust periodontium is pivotal for efficient masticatory function and oro-motor competence, ensuring effective food processing and speech articulation[15,16]. Our findings shed light on the intricate connection between periodontal health and the overall well-being of individuals with diabetes. The majority of study participants were female in both diabetic and non-diabetic groups with the mean age of 39.07 ± 5.96, which is different from the previous study in which the mean age was 56 years[17].

Research outcomes suggest an elevated prevalence and severity of periodontal disease in individuals with diabetes compared to those without the condition. The potential mechanistic connections between diabetes and periodontitis are established through interactions involving advanced glycation end products and their receptors, along with pathways mediated by oxidative stress[18]. To determine the severity of periodontal diseases and evaluating the periodontal health, clinical attachment loss is used as important indicator[19]. Clinical Attachment Loss (CAL) staging is commonly used in periodontics to assess the severity of periodontal diseases. CAL was categorized into three levels: Slight attachment loss was defined as 1–2 mm, moderate attachment loss as 3–4 mm, and severe attachment loss as 5 mm or more. For the study's objectives, CAL was categorized as < 3 mm, signifying slight attachment loss, and = 3 mm, indicating moderate or severe attachment loss. In our study, there was a significantly higher number of diabetic participants (42.5%) with moderate to severe attachment loss, compared to non-diabetic group (25%) ; p value (0.001). This finding is consistent with the results from a study by Nadia Khalifa et al. in which diabetic group has higher CAL (23%) than non-diabetic patients (10%)[20]. These statistics further support the notion that diabetes may elevate the likelihood of developing periodontitis.

Various domains of OHIP-14 were evaluated in study and determined the OHRQoL. Our results revealed a significant association between poor periodontal health and diminished oral health-related quality of life in few domains of OHIP-14. Mean score of both groups had significant association in Functional Limitations, Psychological Discomfort and Psychological Disability. These findings contrast with the results reported in earlier studies of Shahla Kakoei et al and Yuan-Jung Hsu et al[21,22]. However, most of the studies support

Table 1: Relationship Between Diabetes Status and OHIP-14 Domains

Domain	Diabetic Mean (SD)	Non-Diabetic Mean (SD)	p-value*
Impaired functionality (difficulty articulating words/ intensified deterioration in taste)	3.2(0.84)	1.7(1.06)	0.01
Physical Impairment (oral pain or discomfort during meals)	3.3(0.86)	2.1(0.98)	0.46
Emotional Discomfort (sense of tension/ self-consciousness)	3.6(0.80)	2.6(1.2)	0.95
Psychological Discomfort (feeling tense/self conscious)	2.05(1.48)	1.9(1.14)	0.01
Emotional Impairment (difficulty in relaxing/experiencing embarrassment)	1.47(1.35)	1.7(1.06)	0.01
Social Impairment (irritability/challenges in performing regular tasks)	1.45(1.44)	1.77(1.02)	0.005
Handicap (functional Impairment/life less gratifying/ difficulty in functioning)	1.6(0.9)	1.45(1.03)	0.91

** Denotes P-value 0.001, based on chi-square test*

our results, indicating that diabetic group has poorer quality of life than non diabetic group[23]. Regarding other parameters of OHIP, Physical Disability interrupting normal meals and eating had no significant association in diabetic and non-diabetic patients. The findings were very close to another study of Rokhsareh Sadeghi et al that concluded insignificant association of diabetes on OHRQoL parameters[24].

The other important domain of OHIP-14 which influences quality of life is Physical Pain including oral pain and discomfort while eating. More patients in diabetic group were affected by pain during eating; however, similar to other studies, no significant association between diabetic and non-diabetic individuals was found[25]. Periodontal diseases can also contribute to psychological discomfort and disability, impacting individuals emotionally and psychologically. Individuals may become self-conscious about the shape of their teeth and surrounding tissue, leading to feelings of embarrassment and tension, especially in social situations. The current study showed a significant association of diabetes with these parameters of OHIP-14, but a previous study has found little impact of diabetes on psychological discomfort and disability[26].

Periodontal disease and diabetes can have implications for social disability and feelings of handicap, impacting individuals emotionally and functionally. Chronic pain, discomfort, and inflammation associated with periodontal disease can contribute to irritability. Individuals may find it challenging to cope with persistent oral health issues, leading to increased emotional stress. However, our study did not find strong association of variable between diabetic and non-diabetic patients. Elevated blood sugar levels create an environment conducive to bacterial growth and inflammation, exacerbating periodontal disease. Through effective glycemic control, patients can attenuate inflammation and optimize the health of periodontal tissues.

The study is limited by its sample size and the characteristics of the study participants may not comprehensively capture the diversity present in the broader population of individuals with diabetes mellitus. Additionally, the study might have overlooked all possible confounding factors that could impact the relationship between periodontal health and the oral health-related quality of life in patients diagnosed with diabetes mellitus. Factors like socioeconomic status, comorbidities, and treatment adherence could confound the results.

CONCLUSION

In conclusion, our research, exploring the intricate correlation between periodontal health and the oral health-related quality of life among individuals with diabetes mellitus, contributes meaningful insights into the multifaceted dynamics of these interconnected factors. The association between good glycemic control and oral hygiene underscores the critical interplay between diabetes management and oral health. Effective glycemic control is an integral component of diabetes management, for patients and healthcare providers. It can proactively address the multifaceted challenges posed by diabetes-related oral health complications. The results highlight the substantial influence of periodontal health on the general well-being of individuals with diabetes. The recognition of periodontal health as a vital component in enhancing the overall quality of life for diabetes mellitus patients underscores the necessity for integrated and interdisciplinary healthcare approaches.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contributions: SAK conceptualized the study, provided supervision throughout the research process, and contributed to the review of the manuscript; NS was primarily responsible for drafting the manuscript, developing the methodology, conducting literature reviews, and overseeing data collection; AW contributed to drafting the manuscript, conducted data collection and analysis, and participated in the editing process; M focused on editing and reviewing the manuscript to ensure clarity, coherence, and accuracy in the final version.

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ORIGINAL ARTICLE

Triple-Negative Breast Cancer (TNBC): Uncommon in Pakistan?

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ABSTRACT

Objectives: To evaluate the incidence of triple-negative breast cancer (TNBC) and elucidate the factors associated with triple-negative breast carcinoma.
Methodology: It is a retrospective study, that includes breast cancer patients presenting to the outpatient department (OPD) for three years from January 2020 to January 2023.
Results: A total of 946 biopsy-proven breast carcinoma cases were included, out of which, 220 (23.2%) were identified as triple-negative breast cancer. The predominant age range among TNBC patients was 40 to 60 years at the time of diagnosis. A total of 58.2% were postmenopausal, while 41.8% were pre-menopausal. Histopathologically, TNBC cases primarily exhibited ductal carcinoma (91.4%), metaplastic carcinoma (7.7%), and lobular carcinoma (0.9%). Tumor grading within the TNBC group revealed that the majority (71.4%) were poorly differentiated (Grade 3), while 26.8% were moderately differentiated (Grade 2), and 1.8% were well differentiated (Grade 1). Concerning family history, 12.7% of TNBC patients had a positive first-degree relative with breast cancer, 5.9% had a positive 2nd-degree family member, and 81.4% had no family history of breast cancer, indicating a significant association with TNBC. This study also revealed the ethnicity of TNBC patients that the majority (85%) identified as Urdu-speaking, Sindhi (6.4%), Pakhtoon (4.1%), Punjabi (3.6%), and Balochi (0.9%) backgrounds.
Conclusion: Our results showed, that TNBC primarily affected individuals aged 40 to 60 with high-grade tumors, showing associations with menopausal status and histopathology. Family history displayed no significant correlation while Urdu-speaking ethnicity was prominent. As TNBC is an aggressive neoplastic entity. By determining the incidence of TNBC, we can adapt interventions and allocate resources more effectively, thereby enhancing patient care and ultimately advancing survival rates.

Key Words: Age, grade, TNBC, postmenopausal

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INTRODUCTION

Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of three receptors commonly found in other types of breast cancer: estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). TNBC is known for its aggressive behavior, limited treatment options, and higher rates of recurrence compared to other breast cancer subtypes. Understanding the incidence of TNBC holds paramount importance in the realm of healthcare and oncology. According to GLOBACAN 2020, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer with an incidence worldwide of 2,261,419. Interestingly, Asia is top of the list with a high incidence of 1,026,171 for breast cancer[1]. Breast cancer is a momentous health concern globally, and Pakistan is no exception. In Pakistan, the situation is getting alarming due to the increase in the number of cases. Every 9th woman is prone to get breast cancer in Pakistan[2,3]. In a described data from Karachi, the incidence of breast cancer in 1998- 2002 was 69.1%, however in 2010–2012; it was 79.2%[4].

