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Clinicopathological Characteristics of Hirschsprung's Disease With Emphasis on Diagnosis and Management: A Single-Center Study in the Kingdom of Saudi Arabia

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Abstract

Introduction: Hirschsprung's Disease (HD) is a motor disorder of the gut caused by the failure of neural crest cells to migrate craniocaudally into the bowel during intestinal development, resulting in a functional obstruction. The majority of patients with HD are diagnosed in the neonatal period when they present with symptoms of distal intestinal obstruction. *Aim*: This study aims to identify the clinic-pathological characteristic of HD patients in our institution in KSA and comparing it with local and international data. *Materials and Methods*: This retrospective cohort study was conducted in King Abdulaziz Medical City (KAMC), a tertiary care center in Riyadh, Kingdome of Saudi Arabia (KSA). *Results*: A total of 54 patients (72% male) were diagnosed with HD. Forty-eight patients (89%) were born at term, and 6 were pre-term. Sixty-three percent of the patients presented in the neonatal period. Twenty-two patients (41%) underwent one-stage endorectal pull-through procedure, 23 patients (43%) two-stage endorectal pull-through, and 9 patients (16%) had three-stage endorectal pull-through. Five out of 54 patients had ganglion cells seen on FS but were absent in the permanent section. Therefore, the concordance rate was 90.8%. *Conclusion*: FS biopsy is a necessary method to determine the level of aganglionosis intraoperatively in HD, but the definitive diagnosis should be with permanent section. Also, the choice of surgical operation type (single-stage or multi-stage pull-through) depends on the patient's clinical condition.

Keywords

Hirschsprung's disease, megacolon, aganglionosis, endorectal pull-through, neonatal intestinal obstruction, neural crest disorder

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Introduction

Hirschsprung's disease (HD) was described initially by a Dutch anatomist "Frederik Ruysch" in 1691 and was given more attention by Dr Hirschsprung in 1886. During the mid-20th century, a study of case series by Whitehouse and Kernohan concluded that the functional intestinal obstruction was due to intestinal aganglionosis.

Swenson was the first to describe a definitive management procedure, rectosigmoidectomy with coloanal anastomosis in 1949. Soon after, other operative methods were reported such as the Duhamel and Soave techniques and, recently, transanal procedure.[1]

The aganglionosis in HD is due to failure of neural crest cells (the neuroblasts) to migrate completely from the neural crest to the bowel in the craniocaudal direction during intestinal development. Alternatively, when normal neuroblasts migrate to the colon, then the defect may be in their proliferation or differentiation because of lack of the availability of certain factors/molecules in the intestinal stroma. All these abnormalities can

lead to motor dysfunction of the affected intestinal segment, which fails to relax, leading to functional obstruction.[1-3] Since 2011, several studies have discovered gene abnormalities that are claimed to be the underlying cause of HD. Those genes, including *RET, GDNF, GFRα1, NRTN, EDNRB, ET3, ZFHX1B, PHOX2b, SOX10*, and *SHH*, are present in approximately 50% of HD patients[4,5] and tend to have a poorer prognosis.[1]

Short-segment HD is the most frequent type and affects mainly the rectosigmoid colon. The long-segment HD can affect the entire colon in approximately 5% of patients. In rare cases, the small bowel may be affected. The exact worldwide incidence of HD is unknown. Many studies from different countries have reported incidence rates ranging from approximately 1 case per 1500 to 7000 newborns.[5] With regard to the prevalence in the Kingdom of Saudi Arabia, although it is not known, there are a few reports of single-center studies in the literature.[6,7] The overall male-to-female ratio of HD is 4:1.[3,8] Although some studies claim that there is no race preference,[2] others indicate that it is more common in Asian-Americans.[1]

Majority of patients with HD are diagnosed in the neonatal period when they present with clinical features of distal intestinal obstruction that include bilious emesis, abdominal distension, and failure to pass meconium within the first 48 hours after birth. Rectal examination may demonstrate a tight anal sphincter and explosive discharge of gas and stool.[9,10] Although most patients present in infancy and early childhood, some patients may not be diagnosed until later in life. The diagnostic procedures include imaging studies and rectal biopsy. The mainstay of HD diagnosis is through rectal biopsy, either by full-thickness or suction.

