Original Article

# Bilirubin Profiles and Symptomatology in Neonates: Unraveling Gender and Location Specific Trends in Shaheed Benazirabad

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## ABSTRACT

**OBJECTIVE: To assess the levels of bilirubin in male and female neonatal jaundice patients in both urban and rural areas of the Shaheed Benazirabad district, Sindh, Pakistan.**

**METHODOLOGY: A descriptive cross-sectional study was conducted at Mother and Child Health Hospital, Shaheed Benazirabad, targeting neonatal patients with bilirubin/jaundice between January and December 2024. A consecutive nonprobability sampling method was used to select 200 patients. Neonates, specially the first and second week of their birth, were included in the study with clear signs of neonatal jaundice. The neonates were included following their parental consent. SPSS and GraphPad Prism software were used for data analysis.**

**RESULTS: The current study included 200 neonates (136 male, 64 female), of whom 119 were urban and 81 rural. Urban neonates were younger on average (4.57 days) than rural neonates (6.33 days for males, 6.25 days for females). Bilirubin levels significantly differed between rural and urban males. Neonatal jaundice symptoms varied by gender and location, with high-pitched cry most common in urban males and fever in rural males. Phototherapy was the primary treatment, especially in urban males (38). Rural males showed more jaundice symptoms, especially in the eyes, face, and palms. Jaundice was most prevalent in the first week of life, particularly on the palms and soles.**

**CONCLUSION: This study highlights gender and location disparities in neonatal characteristics, bilirubin levels, and NNJ symptoms and treatments. Phototherapy emerged as the primary treatment, particularly for urban males. Understanding these differences informs effective management strategies for neonatal jaundice.**

**KEYWORDS: Bilirubin, Neonatal jaundice, Hyperbilirubinemia, Gender, Urban, Rural.**

## INTRODUCTION

Hyperbilirubinemia, characterized by elevated bilirubin levels in neonates during their first week of life, is a common clinical problem[1]. Bilirubin, a potentially toxic heme metabolite, plays a crucial role in coordinating iron in proteins and is essential for detoxification. It exists in direct and indirect forms, primarily binding to serum albumin[2]. The process involves heme oxygenase converting heme into biliverdin and carbon monoxide, which is then transformed into indirect bilirubin by biliverdin reductase. Uridine Diphosphate Glucuronosyl Transferase 1A1 is responsible for encoding the key enzyme involved in indirect bilirubin production[3,4].

Neonatal jaundice, caused by elevated total serum bilirubin, often leads to hospital readmission, affecting 60-80% of newborns within the first two weeks of life. Lowering bilirubin production is a therapeutic strategy, particularly for infants with genetic deficiencies or defective elimination pathways[5]. This condition, characterized by skin and sclera discoloration, poses a significant risk, with over 100,000 infants dying annually from complications. Untreated or uncontrolled jaundice can result in severe disabilities or death[6-8]. The World Health Organization (WHO) has identified vulnerability signs for neonatal diseases, including feeding difficulties, convulsions, and high respiration rates[9]. In settings with high neonatal mortality rates, hyperbilirubinemia presents potential risks, including neuro-cerebral complications, hepatic lesions, and renal injury[10].

The synthesis and removal of bilirubin can become imbalanced, leading to neonatal indirect hyperbilirubinemia (IHB). Approximately 60% of term and 80% of preterm babies experience jaundice during their first week of life[11]. Ongoing discussions focus on bilirubin metabolism and transport systems, with recent discoveries shedding light on hepatic membrane transporters and hereditary abnormalities in bilirubin metabolism. Understanding these processes has improved, with research indicating that even in cases of normal physiological jaundice without clinical issues, some conjugated bilirubin is eliminated by the renal system instead of the intestinal system[12].

Bilirubin, a waste product derived from heme breakdown, is produced daily at a rate of 0.2 to 0.3 grams[13]. There are various steps involved in the

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metabolism of bilirubin, including: Production of bilirubin, Mechanism of hepatic (liver) transport, Conjugation, Detoxification into bile, and Degradation in the gastrointestinal tract.

Hepatocytes absorb water-insoluble bilirubin from blood plasma, which is carried by albumin throughout the body. Albumin binding prevents bilirubin from escaping blood vessels, facilitating its entry into the liver without binding and ensuring consistent concentration measurement. Hepatocytes, crucial for metabolism, protein synthesis, and bilirubin clearance, produce proteins that bind bilirubin, preventing its diffusion back into tissues. Bilirubin enters hepatocytes through passive diffusion and receptor-mediated endocytosis, with unconjugated bilirubin entering via the periportal area and some returning to the sinusoidal space. Conjugated bilirubin is discharged in urine[14].