The immunohistochemistry analysis of ER, PR receptor, and HER 2 neu receptor provides significant prognostic

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and predictive knowledge[5]. Numerous characteristic distinctions manifest among the four molecular subtypes concerning their incidence, responsiveness to therapeutic interventions, disease trajectory, survival rates, and even radiological attributes. Luminal A tumors exhibit the most promising prognosis within the spectrum of breast cancer subtypes, whereas luminal B, HER2-enriched, and basal-like tumors demonstrate inferior clinical outcomes. Among all molecular subtypes of breast cancer, TNBC is considered the more aggressive phenotype[6]. In Western data, Moss JL et al. reported the incidence of TNBC at 13.7 per 100,000 women (range = 4.5–26.3), notably elevated among African American women[7]. On the other hand, our local data indicates a local incidence ranging from 8.98% to 14% of triple-negative breast cancer cases[8]. However, our frequent encounter at OPD with TNBC seems to be higher than reported. Thus, we conducted this study to determine the incidence of TNBC and its associated variables presented to our hospital.

METHODOLOGY

This was a retrospective study carried out at our oncology department in a tertiary care hospital in Karachi, from January 2020 to January 2023 after the approval of the ethical review committee (ERC). It included the breast cancer patients who presented in our department with their histopathological reports. The data was collected for estrogen receptor (ER), progesterone receptor (PR), and HER-2 neu receptor. Reports with complete records of all three receptors were considered for study. The incidence of TNBC with its associating factors including age, menopausal status, and family history, and the association of grading of tumor at the time of diagnosis, was assessed. The sample size (n) was calculated with Open Epi version 3, according to the formula: n = z2 * p * (1 - p) / e2, (with Z=1.96 for 95% CI), resulting in a total sample size of 220. The inclusion criteria were biopsy-proven triple-negative breast cancer, age above 18 years, weak ER/PR status i.e. ER/PR status less than 3 was considered negative, patients with HER 2 neu 0-2 or FISH amplification of HER 2 neu not detected along with negative ER/PR receptors. The exclusion criteria were patients who were on any hormonal therapy and the patients whose ER/PR and HER 2 neu statuses were not clear.

RESULTS

Out of 946 biopsy-confirmed cancer patients with biopsy-confirmed breast carcinoma with complete ER, PR, and HER 2 neu receptors status, two hundred and twenty patients (23.2%) were identified with TNBC. The majority age array of TNBC patients was 40 to 60 years in our study. The mean age of diagnosis of TNBC was 49.64 ± 14.46 years. Out of 220 patients, about 128 patients were postmenopausal (58.2%) and 92 patients were pre-menopausal (41.8%) with a p-value of 0.0001 (Table 2). Regarding histopathology, 201 patients (91.4%) had ductal carcinoma; however, 17 patients (7.7%) had metaplastic carcinoma and only 2 patients (0.9%) were diagnosed with TNBC lobular carcinoma (Table 3). Concerning grading of TNBC, 157 patients (71.4%) were diagnosed with poorly differentiated (Grade 3) tumors, 59 patients (26.8%) had moderately differentiated (Grade 2) and 4 patients (1.8%) had well differentiated (Grade 1) tumors (p-value 0.005) (Table-4). Relating family history, 28 patients (12.7%) had positive 1st-degree relative breast cancer, 13 patients (5.9%) had positive 2nd-degree relative breast cancer, and 179 patients (81.4%) had no family history for breast cancer (p-value 0.001) (Table-5). As we included the ethnicity of only TNBC patients in this study, about 187 patients (85%) were Urdu speaking, 14 patients (6.4%) were Sindhi, 9 patients (4.1%) were Pakhtoon, 8 patients (3.6%) were Punjabi, and 2 patients (0.9%) were Balochi.

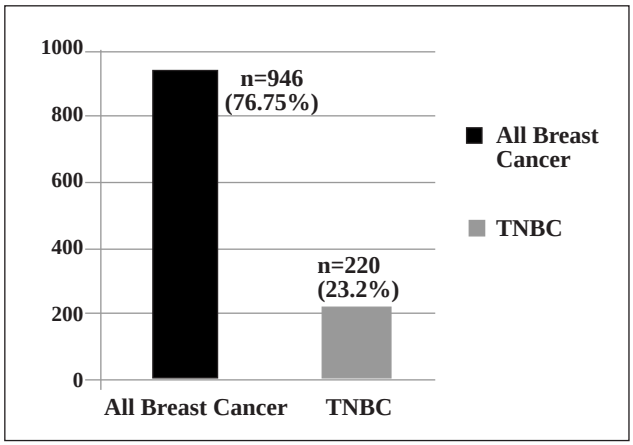

Fig. 1: Incidence of TNBC

Table 1. Frequency of TNBC According to Age

Age	Frequency	Percent	Cumulative Percent
18-30 Years	19	8.6	8.6
31-40 Years	42	19.1	27.7
41-50 Years	55	25.0	52.7
51-60 Years	56	25.5	78.2
61-70 Years	30	13.6	91.8
71-80 Years	14	6.4	98.2
Above 80 Years	4	1.8	100.0
Total	220	100.0	

Table 2. Frequency of TNBC According to Menopausal Status

Menopausal Status	Frequency	Percent	Cumulative Percent	p-value
Pre-menopausal	92	41.8	41.8	<0.0001
Post-Menopausal	128	58.2	100.0	
Total	220	100.0		

Table 3. Histopathological Types Among TNBC

Histopathology Type	Frequency	Percent	Cumulative Percent	p-value
Ductal Carcinoma	201	91.4	91.4	=0.04
Lobular Carcinoma	2	.9	92.3	
Metaplastic Carcinoma	17	7.7	100.0	
Total	220	100.0		

Table 4. Grade of Tumor According to Age

Tumor Grading	Age (Years)					Percent (%)	p-value
	18-30	31-40	41-50	51-60	61-70		
Well Differentiated	2	1	1	0	0	1.8	=0.005
Moderately Differentiated	9	11	16	12	8	26.8	
Poorly Differentiated	8	30	38	44	22	71.4	
Total	19	42	55	56	30	100	

Table 5. TNBC Relation with Family History

Family History	Frequency	Percent	Cumulative Percent
1st Degree Relative Positive for Breast Cancer	28	12.7	12.7
2nd Degree Relative Positive for Breast Cancer	13	5.9	18.6
Negative for Breast Cancer	179	81.4	100.0
Total	220	100.0	

DISCUSSION

Early detection and intervention are paramount in improving patient outcomes and reducing mortality rates associated with TNBC. Besides, recognizing the incidence of TNBC enables healthcare providers to allocate resources effectively, develop targeted screening programmes, and implement preventive measures to mitigate the burden of this aggressive subtype of breast cancer on our healthcare system and society. By gaining insights into the epidemiology of TNBC, we can adapt interventions and allocate resources more efficiently to optimize patient care and ultimately improve survival rates for individuals affected by this challenging disease.

The National Cancer Registry of Pakistan collected data to reveal the top ten cancers in Pakistan from 2015 to 2019, in which breast cancer ranked as the number one malignancy in females with a total of 38.8% of cases[9]. Research regarding the prevalence of TNBC in Asia remains relatively scarce as compared to the West. However, according to Wang et al, the incidence of TNBC in Asia is 10-17% of all breast cancer[10]. Moreover, gaining insights into the distribution of TNBC cases across various demographic groups and geographical regions, facilitates the identification of potential risk factors and disparities, subsequently informing the development of public health initiatives and targeted interventions. Ultimately, an accurate grasp of TNBC incidence empowers the medical community to address this challenge with precision, offering improved patient outcomes and a more comprehensive approach to breast cancer management. TNBC exhibits substantial heterogeneity, both at the histological and molecular levels, resulting in distinct behavioral variations among its subtypes[11].

In our comprehensive analyses, it was revealed that the incidence of TNBC was approximately 23.2% (Table-1); when we compare our study of a greater sample size with another local study of only 120 patients, it showed a 14% incidence of TNBC[12]. Another study in Pakistan regarding the prognostic factors of TNBC showed approximately 45 patients (16.07%) with TNBC out of 280 patients[13]. Given the unfavorable prognostic associations with TNBC as a breast carcinoma subtype, it is noteworthy that Pakistan exhibits a relatively low prevalence of TNBC patients as compared to non-TNBC. This epidemiological observation can be considered a favorable aspect, as it suggests a lower burden of this aggressive malignancy within the population.

In our studied population, comprising 220 individuals diagnosed with TNBC, the predominant demographic consisted of subjects within the age range of 40 to 60 years, exhibiting a central tendency represented by a mean age of 49.6 years. Hussain.S. et al.'s study which is comparable to our study, also showed the peak age of TNBC ranging from 46 to 60 years of age[12]. About the age of TNBC diagnosis, it is frequently observed in women who are under the age of 40, of Black racial background, and who possess BRCA1 gene mutations[14]. In an Indian meta-analysis, 20 of the 34 studies reported mean age at incidence for TNBC as 47.52 ± 3 years, which is meaningfully younger than that for non-TNBC[15]. TNBC diagnosed at a young age can exhibit an exceptionally aggressive nature. A meta-analysis of 36 studies verified that patients with an established diagnosis of TNBC at less than 40 years of age are at

greater risk of locoregional and distant recurrences linked to those identified as older than 40 years of age[16].