Once the diagnosis of HD is confirmed, the treatment is surgical resection of the aganglionic segment of bowel. The surgical treatment of HD initially involved a 3-stage procedure, that is, colostomy, endorectal pull-through, and subsequently colostomy closure. Later, surgeons performed a 2-stage procedure of initial colostomy and subsequent pull-through, thus avoiding the need for colostomy closure. Recently, primary endorectal pull-through in the newborn and older patients are performed in one stage.[11] Frozen section (FS) intraoperative diagnosis on sigmoid and colonic biopsies at the time of the pull-through is necessary to indicate the level of aganglionosis.[12,13] The extent of FS biopsies will be dictated by the extent of the aganglionic segment. FS specimens as well as the resected aganglionic segment are sent for permanent section confirmation. In contrast to FS diagnosis, which is usually done in 20 to 60 minutes depending on the number of biopsies submitted for interpretation, the permanent sections are prepared by placing the tissue in formalin to preserve it, followed by processing, cutting, and staining. This process usually takes between 48 and 72 hours.[8,9]

This study aims to identify the clinicopathological characteristics of HD patients in our center in the Kingdom of Saudi Arabia and compare it with local and international data. The specific objective is to evaluate the effectiveness of FS biopsy in confirming the level of aganglionosis of HD compared with permanent section biopsy.

Methodology

All patients, male and female, Saudi and non-Saudi, with a confirmed tissue diagnosis of HD who were admitted to our institution from 1992 to 2012 were studied. Fifty-four of the study subjects were identified from the surgical pathology reports of the department of pathology and laboratory medicine by searching for all cases coded as "Hirschsprung's Disease." The medical charts of the study subjects were reviewed, and data regarding demographics, clinical features, pathology results, management, complications, and short-term follow-up were

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Table 1. The Age of Hirschsprung's Disease Patients at the Time of Diagnosis (N = 54).

<30 days	34 patients
30 days to <90 days	7 patients
90 days to <180 days	4 patients
180 days to <1 year	2 patients
>1 year	7 patients

collected. A case report form was formulated, validated by 2 expert consultants, and used for the data collection.

The sample size of this study was calculated using the Raosoft sample size online calculator. The recommended sample size was 48 patients, so, all 54 patients were included.

Ethical Approval and Informed Consent

This study was conducted with the ethical standards mentioned by the National Guard Health Affairs (NGHA) and King Abdullah International Medical Research Center (KAIMRC), Reference #: IRBC/058/14. All the data collection forms were kept under strict confidentiality, accessible only to the researcher. The study did not anticipate any harm to the participants as a result of participating in the study. Ethical approval for this study was obtained from the NGHA, KAIMRC, Saudi Arabia.

Results

Fifty-four patients were diagnosed and managed with HD. There were 39 boys (72%) and 15 girls (28%), with a male-to-female ratio of 3:1. Forty-six patients (85%) had normal birth weight and 8 patients (15%) had low birth weight. Forty-eight patients (89%) were born at term, and 6 patients (11%) were preterm.

Details of the age of the HD patients at the time of diagnosis are given in Table 1. The mean number of admission per patients was 4, and the range of hospital stay was 1 to 12 days.

The clinical features included abdominal distension in 47 patients (87%), vomiting in 35 patients (65%), constipation in 27 patients (50%), failure to pass meconium in 21 patients (39%), enterocolitis in 16 patients (30%), diarrhea in 8 patients (15%), and Down syndrome in 11 patients (20%; Figure 1).

The level of aganglionosis was localized to the sigmoid colon in 34 patients (63%; Figure 2).

Five out of 54 patients had ganglion cells identified on FS; however, they were absent on permanent section. Therefore, there was a 9% false-negative diagnosis of HD (Figure 3). Twenty-two patients (41%) underwent 1-stage endorectal pull-through procedure, 23 patients (43%) had 2-stage procedure, and 9 patients (16%) received 3-stage endorectal pull-through procedure (Figure 4).

