Review Article

Coronavirus (COVID-19) pandemic: Outbreak, current scenario and impact on human physiology in Pakistan

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Abstract

Coronavirus that is also known as COVID-19 disease is produced by SARSCoV-2. This causative agent is highly contagious and can cause potentially fatal pneumonia worldwide with serious public health concerns. In the beginning among infected individuals, most of them were those who were mainly shown to the wet animal market in a big city of China known as Wuhan. So, it was suggested that this was almost certainly the zoonotic source of COVID-19 illness. The transitional source of origin and their mode of transmission to humans were not known obviously. Conversely, from human to human rapidly transformation have been confirmed generally. Currently, there is no availability of FDA approved clinically antiviral drugs and/or vaccines to be used against the COVID-19. Afterward, SARS-CoV and MERS-CoV, the occurrence of SARS-CoV-2 has been manifested as the third sketch of an enormously pathogenic coronavirus into human population globally. In this review, we provide a brief overview of the history of COVID-19 in Pakistan up-to 24th weeks after beginning, current situation, epidemiology, and its impact on the human population. Moreover, we focused on physiological variation during the incubation period, genome analysis of SARS-CoV2, supportive treatment approaches, and safety measures in the Pakistani population, which may be supportive for combating the risk of COVID-19 epidemic. We also reviewed the future approaches for the development of therapeutic interventions and vaccines to cope with the COVID-19 epidemic.

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Acute Respiratory Syndrome Coronavirus 2; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; H1N1: Hemagglutinin Type 1 and Neuraminidase Type 1; H5N1: Hemagglutinin Type 5 and Neuraminidase Type 1; MHS: Ministry of Health Services; OPDs: Out-Patient Departments; ARDS: Acute Respiratory Distress Syndrome; 1ORF1: The Open Reading Frame; PCR: Polymerase Chain Reaction; MM: Molecular Mass; ACE-2: Angiotensin–Converting Enzyme-2; GSK: Glaxo Smith Kline; RdRp: RNA-dependent RNA polymerase; KPK: Khyber Pakhtunkhwa; AJK: Azad Jammu and Kashmir; ICT: Islamabad; GB: Gilgit-Baltistan; ARDS: Acute Respiratory Distress Syndrome; IL-6: Interleukin 6; CRP: C-Reactive Protein; NDMA: The National Disaster Management Authority; NIH: National Institute of Health; ssRNA: single-stranded RNA; WHO: World Health Organization

Introduction

Viruses can lead to dangerous lives; they threaten people and...
Coronaviruses are the largest among RNA Coronaviridae, Roniviridae and Families Arteriviridae. Coronavirinae is not segmented; 3'-polyadenylated and 5'-encapsulated positive single-stranded RNA viruses cause various respiratory diseases in people [2]. The coronaviruses' diameter is approximately 65-125 nm and the capsid material of the corona contains a single-stranded RNA. The sub-categories of coronavirus are including alpha [α], beta [β], gamma [γ], and delta [δ] coronavirus. The genomic sequence of SARS-CoV-2 has shown a 99% similarity to the genome of SARS-CoV. Historically, SARS-CoV and MERS-CoV, H1N1, and H5N1 influenza-A are the major known epidemics causing acute respiratory distress and lung injury, leading to pulmonary failure and mortality, and morbidity [3,4]. Coronaviruses were considered to infect only animals until 2002 when the world has seen a SARS CoV disease caused by SARS-CoV in Guangdong, China [5,6]. SARS was ultimately controlled utilising rapid isolation of patients, strict execution of infected person to quarantine along with their associates, inter-connecting of all person to person transmission is controlled, and all these precautionary measures successfully and efficiently eliminated the risk of SARS-CoV [7]. During the last quarter of 2019, coronavirus, which was named as novel coronavirus SARS-CoV-2, occurred in Wuhan, China, that have killed over a large population due to the rapid spread of coronavirus infection [8]. On Mar 30, 2021, COVID-19 is affecting 219 countries and territories all around the world. There are still many un-known mechanisms associated with the COVID-19 outbreak; all these are causing severe illness. Even subsequently, several deaths have been reported in China, the USA, Spain, Italy, Pakistan, and other worldwide countries [9]. In this mini-review, we analysed a brief overview about the history of COVID-19 new confirmed cases and death cases according to per weeks in Pakistan. Current situation of COVID-19 in Pakistan and countries comparison analysis of COVID-19 outbreak. Moreover, focused on physiological variation during different stages of incubation periods and WHO supportive treatment strategies and safety measure during SARS-CoV2 viral replication cycles, which may be supportive for combating the risk of COVID-19 epidemic. We also reviewed the future approaches for development of therapeutic interventions and vaccines to cope with the COVID-19 epidemic.

