

Analyses of ABO blood groups with susceptibility and symptomatic variations of COVID-19 infection, a questionnaire-based survey

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Coronavirus disease 2019 (COVID-19) is a novel respiratory disease that has led to a global pandemic and created a havoc. The COVID-19 disease severity varies among individuals, depending on fluctuating symptoms. Many infectious diseases such as hepatitis B and dengue hemorrhagic fever have been associated with ABO blood groups. The aim of this study was to explore whether ABO blood groups might serve as a risk or a protective factor for COVID-19 infection. Moreover, the symptomatic variations of COVID-19 infection among the individuals with different blood groups were also analyzed. An online questionnaire-based survey was conducted in which 305 partakers were included, who had successfully recovered from coronavirus infection. The ABO blood groups of 1294 healthy individuals were also taken as a control. The results of the current study demonstrated that antibody A containing blood groups (blood group B, p-value: 0.049 and blood group O, p-value: 0.289) had a protective role against COVID-19 infection. The comparison of symptomatic variations among COVID-19-infected subjects showed that blood group O subjects had lower chances of experiencing severe symptoms relating to respiratory distress, while subjects with AB blood group were more prone to develop symptoms, but the differences in both groups were found to be statistically non-significant. In conclusion, subjects who do not have anti-A antibodies in their serum (i.e., subjects with group A and AB) are more likely to be infected with COVID-19. The current data showed that there was no significant association of signs and symptoms variations of COVID-19 infection among individuals with different blood groups.

Key words: association; blood; COVID-19; pandemic; prone; symptoms.

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INTRODUCTION

The novel coronavirus disease; COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan city of China in December 2019. Soon, COVID-19 infection turned into a global pandemic affecting almost all

countries and became a public health concern [1]. Despite many preventive measures taken by all countries worldwide, the virus crossed the barriers and engulfed thousands of innocent lives. Till to date, seven different coronaviruses including SARS-CoV-2 is known to cause infection in humans, two of these coronaviruses have already caused

pandemics in the recent past, that is, SARS coronavirus and the Middle East respiratory syndrome (MERS) coronavirus [2-5]. According to the recent epidemiological research, the incubation period of this novel coronavirus is 1–14 days; however, in some cases, the incubation period over 14 days has also been reported [6, 7]. The infected individuals can transmit the virus during the incubation period and asymptomatic infected individuals can also transmit infection. Transmission is most likely through the inhalation of respiratory droplets or close contact with the infected individual. The infection is clinically characterized by fever, dry cough, and fatigue. In severe cases, the affected individuals may experience acute respiratory distress syndrome (ARDS), septic shock, and even death [8, 9].

In January 2020, the government of Pakistan took several precautionary measures to examine whether the passengers coming from China had no signs of COVID-19 infection. The first case of COVID-19 infection in Pakistan was reported on February 26, 2020 [10]. Iran is a religiously and culturally significant country for Pakistani people. Annually, millions of people go to Iran for religious rites. As the numbers of COVID-19 cases begin to increase, Pakistan closed its borders with Iran in February 2020, but hundreds of Pakistanis get back by other means. It was later found that the first two cases reported by the health ministry of Pakistan had recently returned from Iran [11]. To prevent the spread of the infection, officials decided to quarantine all the tourists. Despite the careful precautionary measures, the outbreak rose and created a wave of distress among the public.

Serological studies are mainly based on identifying and understanding the structure, functions, and interactions of serum antibodies and blood group antigens [12]. The blood group antigens are either sugar or protein and found on red blood cells (RBCs), platelets, leukocytes, plasma proteins, certain tissues, and cell surface enzymes [13]. These antigens are also found in soluble form in various secretions such as breast milk, sweat, saliva, urine, gastric secretions, seminal, and amniotic fluid [14]. So far, hundreds of blood groups antigens have been discovered and classified into more than 30 blood groups [14]. Since the discovery of the ABO blood group system by Landsteiner in the early 1900s, it is confirmed that both RBCs antigens and antibodies are inherited characteristics [15]. The ABO blood group antigens were the first to be identified and perhaps the most widely studied and important among the blood group antigens [16]. The ABO blood groups include four blood types namely, A, B, AB, and O, and its gene is positioned

on chromosome 9 [17,18]. People with blood group A have antigen A on their red blood cells and anti-B antibodies in their serum. Similarly, people with blood group B have antigen B on their red blood cells and anti-A antibodies in their serum. An individual with AB blood group possesses both A and B antigens on the surface of RBCs, but there is neither anti-A nor anti-B antibodies in the serum. On the other side, individuals with blood group O possess no antigen A or B on RBCs surface and antibodies against both antigens A and B [19].