Discussion

The total number of patients diagnosed with HD in this study is 54, of which 72% were male, with a male-to-female ratio of 3:1. In a study conducted in Mansoura University, Egypt, over a 9-year period, 33 (63.4%) out of 52 patients were male.[6] In a 6-year study reported by Izadi et al in Iran, 39 (67.2%) of 58 patients were male. The male-to-female ratio in both studies is approximately 2:1, unlike our result of 3:1.[2,5] Although the literature indicates a male predominance, our findings and those from other Middle Eastern countries are variable.[1] A report from King Abdulaziz Hospital, Jeddah, Kingdom of Saudi Arabia, concluded that the male-to-female ratio is 6:1.[14] This variability between 2 centers in the Kingdom of Saudi Arabia is worth further investigation. One reason for the low number of cases in the tertiary care center in Riyadh, Kingdom of Saudi Arabia, is that there was limited pediatric surgery service in 1992.

In our study, neonatal diagnosis was established in 63% of patients; however, most studies indicate that approximately 90% of patients with HD are diagnosed in this period.[1] The delay in the diagnosis of HD in our study might be explained by the lack of awareness of the disease by the families or delay in getting access to a tertiary care center for treatment.

HD is uncommon in premature infants. Ryan and colleagues study found that approximately 7% of children with HD had been born prematurely while our study revealed 11% of our patients as premature[15] (Figure 5).

A study by Alessio et al showed that HD was localized to the rectosigmoid region in about 75% of cases, which is almost the same as our result of 72%.[16] Alessio et al and Ryan et al have separately reported the association of congenital anomalies and syndromes with HD, as listed in Table 2. In our study, abnormalities were not included in the review. The study by Alessio and his colleagues was a prospective study of 106 patients diagnosed over 2 years, and they identified 112 anomalies in 61 patients (57%). The anomalies were not affected by gender or the length of aganglionosis.[1,5,15,16] Also, Teerlink et al in their study observed significantly elevated risks of Down syndrome, Bardet-Biedl syndrome, and atrial and ventricular septal defects.[17] Therefore, it is important to look for these anomalies in any patients diagnosed with HD. Syndromes associated with HD include Down syndrome (trisomy 21), neurocristopathies, Waardenburg-Shah

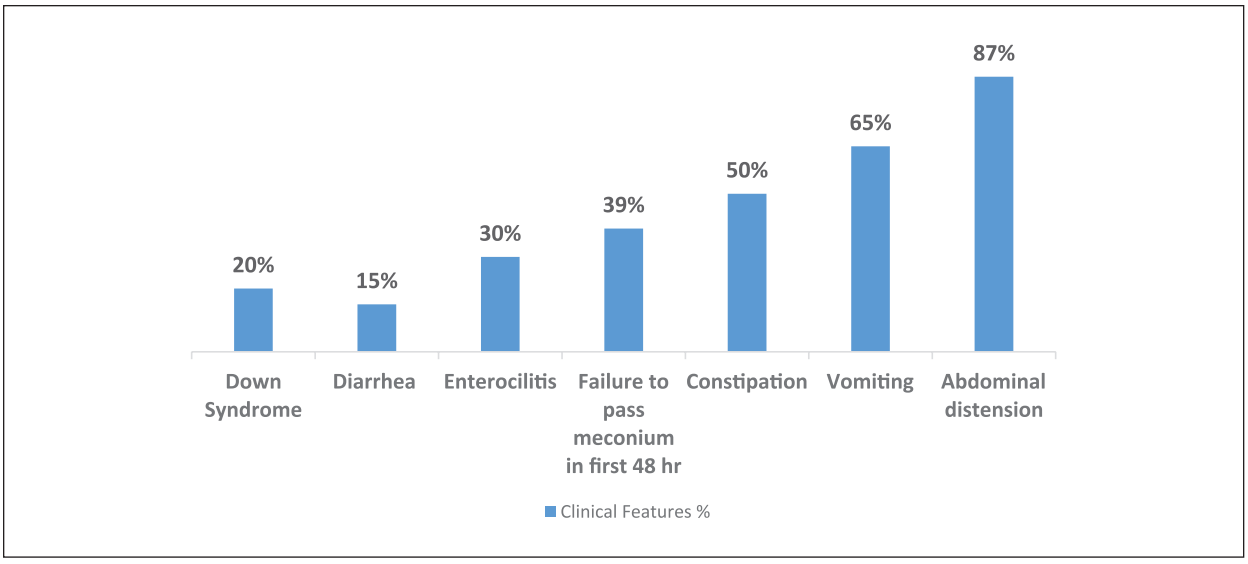

Figure 1. Clinical features of the 54 patients diagnosed with Hirschsprung's disease.