Emerging and current scenario of COVID-19 in Pakistan

New confirmed cases of COVID-19 per weeks in Pakistan: In Pakistan, after detecting the first 2 cases of COVID-19 on Feb 26, 2020, in Sindh Province, the number of coronavirus infected patients was gradually increased up to the 8th weeks. In 1st week, 4 cases of COVID-19 were reported in Sindh, in 2nd week, by the Ministry of Health Services (MHS), a total of 15 no. of COVID-19 cases in different provinces and cities of Pakistan such as 10 cases in Sindh, 1 case in Baluchistan, 2 cases in both Gilgit-Baltistan (GB) and Islamabad (ICT) were reported. In the 3rd week, the no. of new reported cases was increased up-to 219 in different provinces and cities of Pakistan such as in Punjab, Sindh, Baluchistan, KPK, GB, and ICT are 26,158,14, 17,1 and 3 cases respectively. In the 4th week, a total of 762 new confirmed cases were reported in Punjab, Sindh, Baluchistan, GB, KPK, ICT, and AJK are 270, 241, 100, 78, 61,1 and 1 respectively, in 5th week, a total of 1039 no. of cases were reported in the different large area of cities such as in ICT and GB; the announced confirmed cases of COVID-19 are 38 and 103, and in provinces such as Punjab, Sindh, KPK and Baluchistan are 412, 263, 175 and 43 cases of coronavirus were reported respectively, in 6th week the outbreak of novel coronavirus were increased gradually. New reported cases in the 6th week are reached up-to-digit 1,322. In the 7th week total of 1,915 new cases of COVID-19 were reported in provinces and different cities in Pakistan such as Punjab, Sindh, Baluchistan, AJK, GB, and ICT are 915, 532, 336, 25, 27, 22, and 48 respectively. Similarly, in the 8th week total of 3786 new cases were reported in Punjab, Sindh, KPK, Baluchistan, AJK, GB, and ICT are 1383, 1555, 505, 255, 54, 49, and 5, respectively. Similarly, in the 9th week total of 5114 confirmed new cases were reported in Sindh, Punjab, KPK, Baluchistan, ICT, Gilgit-Baltistan, and AJK 2388,1499,793,420,103,47 and 14, respectively. Similarly, at the end of the 31st weeks (Oct 6, 2020) total no of 315,727 confirmed cases of COVID-19 was reported in Pakistan. Similarly, at the end of 36th weeks (end of October 2020) total no of 333,970 confirmed cases of COVID-19 was reported in Pakistan (Figure 1) [10-12].

Death cases of COVID-19 per weeks in Pakistan

The first death case was reported in the 4th week, Pakistan, a total no. 7 death cases were reported in a week, 3 in KPK and 4 death cases were declared in Punjab, Sindh, Baluchistan, and GB. Similarly, in the 5th, 6th, 7th, 8th, and 9th weeks, the reported deaths were steadily increased up-to 19, 31, 50,102, 118, respectively. Similarly, at the end of the 31st week, a total of 6523 death cases were announced. Similarly, at the end of the 36th week, a total of 6823 death cases were announced (Figure 2).

The effectivity of the COVID-19 situation comparatively significantly distinct in a different province of Pakistan (Table 1). The highest COVID-19 cases were reported in Sindh province, while the lower COVID-19 cases were reported in AJK [13,14].