There is compelling evidence that blood group antigens can play an important role in pathogenesis [20]. The blood group antigens not only enable the pathogen uptake and signal transduction but are also known to modulate the responses exerted by the innate immune system [21-24]. Mohammad Ali *et al.* reported that the risk of hepatitis B virus infection (HBV) was significantly less in the individuals with blood group O [20]. Elnady *et al.* discovered that rota-positive status for rotavirus gastroenteritis was predominant in blood type A individuals and significantly lower in blood type B [25]. In another study by Degarege *et al.*, it was observed that blood group A malarial individuals had a higher risk of anemia as compared to non-A phenotypes [26]. Similarly, Murugananthan *et al.* found that patients with AB blood group had 2.5 times higher risk of developing dengue hemorrhagic fever than any other blood type [27]. Recently, a meta-analysis showed that individuals with blood type O are more susceptible to coronavirus infection [6]. Cheng *et al.* also reported that subjects with blood group O were less likely to become corona infected as compared to non-O blood group individuals [28]. As SARS-CoV-2 is a novel virus, it is still not well established that whether the ABO blood groups affect individual's susceptibility or severity to infection. The current study was conducted to explore whether COVID-19 infection is also influenced by ABO blood groups. Moreover, the symptomatic variations among COVID-19 infected subjects with different blood groups were also analyzed.

METHODS

Selection of studied subjects

The subjects for this study included both male and female individuals who had successfully recovered from COVID-19 infection from April 4, 2020 to August 4, 2020 in Pakistan. The subjects were approached to fill out the survey questionnaire through multiple social media applications and via phone calls. The hard copies of the questionnaire were also distributed among the successfully recovered COVID-19-infected subjects. The inclusion criteria of the

study involved subjects whose COVID-19 infection was positively diagnosed by quantitative real-time polymerase chain reaction (Q-PCR) both on pharyngeal and nasal swabs from the patients. Only those COVID-19 subjects were included in the study, which ABO blood group was already known. There was no age and gender restriction; however, COVID-19 subjects with comorbidities were excluded from the current study. The age of the recovered subjects in the current study ranged, 14–60 years. The study also involved 1294 healthy individuals to compare the distribution of the ABO blood group with the infected individuals. The healthy individuals were all blood donors with the age ranging from 18 to 60 years, and their blood was screened for hepatitis B, C, and HIV infections. The data of both COVID-19 infected and healthy subjects were collected from major cities of Pakistan including Lahore, Rawalpindi, Sargodha, Multan, Mardan, Swat, and Quetta.

Questionnaire

The survey questionnaire included personal information such as names, gender, contact information, and age. The participants were asked about their blood groups and the symptoms, they experienced during the COVID-19 infection. The list of 8 major symptoms was given to the respondents, and they were asked to mark the symptoms, they experienced. The symptoms list included fever, sour throat, difficulty in breathing, chest pain or pressure, loss of smell or taste sense, dry cough, and loss of movement or speech. The respondents were also asked whether they experienced no symptoms at all. These major signs and symptoms of COVID-19 infection were selected on the basis of the literature search and experience of local clinicians [29].

Statistical analyses of the data

Categorical variables were described as frequency rates and percentages. The continuous variables were described by the use of mean and median. Descriptive statistics were performed to present the data. Association analysis of blood groups and COVID-19 symptoms was performed using the chi-square test. A $p < 0.05$ was considered to be significant.

RESULTS

Gender and age distribution

The survey was not restricted to any particular gender; however, most of the responses were received from male patients. Out of 305 individuals, 206 (67.540%) were male and 99 (32.459%) were female. The least age recorded in the survey was 3 years old, and the eldest was 74 years old (median age = 30). The data revealed that most of the infected subjects were in their twenties, that is, 126 (41.311%). The age and gender of COVID-19-infected group and healthy control were not compared as it was not the study focus.

Blood group distribution

The majority of COVID-19 infected patients had blood group B, that is, 101 (33.11%). The individuals with blood groups A, AB, and O were 77 (25.24%), 51 (16.72%), and 76 (24.91%), respectively. The distribution of blood groups in both genders is shown in Fig. 1.