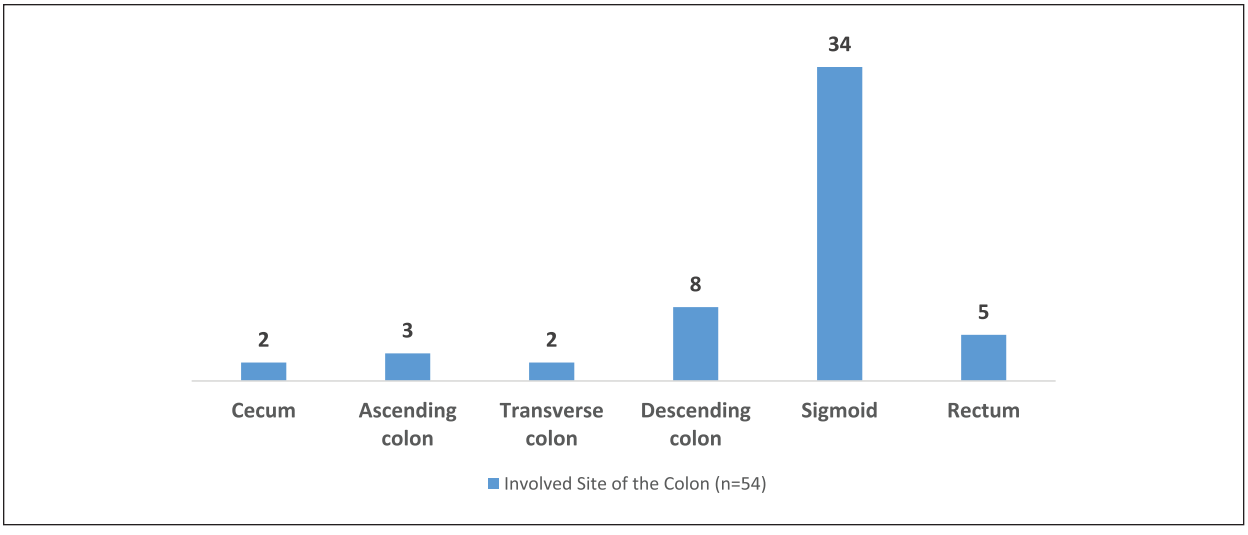

Figure 2. Incidence of Hirschsprung's disease in different parts of the large bowel (54 cases).

syndrome, Yemenite deaf-blind hypopigmentation syndrome, piebaldism, multiple endocrine neoplasia type II (MEN2), and congenital central hypoventilation syndrome.

Out of 54 patients, we found 11 patients with Down syndrome (20%) while other anomalies were not investigated.

In our study, the number of patients treated with the single-stage pull-through procedure were 22 (41%), 2-stage procedure 23 (43%), and 3-stage procedure 9 (16%). The selection of the operative procedure was dependent on the patient's clinical condition based on the age and time of first presentation, state of nutrition, and any associated complications of HD.

According to Justin's review, the most common postoperative complications are anastomotic leakage and stricture formation in 5% to 15%, wound infection (10%), intestinal obstruction (5%), pelvic abscess (5%), and reoperation in 5% of patients. Stoma complications that might develop after surgery include prolapse, herniation, and stricture, HD-associated enterocolitis, chronic obstruction, fecal incontinence, anastomotic stricture, and constipation. Enterocolitis is a complication of HD that is associated more with