Beginning and pathway analysis of Coronavirus' transmission

Human diseases are transmitted due to interactions of host and environmental factors (droplets, polluted air, etc.). Although few diseases are mainly genetic in origin and nearly all disease consequences occur from an interaction of several environmental, behavioral, and genetic factors, genetic factors are responsible for extents of variations in different diseases/infections. Various underlying protocols are mainly responsible for the transmission of infections. Hence in the current review, we also discuss the approaches of infection origin and their transmission mode. Coronavirus infection-19 is an extremely pathogenic and contagious viral disease. Previously, Chinese people were infected with a respiratory virus causing SARS in
2003 in Guangdong province, China. People infected with SARS-CoV developed pneumonia symptoms and alveolar damage in the lungs that led to ARDS [15]. Secondly, a decade later, several Saudi Arabian peoples were inspected to be diseased with another kind of coronavirus in 2012. The isolated virus belonged to the class of coronaviruses and was entitled to the MERS-CoV. The MERS-CoV infection causes a minor upper respiratory tract injury and leads to severe respiratory infection/disease [16]. In December 2019, the Chinese government informed the World Health Organization about numerous pneumonia and unaware aetiology cases. The transmission of COVID-19 is based on huge numbers of the Chinese population in Wuhan city, China. In the human seafood market, where the animals such as frogs, bats, birds, rabbits, snakes, and marmots were frequently sold, and it is proposed that all these probably belong to the zoonotic origin of coronaviruses. The first report recognised that few bats and snakes could be a potential source of coronaviruses, but claims are still under discussion and require more subnational research to prove it [17-19]. Only α and β sub-categories of coronaviruses can cause disease in...
humans; the feeding of infected animals, mainly bats, and
snakes are the main food sources for Chinese peoples. And this
route is the main source of virus transmission from animal to
human due to close contact with the infected person; the virus
is also transmitted to healthy people (Figure 3). Various surveys
have recommended that human-to-human contact, mainly
by sneezing and coughing, is a possible route for COVID-19
infection transmission [20].

Approved diagnostic test for COVID-19 in Pakistan

On Mar 12, 2020, The National Institute of Health in Pakistan
had recommended Reverse transcriptase, Polymerase chain
reaction (RT–PCR) test to better diagnose and detect SARS-
CoV2. Different countries across the country have established
with RT–PCR system that facilitates the free test for COVID-19
(Table 2). Up to 18–weeks, till Jun 30, 2020, in Pakistan, a total
of 3,702,607 tests were conducted for COVID-19 detection, and
about 315,727 were reported as positive, respectively (Figure
4). The ratio of confirmed cases of COVID-19 was progressively
increasing in different provinces of Pakistan, such as in Punjab,
Sindh, KPK, Baluchistan, ICT, Gilgit–Baltistan, and AJK are
36.06%, 39.16%, 12.47%, 4.98%, 6.70%, 0.70%, and 0.50%
respectively (Figure 5). The NDMA works with the NIH to
increasing the research laboratories for detection of COVID-19
from 15 to 50 in mandate to boost the research quality. The
new research laboratories will be established in different cities
all over the country. Similarly, Pakistan is starting a training
program for paramedics and laboratory staff to resolve
the shortfall. NDMA will recruit 100 molecular-biological
laboratory technicians [21,22–24].

Impact of COVID-19 on human physiology

The incubation duration of COVID-19 is nearly 5/2 days, and
the symptoms of COVID-19 exhibit after the incubation period.
The approximate duration from the symptoms’ appearance to
death can range from 0 to 14 days [25]. Mainly the duration
is dependent on the patient’s immunity and age. The impact
of COVID-19 on human physiology was appearing in the
forms of influenza, runny nose, coughing, fever, headache,
dyspnea, diarrhoea, shortness of breath, and lymphopenia
[26–30]. Medical features exposed by a CT-scan of the chest
were symbolised as pneumonia, contrariwise others infrequent
sorts such as acute cardiac injury and acute respiratory distress
syndrome prevalence; that led to death (Figure 6) [31,32].

Structure and genomic analysis of SARS CoV-2

The genomic sequence of the SARS-CoV-2 has been
reported to have more than 80% similarity to the previously
detected human coronaviruses SARS-CoV [34]. The genome of
SARS-CoV-2 comprises of10 open reading frames (ORFs). In
SARS-CoV-2 the biggest genes which encode the proteolytic
processing (pp1ab) protein and 15 naps (non-structural
proteins) for viral replication are the ORFib genes [35,36]. In
SARS-CoV and MERS-CoV, two pp1a and pp1ab polyproteins
are translated into seventeen non-structural proteins (nsp1–
nsp16), which form the transcriptase complex viral replicas
that initiate viral transcription and replication [37,38]. Similarly, SARS-CoV-2 ORFs on the 1/3 of the genome encodes
four core structural proteins such as spike (S), membrane
(M), nucleocapsid (N), and envelope (E) proteins that may
be involved in viral replication [39,40]. Accordingly, some
previous investigations and few current studies showed that
COVID-19’s genomic research associates the β-coronavirus
genus (Figure 7) [41,42].