Symptoms of COVID-19 infection

The study showed that 11.1% (34/305) of COVID-19-infected subjects were asymptomatic. The remaining 89% COVID-19-infected subjects demonstrated symptoms of varying degree as shown in Fig. 2.

Association of COVID-19 symptoms with different blood groups

COVID-19 symptoms in blood group A subjects

Out of 77 individuals belonging to blood group A, only 10.38% ($n = 8/77$) experienced no symptoms of the infection. Out of all COVID-19 blood group A individuals, 71.4% ($n = 55/77$) had fever, 46.7% ($n = 36/77$) suffered from sour throat, 54.54% ($n = 42/77$) had dry cough, 18.1% ($n = 14/77$) had chest pain, 35% ($n = 27/77$) had lost smell and taste sense, 25.9% ($n = 20/77$) had difficulty in breathing, and 6.4% ($n = 5/77$) experienced the loss of speech or movement as shown in Table 1.

COVID-19 symptoms in blood group B subjects

The total infected subjects in blood group B were 101. The asymptomatic subjects were 15.8% ($n = 16/101$). Fever was noticed in 74.2% ($n = 75/101$), 51.4% ($n = 52/101$) suffered from sour throat, 48.5% ($n = 49/101$) reported dry cough, and 29.7% ($n = 30/101$) felt difficulty in breathing during the infection. Chest pain and loss of smell and taste sense were experienced by 15.8% ($n = 16/101$) and 33.6% ($n = 34/101$) subjects, respectively. Only 6.9% ($n = 7/101$) felt loss of movement and speech (Table 1).

COVID-19 symptoms in blood group AB subjects

The total COVID-19-infected subjects in blood group AB were 51. The infection was asymptomatic in 7.84% ($n = 4/51$) individuals. Out of 51 AB blood group subjects, 80.4% ($n = 41/51$) had fever, 68.6% ($n = 35/51$) experienced sour throat, 11.76% ($n = 6/51$) felt chest pain, and 58.8% ($n = 30/51$) individuals reported dry cough. Loss of taste or smell sense was experienced by 15.68% ($n = 8/51$), and difficulty in breathing was noticed in 18.42% ($n = 14/51$). Only one patient (1.9%) of AB blood

Distribution of blood group system among 305 COVID-19 infected male and female individuals

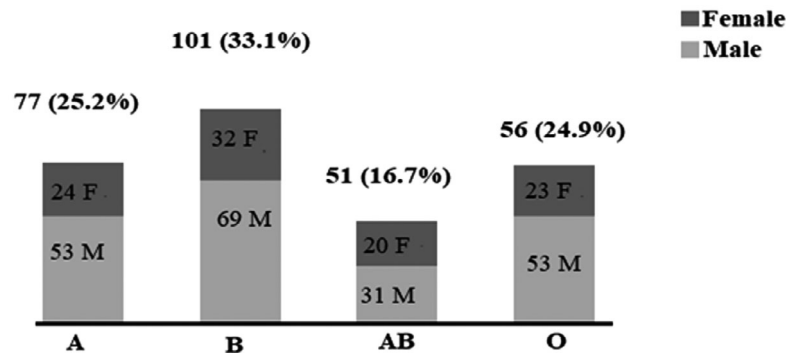


Fig 1. Number of COVID-19-infected individuals (males and females) belonging to different blood groups depicting that majority of subjects belonged to blood group B (33.1%). The AB blood group is the least represented among the series of patients cured of COVID-19 infection (16.7%).

Signs and symptoms of 305 successfully recovered COVID-19 infected subjects

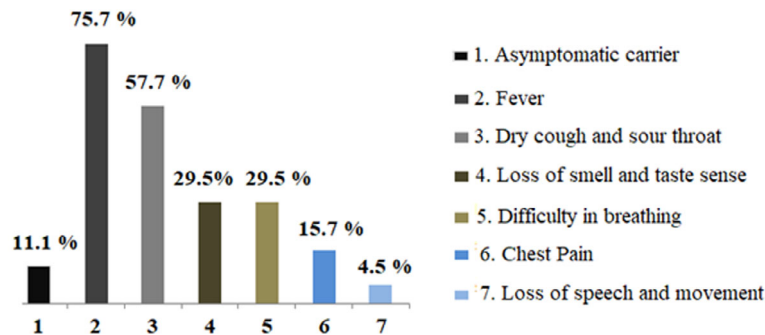


Fig 2. Trend of symptoms reported by 305 COVID-19 individuals illustrating fever as the most common symptom (75.7%). Loss of speech and movement was the least common symptom (4.5%).

group individuals experienced loss of speech and movement (Table 1).