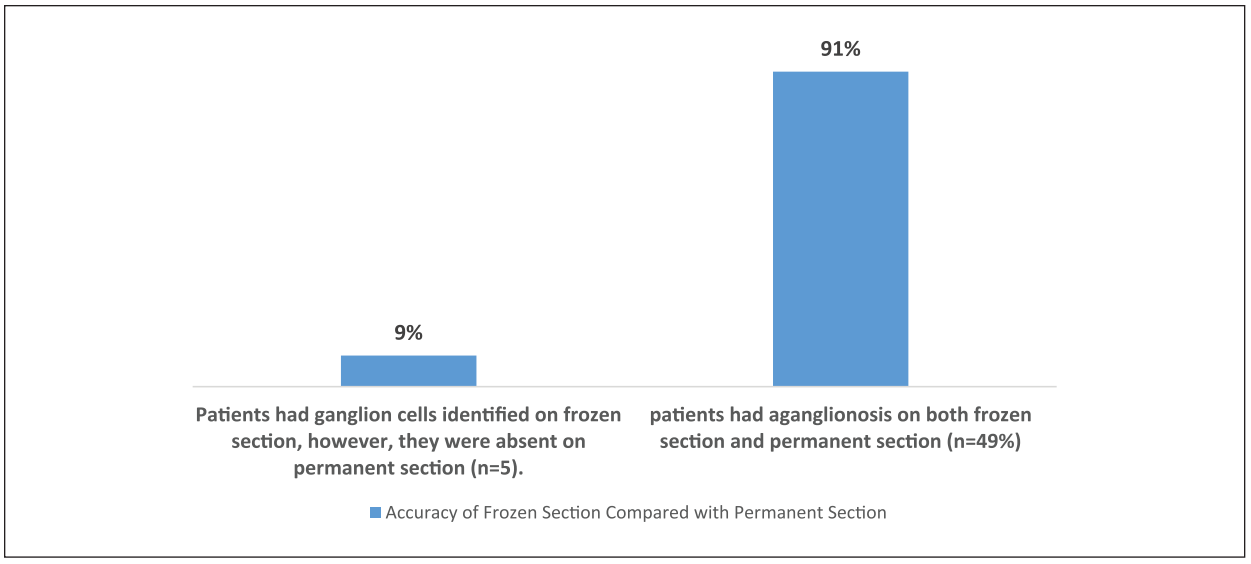

Figure 3. Accuracy of frozen section biopsy compared with permanent full thickness.

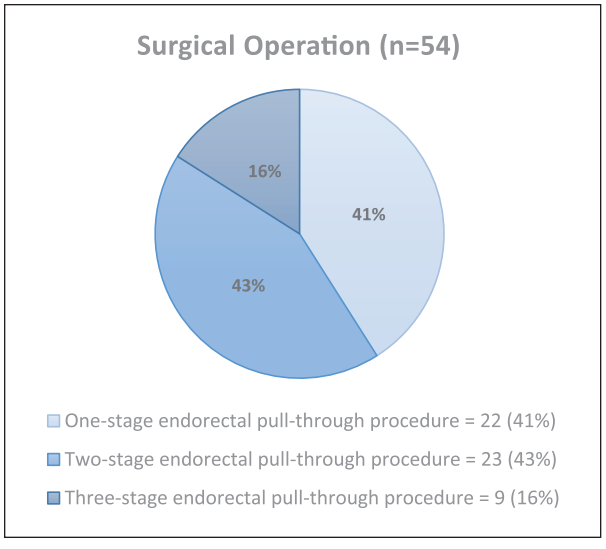

Figure 4. Surgical procedures for the 54 patients with Hirschsprung's disease.

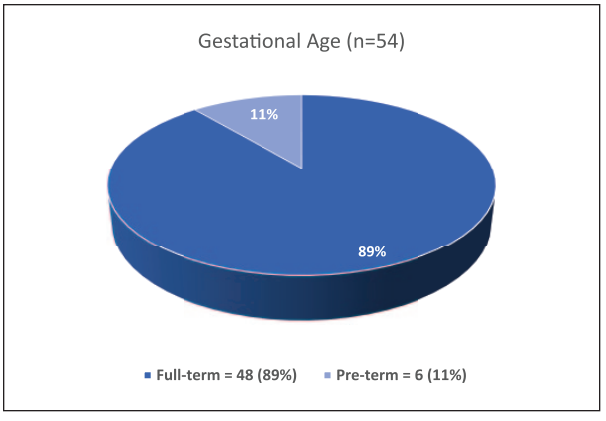

Figure 5. Gestational age of the 54 study patients diagnosed with Hirschsprung's disease.

long-segment disease, and its risk does not decrease with surgical correction.[1,5] In a study of 102 patients with HD, Alessio et al found 22 patients with total colonic aganglionosis, a significantly higher incidence of complications compared with the patients with classic rectosigmoid cases (100% vs 38.5%). This result confirms that the length of aganglionosis has significant impact on the overall surgical outcome.[15]

A definitive diagnosis of HD is made by the absence of ganglion cells in a rectal biopsy specimen. The FS technique for rapid microscope diagnosis of surgical specimens is widely used in hospitals.[11,18] However, a FS biopsy is more difficult to interpret than a permanent biopsy. Our result shows that there is 9% false-negative diagnosis of HD on FS. After permanent sections are examined and the absence of ganglion cells confirmed (misdiagnosis on FS), the surgeon proceeded with the second stage of surgery, which is resection and pull-through. Reasons attributed to this false-negative result might be one of the following: pathologists' misdiagnosed endothelial cells with prominent nuclei or macrophages with large nuclei for ganglion cells, or ganglion cells were seen on the FS, but after cutting deeper sections on the same biopsy to prepare for the permanent sections, the

Table 2. Congenital Anomalies Associated With HD.