A majority—128 individuals (58.2%)—were identified as postmenopausal, whereas 92 patients (41.8%) were classified as premenopausal in our study group (Table 2). The statistical analysis yielded a highly significant p-value of 0.0001, indicating a substantial association or difference between menopausal status and the patient population under investigation. Regrettably, the study lacks a sufficient quantity of data to establish a meaningful association between menopausal status and TNBC. However, a study published from China revealed, that out of 249 TNBC patients, 196 patients (78.7%) were pre-menopausal and 53 patients (21.3%) were postmenopausal[17]. An Indian cohort analysis of hazard risk between pre and postmenopausal breast cancer revealed a significant relation of TNBC with postmenopausal patients with a p-value of 0.001, but TNBC tumors within the premenopausal group did not show any relationship with the hazard in multivariate analysis[18]. Conclusively, it is essential to consider the menopausal status as a crucial factor when contemplating the breast cancer phenotype.

Next, we analyzed the relationship of the histopathology of TNBC and the grading of the tumor in our population. A majority of patients i.e. 91.4%, exhibited intraductal carcinoma (IDC) pathology, while 7.7% presented with metaplastic carcinoma, and only 0.9% were diagnosed with lobular carcinoma (Table-3). It is a significant investigating point to explore the association between metaplastic and non-metaplastic pathologies in the context of TNBC because, in comparison to the triple-negative invasive ductal carcinoma (TN-IDC), the triple-negative metaplastic breast carcinoma (TN-MBC) group exhibits a notably inferior prognosis[19,20]. A congruent study from Punjab, Pakistan has unveiled results that align with our findings regarding the prevalence of IDC within the landscape of TNBC[21]. Nonetheless, it is accurate to acknowledge that IDC remains a prevalent histopathological subtype, even within the context of TNBC[22-24].

Regarding grading of tumors, it is noteworthy that TNBC is frequently diagnosed as a high-grade tumor, characterized by poor differentiation of cells. TNBC is recognized for its aggressive behavior, characterized by rapid cell proliferation, high mitotic activity, and a tendency for early metastasis. These aggressive features often contribute to a higher histological grade. Likewise, it has also come to our attention through clinical observation that the diagnosis of Grade 1 or Grade 2 TNBC is an infrequent phenomenon. In the context of this cohort analysis, it was determined that about 71.4% of patients presented with TNBC characterized by poor differentiation (Grade 3), while 26.8% of patients exhibited moderate differentiation (Grade 2) (Table 4). A minority of patients i.e. 1.8% were diagnosed with well-differentiated (Grade 1) tumors. In a comprehensive database encompassing 38,628 patients diagnosed with TNBC and published in 2016, it was ascertained that approximately 79.8% of these patients exhibited Grade 3 disease[25]. Furthermore, in the Pakistani study, it was observed that among the 246 cases analyzed, a significant portion of 56.5% was diagnosed with Grade 3 tumors[22]. Certainly, a discernible correlation exists between TNBC and high-grade tumors, given that TNBC is commonly recognized as an aggressive malignancy. Unfortunately, there is an inadequacy of studies that provide a comprehensive assessment of prognostic differences between low-grade and high-grade TNBC, however, it has been observed in several studies that TNBC, majority of the time was diagnosed as a high-grade tumor.

Within this study, we also attempted to recognize the impact of a family history of breast cancer on the occurrence of TNBC. In this analysis, our outcomes have not revealed a substantial correlation between a family history of breast cancer and the occurrence of TNBC. Only 12.7% of patients had 1st degree family history positive for breast cancer, 5.9% had a positive 2nd degree relative to breast cancer, and about 81.4% had no family history of breast cancer (Table 5). Multiple research studies have demonstrated an inverse relationship between TNBC and a positive family history of the disease[26-28]. Moreover, the prevalence of BRCA mutations in TNBC was also found to be lower among patients, in contrast to those who were non-BRCA carrier TNBC patients[29]. Remarkably, the presence of a germline BRCA mutation emerges as a favorable prognostic factor for individuals diagnosed with TNBC[30].

Umair-ul-Islam et al studied the incidence of TNBC among Pakistani ethnicity and 160 TNBC patients; Urdu-speaking and Punjabis were the most affected ethnic groups[31]. Our study showed that among 220 TNBC-diagnosed patients, about 85% of patients were Urdu speaking followed by Sindhi 6.4%, Pakhtoon 4.1%, Punjabi 3.6%, and Balochis 0.9% (Table 6). This phenomenon may be attributed to the predominant geographical locations. An additional study published in March 2022 indicated a higher incidence of breast cancer, inclusive of all subtypes, among Urdu-speaking patients when compared to other ethnic groups[32]. Despite the multitude of studies conducted in Pakistan concerning TNBC, the influence of ethnicity specifically

within the Pakistani population remains an enigmatic aspect that warrants further investigation with a larger sample size.

CONCLUSION

The conclusion drawn from our study is that TNBC predominantly affected individuals aged 40 to 60 years, often presenting as high-grade tumors. Menopausal status and histopathology showed significant associations with TNBC and displayed no significant correlation between family history and TNBC. Ethnicity distribution highlighted a predominant Urdu-speaking population. These findings provide valuable insights into the demographic and clinical characteristics of TNBC in the study cohort. The cornerstone of enhancing patient outcomes and decreasing mortality rates linked to TNBC lies in early detection and intervention. This necessitates the establishment of targeted screening initiatives and the implementation of preventive measures to alleviate the burden posed by TNBC.

Limitation of study: The study's limitations include single-center data collection and its retrospective nature.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contributions: HS wrote original manuscript and data analysis; ZM supervise, provided guidance, and final manuscript; TL and AA worked on data collection; JAM worked on validation.

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ORIGINAL ARTICLE

Clinical Course, Behaviour and Staging of Breast Cancer at the Time of Presentation During the Era of COVID-19 Pandemic

Muhammad Ahmad Mukhtar[1], Aeimen Khalid[1], Naila Tariq[1], Syed Raza Haider[2], and Rubina Mukhtar[3]

ABSTRACT

Objective: To explore the repercussions of COVID-19 pandemic on clinical course, behaviour, and staging of breast cancer

Methodology: This observational study, during the span of COVID-19, included all patients reported as breast cancer on histopathology in breast care clinic of MINAR Cancer Hospital, Pakistan. Clinical behaviour, details of histopathology including tumor type, Estrogen Receptors (ER), HER 2 Neu, and stage of disease at the time of presentation were recorded and analyzed for frequency and percentages.

Results: Mean age of diagnosis was 45.6 years with STD of ±10.75 with parity range of 0 to 8. Lesion was most frequent on left side. Only 37% patients were diagnosed at early stage. Total 63% patients presented with advanced disease with 13% patients having distant metastasis with bones being the commonest site. As many as 79% patients reported positive for ER and 74% for HER 2 Neu, while 84% patients breastfed children. Hormone intake history was positive in 32% patients.

Conclusion: COVID 19 pandemic has had a drastic effect on the outcome of breast cancer by hindering early diagnosis in our population. Adding to the preexisting paucity of screening programmes and deficit in infrastructure for early diagnosis, COVID 19 pandemic led to an increase in the preexisting high mortality rate.

Key Words: Breast cancer, COVID-19, delay in diagnosis, early detection, pandemic

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INTRODUCTION

Being the most common type of cancer in women worldwide[1], Breast Cancer is always a topic of discussion for international researchers. It gains importance because the main prognostic factor is the stage of the disease at the time of diagnosis[2]. The earlier the diagnosis, the better is the treatment with 5 years survival rate[3]. Breast Cancer has variable clinical presentations. Although mass screening and awareness programmes have lead to an increasing number of patients being diagnosed pre symptomatically worldwide, but these programmes are still deficient in our region[4]. Low literacy rate, beliefs in myths, poverty, and shortage of resources are aiding factors in late presentation. Lack of awareness for early warning signs and beliefs in myths are the most common recognized factors for delay in diagnosis in Pakistani women. Other factors for delay in early detection are a lack of effective mass screening programmes and scarce availability of diagnostic facilities at public sector institutes[5].

During the COVID-19 pandemic, lock-down was practiced worldwide as an attempt to control dissemination of disease by forcing people to stay confined at homes[6]. Fear of catching disease and strict restrictions on public transportation led to patients facing hindrances in approaching diagnostic medical facilities. Moreover, the convergence of most of the medical force towards control of the pandemic, led to a shortfall in medical services available to non-COVID patients. We initiated this research to analyze the influence of the COVID-19 pandemic on timely detection of breast cancer and to ascertain the number of individuals experiencing diagnostic delays attributable to COVID-19, while also considering existing factors that impede early detection.

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METHODOLOGY

After having approval from ethical committee with Ref No: M-3(13)/2018 of the institution, this observational study was conducted from January 2020 to June 2021 at the breast care clinic of MINAR Cancer Hospital Multan, Pakistan. It might reflect the total population sampling as it is the only institute in public sector of Southern Punjab with fully equipped breast imaging and breast cancer diagnostic facilities. Total population sampling helps to elaborate the complete picture of factors. Information was collected using a pro forma during the history-taking process. This data collection method ensured anonymity, maintained patient confidentiality, and avoided the disclosure of any identifying information.

All new patients presenting to breast care clinic with different breast related symptoms, were evaluated by triple assessment technique, including initial assessment on clinical examination and imaging followed by pathological evaluation.

Patients earning less than 20,000 PKR monthly were considered poor, those earning between 20,000 to 50,000 PKR lower-middle class, and those above 50,000 PKR were categorized as upper-middle class[7].