COVID-19 symptoms in blood group O subjects
Out of 76 blood group O subjects, 7.8 % ($n = 6/76$) subjects experienced no symptoms of COVID-19 infection, 78.9% ($n = 60/76$) suffered from fever, 53.94% ($n = 41/76$) suffered from sour throat, and 56.5% ($n = 43/76$) had dry cough. Difficulty in breathing and loss of taste or smell sense were noticed in 18.4% ($n = 14/76$) and 27.6% ($n = 21/76$), respectively. Chest pain or pressure was observed in 15.78% ($n = 12/76$), and only one patient experienced the loss of speech or movement (Table 1).

It was observed in the current study that dyspnea was the least common in blood group O patients as compared to non-O blood group individuals. Fever, sour throat, and dry cough were more common in AB blood group individuals. However, statistically,

there was no significant difference in overall clinical manifestations of COVID-19 patients with different blood groups ($p > 0.05$).

Association of ABO blood group system with COVID-19 infection

The blood group distribution of COVID-19 cured individuals ($n = 305$) was compared with healthy blood group individuals ($n = 1294$) to explore any association of blood groups with less or more susceptibility to infection. In the current study, blood type B was the most common group both in the healthy controls ($n = 542/1294$; 41.88%) and the patients group ($n = 101/305$; 33.11%), whereas type AB was the least common both in the healthy controls ($n = 117/1294$; 9.04%) and patients group ($n = 51/305$; 16.72%) as shown in Table 2. The frequency of COVID-19 patients with type A blood was higher in the patients group than the control

Table 1. Association of ABO blood group distribution with the clinical features in COVID-19 subjects

| Clinical characteristics | Blood Group A (N=77) | Blood Group B (N=101) | Blood Group AB (N=51) | Blood Group O (N=76) | χ^2 | p-value |
|-----------------------------|-------------------------|--------------------------|--------------------------|-------------------------|----------|---------|
| Gender | | | | | | |
| Male | 53 (68.831%) | 69 (68.316%) | 31 (60.784%) | 53 (69.736%) | 1.315 | 0.725 |
| Female | 24 (31.168%) | 32 (31.683%) | 20 (39.215%) | 23 (30.263%) | | |
| Asymptomatic infection | | | | | | |
| Yes | 8 (10.389%) | 16 (15.841%) | 4 (7.843%) | 6 (7.894%) | 3.665 | 0.299 |
| No | 69 (89.610%) | 85 (84.158%) | 47 (92.156%) | 70 (92.105%) | | |
| Fever | | | | | | |
| Yes | 55 (71.428%) | 75 (74.257%) | 41 (80.392%) | 60 (78.947%) | 1.925 | 0.587 |
| No | 22 (28.571%) | 26 (25.742%) | 10 (19.607%) | 16 (21.052%) | | |
| Sour Throat | | | | | | |
| Yes | 36 (46.753%) | 52 (51.485%) | 35 (68.627%) | 41 (53.947%) | 6.267 | 0.099 |
| No | 41 (53.246%) | 49 (48.514%) | 16 (31.372%) | 35 (46.052%) | | |
| Dry Cough | | | | | | |
| Yes | 42 (54.545%) | 49 (48.514%) | 30 (58.823%) | 43 (56.578%) | 1.905 | 0.592 |
| No | 35 (45.454%) | 52 (51.485%) | 21 (41.176%) | 33 (43.421%) | | |
| Loss of taste or smell | | | | | | |
| Yes | 27 (35.064%) | 34 (33.663%) | 8 (15.686%) | 21 (27.631%) | 6.794 | 0.078 |
| No | 50 (64.935%) | 67 (66.336%) | 43 (84.313%) | 55 (72.368%) | | |
| Difficulty in breathing | | | | | | |
| Yes | 20 (25.974%) | 30 (29.702%) | 14 (27.450%) | 14 (18.421%) | 3.048 | 0.384 |
| No | 57 (74.025%) | 71 (70.297%) | 37 (72.549%) | 62 (81.578%) | | |
| Chest pain or pressure | | | | | | |
| Yes | 14 (18.181%) | 16 (15.841%) | 6 (11.764%) | 12 (15.789%) | 0.954 | 0.812 |
| No | 63 (81.818%) | 85 (84.158%) | 45 (88.235%) | 64 (84.210%) | | |
| Loss of movement and speech | | | | | | |
| Yes | 5 (6.493%) | 7 (6.931%) | 1 (1.960%) | 1 (1.315%) | 4.566 | 0.206 |
| No | 72 (93.506%) | 94 (93.609%) | 50 (98.039%) | 75 (98.684%) | | |