Central nervous system
Down's syndrome
Dandy Walker syndrome
Gross malformation of the skull
Clinical mental retardation
Cardiac
Ventricular septal defect
Tetralogy of Fallot
Patent ductus arteriosus
Endocardial cushion defect
Persistent atrioventricular canal
Genitourinary
Bilateral inguinal hernias
Cryptorchidism
Hypospadias
Solitary kidney and bilateral inguinal hernias
Urethral rectal fistula
Megaloureter
VATER syndrome
Bifid kidney with double left ureter and pelvis; hypospadias; and **bilateral inguinal hernias**
Gastrointestinal
Imperforate anus, isolated
Imperforate anus in VATER syndrome with ileal atresia
Malrotation of the gut
Patent vitelline duct
Meckel's diverticulum
Sacral rectal fistula

Abbreviations: HD, Hirschsprung's disease; VATER, vertebrae, anus, trachea, esophagus, renal.

ganglion cells disappeared.[19] This scenario can happen especially in the ultrashort segment of HD. The false-negative diagnosis for HD was of no consequence to our patients. However, it delayed the corrective surgery and might have changed the surgeon's plan from 1-stage procedure to 2-stage or 3-stage procedure. A study conducted at the University of North Carolina Hospitals explained some difficulties encountered during FS examination.[20] They found that FS biopsies may only demonstrate the superficial segment of the submucosal (Meissner's) plexus and does not contain the deep myenteric (Auerbach) plexus, which is more ganglionated. In the permanent (usually full-thickness) biopsy, both plexuses are present, and the staining of a formalin-fixed section is easier to examine than the quickly stained FS. So the likelihood to give a false-negative diagnosis of HD may occur, which will have a serious outcome on the patients, resulting in an unnecessary procedure. Other causes of discrepancy between biopsy and resection specimens might be related to the location of the initial biopsy; either too low or too high in the rectum or at the anorectal junction, which is usually hypoganglionated. Also, the ganglion cells of very young newborns and premature infants are small and immature, which make their recognition in FS difficult.[19]

Conclusion and Recommendations

The prevalence of HD in the Kingdom of Saudi Arabia remains unclear. Some small-scale, single-center studies for the demography of HD have been conducted and showed variability. A study of 54 patients over a 20-year period means a low incidence of HD in Saudi Arabia. In comparison, a study conducted in Boston (USA) over 25 years found 179 cases, which is triple our number.[15] Therefore, multicenter collaborative work in Saudi Arabia is needed to identify the magnitude of this problem. Furthermore, an awareness campaign to the public to orient them with the clinical features of this disease and its association with other congenital diseases might help patients to present earlier to health care centers. The difference in surgical procedure

outcomes and complications should be included in future studies. The fact that the Kingdom of Saudi Arabia has high consanguineous marriages emphasizes the importance of genetic studies for all patients with this disease and exploring the relation of consanguineous marriage to the magnitude of this problem. Finally, the practice of using FS to plan for surgery is safe and dependent on the experience of the pathologists.

Author Contributions

Abdulaziz Howsawi (Conceived and designed the analysis, performed the analysis, and wrote the paper).
Hanaa Bamefleh (Corresponding author).
Saud Al Jadaan (Contributed data tools).
Stanley Crankson (Performed the analysis and contributed in paper writing).
Rakan Al Khilaiwi (Collected the data).
Rakan Al Essa (Collected the data).
Fares Aljahdali (Collected the data).
Jameel Al Nemari (Contributed data tools).
Khalid Al Aqeely (Collected the data).
Sultan Al Howti (Collected the data).
Majed Al Juhaiman (Collected the data).
Nayef Bin Dajim (Contributed the analysis).

Declaration of Conflicting Interests

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