Bilirubin undergoes conjugation with glucuronic acid in hepatocytes, catalyzed by UDPGT. This process makes bilirubin more water-soluble. Mutations in UDPGT can lead to hyperbilirubinemias, Gilbert's syndrome, and Crigler-Najjar syndromes[15]. Conjugated bilirubin is excreted into bile via transporters in the canalicular membrane, primarily multidrug resistance-associated protein 2 MRP2. A fraction may be reabsorbed into hepatocytes or transported into the bloodstream. Conjugation alters bilirubin's properties, making it more soluble in water. Conjugated bilirubin is partially reabsorbed across the small intestine and converted by gut microbiota into urobilinogen. Urobilinogen is excreted as stercobilinogen in faeces, with some being reabsorbed into the circulation or undergoing an intrahepatic cycle, contributing to bilirubin recycling and potentially causing jaundice. Bilirubin's glucuronidation controls its passage across the blood-brain barrier. This comprehensive process ensures efficient bilirubin elimination and maintenance of physiological balance.

Pakistan is a developing country, and most of the medical diagnostic facilities are concentrated in urban areas. Furthermore, in rural areas, due to the unavailability of diagnostic facilities and a lack of awareness, traditional and classical treatments are still practiced by untrained personnel. We hypothesized that mishandling elevated levels of bilirubin in neonates, a potential risk factor, may cause irreversible health conditions if left untreated. The objective of the study was to assess the levels of bilirubin in male and female neonatal jaundice patients in both urban and rural areas of the Shaheed Benazirabad district.

## METHODOLOGY

The descriptive cross-sectional study was designed to evaluate the level of bilirubin in jaundice patients among neonates, comparing gender and urban-rural differences. The study was carried out at the Mother and Child Hospital (MCH) of Shaheed Benazirabad district, Pakistan, between January and December 2024.

The consecutive nonprobability sampling method was used of select neonates presenting to the hospital's outpatient department (OPD) in Shaheed Benazirabad, which serves both urban and rural populations. A total of 200 neonates (1–14 days old) with clinical jaundice were enrolled. Participants were enrolled from the MCH OPD. Neonates between the ages of 1–14 days with jaundice signs, parents'/ guardians' willingness to participate through written informed consent. Parents'/guardians' refusal of consent and unclear jaundice signs in neonates were excluded. A standardized questionnaire was used to collect demographic information (gender, age, domicile), mothers' level of awareness of jaundice, clinical features (e.g., fever, high-pitched cry), and forms of treatment (e.g; phototherapy). Parental permission was taken before recruitment. Venipuncture with a sterile needle was performed to collect 2–3mL of venous blood. Serum was separated and stored in the dark to prevent bilirubin breakdown.

***Bilirubin Test Collection and Assay Principles***

**Collection Method:** A venipuncture tool was used to collect blood samples by inserting a needle into a vein through the skin of the arm.

**Assay Principle:**

• Red-colored azobilirubin is produced when the sample's conjugated (direct) bilirubin combines with diazotized sulfanilic acid.

• In the presence of caffeine, the sample's conjugated (direct) and unconjugated (indirect) bilirubin combine with diazotized sulfanilic acid to generate reddish-colored azobilirubin.

Reagents:

• R1 Bilirubin Total Reagent: Sulfanilic acid 30.0 mmol/l, HCl 0.20N, Caffeine 260nmol/l, Sodium Benzoate 520mmol/l

• R1 Bilirubin Direct Reagent: Sulfanilic acid 30.0 mmol/l, HCl 0.20N

• R2 total and direct bilirubin: Sodium nitrite 30.0 mmol/l

Specimen:

• The preferred specimen is serum.

• Specimens should be analyzed as soon as possible after collection.

• Specimens should be shielded from light exposure if testing is postponed.

***Protocol:***

• Total Bilirubin: 546 nm wavelength, 1 cm cuvette light path, temperature: 20–25 □.

• Procedure: Total Bilirubin: 1 ml of R1 reagent, 1 drop of R2 reagent, 100 µl of specimen, mix well, let stand 10 minutes at room temperature.

