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Editorial

MONKEY POX: A GLOBAL HEALTH HAZARD

Momal Khan[1], Noor-ul-Ain Liaqat[2]

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The monkeypox virus was declared a global health hazard by WHO in 2022, affecting six WHO regions with 110 countries reporting almost 87 thousand cases and 112 deaths worldwide.[1] The virus belongs to the genus Orthopoxvirus and has two clades, clade I and clade II. The recent monkeypox outbreak in 2022-2023 was caused by the clad IIb strain.

The first human case was reported back in 1970 in Congo, Africa.[2] Monkeypox was endemic in Africa but did not gain much recognition until its outbreak in the United States of America in 2003. The virus spread to the United Kingdom (UK) when a British citizen visited Nigeria and contracted the disease, resulting in becoming an index case in the UK.[3] As of January 2023, 85,142 cases have been reported worldwide with the highest number of cases reported in the USA (29980).[2] In Southeast Asia, the outbreak began on 18th August 2022 and India reported 12 cases and 1 death till September 2022.[4] In Pakistan 2 cases have been reported in Jinnah Hospital Lahore resulting in WHO declaring it a global health hazard in 2022.[5] Worldwide, most deaths were reported in the United States (21) followed by Brazil (14), Peru confirmed 12 deaths, Nigeria 7, while Mexico and Ghana reported 4 deaths each and Spain and Cameroon each had 3 deaths.[3] The virus multiplies in rodents and small mammals which is then transmitted to humans via direct contact with infected animals having open wounds and scabs.

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In humans, it is transmitted by direct contact with infected lesions, droplet infection, fomites and sexual transmission especially in homosexual males.[6] The individuals most likely to be at risk are male homosexuals, people with multiple sex partners, sex workers, and healthcare workers. Children, pregnant females, HIV patients and those who are immunosuppressed are most likely to have more severe disease.

The mean incubation period of the disease is 9 days.[7] The infected patient may experience nonspecific symptoms such as fever, headache, chills and backache. There can be lymphadenopathy and skin rash is a hallmark of the disease. The rash is vesiculopapular in nature and can lead to permanent scarring and discoloration, which can have a huge psychological impact on the affected individual. The rash can be swabbed and sent to the lab for PCR to reach the final diagnosis.[8] The disease can progress to severe complications such as cellulitis, abscess, pneumonia, diarrhoea, sepsis or septic shock, keratitis and encephalitis.[9] Once diagnosed, the patient is isolated. Most people recover with hydration and supportive treatment with no need for pharmacological therapy, while a few people might need antivirals. Cidofovir and tecovirimat are currently approved for the treatment of people showing severe signs and symptoms of monkeypox. Active immunization can be achieved in susceptible patients via the vaccinia virus vaccine which is the same vaccine used for protection against smallpox. In immunosuppressed patients, vaccinia immunoglobulins can be used for restraining the disease.[10] As with any other disease or health hazard, prevention is considered a far

better option than treatment. The same is the case with monkeypox, the precautionary measures that are advised for the control and prevention of the disease are surveillance, isolation, and contact tracing. Personal preventive measures advised for prevention of the disease are to avoid close contact with the patient, disinfect the household items used by the affected individual, repeated handwashing, wear disposable gloves and masks, avoid contact with wild animals and unprotected homosexual activity.[9] Mass Vaccination is not recommended for the general population as a preventive measure, but it is indicated for healthcare workers who are constantly involved in working with patients suffering from Monkeypox.[11] The psychological load connected with this disease's treatment poses a challenge for institutions and will most likely require a long-term commitment.[12] Government of Pakistan has requested WHO to provide the Monkeypox vaccine for frontline Health care workers. WHO has promised to provide Mpox vaccine despite its short supply globally and will also assist the Pakistani government in lab testing and provision of testing kits.

Pakistan, being a developing country and already combating diseases that have been eradicated worldwide such as polio, must be hypercautious for infections that can be controlled in the initial stages. The coronavirus pandemic has already drained the country of its resources and being struck by another pandemic would leave us in shambles. Henceforth, it is the need of the hour to be foresighted and be aware of the disastrous effects it can have on the social, financial, mental, and emotional status of the country. Health education is the key to halting the progress of the disease as it is the best way to control any infectious disease.

REFERENCES

1. Mpox (monkeypox) (no date) World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/monkeypox-07 June 2023
2. Bukhari MH. The truth of monkeypox outbreak: a guide for the diagnostic laboratories, health care workers and community in Pakistan. Biomedica. 2022 Jun 10;38(2):53-6. doi: 10.51441/biomedica/5-734
3. Karagoz A, Tombuloglu H, Alsaeed M, Tombuloglu G, AlRubaish AA, Mahmoud A, et al. Monkeypox (mpox) virus: Classification, origin, transmission, genome organization, antiviral drugs, and molecular diagnosis. J Infect Public Health. 2023 Feb 9. https://doi.org/10.1016/j.jiph.2023.02.003,
4. Siddiqui JA, Aamar H, Rija A, Essar MY. Preparedness of Pakistan in view of monkeypox emergence: a call for action. *Int* J Surg. 2023 Jan 1;109(1):34-5.
5. Abdullah, Ali S, Cancado FA, de Oliveira CA. The emergence of Monkeypox virus, new challenges to the healthcare settings in Pakistan. J Med Virol. 2023 Jan;95(1):e27899. doi: 10.1002/jmv.27899.
6. Wang Y, Leng P, Zhou H. Global transmission of monkeypox virus—a potential threat under the COVID-19 pandemic. Front Immunol. 2023;14. doi: 10.3389/fimmu.2023.1174223.
7. Miura F, van Ewijk CE, Backer JA, Xiridou M, Franz E, de Coul EO, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. Eurosurveillance. 2022 Jun 16;27(24):2200448. https://doi.org/10.2807/1560-7917.ES.2022.27.24.2200448.
8. Altindis M, Puca E, Shapo L. Diagnosis of monkeypox virus–An overview. Travel Med. Infect. Dis 2022 Sep 13:102459. https://doi.org/10.1016/j.tmaid.2022.102459.
9. Jiang RM, Zheng YJ, Zhou L, Feng LZ, Ma L, Xu BP, et al. Diagnosis, treatment, and prevention of monkeypox in children: an experts' consensus statement. World J Pediatr. 2023 Mar;19(3):231-42.
10. Khani E, Afsharirad B, Entezari-Maleki T. Monkeypox treatment: current evidence and future perspectives J Med Virol. 2023 Jan;95(1):e28229.
11. Reina J, Iglesias C. Vaccines against monkeypox. Medicina clinica (English ed.). 2023 Apr 6;160(7):305-9. doi: 10.1016/j.medcle.2023.01.005

12. Hirani R, Rashid D, Lewis J, Hosein-Woodley R, Issani A. Monkeypox outbreak in the age of COVID-19: a new global health emergency. Mil Med Res. 2022 Dec;9(1):1-2. https://doi.org/10.1186/s40779-022-00419-7

Original Article

COMPARISON OF THE EFFICACY OF GLASS IONOMER AND RESIN BASED SEALANTS IN PERMANENT 1ST MOLARS IN 7-12 YEARS OLD CHILDREN

Syeda Afshan Manzoor[1], Amara Nazir[2], Sadiq Amin Ahmad Rana[3], Faisal Asghar[4], Humaira Iqbal[5], Muhammad Kashif[6]

ABSTRACT

Background: The present investigation sought to compare the retention rates of glass ionomer and resin-based sealants in the permanent first molars of children aged seven to twelve years old.

Material and Methods: A total of 112 participants were recruited and randomly allocated to either Group A (glass ionomer sealants) or Group B (resin-based sealants), with retention rates for the sealants assessed after one year.

Results: The findings demonstrated that glass ionomer sealants' retention rate was significantly lower than resin-based sealants' ($p < 0.05$). Glass ionomer sealants had a retention rate of 57.1% compared to 81.3% for resin-based sealants.

Conclusion: These results imply that resin-based sealants might be more successful in protecting the permanent first molars of kids between the ages of 7 and 12 against dental caries. This information can be useful to dental practitioners and policymakers in making decisions about the optimal material for pi and fissure sealant application in this population.

Key Words: Dental caries, Molar, Population

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INTRODUCTION

Among dental diseases, caries is the most prevalent affecting millions of children worldwide. According to a study by the World Health Organization (WHO), dental caries affects up to 90% of school-aged children globally.[1]

The rate of dental caries varies among different populations and countries, with some populations having higher rates than others.[2] The high rate of dental caries in children highlights the importance of effective prevention measures, such as dental sealants.

Pit and fissure caries in youngsters can be prevented from starting and progressing with the use of dental sealants.[3] Sealants, which are slender plastic coatings, are applied to the occlusal surfaces of molars and premolars. This application creates a physical barrier that effectively prevents bacterial and food particle build-up within the crevices and grooves of the teeth.

Evidence suggests that dental sealants reduced the incidence of dental caries by up to 70%.[4]

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Sealants are particularly important for children as they may not have developed adequate oral hygiene habits and may consume sugary foods and drinks more frequently than adults. Dental sealants can stop dental cavities in youngsters from developing and progressing, preventing the need for more intrusive and expensive dental operations.[5]

Dental sealants include glass ionomer and resin-based sealants. Glass ionomer sealants are made of a mixture of glass and acrylic acid, which chemically bond to the tooth surface. Resin-based sealants consist of a mixture of resin and other materials, which bond to the tooth surface.[6] Both materials are effective in halting dental caries progression, but the optimal material for sealant application remains unclear. The selection of sealant material may depend on various factors, such as operator preference, patient characteristics, and tooth morphology.[7]

The research focus of this study is to compare the efficacy of glass ionomer and resin-based sealants in terms of retention rate at 12 months in children aged 7-12 years. Previous studies have reported conflicting results regarding the efficacy of these two materials. For example, some researchers reported that retention of resin-based sealant group is higher than glass ionomer group after 12-36 months.[7,8] In contrast, in another randomized controlled trial, researchers found insignificant differences in the retention rates of glass ionomer sealants and resin-based sealants.[6]

In consideration of the elevated incidence of caries amongst children between the ages of seven and twelve, it is of utmost importance to evaluate the efficacy of glass ionomer and resin-based sealants within this specific age cohort. The first permanent molars usually erupt between the ages of 6 and 7 and are vulnerable to dental caries due to their complex occlusal morphology, which makes them difficult to clean. The first permanent molars are also most commonly affected by dental caries in children.[9]

Additionally, the choice of sealant material is crucial in achieving a successful outcome. The retention rate of the sealant is an essential factor to consider as it affects the longevity of the sealant and its ability to provide long-term protection against dental caries. To select the most suitable material for sealant application in the aforementioned demographic, it is imperative to undertake a comparative assessment of the retention rates of glass ionomer and resin-based sealants over 12 months in the permanent first molars of children aged between seven and twelve years old. The results obtained from this inquiry hold the potential to enhance clinical practice and optimize preventive measures against caries in this population subset.

MATERIAL AND METHODS

The study was conducted at the Department of Paedodontics, Bakhtawar Amin Hospital, Multan, Pakistan. A total of 112 children, aged 7 to 12 years, with pits and fissure caries in permanent first molar teeth were enrolled. Children who were physically or mentally handicapped had known diabetes mellitus, or were allergic to resins were excluded. After taking consent from the parents, the children were allocated into two groups: Group A (glass ionomer sealants) and Group B (resin-based sealants).

Tooth surfaces were prepared for sealant application by prophylactic cleaning using pumice slurry on a bristle brush. After cleaning tooth surfaces were rinsed and air dried. Followed by rubber dam isolation. In Group A, the tooth surface was conditioned using 20% polyacrylic acid for 10 seconds, which was then removed by air-water spray. Glass ionomer sealant was then placed on the pits and fissures of the permanent first molar. Excess sealant was wiped off using a cotton pellet, and petroleum jelly was applied. Occlusal adjustments were made, if necessary, using an articulating paper. Flossing was done to ensure that no sealant was left in contact areas. The patient was advised to avoid eating for one hour.

In Group B, following tooth preparation, etching was performed utilizing 37% phosphoric acid for 15-30 seconds. The acid was then rinsed for 20 seconds and air-dried,

subsequently inspected for the manifestation of a frosted appearance. Next, resin sealant was administered to the pits and fissures of the permanent first molar and cured for 15 seconds. Occlusal adjustments were made, if necessary, using an articulating paper.

Follow-up was conducted after 6 months to evaluate sealant retention in pits and fissures. The retention of sealants was checked under illumination using a mirror and explorer. If the sealant was present in all parts of pits and fissures it was noted as complete retention and the absence of sealant when it was lost from the pits and fissures.

Data were entered and analyzed using SPSS version 22.0. The mean and standard deviation were presented for the duration and age of the disease. Qualitative variables, such as residence (rural/urban), monthly income (<20000 or >20000), brushing teeth more than two times a day (yes/no) and efficacy, were presented by percentage and frequency. The Chi-square test was used to compare the effectiveness of both groups, and a p-value of < 0.05 was regarded as significant. Effect modifiers were checked by an assortment of data based on age, duration of disease, residence (urban/rural), socio-economic status (poor, middle, upper), and brushing teeth (yes/no). After assortment chi-square was applied to determine the effect of these factors on efficacy, and a p-value of ≤ 0.05 was marked significant.

RESULTS

In this study, the range of age was from 7-12 years having a mean age of 9.24 ± 1.38 years. The mean age in group A was 9.23 ± 1.39 years and in group B was 9.29 ± 1.38 years. The majority of patients 64 (57.14%) were between 7-9 years of age. Out of 112 patients, 58 (51.79%) were male and 54 (48.21%) were female having male to female ratio of 1.1:1. Distribution of patients according to place of living and tooth brushing frequency is given in Table 1.

Table-1: Demographic characteristics of study participants

Variables	Group A (n/%)	Group B (n/%)
Gender Male Female	 27 (48.21) 29 (51.79)	 31 (55.36) 25 (44.64)
Living status Rural Urban	 23 (41.07) 33 (58.93)	 22 (39.29) 34 (60.71)
Mean Age (years ±S.D)	9.23 1.39	9.29 ± 1.38

In group A, sealant was present in 17 patients after 12 months period and in 39 patients sealant was lost whereas in group B, after 12 months, resin sealant was retained in 31 patients, and 25 patients, sealant was lost.

In Group A, 19 patients in the age group of 7-9 years showed complete retention of sealants. In the same age group in Group B, 8 patients showed complete retention. The difference in efficacy between the two groups in the 7-9 age group was found to be statistically significant (p=0.010). In the age group of 10-12 years, 12 patients in Group A showed complete retention and in Group B, 9 patients showed complete retention. The difference in efficacy between the two groups in the 10-12 age group was not found to be statistically significant (p=0.259).

In Group A, 17 (30.36%) males and 14 (25%) females had complete retention of the sealant. In Group B, 12 (21.43%) males and 5 (8.93%) females had complete retention of the sealant. The p-value was 0.065 for males and 0.030 for females. These results suggest that gender may be an effect modifier for the efficacy of sealants in terms of retention rate. Regarding the place of living, the urban group showed a higher efficacy than the rural group in both Group A and Group B. The p-value for Group B was statistically significant (p=0.037), indicating a significant difference in efficacy between the urban and rural groups in Group B

Table-2: Comparison of efficacy between both Groups (n=112).

Variables	Group A (n/%)	Group B (n/%)	*p*-Value
Efficacy/retention frequency			
Yes	17(30.36)	31(55.36)	0.028
No	39(69.44)	25(44.64)	0.129
Efficacy in Age groups			
7-9	19	8	0.010
10-12	12	9	0.259
Efficacy in Gender			
Male	17	12	0.065
Female	14	5	0.030
Efficacy concerning the place of living			
Rural	13	7	0.095
Urban	18	10	0.037

DISCUSSION

Caries are a common dental health issue, and dental sealants proved to be effective against their progression.[10-12] The present investigation sought to contrast the effectiveness of glass ionomer and resin-based sealants on retention rates within the permanent first molars of children aged between seven and twelve years old. Our study's results indicate that resin-based sealants exhibit a superior retention rate compared to glass ionomer sealants ($p<0.05$), with a recorded retention rate of 81.3% for the former and 57.1% for the latter. This finding aligns with earlier research studies that also found resin-based sealants to possess a higher retention rate compared to their glass ionomer counterparts.[6,13,14] Our study provides further evidence that resin-based sealants could be a better choice to prevent dental caries in permanent first molars of children aged 7-12 years. Various scientific justifications exist to substantiate the observed superior retention rate of resin-based sealants over glass ionomer sealants in the present study. One such rationale pertains to the augmented adhesive strength exhibited by resin-based sealants, which stems from their ability to bind to both enamel and dentin. In contrast, glass ionomer sealants possess weaker adhesive properties, which could account for their comparatively inferior retention rate.[15-17] The chemical bonding between the resin-based sealant and the tooth structure creates a stronger, more durable bond than the ionic bond formed by glass ionomer sealants. Other reasons are polymerization. Resin-based sealants are cured by a chemical process called polymerization, which results in a hard and durable surface.[18,19] Glass ionomer sealants, on the other hand, are set through a process called acid-base reaction, which results in a surface that is softer and more prone to wear and tear. Furthermore, Resin-based sealants are more wear-resistant than glass ionomer sealants due to their higher hardness and durability. Resin-based sealants are less likely to chip, crack or break, and can withstand the forces of chewing and grinding better than glass ionomer sealants.[20,21]

An examination of efficacy stratification by age group illustrated that the observed disparity in effectiveness between glass ionomer and resin-based sealants was statistically significant (p=0.010) for the 7-9 age group. This outcome corroborates a prior investigation's finding that the retention rate of glass ionomer sealants was less favorable amongst younger age cohorts.[22] The results of our study suggest that resin-based sealants may be a better choice for younger children.

One limitation of our study is that it only evaluated retention rates after 12 months. Long-term studies are needed to evaluate the efficacy of both types of sealants in preventing dental caries in the permanent first molars of children aged 7-12 years.

Based on the findings of this study, recommendations can be made for future research and clinical practice. Firstly, future research could investigate the long-term efficacy of glass ionomer and resin-based sealants beyond the 12 months. Longer-term studies may provide more insights into the durability and efficacy of these sealants in preventing dental caries.

Secondly, more research is needed to identify the factors that influence the retention of sealants in children. This could include investigating the impact of tooth

morphology, oral hygiene habits, and dietary habits on the retention of sealants. Thirdly, the use of a combination of glass ionomer and resin-based sealants could be explored in future research. This may provide a more effective remedy for preventing dental caries in children. Fourthly, given the importance of early prevention of dental caries, policymakers should consider implementing national programs to provide dental sealants to children at high risk of developing dental caries.

Finally, dental practitioners should consider the age and clinical needs of the patient when deciding on the type of dental sealant to use. For children with a higher risk of developing dental caries, resin-based sealants may be the optimal choice. However, for children who are less cooperative or have special needs, glass ionomer sealants may be more suitable.

CONCLUSION

To summarize, our investigation has produced empirical evidence indicating that resin-based sealants exhibit a superior retention rate relative to glass ionomer sealants within the permanent first molars of children aged between seven and twelve years old. As such, it could be argued that the implementation of resin-based sealants may be more efficacious in averting dental caries among younger age groups. Nevertheless, future research endeavors are required to ascertain the long-term efficacy of both sealant types.

AUTHOR'S CONTRIBUTION

SAM: Conception, data analysis, Clinical methods and final drafting

AN: Conception, data analysis, Clinical methods and final drafting

SAAR: Conception, data analysis, Clinical methods and final drafting

FA: Sample collection, data analysis and drafting

HI: Sample collection, data analysis and drafting

MK: Clinical methods, data collection, analysis and final review

REFERENCES

1. Goodarzi A, Heidarnia A, Tavafian SS, Eslami M. Association between dental caries and body mass index-for-age among 10-12-year-old female students in Tehran. Int J Prev Med 2019;10. doi: 10.4103/ijpvm.IJPVM_528_18.
2. Cheng YH, Liao Y, Chen DY, Wang Y, Wu Y. Prevalence of dental caries and its association with body mass index among school-age children in Shenzhen, China. BMC Oral Health. 2019 Dec;19:1-9. https://doi.org/10.1186/s12903-019-0950-y
3. Yu OY, Lam WY, Wong AW, Duangthip D, Chu CH. Nonrestorative management of dental caries. Dent. J 2021 Oct 18;9(10):121. https://doi.org/10.3390/dj9100121.
4. Baik A, Alamoudi N, El-Housseiny A, Altuwirqi A. Fluoride varnishes for preventing occlusal dental caries: A review. Dent J. 2021 Jun 3;9(6):64. https://doi.org/10.3390/dj9060064.
5. Ibrahim MS, Garcia IM, Vila T, Balhaddad AA, Collares FM, Weir MD, et al. Multifunctional antibacterial dental sealants suppress biofilms derived from children at high risk of caries. Biomater Sci. 2020;8(12):3472-84. doi https://doi.org/10.1039/D0BM00370K
6. Alsabek L, Al-Nerabieah Z, Bshara N, Comisi JC. Retention and remineralization effect of moisture tolerant resin-based sealant and glass ionomer sealant on non-cavitated pit and fissure caries: Randomized controlled clinical trial. J Dent 2019 Jul 1;86:69-74. https://doi.org/10.1016/j.jdent.2019.05.027.
7. Prathibha B, Reddy PP, Anjum MS, Monica M, Praveen BH. Sealants revisited: An efficacy battle between the two major types of sealants–A randomized controlled clinical trial. J Dent. Res. 2019 Jan;16(1):36.
8. Gupta A, Agrawal A, Rawal A, Gujarkar S. Evaluating the Retention of Resin-Based Sealant and a Glass Ionomer Sealant among 7-10 Year-Old Children: A Randomized Controlled Trial. Int J Oral Dent Health. 2020;6:115. doi: 10.23937/2469-5734/1510115.
9. Emmanuelli B, Knorst JK, Menegazzo GR, Mendes FM, Ardenghi TM. The Impact of Early Childhood Factors on Dental Caries Incidence in First Permanent Molars: A 7-Year Follow-Up Study. Caries Res. 2021;55(3):167-73.

https://doi.org/10.1159/000515083
10. Kashbour W, Gupta P, Worthington HV, Boyers D. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in the permanent teeth of children and adolescents. CDSR. 2020(11).
11. Schraverus MS, Olegário IC, Bonifácio CC, González AP, Pedroza M, Hesse D. Glass ionomer sealants can prevent dental caries but cannot prevent posteruptive breakdown on molars affected by molar incisor hypomineralization: one-year results of a randomized clinical trial. Caries Res. 2021;55(4):301-9. https://doi.org/10.1159/000516266.
12. Cheng L, Zhang L, Yue L, Ling J, Fan M, Yang D, et al. Expert consensus on dental caries management. Int. J. Oral Sci 2022 Dec;14(1):17. https://doi.org/10.1038/s41368-022-00167-3.
13. Alsabek L, Al-Hakeem A, Alagha MA, Comisi JC. Efficacy of hydrophilic resin-based sealant: A systematic review and meta-analysis. J Dent. 2021 Nov 1;114:103816. https://doi.org/10.1016/j.jdent.2021.103816.
14. Lam PP, Sardana D, Lo EC, Yiu CK. Fissure sealant in a nutshell. evidence-based meta-evaluation of sealants'effectiveness in caries prevention and arrest. J. Evid. Based Dent. Pract. 2021 Sep 1;21(3):101587. https://doi.org/10.1016/j.jebdp.2021.101587.
15. Gogos C, Economides N, Stavrianos C, Kolokouris I, Kokorikos I. Adhesion of a new methacrylate resin-based sealer to human dentin. J Endod. 2004 Apr 1;30(4):238-40. https://doi.org/10.1097/00004770-200404000-00014.
16. De Pinho Quintão C, Costa ST, Lacerda MF, Girelli CF, Oliveira C. Adhesion capacity of bioceramic and resin-based root canal sealer to root dentin: An integrative review. Rev. Bras. Odontol. 2020;77:e1758. doi: http://dx.doi.org/10.18363/rbo.v77.2020.e1758.
17. Ekambaram M, Yiu CK, Matinlinna JP. Bonding of adhesive resin to intraradicular dentine: A review of the literature. Int J Adhes Adhes. 2015 Jul 1;60:92-103. https://doi.org/10.1016/j.ijadhadh.2015.04.003.
18. Kitchens B, Wells M, Tantbirojn DA, Versluis A. Depth of cure of sealants polymerized with high-power light emitting diode curing lights. Int J Paediatr Dent. 2015 Mar;25(2):79-86. https://doi.org/10.1111/ipd.12102.
19. De Nys S, Duca RC, Vervliet P, Covaci A, Boonen I, Elskens M, et al. Bisphenol A release from short-term degraded resin-based dental materials. J Dent. 2022 Jan 1;116:103894. https://doi.org/10.1016/j.jdent.2021.103894.
20. Kaverikana K, Vojjala B, Subramaniam P. Comparison of Clinical Efficacy of Glass Ionomer-based Sealant Using ART Protocol and Resin-based Sealant on Primary Molars in Children. Int J Clin Pediatr Dent. 2022 Nov;15(6):724. doi: 10.5005/jp-journals-10005-2450.
21. Saveanu CI, Dragos O, Armencia A, Bamboi I, Saveanu AE, Tanculescu O. Characterization of Sealing Materials by Energy Dispersive X-ray Spectrometry and Scanning Electron Microscopy. REVISTA DE CHIMIE. 2019 Oct 1;70(10):3657-9.
22. Morales-Chávez MC, Nualart-Grollmus ZC. Retention of a resin-based sealant and a glass ionomer used as a fissure sealant in children with special needs. J Clin Exp Dent. 2014 Dec;6(5):e551. doi:10.4317/jced.51688

Original Article

KNOWLEDGE AND PRACTICES OF MOTHERS REGARDING INTEGRATED MANAGEMENT OF NEONATAL AND CHILDHOOD ILLNESS COMMUNITY COMPONENT IN THE PERI URBAN AREA OF LAHORE

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ABSTRACT

Background: The Integrated Management of Childhood Illness (IMCI) strategy was created in 1992 by the World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF) to address the five major causes of child mortality: diarrhoea, pneumonia, malaria, measles and malnutrition. Its community component (IMCI-C) focuses on important health practices within households and communities for child survival. The current study aimed to assess the knowledge and practices of IMCI-C among mothers in a peri-urban area of Lahore, Pakistan.