Supportive treatment and preventive measure against
COVID-19 in Pakistan

There is no availability of vaccines and approved antiviral
drugs against COVID-19 worldwide. Specialized Department
of Health and Medical Education, Government of Punjab, Pakistan,
provides supportive management for PCR-positive COVID-19 infected patients, including oxygen saturation and inhalation, vitals monitoring, and supportive management use of I/V fluid. (Table 3). In Pakistan, there are different strategies followed to overcome the effect of COVOD-19. The government focuses on wearing a mask when you go to outside homes, social places, and marketplaces. During this should people maintain the stay 6 feet away/ social distance in the market or crowded places. While during daily life, people should wash their hands with hand sanitisers properly.

### Table 2: The COVID-19 test facilities in different laboratories at distinct areas of Pakistan.

| Sr.no | Province | City | Functional Lab/Category |
|-------|----------|------|-------------------------|
| 1     | Punjab   | Faisalabad | Allied hospital |
| 2     | Punjab   | Faisalabad | Abwa Hospital & Research Centre |
| 3     | Punjab   | Lahore | Punjab Forensic Science Auth Lab |
| 4     | Punjab   | Lahore | Punjab AIDS Control Program incl Hepatitis Lab |
| 5     | Sindh    | Karachi | Liaquat National Hospital |
| 6     | Sindh    | Karachi | Dow University |
| 7     | Sindh    | Karachi | PCMD Karachi University |
| 8     | Sindh    | Karachi | Civil Hospital |
| 9     | Sindh    | Karachi | Jinnah PG Medical Institute |
| 10    | Sindh    | Karachi | Civil Hospital North Karachi |
| 11    | Sindh    | Karachi | Indus Hospital (Pvt) |
| 12    | Sindh    | Karachi | Chughtai Lab |
| 13    | Sindh    | Karachi | Hashmanis |
| 14    | Sindh    | Karachi | Essen Lab |
| 15    | Sindh    | Karachi | LUMHS |
| 16    | Sindh    | Karachi | SASIMS |
| 17    | Sindh    | Karachi | Forward Medical Co. |
| 18    | Sindh    | Karachi | Mohammad Ali Hospital |
| 19    | Sindh    | Karachi | Hayatabad Medical Complex |
| 20    | Baluchistan | Quetta | Bolan Medical College |
| 21    | Baluchistan | Quetta | Regional Blood Centre (RBC) |
| 22    | Baluchistan | Quetta | Fatima Jinnah Hospital |
| 23    | Gilgit-Baltistan | Gilgit | Mobile Diagnostic Unit |
| 24    | Gilgit-Baltistan | Gilgit | DHQ |
| 25    | Gilgit-Baltistan | Gilgit | Public |
| 26    | Gilgit-Baltistan | Gilgit | Public |
| 27    | Gilgit-Baltistan | Gilgit | Public |
| 28    | AJK      | Rawalpindi | Rawalpindi Medical University |
| 29    | AJK      | Rawalpindi | Benazir Bhutto Hospital (BBH) |
| 30    | AJK      | Rawalpindi | National Institute of Health |
| 31    | AJK      | Rawalpindi | Private |
| 32    | AJK      | Rawalpindi | Excel Labs |
| 33    | AJK      | Rawalpindi | Maroof Hospital |
| 34    | AJK      | Rawalpindi | Shaafi Hospital |
| 35    | AJK      | Rawalpindi | Nayyab |
| 36    | AJK      | Rawalpindi | Kulsum Int Hosp |
| 37    | AJK      | Rawalpindi | Biogene |
| 38    | AJK      | Rawalpindi | MedAsk |
| 39    | AJK      | Rawalpindi | Public |
| 40    | AJK      | Rawalpindi | Private |
| 41    | AJK      | Rawalpindi | Public |
| 42    | AJK      | Rawalpindi | Public |
| 43    | AJK      | Rawalpindi | Public |
| 44    | AJK      | Rawalpindi | Public |
| 45    | AJK      | Rawalpindi | Public |
| 46    | AJK      | Rawalpindi | Public |
| 47    | AJK      | Rawalpindi | Public |
| 48    | AJK      | Rawalpindi | Public |
| 49    | AJK      | Rawalpindi | Public |
| 50    | AJK      | Rawalpindi | Public |
| 51    | AJK      | Rawalpindi | Public |
| 52    | AJK      | Rawalpindi | Public |
| 53    | AJK      | Rawalpindi | Public |
| 54    | AJK      | Rawalpindi | Public |
| 55    | AJK      | Rawalpindi | Public |
| 56    | AJK      | Rawalpindi | Public |
| 57    | AJK      | Rawalpindi | Public |
| 58    | AJK      | Rawalpindi | Public |
| 59    | AJK      | Rawalpindi | Public |
| 60    | AJK      | Rawalpindi | Public |
| 61    | AJK      | Rawalpindi | Public |
| 62    | AJK      | Rawalpindi | Public |
| 63    | AJK      | Rawalpindi | Public |
| 64    | AJK      | Rawalpindi | Public |
| 65    | AJK      | Rawalpindi | Public |
| 66    | AJK      | Rawalpindi | Public |
| 67    | AJK      | Rawalpindi | Public |
| 68    | AJK      | Rawalpindi | Public |
| 69    | AJK      | Rawalpindi | Public |
| 70    | AJK      | Rawalpindi | Public |
| 71    | AJK      | Rawalpindi | Public |
| 72    | AJK      | Rawalpindi | Public |
| 73    | AJK      | Rawalpindi | Public |
| 74    | AJK      | Rawalpindi | Public |
| 75    | AJK      | Rawalpindi | Public |
| 76    | AJK      | Rawalpindi | Public |
| 77    | AJK      | Rawalpindi | Public |
| 78    | AJK      | Rawalpindi | Public |
| 79    | AJK      | Rawalpindi | Public |
Figure 4: Represent that the analysis of COVID-19 reported test in Pakistan.

