

#### ORIGINAL RESEARCH

# Assessing the Impact of COVID-19 on the Mental Health of Healthcare Workers in Three Metropolitan Cities of Pakistan

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Purpose: The COVID-19 (coronavirus disease-2019) has been associated with psychological distress during its rapid rise period in Pakistan. The present study aimed to assess the mental health of healthcare workers (HCWs) in the three metropolitan cities of Pakistan.

Methods: A cross-sectional, web-based study was conducted in 276 HCWs from April 10, 2020, to June 5, 2020. Depression, anxiety, and stress scale (DASS-21) were used for the mental health assessment of the HCWs. Multivariable logistic regression analysis (MLRA) was performed to measure the association between the demographics and the occurrence of depression, anxiety, and stress (DAS).

Results: The frequency of DAS in the HCWs was 10.1%, 25.4%, and 7.3%, respectively. The MLRA showed that the depression in HCWs was significantly associated with the profession (P<0.001). The anxiety in HCWs was significantly associated with their age (P=0.005), profession (P<0.05), and residence (P<0.05). The stress in HCWs was significantly associated with their age (P<0.05).

**Limitation:** This study was conducted in the early phase of the COVID-19 pandemic, when the number of COVID-19 cases was on the rise in Pakistan and it only represents a definite period (April to June 2020).

Conclusion: The symptoms of DAS are present in the HCWs of Pakistan and to manage the psychological health of HCWs, there is a need for the initiation of psychological well-being programs.

Keywords: depression, anxiety, stress, pandemic, DASS-21

#### Introduction

A cluster of acute respiratory illnesses with unknown etiology was reported in Wuhan, Hubei province, China in December 2019. 1,2 Chinese health committees later confirmed that respiratory illness was caused due to a novel coronavirus and shared its viral genome sequence with the world.<sup>3,4</sup> China confirmed the first human-to-human transmission of novel coronavirus on the 21st of January 2020 in the healthcare workers (HCWs) of Wuhan.<sup>5</sup> The World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (PHEIC) on 30th of January 2020.6 The WHO named this disease as coronavirus disease 2019 (COVID-19) on 12th of February 2020,7 and declared it a global pandemic on 11th of March 2020, as it was spreading at a very high rate around the globe. In Pakistan, the first case of COVID-19 was reported on February 26, 20209 and since then the number of confirmed cases is on the rise by every passing day.

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As of May 31, 2020, the number of confirmed cases in Pakistan was 72,460 with 1543 deaths, and with 26,083 patients recovered from the disease. 10 This increase in reported COVID-19 cases in Pakistan has significantly amplified patient load in the hospitals and resultantly, there is a situation of national health emergency and the HCWs must work at their full capacity.

Psychological distress is known to be associated with the spread of infectious diseases 11-14 and similarly, it is also reported with COVID-19. 15-18 The COVID-19 can cause a serious impact on the mental and physical health of healthy and disease populations. Several studies have reported psychological symptoms like depression, anxiety, and stress (DAS) among general people during the outbreak of COVID-19 especially in those who are in contact with the infected patients. <sup>16,19,20</sup> The frontline HCWs are at a higher risk for COVID-19 as they are in direct contact with the infected patients and they have higher psychological stress as compared to the general population. 15,17,21,22 Similarly, during the SARS (Severe Acute Respiratory Syndrome) MERS (Middle East respiratory syndrome) breakout, mental health problems were reported in HCWs and the survivors. 11,13,14,23 To protect themselves from the infected people, the HCWs must be provided with personal protective equipment (PPE), but due to the shortage of PPE in Pakistan, the HCWs were forced to work without it, that has resulted in enormous work-related stress amongst them.<sup>24</sup> The number of HCWs infected by coronavirus is increasing alarmingly by every passing day in Pakistan. <sup>25</sup> Recently, due to the high workload and fear of being infected by a coronavirus. a young doctor has committed suicide in Pakistan.<sup>25</sup> To date, no study has been reported in Pakistan that has focused on the COVID-19 related psychological stress in the HCWs. Therefore, if a study that can identify job-related DAS is conducted in Pakistan, it can provide support to the health administration to design and implement targeted interventions for adopting policies that can improve the psychological health of the HCWs during this pandemic.

The present study was conducted to assess the occurrence of DAS among the HCWs and their determinants during the rapid rise period of the COVID-19 pandemic in Pakistan.