Material and Methods: A cross-sectional study was conducted in Shah di Khoi, Johor Town, Lahore involving 1250 mothers' of 2932 children under the age of five; 180 mothers were selected using systematic random sampling. Information about the mothers' sociodemographic characteristics, knowledge and practices related to IMCI-C was collected. The data were analysed using SPSS version 21. The frequency percentages for outcome variables of overall knowledge and practices of IMCI-C were calculated; the chi-square test was applied for statistical significance with a p-value ≤ 0.05.

Results: Overall knowledge and practices of mothers regarding IMCI-C were 91.1% and 95% respectively, with a significant association between the age of the child and the mother's knowledge regarding IMCI-C (χ 2 =7.935, p-value=0.019). No statistical significance of age, education, occupation income of mothers and their knowledge and practice of C-IMNCI was observed.

Conclusion: A high level of knowledge and practices was reported among the mothers highlighting a good literacy rate (73%) and the role of lady health workers in promoting the health of children under five.

Key Words: Knowledge, Pneumonia, Malaria, Literacy

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INTRODUCTION

The world has made significant progress in reducing the under-five mortality rate, decreasing it from 93 deaths per 1000 live births in 1990 to 37 deaths per live births in 2020.[1]

A large portion of under-five deaths in 2020 were concentrated in two regions: sub-Saharan Africa, where 55% of deaths occurred and South Asia, where 27% of deaths occurred. These deaths were mainly due to preventable and treatable infectious diseases.[1] The mortality rate of children under five years of age per thousand live births in Pakistan was 65.2 per 1000 live births in 2020.[2] In 1992, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) developed the Integrated Management of Childhood

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Illnesses (IMCI) strategy to address the major causes of child mortality including diarrhea, pneumonia, malaria, measles and malnutrition. The strategy was introduced in the Eastern Mediterranean Region in 1996.[3]

The Integrated Management of Childhood Illnesses (IMCI) strategy has three main components: Improving the clinical and communication skills of health workers; Improving overall health systems, including policy, planning and management, financing, human resources, medicines and supplies, referral, monitoring, and health information systems, supervision, evaluation, and research and Improving family and community health practices. These practices related to child health and development when implemented in targeted communities, would improve child survival, growth, and development.[4] In Pakistan, IMCI was introduced in September 1998, and its community component was launched in March 2002.[5]

Care for newborns was included in IMCI in 2003and the strategy was retitled IMNCI.[6]

The WHO-UNICEF package for community care includes newborn care at home, care for a child, healthy growth and development, and care for the sick child in the community.[7] Families need knowledge and skills to provide suitable care, motivation to sustain new practices, and support from the community and the health system.[8]

IMNCI is a holistic approach that addresses the key factors influencing childhood health and mortality. It provides a framework for effective case management, disease prevention, and comprehensive care, while also engaging communities to promote positive childcare practices and support the well-being of children.[4]

The integration of community-level interventions into comprehensive primary child health care strategies, aligned with the principles of primary health care (PHC), has faced delays in many countries. This delay hampers the effective coordination of childcare interventions between the health system and the community and it prevents reaching the most vulnerable populations.[4]

The current global architecture, including the transition from Millennium Development Goals (MDGs) to Sustainable Development Goals (SDGs), emphasizes Universal Health Coverage (UHC), revitalized PHC and the UN Secretary-General's Global Maternal, Newborn, and Child Health (MNCH) Strategy. This shift places greater emphasis on health determinants and recognizes the need for community engagement and interventions that go beyond the health sector.[9]

The IMCI community component advocates for community participation as a means of achieving sustainability, in line with the principles of PHC. It recognizes the need for the active involvement of families and communities in planning and implementing childcare interventions. This approach is crucial for achieving the Sustainable Development Goal target 3.2, which aims to reduce child mortality to 25 or fewer deaths per 1000 live births by 2030. It is especially important to implement key components of IMCI at scale in countries with a high burden of preventable childhood mortality.[10]

In a study conducted in Northern Uganda, the overall knowledge of caregivers about the community component of IMCI was found to be 13.3% (n=59). The study found that 59% (n=261) had adequate knowledge of breastfeeding,17% (n=75) on complementary feeding/weaning. Knowledge was found to be better regarding immunization, where 85.3% (n=377) had adequate knowledge.[11] A study conducted among rural nursing mothers in Nigeria reported that the majority (90.5%) of the mothers had high knowledge about IMCI-C practices. The IMCI-C practices utilization among the mothers was rated according to mean. The most used IMCI-C practices were found to be child immunization (mean=2.98) and the use of insecticide-treated mosquito nets (mean=2.97).[12]

Few studies have been conducted related to the community component of IMCI in Pakistan including knowledge and practices with all four domains. A study conducted in Gadap Town, Karachi, found 67.4% knowledge and 68.8% practices by respondents which had positive results in reducing diarrhea morbidity.[13] Another study conducted in a slum community of Karachi reported that only15.8% of women had fair knowledge about pneumonia and 19.2% of mothers knew its preventive measures including immunization. Additionally, 60.8% of respondents were unable to recognize the signs and symptoms of pneumonia.[14] The objective of the present study is to assess the knowledge and practices related to the community component of IMNCI among mothers in a peri-urban area of Lahore. The rationale behind this study is to have a baseline assessment of the current knowledge and practices of IMNCI-C among respondents as they are the primary caregivers of their children and data on these parameters are scarce for this population.

MATERIAL AND METHODS

A cross-sectional study was conducted in Shah di Khoi, a peri-urban area in Lahore, Johar Town, Lahore from November 2016 to December 2016. There were 2079 houses and 1250 mothers' of 2932 children under the age of five residing in the study universe. The sample size was calculated using a standard formulation $n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$ (EPI info) based on the prevalence of overall adequate knowledge of the community component of IMCI among mothers i.e.13.3% with a 95% confidence level and a 5% margin of error.[11] A total of 180 mothers who met the inclusion criteria were selected through systematic random sampling, where every seventh mother was enrolled. The researcher maintained the confidentiality of the participants and obtained written consent from the respondents and approval from the Institutional Ethical Committee of Allama Iqbal Medical College, Lahore. (Letter no 25.05/ERB/25th)

Data were collected using a pre-tested, self-structured, close-ended questionnaire that included questions related to the knowledge and practices of mothers about the community component of the Integrated Management of Neonatal and Childhood Illness (IMNCI-C). Each question had four choices and each correctly answered question earned one point. The data were checked by the investigator at the point of data entry concerning predetermined correct responses developed from the latest WHO recommendations.[8]

The dependent variables in this study were the knowledge and practices of mothers regarding the IMNCI-C. Independent variables included the age of the respondent, education, occupation, total family income and age of the child. The overall knowledge of the study respondents regarding IMNCI-C was assessed through 19 questions in four domains: physical growth and mental development, disease prevention, appropriate home care, and seeking care. Knowledge was scored as adequate (score $\geq$ 10) or inadequate (score < 9.0). Adequate knowledge was defined as achieving a minimum of 50% of correct answers. The overall practices of study respondents regarding IMNCI-C were evaluated through 16 questions in four domains. Practice was scored as adequate (score $\geq$ 8) or inadequate (score < 7) with a minimum 50% of correct answers defined as adequate practice.

The data were entered and analysed using SPSS version 21.0. Simple frequency distribution tables were generated for sociodemographic variables such as age, education, occupation, total family income, and age of the child, as well as overall knowledge and practices of the respondents regarding each of the four main areas of the community component of IMCI-C. Cross tabulation was done for variables of interest such as age, education, occupation, total income and age of the child affecting knowledge and practices among mothers. The chi-square test was applied to determine any statistically significant effect of these factors on knowledge and practices among

mothers regarding the community component of IMCI-C. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

About 84 (46.7%) respondents were 26-30 years of age having a mean age of 27.86±4.214 years whereas 119 (66.1%) children belonged to 6-24 months of age. Out of 180 children, 90 (50%) were males. Regarding the educational status of respondents, 48 mothers (26.7%) were illiterate whereas the rest had some formal education from primary to above matric level. The educational status of the fathers showed that 41 (22.8%) were illiterate whereas the rest had some formal education from primary to above matric level. Of 177(98.3%) mothers out of 180 were housewives. The economic status of the study participants showed that 168(93.4%) had a total family income≤ of 6,000 PKR per capita. (Table -1)

Table-1: Sociodemographic characteristics of study respondents regarding IMNCI_C Knowledge and Practices (n=180)

Characteristics	Frequency	Percentage (%)
Age of mother		
20-25 years	58	32.2
26-30 years	84	46.7
31-35 years	35	21.1
Mean age = 27.86 years + 4.214		
Age of children		
6 months – 24 months	119	66.1
25 months -42 months	49	27.2
43 months – 60 months	12	6.7
Mean age = 22.23 months +12.30		
Educational status of respondents		
Illiterate	48	26.7
Literate	132	73.3
Educational level of fathers		
Illiterate	41	22.8
Literate	139	77.2
Occupation of respondents		
House wife	177	22.8
Others	3	77.2
Occupation of Fathers		
Private employee	74	41
Others	106	59
Sex of children		
Male	90	50
Female	90	50
Income per capita (PKR)		
<6000	168	93.4
>6000	12	6.6

Overall Knowledge of study respondents regarding IMNCI – C:

Out of 180 mothers, 161(91.1%) had overall adequate knowledge of IMNCI-C. About 152 (84.4%) and 134 (74.4%) mothers had adequate knowledge about physical growth/mental development and home management of illness among children under five respectively. (Figure-1). For physical growth and development, almost all mothers180 (100%) regarded breastfeeding as the best food for babies up until 6 months. Regarding the disease prevention component, 170 (94.4%) had adequate knowledge about the schedule of the first vaccine for a newborn whereas 169 (93.9%) had adequate knowledge about home treatment of diarrhea. However, only 83 (46.1.%) had adequate knowledge regarding care-seeking and treatment (Table -2).

Table-2: Knowledge regarding the four main components of IMNCI-C among study respondents

Knowledge: the four main areas of IMNCI – C among respondents		**Adequate knowledge** N (%)	**Inadequate knowledge** N (%)
Knowledge: Physical growth and mental development ***Adequate knowledge*** *(Score 5-8)* **-** ***Inadequate knowledge*** *(Score ≤ 4.0)*			
i)	The best food for baby during the first 6 months of life **(Mother's milk)**	180(100%)	0
ii)	The term exclusive breastfeeding means **(Only breast milk along with medicine or vitamin/mineral drops**)	46 (25.6%)	134(74.4)
iii)	The optimal duration of exclusive breastfeeding **(6 months)**	146(81.1%)	34(18.9%)
iv)	The importance of exclusive breast feeding**(It gives an infant the best chance to grow and stay healthy)**	140(77.8%)	40 (22.2%)
v)	The minimum frequency of breast feeding for a young infant of 6 months /day**(At least 8 times/day)**	50(27.8%)	130(72.2%)
vi)	The appropriate weaning age **(6 months)**	148(82.2%)	32(17.8%)
vii)	Common types of weaning foods offered initially (**Kitchri/dalia/mashed banana, boiled potatoes etc)**	174 (96.7%)	6(3.3%)
viii)	Total duration of breast feeding along with weaning foods**(24 months /2 years)**	154(85.6%)	26(14.4%)
Total		**152(84.4%)**	**28(15.6%)**
Knowledge: Disease prevention ***Adequate knowledge*** *(Score 2.5-5.0)* **-** ***Inadequate knowledge*** *(Score ≤ 2.5)*			
i)	The best method of prevention from childhood infections(**Immunization)**	89(49.4%)	91(50.6%)
ii)	Diseases for which the child is immunized by EPI schedule **(Any 4 or more) Tuberculosis, Diphtheria, Pertussis, Tetanus, Polio, Pneumonia, Meningitis, Hepatitis B, Measles**	38(21.1%)	142(78.9%)
iii)	The schedule of the first vaccine for a newborn **(At birth)**	170(94.4%)	10(5.6%)
iv)	The schedule of the first measles vaccine for an infant **(At 9 months)**	62(34.4%)	118(65.6%)
v)	The best precaution before feeding the child(**Hand washing)**	165(91.7%)	15(8.3%)
Total		**118(65.6%)**	**62(34.4%)**
Knowledge: Home management of childhood illness ***Adequate knowledge*** *(Score 1.6 - 3)* **-** ***Inadequate knowledge*** *(Score ≤ 1.5)*			
i)	Feeding during illness **(More breast milk and other fluids to be offered to a sick child)**	68 (37.8%)	112 (62.2%)
ii)	Home treatment of child having diarrhea (**Oral Rehydration Solution)**	169 (93.9%)	11 (6.1%)
iii)	Home treatment of a child with cough and cold**(Keep the child warm and dry, safe home remedies to soothe throat)**	133 (73.9%)	47 (26.1%)
Total		**134(74.4%)**	**46(25.6%)**
Knowledge: Care seeking and treatment ***Adequate knowledge*** *(Score 1.6 - 3)* **-** ***Inadequate knowledge*** *(Score ≤ 1.5)*			
i)	Care seeking for a sick child suffering from diarrhea**(Child is not able to drink or breastfeed , sunken eyes**)	73 (40.6%)	(59.4%)
ii)	Care seeking for a sick child suffering from cough and cold **(Child is having fast breathing, lower chest in the drawing)**	89(49.4%)	91(50.6%)
iii)	Importance of follow up **(If treatment prescribed is effective)**	97(53.9%)	83(46.1%)
Total		**83(46.1%)**	**97(53.9%)**

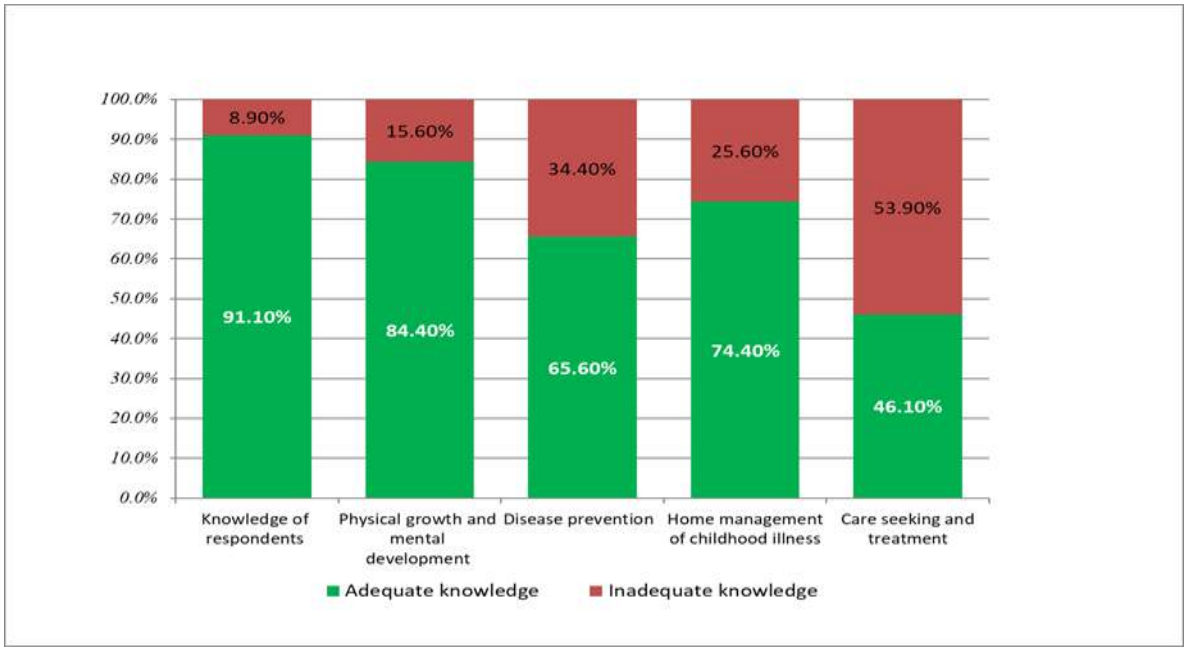

Figure 1: Overall Knowledge of study respondents regarding IMNCI – C

Overall Practices of study respondents regarding IMNCI – C:

As regards the practices of IMNCI-C, the majority of mothers 171 (95%) had adequate practices. Adequate practices in the domain of physical growth/development and care seeking / treatment were reported by 113(62.8%) and 126(70%)mothers respectively. (Figure-2). About 100 (55.6%) and 106(58.9%) mothers had adopted age-appropriate breast feeding and weaning practices respectively. In the area of disease prevention, BCG vaccination against tuberculosis was confirmed by immunization scar in 162(90%) children. Oral polio vaccine coverage was reported by all respondents. Regarding home management of childhood diarrhoea, 163(90.6%) children were offered extra fluids. (Table -3)

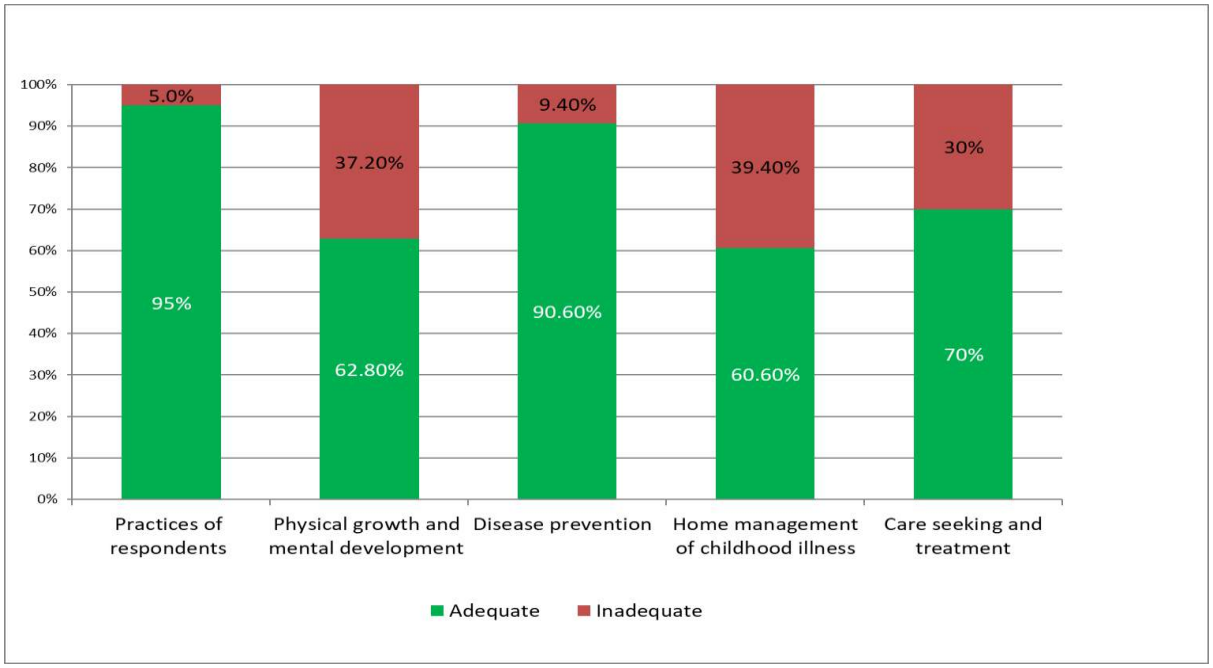

Figure-2: Overall Practices of study respondents regarding IMNCI – C

Table-3: Practices regarding the four main areas of IMNCI – C among study respondents

Practices: the four main areas of IMNCI – C among respondents		**Adequate Practice N (%)**	**Inadequate Practice N (%)**
Practice: Growth and development ***Adequate Practice (Score 2.5-5.0) - Inadequate Practice (Score ≤ 2.5)***			
i)	Breast feeding for 6 months**(exclusive breast feeding)**	103(57.2%)	77(42.8%)
ii)	Total duration of breast feeding**(according to age)**	100(55.6%)	80 (44.4%)
iii)	Starting age of complementary feeding **(6 months)**	106(58.9%)	74(41.1%)
iv)	Types of common weaning foods offered to the child in the last 24 hours	177(98.3%)	3(1.7%)
v)	Frequency of food serving according to age	32(17.8%)	148(82.2%)
Total		**113(62.8%)**	**67(37.2%)**
Practice: Disease prevention ***Adequate Practice****(Score3-4) -* ***Inadequate Practice****(Score ≤ 2)*			
i)	BCG vaccination against tuberculosis **(by immunization scar)**	162(90%)	18(10%)
ii)	Confirmation of Immunization status **(by card)**	101(49.1%)	79(43.9%)
iii)	Oral polio vaccination **(drops in the mouth every)**	180(100%)	00.0
iv)	Hand washing practice (Any 3 or more options)	173(96.15)	7(3.9%)
Total		**163(90.6%)**	**17(9.4%)**
Practice: Home management of childhood illness ***Adequate Practice****(Score 2.5-5.0) -* ***Inadequate Practice****(Score ≤ 2.5)*			
i)	Feeding during illness**(more frequently and for longer)**	39(21.7%)	141 (78.3%)
ii)	The extra fluid after each loose stool(**Yes)**	163 (90.6%)	17 (9.4%)
iii)	Method of giving ORS to a sick child(**Frequent small sips from a cup or spoon)**	97 (53.9%)	83(46.1 %)
iv)	ORS after the child vomited **(wait 10 minutes before giving more fluid, give slowly)**	87(48.3%)	93 (51.7%)
v)	Home management of cold and cough **(Any one option) (Keep the child warm and dry, safe home remedies to soothe throat)**	136(75.6%)	44(24.4%)
Total		**109(60.6%)**	**71(39.4%)**
Practice: Care seeking and treatment ***Adequate Practice****(Score 1-2) -* ***Inadequate knowledge*** *(Score ≤ 0)*			
i)	Recognition of 2or more danger signs	172 (95.6%)	8 (4.4%)
ii)	Follow up visit	133(73.9%)	47(26.1%)
Total		**126(70%)**	**54(30%)**

There was a significant statistical association between the age of children and mothers' knowledge regarding IMNCI-C ($\chi 2$ =7.935, P value =0.019). No statistical significance of age, education, occupation, or income of mothers was reported in association with their knowledge and practices of C-IMNCI.(Table-4)

Table-4: Relationship of age, education, occupation, income per capita and age of the child with overall knowledge regarding IMNCI-C among respondents.