In this study, individuals with a graduation level were noted as highly educated, while those with undergraduate qualifications were considered to have lower levels of education[8].

All patients diagnosed for breast cancer on histopathology during this period were included in the study and were evaluated for liver, lung, bone, or brain metastasis by Abdominal Ultrasound, Bone Scan, Ct Scan/ X-ray chest, and CT Scan of Brain. All already diagnosed patients on follow up or treatment, non-cancer patients and patients who lost follow up were excluded from study.

Details of demographic features including age, family history, marital status, parity, education level, socioeconomic status and work status were recorded. Answer to questions were recorded in pre-designed pro forma. Time of onset of symptoms, reasons for delay in seeking medical advice, knowledge about breast cancer and significance of early detection, beliefs in myths, and social or cultural values were gathered.

SPSS 26 software was used for data analysis. Frequency was expressed in percentages. Relationships between variables were determined by Chi Square test.

RESULTS

Total 3,864 patients reported to the breast care clinic of MINAR Cancer Hospital, Multan. Out of these, 379 patients were found to have (Breast Imaging-Reporting and Data System) BIRADS 5 lesions on mammography and ultrasound. All patients with BIRADS 5 lesions were subjected to ultrasound guided Trucut biopsies for histopathology correlation. Total 297 biopsies turned out to be carcinoma. Patients diagnosed with carcinoma were of ages from 20 to 70 years with the mean age of 45.6 years with STD of ±10.75. Age-wise distribution is shown in Table 1. Parity ranged from 0 to 8 while mean value for parity was 4 with STD of ± 1.75. Fifty-two per cent (154) patients had lesions in left breast. Only 37% (109/297) patients were diagnosed at an early stage that is defined as stages I and II. Sixty-three per cent (188/297) patients were categorized in late stages i.e. Stage III and IV. Prevalence of group staging is shown in Table 2 and Graph 1. Thirty per cent (89/297) patients had positive nodal disease at the time of presentation. Nodal involvement is shown in Graph 2. Total 13% (39/297) patients were having distant metastasis. Bones were the commonest site for distant metastasis at the time of presentation. Out of these, 18 were positive for bones, 15 for lungs, and 6 for liver metastasis. Summary of clinical course and behaviour are shown in Table 3. Relevance of the stage of disease to literacy, socioeconomic status, and living areas is shown in Table 4. Receptor status of tumor cells revealed positive estrogen receptor (ER) in 79% (235) cases while progesterone receptor (PR) was positive in 74% (220) and HER 2 was positive in 70% (208) cases. Invasive ductal carcinoma remained the most frequent histology type forming 82% of total. Other types in descending frequency were medullary, lobular, mucinous, and papillary carcinomas.

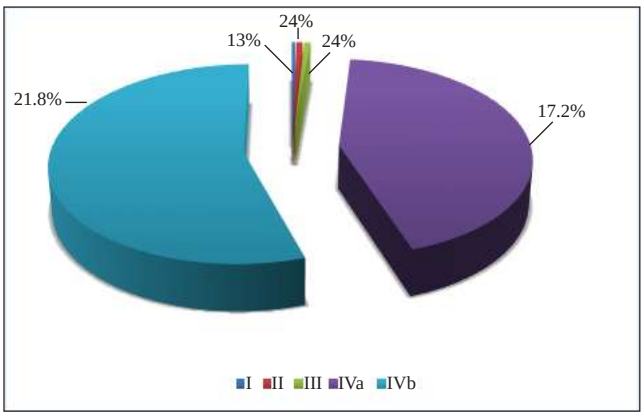
We subdivided delays in two types:

a. Delay on the patients' part
b. Delay on the system's part

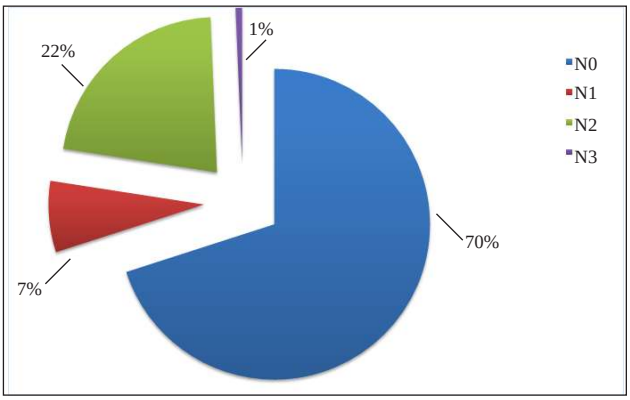
As our system is providing services for diagnosis of breast cancer on one to two days' delay, that was not significant. So, the main part of delay shown in our study was late reporting of patients for diagnostic services. Lack of awareness for relevance of successful treatment on early detection remained the most common factor. Other factors were low literacy rate, beliefs in myths, and belief that breast cancer is untreatable. COVID-19 lockdown further added to this delay. Moreover, patients were not sure whether they would be entertained in hospitals for diagnostic services during the pandemic, so they postponed their medical check ups.

Table 1: Age Distribution

Sr. No.	Age group	Frequency	Percentage
1	<30	24	8%
2	31-40	78	26%
3	41-50	102	35%
4	51-60	78	26%
5	>60	15	5%



Graph 1: Stages of Breast Cancer



Graph 2: Nodal Stage

DISCUSSION

Breast cancer is a health issue of concern worldwide because of its high frequency. It is the third most common cancer after lung and stomach, and remains the most common female malignancy worldwide. Primary breast cancer, being the most common female malignancy, constitutes 30 % of total cancers[1]. It is the all-time feared malignancy among women owing to high mortality rate, being the second most common cause of death. The prime recognized cause of high mortality is late presentation. Outcome of breast cancer treatment highly depends upon the variation in stage at the time of presentation or diagnosis[9]. Probability of five years survival rate is calculated on the presenting stage. Breast cancer is staged by TNM, T1 (tumor size less than 2 cm), T2 (tumor size between 2 to 5 cm), T3 (Tumor size > 5), T4 (locally invaded to chest wall or skin or has distant metastasis[10,11].

Table 2: TNM Staging

T Stage Depends upon size of tumor	T1 <2 cm	39	13%
	T2 bet 2-5 cm	71	24%
	T3 > 5 cm	136	45.8%
	T4 Extend to skin or chest wall	51	17.2%
N Stage Depends upon involvement of lymph nodes	N0 No lymph node	208	70%
	N1 Ipsilateral moveable	22	7.4%
	N2 Ipsilateral fixed matted or IM	65	21.9%
	N3 Infra or supra clavicular or Bi/contralateral	2	0.7%
M Stage	M0 No distant mets	278	93.%
	M1 Distant mets present	39	13%

Combinations of TNM stages define group staging of invasive breast cancer[10].

Over all, 5 years survival rate in USA has been shown in a study to be up to 96.8% for localized lesions or early stage, while it is very poor, up to 10%, in stage IV patients[12]. Stage IV is taken as advanced stage and is considered to be incurable. Over all survival at this stage without treatment is less than 2.7 years. Stages I and II are defined as early stages[13,14]. Developing countries also show marked outcome variation by the differences in stage at diagnosis. Worldwide, efforts are being made to promote early diagnosis of breast cancer. Following the proven fact that breast cancer has high survival rate if diagnosed and treated at early stage, developed countries have reduced mortality rate to a great extent by enhancing early detection through mass screening and awareness programmes but it is still distressing in developing countries like ours[15,16]. Most prevalent reason is late presentation of patients by virtue of poverty, illiteracy, superstitions and lack of resources and infrastructure for early detection of breast cancer.

COVID-19 pandemic was the most urgent challenge worldwide in early 2020. It emerged in China and then spread in the whole world[17]. Millions of COVID-19 related deaths have been recorded[18]. It led to worse

Table 3: Clinical Course

Sr. No.	Features	Frequency of Positive	Percentage	Frequency of Negative	Percentage	Total
1	H/O Breast feeding	249	84%	48	16%	100%
2	H/O hormone therapy	95	32%	202	68%	100%
3	Family History	12	4%	285	96%	100%
4	Lymph nodes	89	30%	208	70%	100%
5	ER Estrogen receptors	50	17%	247	83%	100%
6	Progesterone receptors (PR)	57	19%	240	81%	100%
7	HER 2 Neu	30	10%	267	90%	100%

Table 4: Relevance of Stages

Features			Number of Patients	Percentage
Socioeconomic status	Early stage	Poor	6	5%
		Middle to high	103	95%
		Total	109	100%
	Late stage	Poor	173	92%
		Middle to high	15	8%
		Total	188	100%
Residence	Rural		267	90%
	Urban		30	10%
	Total (N)		297	100%
Education	Early stage	Literate	96	88%
		Illiterate	14	12%
		Total	109	100%
	Late stage	Literate	4	2%
		Illiterate	184	98%
		Total	188	100%

economic, physical, and psychological consequences[6]. It is a communicable viral disease that spreads through direct communication, coughing, and sneezing. In the absence of a definitive treatment or vaccine during the initial phase, the primary approach was to curb its spread by strictly adhering to social distancing and self-quarantine measures, along with employing additional protective measures such as wearing face masks and practicing frequent hand washing[19]. Lock down and priority shifting of health resources towards control of COVID-19 pandemic not only hindered effective screening but also created a gap between presentation and diagnosis of breast cancer, ultimately leading to failure of early detection of breast cancer.