Figure 5: The Current scenario of COVID-19 in Pakistan.

Figure 6: Represent the clinical sign and symptoms of COVID-19 infection at different stages during their incubation period of viral infection [33].

Figure 7: Representing coronaviruses type enveloped and 100-160 nm diameter spherical particles. They contain an ssRNA genome 26-32 kb in size. (B) Reflect all of the SARS-CoV2 genome sequences. In SARS-CoV-2, ORF1a/b encoded polyproteins are two-thirds of the 5'-5'-terminal genome, forming the viral replicase transcriptase complex. The four major structural proteins, Boll, shell, nucleocapsid, and membrane encoded by the other one-third ORF genome and some accessory proteins [43].

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The government of Pakistan also initiates the vaccination in different trials. In the first phase, the vaccination was used by premedical’s staff, and in the second phase, the older adults whose age was more than 65 were vaccinated without any cost. In the third phase, the government will use the vaccination for more than 40 years. So, using these strategies government of Pakistan is trying to combat the COVID-19.

**Drug availability**

At the onset of the pandemic, no new COVID-19 therapeutics or vaccinations were eligible. Several treatments are being tested, including remdesivir and favipiravir, but their antiviral effectiveness is unknown. During the 2014 Ebola virus outbreaks, convalescent plasma was recommended as an alternative therapy. In 2015, a guideline for using convalescent plasma to treat the Middle East respiratory syndrome coronavirus was developed. Other viral infections, such as SARS-CoV, avian influenza, and H1N1 influenza, were treated similarly, indicating that transfusion of convalescent plasma was successful. In previous studies, most patients obtained convalescent plasma from a single transmission [44].

Furthermore, hydroxychloroquine is another treatment for Covid-19, according to the researcher. In vitro, it has antiviral activity against SARS-CoV-2. In ICU Covid-19 patients, the Surviving Sepsis Campaign recommendations stated that there was inadequate data to prescribe antiviral drugs and hydroxychloroquine. Furthermore, the usage of two separate dosing regimens for these medications has little impact on chronically ill patients’ results [45].