	Knowledge Score		P -Value	χ^2
	Inadequate knowledge (Score ≤ 9.0)	Adequate knowledge (Score 10 -19)		
Age of Mothers				
20-30 years	14(87.5%)	127 (77.4%)	**0.351**	**0.869**
31+	2(12.5%)	37(22.6%)		
Education of Mothers				
Illiterate	5(31.1%)	43(26.2%)	**0.664**	**0.189**
Literate	11(68.8%)	121 (73.8%)		
Occupation of Mothers				
Housewife	16(100%)	161(98.2%)	**0.585**	**0.298**
Working	0(0.00%)	3 (1.7%)		
Income per capita				
PKR1000-6000	16(100%)	152(92.7%)	**0.263**	**1.254**
PKR 6001and	0(0.00%)	12 (7.3%)		
Age of Child				
6-24 months	7 (43.8%)	112(68.3%)	**0.019**	**7.935**
25-42 months	9(49.3%)	40(24.4%)		
43-60 months	0(0.0%)	12(7.3%)		
Total (180)	16	164		

DISCUSSION

In our study, adequate overall knowledge of IMNCI-C was reported in 91.1% of mothers. It might be due to the flexible knowledge scale used and better literacy rate among mothers as 73% of respondents were having some formal education from primary level to master. It agrees with a study conducted in Nigeria which stated that 90.5% of the mothers had a piece of high knowledge about IMCI-C practices and the respondents were fairly educated.[12]

A high level of knowledge may be attributed to various other factors such as guidance transferred from family members like grandmothers, mothers, elder sisters and friends. Also, our religion provides advice about breast feeding and cleanliness. Our study area was in the vicinity of a tertiary care hospital from where many of our respondents might get information regarding the care of their children. The role of the lady health worker is very important especially in our area of research as she focused on health education regarding nutrition (breast feeding, weaning) and vaccination advice. The study aligns with previous research conducted in India, which assessed the effectiveness of structured teaching on knowledge of IMCI guidelines among mothers. The study found that 90% of mothers had average knowledge, 10% had good knowledge scores in the pre-test, and after structured teaching, 66% of mothers were in the excellent grade and 34% had good knowledge grades.[15]

The community component of IMNCI focuses on the role of sixteen key health practices within the household and community for child survival, growth and development, divided into 4 main areas. This study assessed the knowledge of these four areas among the participating mothers and showed that three of the fourth mothers had adequate knowledge regarding the physical growth and mental development of children under five. Mothers' knowledge of breast feeding is a good indicator to achieve breastfeeding practices. All mothers knew that mother's milk is the best food for a baby during the first six months of life which is consistent with a study conducted in India.[16] Weaning is often beneficial in reducing early infant mortality. The current study found that

above eighty percent of mothers knew the appropriate age for weaning and knowledge of common weaning foods which is consistent with a study conducted in Nigeria which found that most of the mothers possessed a good knowledge of feeding and weaning.[17]

Additionally, our study found that nearly two third mothers had adequate knowledge of disease prevention, mothers agreed that immunization is the best method to prevent childhood infections which is in line with studies conducted in Cyprus (64%)[18] and Georgia (68%).[19] Proper hand washing is considered the first line of defence against the spread of many illnesses. In this study, the majority of mothers considered hand washing as the best precaution before feeding their child congruent with the studies done in Ethiopia (47.8%)[20] and Saudi Arabia (83.8%)[21]

Our study concluded that three fourth of respondents had adequate knowledge of home management for diarrhea and pneumonia. It aligns with a study conducted in Eastern Ethiopia.[22] A community-based study in Al Mukalla, Yemen found that about eighty percent of urban mothers had good knowledge of pneumonia prevention.[23] A study conducted in Myanmar also found that mothers had high levels of knowledge of childhood pneumonia and moderate overall self-efficacy in-home care for children with pneumonia.[24]

Appropriate care-seeking behaviour refers to mothers who seek out care for their children with general danger signs from proper healthcare providers. The current study found that less than half of mothers had adequate knowledge of care-seeking and treatment similar to a study in Ethiopia where 44.7% of mothers had good knowledge of the general danger signs for care seeking of common childhood illnesses.[25]

Regarding the practice of IMNCI-C, a high majority of mothers had overall adequate practices. Practices of IMNCI-C are profoundly affected by the mothers' knowledge. Higher knowledge about IMNCI-C among mothers leads them to utilize IMNCI services more. A high level of knowledge and an even better level of practice were reported in our study. A variety of psychological and social factors responsible for better maternal awareness and its application include beliefs, cultural experiences, norms and expectations, available support and existing attitudes. It could be due to the better education, guidance by experienced family members and awareness imparted by lady health workers. The four key area practices were reported as growth and development, disease prevention, home management and care seeking. A study conducted in Colombia evaluated the 18 key practices of the IMCI-C strategy among caregivers, the most used practices were related to disease control (80% to 99.3%), although a high percentage of caregivers did not recognize the warning signs. Less commonly used practices were related to health promotion and disease prevention (23% to 57.9%) as caregivers thought them unworkable.[26]

A recent study found that above sixty percent of mothers had adequate practices in growth and development promoting activity specifically in optimal breast and complementary feeding. This is supported by the demographic and health survey of Pakistan, which reported that exclusive breastfeeding among children under 6 months of age has increased from 38% in 2012-13 to 48% in 2017-18.[27] Age-appropriate breastfeeding practices by mothers reported in our study were following the demographic and health survey of Pakistan(54%).[27] Appropriate complementary feeding and weaning depend on precise information and proficient assistance from the family, community and healthcare system. The age-appropriate weaning practices by mothers found in our study are consistent with studies conducted in Sudan[28] and South India[29] where 62% and 63.35% of mothers started weaning their children promptly, respectively.

Above ninety percent of mothers had adequate practices regarding disease prevention in our study. BCG vaccination

was confirmed by scar in the majority of children and Oral polio vaccination was reported by all. Basic Immunization status (by card) was less than fifty percent in contrast to a study conducted in Urban Multan where 91% of children received age-based full basic immunization.It might be due to the difference in the study area.[30] The overall coverage for completely immunized children between the ages of 12-23 months in Pakistan is 66%, with significant inequality among provinces.[27] A study conducted in 8 districts of southern Pakistan found that only 30.8% of children were fully vaccinated, 46% were incompletely vaccinated, and 23% were non-vaccinated.[31] Proper handwashing practices have a vital role in reducing the burden of childhood diseases. The present study found that above ninety percent of mothers practised handwashing adequately in contrast to a study from Northwest Ethiopia where only 39.1% of mothers practised good handwashing probably because of their lower socioeconomic status.[32]

The study established that about sixty percent of mothers had adequate practices related to the home management of childhood illnesses, and most of the mothers gave extra fluids to their sick child which is similar to a study in Nepal[33] where mothers gave more fluids than usual to their child during diarrhea. However, a study from Saudi Arabia found that although 62% of mothers knew about oral rehydration therapy, only 23.5% of them used it. The reason was an inadequate level of awareness of respondents and insufficient public info on the subject.[34] A study conducted in Ethiopia revealed that 58% of mothers had poor practices in home-based diarrhea management, it might be because 45% of mothers were illiterate.[22] The current study found that three fourth of mothers correctly managed their child's cold and cough at home in agreement with a study from Yemen where rural mothers used home remedies (61.3%).[23]

The health-seeking behaviour of mothers for childcare depends on the proper recognition of key symptoms of illness. Adequate practices of care seeking and treatment were reported by two thirds of caretakers similar to a study in Kenya where 56.9% of the respondents brought the child to the hospital immediately after observing danger signs.[35] The differences observed in the results of various studies could be because mothers were exposed to different types and amounts of information due to variable sociodemographic and cultural patterns. Moreover, different scales were used to determine adequate and inadequate practices of C-IMNCI in the various studies.

There was a significant statistical association between the age of children and mothers' knowledge regarding IMNCI-C in the current study. Mothers of children between the ages of 2 to 5 years were less likely to have adequate knowledge than mothers of children between 6 and 24 months. It is supported by other studies done in Burkina Faso[36] and Bangladesh[37] that found that mothers/caregivers of children between 2-5 years old engaged in less care-seeking behaviours. Mothers might think age below two years is a crucial period for children with the illness so they tend to take care of their younger children more than the older ones.

No statistical significance was specified regarding the age, occupation and income per capita of mothers and their knowledge and practices of IMNCI-C**.** The same is true for the education of mothers and their knowledge and practice of IMNCI-C in contrast to the studies conducted in Nigeria[12], Ethiopia[38] and Zimbabwe[39] which have shown that the education of the child's mother or caregiver is an important factor for optimal childrearing and improving child survival.

Improvement in family and community participation is very important for IMNCI to be successful. Successful implementation of the IMNCI strategy requires raising awareness of the benefits of IMNCI among policymakers, healthcare providers, professional associations, non-governmental organizations, the private sector, donors, and the general public.

It is important to tailor interventions and strategies to the specific circumstances of a given country. Further research on family and

community behaviours can help to develop effective interventions for the prevention and management of childhood illnesses in the home and community setting.

It was a community study in peri urban setting which focused on all four domains of IMNCI-C. The systematic random sample selection and a complete lack of non-consenters added strength to our study.

One limitation of this study is that it relied on mothers' self-report of their knowledge and practices regarding the community component of IMNCI, rather than observing them directly. As a result, their responses may not fully reflect their actual practices. Additionally, the results cannot be generalized as this was a cross-sectional study done in a peri urban setting.

CONCLUSION

Overall knowledge and practices of mothers in peri urban areas, regarding IMCI-C were adequate, with a significant association between the age of the child and the mother's knowledge regarding IMCI-C. No statistical significance of age, education, occupation income of mothers and their knowledge and practice of C-IMNCI was appreciated.

AUTHORS CONTRIBUTION

MJK: Contributes to the conception, design, execution and analysis and final interpretation of data, article writing (abstract, objective, introduction, discussion) accountable for all aspects of the manuscript.

SH: Supervised all the activities of the study. Participated in drafting and revising the manuscript critically. Finally approved the manuscript.

ZPB: Assisted in SPSS data entry, data analysis, result writing up and interpretation of results.

SA: Helped in editing, and assisted in writing the final results for the manuscript conclusion and recommendations.

REFERENCES

1. Child survival / Under five mortality [Internet]. December 2021. Available from: https://data.unicef.org/topic/child-survival/under-five-mortality/#sthash.
2. Pakistan (PAK) -Demographics,Health &Infant mortality [Internet]. 2020. Available from: https://data.unicef.org/country/pak/.
3. Julia Ross KLaLW. Community-based Integrated Management of Childhood IllnessPolicy Guidance. In: (USAID) CGaUSAID, editor. January 2009.
4. IMCI | Child and adolescent health: WHO Regional Office for the Eastern Mediterranean; [Available from: https://www.emro.who.int/child-adolescent-health/imci/index.html.
5. Implementation of IMCI in Pakistan. Strategy-implementation. Child health and development.: WHO Regional Office for the Eastern Mediterranean; [Available from: https://www.emro.who.int/child-health/strategy-implementation/implementation-of-imci-in-pakistan.html.
6. (MCSP) TMaCSP. Review of Newborn Health Content in Integrated Management of Newborn and Childhood Illnesses and Integrated Community Case Management Training Materials and Job Aids in Seven Maternal and Child Survival Program Countries. 2019 September 17.
7. Community based interventions|Child and Adolescent health: WHO Regional Office for the Eastern Mediterranean; [Available from: https://www.emro.who.int/child-adolescent-health/community-based-interventions/index.html.
8. World Health Organization. Framework for the community component of the integrated child care strategy. WHO. Regional Office for the Eastern Mediterranean; 2002.
9. Qazi S. WHO/UNICEF Integrated Management of Childhood Illness (IMCI) and Child Health Redesign. 2019.
10. Integrated management of childhood illness [Internet]. Available from: https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/child-health/integrated-management-of-childhood-illness.
11. Mukunya D, Kizito S, Orach T, Ndagire R, Tumwakire E, Rukundo GZ, et al. Knowledge of integrated management of

childhood illnesses community and family practices (C-IMCI) and association with child undernutrition in Northern Uganda: a cross-sectional study. BMC Public Health. 2014 Dec;14:1-7. https://doi.org/10.1186/1471-2458-14-976
12. Akwataghibe NN, Ogunsola EA, Broerse JE, Popoola OA, Agbo AI, Dieleman MA. Exploring factors influencing immunization utilization in Nigeria—a mixed methods study. Frontiers in public health. 2019 Dec 20;7:392.
13. K Khaliq A, Amreen, Jameel N, Krauth SJ. Knowledge and practices on the prevention and management of diarrhea in children under-2 years among women dwelling in urban slums of Karachi, Pakistan. Matern Child Health J. 2022 Jul;26(7):1442-52. https://doi.org/10.1007/s10995-022-03391-9
14. Eliyas A, Sherali S, Khan I, Khan K, Hashmi F. Mothers knowledge related preventive measure of pneumonia in slum community, Karachi, Pakistan. Pak J Health. 2018 Dec 11;8(3):156-9. https://doi.org/10.32413/pjph.v8i3.181.
15. Dani MR, Pandhare MP. Effect of Structured Teaching on Knowledge Regarding Management of Diseases as per IMNCI Guidelines among the Mothers of Under-Five Children's At Anganwadis. Nveo-natural volatiles & essential OILS Journal| NVEO. 2021 Nov 27:8767-73.
16. Siddha S. A cross sectional study on breastfeeding and weaning practices among pregnant and lactating women. METHODOLOGY. 2018 Jun;5(06).
17. Akpor O, Oluwadare T, Taiwo O, Aladenika B, Akpor O. Feeding and weaning practices among mothers of under-five children in selected primary health care centres in ado-ekiti, ekiti, nigeria. Potravinarstvo. 2020 Jan 1;14(1).
18. Kyprianidou M, Tzira E, Galanis P, Giannakou K. Knowledge of mothers regarding children's vaccinations in Cyprus: A cross-sectional study. PLoS One. 2021 Sep 20;16(9):e0257590. https://doi.org/10.1371/journal.pone.0257590
19. Verulava T, Jaiani M, Lordkipanidze A, Jorbenadze R, Dangadze B. Mothers' knowledge and attitudes towards child immunization in Georgia. Open Public Health J. 2019 May 31;12(1). doi: 10.2174/1874944501912010232
20. Dagne H, Bogale L, Borcha M, Tesfaye A, Dagnew B. Hand washing practice at critical times and its associated factors among mothers of under five children in Debark town, northwest Ethiopia, 2018. Ital J Pediatr. 2019 Dec;45:1-7. https://doi.org/10.1186/s13052-019-0713-z.
21. Ayaz WO, Priyadarshini A, Jaiswal AK. Food safety knowledge and practices among Saudi mothers. Foods. 2018 Nov 25;7(12):193.. https://doi.org/10.3390/foods7120193
22. Workie HM, Sharifabdilahi AS, Addis EM. Mothers' knowledge, attitude and practice towards the prevention and home-based management of diarrheal disease among under-five children in Diredawa, Eastern Ethiopia, 2016: a cross-sectional study. BMC pediatrics. 2018 Dec;18:1-9. https://doi.org/10.1186/s12887-018-1321-6
23. Al-Noban MS, Elnimeiri MK. Mothers knowledge, attitude and practices regarding acute respiratory infection in children under five years/urban and rural Areas-Al Mukalla city-2022. EJUA-BA 2022 Jun 30;3(2):93-100. https://doi.org/10.47372/ejua-ba.2022.2.157
24. Naing MP, Payakkaraung S, Sanasuttipun W. Factors Predicting Mothers' Self-efficacy in Providing Home Care for Children with Pneumonia in Yangon, Myanmar. Nurs Sci J Thai. 2022 May 17;40(3):120-34.
25. Gebreslasie S, Welu G, Berhane B, Gebresilassie B, Fseha B, Tsegay T, et al. Exploring knowledge on danger signs of common childhood illnesses and associated factors among mothers of under-five children in Central Tigrai, Ethiopia: a cross-sectional study. Germs. 2020 Mar;10(1):9. doi: 10.18683/germs.2019.1175
26. Padilla-Choperena C, Amador-Ahumada C, Puello-Alcocer E. Effectiveness of the implementation of community IMCI strategy in Montería, Colombia. Enfermería Global. 2018 Oct 1;17(4):265-77.
27. National Institute of Population Studies - NIPS/Pakistan, ICF. Pakistan Demographic and Health Survey 2017-18. Islamabad, Pakistan: NIPS/Pakistan and ICF; 2019.
28. Ahmed AA. Complementary Feeding and Weaning Practices among Women In Omdurman Althora Locality And Their Influencing Factors. 2021.

29. J Jabeen A, Amberina AR, Gayathri V, Eshwar MD, Dodda S, Begum GS, et al. Assessment of breastfeeding, weaning, and complementary feeding practices among women attending a Tertiary care teaching hospital in South India. Cureus. 2022 Sep 5;14(9).
doi: 10.7759/cureus.28791
30. Ijaz B, Javed R, Iqbal S, Yousaf R, Raza A. Knowledge, attitude & practices among parents living in urban areas of multan about routine vaccination of their children under five years of age. JNMU. 2019;2(1):9-14.
31. Riaz A, Husain S, Yousafzai MT, Nisar I, Shaheen F, Mahesar W, et al. Reasons for non-vaccination and incomplete vaccinations among children in Pakistan. Vaccine. 2018 Aug 23;36(35):5288-93. https://doi.org/10.1016/j.vaccine.2018.07.024.
32. T Taddese AA, Dagnew B, Dagne H, Andualem Z. Mother's handwashing practices and health outcomes of under-five children in Northwest Ethiopia. Pediatric health, Med. Ther. 2020 Mar 11:101-8.
doi: 10.2147/PHMT.S238392.
33. Shah S, Shreshta M, Sharma B, Pandey N, Dahal S. Knowledge and Practice on Childhood Diarrhea among Mothers having Children Under Five Years of Age in Madhuban, Sunsari-Nepal. Religion. 2019;20(42):29-1.
34. Alghadeer S, Syed W, Alhossan A, Alrabiah Z, Babelghaith SD, Al Arifi MN, et al. Assessment of Saudi mother's knowledge and attitudes towards childhood diarrhea and its management. Int J Environ Res Public Health. 2021 Apr 9;18(8):3982. https://doi.org/10.3390/ijerph18083982.
35. Wambui WM, Kimani S, Odhiambo E. Determinants of health seeking behavior among caregivers of infants admitted with acute childhood illnesses at Kenyatta National Hospital, Nairobi, Kenya. Int. J. Pediatr. 2018 Dec 16;2018. https://doi.org/10.1155/2018/5190287.
36. Badolo H, Bado AR, Hien H, Méda N, Susuman AS. Factors associated with mothers' health care-seeking behaviours for childhood fever in Burkina Faso: findings from repeated cross-sectional household surveys. Glob Health Res Policy. 2022 Dec;7(1):1-2.
https://doi.org/10.1186/s41256-022-00270-2.
37. Akter S, Banna MH, Brazendale K, Sultana MS, Kundu S, Disu TR, et al. Determinants of health care seeking behavior for childhood infectious diseases and malnutrition: a slum-based survey from Bangladesh. J Child Health Care. 2022 Feb 14:13674935211057714.
https://doi.org/10.1177/13674935211057.
38. Dessie ZB, Fentie M, Abebe Z, Ayele TA, Muchie KF. Maternal characteristics and nutritional status among 6–59 months of children in Ethiopia: further analysis of demographic and health survey. BMC pediatrics. 2019 Dec;19(1):1-0. https://doi.org/10.1186/s12887-019-1459-x.
39. James N, Acharya Y. Integrated management of neonatal and childhood illness strategy in Zimbabwe: An evaluation. Glob Public Health. 2021 Nov 22;1(11):e0000046.

Original Article

RELATIONSHIP OF AGE WITH INTRAOCULAR PRESSURE AND CENTRAL CORNEAL THICKNESS IN HYPERTENSIVE AND NON-HYPERTENSIVE PATIENTS

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ABSTRACT

Background: Increased Intraocular Pressure (IOP) is the main risk factor for glaucoma and a principal cause of permanent blindness throughout the world. Glaucoma has been significantly linked with aging. The objective of this study is to correlate the effect of age on IOP and Central Corneal Thickness (CCT) in hypertensive and non-hypertensive subjects of the Pakistani population.

Material and Methods: 54 hypertensive and 54 non-hypertensive subjects, taken from Eye OPD Mayo Hospital, were studied. A mercuric sphygmomanometer was used to determine the blood pressure after written informed consent. Assessment of IOP was done by Goldmann applanation tonometer by using 2% fluorescein strips. An ultrasound pachymeter was used for the measurement of CCT.

Results: IOP decreased with age and depicted a weak and negative association in patients with hypertension while CCT showed a weak and positive association with age among hypertensives.

Conclusion: As age increases, the levels of IOP decrease and CCT shows a weak and positive correlation with age in hypertensive patients.

Key Words: Hypertension, Patients, Intraocular pressure, Body mass index

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INTRODUCTION

Intraocular pressure (IOP) is the pressure felt in the eye. Due to the aqueous humor generation and drainage, it is controlled and kept in balance. Its value lies between 11 and 21 mmHg.[1]

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Age, blood pressure, CCT, diabetes, vascular disease, and myopia-related refractive error all affect it differently.[1] Since central corneal thickness (CCT) is the primary predictor of IOP and flattening of the cornea is associated with IOP measurement. Its normal thickness in the center is from 490 to 560 mmHg.[2] Clinically, CCT measurement is directly involved in the therapy of 15% of glaucoma patients.[3]

Hypertension is the foremost cause of renal failure, heart attacks and stroke. Predictably, almost about 17 million deaths every year occur due to cardiovascular diseases globally, of which 9.4 million are due to hypertension complications. Low physical activity, tobacco

use, a poor diet and a high salt intake all raise the risk of hypertension. Aging is a significant additional risk factor for hypertension.[4] Literature review shows that there is a strong correlation between age, IOP, central corneal thickness, and blood pressure.[5] A few studies concluded that with younger age, and with high systolic blood pressure, IOP increases.[6] Whereas a different study proved that IOP decreases with age.[7] Additionally, a different study found no link between CCT and age, gender, IOP, or hypertension.[8] Furthermore, the research found no evidence of a significant relationship between IOP and body mass index or age.[9]

The main risk factor for glaucomatous optic neuropathy is increased intraocular pressure (IOP), however moderate to high myopia and thinner central corneal thickness (CCT) are also risk factors.[10] along with some other ocular factors are also known to be the cause of glaucoma. In patients with elevated IOP, CCT plays a crucial part for being a parameter for determining the risk of developing glaucoma.

Increased IOP is the main, and the only modifiable risk factor for glaucoma, and a principal cause of permanent blindness throughout the world.[11] Glaucoma has been significantly linked with aging.[12] Much cross-sectional research has already investigated the link between IOP and age. Some studies concluded an increase in IOP with age among South Asian and Japanese people.[6-9] On the contrary, most studies concluded a decrease in IOP as Asian people aged.[13-15] The relationship between age with IOP and CCT is still uncertain because of controversial results found in the literature review. Hence, the current study was done to determine the relationship between age with IOP and CCT among hypertensives versus non-hypertensives Pakistani population.

MATERIAL AND METHODS

After taking approval from the Ethical committee of KEMU we conducted this Case control study at the Physiology Department of KEMU, Lahore in collaboration with the Ophthalmology Department of Mayo Hospital, Lahore. A total of 108 subjects (54 controls and 54 hypertensives) were enrolled in our study. Informed written permission was taken from the patient aged between 45-65 years. Non-Probability purposive sampling was done. Registered and physician diagnosed cases of hypertension were included. Patients were excluded who have pre-existing ocular surface pathologies (like a corneal ulcer, corneal opacity) on slit lamp examination, history of contact lens wear during the last 6 months, history of intraocular surgery, laser or trauma during the last 6 months, Corneal astigmatism ≥3 diopters checked by autorefractor. A complete eye examination was done. Blood pressure was measured with a mercuric sphygmomanometer in a sitting position and an average of three readings was taken. IOP was measured by a Goldmann applanation tonometer after anesthetizing the eye with topical proparacaine 0.5% and 2% fluorescein strips. Three consecutive readings were recorded. 5 ml of blood sample was drawn using an aseptic measure for the determination of serum electrolytes by Easylyte Plus Na/K/Cl Analyzer.

SPSS 25 was used for data entry and analysis. Mean and SD was reported for normally distributed variables. Median and IQR were given for non-normally distributed variables. T-test was used to compare the mean between the two groups. Pearson correlation was applied to find out any correlation between variables. p-value ≤ 0.05 was considered statistically significant.

RESULTS

The mean age of both groups hypertensive and non-hypertensive patients was 56.37±6.71 years and 52.35±5.92 years respectively. Gender distribution showed that there were 60 males and 48 females included in the study. i.e. (Hypertensive: Male: 30 & Female: 24 & Non-

Hypertensive: Male: 30 & Female: 24). Comparison of study variables in both groups is given in Table 1 and Table 2 showed the correlation of study variables.