•Direct Bilirubin: 546 nm wavelength, 1 cm cuvette light path, temperature: 20–25 □.

• Procedure: Total Bilirubin: 1 ml of R1 reagent, 1 drop of R2 reagent, 100 µl of specimen, mix well, let stand 5 minutes at room temperature.

***Calculation:***

Total Bilirubin Concentration = Specimen absorbance X 13 = mg/dl.

Direct Bilirubin Concentration = Specimen absorbance X 13 = mg/dl

Indirect bilirubin Concentration = Total Bilirubin level - Direct Bilirubin level

***Statistical Analysis***

Research data were analyzed using Excel, SPSS, and GraphPad Prism. Analysis of variance (ANOVA) was used to determine statistical significance in bilirubin levels between male and female neonates of urban and rural areas. Student's t-test used to compare the difference of bilirubin levels between the first and second weeks of neonates. Frequencies were calculated of demographics, gender, patient age, neonatal parent level of awareness, causes/ Symptoms, neonatal jaundice first noticed in patients, and different treatment modalities of neonatal jaundice patients. In all statistical tests, a p-value < 0.05 is considered statistically significant based on parametric and non-parametric test results.

**Ethical Considerations**: Ethical approval was presumed based on parental consent. Participant data were kept confidential in the course of the study. The Institutional Review Board at Shaheed Benazir Bhutto University, Shaheed Benazirabad, approved the study.

## RESULTS

Bilirubin levels were measured in both urban and rural neonates, including males and females, as well as across the first and second weeks after birth (**Figure 1A**). It was observed that the total bilirubin levels of rural female, urban female, and rural male neonates were not statistically different from each other. However, the total, direct, and indirect bilirubin levels were significantly different between rural and urban males, contradicting the earlier statement that no significant differences were found among females. Overall, analysis of variance (ANOVA) between neonates total bilirubin (P=0.0163), direct bilirubin (P=0.0175) level among rural (female and male), and urban (female and male) observed different significantly (**Figure 1A, 1B**) except indirect bilirubin (P=0.0761) noted non-significant among rural (female and male), and urban (female and male).

The average levels of total, direct, and indirect bilirubin were measured between the first and second weeks of neonates, regardless of gender. The total and indirect bilirubin levels between neonates in the first and second weeks were not significantly different (**Figure 2A, C**). In contrast, the direct bilirubin levels showed a slight but significant difference (P<0.046) (**Figure 2B**).

The signs and symptoms of neonatal jaundice (NNJ) varied across genders. High-pitched cry was highest in urban males (21), fever was most prevalent in rural males (26), and reluctance to feed was equally common in rural males and urban males (16 and 29, respectively) (**Figure 3A**).

In **Figure 3B**, the most common treatment for neonatal jaundice in urban males was phototherapy (38), followed by sunlight exposure (25) and blood transfusion (12). Similarly, in urban females, phototherapy was the most frequent treatment (17), followed by sunlight exposure (22) and blood transfusion (5).

**Figure 1: Different Concentrations of bilirubin in neonates, A. Total bilirubin. B. Direct bilirubin and C. Indirect level of bilirubin (mg/dL)**

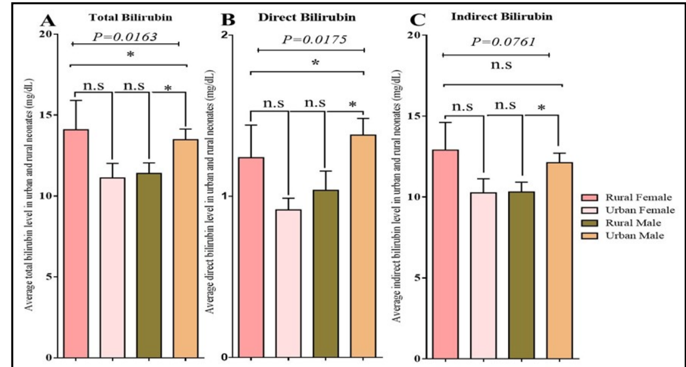



**Figure 2: Comparison of bilirubin levels between the first and second week, A. direct bilirubin in the first and second week of neonatal jaundice patients, B. indirect bilirubin in the first and second week of neonatal jaundice patients and C. Total bilirubin in the first and second week of neonatal jaundice patients**