Patients who are seriously ill with COVID-19 are being handled with convalescent plasma, according to recent research. Within days after receiving convalescent plasma, viral load decreased, and these patients’ health outcomes increased, as shown by lower body temperatures and improved chest imaging. Nine days after consuming plasma, four patients on mechanical ventilation no longer needed it (Yeh, et al. 2005) (Figure 8) [44-46]. Outcomes of continuing clinical trials are impatiently awaited. Self-protection from COVID-19 was confirmed by using gloves, glasses, hand sanitiser, and N-95 masks. Also, plenty of water and organ juice intake played a significant role in boosting human immunity.

**Future prospects**

Furthermore importantly, working on human COVID-19 targeting antiviral drugs and vaccines should be designed to be used against viral epidemics. Many companies such as Inovio California, Cancino Bio China, Pfizer & Biotech, Sanofi, and GSK effectively develop the vaccine against SARS-CoV-2. Researchers are working hard to advance/develop the required successful therapeutic approaches to manage the novel COVID-19. COVID-19 vaccinations have been provided to millions of citizens in the United States, and they have undergone the most rigorous safety testing in the country’s history. To ensure that COVID-19 vaccinations are secure, this surveillance requires both existing and new protection monitoring systems. The European Medicines Agency (EMA) has licensed these

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| Sr.no | Antiviral Drugs Under Evaluation for the Treatment of COVID-19 | Duration/Effects |
|-------|---------------------------------------------------------------|-----------------|
| 1     | Remdesivir                                                   | 5-10 days       |
| 2     | Chloroquine                                                  | 600 mg twice daily for ten days |
| 3     | Hydroxychloroquine                                           | In combination with azithromycin to better manage COVID-19 |
| 4     | Lopinavir                                                    | Under clinical trial but used against COVID-19 |
| 5     | Ritonavir                                                    | Under clinical trial but used against COVID-19 |
| 6     | Ivermectin                                                   | Under clinical trial but used against COVID-19 |

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**Figure 8:** The mood of action of treatment strategies is announced by WHO and their interaction with different steps in the coronavirus replication cycle [47].
vaccinations, which has previously only authorised vaccines from Pfizer/BioNTech, Moderna, and AstraZeneca. According to forecasts, the Covid-19 vaccine could decrease morbidity and mortality rates while also enhancing health outcomes in efficacy and safety management. Lockdown, mask wear, social distance, exact evaluation, proper treatment, and vaccine are only a couple of the precautionary steps that the government can take to minimise the danger of Covid-19. The transmission of COVID-19 influences the population to save several human lives if we adopt aggressive preventive measures. A government recommended guideline should be practised, diminishing the transmission from one person to another of COVID-19 and regulates the viral epidemic. The exact diagnosis will help monitor the rapid spread of the infection in the early stages of the epidemic. Pakistan and all other countries will adopt primary anticipatory, control, and preventive measures explicitly focusing on travel screening to regulate the further transmission of the outbreak of SARS-CoV2.

Conclusion

China faced COVID-19 in December 2019 and has been confirmed to clear the spread of coronavirus approximately after months; few other countries, such as South Korea, have been capable enough to manage the outbreak of COVID-19, but numerous developing countries, mainly Pakistan, has not been well-off. The pandemic of COVID-19 is looking more catastrophic and disaster effect than the 2nd World War. Pakistan would be affected by the COVID-19 outbreak and mainly impact the socio-economic situation in different fields/sectors. In this review, we concluded the coronavirus epidemic up-to 18 weeks (30-June, 2020) in Pakistan, and their outbreak was gradually increased in different provinces of Pakistan. A large no. of COVID-19 cases was seen in Sindh.

Similarly, overall, about 2.06% of the death ratio due to COVID-19 in Pakistan was reported. COVID-19 mortality rate accordingly to area division progressively increased in-order such as in Punjab, Sindh, Baluchistan, Gilgit-Baltistan, and ICT are 2.28%, 1.64%, 1.90%, 2.62%, and 1.00%, respectively. The mortality rate was highly testified in KPK about 3.58%, and test conductance rate was reported fewer in KPK. This situation should be noticeable. Appropriate implementation of preventive measures and control of the COVID-19 outbreak now—a-day become a challenging phase for the Pakistan population.

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Author’s contributions

All authors have contributed significantly to this for the conception, design, analysis and Data interpretation, review and approval of the final version of the manuscript and agree to be responsible for its content.

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