Table-1: Comparison of IOP and CCT in hypertensives and non-hypertensive subjects

Parameters	Hypertensives	Non-hypertensives	p-value
Age (n=54)	56.37±6.71	52.35±5.92	
IOP (right eye)	17.38±3.99	14.05±3.98	0.000
IOP (left eye)	18.77±6.86	15.09±2.84	0.000
CCT (Right eye)	52.80±30.16	529.57±42.51	0.606
CCT (left eye)	52.42±28.84	533.38±37.93	0.285

Table-2: Correlation of IOP and CCT in hypertensive and non-hypertensive subjects

Parameters		Age	
		HTN	NON-HTN
IOP (right eye)	r / rho	-0.204	0.271
	p-value	0.140	0.048
	N	54	54
IOP (left eye)	r / rho	-0.291	0.001
	p-value	0.033	0.992
	N	54	54
CCT (right eye)	r / rho	0.025	-0.303
	p-value	0.857	0.026
	N	54	54
CCT (left eye)	r / rho	0.087	-0.267
	p-value	0.533	0.051
	N	54	54

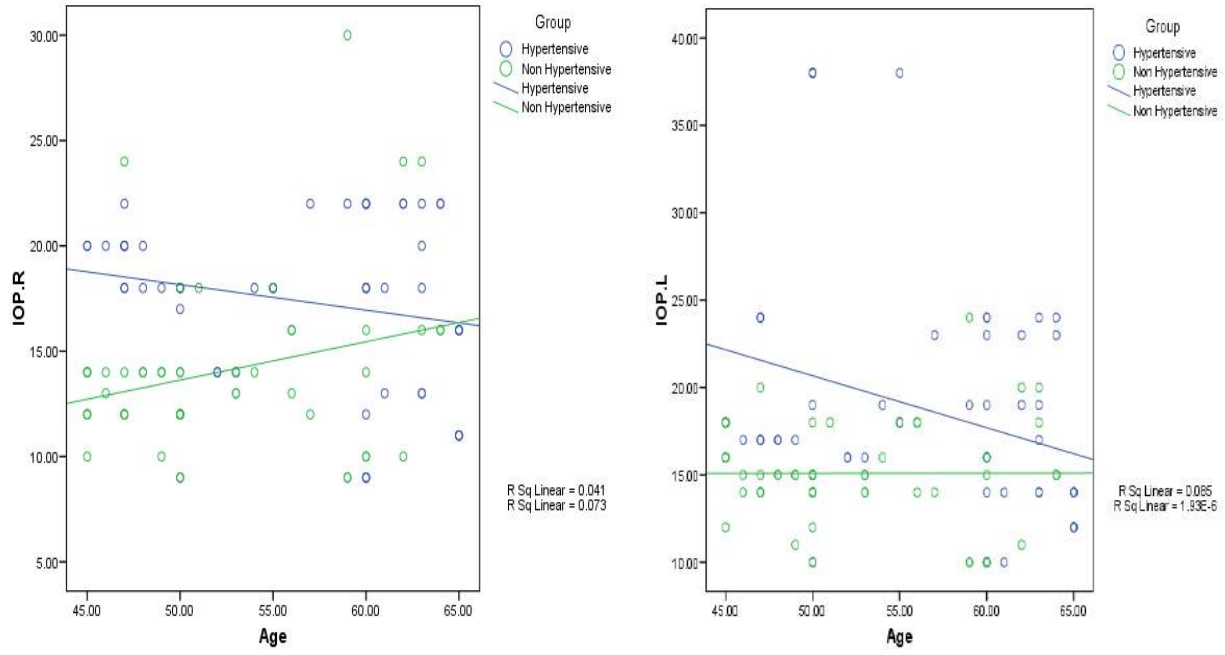
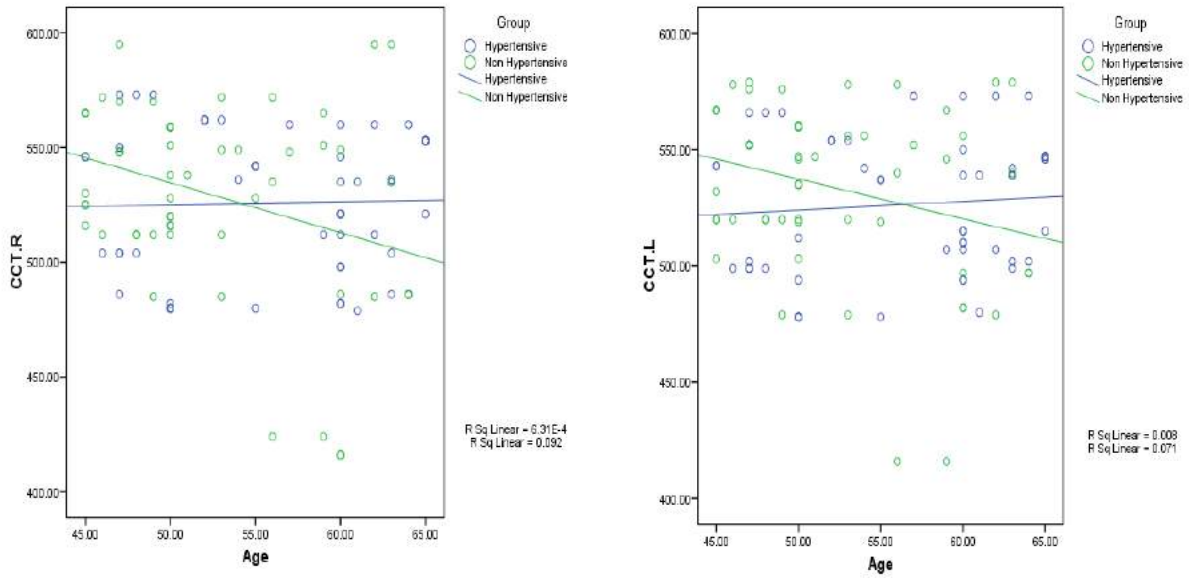


Figure-1: Correlation between age and IOP in hypertensive and non-hypertensive subjects



Fugure-2: Correlation between CCT and age in hypertensive and non-hypertensive subjects.

IOP was statistically high in hypertensives as compared to non-hypertensives in right and left eye. CCT was statistically the same in right and left eye in hypertensives and non-hypertensive patients. IOP showed weak and negative correlation with age in hypertensives. CCT showed weak and positive correlation with age in hypertensives. In normotensive subjects, IOP showed weak and positive correlation with age and CCT showed weak and negative correlation with age.

DISCUSSION

In hypertensive individuals, there is a link between age and IOP, according to our findings. IOP in the left eye exhibits a negative relationship with age among hypertensives. Many studies found a negative relationship between IOP and age.[13-15]

Our study along with research done on the East Asian population showed that IOP decreased with aging in Asians. [16-18]

IOP showed a significant positive correlation with age in non-HTN. The majority of the cross-sectional and longitudinal research done in Europe and America found that IOP rises with age. One study found that the trabecular meshwork's age-related structural alterations considerably compensated for an individual's declining aqueous humor production.[19-20] Some research done in Africa came up with a similar correlation as well.[21,22] On the other hand, Asian studies have different results.[23] In China, the Handan Eye Study discovered an inverted U-shaped relationship between IOP and age.[24]

Yoshida and Fukuoka recognized the mismatch of Asian research findings with other, comparable studies and ascribed it to ethnic and environmental factors.[25] They hypothesized that in Europeans and Americans, the hypertensive effects of increased BP and BMI outweighed the hypotensive effects of age, leading IOP to seem to rise with age.[25] In contrast, because obesity and hypertension are less common in Japan, age-related hypotensive effects may predominate, causing an apparent drop in IOP with age.[26]

CCT showed a weak and positive correlation with age in HTN. CCT showed a significant negative correlation with age in non-HTN. CCT in the right and left eye showed a negative correlation with age in non-hypertensives.

Another Study has also shown a negative correlation between age and CCT.[26]

Cross-sectional studies conducted in the past have investigated the effect aging has on CCT but the results have been varying. Most of these concluded that there is no association,[27] while a negative association was found in the rest,[28] and only one research proved a positive association[29] of age and CCT. All the studies that had found a decrease in CCT with age had their thinning rates less than -one μm/year. The age-dependent CCT was done in some cross-sectional studies and the outcome is influenced by causes such as survival effects and age of cohorts.[29,30] It is increasingly acknowledged that as people get older, the function of aqueous humor production and outflow changes and IOP measurements on a representative group of older Asian populations are deficient. [31,32] Simultaneously, the rates of numerous systemic and chronic disorders and the use of systemic medication rise dramatically among people aged 40 and up. As there is a proven constant relationship between hypertension (HTN) and blood pressure (BP) levels with IOP,[33] the influence of BP and age on IOP is complex.

As of now, the evidence shows that the central cornea does get thinner with an increase in age, but the magnitude of change of CCT needs further explanation as to why is there a difference in untreated and healthy glaucomatous eyes.

CONCLUSION

With aging, IOP displays a physiologic decline. We also discovered that IOP changes are related to changes in systemic BP in a direct and significant manner, particularly in patients with hypertension. Our findings emphasize the importance of BP management in glaucoma patients since this will result in a reduction in IOP over time. Given that high IOP is a key risk factor for glaucoma, it emphasizes the need of regulating blood pressure in older patients, who have a higher glaucoma burden.

AUTHOR'S CONTRIBUTION

FI: Research proposal development, data collection, analysis, article writing & reviewing

RKA: Research proposal development, analysis, article writing & reviewing

HS: Research proposal development & data collection

MI: Analysis, article writing & reviewing

MAN: Data collection, analysis & article writing

HS: Analysis, Article writing & reviewing

REFERENCES

1. Kanski JJ, Bowling B. Clinical ophthalmology: a systematic approach. Elsevier Health Sciences; 2011 Apr 28.
2. Park HM, Choi J, Lee WJ, Uhm KB. Rate of central corneal thickness changes in primary angle closure eyes: long-term follow-up results. BMC ophthalmology. 2021 Dec;21(1):1-0.
3. World Health Organization. Global Status Report on Noncommunicable Diseases 2014. WHO 2014. https://www.ahajournals. org/doi/full/10.1161 /STROKEAHA. 115. 008097
4. Hashemi H, Heydarian S, Aghamirsalim M, Yekta A, Hashemi A, Sajadi M, et al. Distribution and associated factors of intraocular pressure in the older population: Tehran Geriatric Eye Study. International Journal of Ophthalmology. 2023;16(3):418.
5. Ma D, Wei S, Sun Y, Li SM, An WZ, Hu JP, et al. Distribution of IOP and its relationship with refractive error and other factors: the Anyang University Students Eye Study. International Journal of Ophthalmology. 2021;14(4):554.
6. Habib R, Javed MM, Ijaz F, Aftab K, Sohail H, Aftab RR. Intra ocular pressure and central corneal thickness in hypertensive and non-hypertensive patients. Pakistan Journal of Physiology. 2020 Mar 31;16(1):3-5.
7. Fortepiani L, Foutch BK, Wilson MR. The effects of sex, oral contraception, and menstrual cycle phase on intraocular pressure, central corneal thickness, and foveal thickness: a descriptive analysis. Vision. 2021 Oct 18;5(4):48.

8. Pileggi C, Papadopoli R, De Sarro C, Nobile CG, Pavia M. Obesity, blood pressure, and intraocular pressure: a cross-sectional study in Italian children. Obesity facts. 2021;14(2):169-77.
9. Sayah DN, Lesk MR. Ocular Rigidity and Current Therapy. Current Eye Research. 2022 Jul 5:1-9.
10. Rong SS, Lu SY, Matsushita K, Huang C, Leung CK, Kawashima R, et al. Association of the SIX6 locus with primary open angle glaucoma in southern Chinese and Japanese. Experimental Eye Research. 2019 Mar 1;180:129-36.
11. Cimaglia G, Votruba M, Morgan JE, André H, Williams PA. Potential therapeutic benefit of NAD+ supplementation for glaucoma and age-related macular degeneration. Nutrients. 2020 Sep 19;12(9):2871.
12. Kuo CY, Ko YC, Kuang TM, Chou P, Chiou SH, Liu CJ. Prevalence of glaucoma in the elderly population in Taiwan: The Shihpai Eye Study. Journal of the Chinese Medical Association. 2020 Sep;83(9):880.
13. Hanyuda A, Sawada N, Yuki K, Uchino M, Ozawa Y, Sasaki M, et al. Relationships of diabetes and hyperglycaemia with intraocular pressure in a Japanese population: the JPHC-NEXT Eye Study. Scientific reports. 2020 Mar 24;10(1):5355.
14. Egorov EA, Petrov SY, Gorodnichy VV, Kuroyedov AV, Alekseev VN, Amirov AN, et al. Tonometric intraocular pressure in adult population: a population study. National Journal glaucoma. 2020 Oct 9;19(2):39-50.
15. Asaoka R, Obana A, Murata H, Fujino Y, Omoto T, Aoki S, et al. The Association Between Age and Systemic Variables and the Longitudinal Trend of Intraocular Pressure in a Large-Scale Health Examination Cohort. Investigative Ophthalmology & Visual Science. 2022 Oct 3;63(11):22-.
16. Zhao D, Kim MH, Pastor-Barriuso R, Chang Y, Ryu S, Zhang Y, Rampal S, et al. A longitudinal study of age-related changes in intraocular pressure: the Kangbuk Samsung Health Study. IOVS. 2014 Oct 1;55(10):6244-50. doi:https://doi.org/10.1167/iovs.14-14151.
17. Wang YX, Xu L, Zhang XH, You QS, Zhao L, Jonas JB. Five-year change in intraocular pressure associated with changes in arterial blood pressure and body mass index. The beijing eye study. PloS one. 2013 Oct 11;8(10):e77180. https://doi.org/10.1371/journal.pone.0077180.
18. Åström S, Stenlund H, Lindén C. Intraocular pressure changes over 21 years–a longitudinal age-cohort study in northern Sweden. Acta ophthalmologica. 2014 Aug;92(5):417-20. https://doi.org /10.1111/aos.12232.
19. Kaplan M, Abacýoglu OO, Yavuz F, Kaplan GI, Düzen B, Bursa N, et al. Intraocular pressure predicts premature coronary atherosclerosis. Revista da Associação Médica Brasileira. 2020 Dec 16;66:1707-11.
20. Hennis A, Wu SY, Nemesure B, Leske MC, Barbados Eye Studies Group. Hypertension, diabetes, and longitudinal changes in intraocular pressure. Ophthalmology. 2003 May 1;110(5):908-14. https://doi.org/10.1016/S0161-6420(03)00075-7.
21. Dohvoma VA. Emilienne Epee, Côme Ebana Mvogo. Clinical Characteristics of Patients Newly Diagnosed with Primary Open Angle Glaucoma at The Yaoundé Central Hospital-Cameroon. Journal of Ophthalmology and Research. 2020;3:1-7.
22. Wang D, Huang W, Li Y, Zheng Y, Foster PJ, Congdon N, et al. Intraocular pressure, central corneal thickness, and glaucoma in Chinese adults: the Liwan Eye Study. Am. J. Ophthalmol. 2011 Sep 1;152(3):454-62. https://doi.org/10.1016/j.ajo.2011.03.005.
23. Liang YB, Friedman DS, Zhou Q, Yang X, Sun LP, Guo LX, Handan Eye Study Group. Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. IOVS. 2011 Oct 1;52(11):8250-7. doi:https://doi.org/10.1167/iovs.11-7472.
24. Yoshida M, Take S, Ishikawa M, Kokaze A, Karita K, Harada M, et al. Association of smoking with intraocular pressure in middle-aged and older Japanese residents. Environ Health Prev Med. 2014 Mar;19:100-7. https://doi.org/10.1007/s12199-013-0359-1. https://link.springer.com/article/10.1007/s12199-013-0359-1
25. Choudhari NS, George R, Sathyamangalam RV, Raju P, Asokan R, Velumuri L, et al. Long-term change in central corneal thickness from a glaucoma perspective. Indian J.

Ophthalmol. 2013 Oct;61(10):580. doi: 10.4103/0301-4738.119338.
26. Hoffmann EM, Lamparter J, Mirshahi A, Elflein H, Hoehn R, Wolfram C, et al. Distribution of central corneal thickness and its association with ocular parameters in a large central European cohort: the Gutenberg health study. PloS one. 2013 Aug 1;8(8):e66158.
27. Pan CW, Li J, Zhong H, Shen W, Niu Z, Yuan Y, Chen Q. Ethnic variations in central corneal thickness in a rural population in China: the Yunnan minority eye studies. PLoS One. 2015 Aug 14;10(8):e0135913. https://doi.org/10.1371/journal.pone.0135913.
28. Schuster AK, Fischer JE, Vossmerbaeumer U. Central corneal thickness in spectral-domain OCT and associations with ocular and systemic parameters. J Ophthalmol 2016 Jan 1;2016. https://doi.org/10.1155/2016/2596956
29. Rushood AA, Zahrani MH, Khamis A, Rushood AA. Central corneal thickness in full-term Saudi newborns. Acta Ophthalmologica. 2012Aug;90(5):e355-8.. https://doi.org/10.1111/j.1755-3768.2012.02412.x.
30. Posarelli C, Ortenzio P, Ferreras A, Toro MD, Passani A, Loiudice P, et al. Twenty-four-hour contact lens sensor monitoring of aqueous humor dynamics in surgically or medically treated glaucoma patients. Journal of Ophthalmology. 2019 Jan 27;2019.
31. Ho H, Shi Y, Chua J, Tham YC, Lim SH, Aung T, et al. Association of systemic medication use with intraocular pressure in a multiethnic Asian population: the Singapore Epidemiology of Eye Diseases Study. JAMA ophthalmology. 2017 Mar 1;135(3):196-202..
32. Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. Am J Ophthalmol. 2014 Sep 1;158(3):615-https://doi.org/10.1016/j.ajo.2014.05.029.
33. David DS, Arun S, Sivaprakash S, Raja PV, Sharma DK. Enhanced detection of glaucoma on ensemble convolutional neural network for clinical informatics. CMC-Computers, Materials & Continua. 2022 Jan 1;70(2):2563-79.

Original Article

RESTLESS LEGS SYNDROME: DIFFERENCE IN QUALITY OF LIFE PARAMETERS BETWEEN HEMODIALYSIS PATIENTS WITH AND WITHOUT RESTLESS LEGS SYNDROME

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ABSTRACT

Background: The majority of abnormal motions that happen during sleep often involve the movement of legs, the most prevalent of which is Restless Legs Syndrome (hereinafter referred to as "RLS"), also known as "Willis Ekbom Disease". Hemodialysis therapy causes a variety of side effects in individuals with chronic renal disease, notably Restless Legs Syndrome, which can be quite distressing forthis patient population. This study seeks to ascertain the incidence of restless legs syndrome amongst people with chronic renal disease receiving hemodialysis in Lahore health facilities.

Material and methods: A non-probability convenience sample of 70 patients with chronic kidney disease receiving hemodialysis was taken in an observational (cross-sectional) research at the Shaikh Zayed National Institute of Kidney Diseases and the Jinnah Hospital in Lahore. Using the widely accepted IRLSSG diagnostic criteria, restless legs syndrome was identified in respondents who answered yes to all questionnaire items. The WHOQOL BREF (World Health Organization QoL Brief Version) assessment was used to examine one's quality of life.

Results: Participants' mean ages ranged from 54.97±9.54 years. 46 (65.7%) of the 70 participants were men, and 24 (34.3%) were women. RLS was observed to be more common in men (62.2%) than that in women (37.8%). Restless legs syndrome was found to be hurting the quality of life in hemodialysis patients, especially in physical and psychological domains.

Conclusion: The quality of life of hemodialysis patients is negatively affected by RLS, with considerable influence on their psychological and physical well-being. As a consequence, medical practitioners ought to do everything possible to recognize and treat RLS symptoms in this demographic at risk.

Key Words: Restless legs syndrome, hemodialysis, quality of life

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INTRODUCTION

Different types of bodily movements may affect a person. The preponderance of these sorts of movements usually concerns the legs as you sleep and the most frequent of them is restless legs syndrome[1], often referred to as the "Willis Ekbom Disease". It is a chronic sensorimotor neurological condition[2] that is characterized by "an unusual sensation of numbness, puffiness, stiffness, discomfort, burning, irritation and pain, in the legs,

accompanied bya desire to move the involved lower extremity".[3] Symptoms generally appear at times of rest and wither away once you move. Hemodialysis therapy can cause several problems in individuals with chronic kidney disease, including RLS[4], which can be very distressing for this patient population. Iron deficiency brought on by frequent blood loss during dialysis is most likely to be the cause.[5] A decline in the brain's iron levels causes disruptions of dopaminergic pathways, which leads to sensorimotor symptoms.[6]

Research on restless legs syndrome in hemodialysis patients showed that this condition is more widespread in such patients compared to the regular populace, with an incidence range of 8% to 52% and a mean frequency of 30%.[7] Restless legs syndrome was identified as being linked with a poorer quality of life and a higher rate of dialysis discontinuations because patients with RLS encounter more fatigue and sleep disturbance than patients without RLS.[8] Quality of life is a dynamic construct that is affected by one's surroundings, physical, sociocultural, and subjective values.[9] Furthermore, because of alterations in nocturnal hemodynamics and variations in the structure and function of the left ventricle, restless legs syndrome can also have a detrimental impact on one's cardiovascular health.[8]

To enable both patients and medical professionals to comprehend the importance of this syndrome, and to profit from its care and therapy, it is fundamental to have reliable statistics about the incidence of RLS, as well as, the correlation between RLS symptoms, quality of life and preservation. Within and between hemodialysis patients.

This research intends to investigate the incidence of restless legs syndrome across chronickidney disease patients who received hemodialysis in Lahore health facilities and to contrast quality of life measures between diagnosed and undiagnosed patients.

MATERIAL AND METHODS

Cross-sectional research on a population of 70 patients with chronic kidney disease taking hemodialysis was carried out at the Shaikh Zayed National Institute of Kidney Diseases and The Jinnah Hospital in Lahore over 8 months. The participants were chosen by non-probability convenience sampling. This research included male and female subjects over 40 with chronic kidney disease undergoing hemodialysis. This research excluded participants with rheumatologic diseases, chronic neurological ailments, and chronically painful symptoms including neuropathy.[2]

The equation N= [(-Za/2)2 x P (1-P)] / d2 was employed to assess the sample group based on the results of prior research.[10] By using widely accepted IRLSSG diagnostic criteria, restless legs syndrome was considered to be present in participants who answered 'Yes' to all four questions. Whereas, the WHOQOL BREF instrument, developed by the World Health Organization, was implemented to assess the quality of life.

For said quality of life profile, the WHOQOL-BREF was adopted. The questionnaire comprises 26 items, subdivided into four aspects. Each domain represents how an individual feels about their quality of life. The scale for domain scores is positive (i.e. higher scores denote higher quality of life). The mean score of the elements in each domain was used to determine the domain score.

Using the IRLSSG's internationally accepted diagnostic criteria, individuals who answered "yes" to all four queries, were deemed to have restlesslegs syndrome.[2]

Restless legs syndrome was identified using internationally recognized criteria. Participants respondingto all four questions were diagnosed as having Restless legs syndrome.

An impulse to do movements of legs with an unpleasant and uncomfortable sensation.

Symptoms begin or worsen when the patient is

at rest or in a state of inactivity such assitting or lying down.
Complete or partial relief of symptoms by movement.
Worsening of symptoms in the night or evening time than during the day.
IBM SPSS Statistics 20 was employed to evaluate the data. The mean, standard deviation, range, and histogram were utilized to show the quantitative variables. Categorical factors were analyzed using cross-tabulation, frequency, percentages (%), bar charts, and pie charts. To determine the quality of life in both groups—those with and without diagnoses—an independent sample t-test was applied.
Whereas, to conduct the research, approval from the institutional ethical committee was obtained.

RESULTS:

In the present study, 70 hemodialysis patients were questioned to complete the WHO quality of life questionnaire and the diagnostic criteria for restless legs syndrome. The individuals' average age was54.97±9.54 years. 46 (65.7%) of the 70 individuals were men and 24 (34.3%) were women. Restless legs syndrome was found in 52.86% of the cases.