We conducted this study to find the damaging effects of COVID pandemic on clinical course, behaviour and stage of breast cancer at the time of presentation. Stage of disease at the time of presentation is most important predictive factor for 5 years survival[10]. The earlier the diagnosis, the better is the prognosis. Literature narrates different definitions for early stage of breast cancer but most accepted definition is Stage I and II elaborating tumor limited to breast with or without involvement of few (1-3 in numbers) axillary lymph nodes[20,21]. In developed countries, 70 % of breast cancer are diagnosed at early stages, while the figure is low in developing countries. In Pakistan, the figure is 60% for early stage (stage I and II) diagnosis and 40% for advanced stage (III and IV)[22]. Our study shows only 37% patients presented at early stage of I and II. Total 63% presented at advanced stages of III and IV, and 21.8% of our patients presented with distant metastasis. This indicates that the COVID pandemic crisis with lock-down badly affected the already compromised early diagnosis of breast cancer and might have enhanced the preexisting high mortality rate in our population.

Studies correlated variation in early diagnosis with age of the patient. Early diagnosis at younger age is better later[23]. Mean age of presentation in our study is 45.6 years with 59% of total patients presented being below the age of 40 years, while 70% patients diagnosed at early stage fell into age group below 40 years indicating good self-consciousness for health care.

A family history of breast cancer is a significant factor in early detection, as it provides firsthand insight into the challenges and consequences associated with delayed diagnosis. All this compels one to seek medical attention earlier in case of symptoms[24]. As many as 18.4 % patients were shown to have family history of breast cancer in a study conducted by A Tazzite, H Jouhadi in 2013[25]. But our study shows that only 4% had family history of breast cancer that does not correlate with literature.

Illiteracy and low socioeconomic status are recognized delaying factors. Higher education level is correlated with less delay. Less literate people have poor decision making abilities for their health issues. Many studies support this fact. Jasem et al noted the same in his study[26]. A study by Imran Majeed showed that low income status is highly correlated with delay in diagnosis and treatment as people with low income put health at the bottom level of priorities as compared to other basic necessities of life[23]. Our study also shows the same correlation. As many as 88% and 95% patients diagnosed at early stages were literate and belonged to middle to high socioeconomic status respectively. On the other hand, 98% and 92 % patients with late stage diagnosis corresponded to the low literacy and low socioeconomic status group. In our country, the costs of Mammography, Biopsy and Histopathology are high and the infrastructure for screening and diagnosis of breast cancer is deficient. People expect to have all medical services free from the Government and are not able to spend money for their healthcare.

Similarly, patients from rural areas neither have easy approach to health system nor are aware of the magnitude of this disease. Moreover, healthcare system in Pakistan is not built to provide medical cover at elementary level. More than 90% of our patients with advance stage diagnosis fall in this category. All of these factors contributed to a pervasive fear of contracting the deadly communicable disease, leading to widespread confinement at home. This not only impeded hospital visits but also significantly impacted businesses due to lockdown measures, resulting in a financial crisis for many.

This situation is alarming, possibly an aftermath of the COVID-19 pandemic, posing a significant barrier to screening and diagnosis, especially for symptomatic patients. This may contribute to an increase in the already high mortality rate of breast cancer in our population. Urgent efforts should be made to address this pressing concern.

The gist of all predisposing factors for delay in early diagnosis comes out to be a lack of awareness. Awareness campaigns are run in the month of October but are not very effective. Early detection of breast cancer should be encouraged through public awareness. Early diagnosis would ultimately bring about decrease in mortality rate. Moreover, there is an intense need to expand the diagnostic facilities for breast cancer at the level of basic health units.

CONCLUSION

The COVID-19 pandemic has significantly impacted the already high mortality rates from breast cancer by obstructing early diagnosis. This disruption has occurred not only due to hindrances in already insufficient screening programmes but also because of delays in diagnosing symptomatic patients caused by lockdowns and the reallocation of healthcare resources to pandemic control. In our population, which already suffers from a compromised healthcare system, it is crucial to implement effective public awareness and screening programmes to reduce the mortality rate to levels comparable to those in developed countries.

Limitation of Study: It is a single institute based study that does not represent whole population of country but only a part of a province.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contribution: RM led the manuscript writing and provided the primary idea; MAM, AK, NT, and SRH contributed to data recording, analysis, and manuscript writing, and provided critical review.

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REVIEW ARTICLE

Biochemical and Other Mechanisms Associated With Olfaction and Taste Abnormalities in Covid-19

Loung V Umedani[1] and Quratulain Javaid[2]

ABSTRACT

Coronavirus (SARS-CoV-2) spreads from its initial nasal reservoir to produce respiratory problems and neurological manifestations. Viral spike protein-S binds with host receptor angiotensin-converting enzyme 2 with the assistance of membrane fusion protease. Average smell and taste disorders prevalence was 18.8% and 14.1% respectively.

The objective of this narrative retrospective study was to explore mechanisms underlying olfactory and gustatory manifestations. For obtaining novel information, we selected articles from January 2021 to January 2023. We searched terms like neurological manifestations, anosmia, loss of taste in COVID-19, and SARS-CoV-2 as keywords using PubMed. After scrutiny, we excluded articles with accessory and non-relevant information and finally selected 23 articles.

Various immune mechanisms like cytokine storm and direct neuroinvasions result in neurological manifestations. Role of various micro RNAs in molecular pathology point towards future research to explore epigenetic neuropathological mechanisms to help in designing novel therapeutic remedies. Global awareness and vaccination protocols had greatly reduced occurrence of disease.

Key Words: Ageusia, anosmia, biochemical, COVID-19, mechanisms

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INTRODUCTION

A new strain of SARS-CoV-2 was isolated in China at the end of December 2019 resulting in serious pneumonia[1]. The World Health Organization declared it as a pandemic in March 2020. In a highly alarming report, the American Association for Cancer Research and COVID-19 announced that by January 2022, =289 million subjects were identified globally to have COVID-19 and =5.4 million had expired from the disease[2]. The higher genomic size gives more possibilities of flexibility resulting in recombinations and mutations favoring genetic diversity and spread of corona virus to other species[3].

The method of SARS-CoV-2 entry in the target cells is membrane fusion or endosomal pathway. This occurs once the spike (S) protein of virus binds with the receptor angiotensin-converting enzyme 2 (ACE2) located in the lungs, liver, blood vessels, nervous system, and other places with the assistance of membrane fusion protease (TMPRSS)[4].

COVID-19 presented with multiple stages of severity. It could be asymptomatic or may commence with upper respiratory tract symptoms like pyrexia, myalgia, tiredness, sneezing, nasal secretions, and irritation in throat. When it progressed to moderate stage, cough and fever due to pneumonia occurred with or without hypoxemic spells. At this stage, chest radiography mainly CT scans showed the lesions. In severe stage, there was pneumonia with hypoxemia (SpO2 <92%). These were followed by highly serious states like acute respiratory distress, cardiac injury or failure and shock; and could be accompanied by acute renal injury, encephalopathy and clotting problems. Such cases required an emergency intensive care unit admission[4].

It is in the moderate to severe stage of the disease that the CNS injury occurs as pronounced feature[5]. The prevalence of anosmia was 49%. In different studies, about 60 days post COVID-19, the average prevalence of anosmia and loss of taste was 18.8% and 14.1% respectively in 2021. The taste variations were ageusia

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and hypoguesia. The average anosmia duration was about 10 days in mild disease, which settled completely in about 89% cases in four weeks[6]. Some 5% of cases showed a prolonged course or no improvement[7]. There could be a combined loss of smell and taste.

The other lesions coexisting with dysgeusia were tongue and palatal ulcers, gingivitis, halitosis, fissures in tongue, hyperplasia of papillae, candidiasis, dry mouth, and lingual plaques. These symptoms could be attributed to lower immune system and simultaneous antibiotic usage[8].

This review contains general information about the causative virus and COVID-19 disease itself followed by the general information about the mechanisms for smell and taste manifestations. This review in particular highlights the said mechanisms in COVID-19 for gaining guidelines for the future researchers to explore the treatment strategies for these cases.

General Background of Mechanisms in Neurological Complications:

The initiators of infectivity existed on both sides i.e. virus and host cell (viral spike protein variations and host cell surface proteins, mainly ACE2 and TMPRSS2)[9].

There are four types of viral structural proteins called Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N) proteins.

The RNA genome lies in N protein where as S, E and M collectively form viral envelope. S1 and S2 are type-1 membrane glycoproteins. S1 helps in attachment of virus and S2 works for its fusion with host cell membrane. On the host cell, ACE2 has affinity for S proteins. This is followed by host serene proteases called TMPRSS2, TMPRSS4, furin, endothelial cathepsins helping in membrane fusion by protein catalysis and viral entrance in target cells[10]. The viral inhabitance and infectivity is determined by the Receptor Binding Domain (RBD) of the subunit S1 viral spike protein that attaches by increased affinity to the peptidase domain of ACE2. The genetic mutations at RBD determine variations of infectivity between various regions of the world. The variations outside RBD like single nucleotide polymorphism G614 results in generation of dominant viral strain in the pandemic and need further research[9]. After the entrance of the viral genome in cell, it replicates its polyproteins 1a and 1ab tagged with genes pertaining to open reading frame called ORF-1a and ORF-1b. These mechanisms take over the control of target cell ribosomal functions[11].