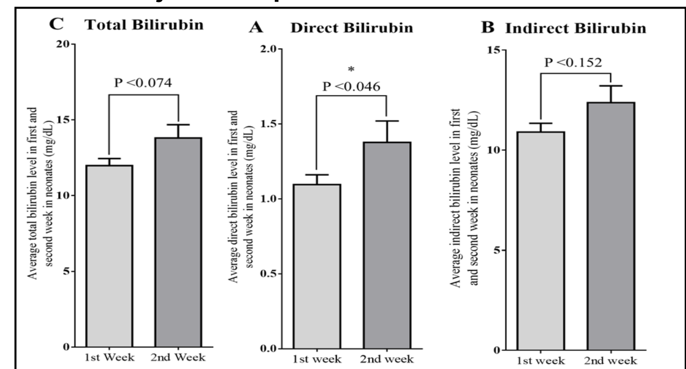
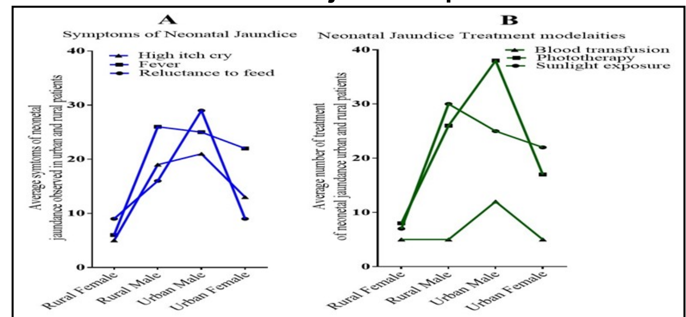
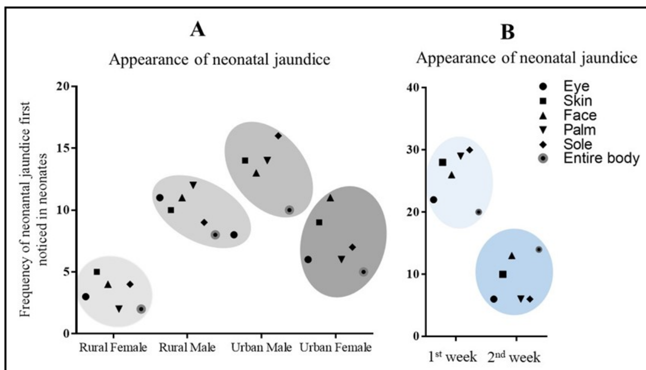



**Figure 3: Neonatal Jaundice among female and male urban and rural patients, A. Symptoms of neonatal jaundice. B. Neonatal jaundice was first noticed in the patient, and C. Different treatment modalities of neonatal jaundice patients**



In **Figure 4A**, rural male neonates had the highest counts of neonatal jaundice symptoms, particularly in the eye (11), face (11), and palm (12). In Figure 4B, the appearance of neonatal jaundice was more prevalent in first-week neonates across all body parts, with the highest counts in the palm (29) and sole (30).

**Figure 4: Appearance frequency of neonatal jaundice and first noticed across the patients with groups and in the first and second week, A. neonatal jaundice first notice in different groups among rural female, rural male, urban male and urban female, B. as a result of elevated bilirubin, neonatal jaundice appearance during the first and second week after birth**




## DISCUSSION

In the initial study conducted in Shaheed Benazirabad, the bilirubin levels were compared across different genders and demographic characteristics. The results of the research revealed valuable insights into neonatal health, particularly bilirubin levels.

In this study, 200 neonates participated, comprising 136 males (68%) and 64 females (32%). Neonates ranged in age from 1 to 14 days. They were categorized by urban and rural settings, with 119 urban and 81 rural neonates. The average age of urban neonates was 5.7 days, while rural neonates averaged 6.3 days in age. Overall, the average age of neonates was 8.7 days (± 3.3), as reported[16].

In terms of awareness about neonatal jaundice, a total of 65% of mothers were aware. When considering urban and rural areas separately, 36% of mothers in urban areas and 29% of mothers in rural areas were mindful of neonatal jaundice. It has been reported that 52.3% of participants had sufficient knowledge about neonatal jaundice[17]. Studies from various developing nations show inconsistent frequencies of correct responses regarding knowledge related to neonatal jaundice: Ethiopia (63.5%)[18], Nigeria (57%)[19], Iran (77%), Ethiopia (46%)[20], and Turkey (46%)[21].