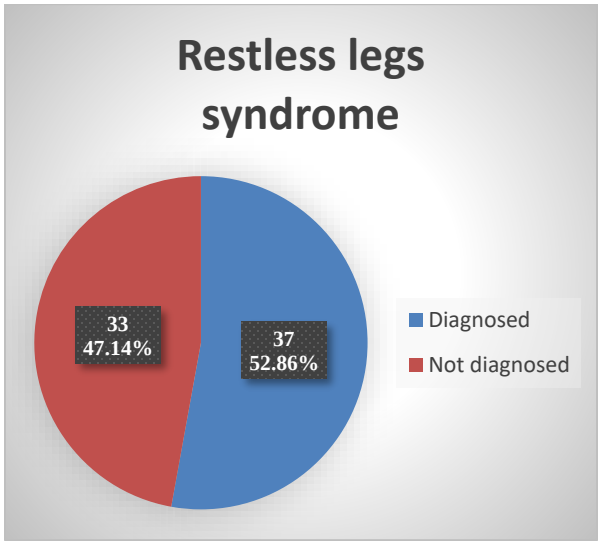

Figure-1: Prevalence of restless legs syndrome

Out of 70 hemodialysis patients 37(52.86%) had restless legs syndrome.
Men had a greater prevalence of RLS (62.2% than women (37.8%). **(Table 1)**

Table-1: Frequency distribution of hemodialysis patients with and without restless legs syndrome in terms of gender

Restless legs syndrome		**Frequency**	**Percentage**
Diagnosed	Male	23	62.2%
	Female	14	37.8%
Not diagnosed	Male	23	69.7%
	Female	10	30.3%
Total	Count	46	24

The mean duration of hemodialysis in 70 patients was 57.73 months, out of 70 patients, 42 (74.29%) had hypertension and 41 (58.6%) had diabetes. Utilizing an independent samples t-test, it was discovered that individuals with and without restless legs syndrome had varying physical and psychological health, with non-diagnosed patients having a higher mean score. The environmentaland social life domains did not differ between the two groups (P>0.05). As a result, a significant difference between patients with and without restless legs syndrome was discovered in the qualityof life indicators (physical, psychological) (**Table 2**), with the impact on patients undergoing hemodialysis being more detrimental.

Table-2: A Comparison of quality of life in diagnosed and non-diagnosed groups.

	Restless legs syndrome	N	Mean	Std. Deviation	p-value
Physical health	Diagnosed	37	18.46	6.92	0.008
	Not diagnosed	33	22.88	6.60	
Psychological	Diagnosed	37	19.51	5.82	0.024
	Not diagnosed	33	22.58	5.16	
Social relationships	Diagnosed	37	10.78	2.45	0.712
	Not diagnosed	33	11.00	2.42	
Environment	Diagnosed	37	28.89	6.19	0.104
	Not diagnosed	33	31.24	5.68	

DISCUSSION

One of the most debilitating issues that hemodialysis individuals encounter is restless legssyndrome. It is more prominent in hemodialysis patients than in the regular populace.[2] According to the RLS criteria used in this research, 52.9% of individuals (n=70) had restless legs syndrome.

According to cross-sectional research in 2018, hemodialysis patients had an RLS prevalence of 19%.[2] A Prevalence of 10.3% was observed by Ramachandran et al. in 2018.[11] Turk's investigation revealed the prevalence of restless legs syndrome of 16.8%.[12] Whereas, a 2017 meta-analysis reported that 34% of patients had restless legs syndrome.[13]

The prevalence of restless legs syndrome (52.68%) was determined to be nearer to the prevalence of previous studies (mean 30%, range 8%-52%).[7] Diverse demographics, races, diagnostic criteria for restless legs syndrome, variations in dialysis procedures, and research methods might each have an impact on the variance in the frequency of RLS amongst patients with end-stage kidney disease.

Among 70 participants, 24 (34.3%) were women and 46 (65.7%) were men. Males (62.2%) were reported to have restless legs syndrome more frequently than females (37.8%). Whilst Chavoshi et al.claimed that the incidence was higher in the female population.[7] Gender and restless legs syndrome were not strongly associated (P>0.05). The variation in the male-to-female ratio between participants throughout sampling could be the cause of the discrepancy in gender incidence.

According to the WHO Quality of Life (WHO QOL) questionnaire, patients with and without restless legs syndrome diverged in all four areas related to the quality of life (physical, psychological,social, and environmental), with non-diagnosed individuals receiving higher mean scores. As a direct consequence, patients on hemodialysis have a poorer quality of life due to restless legs syndrome, with considerable negative effects on their physical (P<0.05) and psychological (P<0.05)wellness. Restless legs syndrome negatively influences hemodialysis patients' physical health, according to Kutlu et al.[2] Whereas, Tuncel D et al. observed that instead of physical factors, the minimum level of quality of life reported by those with RLS is induced by mental health and sleep-related factors.[14]

Such differences in results could represent the reflection of the quality of life assessment taking into account a variety of factors. Thus, individuals who adopt or receive considerable social and family support would be able to deal with their disease more speedily with less influence on their quality of life.

Thus, medical professionals should use their medical knowledge to create assorted medication and exercise therapeutic strategies to improve overall symptoms and in turn, the quality of life for such patients. They should

perhaps take every measure to diagnose and treat restless legs syndrome symptoms in this at-risk population.

CONCLUSION

Restless legs syndrome is a prevalent condition among chronic kidney disease patients undergoing hemodialysis treatment. The quality of life is strongly influenced by restless legs syndrome, both physically and psychologically in these patients and so they need special attention so that their quality of life can be improved.

AUTHOR'S CONTRIBUTION

MP: Main author, Data analysis and discussion writing
EH: Research Supervisor and Data analysis
MNJ: Article writing
SS: Data collection and manuscript writing
SA: Data collection and manuscript writing

REFERENCES

1. Hein M, Lanquart JP, Hubain P, Loas G. Risk of resistant hypertension associated with restless legs syndrome and periodic limb movements during sleep: a study on 673 treated hypertensive individuals. Sleep Med. 2019 Nov 1;63:46-56. https://doi.org/10.1016/j.sleep.2019.05.013
2. Kutlu R, Selcuk NY, Sayin S, Kal O. Restless legs syndrome and quality of life in chronic hemodialysis patients. Niger J Clin Pract. 2018;21(5):573-7. DOI: 10.4103/njcp.njcp_84_17.
3. Tsai LH, See LC, Chien CC, Chen CM, Chang SH. Risk factors for restless legs syndrome in hemodialysis patients in Taiwan: A case–control study. Medicine. 2019 Dec;98(51) doi: 10.1097/MD.0000000000018450.
4. Ajorpaz NM, Rahemi Z, Aghajani M, Hashemi SH. Effects of glycerin oil and lavender oil massages on hemodialysis patients' restless legs syndrome. J Bodyw Mov Ther. 2020 Jan 1;24(1):88-92. https://doi.org/10.1016/j.jbmt.2019.06.012.
5. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB, International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep med. 2014 Aug 1;15(8):860-73. https://doi.org/10.1016/j.sleep.2014.03.025
6. Rizzo G, Li X, Galantucci S, Filippi M, Cho YW. Brain imaging and networks in restless legs syndrome. Sleep med. 2017 Mar 1;31:39-48. https://doi.org/10.1016/j.sleep.2016.07.018.
7. Chavoshi F, Einollahi B, Haghighi KS, Saraei M, Izadianmehr N. Prevalence and sleep related disorders of restless leg syndrome in hemodialysis patients. Nephro-Urol Mon. 2015 Mar;7(2). doi: 10.5812/numonthly.24611.
8. Novak M, Winkelman JW, Unruh M. Restless Legs Syndrome in Patients With Chronic Kidney Disease. In Semin Nephrol 2015 Jul 1 (Vol. 35, No. 4, pp. 347-358). Elsevier.. https://doi.org/10.1016/j.semnephrol.2015.06.006
9. Hemati Z, Alidosti M, Reisi M. The relation between the quality of life and restless legs syndrome in patient sunder going hemodialysis is dialysis centers in chahar mahal and bakhtiari, 2011..
10. Micozkadıoglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. Ren Fail. 2004 Jan 1;26(4):393-7. https://doi.org/10.1081/JDI-120039823
11. Ramachandran P, Devaraj U, Sebastian S, Krishnaswamy UM, D'Souza GA. Restless legs syndrome in patients with chronic renal failure on hemodialysis: Does peripheral iron status matter?. Ann Mov Disord. 2018 Jan 1;1(1):39.
12. Turk AC, Ozkurt S, Turgal E, Sahin F. The association between the prevalence of restless leg syndrome, fatigue, and sleep quality in patients undergoing hemodialysis. Saudi Med J. 2018 Aug;39(8):792. doi: 10.15537/smj.2018.8.22398.

13. Gheshlagh RG, Farajzadeh M, Zarei M, Baghi V, Dalvand S, Sayehmiri K. The prevalence of restless legs syndrome in patients undergoing hemodialysis: a systematic review and meta-analysis study. Basic Clin Neurosci. 2017 Mar;8(2):105. doi: 10.18869/nirp.bcn.8.2.105.

14. Tuncel D, Orhan FÖ, Sayarlioglu H, Isık IO, Utku U, Dinc A. Restless legs syndrome in hemodialysis patients: association with depression and quality of life. Sleep Breath. 2011 Sep;15:311-5. https://doi.org/10.1007/s11325-010-0382-z

Original Article

"TREATMENT SUCCESS OF SOFOSBUVIR AND DACLATSVIR WITH OR WITHOUT RIBAVIRIN IN PATIENTS OF HEPATITIS C VIRUS"

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ABSTRACT

Background: To compare the frequency of responders achieving SVR12 after taking sofosbuvir and daclatasvir with vs without ribavirin.

Material and Methods: Total 180 patients meeting inclusion criteria were enrolled in the study from Department of Medicine, Government Teaching Hospital Shahdara, Lahore.This randomized controlled trial was conducted from March 25, 2021, to September 24, 2021. Treatment naive cases were given tablet sofosbuvir & daclatasvir for 12 weeks. Treatment-experienced and naive with cirrhosis were given ribavirin based on their body weight along with sofosbuvir and daclatasvir for 12 weeks. After 3 months of treatment, patients were called for follow up at 12th week post-treatment for HCV RNA PCR to see if patient has achieved SVR12 or not. Statistical analysis was performed using SPSS v25.0. Frequency of responders was compared using the Chi-square test. P-value less than or equal to 0.05 was considered statistically significant.

Results: In group-A, 54(60.0%) patients were males and 36(40%) patients were females. In group-B, 52(57.8%) patients were males and 38(42.2%) were females. The mean age in patients of group-A was 45.69±12.481 years while that was 44.99±14.590 years in group-B. In group-A (Sofosbuvir and daclatasvir with ribavirin), 81(90.0%) patients had a response rate and in group B (Sofosbuvir and daclatasvir), 65(72.2%) patients had a response rate with p-value (p=0.002).

Conclusion: It was concluded that sofosbuvir & daclatasvir with ribavirin was found more efficacious than sofosbuvir & daclatasvir alone in achieving SVR 12 in patients of chronic hepatitis C infection, so it will help in delaying disease process and improving quality of life, especially in the developing world.

Key Words: Sofosbuvir, Daclatasvir, Ribavirin, Hepatitis C

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INTRODUCTION

Hepatitis C virus (HCV) is a single-stranded RNA virus. About 64 and 103 million people are chronically infected globally with HCV.[1] Chronic HCV poses a global threat, infecting more than 71 million people worldwide according to WHO report in 2015 with 400,000 deaths per year. HCV prevalence is highest in Central, South and East Asia more than 50% HCV infected cases belongs to Asian regions[2,3] National survey done in 2007-2008 in Pakistan reported 4.8% HCV prevalence.[4] Chronic HCV infection if untreated can lead to decompensated liver changes, extra-hepatic manifestations and hepatocellular carcinoma with early mortality.[5] Standard treatment for chronic HCV infection from the late 1990s to the early 2010s was a combination of

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peginterferon and ribavirin but they resulted in less viral clearance and more adverse effects. With the advent of science, new HCV treatment therapy with host targeting, oral and direct acting, anti-viral (DAA) agents have been recognized and approved by FDA in 2018. These newer drugs lead to early HCV elimination along with regression of hepatic fibrosis and hence decrease the risk of hepatocellular carcinoma.[6,7]

It has also been shown to be beneficial in the treatment of cryoglobulinemia associated with HCV, decreased cardiovascular events, and improved neurocognition.[8] Direct-acting, antiviral therapy includes several types of agents like HCV protease inhibitors, HCV polymerase inhibitors. Daclatasvir is a potent, pan genotypic NS5A inhibitor, it disrupts HCV replication complex formation. Sofosbuvir is a potent, pan genotypic, NS5B polymerase inhibitor thus inhibits HCV-RNA synthesis. Ribavirin is a guanosine analogue and works by immunomodulation and inhibits the initiation and elongation of RNA fragments.[9]

An Indian study showed over 90% SVR12 achievement with all oral-DAA therapy.[10] Similarly 12 week treatment with sofosbuvir and daclatasvir resulted in 90% SVR12 in treatment naive patients, 86% in treatment experienced, while 96% in patients without cirrhosis and 63% in cirrhotic having HCV genotype 3 but with treatment relapse in 16 patients.[11] Comparable SVR12 results were observed in two treatment groups in large real world cohort study regardless of liver status or prior treatment.[12] This therapy almost exhibited similar results in HCV mono-infected, HIV co-infected, and fibrotic cases except decompensated cases having less virological clearance.[13,14] The SVR12 rate was 97.5% in group without ribavirin and 87.7% in group with Ribavirin.[15] this study aims to assess the response of HCV infected patients treated with sofosbuvir and daclatasvir with or without ribavirin. It may represent different response in our population due to ethnic differences or comparable with other Asian groups showing high SVR rates.[14] It may show different responses in our elderly population due to different prevalent diseases as compared to a study by Tamer Elbaz.[15] No recently published local data is available regarding this. It may provide local evidence regarding DAA therapy and may add productive data to the existing body of knowledge and help for further research work. Patients who achieved SVR12 with treatment i.e Sustained Virological Response 12 (SVR12) the endpoint of treatment defined by undetectable levels of HCV RNA in blood 12 weeks after the end of therapy as assessed by a sensitive molecular method like PCR with a lower limit of detection at 15 IU/ml. HCV patients who were treated successfully with sofosbuvir and daclatasvir with or without ribavirin and achieved SVR 12 will be labelled responders while HCV patients who did still show detectable viral load on HCV PCR 12 weeks after the end of treatment will be labelled as non-responders. There is a difference in the frequency of responders after treatment with sofosbuvir and daclatasvir with vs. without ribavirin in hepatitis C infected patients.

MATERIAL AND METHODS

It was conducted in the Department of Medicine, at Government Teaching Hospital Shahdara, Lahore. It was performed from March 25, 2021 to September 24, 2021. It was a randomized controlled trial. Non-probability consecutive sampling technique was used. A sample of size 180 (90 in each group) was calculated according to the WHO formula with an expected SVR12 rate 87.7% in sofosbuvir and daclatasvir with the ribavirin group and 97.5% in sofosbuvir and daclatasvir without ribavirin group at 12 weeks in patients with hepatitis C virus infection with 80% power of the test and 5% level of significance.[15] Patients between the ages of 18 and 90 with detectable HCV RNA burden on quantitative HCV RNA PCR with a lower limit of detection at 15 IU/ml and positive anti-HCV antibodies on screening were included while patients with diagnosed hepatocellular carcinoma or any other malignancy, having concomitantly Hepatitis B or HIV with HCV, those who are currently

on interferons or other oral anti-viral drugs, those of chronic renal disease (with serum creatinine > 2.5mg/dl), with any organ transplantation, on haemodialysis, pregnant females and critically sick patients in ICU were ***excluded***. After approval from the ethical committee of the Hospital, informed consent was taken from 180 patients meeting the inclusion criteria as mentioned above and they were enrolled in a study from the Outdoor Department of Medicine, Government Teaching Hospital Shahdara, Lahore.

These patients were given treatment according to EASL recommendations 2018. Patients who taking anti-viral therapy for the first time in life were labelled as treatment naive cases and it was the control group of the study. Those who had taken interferons, ribavirin or DAA therapy in past but hadn't achieved SVR12 were labelled as treatment experienced cases. Treatment naive cases were given tablet sofosbuvir (Sofos, Genix Pharma, Karachi, Pakistan, 400mg orally once daily) and daclatasvir (Daclit, Genix Pharma, Karachi, Pakistan 60mg orally once daily) for 12 weeks. Treatment experienced and naive with cirrhosis were given ribavirin based on their body weight (Ribavil, Genix Pharma, Karachi, Pakistan 1200mg or 1000mg orally daily if greater than 75kg and 75kg or less body weight respectively) along with sofosbuvir 400mg orally daily and daclatasvir 60mg orally daily for 12 weeks. Data were collected from patients on the first visit including their age, gender, baseline viral load on quantitative HCV RNA PCR, treatment naive or treatment experienced cases. Treatment was prescribed as above and entered on proforma and patients were followed monthly for 3 months for checking treatment compliance, adverse effects and supply of next month's drugs.

After 3 months of treatment, patients were called for follow up at 12^{th} week post-treatment for HCV RNA PCR to see if the patient has achieved SVR12 or not and their results were entered on her/his proforma. Responders were labelled (as per operational definition).

All the data were collected and analysed by the trainee himself and all the investigations were done from the hospital laboratory and reported by the same fellow pathologist having five years' experience to eliminate bias and confounding variables were controlled by exclusion. Patients who did not achieve SVR12 were advised further workup and retreatment. Statistical analysis was performed using SPSS version 25.0. Mean and standard deviation was calculated for quantitative variables like age and viral load. Frequency and percentage were calculated for gender, treatment naive and treatment experienced cases, responders and non-responders. The frequency of responders was compared using the Chi-square test. Data were stratified for age, gender, treatment naïve vs. already treatment taken for the two treatment groups. Poststratification, the Chi-square test was applied and p-value less than or equal to 0.05 was considered statistically significant.

RESULTS

In this study, we enrolled 180 patients (90 in each group) with hepatitis C virus. In group-A (Sofosbuvir and daclatasvir with ribavirin), 54(60.0%) patients were males and 36(40.0%) patients were females. In group-B (Sofosbuvir and daclatasvir), 52(57.8%) patients were males and 38(42.2%) patients were females

The mean age of patients in Group-A (Sofosbuvir and daclatasvir with ribavirin) was 45.69±12.481 years and 44.99±14.590 years in Group B (Sofosbuvir and daclatasvir). In Group-A (Sofosbuvir and daclatasvir with ribavirin),

63(70.0%) patients had ages ≤50 years and 27(30.0%) patients had >50 years. In Group-B (Sofosbuvir and daclatasvir),

64(71.1%) patients had ages ≤50 years and 26(28.9%) patients had >50 years

In group-A, 61(67.8%) patients had new treatment and 29(32.2%) patients had experienced treatment. In-group-B, 64(71.1%) patients had new treatment and 26(28.9%) patients had experienced treatment **(Table-1)**.

In Group-A (Sofosbuvir and daclatasvir with ribavirin), 81(90.0%) patients had a response rate and in Group B (Sofosbuvir and daclatasvir), 65(72.2%) patients had a response rate with p-value (p=0.002) **(Table-2)**. According to the stratification of responders between groups concerning gender, there is a significant difference in responders between groups of either gender (p<0.05) . According to the stratification of responders between groups concerning age, there is a significant difference in responders between groups in either age group (p<0.05) . According to the stratification of responders between groups concerning the treatment group, there is a significant difference in efficacy between groups in the treatment group (p<0.05) **(Table-3)**.

Table-1: Comparison of treatment group distribution between groups

Treatment group	Groups		Total
	Sofosbuvir and daclatasvir with ribavirin	Sofosbuvir and daclatasvir	
New	61	64	125
	67.8%	71.1%	69.4%
Experienced	29	26	55
	32.2%	28.9%	30.6%
Total	90	90	180
	100.0%	100.0%	100%

Table-2: Comparison of responders between groups

Responders	Groups		Total	p-value
	Sofosbuvir and daclatasvir with ribavirin	Sofosbuvir and daclatasvir		
Yes	81	65	146	0.002
	90.0%	72.2%	81.1%	
No	9	25	34	
	10.0%	27.8%	18.9%	
Total	90	90	180	
	100.0%	100.0%	100%	

Table-3: Stratification of responders between groups concerning treatment group

Treatment group	Responders	Groups		Total	p-value
		Sofosbuvir and daclatasvir with ribavirin	Sofosbuvir and daclatasvir		
New	Yes	57	42	99	0.001
		93.4%	65.6%	79.2%	
	No	4	22	26	
		6.6%	34.4%	20.8%	
	Total	61	64	125	
		100.0%	100.0%	100%	
Experienced	Yes	24	23	47	0.549
		82.8%	88.5%	85.5%	
	No	5	3	8	
		17.2%	11.5%	14.5%	
	Total	29	26	55	
		100.0%	100.0%	100%	

DISCUSSION

The use of drugs known as direct acting antivirals (DAAs) has truly revolutionized the way that chronic HCV is treated, but their high market costs have long been a cause for grave worry. This is even though every effort has been made to give patients, particularly those in developing countries, access to these medications at affordable prices.[16] One such strategy that has significantly lowered the cost of DAAs is the decision to permit generic drugs in around 101 developing nations[17], but the safety and efficacy of these generics constituted a significant problem that requires scientific analysis. At the end of the course of treatment, the overall SVR12

rate was 81.1%. Similar to this, patient subgroups with characteristics that are regarded as being significantly more challenging to treat, like decompensated chronic liver disease and genotype 3 HCV infection with decompensated chronic liver disease, demonstrated substantial SVR12 rates. Patients with Child-Pugh C had lower SVR12 rates, which is consistent with past studies, and as a result, markers of advanced liver disease, such as a low platelet count or low serum albumin level, were linked to a higher risk of treatment failure.[18] However, a significant percentage of this gap was caused by pre-existing severe chronic liver disease rather than poor virological efficiency. After excluding individuals who had a non-virological failure, the majority of them died from advanced chronic liver disease. Those with decompensated chronic liver disease had a 90% SVR12 rate. All Child-Pugh classes had similar rates and advanced chronic liver disease signs did not significantly increase the probability of virological failure.

The study's results are excellent and strikingly similar to data that is widely available. Contrary to this research, ALLY 3+, a top study that evaluated sofosbuvir and daclatasvir in individuals with genotype 3 reported an SVR12 of 90%. SVR12 is 86.01% in chronic liver disease that has decompensated and 87.01% in chronic liver disease that has received therapy, according to this study.[19] In another study, the same combination was used to treat genotype 3 HCV patients, and the outcomes showed an overall SVR12 of 88%, 92% in patients who had never received treatment, 84% in those who did, and 89% in cirrhotics.[20] In patients with genotype 3, a trial from Iran showed the efficacy of generic daclatasvir and sofosbuvir, although their outcomes were significantly better with an SVR12 of 98%. Additionally, they only include cirrhotic individuals in their trial, and a 12-week course of the generic medication costs roughly $1,890.[21]

In Indian research, all oral-DAA medications achieved an SVR12 of above 90%.[10] Similar to this, a 12-week course of sofosbuvir plus daclatasvir therapy produced 90% SVR12 in patients who were treatment naive, 86% in patients who had received previous therapy, 96% in patients without cirrhosis, 63% in cirrhotics with HCV genotype 3 and treatment relapse in 16 individuals.

Regardless of liver function or prior therapy, comparable SVR12 results were seen in two treatment groups in a significant real-world cohort trial.[12] Except for decompensated individuals having poorer virological clearance, this therapy almost produced equivalent results in HCV mono-infected, HIV co-infected, fibrotic cases.[13,14] The SVR12 rate was 87.7% in the group receiving ribavirin against 97.5% in the group not receiving it.[15] Daclatasvir and sofosbuvir were generally well tolerated, both with and without ribavirin, and their safety profile was comparable to that of phase III trial results. Even though a large number of patients had severe chronic liver disease—a population that frequently has decreased tolerance to HCV therapy, particularly those involving injectable interferon— no unusual safety events were discovered. There were very few cases of treatment termination due to adverse events and it is not surprising that in a population with advanced chronic liver disease, the majority of serious adverse events and treatment termination were most likely brought on by the disease's natural course rather than medication. Safety results were largely comparable between the two medication groups, except for a higher incidence of typically moderate haematological events, such as hemolysis resulting in anaemia, in the ribavirin group.

CONCLUSION

To achieve SVR 12 in patients with chronic hepatitis C infection, sofosbuvir and daclatasvir with ribavirin were found to be more effective than sofosbuvir and daclatasvir alone. This will aid in slowing the progression of the disease and enhancing the quality of life, particularly in the developing world.