The host cell apoptosis occurs by ORF3a, ORF3b, ORF6 and ORF7a. The expression of cytokines is increased by viral ORF7a. Host cell interferon production is inhibited by ORF6, host cell autophagy by mitochondrial dysfunction due to ORF9b effects. The effects such as activation of inflammasome complex, release of interleukin-1 beta, stress response of endoplasmic reticulum, malfunction of lysosomes, caspase-independent cell necrosis is produced by ORF8b[12].

The viral invasion of nervous tissue by inflammatory state caused by cytokines produced neurological manifestations[13]. T cell infiltration also had role in neuroinflammation in about 70% of subjects, which showed $CD8^+$ T-cell infiltration. The infiltration of neutrophils, T-cells with the activated microglial cells producing microgliosis were also found in brain autopsies of such cases[14]. The immune system autoantibodies, molecular, cellular and biochemical mechanisms were noted in various neurological complications[15]. Apart from olfaction and gustation, the other neurological manifestations were also found such as stroke, neuropathy, damage to choroid plexus, blood brain barrier damage, direct cranial nerve damage, gene regulation problems, glial cell damage, and audio-vestibular problems. These problems had various underlying mechanisms which are not addressed in this review.

The severity of disease was related to complement mainly C3, C5a and C5b, their hyper activation caused clotting, formation of thrombi and damage to endothelial cells[13]. The interleukins (IL6, IL8, IL17A), TNF-α, activated perivascular astrocytes, and the endothelial cells were found implicated in the cytokine storm. The immune process damaged the endothelium. This was shown by raised levels of D-dimers, soluble vascular cell adhesion molecules, plasma fibrinogen, thrombomodulin, von Willebrand factor, TNF receptor 1, haparan sulphate, alpha-2 antiplasmin and plasminogen activator inhibitor[16,17].

Mechanism by retrograde axonal transport of virus:

The virus can travel through trigeminal, olfactory, facial, glossopharyngeal, and vagus nerves to infect parts of the brain[18]. The autopsies from frontal lobe and cerebellar cortex, trigeminal ganglion, olfactory bulb, medulla oblongata, and olfactory nerves showed presence of SARS-CoV-2[19]. The inoculation of SARS-CoV-2 in olfactory epithelium of mice revealed entry of virus in the cerebral cortex and hippocampus, and in other experiments, the viral antigen was detected in the neuroglial and nerve cells[20].

METHODOLOGY

In this retrospective narrative review, the mechanisms underlying neurological manifestations related to COVID-19 subjects were analyzed. As less work was done in the initial periods of COVID-19 due to a lack of in-depth research aimed to explore the underlying mechanisms, therefore we targeted the articles that were published in the most recent years. For this purpose, the related articles were searched from January 2021 to January 2023. We utilized PubMed for this task.

The methods utilized to seek these articles were carried by using group of search items. First by putting the term COVID-19 followed by the type of neurological complication and mechanism like COVID-19 anosmia mechanisms, COVID-19 biomarkers in neurological complications, COVID-19 biomarkers in olfactory complications, and COVID-19 dysgeusia mechanisms. Most of these articles included comprehensive reviews, original research manuscripts, and case studies. The articles indicating six months post COVID period and thereafter for the presence of neurological complications, were included in this review.

In each search output, we sorted out the underlying molecular mechanisms also. We also looked at the references of all the articles found and tried to get the related molecular mechanisms. Further, the bibliographies of related articles were assessed to observe and search the pertinent literature. More emphasis was given to articles published in year 2022 so that latest information could be obtained. After getting all the pertinent information, we set the concluding remarks in discussion section to get further research track for future workers. The inclusion criteria were year of publication, relevance with the title, and aim of related article. The exclusion criterion was accessory and non-relevant information.

After scrutiny and exclusion, the total number of articles selected was 23. We found 16 articles related to anosmia and altered sense of olfaction and seven articles for gustatory deficits. For each major deficit, we explored the related mechanism underlying it in these published papers.

SPECIFIC MECHANISMS AT VARIOUS LEVELS ALONG THE OLFACTORY PATH

From the site of olfactory epithelium up to the olfactory cortex

(i) Mechanisms at the Level of Olfactory Epithelium:

The infection starts at the nasal passage where the narrow olfactory cleft could be occluded by congestion and mucus to produce conduction block for smell. This mechanism was not operable because some cases showed anosmia before nasal symptoms and its recovery before olfactory cells's regeneration. Normally, the olfactory stem cells regenerate to produce the olfactory sensory cells and the sustentacular (supporting) cells. The SARS-CoV-2 mainly infects the supporting cells and the stem cells to express ACE2[21]. During supporting cell's regeneration in about eight days, the olfactory cell dendrites mature producing recovery of smell[9].

Molecular mechanisms involving *expression of ACE2 and trans-membrane serine protease 2 (TMPRSS2) in the supporting cells* was found as the main cause of anosmia[22]. The viral protein Nsp13 binds with ciliary centrosomes to produce ciliary damage and anosmia[23] (Table 1). The ACE gene has many genetic variations producing delta and omicron strains. Serene protease inhibitors like camostat mesylate and nafamostat mesylate could help treating anosmia and also reduce viral infection (Table 1)[22,24]. Some authors have indicated that TMPRSS2 expression occurs in scanty amounts in the olfactory cells[25].

(ii) Variation in Enzymatic Metabolism of Sustentacular Cells:

The sustentacular cells normally produce soluble proteins which mix with secretions of olfactory glands so that the receptor cells of sensory neurons can detect the sense of olfaction. When the sustentacular cells get infected with the virus, the function of enzymatic metabolism gets disturbed. These effects produce degradation of odorant molecules resulting in decreased sense of smell (Table 1)[26].

(iii) Mechanisms Based on the Effects of Cytokine Storm on Sustentacular Cells:

The cytokines are released at the olfactory epithelial ACE2 receptors like interleukin-6, IL 1β[6]. After the virus binds with toll-like receptors, the IL 1β is released which is cleaved by caspase-1 leading to activation of inflammosomes, apoptosis through TNF-α or neuropilin to produce anosmia[27]. After three months of post-COVID Syndrome (PCS), the low-grade inflammation, high neutrophil count, pro-inflammatory response, and decreased local immunity could prolong anosmia[28].

(iv) Effect on Stem Cell Regeneration:

Due to inflammation and apoptosis of the stem cells because of complementing factors, neutrophils, and cytotoxic cells around them, a prolonged span of anosmia can occur (Table 1)[6].

(v) Mechanism by Direct Effects on the Sensory Neurons:

The sensory cells showed replication of viral genes, non-structural protein genes such as nsp14 and RNA-dependent RNA-polymerase genes like RdRp in real time. Some therapeutic target genes viz. chemosensory modulator bromodomain-containing protein 2 (BRD2) and early-growth response gene (EGR1) manifested higher expression in human peripheral neurons following COVID-19[29]. Expression of immature class III β-tubulin and mature olfactory membrane protein in the olfactory epithelium was also noted (Table 1). Autopsy examination of 19 cases of such infection carried out for sensory neuron membrane proteins showed positive results[30]. The olfactory sensory neurons gave reduced receptor gene expression of adenylyl cyclase 3 and other key olfactory transcripts that caused hyposmia (Table 1)[31]. However, some asthmatics were protected due to respiratory allergen exposure causing less ACE2 expression in upper air passages[32].

(vi) Damage to Olfactory Bulb:

The olfactory bulb neurons are regarded as 2nd order neurons in the olfaction pathway. In COVID-19 cases, it showed an abnormal enhancement on magnetic resonance images. A mechanism in the form of upstream movement of virus through the cribriform plate towards olfactory bulb and from here to other parts of brain was also proposed (Table 1)[33]. The human olfactory bulb autopsies also revealed the presence of virus in peripheral neurons[30].

(vii) Mechanism of Viral Spread to Hypothalamus **by** *Nervus Terminalis (XIII Cranial Nerve)*:

This nerve is a microscopic plexus of unmyelinated nerves projecting to olfactory trigone by passing under the medial olfactory gyrus. It was proposed that the expression of ACE2, cathepsin B, and cathepsin L in this nerve, causes facilitation of viral transmission through it to nearby brain structures. At the lamina terminalis, this nerve facilitates entry of virus to preoptic area and hypothalamic arcuate nucleus to disturb the pituitary hormone secretion, thermoregulation, and autonomic responses[34].

Mechanisms Involved in Gustatory Dysfunctions

(i) Direct Effect on Gustatory Receptor Cells:

There was a direct mode of infection of gustatory receptor cells due to ACE2 and TEMPRSS2 as compared to olfactory, where it was an indirect effect coming from the infection of the supporting cells (Table 2)[35]. This was reported in harvested circumvallate papillae immune staining experiments on Sprague-Dawley rat cells, which showed ACE2 expression causing decrease in bud cells and taste bud numbers supporting ageusia[36]. Different types of tastes (salt, sweet, bitter, sour, and umami) had variable mechanisms supported by some authors and not favored by others[37,38].