Table 2. Comparison of ABO blood group distribution in general population against COVID-19 patients in Pakistan.

| Blood Group | COVID-19-positive (N=305) | Control (N=1294) | p-value |
|----------------|------------------------------|---------------------|--------------------------------|
| Blood group A | 77 (25.24%) | 273 (21.09%) | 0.114 (At risk of infection) |
| Blood group B | 101 (33.11%) | 542 (41.88%) | 0.049* (Protective effect) |
| Blood group AB | 51 (16.72%) | 117 (9.04%) | <0.001* (At risk of infection) |
| Blood group O | 76 (24.9%) | 362 (27.97%) | 0.289 (Non-significant) |

group (25.24% vs. 21.09%; p-value = 0.114), while the frequency of patients with COVID-19 infection with type O blood was lower as compared to the control group (24.9% vs. 27.97%; p-value = 0.289). However, statistically, both the differences were found to be non-significant. On the other hand, the risk of COVID-19 infection was significantly higher in patients with blood group AB as compared to the control (16.72% vs. 9.04%; p-value < 0.001). Patients with blood group B had significantly a lower risk of COVID-19 infection (33.11% vs. 41.88%, p-value = 0.049).

DISCUSSION

Since the discovery of the ABO blood group system by Karl Landsteiner in 1901, researchers are

constantly searching for the association of ABO blood group system with various diseases [30]. The association between ABO blood group system with many diseases including bacterial and viral diseases has been extensively studied [31-36]. Now, it is well established that the ABO blood group system is related to many diseases [37]. Recently, several studies of COVID-19 infection in China and America have demonstrated a relationship between the ABO blood groups and infection severity and demise. These studies demonstrated that individuals with blood group A are at higher risk for acquiring COVID-19 infection, while individuals with blood group O are at lower risk for acquiring COVID-19 infection. The disease severity may also be affected by blood type. The risk of intubation was decreased in individuals with blood type A than other blood types [9, 38].

The results of the current study showed that blood group distribution in 305 COVID-19 cured subjects and 1294 healthy control for blood group A was; 25.24 % vs 21.09% p-value = 0.114, for blood group B, 33.11 % vs 41.09% p-value = 0.049, for blood group AB, 16.72 % vs 9.04% p-value = 0.001, and for blood group O, 24.9 % vs 27.97% p-value = 0.289. The results showed that compared with the control series, the subjects of group AB are significantly over-represented ($p < 0.001$) in the series of cured patients. Similarly, Wu *et al.* observed that individuals possessing blood group AB (7.49%) were least common in COVID-19-infected subjects (16.72%) [39]. The frequency of COVID-19 subjects with blood group A in the current study was also higher; however, the p -value was found to be statistically non-significant, that is, 0.114 in the present study. Previously, it was reported by Zhao *et al.* that individuals with A blood group were at higher risk of getting COVID-19 infection [9]. In this study, blood group B was significantly lower in COVID-19-infected subjects than control group, that is, $p = 0.049^*$. A recent study by Gérard *et al.* demonstrated that subjects with antibody A in serum (B and O) are significantly less represented in the COVID-19 group [40]. However, the current study failed to show any association of blood group O with COVID-19 infection, $p = 0.289$. Gerard *et al.* compared the supposed protective effect of anti-A from blood type O and B groups. The results showed that both blood group O and B patients possess circulating serum anti-A, which confers anti-COVID-19 features. The study further demonstrated that the anti-A of O subjects are significantly more "protective" against the coronavirus than the anti-A of B subjects [40]. This partially agrees with the results of the current study. The partial differences in the current study with some other reported studies may be due to difference in sample size, sampling strategies, regional variability, ethnic differences, and even strain of coronavirus.