AUTHOR'S CONTRIBUTION

CAAA: Supervised the research
MN: Data collection and analysis
SBS: Prepared the manuscript
SC: Final review of the article
ZM: Data analysis
MR: Help in data analysis and SPSS

REFERENCES

1. Manns MP, Buti M, Gane ED, Pawlotsky JM, Razavi H, Terrault N, Younossi Z. Hepatitis C virus infection. Nat Rev Dis Primers. 2017 Mar 2;3(1):1-9. https://doi.org/10.1038/nrdp.2017.6.
2. Pradat P, Virlogeux V, Trépo E. Epidemiology and elimination of HCV-related liver disease. Viruses. 2018 Oct 6;10(10):545. https://doi.org/10.3390/v10100545
3. Kao JH, Ahn SH, Chien RN, Cho M, Chuang WL, Jeong SH, et al. Urgency to treat patients with chronic hepatitis C in Asia. J. Gastroenterol. Hepatol. 2017 May;32(5):966-74. https://doi.org/10.1111/jgh.13709.
4. Al Kanaani Z, Mahmud S, Kouyoumjian SP, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Pakistan: systematic review and meta-analyses. Royal Soc Open Sci. 2018 Apr 11;5(4):180257. https://doi.org/10.1098/rsos.180257.
5. Cacoub P, Comarmond C. Considering hepatitis C virus infection as a systemic disease. In Semin Dial. 2019 Mar (Vol. 32, No. 2, pp. 99-107). https://doi.org/10.1111/sdi.12758
6. Rivero-Juarez A, Brieva T, Frias M, Rivero A. Pharmacodynamic and pharmacokinetic evaluation of the combination of daclatasvir/sofosbuvir/ribavirin in the treatment of chronic hepatitis C. Expert Opin Drug Metab Toxicol. 2018 Sep 2;14(9):901-10. https://doi.org/10.1080/17425255.2018.1506765.
7. Roche B, Coilly A, Duclos-Vallee JC, Samuel D. The impact of treatment of hepatitis C with DAA s on the occurrence of HCC. Liver Int. 2018 Feb;38:139-45. https://doi.org/10.1111/liv.13659.
8. Lledo G, Benítez-Gutiérrez L, Arias A, Requena S, Cuervas-Mons V, de Mendoza C. Benefits of hepatitis C cure with antivirals: why test and treat?. Future Microbiol. 2019 Mar;14(5):425-35. https://doi.org/10.2217/fmb-2019-0041.
9. Kurniawan J, Gani RA, Hasan I, Sulaiman AS, Lesmana CR, Jasirwan CO, et al. Comparative efficacy of sofosbuvir-ribavirin versus sofosbuvir-daclatasvir for treatment of chronic hepatitis C in an area with limited NS5A inhibitor availability. Indian J Gastroenterol. 2018 Nov 13;37:520-5. https://doi.org/10.1007/s12664-018-0921-2.
10. Goel A, Bhargava R, Rai P, Aggarwal R. Treatment of chronic genotype-3 hepatitis C virus infection using direct-acting antiviral agents: An Indian experience. Indian J Gastroenterol. 2017 May;36:227-34 https://doi.org/10.1007/s12664-017-0763-3..
11. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015 Apr;61(4):1127-35. https://doi.org/10.1002/hep.27726.
12. Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort Gut. 2016 Nov 1;65(11):1861-70. http://dx.doi.org/10.1136/gutjnl-2016-312444.
13. Cheng PN, Chiu YC, Chien SC, Chiu HC. Real-world effectiveness and safety of sofosbuvir plus daclatasvir with or without ribavirin for genotype 2 chronic hepatitis C in Taiwan. J Formos Med Assoc. 2019;118(5):907-913.
14. Ji F, Wei B, Yeo YH, Ogawa E, Zou B, Stave CD, et al. Systematic review with meta-analysis: effectiveness and tolerability of interferon-free direct-acting antiviral regimens for chronic hepatitis C genotype 1 in routine clinical practice in Asia. Aliment Pharmacol Ther. 2018 Mar;47(5):550-62. https://doi.org/10.1111/apt.14507.
15. Elbaz T, Abdo M, Omar H, Hassan EA, Zaghloul AM, Abdel-Samiee. Efficacy and safety of sofosbuvir and daclatasvir with or without ribavirin in elderly patients with chronic hepatitis C virus infection. J Med Virol. 2019 Feb;91(2):272-7 https://doi.org/10.1002/jmv.25287.

16. Hill A, Cooke G. Hepatitis C can be cured globally, but at what cost?. Science. 2014 Jul 11;345(6193):141-2. doi: 10.1126/science.1257737.
17. Gilead Sciences Inc. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries. 2015. Available from: http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf.
18. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016 May;63(5):1493-505. https://doi.org/10.1002/hep.28446.
19. Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized phase III study (ALLY-3+). Hepatology. 2016 May;63(5):1430-41. https://doi.org/10.1002/hep.28473.
20. Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut. 2016 Nov 1;65(11):1861-70. http://dx.doi.org/10.1136/gutjnl-2016-312444
21. World Health Organization. Prequalification of medicines by WHO. Available from: http://www.who.int/mediacentre/factsheets/fs278/en/. 2018.

Original Article

FREQUENCY OF HEMOGLOBINOPATHIES AND ITS RELATION WITH CONSANGUINITY AT TWO HEALTHCARE CENTERS OF PESHAWAR

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ABSTRACT

Background: One of the most prevalent genetic disorders and major problems in Pakistan is hemoglobinopathies. Every year, 5,000 additional patients are added to the pool. Considering the medical and social implications of this familial condition, it is important to evaluate the prevalence of hemoglobinopathies across members of the family.

Material and Methods: This cross-sectional study included 263 samples with the diagnosis of anemia and complete blood count referred for screening of HB disorder from March 2021 to February 2022 at two general hospitals Rehman medical institute (RMI) and Peshawar Institute of medical sciences (PIMS). The institutional review board approved the study then blood specimens were collected in EDTA anti-coagulated tube: a complete blood picture with a peripheral blood smear was stained with a Leishman stain was performed. Hemoglobin electrophoresis was performed at pH 8.8 (Fisher Biotech) using a commercially available electrophoresis kit.

Result: Out of 263 Samples, Hemoglobinopathies affected 111(42.2%) people; the remaining 152(57.8%) people had a normal profile of Hb Electrophoresis. Of these 111 people with hemoglobinopathies, 86 (32.7%) had minor B-thalassemia and 22 (8.4%) had major B-thalassemia, while the rate of recurrence of sickle cell disease was 3 (1.1%). Among these, 40.3% of patients' parents are relatives with which consanguinity frequency was 37.3% and 22.4% of patients' parents are not relatives or cousins.

Conclusion: According to our research, cousin marriages frequently have a significant role in the development of B thalassemia minor, which affects the majority of patients. Relatives of known cases of thalassemia can be screened for hemoglobinopathies to reduce the financial and medical burden of transfusions and treatment.

Key Words: Electrophoresis, Hemoglobinopathies, Thalassemia, Sickle cell disease

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INTRODUCTION

Sickle cell diseases (SCDs), α and β-thalassemia, and other inherited blood illnesses known as hemoglobinopathies are caused by abnormalities in the globin genes.[1] Hemoglobinopathies are a genetic disorder of the globin component of the hemoglobin protein. genetic modification of the globin protein code that alters protein output produces thalassemia syndrome.[2] They currently occur most commonly in the tropical belt; a type of micro mapping will be necessary to determine their true prevalence and the likely cost of management for the governments of these countries.[3] Sickle cell disease (SCD) is a term used to describe a collection of inherited blood disorders characterized by chronic anemias and a variety of acute and chronic issues, such as

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episodes of discomfort, strokes, and early death.[4]

Thalassemia, which is a widespread genetic illness around the world, is mostly caused by a variety of mutations in the globin genes. Though it varies greatly from region to region, Iran has a high gene frequency of -thalassemia. The North and South coasts show the highest prevalence, which can exceed 10% in some places. Iran has more than 50 distinct mutations, which shows how the population's genotype is diverse.[5,6] One of the most common heredity hemoglobinopathies in Pakistan is thalassemia major (TM). With an essential 100,000+ current cases. It has one of the largest prevalences of transfusion-dependent TM patients worldwide.[7]

Some Hemoglobinopathies particularly having mutations in regulatory regions such as promoters and enhancers alters the globin protein production and leads to a well-known disorder thalassemia syndrome. If mutations are in the regulatory regions of globin, then globin proteins are normally made but at a modified rate. On the contrary, if the mutations are in the coding regions, then proteins may be produced in normal amounts, but proteins will not be normal as amino acid sequences are altered and lead to a decrease in the quality of globin proteins. Quantitative defects present as thalassemia, while the qualitative changes are collectively known as Hb variants, which result in great health problems ranging from sickle cell disease to unstable Methemoglobinemia encompassing many variants.[8] There have been more than 200 distinct point mutations and uncommon deletions of the gene described to date. Consanguineous marriage patterns, high birth rates, high fertility rates, poor levels of education, and early marriages without consent have contributed to Pakistan having one of the highest rates of transfusion-dependent Thalassemia in the world. A lack of screening facilities and 40% of cousin marriages in cultural norms have increased the likelihood of congenital transfer of the thalassemia trait.[9]

Our main purpose of the study was to discover the different types of hemoglobin disorders, consanguinity ratio, and their prevalence of Peshawar in the northern part of Pakistan which may be beneficial in various techniques for potent management and prevention of this hereditary disease in the general population of Khyber Pakhtunkhwa

MATERIAL AND METHODS

This cross-sectional study included 263 samples with the diagnosis of anemia and Complete Blood Count (CBC) referred for screening of Hb disorder from March 2021 to February 2022 at two general hospitals Rehman Medical Institute (RMI) and Peshawar Institute of Medical Sciences (PIMS). A reference lab that gets samples for the evaluation and diagnosis of hemoglobinopathies from the OPD and numerous minor labs. The study was given institutional review board approval, and after obtaining patient consent, information about their age, gender and marital status (consanguinity) was recorded.

Blood samples were collected from patients of low HB, with suspicion of hemoglobinopathies who visited these two healthcare hospitals. Using a completely automated blood cell counter, samples were examined within 120 minutes of being taken. (Sysmex KX-21), Leishman's stain was used to stain peripheral blood smears, and the conventional criteria were followed for evaluating the presence of hyperchromasia, anisocytosis, microcytosis, macrocytosis, and polychromasia.

For Thalassemia and sickle cell anemia samples, hemoglobin electrophoresis was performed at pH 8.8 (Fisher Biotech) using a commercially existing electrophoresis set with a cellulose acetate membrane in a tris-EDTA-borate buffer. Band density is measured by the Turboscan Digital Densitometric Analysis System (Fisher Biotech). Beta-thalassemia symptoms are considered present if the HbA2 measurement is greater than 3.5%. Red blood cell counts are positive for thalassemia in all

circumstances where the HbA2 gene is elevated.

RESULT

There were 140 (53.2%) Females and 123(46.8%) males in this study. Among these patient's majority were children (1-10 years) 85 (32.4%), Adults (18-30 years) 28 (10.7%), and more than 30 years old 58 (22.1%), Infant (1-12 months) 28 (10.7%), 12-18 years' children's 20 (7.6%). The socio-demographic profile has been identified in (Table-1). Out of 263 Samples, Hemoglobinopathies affected 111(42.2%) people; the remaining 152(57.8%) people had a normal profile of Hb Electrophoresis. Of these 111 people with hemoglobinopathies, 86 (32.7%) had minor B-thalassemia and 22 (8.4%) had major B-thalassemia, while the rate of recurrence of sickle cell disease was 3 (1.1%). Diverse Hemoglobinopathy wise distributions are shown in Table-2.

Among these 111, 40.3% of patients' parents are relatives with which consanguinity frequency was 37.3% and 22.4% of patient's parents are not relatives or cousins. The parent's relative, consanguinity frequency was described in table-3.

Table-1: Socio-demographic profile of study participants

		Frequency	Percent
Gender	Female	140	53.2
	Male	123	46.8
	Total	263	100
Age	1-10 years	82	31.1
	18-30 years	72	27.3
	Above 30 years	59	22.3
	1-12 months	29	11
	12-18 years	21	8
	Total	263	100

Table-2: Diverse Hemoglobinopathy in study participants

	Frequency	Percent
Normal patients	152	57.8
Beta thalassemia minor	86	32.7
Beta thalassemia major	22	8.4
Sickle cell disease	3	1.1
Total	263	100.0

Table-3: Consanguinity Frequency in study participants

	Frequency	Percent
Relatives	106	40.3
Cousins	98	37.3
Not relatives or Cousins	59	22.4
Total	263	100.0

DISCUSSION

In Pakistan, family marriages are more frequent, particularly marriages to first cousins who have a family history of hemoglobinopathy while also being homozygous. Thalassemia is the most prevalent hemoglobin disorder in one situation. There are more than 5000 homozygotes born in Pakistan every year, and they may be found all around the nation. In numerous areas of the country, the prevalence of Carriers varies from 4.0% to 5.0% for various populations. A family with a main patient of beta thalassemia is more likely to have more than 30% carriers.[10] In our study 111 (42.2%) people with hemoglobinopathies, 86 (32.7%) had minor B-thalassemia, and 22 (8.4%) had major B-thalassemia, while the rate of recurrence of sickle cell disease was 3 (1.1%). According to a study done in Lahore, the prevalence of various thalassemia diseases is 61%, with - Thalassemia trait at 51.9%.[9] Thalassemia major and minor were highly common at; 36.5% (n=301) and 47.5% (n=301)

respectively.[11] According to a 2020 study by Huma Riaz, 115 (32.9%) patients received a diagnosis of beta thalassemia trait, 45 (12.9%) patients received a diagnosis of beta thalassemia major, and 3 (0.8%) patients received a diagnosis of sickle cell anemia.[8] Which is close to our result. First cousin marriages accounted for 68.69% of consanguineous unions in the Moroccan study and 49 (18.1%) families had more than one child with thalassemia major. The study found that the rate of consanguinity in the parents' generation of children with hemoglobinopathies was 50.25 percent.[12,13] And according to our study 40.3% of patients' parents are relatives with which consanguinity frequency was 37.3%. Another study was conducted in Karachi, where minor beta thalassemia made up 51.8% of cases, major beta thalassemia 24.1%, HbD trait 6.7, sickle cell disease 3.9%, and sickle/beta thalassemia 4.5%. Another investigation was conducted in western Iran, where 56 (16.2%) of the patients had minor beta thalassemia.[2,14] Hemoglobinopathies were reported to affect 3.7% of the population in the 2014–15 Brazilian National Health Survey. Thalassemia mild (0.30%), probable thalassemia major (0.80%) and sickle cell trait (2.49%) were the most prevalent.[15] According to a study done in Saudi Arabia, the prevalence of the -thal trait is higher in the adult population of Al Majma'ah than that of the sickle cell trait[16] In 2018 another study conducted in Islamabad in which out of the 175 participants, 33 (or 18.9%) had hemoglobinopathies. the most common hemoglobinopathies were thalassemia major 8 (4.6%) and thalassemia trait 18 (10.1%).[17] Additionally, this research supports the hypothesis that thalassemia minor is the most prevalent hemoglobinopathy in Pakistan.

Although precise statistics on the prevalence of hemoglobin disorders in Pakistan are not yet available, it is possible to reduce their vertical transmission by conducting population surveys, inductive screenings using the HPLC technique and special care facilities in major cities that provide access to genetic counseling, prenatal diagnosis, genetic studies, diagnostic services, and treatment using cutting-edge techniques for restriction enzyme analysis and management. Young individuals must become aware of their carrier status as early as possible to weigh all of their options, including getting married and having children.

CONCLUSION

According to our research, cousin marriages frequently have a significant role in the development of B thalassemia minor, which affects the majority of patients. Relatives of known cases of thalassemia can be screened for hemoglobinopathies to reduce the financial and medical burden of transfusions and treatment to create a regional database, further investigation on the prevalence of various features is needed.

AUTHOR'S CONTRIBUTION

MT: Manuscript writing & data collection
FR: Conceived design, and final approval
AR: Performed data analysis
MH: Manuscript writing
SU: Manuscript writing
SA: Performed data analysis and data collection

REFERENCES

1. Hulihan MM, Feuchtbaum L, Jordan L, Kirby RS, Snyder A, Young W, et al. State-based surveillance for selected hemoglobinopathies. Genet Med 2015 Feb;17(2):125-30. https://doi.org/10.1038/gim.2014.81.
2. Shabbir S, Nadeem M, Sattar A, Ara I, Ansari S, Farzana T, Taj M, et al. Type and frequency of hemoglobinopathies, diagnosed in the area of Karachi, in Pakistan. Cogent Med. 2016 Dec 31;3(1):1188875. https://doi.org/10.1080/2331205X.2016.1188875
3. Weatherall DJ. The evolving spectrum of the epidemiology of thalassemia. Hematol Oncol Clin. 2018 Apr 1;32(2):165-75. https://doi.org/10.1016/j.hoc.2017.11.008
4. Snyder AB, Zhou M, Theodore R, Quarmyne MO, Eckman J, Lane PA. Improving an administrative case definition for

longitudinal surveillance of sickle cell disease. Public Health Rep. 2019 May;134(3):274-81
doi: 10.1177/0033354919839072.
5. Zulfiqar B, Jillani K, Shaikh F, Fahim MF. Frequency of Beta Thalassemia and Iron Deficiency Anemia in Moderate Anaemic Pregnant Patients Visiting to Tertiary Care. electrophoresis. 2017;18:13.
6. Alizadeh S, Bavarsad MS, Dorgalaleh A, Khatib ZK, Dargahi H, Nassiri N, et al. Frequency of beta-thalassemia or beta-hemoglobinopathy carriers simultaneously affected with alpha-thalassemia in Iran. Clin Lab. 2014 Jun;60(6):941-.
doi: 10.7754/Clin.Lab.2013.130306)-
7. Ehsan H, Wahab A, Anwer F, Iftikhar R, Yousaf MN. Prevalence of transfusion transmissible infections in beta-thalassemia major patients in Pakistan: a systematic review. Cureus. 2020 Aug 27;12(8). doi:10.7759/cureus.10070.
8. Riaz H, Shah MA, Rehan G, Azeem R. Types and frequency of hemoglobinopathies, diagnosed by HB electrophoreses in the lady reading hospital Peshawar, Pakistan. Khyber J Med Sci. 2020 Jan;13(1):39-42.
9. Majeed T, Akhter MA, Nayyar U, Riaz MS, Mannan J. Frequency of β-thalassemia trait in families of thalassemia major patients, Lahore. JAMC. 2013 Jul 1;25(3-4):58-60.
10. Hussain J, Arif S, Zamir S, Mahsud MA, Jahan S. Pattern of thalassemias and other hemoglobinopathies: A study in district Dera Ismail Khan, Pakistan. Gomal j med sci. 2013 Jul 1;11(2).
11. Abbasi S, Qadri F, Jawed M, Ujjan ID, Abbasi S, Jawed K. Pattern of Hemoglobinopathies And Thalassemia in Children by Using HPLC At LUMHS Jamshoro Hyderabad Sindh. APMC. 2019 Sep 30;13(3):245-8.
https://doi.org/10.29054/apmc/2019.759
12. Laghmich A, Ismaili FZ, Zian Z, Barakat A, Nourouti NG, Mechita MB. Hemoglobinopathies in the north of Morocco: Consanguinity pilot study. BioMed res int. 2019;2019.
https://doi.org/10.1155/2019/6857417
13. Hashim S, Sarwar M, Arsalan A, Awan I, Naseem S. Frequency of carrier screening and preventive orientation among first degree relatives of Thalassaemia patients. JPMA. 2018 Jan 1;68(1):50-4.
14. Payandeh M, Rahimi Z, Zare ME, Kansestani AN, Gohardehi F, Hashemian AH. The prevalence of anemia and hemoglobinopathies in the hematologic clinics of the Kermanshah Province, Western Iran. Int J Hematol Oncol Stem Cell Res. 2014;8(2):33.
15. Rosenfeld LG, Bacal NS, Cuder MA, Silva AG, Machado ÍE, Pereira CA, et al. Prevalence of hemoglobinopathies in the Brazilian adult population: National Health Survey 2014-2015. Revista Brasileira de Epidemiologia. 2019 Oct 7;22:E190007-SUPL.
https://doi.org/10.1590/1980-549720190007.supl.2.
16. Mir SA, Alshehri BM, Alaidarous M, Banawas SS, Dukhyil AA, Alturki MK. Prevalence of hemoglobinopathies (β-thalassemia and sickle cell trait) in the adult population of Al Majma'ah, Saudi Arabia. Hemoglobin. 2020 Jan 2;44(1):47-50. https://doi.org/10.1080/03630269.2020.1729175.
17. Khan SA, Aaraj S, Hussain SN. Frequency and types of haemoglobinopathies in children with microcytic anaemia. JPMA. 2021 Jan 1;71(1 (A)):78-80.

Original Article

LEVEL OF JOB SATISFACTION IN HEALTHCARE PROFESSIONALS WORKING AT KHYBER TEACHING HOSPITAL PESHAWAR, PAKISTAN

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ABSTRACT

Background: An effectively working institution depends on its skilled, motivated and well supported employees which are determined by said workers' working conditions, circumstances and environment. This is especially true for doctors and nurses whose work performance is closely linked to patient safety and quality patient care. Job satisfaction is defined by how employees feel about different aspects of their jobs. Different factors are involved in job satisfaction in different settings.

Material and Methods: It was a cross sectional study conducted in Khyber Teaching Hospital Peshawar involving health care Personnel's selected through Non probability quota sampling technique. Total 335 health care Personnel's were interviewed using structured questionnaire. Data was analyzed using SPSS version 20.

Results: Overall, 73.6% of participants were satisfied with the different factors of their working conditions. The results of the study revealed the major factors were Support from senior colleague (83.3%), Amount of hours health care workers work (82.7%), salary and vacation time (82.4%), On Job Training (76.1%). Other factors were presence of feedback system, involvement in decision making, good use of skills, promotion and job security.

Conclusion: The overall satisfaction level was high. Support from seniors, Salary and vacation time, Promotion in job and colleagues support is important motivators for job satisfaction.

Key Words: Job satisfaction, Health personnel, Working environment

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INTRODUCTION

Approximately 59 million healthcare personnel worldwide work collaboratively to cater to the public's health needs.[1] Around the time of The Great Depression (early 1930's) was the first instant of research into job satisfaction.[2] Many insights and information regarding job satisfaction arose after this time, notably the four theories of job satisfaction: Maslow's needs hierarchy theory, Herzberg's motivator-hygiene theory, the Job Characteristics Model, and the dispositional approach.[3]

Simply put, job satisfaction is defined by how employees feel about their jobs and different aspects of their jobs.[4] Competitive pay, good human resource, a nice working environment, opportunities for personal and professional growth, a less workload are the factors contributing towards job satisfaction. Supervision, recognition, autonomy on the job, job security, career advancement act further to improve job satisfaction.[5,6] Job satisfaction is important to an organization in terms of its positive relationship with individual performance, employee relations, physical and mental health and satisfaction.[7] Thus, more satisfied employees tend to be more creative and productive.[8] Presence of highly productive and motivated personnel increases quality of service.[9] About the

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healthcare field, the job satisfaction of healthcare workers has a positive association with patients'satisfaction.[10,11] There is relative shortage of healthcare workers globally.[12,13] WHO has predicted that, as the population of the world increases, there will be a decline of about 18 million skilled healthcare staff by 2035.[14]

According to the Pakistan Medical Commission, there are currently 281,072 doctors in Pakistan, which is severely lacking for a country with a population of 211.7 million.[15] The background factors triggering this shortage of healthcare staff being fewer people enrolling in health related fields, change of profession, irrational distribution of human resources and feeling of insecurity with their jobs.[16]

To determine factors contributing to job dissatisfaction among healthcare personnel. Limited work has been done especially in Khyber Pakhtunkhwa province to know about the common factors for job dissatisfaction. This study will help to know about the insight of the issue.

MATERIAL AND METHODS

It was a Cross sectional descriptive study conducted in Khyber Teaching Hospital Peshawar after taking approval from ethical board of Khyber Medical College. Total 335 health care Personnel's were interviewed selected through non probability quota sampling technique. Twenty wards were chosen from the hospital: Surgery 4 units, Medicine 4 units, Eye 2 units, ENT 2 units, Gynecology 3 units, Pediatrics 3 units, Pulmonology and Cardiology. Data was collected using a structured questionnaires designed. Data was analyzed using SPSS version 20 and Microsoft Excel (2018). Those healthcare professionals currently employed by the hospital i-e doctors, nurses and paramedics who consent to participate in the study were included. In contrast, those healthcare professionals who were currently enrolled post graduate training or near to their retirement were excluded from the study.