(ii) Mechanisms based on the effects of Cytokine storm

This was explained in Table 1.

(iii) Effect on Non-gustatory Cells of Tongue:

A different type of taste sensation called chemesthesis (feeling of coldness after eating mint or heat from chilies) was decreased. This was due to inflammatory effects on non-gustatory cells, which are normally involved in transmitting general sensations. This had a separate trigeminal general sensory path, as it does not start from taste buds, mechanism was unknown or may be due to cytokines, all the three senses (olfaction, taste and chemesthesis) may be affected simultaneously[39].

(iv) Effect on Salivary Glands:

The glandular epithelium of the salivary glands express ACE2. The subsequent damage to this epithelium causes reduction in saliva and dry mouth due to ACE2 effects resulting in decreased sense of taste.

(v) Effect of SARS-CoV-2 on Nerves Carrying Taste Sensation:

The branches of facial, glossopharyngeal, and vagus nerves carry taste sensations. These fibers along their path also join other nerves such as branches of the trigeminal nerve. The direct damage to these cranial nerves by the viral pathology were also considered as an important cause to produce gustatory manifestations (Table 2)[8].

(vi) Mechanism of Furin Expression:

The furin is a cytoplasmic enzyme involved in the priming of the virus. The expression of furin was noted in the fungiform papillae, neural tissue, and salivary glands (Table 2)[40].

(vii) Mechanism Indicating Effects on Zinc Chelation:

The inflammatory effects of viral infection on the taste buds can result in zinc environment alteration[8,41]. Conduction of taste in nerves and gustatory perception is based on the role of zinc, which acts as cofactor for alkaline phosphatase to maintain taste[42]. Zinc dependent enzyme (Gustine) is influenced by carbonic anhydrase

Table 1. Main Mechanisms Involved in Olfactory Manifestations with Their Therapeutic Aspects

Anosmia and Hyposmia	**Mechanisms**	**Therapeutic Comments**
	-Expression of ACE2 and TMPRSS2 in the supporting cells	-Camostat mesylate and Nafamostat mesy late to reduce infectivity
	-Polymorphism of ACE2 and TMPRSS2 genes and/or variations of viral S-protein	-**
	-Nasal enzymes metabolic genetic variation for odorants by supporting cells	-Enzymatic inhibitors need to be explored**
	-Cytokine storm (TNF-α, IL-1β and IL-6 levels) causing apoptosis	-Cortisone in early and late stages with care about their side effects
	-Expression of non-structural protein gene (nsp14)	-Inhibitors**
	-Expression of RNA-dependent RNA-polymerase (RdRp) gene	-Remdesivir, other Inhibitors**
	-Viral protein Nsp13 binding to ciliary centrosomes	-**
	-Inflammation and apoptosis of stem cells by complement factors, neutrophils and cytotoxic cells around them	-Eculizumab to decrease inflammation
	-Neuronal genes overexpression (Bromodomain-containing protein 2 (BRD2)	-BRD2 inhibitors still in clinical trial, **
	-Early-growth response gene (EGR1), has role in infection and inflammation	-**
	-Immature class III β-tubulin expressed by olfactory neuronswhich, upon infection are phagocytosed by macrophages	-Colchicine / others are under trial but**
	-Under expression of adenylyl cyclase 3 (Neuronal receptor gene)	-Endosome inhibitors chloroquine, azithromycin showed limited efficacy**
	-Olfactory bulb (second order) neuronal inflammatory damage	-** Cortisone with precautionary measures.

Legend: **Needs further research

Table 2. Main Mechanisms Involved in Gustatory Manifestations with Their Therapeutic Aspects

Ageusia and Dygeusia	**Mechanisms**	**Therapeutic Comments**
	-Direct effect on gustatory receptor cells (expression of ACE2 and TMPRSS2) resulting in damage and improper differentiation	-Protease inhibitors, Corticoids
	-Similar mechanism on salivary gland's ACE2 receptors resulting in dry mouth	-Protease inhibitors
	-Cytokine storm	-Cortisone in early and late stages with care about their side effects
	-ACE2 mediated damage of cranial nerves VII, IX and X resulting in taste problem	-Corticoids, antivirals
	-Furin expression (proteolytic enzyme) by fungiform papillae with role in priming of virus	-**
	-Zinc chelation by taste bud inflammation	-Zinc therapy
	-Gustatory center's viral infiltration	-**
	-Polymorphism of uridine diphosphate (UDP) glycosyltransferase genes causes hypogeusia	-**

Legend: **Needs further research

for production of taste buds. Oral zinc stimulates the food intake by its effect on the hypothalamus with its role in taste disorders therapy. The zinc deficiency causes taste problems (Table 2)[35].

(viii) Direct Infiltration of Virus on Neurons in Taste Centers:

Like direct effects of SARS-CoV-2 on olfactory center, the centers for taste perception can also be affected directly. This can be based on factors which produce neuropathy[42].

(ix). Genetic Mechanisms:

The *polymorphism in uridine diphosphate (UDP) glycosyltransferase family of gene loci* with a role to eliminate toxic products was noted mainly UGT2A1 and UGTA2 genes as factors for ageusia and anosmia (Table 2)[43].

DISCUSSION

The mechanisms underlying neurological manifestations in COVID-19 are multifaceted. The direct infection of the virus on peripheral sensory neurons happened through the entry component ACE2. This is followed by the events involved in the lifecycle of virus ahead like the molecular mechanisms. The genes associated with chemosensory functions get changed and undergo expression by the viral infection. The pattern of gene expression needs further exploration to understand the basic background to design appropriate therapeutic remedies against such infections.

COVID-19 is characterized by predominance of the pulmonary as opposed to neurological signs that are lesser. Since the neurological signs can occur during the active phase as well as long afterwards in the post COVID-19 phase with unfavorable consequences and morbidity so they should never be ignored and must be diagnosed and remedied early.

A regional variation was also noted related to COVID-19. Researchers have found the main reason for lower prevalence in Asia as compared to the West, which could be due to a genetic variation either in the viral spike proteins (S-protein) or host cell surface proteins. There can be genetic polymorphism at the level of ACE2 or at transmembrane serine protease 2 (TMPRSS2) (Table 1). It is found that different populations have variations in degree of the individual complications, for instance, anosmia variations occurred due to dissimilarities in S proteins of the viral genealogic lineage at one hand and dissimilar host proteins on the other end. This will certainly modify the entrance of virus and overall level of infectivity[9].

Although various mechanisms were pointed by different workers to produce anosmia but the overall findings for it gave importance to the damaged sustentacular cells than the olfactory receptor cells. Viral spread from sustentacular cells through cribriform plate into nearby cerebrospinal spaces and from there to adjacent brain regions, is accepted as final mechanism till date[44]. This does not ignore the effects due to olfactory sensory neurons totally as some workers found damage of cilia of these neurons and presence of viral particles in neurons. In addition, the other supplementary effects like the radiological evidence of damage to olfactory bulb and reduction in size of the olfactory cortical area cannot be ignored because these structures form part of the olfactory path.

The experimental evidence of expression of ACE2 in oral mucosal cells and cell membranes of taste buds can easily explain the direct damage occurring at taste receptor cells as well as secondary pathogenesis of inflammation due to cytokines at mainly local and systemic levels to induce hypogeusia, dysgeusia, or ageusia. Various consequences of SARS-CoV-2 infection in oral region in the mucosa itself and gingiva with problems in taste sensations need further research to approve a relation among these stated lesions and disease. Exploration of the nature of these lesions for being a kind of primary manifestation of the disease versus the possibilities operating due to secondary effects is mandatory.

One cannot ignore the secondary effects on taste; like use of medications, decreased immune system mechanisms, reduction in local blood supply, inflammatory effects at both local and systemic levels, and abandoned personal oral health care. The secondary effects due to reduced salivary secretion (dryness of mouth) and direct effects on nerves involved in the path of taste sensation were also noted. The treatments for taste disorders are currently taken as arbitrary as they still need further research workup. The ageusia and anosmia has long duration effects like perceptivity about food, dietary practice of the individual and the way one communicates at societal or social level.

The parameters of the quality of life are affected negatively by the neurological complications in the form of smoke inhalation and consumption of spoiled food in case of olfactory dysfunction. This can cause decrease in appetite and lacking interest in eating one's own favorite foods, malnutrition, and decreased social life. Such effects point to the need for further research and explore treatment remedies against these complications.

This emphasizes the need to diagnose the problems meticulously. Hence, an essential earlier screening, diagnosis at clinical as well as laboratory levels for assessment of these problems, followed by their effective management, is mandatory.

CONCLUSION

This review had enumerated proteins, enzymes related to SARS-CoV-2 entrance, various receptors and mechanisms. The sequelae of cytokine related pathogenesis, immune mechanisms and direct

neuroinvasion result in neurological complications. It was necessary to explore the molecular mechanisms operating in SARS-CoV-2 infection, define research gaps to direct further research to predict the diagnosis, identify the patient stratifications, timely target the preventive steps, to arrange medical services, to design appropriate treatment strategies, and seek an improved prognostic assessment. The role of various micro RNAs in the molecular pathology of inflammatory process point towards future research targeted to explore the epigenetic mechanisms to help in designing the new treatment modalities. The incidence of this disease was reduced by the extensive measures taken globally such as surveillance, isolation, and data about contacts, discouraging public movements, social distancing, frequent hand washing, increased awareness, and most importantly, the vaccination protocols.