#### **Materials and Methods**

## Study Population

According to the statistics division of the Government of Pakistan, the estimated number of HCWs in Pakistan is 302,868 and amongst them 91, 696 are working in Punjab.<sup>26</sup> This study was conducted among the HCWs,

including physicians, pharmacists, nurses, and supporting staff working in different metropolitan cities of Pakistan (Multan, Lahore, and Faisalabad), where the reported COVID-19 cases were highest.

### Data Collection

A cross-sectional web-based survey was conducted from April 10 to June 5, 2020. An online questionnaire was designed using Google forms (Google LLC. USA) and its online link was shared through e-mail and different social media platforms (WhatsApp, Facebook). The participants could view the question by simply clicking on the shared link and answer the questions. The first page of the questionnaire comprised a short introduction regarding the objectives, procedures, declaration of confidentiality and anonymity, and the volunteer nature of the participation, which is in accordance with the Declaration of Helsinki. To avoid redundant answers and nonserious participants, the responses completed in less than 2 minutes were excluded from the final analysis. The CHERRIES Guidelines for web-based survey was followed throughout the data collection phase of the study as shown in Supplementary Table S1.<sup>27</sup>

A total of 624 questionnaires were distributed, and 295 responses were collected, 19 questionnaires were excluded from the final analysis. The response rate for the study was 47.2%. The process of data collection can be seen in Figure 1.

# Study Instrument

Socio-demographic data were collected on age, gender, marital status, profession, and residence. Mental health status was measured using the depression, anxiety, and stress scale (DASS-21)<sup>28</sup> presented in Supplementary Table S2. Questions 3, 5, 10, 13, 16, 17, and 21 formed the depression subscale. The total depression subscale score was divided into normal (0-9), mild depression (10–12), moderate depression (13–20), severe depression (21–27), and extremely severe depression (28–42). Questions 2, 4, 7, 9, 15, 19, and 20 formed the anxiety subscale. The total anxiety subscale score was divided into normal (0-6), mild anxiety (7-9), moderate anxiety (10-14), severe anxiety (15–19), and extremely severe anxiety (20-42). Questions 1, 6, 8, 11, 12, 14, and 18 formed the stress subscale. The total stress subscale score was divided into normal (0-10), mild stress (11-18), moderate stress (19–26), severe stress (27–34), and extremely severe stress (35–42). In the present study, the scores of  $\geq$ 10, 07, and 11 in the subscales were considered to depict elevated depressive, anxiety, and stress symptoms, respectively.

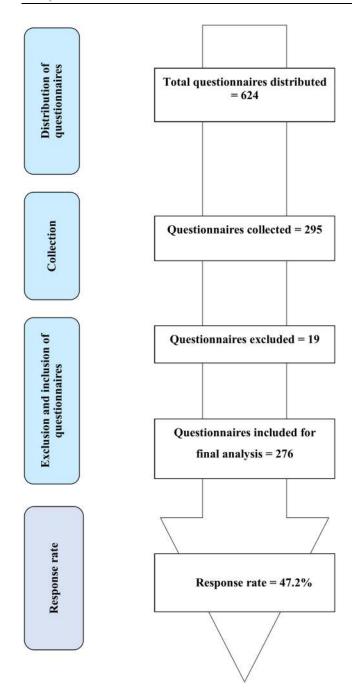


Figure I The process of data collection for the conducted study.

# Ethical Approval and Consent to Participate

This research involved online data collection from the participants. Every participant gave an online informed consent before filling the study questionnaire. The formal approval of the study was given by the ethical committee of the department of pharmacy practice, faculty of pharmacy, Bahauddin Zakariya University, Multan with reference number Acad/33/20/5.

# Statistical Analysis

Descriptive statistics were used for analyzing sociodemographic characteristics and the association between different parameters was found by applying the chi-square test (x²) and Fisher exact test (where applicable). The multivariate logistic regression was used to determine the association between demographics and DAS along with their odds ratios (OR) and 95% confidence intervals (95% Cl). The linear regression model was also used to estimate the possible demographic predictors of DAS by using an unadjusted and adjusted model for age, gender, marital status, profession, and residence. All the applied statistical tests were two-tailed and a p-value of <0.05 was considered statistically significant. All the analysis was performed using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Statistics, New York, United States).