RESULTS

There were 355 participants in this study. The mean age of the participants was 28 years with a standard deviation of 6.89 years. There were 127 (37.91%)Males and 208 (62.08 %) Females. Data collected through the structured questionnaire were analyzed in the following table. Only the responses of strongly agree and agree (not neutral) were classified as satisfied following Herzberg's motivator-hygiene theory.

Level of job satisfaction based on different variables						
	Strongly Agree	Agree	Satisfied %	Neutral	Disagree	Strongly Disagree
I am satisfied with my **Salary** for the work that I do	46	122	82.4%	30	73	64
The chance of **promotion** is very high	53	106	47.5%	66	85	25
My job provides me with additional **training/education**	92	163	76.1%	35	41	04
I have **job security** in my place of work	57	126	54.6%	38	69	45
I feel I can get **vacation time** easily	106	170	82.4%	26	24	09
My workplace has an adequate **feedback process** in place	74	160	69.8%	66	27	08
The amount of **hours** I work play an important part in my satisfaction at work	88	189	82.7%	39	15	04
I believe I get good **Support** from my senior colleagues at work	129	150	83.3%	19	25	12
I feel I am involved in **decision making** at my place of work	89	144	69.5%	48	39	15
My job makes **good use of my skills and abilities**	104	161	79.1%	32	31	07
My **colleagues create an environment** that allows me to work to the best of my ability	115	161	82.4%	27	24	08
Overall Satisfaction			73.6%			

DISCUSSION

The study's results showed that the variable relationships had the highest fraction of satisfied healthcare workers (73.6%), which has been seen in other studies worldwide.[17,19] The results of the study revealed that healthcare personnel were satisfied with the variable personal satisfaction; this variable was an amalgamation of the individual's satisfaction with the recognition they get for the effort they put in, the extent to which their skills are used in their job, how involved they feel in decision making and whether or not they have a variety of tasks to perform in the workplace.

Yaseen corroborated these results.[20] From the study's results, 82.4% of individuals were satisfied with their Salary and advancement in career. More specifically, the majority of healthcare personnel's were satisfied with their Salary, and 82.4% believed it was an important factor to their satisfaction at their workplace. Rahman et al corroborated this finding, reporting that 64.4% of Ayub Teaching Hospital Abbottabad nurses were satisfied with their salaries.[21] In regards to job security, 54.6% of individuals in the study were satisfied with it and 84.2% of them believed it was an important factor to their job satisfaction; meaning overall, most healthcare professionals were satisfied with their job security and believed it was important in their job satisfaction. These results were supported by Eiche et al.[19] From the study results, the number of individuals that believed being promoted at work was feasible was 47.5% and 89.3% believed that being promoted was an important factor to their satisfaction. These results were mirrored in international studies such as Fogarty et al.[20] Additionally, Hamid et al. reported that nurses from private and public sector hospitals desired promotion but the private hospital provided more growth based on performance.[21]

The study results revealed 76.1% of individuals believed they received additional training and 79.7% believed additional training was important to their job satisfaction. This was validated by results from Rahman et al. where a majority (56.5%) of nurses in Ayub Teaching Hospital agreed that the hospital provided them with some training. Overall, 73.6% of participants were satisfied with their working conditions and believed it was an important factor in their satisfaction at work, meaning a majority of individuals was satisfied with their working conditions.

CONCLUSION

The overall satisfaction level was high. 73.6% of participants were satisfied with the different factors of their working conditions. The major factors were Support from senior colleagues, Amount of hours health care workers work, Salary and vacation time, On Job Training. Other factors were presence of a feedback system, involvement in decision-making, good use of skills, promotion and job security.

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AUTHOR'S CONTRIBUTION

HMK: Data analysis and proposal development
JH: Proposal development and data analysis
AAA: Data collection and manuscript writing
NK: Data entry and manuscript writing
ZW: Data analysis and interpretation
MA: Data collection and data analysis

REFERENCES

1. Joseph B, Joseph M. The health of the healthcare workers. Indian J Occup Environ Med 2016 May;20(2):71. doi: 10.4103/0019-5278.197518.
2. Weiss HM, Merlo KL. Job Satisfaction. In: Wright JD, editor. International Encyclopedia of the Social & Behavioral Sciences. 2nd ed. [place unknown]: Elsevier; 2015. p. 833–838.
3. Hassard J, Teoh K, Cox T. Job satisfaction: Theories and definitions. Available at:[CrossRef] [Accessed Oct 4 2020]. 2016

Sep..https://oshwiki.eu/wiki/Job_satisfaction:_theories_and_definitions [Accessed 20th February 2022].
4. Wang W, Houston M. Teaching as a career choice: the motivations and expectations of students at one Scottish University. Educational Studies. 2021 May 11:1-8.
5. Dzimbiri GL, Molefi A. The impact of talent management on job satisfaction of registered nurses in Malawian public hospitals. SA Journal of Human Resource Management. 2021 Aug 23;19:9.
6. Latzke M, Putz P, Kulnik ST, Schlegl C, Sorge M, Mériaux-Kratochvila S. Physiotherapists' job satisfaction according to employment situation: Findings from an online survey in Austria. Physiotherapy Research International. 2021 Jul;26(3):e1907.
7. Lal A, Tharyan A, Tharyan P. The prevalence, determinants and the role of empathy and religious or spiritual beliefs on job stress, job satisfaction, coping, burnout, and mental health in medical and surgical faculty of a teaching hospital: A cross-sectional survey. La Revue de medecine interne. 2020 Apr 1;41(4):232-40.
8. Karem MA, Mahmood YN, Jameel AS, Ahmad AR. The effect of job satisfaction and organizational commitment on nurses' performance. Journal of Humanities and Social Sciences Reviews. eISSN. 2019:2395-6518.
9. Hinojosa-López JI. The mediating role of job satisfaction between quality in work factors and work engagement. Revista de Administração de Empresas. 2022 Jun 27;62.
10. Hooker RS, Moloney-Johns AJ, McFarland MM. Patient satisfaction with physician assistant/associate care: an international scoping review. Human Resources for Health. 2019 Dec;17:1-1.
11. Gu J, Zhen T, Song Y, Xu L. Job satisfaction of certified primary care physicians in rural Shandong Province, China: a cross-sectional study. BMC health services research. 2019 Dec;19:1-1.
12. Grembowski D, Ulrich CM, Paschane D, Diehr P, Katon W, Martin D, Patrick DL, Velicer C. Managed care and primary physician satisfaction. JABFP. 2003 Sep 1;16(5):383-93..
doi: https://doi.org/10.3122/jabfm.16.5.383
13. Black C. Global shortage of health workers expected to keep growing, UN agency warns. UN News [Internet]. 2013 Nov 11.
14. Merga H, Fufa T. Impacts of the working environment and benefits packages on the health professionals' job satisfaction in selected public health facilities in eastern Ethiopia: using principal component analysis. BMC Health Serv Res. 2019 Jul 16;19(1):494. DOI: 10.1186/s12913-019-4317-5.
15. Mustafa ZU, Haroon S, Aslam N, Saeed A, Salman M, Hayat K, Shehzadi N, Hussain K, Khan AH. Exploring Pakistani Physicians' Knowledge and Practices Regarding High Alert Medications: Findings and Implications. Front Pharmacol. 2022;13. doi: 10.3389/fphar.2022.744038.
16. Abdullah MA, Mukhtar F, Wazir S, Gilani I, Gorar Z, Shaikh BT. The health workforce crisis in Pakistan: a critical review and the way forward. World Health Popul. 2014 Jan 1;15(3):4-12..
17. Lu Y, Hu XM, Huang XL, Zhuang XD, Guo P, Feng LF, Hu W, Chen L, Hao YT. Job satisfaction and associated factors among healthcare staff: a cross-sectional study in Guangdong Province, China. BMJ open. 2016 Jul 1;6(7):e011388. http://dx.doi.org/10.1136/bmjopen-2016-011388.
18. Singh T, Kaur M, Verma M, Kumar R. Job satisfaction among health care providers: A cross-sectional study in public health facilities of Punjab, India. J Family Med Prim Care. 2019 Oct;8(10):3268. doi: 10.4103/jfmpc.jfmpc_600_19.
19. Eiche C, Birkholz T, Konrad F, Golditz T, Keunecke JG, Prottengeier J. Job Satisfaction and Performance Orientation of Paramedics in German Emergency Medical Services—A Nationwide Survey. IJERPH. 2021 Nov 26;18(23):12459.. https://doi.org/10.3390/ijerph182312459
20. Fogarty L, Kim YM, Juon HS, Tappis H, Noh JW, Zainullah P, Rozario A. Job satisfaction and retention of healthcare providers in Afghanistan and Malawi. Hum Resour Health. 2014 Dec;12:1-2. https://doi.org/10.1186/1478-4491-12-11.
21. Samad A, Memon SB, Ali I. Despotic leadership and job satisfaction among nurses: role of emotional exhaustion. Indep J Manag Prod. 2021 Feb 6;12(1):127-42.

Review Article

ROLE OF INDOLAMINE-2,3-DIOXYGENASE IN THE PATHOGENESIS OF CANCER AND HEPATITIS

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Summary

The gene responsible for Indolamine-2,3-dioxygenase (IDO) in humans is located at chromosome 8, it controls the tryptophan breakdown via the kynurenine pathway. IDO is actively expressed in epithelial cells, monocytes, tumor cells, macrophages, and the vascular endothelium. This enzyme exclusively converts L-tryptophan to L-kynurenine. Normally, it is produced in lower concentration. But overexpression of IDO suppresses the immune system of the body by reducing the metabolic fuel, tryptophan, required for immune activity. The function of the immune system can be suppressed by the upsurge of T regulatory cells and a decline in effector T cell activity. That is why it is known to be an important enzyme in the immune system, in cancer development, and viral and bacterial infection. Various studies have documented high levels of IDO expression in diverse types of cancers, bacterial infections, and viral infections. Nevertheless, the increased synthesis of IDO induces a tolerogenic effect, aiding the affected cells in evading immune responses. Consequently, IDO possesses the potential as an exceptional therapeutic agent for combating cancer and eliminating virus-infected cells.

Key Words: Indolamine, Dioxygenase, Tryptophan, Immune system

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INTRODUCTION

Indolamine-2,3-dioxygenase (IDO), an intracellular enzyme containing a heme group, is directly involved in the synthesis of kynurenine as a result of tryptophan breakdown.[1,2] The primary site for the kynurenine pathway is the liver, which holds all the essential enzymes for the transformation of tryptophan into NAD+.

In normal circumstances, approximately 90% of tryptophan degradation in the liver or hepatic cells is attributed to the kynurenine pathway.[3]

The initial steps of the kynurenine pathway in the liver are regulated by Tryptophan 2,3-dioxygenase (TDO) and exhibit a higher degree of substrate specificity compared to IDO.[4]

Normally, IDO accounts for approximately 5-10% of tryptophan degradation[5], but its significance increases during immune activation.[6,7] IDO serves as an essential enzyme to promote tolerance and suppress adaptive immunity as it converts tryptophan into L-kynurenine.[8] There are two isoforms of IDO: IDO1 and IDO2. IDO1, which plays an important role in the immune, has become a focal point of the research system as it exhibits higher expression levels than IDO2.[9] In this article, the term "IDO" specifically refers to IDO1.

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Normally, IDO1 has a limited role in tryptophan metabolism.[10] However, during inflammation, bacterial and viral infections, the release of interferons and other cytokines leads to increased activation of IDO, resulting in its up-regulation.[11] By controlling the level of tryptophan in the body, IDO synchronizes the immune function. Tryptophan is one of the vital amino acid beings is required for cellular growth as well as for immune function. Overexpression of IDO suppress the immune system of the body by reducing the metabolic fuel, tryptophan, required for immune activity. The high expression of IDO contributes to the up-regulation of T regulatory cells and the low expression of effector T cell activity, resulting in immune system suppression.[12,13] In essence, the high expression of IDO leads to immunosuppression. It assumes a pivotal role in various malignancies, infections, and autoimmune diseases.[14] Numerous studies demonstrate that the levels of IDO and tryptophan in the blood are involved in the diagnosis and treatment of various diseases.

Role of IDO as an immunosuppressive enzyme associated with the development of cancer:

Overexpression of IDO helps cancerous cells to outflow from the immune system. Being an immunosuppressive molecule it helps in the prognosis of tumors. Different studies show that IDO expression is increased in different cancer which helps the cancerous cell to escape from the anti-tumor immune response.[15] IDO up-regulates the growth and spread of tumors, by serving as an important link between inflammation, vascularization, and immune evasion.[16] Excessive production of IDO has been observed in the lymphatic drainage regions of multiple deadly cancers, including stomach carcinomas[7], colorectal cancer[17], ovarian cancer[18,] and various others.[19]

IDO and ovarian cancer:

Elevated expression of IDO results in an increase in pro-inflammatory cytokine levels whereas through tryptophan depletion it is responsible for the reduction of effector T cells within the tumor cells. Further research has indicated that in ovarian cancer, IDO-derived tumor cells are not only involved in the suppression of the ability of tumor-infiltrating effector T cells to fight it but alongside enhance the production of immunosuppressive cytokines in ascites. This creates an environment wherein the cancer cells can spread without any resistance.[20,21]

To create clones of cells overexpressing IDO, they transfected the cDNA of IDO into a murine ovarian carcinoma cell line called OV2944-HM-1, which was then referred to as HM-1-IDO. Control cells were also transfected with a control vector, known as HM-1-mock. Subsequently, both HM-1-mock and HM-1-IDO cells were transplanted into immune-deficient mice of the same strain. The mice that received HM-1-IDO grafts exhibited significantly lower survival rates, increased volume of ascites, and elevated tumor weight in the peritoneal dissemination area compared to the control mice.[21]

The tumor-promoting effect is interrelated with a decline in CD8+ T cells along with natural killer cells within the tumor cells. On the other hand, it results in an upsurge in the levels of transforming growth factor-β along with interleukin-10 in the ascites.[21]

IDO and gastric cancer:

In a study led by Nishi et al., 2018, the levels and mechanism of IDO in stage III gastric cancer were investigated. The study revealed a significantly lower survival rate among patients who tested positive for IDO compared to the IDO-negative group. IDO was found to contribute to immune tolerance and poor prognosis by suppressing Treg activation in gastric cancer. Alongside this, this study established a positive link between IDO and TGF-β expressions. Whereas the TGF-β expression was found to be related to the activity of Foxp3, a known factor involved in the development and function of Treg cells, in patients with stage III gastric

cancer. Li et al., 2019, conducted a study to further verify that the levels of IDO Foxp3 can be used to foretell prognosis in gastric cancer.[22]

IDO and breast cancer:

The overexpression of IDO plays a crucial role in breast cancer. In addition to increased expression, the activity of IDO is remarkably high in paclitaxel-resistant breast cancer cells, leading to poor prognosis and reduced response to chemotherapy. However, IDO also serves as an important biomarker for assessing chemotherapy efficiency, as tryptophan catabolism is associated with tumor response.[23] Asghar et al., 2019 conducted a study to examine the expression of IDO in patients with triple-negative breast cancer (TNBC) at the tissue level.[24] The findings of this study demonstrated that IDO is overexpressed in TNBC patients compared to normal individuals. Furthermore, patients with a high IDO score exhibited lower survival rates than those with a low IDO score. In addition to suppressing the immune response against tumor cells, IDO also promotes angiogenesis in breast cancer.[25]

IDO and Prostate Cancer

IDO activity is also over-expressed in prostate cancer. The progression and prognosis of prostate cancer are influenced by inflammation, as evidenced by histological studies of prostatectomy samples revealing significant inflammation during the early stages of malignancy.

IFN-γ, a pro-inflammatory cytokine, up-regulates the production of IDO. This enhanced production of IDO helps prostate tumor cells circumvention of the immune response.[26] However, the expression of the IDO gene in the urine of men acts as a potential marker for the development of prostate cancer and may reduce the need for prostate biopsies.[27] Banzola et al., 2018 researched the effect of inflammatory triggers on the creation of prostate cancer-related soluble factors, like IDO and interleukin 6 (IL-6). They used IFN-γ and TNF-α to induce IDO and IL-6 genes respectively.[28] Research has shown that IDO expression can be used to accurately predict recurrence-free survival in individuals who are diagnosed with prostate cancer. On the other hand, IL-6 gene expression did not seem to have a significant role in predicting recurrence-free survival among prostate cancer patients.

IDO and Hepatitis:

Hepatitis, also known as viral hepatitis, is characterized by inflammation of the liver and is primarily caused by viral infections. According to epidemiological reports, Hepatitis B Virus (HBV) affects about 350 million people around the world, with more than 780,000 deaths per year due to liver ailments.[29] Patients with HBV infection exhibit higher kynurenine to tryptophan ratios compared to non-infected individuals due to increased activity of IDO.[30] HBV infection impairs the response of virus-specific T-cells by promoting the expansion of myeloid-derived suppressor cells (MDSCs). HBeAg-induced MDSC expansion impairs the function of T-cells through the IDO pathway, facilitating the establishment of persistent HBV infection. Yang et al., 2019 investigated the frequency of circulating myeloid-derived suppressor cells in patients with chronic hepatitis B and healthy individuals.[31] In comparison to healthy individuals, the percentage of myeloid-derived suppressor cells came out to be higher in HBV-infected individuals. Additionally, exposure of peripheral blood mononuclear cells (PBMCs) from healthy donors to HBeAg resulted in significant upregulation of IDO, IL-1β, IL-6, and expansion of MDSCs.[30]

Hepatitis C Virus (HCV) affected almost 170 million people around the world and the infected ones are more vulnerable to developing chronic liver diseases. In comparison to healthy individuals, the HCV-infected patients portray higher IDO levels.[14] IDO expression is enhanced by the synergistic effect of Lipopolysaccharide (LPS), interleukin-1 (IL-1) and tumor necrosis factor (TNF) with interferon-γ (IFN-

γ).[32,14] Upon stimulation with IFN-γ and co-culture with activated T-cells, Huh 7 cells, which support HCV replication, exhibit higher levels of IDO mRNA expression compared to healthy individuals.[33,34] HCV infection induces the production of MDSC-like monocytes through the TLR2/PI3K/AKT/STAT3 pathway. These monocytes suppress the activation of CD4+ T-cells and promote the development of CD25+, Foxp3+, and CD4+ regulatory T-cells (Tregs) in the presence of IDO, leading to the accumulation of kynurenine.[35]

Therapeutics of IDO

It is obvious from the above explanation that IDO helps in the escape of tumor cells and virus-infected cells from the immune response. So, IDO can act as a marvelous therapeutic agent for the cure of cancer and viral infections.[36] According to recent studies, IDO can be used as a biomarker to monitor immune status. Zhu et al. (2020) investigated the relationship between IDO activity and clinical diagnosis in patients with early-stage non-small cell lung cancer in patients who underwent stereotactic body radiotherapy (SBRT).[6] They quantitatively analyze the immune activity of IDO in serum before and after SBRT and explore the changes in immune ne activity of IDO mediated by SBRT and its relationship with patient survival. SBRT could alter IDO-mediated antitumor immune activity. The post/pre kynurenine ratio was found to have a direct correlation with higher progression-free survival. The expression of T-regs produced by IDO secreted by dendritic cells decreased in the presence of 1-methyl tryptophan (1-MT)fingolimodimod (inhibitor of IDO). So, 1-MT can be served as one of the best strategies to boost the immune responses in HCV infection.[14] The inhibitors of IDO show anti-cancer behavior in different types of cancer.[37] There are different inhibitors of IDO but three strong inhibitors, indoximod, INCB024360, and NLG-919 are in clinical trials.[38]

CONCLUSION

Millions of people die due to both cancer and infectious disease (whether bacterial or viral) every year in the world. There is no proper treatment to cure these diseases. So, there is a dire need for the development of treatment for these mortal diseases. There is ample evidence of increased production of IDO in cancer, bacterial and viral diseases which help infect cells to escape from the immune response. That is why IDO can act as both an important diagnostic as well as a therapeutic agent to diagnose and cure different cancerous and infectious diseases. Inhibition of IDO will help to drive anti-tumor immune effects and lead to the removal of cancerous and infected cells from the body. Many drugs, which act as inhibitors of IDO, are in clinical trials. To achieve exceptional therapeutic effects in humans, extensive study of the immunological function of IDO is required.

AUTHOR'S CONTRIBUTION

FA: Conception and data collection
MSQ: Conception and proofreading
ZA: Data collection and drafting
AK: Data collection and drafting
ZK: Drafting and proofreading
IG: Final drafting and proofreading
MSA: Final drafting and proof reading

REFERENCES

1. Refaat MM, Abdel Rehim AS, El-Sayed HM, Mohamed NA, Khafagy AG. Serum indolamine 2, 3 dioxygenase as a marker in the evaluation of allergic rhinitis. Am J Rhinol Allergy. 2015 Sep;29(5):329-33. https://doi.org/10.2500/ajra.2015.29.4
2. Wu H, Gong J, Liu Y. Indoleamine 2, 3-dioxygenase regulation of immune response. Mol Med Rep. 2018 Apr 1;17(4):4867-73. https://doi.org/10.3892/mmr.2018.8537
3. Lerch S, Schefold JC, Spinetti T. The Role of Kynurenines Produced by Indolamine-2, 3-Dioxygenase 1 in Sepsis. Pharmacology. 2022;107(7-8):359-67. https://doi.org/10.1159/000523965.
4. Murakami Y, Ito H, Saito K. The Role of L-Tryptophan Kynurenine Pathway Metabolism in Various Infectious Diseases:

Focus on Indoleamine 2, 3-Dioxygenase 1. Tryptophan Metabolism: Implications for Biological Processes, Health and Disease. 2015:95-120. doi: 10.1007/978-3-319-15630-9_5.
5. Badawy AA. Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects. Int J Tryptophan Res 2017 Mar 9;10:1178646917691938. doi: 10.1177/1178646917691938
6. Zhu Y, Jiang C, Liu Y, Li Y, Wu H, Feng J, Xu Y. Association between IDO activity and prognosis in patients with non-small cell lung cancer after radiotherapy. Ann Transl Med. 2020 Sep;8(18). doi: 10.21037/atm-20-5634
7. Li R, Li H, Sun Q, Liu L, Zhang C, Ren X. Indoleamine 2, 3-dioxygenase regulates T cell activity through Vav1/Rac pathway. Mol Immunol. 2017 Jan 1;81:102-7. https://doi.org/10.1016/j.molimm.2016.11.018
8. Hoshi M, Saito K, Hara A, Taguchi A, Ohtaki H, Tanaka R, Fujigaki H, et al. The absence of IDO upregulates type I IFN production, resulting in suppression of viral replication in the retrovirus-infected mouse. J Immunol. 2010 Sep 15;185(6):3305-12. https://doi.org/10.4049/jimmunol.0901150.
9. Ye Z, Yue L, Shi J, Shao M, Wu T. Role of IDO and TDO in cancers and related diseases and the therapeutic implications. J Cance. 2019;10(12):2771. doi 10.7150/jca.31727.
10. Hornyák L, Dobos N, Koncz G, Karányi Z, Páll D, Szabó Z, Halmos G, Székvölgyi L. The role of indoleamine-2, 3-dioxygenase in cancer development, diagnostics, and therapy. Front Immunol. 2018 Jan 31;9:151. https://doi.org/10.3389/fimmu.2018.00151.
11. Sorgdrager FJ, Naudé PJ, Kema IP, Nollen EA, Deyn PP. Tryptophan metabolism in inflammation: from biomarker to therapeutic target. Front Immunol. 2019 Oct 30;10:2565. https://doi.org/10.3389/fimmu.2019.02565.
12. Jung KH, LoRusso P, Burris H, Gordon M, Bang YJ, Hellmann MD, et al. Phase I Study of the Indoleamine 2, 3-Dioxygenase 1 (IDO1) Inhibitor Navoximod (GDC-0919) Administered with PD-L1 Inhibitor (Atezolizumab) in Advanced Solid TumorsNavoximod and Atezolizumab in Advanced Solid Tumors. Clin Cancer Res. 2019 Jun 1;25(11):3220-8. https://doi.org/10.1158/1078-0432.CCR-18-2740.
13. Dillinger B, Ahmadi-Erber S, Lau M, Hoelzl MA, Erhart F, Juergens B, Fuchs D, Heitger A, Ladisch S, Dohnal AM. IFN-γ and tumor gangliosides: Implications for the tumor microenvironment. Cell Immunol. 2018 Mar 1;325:33-40. https://doi.org/10.1016/j.cellimm.2018.01.014.
14. Asghar K, Farooq A, Zulfiqar B, Rashid MU. Indoleamine 2, 3-dioxygenase: As a potential prognostic marker and immunotherapeutic target for hepatocellular carcinoma. World J Gastroenterol. 2017 Apr 4;23(13):2286. doi: 10.3748/wjg.v23.i13.2286.
15. Zhou H, Wang W, Liu M, Xie P, Deng T, Peng J, Xu C. IDO promotes the proliferation and invasion of prostate cancer cells through KYNU. Genes & Genomics. 2023 Mar;45(3):367-76. https://doi.org/10.1007/s13258-022-01316-y.
16. Holmgaard RB, Zamarin D, Li Y, Gasmi B, Munn DH, Allison JP, et al. Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner. Cell Reports. 2015 Oct 13;13(2):412-24. https://doi.org/10.1016/j.celrep.2015.08.077.
17. Puccetti P, Fallarino F, Italiano A, Soubeyran I, MacGrogan G, Debled M, et al. Accumulation of an endogenous tryptophan-derived metabolite in colorectal and breast cancers. PloS one. 2015 Apr 16;10(4):e0122046. https://doi.org/10.1371/journal.pone.0122046
18. Chester C, Dorigo O, Berek JS, Kohrt H. Immunotherapeutic approaches to ovarian cancer treatment. J Immunother Cancer. 2015 Dec;3:1-0. https://doi.org/10.1186/s40425-015-0051-7.
19. Costa F, Das R, Kini Bailur J, Dhodapkar K, Dhodapkar MV. Checkpoint inhibition in myeloma: opportunities and challenges. Front Immunol. 2018 Sep 26;9:2204. https://doi.org/10.3389/fimmu.2018.02204.
20. Tanizaki Y, Kobayashi A, Toujima S, Shiro M, Mizoguchi M, Mabuchi Y, et al. Indoleamine 2, 3-dioxygenase promotes peritoneal metastasis of ovarian cancer by inducing an immunosuppressive

environment. Cancer science. 2014 Aug;105(8):966-73. https://doi.org/10.1111/cas.12445.
21. Ala M. The footprint of kynurenine pathway in every cancer: A new target for chemotherapy. European J. Pharmacol. 2021 Apr 5;896:173921. https://doi.org/10.1016/j.ejphar.2021.173921
22. Li F, Sun Y, Huang J, Xu W, Liu J, Yuan Z. CD4/CD8+ T cells, DC subsets, Foxp3, and IDO expression are predictive indictors of gastric cancer prognosis. Cancer med. 2019 Dec;8(17):7330-44. https://doi.org/10.1002/cam4.2596
23. Ebokaiwe AP, Njoya EM, Sheng Y, Zhang Z, Li S, Zhou Z, Qiang Z, et al. Salinomycin promotes T-cell proliferation by inhibiting the expression and enzymatic activity of immunosuppressive indoleamine-2, 3-dioxygenase in human breast cancer cells. Toxicol Appl Pharmacol. 2020 Oct 1;404:115203. https://doi.org/10.1016/j.taap.2020.115203.
24. Asghar K, Loya A, Rana IA, Tahseen M, Ishaq M, Farooq A, et al. Indoleamine 2, 3-dioxygenase expression and overall survival in patients diagnosed with breast cancer in Pakistan. Cancer Manag Res. 2019;11:475 doi: 10.2147/CMAR.S184221.
25. Li F, Zhao Y, Wei L, Li S, Liu J. Tumor-infiltrating Treg, MDSC, and IDO expression associated with outcomes of neoadjuvant chemotherapy of breast cancer. Cancer Biol Ther. 2018 Aug 3;19(8):695-705. https://doi.org/10.1080/15384047.2018.1450116
26. Zahm CD, Johnson LE, McNeel DG. Increased indoleamine 2, 3-dioxygenase activity and expression in prostate cancer following targeted immunotherapy. Cancer Immunol Immunother 2019 Oct;68:1661-9. https://doi.org/10.1007/s00262-019-02394-w
27. Thüring M, Knuchel R, Picchetta L, Keller D, Schmidli TS, Provenzano M. The prognostic value of indoleamine-2, 3-dioxygenase gene expression in urine of prostate cancer patients undergoing radical prostatectomy as first treatment of choice. Front Immunol. 2020 Aug 14;11:1244. https://doi.org/10.3389/fimmu.2020.01244
28. Banzola I, Mengus C, Wyler S, Hudolin T, Manzella G, Chiarugi A, et al. Expression of indoleamine 2, 3-dioxygenase induced by IFN-γ and TNF-α as potential biomarker of prostate cancer progression. Front Immunol. 2018 May 29;9:1051. https://doi.org/10.3389/fimmu.2018.01051.
29. Pei RJ, Chen XW, Lu MJ. Control of hepatitis B virus replication by interferons and Toll-like receptor signaling pathways. World J Gastroenterol WJG. 2014 Sep 9;20(33):11618. doi: 10.3748/wjg.v20.i33.11618.
30. Koç DÖ, Özhan Y, Acar ET, Bireroğlu N, Aslan F, Keğin M, Sipahi H. Serum neopterin levels and IDO activity as possible markers for presence and progression of hepatitis B. Pteridines. 2020 Jan 1;31(1):91-9. https://doi.org/10.1515/pteridines-2020-0010.
31. Yang Y, Liu K, Chen Y, Gong Y, Liang Y. Indoleamine 2, 3-dioxygenase (IDO) regulates Th17/Treg immunity in experimental IgA nephropathy. Folia biologica. 2019 Mar 1;65(2):101-8.
32. Verghese VP, Robinson JL. A systematic review of hepatitis E virus infection in children. Clin Infect Dis. 2014 Sep 1;59(5):689-97. https://doi.org/10.1093/cid/ciu371.
33. Larrea E, Riezu-Boj JI, Gil-Guerrero L, Casares N, Aldabe R, Sarobe P, et al. Upregulation of indoleamine 2, 3-dioxygenase in hepatitis C virus infection. J Virol. 2007 Apr 1;81(7):3662-6. doi: https://doi.org/10.1128/jvi.02248-06
34. Yang R, Gao N, Chang Q, Meng X, Wang W. The role of IDO, IL-10, and TGF-β in the HCV-associated chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. J Med Virol. 2019 Feb;91(2):265-71. https://doi.org/10.1002/jmv.25083.
35. Zhai N, Li H, Song H, Yang Y, Cui A, Li T, et al. Hepatitis C virus induces MDSCs-like monocytes through TLR2/PI3K/AKT/STAT3 signaling. PLoS One. 2017 Jan 23;12(1):e0170516 https://doi.org/10.1371/journal.pone.0170516
36. Brown ZJ, Yu SJ, Heinrich B, Ma C, Fu Q, Sandhu M, Agdashian D, et al. Indoleamine 2, 3-dioxygenase provides adaptive resistance to immune checkpoint inhibitors in hepatocellular carcinoma. Cancer Immunol Immunother. 2018 Aug;67:1305-15. https://doi.org/10.1007/s00262-018-2190-4.

37. Yap TA, Sahebjam S, Hong DS, Chiu VK, Yilmaz E, Efuni S, et al. First-in-human study of KHK2455, a long-acting, potent and selective indoleamine 2, 3-dioxygenase 1 (IDO-1) inhibitor, in combination with mogamulizumab (Moga), an anti-CCR4 monoclonal antibody, in patients (pts) with advanced solid tumors. Journal of Clinical Oncology. 2018; 36(15). doi: 10.1200/JCO.2018.36.15_suppl.3040.

38. Khalil DN, Budhu S, Gasmi B, Zappasodi R, Hirschhorn-Cymerman D, Plitt T, De Henau O, Zamarin D, Holmgaard RB, Murphy JT, Wolchok JD. The new era of cancer immunotherapy: manipulating T-cell activity to overcome malignancy. Adv Cancer Res. 2015 Jan 1;128:1-68. https://doi.org/10.1016/bs.acr.2015.04.010

Case Report

UNIQUE CASE OF BILATERAL ADRENAL PHEOCHROMOCYTOMAS: DIAGNOSTIC APPROACH

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ABSTRACT

Pheochromocytoma is a neuroendocrine tumor arising from the adrenal medulla. Paragangliomas also originate from neural crest tissue but outside the adrenal gland. The presence of Bilateral adrenal masses is a unique and reportable event. Bilaterality is a treatment dilemma for a clinician whether to operate or not, keeping in mind that it can render patients with life threatening complications, perioperative mortality, and the potential burden of life long medications in some cases. We present a unique case of 28 years old female who presented with left lumbar pain, occasional headaches in her twenties followed by spells of uncontrolled hypertension during pregnancy, referred in post-partum period following a successful pregnancy to urology with suspicion of bilateral adrenal masses ending up with histopathology and immunocytochemistry confirming the diagnosis of Bilateral Adrenal Pheochromocytoma

Key Words: Pheochromocytoma, Adrenalectomy, Pregnancy, Adrenal medulla

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INTRODUCTION

Pheochromocytomas and Paragangliomas are rare tumors of neural crest origin.[1,2] Some of them present with symptoms while most are diagnosed as incidental findings on imaging done for other purposes. Symptoms may include episodic headaches, sweating, tachycardia, flushing, and paroxysms of hypertension.[3] Due to overlaps of symptoms with various other medical conditions there is often seen a delay in patient presentation and correct diagnosis.[3] Diagnostic workup includes measurements of urinary catecholamines secreted by the tumor and imaging including ultrasound, CT scan, MRI and MIBG scans where suited.

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Pheochromocytomas being a rare diagnosis may mimic Renal Cell Carcinoma.[4] It is a diagnostic challenge for the clinician and as well as a difficult pathological diagnosis for the histopathologist sometimes requiring re-reporting of slides by a second pathologist or a second review by outsourcing to confirm the diagnosis. Pheochromocytomas due to the release of Catecholamines during surgical manipulation for resection cause unpredictable fluctuations in blood pressure during the surgery as well as in the immediate post operative period requiring a dedicated anesthesia team and ICU care. Adrenalectomy in such cases should be performed by the senior surgeon as the surgery requires a high set of surgical skills. Surgical resection is further made difficult by the rich blood supply and the potential threat of bleeding with such fluctuating per operative blood pressures.[5]

We present a unique case of 28 years old female presenting with bilateral adrenal masses who underwent bilateral

adrenalectomies with histopathology and further immunostaining confirming the diagnosis of Bilateral Pheochromocytomas.

CASE REPORT

A 28 years old female was referred to us by the gynecologist after a successful pregnancy with spells of uncontrolled hypertension starting from 7-8 weeks of pregnancy and continuing throughout the antenatal period. She underwent an Ultrasound abdomen later during the pregnancy showing evidence of hypoechoic lesions bilaterally in the Suprarenal region with no pathology seen in the kidneys bilaterally. After the successful pregnancy, further workup was advised including a CT abdomen and pelvis with contrast which showed bilateral adrenal masses of more than 5cm in size each showing intense enhancement and nonenhancing areas of necrosis. Nodular calcification was noted on the left side. The fat planes with kidneys were clear. (Figure 1) She had her urinary catecholamines levels done in which Urinary metanephrines levels of 134.6 pg/ml, normetanephrine levels of 800 pg/ml and dopamine levels of 93.4 pg/ml were seen, further supporting the diagnosis of Bilaterally functional or either one functional pheochromocytomas. After meticulous pre operative preparations including blood pressure monitoring she had her Left Open adrenalectomy done with uneventful post operative recovery except for minor fluctuations in blood pressure. This did not require any need for blood transfusions.

Upon histopathology of this left adrenal mass, the Gross cut section showed a yellowish brown lesion with a white gelatinous central nodule. Histopathological examination showed cells arranged in nested and solid patterns with abundant eosinophilic granular cytoplasm with nuclei having salt and pepper chromatin. Typical Zellballen patterns of polygonal cells were also seen. To confirm this rare diagnosis second review of histopathology was done by another pathologist, both suggesting the same. Further immunohistochemical staining of the same slides showed positive results for Chromogranin and negative staining for CK, PAX8, CAIX, SMA, HMB45 and Inhibin. Based upon the above the histopathological diagnosis was confirmed as Pheochromocytoma. (Figure 2, Figure 3)

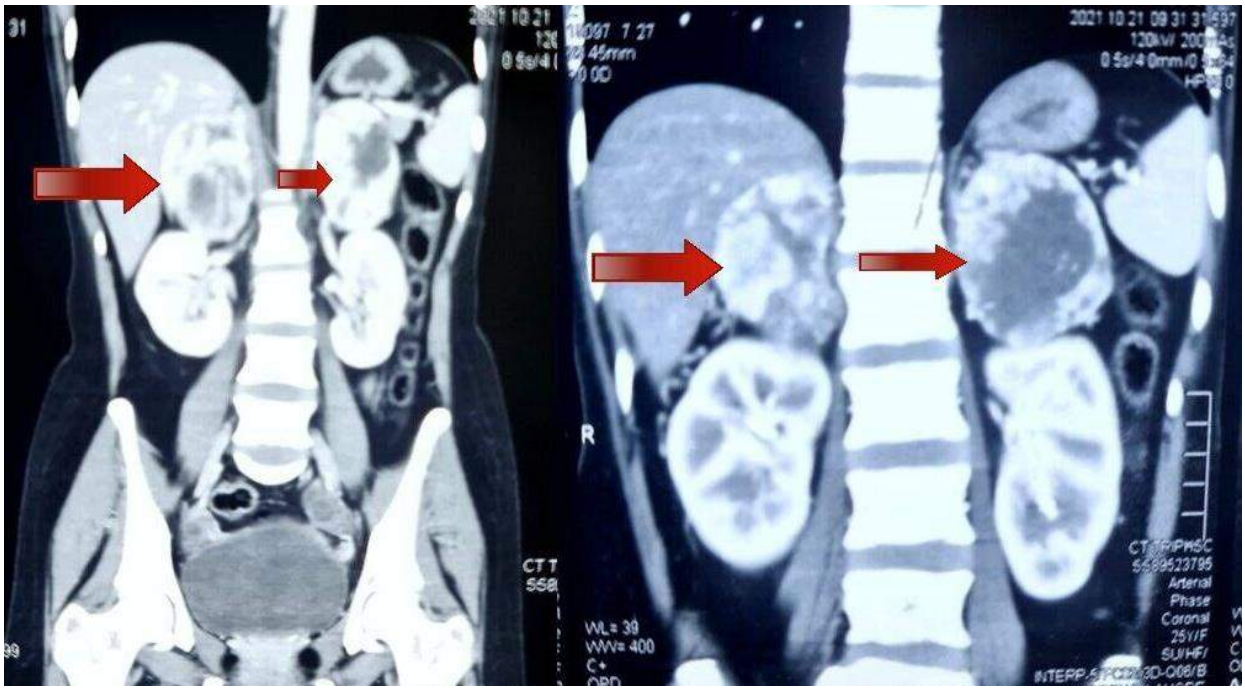

Figure-1: CT Abdomen and Pelvis showing Bilateral Adrenal Masses

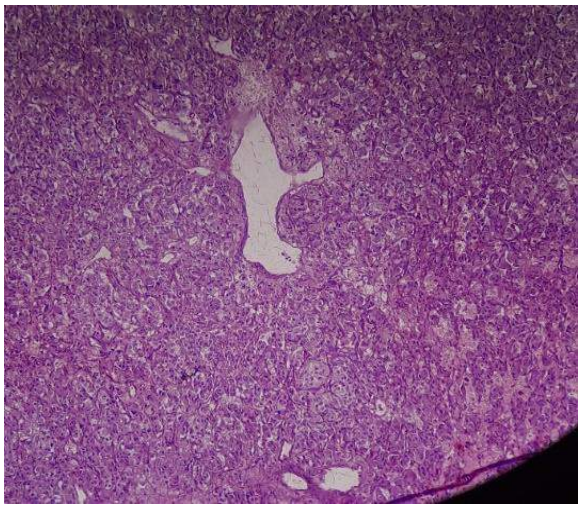

Figure-2: Left adrenal mass low power view (4x) showing packeting of cells zell Ballen pattern.

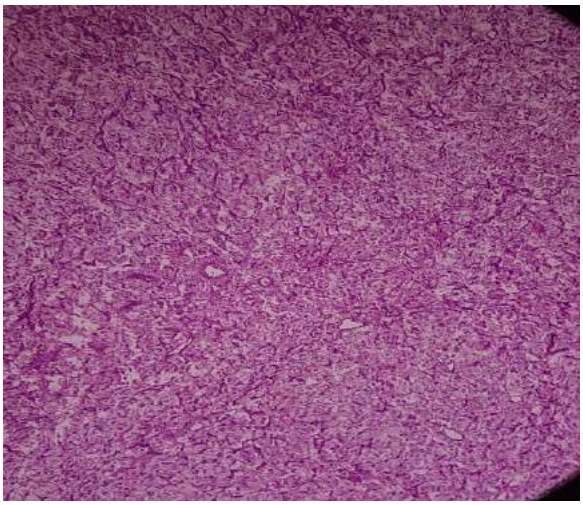

Figure-4: Right adrenal mass. Low power view (4 x) showing the nested pattern and packeting of cells.

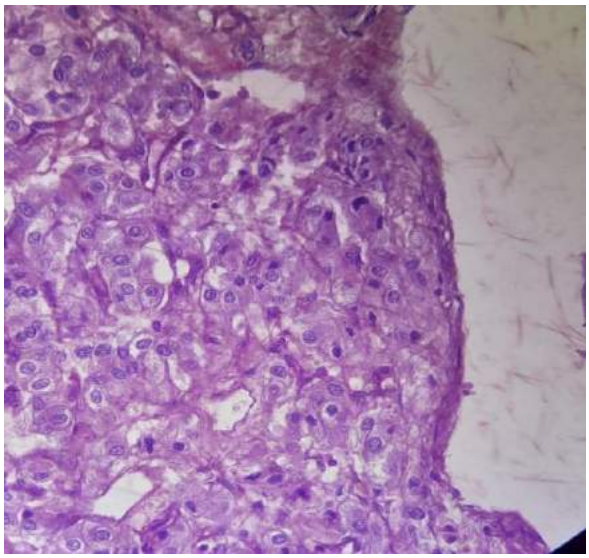

Figure-3: High power view (40x) with polygonal to round cells with abundant cytoplasm. An occasional mitotic figure is seen.

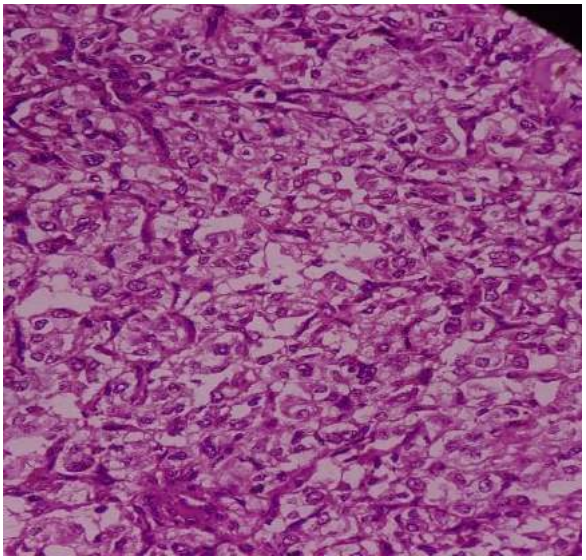

Figure-5: Right adrenal mass high power view (40x) showing polygonal cells arranged in packets with eosinophilic cytoplasm, minimal atypia. No mitotic figures.

After successful recovery from the left adrenalectomy, she underwent a right open adrenalectomy with a cut section showing a brownish encapsulated lesion having a central fibrotic bank. Histological examination showed tumor cells with abundant grey-blue granular cytoplasm and nuclei with granular chromatin, mitotic rate of less than 2 mitosis / 10HPF confirming the histopathological diagnosis of Left pheochromocytoma. (Figure 4, Figure 5)

In the post operative period, the patient had no major complications and was referred to a medical specialist on discharge for lifelong monitoring of Blood pressure and electrolyte balance who advised oral steroids. The six-month follow-up of patients with both us and the medical team was satisfactory.

DISCUSSION

With bilateral adrenal masses being rare, there have been very few documented cases of such nature.[1-3] Establishment of diagnosis can be difficult as tumors may be purely

incidental or may produce symptoms that overlap with a lot of other medical conditions which are generally ignored by patients including episodic headaches, sweating, tachycardia, flushing, paroxysms of hypertension.[3] Bilaterality poses an additional challenge of potential drastic metabolic and electrolyte disturbances that can be life threatening. Diagnostic workup may comprise Urinary catecholamine levels including metanephrines, normetanephrine and dopamine.

Further imaging workup can include Ultrasound Abdomen, CT Scan with contrast, MRI and MIBG scan where suited.[6-8] Bilateral resection of adrenal masses can be achieved in the same session by Laparoscopic approach or we may choose one by one approach through open adrenalectomy.

Histopathology of such rare cases requires a careful approach including a panel of immunostaining to confirm the diagnosis[9,10] as was done in this case. In such cases, a 2nd review from another pathologist in the same setup or outsourcing to obtain a second valid opinion should also be carried out for safe surgical practices and patient welfare, as was done in our case with both sources confirming the diagnosis of Pheochromocytomas.

There are very few cases being documented on bilateral pheochromocytomas and there is a need to gather more data to establish guidelines for diagnosis, histopathological reporting and treatment for such cases.

CONCLUSION

Bilateral Pheochromocytomas is a rare finding and poses a diagnostic and therapeutic challenge. The clinical presentation may be varied including presentation as incidentalomas. The use of a Contrast CT scan and Urinary catecholamines can narrow down the diagnosis with histopathology and immunocytochemistry staining being confirmatory and pathognomonic.

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AUTHOR'S CONTRIBUTION

NAG: Concept, Design and writing with data collection
SH: Data collection and critical review
UA: Data collection

REFERENCES

1. Calissendorff J, Juhlin CC, Bancos I, Falhammar H. Pheochromocytomas and abdominal paragangliomas: practical guidance. Cancers. 2022 Feb 12;14(4):917. doi: 10.3390/cancers14040917.
2. Pacak K, Tella SH. Pheochromocytoma and Paraganglioma. 2018 Jan 4. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 29465938.
3. Garg SK, Garg P, Urumdas M. An interesting presentation of pheochromocytoma. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of ISCCM. 2018 Jan;22(1):40. doi: 10.4103/ijccm.IJCCM_407_17.
4. Wu W, Li SL, Huang KB, Wei QZ. Malignant paraganglioma originating from the kidney: a case report and literature review. South. Med. J. 2011 Jun 1;31(7):1111-3.
5. Doo AR, Son JS, Han YJ, Yu HC, Ko S. Hypertensive crisis caused by electrocauterization of the adrenal gland during hepatectomy. BMC surgery. 2015 Dec;15(1):1-3.
6. Albano D, Agnello F, Midiri F, Pecoraro G, Bruno A, Alongi P, et al. Imaging features of adrenal masses. Insights Imaging. 2019 Dec 1;10(1):1-6. doi: 10.1186/s13244-019-0688-8.
7. Halefoglu AM, Yasar A, Bas N, Ozel A, Erturk ŞM, Basak M. Comparison of computed tomography histogram analysis and chemical-shift magnetic resonance imaging for adrenal mass characterization. Acta Radiologica. 2009 Nov;50(9):1071-9. doi: 10.3109/02841850903207170.

8. Ku EJ, Kim KJ, Kim JH, Kim MK, Ahn CH, Lee KA, et al. Diagnosis for pheochromocytoma and paraganglioma: a joint position statement of the Korean pheochromocytoma and paraganglioma task force. Endocrinol Metab. 2021 Apr 6;36(2):322-38.
9. Juhlin CC. Challenges in paragangliomas and pheochromocytomas: from histology to molecular immunohistochemistry. Endocr. Pathol. 2021 Jun;32(2):228-44. doi: 10.1007/s12022-021-09675-0.
10. Kumaki N, Kajiwara H, Kameyama K, DeLellis RA, Asa SL, Osamura RY, et al. Prediction of malignant behavior of pheochromocytomas and paragangliomas using immunohistochemical techniques. Endocr. Pathol. 2002 Jun;13:149-56. doi: 10.1385/ep:13:2:149.