Neonatal hyperbilirubinemia, marked by jaundice, is common in newborns, particularly in the first days of life. While usually harmless, it can be dangerous if left untreated. Studies show differences in bilirubin levels among rural and urban populations and between male and female neonates. Notably, male neonates from rural and urban areas show a slight but significant difference. Similarly, reported higher bilirubin level among boys[22]. In a study, a higher bilirubin level was significantly associated with male gender, due to their young livers not fully processing bilirubin from red blood cells [23, 24].

In our study, rural areas had higher neonatal total bilirubin levels (12.25 mg/dl) compared to urban areas; our results are consistent with previous findings of 12.21 mg/dl in urban areas[25]. Additionally, median direct bilirubin levels in patients were 1.22 (±2) and mean total bilirubin levels in controls were 10.66 (±5.98)[26]. These variations highlight the importance of understanding regional and demographic differences in managing neonatal hyperbilirubinemia. Moreover, no significant differences in mean bilirubin levels between the two groups based on demographic characteristics[27]. The study noted comparable total and indirect bilirubin levels between neonates in the first and second weeks, with no significant difference. However, direct bilirubin levels showed a slight but significant disparity ($P < 0.046$). Furthermore, higher direct and indirect bilirubin levels were found in the case group compared to the control group ($P=0.000$). Found consistent direct bilirubin levels but significant seasonal variations in indirect and total bilirubin levels among newborns, with higher levels in spring and winter, possibly due to shorter daylight duration in winter, potentially increasing the risk of hyperbilirubinemia[28,29].

In our study, neonatal jaundice manifested with fever in 39.5% of cases, a high-pitched cry in 29% of cases, and reluctance to feed in 31.5% of cases. However, 36% of women were unaware of early warning signals, with 17.6% identifying changes in their infant's feeding and sucking abilities as indicators. Similarly, high-pitched cries are a warning sign of newborn jaundice, yet 44.3% of respondents were unaware of these signs. Additionally, 26.6% of respondents reported their infants refusing to feed[30,31].

In our study, neonatal jaundice treatment primarily involved exposure to sunlight (42%), phototherapy (45%), and exchange blood transfusion (13%). However, 34.7% of mothers stated using phototherapy for jaundice treatment[30]. The variance in treatment methods may be attributed to limited knowledge among primary health workers regarding phototherapy and exchange blood transfusion, as only 24.1% and 16.3% of respondents were knowledgeable about these methods, respectively[32]. Interestingly, nurses and midwives in secondary health institutions demonstrated higher levels of knowledge, with phototherapy and exchange blood transfusion rates of 82.4% and 61.8%, respectively. This echoes findings from earlier research, in which respondents from both health institutions reported substantial use of sunlight phototherapy[32,33].

In this study, jaundice was initially observed in various body parts: eyes (14%), skin (19%), face (19%), palms (17.5%), soles (18%), and the entire body

(12.5%). Notably, 7.5% of participants relied solely on physical appearance for jaundice diagnosis[29]. In contrast, 56.6% of participants recognized the importance of examining the baby's eyes, skin, palms, and soles for jaundice. However, 36% also considered feces or urine color as potential indicators of neonatal jaundice[34].

Bilirubin levels in neonates were evaluated in this study from Shaheed Benazirabad, with a focus on maternal awareness, gender, and geographic location. There were 200 neonates in all, 136 of whom were male (68%) and 64 of whom were female (32%). Consistent with earlier findings, the neonates' average age was 8.7 ± 3.3 days, with a range of 1 to 14 days. In terms of demographics, 81 neonates came from rural areas and 119 from urban areas. Urban neonates had a mean age of 5.7 days, while rural neonates averaged 6.3 days[16].

Our study also focused on maternal awareness of neonatal jaundice. In general, 65% of mothers knew what jaundice was, and in urban areas, awareness was slightly higher (36%) than in rural areas (29%). This level of awareness is somewhat higher than the 52.3% reported in a previous study[17]. Additionally, our results are consistent with those of other international studies. For example, Ethiopia [18], Nigeria [19], and Iran [20] reported maternal awareness rates of 63.5%, 57%, and 77%, respectively. On the other hand, some areas reported significantly lower awareness, with some parts of Ethiopia and Turkey reporting only 46% [20,21]. This regional variation emphasizes the need for context-specific educational approaches to enhance awareness and early detection of neonatal jaundice, particularly in rural populations.