#### Results

The descriptive statistics of the demographic data are presented in Table 1. A total of 276 participants completed the survey, among which 182 (65.9%) were male and 94 (34.1%) were female. Most of the participants were within the age group of 26–30 years 172 (62.3%). Among them, 158 (57.2%) were unmarried and 118 (42.8%) were married. Most of the participants were physicians 112 (40.4%) followed by pharmacists 82 (29.7%), nurses 50 (18.1%), and supportive staff 32 (11.6%). The female HCWs were more depressed than males (female vs male:  $6.47 \pm 2.77$  vs  $4.66 \pm 3.40$ , p <0.001). While in comparison to males, the anxiety symptoms were more common among female HCWs (female vs male:  $5.60 \pm 3.14$  vs  $4.51 \pm 3.35$ , p <0.001).

# Depression

Among the total 276 respondents, 28 (10.1%) showed elevated depressive symptoms. The frequency and correlation using multivariate logistic regression are presented in Table 2. The elevated depressive symptoms were significantly associated with physicians (OR, 0.086; 95%Cl, 0.016—0.473; P =0.005). Among the 50 nurses, 12 (24.0%) showed depressive symptoms. The prevalence of depressive symptoms was more common among nurses as compared to other healthcare professionals.

# Anxiety

Association of anxiety with independent variables using multivariable logistic regression and prevalence is presented in Table 3. 25.4% of the respondents showed symptoms of

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Table I The Demographical Data and Descriptive Statistics

		Overall	Gender	P-value		
		(N=276) n (%)	Male (N=182) n (%)	Female (N=94) n (%)		
Age	21–25 26–30 31–35 36–40	30(10.9%) 172(62.3%) 58(21.0%) 16(5.8%)	16(8.8%) 108(59.3%) 46(25.3%) 12(6.6%)	14(14.9%) 64(68.1%) 12(12.8%) 4(4.3%)	0.034	
Marital status	Married Un-married	118(42.8%) 158(57.2%)	92(50.5%) 90(49.5%)	26(27.7%) 68(72.3%)	<0.001	
Profession	Physician Pharmacist Nurse Supportive staff	112(40.4%) 82(29.7%) 50(18.1%) 32(11.6%)	74(40.4%) 76(41.8%) 6(3.3%) 26(14.3%)	38(40.4%) 6(6.4%) 44(46.8%) 6(6.4%)	<0.001	
Residence	Multan Faisalabad Lahore other	174(63.0%) 14(5.1%) 20(7.2%) 68(24.6%)	110(60.4%) 9(4.9%) 20(11.0%) 43(23.6%)	64(68.1%) 5(5.3%) 0(0.0%) 25(26.6%)	0.002	
Depression Mean(±SD)		5.27±3.3	4.66 ±3.40	6.47 ±2.77	<0.001	
Anxiety Mean(±SD)		4.87±3.3	4.51 ±3.35	5.60 ±3.14	<0.001	
Stress Mean(±SD)		5.59±3.3	5.23 ±3.29	6.30 ±3.23	0.076	

Note: The bold figure shows the results where P-value is < 0.05.

anxiety. The logistic regression analysis showed that the anxiety was significantly associated with age (21–25 years) (OR, 0.505; 95% Cl, 0.313–0.814; P=0.008), pharmacist (OR, 0.155; 95% Cl, 0.046–0.521; P=0.003) and Multan (OR, 3.009; 95% Cl, 1.373–6.593; P= 0.006). The anxiety was more common in the age group  $\geq$ 36 years (37.5%) and the nurses (44%). The respondents from the Multan city showed elevated anxiety levels (31%).

#### Stress

The frequency of stress was the lowest as 7.3% of the respondents were having stress symptoms (Table 4). The multivariate logistic regression analysis showed that stress was significantly associated with the residence (Lahore) (OR, 17.979; 95%Cl, 1.378–234.599; P=0.027) (Table 4). The stress symptoms were more common within the age group of 21–25 years (20.0%).

# Predictors of Depression, Anxiety, and Stress

The linear regression model was used to predict the association of mental symptoms (DAS) with the independent variables (Table 5). Among all the demographic variables, gender was the only common predictor of DAS, with and without adjusting

the predictor variables. The age of the respondents was significantly associated with depression and anxiety. The profession of HCWs was a significant predictor of stress, with and without adjusting the predictor variables.