Although the early research was mainly based on statistical analyses of the association's blood group antigens with infectious diseases, malignancy, and coagulation, these observational studies are now given scientific validation through extensive research on malignancy, infectious diseases, and membrane chemistry [41, 42]. While the exact mechanisms of associations of blood group antigens and known diseases are still to be discovered, however on the basis of existing knowledge about the structures and functions of these antigens, some intriguing clues may be given [37]. Unexpectedly, large number of antigenic structures on the cell surface of RBCs act as a receptor or ligand for

infectious agents and may also play role in the movement of normal and malignant cells throughout the body [41]. These antigenic moieties include carbohydrates, glycosylphosphatidylinositol-anchored proteins, and transmembrane proteins [43]. Due to the presence of extra sugar N-acetyl galactosamine on blood group A RBCs, pathogens get more opportunity to contact with these cells [44]. The other possible reason for A blood group subjects, predisposition to COVID-19 infection is virus successful replication in the gut and respiratory epithelium and the expression of blood group antigens over there. Additionally, the spike (S) protein is a transmembrane protein of SARS-CoV-2 that binds to angiotensin-converting enzyme (ACE-2) receptor [45]. As proposed for SARS-CoV-2 [35], an anti-A antibody might inhibit the attachment of S protein to the ACE-2 receptor on the host cell. This might explain why blood groups O and B (24.9% vs 27.97%; p -value = 0.289 and 33.11% vs 41.88%, p -value = 0.049*, respectively) are least susceptible, whereas blood groups A and AB (25.24% vs. 21.09%; p -value = 0.114 and 16.72% vs. 9.04%; p -value < 0.001 , respectively) are more prone to coronavirus infection in the current study. Thus, according to documented data, SARS virus could be specifically inhibited by anti-A antibodies via blocking the adhesion of SARS-CoV-2 S protein-expressing cells hence providing complete or partial shield [35, 46, 47].

COVID-19-infected individuals with blood groups O and AB showed a deviated clinical spectrum of signs and symptoms as subjects with AB blood group demonstrated slightly higher chances of fever and sore throat and lower incidences of loss of taste and smell sense. Moreover, respiratory distress was the least prevalent (18.42%) among blood group O individuals, although the difference was not much significant. Collectively, there was no significant difference in clinical indices among blood groups which is in accordance with the study of Wu Y *et al.* [48]. The current study demonstrated that COVID-19 infection was more common in males than females (67.54% vs 32.45%, respectively). The most probable reason for this difference seems to be more exposure of male individuals as compared to female individuals in our settings as in Pakistan, females mostly live in villages and restricted to home [49]. This study further adds a piece of evidence to the protective association for anti-A blood types with the COVID-19 infection, which has been revealed previously [50]. The current study has certain limitations which include regional biasedness, small sample size, and no information about the strain of coronavirus.

CONCLUSIONS

The current study reported the association ABO blood groups with susceptibility to COVID-19 infection. The B and O blood group individuals who have anti-A antibodies in their serum are least likely to get COVID-19 infection, while individuals with A and AB blood groups who possess anti-B and no antibodies, respectively in the serum are most likely to get COVID-19 infection. The findings in the current study may have a clinical recommendation that individuals with blood groups A and AB might need to particularly strengthen their immunity and personal protection to reduce the chances of getting COVID-19 infection. The symptoms of COVID-19 infection which demonstrated the trend of variations in different blood groups were; sour throat ($p = 0.099$) and loss of smell and taste ($p = 0.078$). The overall symptoms trends of COVID-19 individuals belonging to different blood groups varied non-significantly. Large replication studies with complete information should be encouraged to pursue and required to verify the present findings.

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CONFLICT OF INTEREST

There is no conflict of interest among the authors.

AUTHORS' CONTRIBUTION

M.I., M.N. and J.A. involved in conceptualization and methodology. A.K. involved in writing the original draft preparation. M.I., M.N., and Y.W. involved in writing the review and editing and data curation. A.K. and M.N. collected data from Multan. J.A. and M.A. collected data from Sargodha. M.J. collected data from Mardan. J.K. collected data from Quetta. F.H. and M.R. collected data from Swat. A.G. and U.A. collected data from Lahore. Y.W. collected data from Rawalpindi. M.I. and M.N. involved in supervision.

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