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CASE REPORT

Complete Excision of Rare Esophageal Tumor; Leiomyosarcoma

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ABSTRACT

Leiomyosarcoma are rare malignant esophageal tumors that remain asymptomatic unless size exceeds 5 cm. They grow at a slow rate and in very few cases have metastasized by the time of their presentation. Here, we present a case of a 65 years old male with progressive dysphagia and occasional dull chest pain for one and half years. Clinical examination was unremarkable. Computed tomography showed an 8 cm mass of the upper and middle thoracic esophagus with lateral wall thickness of 1.5 cm. Fat planes were intact with enlarged subcarinal nodes. Biopsy was suggestive of leiomyosarcoma and Mckeown esophagectomy was performed. Intraoperatively, mass was consistent with radiological findings, however it was adherent to surrounding structure with enlarged carinal nodes. Patient had an uneventful recovery period with histopathological evidence of complete recession of tumor.

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INTRODUCTION

Leiomyosarcomas are among the rare malignant smooth muscle tumors of the esophagus. They make up to 0.5% of all esophageal malignancies[1]. Considering the rarity of tumor, only 165 cases of leiomyosarcomas have been reported till date[2]. Patients are often affected at or after fifty years of age with a slight male preponderance having 2:1 of male to female ratio[3]. As a result of their slow growth rate and late metastasis, they have good survival rate. Diagnosis and management of leiomyosarcomas are challenging as they are rare and no well established guidelines are present[4].

CASE REPORT

A 65 years old male presented to outpatient department with history of progressive dysphagia for one and half year. Initially dysphagia was for solids which later progressed to liquids over twelve months. Patient also complained of occasional dull chest pain with a feeling of sticking sensation in the center of the chest. There was no relevant history of weight loss or regurgitation. Family members reported a change in his dietary habits and frequency of meal over the year.

Patient underwent flexible endoscopy that identified a polypoid mass extending into the lumen with overlying normal mucosa. Biopsy showed spindle cells with spindle shaped hyperchromic nuclei with mild to moderate nuclear pleomorphism, few mitotic figures, and h-Caldesmon positive.

Computed Tomography(CT) revealed a large mass starting from the upper and extending upto the middle thoracic esophagus. Mass was 8 cm in length with lateral wall thickness of 1.5 cm and enlarged carinal nodes (Figure 1). All metastatic work up was negative. After consultation with multidisciplinary team, surgery was advised as preoperative chemoradiotherapy had no role.

After optimization and obtaining informed consent, McKeown esophagectomy was carried out. Operative findings included a large bulky mass extending from lower one third of upper thoracic esophagus up to the junction of lower and middle esophagus. Esophagus was found adherent to the mediastinum and posterior membrane of the trachea. Stations 7 and 8 nodes (subcarinal and esophageal respectively) were visibly enlarged. Tumor was resected completely along with lymphadenectomy without iatrogenic injury to any

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underlying structure. Patient was managed postoperatively in the ward with early commencement of enteral feed via feeding jejunostomy. Nasogastric tube was removed on the third day followed by chest tube removal on day 5. The patient was allowed orally on the 10th postoperative day and discharged without any complication.

At follow up, the patient had no active complaints. Histopathology was consistent with leiomyosarcoma of esophagus showing spindle cells arranged in intersecting fascicles and intervening bundles. Mitotic activity of 2/10 Hpf was noticed. All nodes examined were non-reactive and the resected margins negative for malignancy. Radiological assessment post-surgery showed no evidence of anastomotic leak or metastasis.

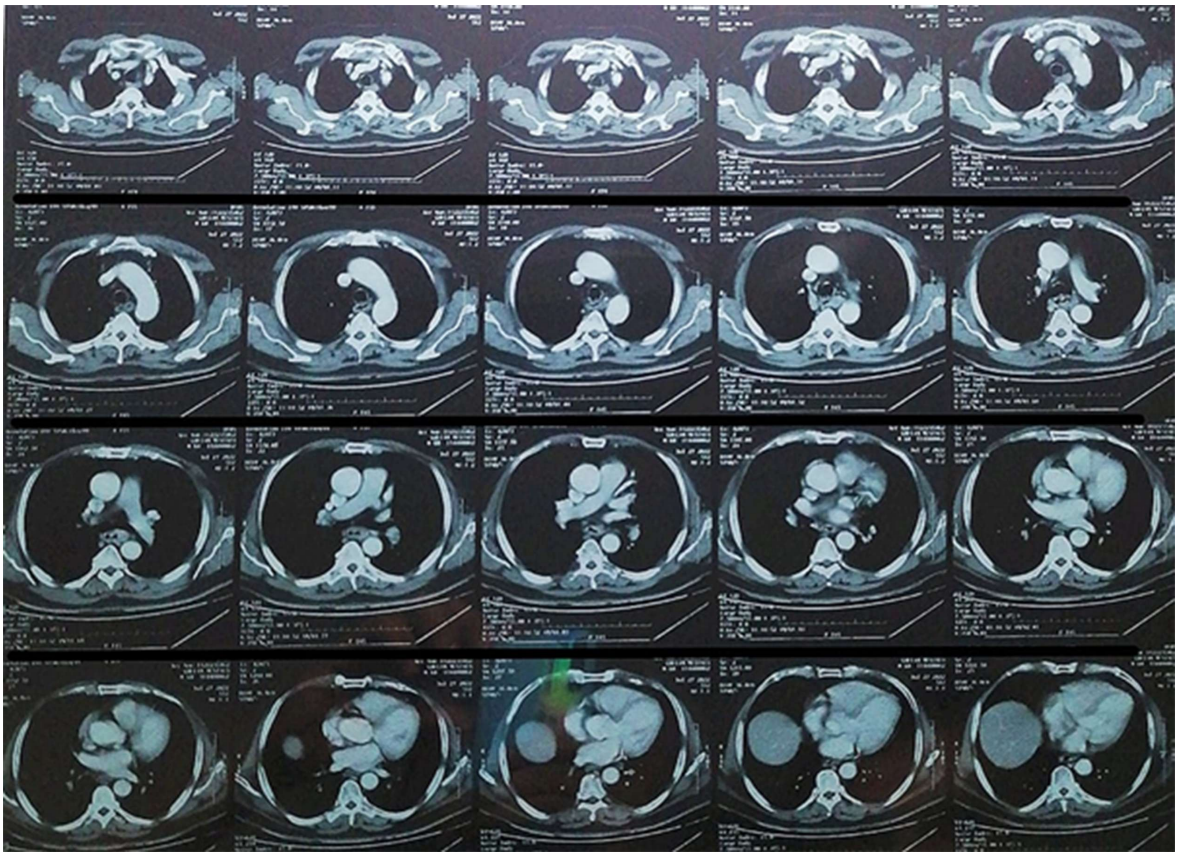

Figure 1: CT scan of leiomyosarcoma

DISCUSSION

Leiomyosarcomas are malignant smooth muscle tumors originating from mesenchymal cells of muscularis propria of the esophagus. Macroscopically, they appear polypoidal, remaining intramural, however in selective cases, they may be infiltrating in nature[3]. In our case, mass was intramural in location. The malignancy has a higher predilection for males in the sixth decade of life[4]. Leiomyosarcomas usually affect middle and lower esophagus as per literature but our patient presented with the involvement of upper and middle esophagus[3,6].

The commonest symptom at presentation is usually dysphagia which occurs in three-fourths of the patients[1]. Other symptoms include retrosternal pain, weight loss, and regurgitation. The tumor has indolent growth pattern due to which patients modify their dietary habits as seen in our case; ultimately one-third of them present with metastasis[3]. They metastasize to the surrounding structures such as lung, pleura, pericardium, diaphragm, and to distant sites as well, such as stomach, liver, and bones[1]. As per literature, 5-year survival is only 20% after metastasis[4].

The accurate diagnosis preoperatively is difficult as differentiation between leiomyoma and leiomyosarcoma is only possible by histopathological examination. Till date, preoperative differentiation of leiomyoma and sarcoma have been possible in few cases only[5]. Differential diagnosis includes spindle cell sarcoma and carcinosarcoma of the esophagus[6,7].

Transthoracic en-bloc esophagectomy with radical lymphadenectomy should be the best surgical option to achieve complete resection. Significant survival

advantages have been achieved with local excision surgery for well localized lesions[1,7]. Role of adjuvant chemotherapy and radiotherapy remains controversial[1,3]. Few authors recommended radiotherapy for treatment of metastatic tumors to prolong survival in cases exhibiting extensive or unresectable metastases[4,6]. In literature, survival rate over 5 to 10 years is 47% and 31% respectively[3].

CONCLUSION

Any patient presenting with prolonged dysphagia should be thoroughly investigated. Although rare but leiomyomas/sarcomas should be given due attention and resected in surgically fit patients for better histopathological assessment. Surgical resection via esophagectomy remains standard treatment. Although leiomyosarcoma exhibits poor sensitivity to radiation, the tumor may be effectively controlled by increasing the radiation dose appropriately.

Conflict of interest: Authors declare that there is no conflict of interest.

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