## **Discussion**

To the best of our knowledge, it is the first study to assess the psychological impact of the COVID-19 pandemic on the mental health of HCWs in the three main metropolitan cities of Pakistan by using the validated tool, DASS-21. The results of our study showed that the prevalence of DAS among HCWs (n=276) was 10.1%, 25.4%, and 7.3%, respectively. These psychological symptoms (depression, anxiety, and stress) showed a significant association with age, profession, and residence in multivariate logistic regression analysis. The result of linear regression analysis showed that the age, gender, and profession of the HCWs were significant predictors of DAS.

In the present study, the percentage of depression among the HCWs was 10.1%, which was significantly associated with the profession and was more common among nurses (24.0% in nurses). The overall depression rates in HCWs from our study were comparable to the

Table 2 Prevalence and Association of Depressive Symptoms by Logistic Regression Analysis

Independent Variables		Depressive Sy n (%)	mptoms	Odds Ratio OR(95% CI)	P-value
		Normal Score ≤9 (N=248)	Elevated Score ≥10 (N=28)		
Age	21-25 (N=30) 26-30(N=172) 31-35(N=58) 36-40(N=16)	26(86.7%) 160(93.0%) 50(86.2%) 12(75.0%)	4(13.3%) 12(7.0%) 8(13.8%) 4(25.0%)	0.353(0.050–2.498) 0.263(0.057–1.223) 0.512(0.115–2.280) Reference	0.297 0.089 0.380 NA
Gender	Male(N=182) Female(N=94)	166(91.2%) 82(87.2%)	16(8.8%) 12(12.8%)	1.324(0.322–5.447) Reference	0.697 NA
Marital status	Married(N=118) Un-married(N=158)	102(86.4%) 146(92.4%)	16(13.6%) 12(7.6%)	1.199(0.411–3.498) Reference	0.740 NA
Profession	Physician(N=112) Pharmacist(N=82) Nurse(N=50) Supportive staff(N=32)	110(98.2%) 74(90.2%) 38(76.0%) 26(81.3%)	2(1.2%) 8(9.8%) 12(24.0%) 6(18.8%)	0.086(0.016-0.473) 0.263(0.064-1.085) 1.658(0.353-7.783) Reference	0.005 0.065 0.522 NA
Residence	Multan(N=174) Faisalabad(N=14) Lahore(N=20) other(N=68)	157(90.2%) 12(85.77%) 16(80.0%) 63(92.6%)	17(9.8%) 2(14.3%) 4(20.0%) 5(7.4%)	1.324(0.428–4.092) 2.061(0.242–17.579) 5.917(0.928–37.715) Reference	0.626 0.508 0.060 NA

**Note:** The bold figure shows the results where P-value is < 0.05.

Table 3 Prevalence and Association of Anxiety Symptoms by Logistic Regression Analysis

Independent Variables		Anxiety n (%)		Odds Ratio OR(95% CI)	P value
		Normal Score ≤06 (N=206)	Elevated Score ≥07 (N=70)		
Age	21-25 (N=30) 26-30(N=172) 31-35(N=58) 36-40(N=16)	28(93.3%) 130(75.6%) 38(65.5%) 10(62.5%)	2(6.7%) 42(24.4%) 20(34.5%) 6(37.5%)	0.505(0.313-0.814) 0.334(0.095-1.174) 0.836(0.367-1.908) Reference	0.008 0.087 0.399 NA
Gender	Male(N=182) Female(N=94)	142(78.0%) 64(68.1%)	40(22.0%) 30(31.9%)	0.836(0.367–1.908) Reference	0.671 NA
Marital status	Married(N=118) Un-married(N=158)	84(71.2%) 122(77.2%)	34(28.8%) 36(22.8%)	0.849(0.402–1.890) Reference	0.728 NA
Profession	Physician(N=112) Pharmacist(N=82) Nurse(N=50) Supportive staff(N=32)	86(76.8%) 70(85.4%) 28(56.0%) 22(68.8%)	26(32.2%) 12(14.6%) 22(44.0%) 10(31.3%)	0.472(0.181–1.229) 0.155(0.046–0.521) 1.182(0.362–3.859) Reference	0.124 <b>0.003</b> 0.781 NA
Residence	Multan(N=174) Faisalabad(N=14) Lahore(N=20) other(N=68)	120(69.0%) 14(100%) 14(70.0%) 58(85.3%)	54(31.0%) 0(0.0%) 6(30.0%) 10(14.7%)	3.009(1.373-6.593) 1.817(0.161-20.500) 11.673(2.522-54.039) Reference	0.006 0.629 0.002 NA