Our study found that male neonates had higher bilirubin levels than females, consistent with other research that attributes this to delayed liver enzyme maturation in males, which hinders bilirubin processing[22-24]. Furthermore, compared to their urban counterparts, rural neonates had higher total bilirubin levels (12.25 mg/dl), which is in line with another study reporting similar rural values (12.21 mg/dl)[25]. Some studies, however, found no significant variations in mean bilirubin levels according to demographic factors[27].

The study also assessed maternal recognition of early signs and symptoms of neonatal jaundice. Mothers most frequently reported fever (39.5%), high-pitched cry (29%), and reluctance to feed (31.5%). However, only 17.6% of mothers identified changes in feeding and sucking behaviours as suggestive of jaundice, and 36% of mothers were unaware of any early warning signs. These results are consistent with earlier studies that found 26.6% of mothers reported feeding refusal as a potential symptom, and 44.3% of mothers were not aware of high-pitched cries as a warning sign[30,31]. This emphasizes the crucial role of health education in helping mothers better recognize the clinical signs of neonatal hyperbilirubinemia.

The most popular treatment approach was phototherapy (45%), followed by exposure to sunlight (42%) and exchange blood transfusions (13%). A related study reported that 34.7% of mothers used phototherapy to treat neonatal jaundice[30]. Another study found that primary health workers had limited awareness, with only 16.3% of them knowing about exchange transfusion and only 24.1% knowing about phototherapy[18]. The knowledge levels of nurses and midwives in secondary health facilities, on the other hand, were noticeably higher, with 82.4% and 61.8%, respectively, being aware of phototherapy and exchange transfusion[32,33]. These variations suggest a lack of primary care training, which could affect the quality of neonatal care in outlying areas.

In our study, mothers were able to visually identify jaundice in several body parts, including the skin (19%), face (19%), palms (17.5%), soles (18%), eyes (14%), and generalized yellowing (12.5%). This contrasts with a study in which only 7.5% of mothers identified jaundice based solely on physical appearance[29]. On the other hand, 56.6% of study participants accurately recognized the importance of examining the baby's skin, eyes, and extremities. However, 36% also considered feces or urine color as potential indicators of neonatal jaundice[34].

Bilirubin levels during the first and second weeks of life were also examined. Our data showed no significant changes in total and indirect bilirubin levels between the first and second weeks of life. Direct bilirubin levels, however, showed a small but statistically significant difference ($P < 0.046$). Other studies that reported seasonal variations in total and indirect bilirubin levels but found stable direct bilirubin levels support this finding. Higher levels were observed in the spring and winter, most likely due of reduced daylight exposure, which could affect natural phototherapy and increase the risk of jaundice during those times of year [28,29].

## CONCLUSION

This study's originality comes from its original examination of neonatal hyperbilirubinemia using the dual viewpoint of gender and geographical differences in Shaheed Benazirabad, Pakistan, an area characterized by severe urban-rural healthcare disparities. Unlike earlier research that often separated demographic factors, this study finds notable differences in direct bilirubin levels between urban and rural male neonates, suggesting region-specific metabolic or environmental effects. It emphasizes systematic gaps in resource-constrained areas where rural communities depend on sunlight exposure, despite constrained access to phototherapy, in contrast to metropolitan reliance on clinical treatments. The study also finds specific symptom patterns, such as higher jaundice incidence in the eyes, face, and palms of rural male neonates and first-week neonates, while noting poor maternal knowledge (29% in rural areas) as a significant public health concern. The study offers practical insights into

customized neonatal care approaches in under-resourced areas by combining clinical, demographic, and sociocultural factors.

**Ethical Permission:** Shaheed Benazir Bhutto University, Shaheed Benazirabad, Sindh, Pakistan, IRB letter No. REF/ORIC/1075.

**Conflict of Interest:** Authors have no conflict of interest.

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**Data Sharing Statement:** The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

## AUTHOR CONTRIBUTION

Altaf M: Research design, data collection and writing of manuscript
Rind KH: Statistical analysis of data, interpretation of results, the overall integrity of the manuscript and supervision of research.
Noreen R: Research methodology design, Literature review, Language Grammar settings of the manuscript.
Rind NA: Investigation, overall review of manuscript, formal analysis, methodology.
Shar AH: Writing literature review and editing of manuscript.
Khuhro GM: Review of the result and discussion section, Reference setting
All authors have read, approved the final version, and are accountable for the integrity of the study.

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