**Note:** The bold figure shows the results where P-value is < 0.05.

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Table 4 Prevalence and Association of Stress Symptoms by Logistic Regression Analysis

Independent Variables		Stress n (%)		Odds Ratio OR(95% CI)	P value
		Normal Score ≤10 (N=256)	Elevated Score ≥ I I (N=20)		
Age	21–25 (N=30) 26–30(N=172) 31–35(N=58) 36–40(N=16)	24(80.0%) 160(93.0%) 56(96.6%) 16(100.0%)	6(20.0%) 12(7.0%) 2(3.4%) 0(0.0%)	3.333(0.278–39.930) 0.791(0.076–8.227) 0.536(0.041–6.940) Reference	0.342 0.845 0.633 NA
Gender	Male(N=182) Female(N=94)	170(93.4%) 86(91.5%)	12(6.6%) 8(8.5%)	2.592(0.533–12.607) Reference	0.238 NA
Marital status	Married(N=118) Un-married(N=158)	112(94.9%) 144(91.1%)	6(5.1%) 14(8.9%)	0.517(0.150–1.775) Reference	0.294 NA
Profession	Physician(N=112) Pharmacist(N=82) Nurse(N=50) Supportive staff(N=32)	110(98.2%) 74(90.2%) 42(84.0%) 30(93.8%)	2(1.8%) 8(9.8%) 8(16.0%) 2(6.3%)	0.360(0.045–2.884) 0.923(0.149–5.714) 6.349(0.845–47.696) Reference	0.336 0.931 0.072 NA
Residence	Multan(N=174) Faisalabad(N=14) Lahore(N=20) other(N=68)	161(92.5%) 12(85.7%) 16(80.0%) 67(98.5%)	13(7.5%) 2(14.3%) 4(20.0%) 1(1.5%)	5.625(0.675–46.904) 3.720(0.250–55.366) 17.979(1.378–234.599) Reference	0.110 0.340 <b>0.027</b> NA

**Note:** The bold figure shows the results where P-value is < 0.05.

studies from Singapore (8.9%), <sup>17</sup> India (12.6%)<sup>29</sup>, and China (13.6%).30 However, three studies from China have reported higher depression rates of 50.4%, 30 34.8%, 31 and 34.6% 32 in their HCWs. The probable reasons behind these lower depression rates in our study could be that China was the epicenter of the pandemic and a high number of patients were admitted to the hospitals during the early stage of the pandemic, which may have resulted in high depression among Chinese HCWs. Additionally, these studies were conducted in Wuhan, when it was the epicenter of the COVID-19 and this may be the reason for the higher prevalence of depression among their HCWs. Furthermore, a nationwide study from Switzerland showed a higher prevalence of depression (20.7%) in their HCWs. 18 The higher depression rates in HCWs of Switzerland may be due to several reasons. Firstly, the study in Switzerland was conducted when the reported COVID-19 cases were very high, as on the closing date of this study, ie, 4th April 2020 there were 21,473 COVID-19 confirmed cases in Switzerland<sup>33</sup> vs 2880 in Pakistan. 10 Secondly, it is known from previous studies that the frequency of depression was higher in HCWs of Europe when compared with that of HCWs of Asia.<sup>34</sup>

In our study, the frequency of anxiety among the HCWs was higher (25.4%) than the reported values in the HCWs of India and Singapore (15.7%),<sup>29</sup> China (16.0% and 12.5%). 32,35 These higher anxiety levels in the presented study may be due to the fact that our HCWs did not have any previous experience in managing epidemics (like SARS) and the HCWs from China and Singapore have faced similar epidemics in the past. 14 Moreover, the health system in China and Singapore is far more advanced than that in Pakistan, the availability of limited health resources and lack of training regarding the management of epidemics are the probable reasons for higher anxiety rates in HCWs of Pakistan. The results of our study were comparable with the reported anxiety levels in the HCWs of Switzerland (25.9%). 18 The similar anxiety levels in the HCWs of Pakistan and Switzerland can also be related to the above-mentioned fact that the HCWs of both countries have no recent experiences in the management of epidemics.

The frequency of stress among the HCWs in the reported study was 7.3%, which is lower than the values reported in Chinese HCWs (30.56% and 71.5%).<sup>30,36</sup> The 16% of nurses showed symptoms of stress in this study

Table 5 Predictors of Depression, Anxiety, and Stress by the Linear Regression Model

Predictors	Unadjusted			Adjusted				
Depression	Beta-Coefficients	Standard Error	t	p value	Beta-Coefficients	Standard Error	Т	p value
Age	0.141	0.278	2.364	0.019	0.174	0.310	2.607	0.010
Gender	0.259	0.406	4.443	<0.001	0.277	0.409	4.715	<0.001
Marital Status	-0.082	0.401	-1.368	0.172	-0.044	0.452	-0.644	0.520
Profession	0.190	0.191	3.208	0.001	0.164	0.186	2.833	0.005
Residence	0.032	0.153	0.533	0.594	0.57	0.144	1.000	0.318
Anxiety								
Age	0.277	0.271	4.769	<0.001	0.341	0.312	5.094	<0.001
Gender	0.156	0.417	2.617	0.009	0.181	0.412	3.075	0.002
Marital Status	-0.085	0.403	-1.417	0.158	0.060	0.455	0.881	0.379
Profession	0.101	0.194	1.675	0.095	0.102	0.187	1.755	0.080
Residence	-0.058	0.154	-0.968	0.334	-0.036	0.145	-0.634	0.527
Stress								
Age	0.079	0.279	1.317	0.189	0.083	0.318	1.216	0.225
Gender	0.149	0.414	2.497	0.013	0.145	0.419	2.392	0.017
Marital Status	-0.083	0.400	-1.382	0.168	-0.056	0.463	-0.804	0.422
Profession	0.229	0.188	3.892	<0.001	0.211	0.190	3.549	<0.001
Residence	-0.074	0.153	-1.226	0.221	-0.058	0.148	-0.988	0.324

**Note:** The bold figure shows the results where P-value is < 0.05.

while the frequency of stress was very high in the nurses working in China (70.9% and 74.5%).<sup>30,36</sup> The higher stress among Chinese HCWs can be related to their long duty hours and high patient load in the hospitals during the rapid rise period of the COVID-19. Moreover, the probable reason behind these less stress levels among HCWs in Pakistan may be that our study was conducted at an early stage of the pandemic, as the number of confirmed COVID-19 cases was low in comparison with other countries.

In this study, we have found predictors for DAS by using multiple linear regression and it was observed that age was significantly associated with anxiety [p=0.000] and depression [p=0.010], gender was associated with depression [p=0.000], anxiety [p=0.002], and stress [p=0.017], while profession was a significant predictor of depression [p=0.005] and stress [p=0.000]. These results were consistent with a study from China where gender was reported as a significant predictor for anxiety [p=0.001], depression [p=0.003], and stress [p=0.01].<sup>30</sup>

#### Limitations

The presented results are from the data collected within the rapid rise period of COVID-19 in Pakistan and it only represents a definite period (April to June 2020). The data for this study were collected online and only those HCWs were included who had access to the internet. Although CHERRIES guideline was used for minimizing bias in the study but since no sensitivity analysis was performed, which may be treated as a limitation of the study. The data related to the mental health of HCWs before the COVID-19 pandemic was not available and the comparison of the DAS was not possible before and during the pandemic. Therefore, we are unable to differentiate between already existing symptoms and new symptoms that may have aroused due to the pandemic.

Finally, this study was conducted in the early phase of the COVID-19 pandemic, when the number of COVID-19 cases was still on the rise in Pakistan.

#### Conclusion

The HCWs in the three major cities of Pakistan showed only mild to moderate symptoms of DAS as no severe symptoms were found. The frequency of DAS was higher in nurses as compared to other HCWs, ie doctors, pharmacists, and supportive staff. Since the number of COVID-19 confirmed cases is on the rise in Pakistan, the frequency of DAS is expected to rise; therefore, follow-up studies are required to measure the DAS levels in the HCWs to assess the impact of the increasing number of COVID-19 on the mental health of the HCWs.

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Moreover, a similar study from Italy has supported the need for implementing prevention strategies and early psychological interventions for reducing DAS symptoms in HCWs.<sup>35</sup>

Lastly, the health regulatory agencies in Pakistan should initiate mental health programs and special sessions for the HCWs on a priority basis so that the frontline HCWs can better cope with the COVID-19-associated mental stress.

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### **Author Contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

#### **Disclosure**

The authors report no conflicts of interest in this work.

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