Immune response of frontline medical workers providing medical support for Wuhan COVID-19 patients, China

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A R T I C L E   I N F O

A B S T R A C T

The outbreak of novel coronavirus disease 2019 (COVID-19) posed a great challenge and stress to frontline medical workers in China. Stress is closely related to immunity. However, the immune response of frontline medical workers providing medical support for COVID-19 patients is unclear. Here, we reported the immune response of 76 frontline medical workers and 152 controls from the Second Affiliated Hospital of Xi'an Jiaotong University. The frontline medical workers were involved in the care for Wuhan COVID-19 patients from February 8 to March 31, 2020 in Tongji Hospital of Huazhong University of Science and Technology. The controls were medical workers of our hospital who had not been in contact with COVID-19 patients during the same period. Demographic and clinical data, including routine blood test data were extracted from the electronic health examination record and retrospectively analyzed. The post-stress frontline medical workers had higher lymphocyte (LYM) count compared with controls or pre-stress. However, the post-stress frontline medical workers had lower monocyte (MONO) count, neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and neutrophil (NEUT) ratio than controls or pre-stress. Interestingly, we found the differences were more significantly in female subgroup and nurse subgroup. Together, these data indicated that changes of immune response were found in frontline medical workers providing medical support for Wuhan COVID-19 patients, especially in females and nurses. Those maybe caused by psychological stress and we recommend to pay more attention to mental health of frontline medical workers, and provide appropriate psychological interventions for them.

1. Introduction

On the end of December 2019, some cases of pneumonia of unknown etiology were found initially in Wuhan, Hubei, China[1]. The World Health Organization (WHO) subsequently termed it COVID-19, which was caused by infection with the novel coronavirus, SARS-CoV-2. On January 30, 2020, the WHO declared the COVID-19 outbreak a public health emergency of international concern. On March 11, 2020, the WHO characterized COVID-19 outbreak as a pandemic because of the rapid global spread of the disease [2].

It is well known that infectious disease outbreaks, such as severe acute respiratory syndrome (SARS) outbreak in 2003, have psychological effects on healthcare workers and the general population [3]. Previous studies reported that healthcare workers underwent psychological stress reactions on the SARS outbreak [4,5]. The critical situation of COVID-19 outbreak caused mental burden on suspected and confirmed patients with COVID-19. Meanwhile, the outbreak of COVID-19 posed a great challenge to healthcare workers in China. A recent study revealed that frontline healthcare workers who were directly involved in the diagnosis, treatment and care for patients with COVID-19 in China experienced psychological burden [6].

The immune system is the body's main defense mechanism against harmful pathogens. The immune mechanism provides effective defense against infections and regulates the autoimmune response [7]. The peripheral circulation is essential for maintaining an effective immune defense network. The white blood cell (WBC) count is usually measured as a non-specific hematological inflammatory marker [8]. The number and proportion of WBC and subgroup immune cells in the blood provide

an important representation of the distribution of WBC in the body and the activation of the immune system. Psychological stress has been shown to have a large impact on the immune system [9–11], and chronic stress usually suppresses the immune system [12]. A previous study demonstrated that inflammation was acutely increased in individuals exposed to psychosocial stressors [13]. However, the immune response of frontline medical workers providing medical support for COVID-19 patients is unclear. This study aimed to assess the immune response of frontline doctors and nurses treating and caring for Wuhan COVID-19 patients.

2. Material and methods

2.1. Participants

This retrospective study included frontline doctors and nurses from the Second Affiliated Hospital of Xi'an Jiaotong University who had provided medical support for Wuhan COVID-19 patients from February 8 to March 31, 2020 in Tongji Hospital of Huazhong University of Science and Technology as stress group. They underwent hematological test on April 10th. The COVID-19 virus and its specific antibody in frontline doctors and nurses were tested. All test results have been negative for COVID-19 infection. Those medical workers were excluded if they have physical diseases and psychiatric diseases such as diabetes, immune-mediated diseases, post-traumatic stress disorder, major depression, anxiety and so on. The other medical workers of our hospital who had not been in contact with COVID-19 patients during the same period were controls. Their age, gender and occupation were matched with those in stress group. The study was approved by the Ethics Committee of Xi'an Jiaotong University College of Medicine according to the principles outlined in the Declaration of Helsinki.

2.2. Data collection

The demographic and clinical data were extracted from the electronic health examination record in our hospital, including age, sex, occupation, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and medical history.

In the stress group, blood test data before and after providing medical support for Wuhan COVID-19 patients were recorded as pre-stress data and post-stress data. A total of 3 mL blood was extracted from every one. Routine blood tests were performed using an automatic blood cell analyzer (XN9000; Sysmex, Japan). Detection was operated according to the manufacturer's instructions. Routine blood tests included WBC count, neutrophil (NEUT) count, lymphocyte (LYM) count, monocyte (MONO) count, eosinophil (EOS) count, basophilic granulocyte (BASO) count, neutrophil ratio (NEUT%), lymphocyte ratio (LYM%), monocyte ratio (MONO %), eosinophil ratio (EOS%), and basophilic granulocyte ratio (BASO%). The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. The monocyte to lymphocyte ratio (MLR) was calculated by dividing the monocyte count by the lymphocyte count. Medical workers in two groups were stratified by sex and occupation to compare differences of immune response.

2.3. Statistical analysis

All analyses were performed using SPSS 19.0. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as absolute values. Student's t-test was used to test the differences of continuous variables and chi-square test was used to test the differences of dichotomous variables between two groups. Participants were divided into different layers on the basis of sex and occupation. One-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test was used to test for differences in levels of immune markers among the controls, pre-press and post-press data. Statistical

significance was considered as $P < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

A total of 76 frontline medical workers and 152 controls were enrolled in this study. Demographic and clinical characteristics of all subjects are presented in Table 1. The mean age of 76 frontline medical workers was 34.9 ± 5.8 years old and the mean age of 152 controls was 35.0 ± 5.0 years old (Table 1). Among 76 frontline medical workers, 17 (22.4%) were doctors, 59 (77.6%) were nurses, 61 (80.3%) were female and 15 (19.7%) were male (Table 1). Among 61 female frontline medical workers, 55 were nurses and 6 were doctors. The age, gender and occupation of the control group were completely matched with stress group. Among 152 controls, 34 (22.4%) were doctors, 118 (77.6%) were nurses, 124 81.6%) were female and 28 (18.4%) were male (Table 1). Among 124 female controls, 112 were nurses and 12 were doctors. There was no statistical difference between two groups in BMI ($P = 0.742$), SBP ($P = 0.505$) and DBP ($P = 0.408$) (Table 1).

3.2. Leukocyte distribution characteristics from stress group and controls

Leukocyte distribution characteristics of all subjects are presented in Table 2. The LYM count and LYM ratio were significantly higher in post-stress (2.18 ± 0.59 × 10^9/L and 39.46 ± 7.90%) compared with the controls (1.89 ± 0.52 × 10^9/L and 34.77 ± 6.80%) or pre-stress (1.77 ± 0.50 × 10^9/L and 32.98 ± 6.77%) (all $P < 0.01$, Table 2). Interestingly, stratification analysis based on sex showed that the post-stress LYM count was significantly higher only in female subgroup while stratification analysis based on occupation showed that the post-stress LYM ratio was significantly higher only in nurse subgroup (Table 2).

The MONO count and MONO ratio were significantly lower in post-stress (0.28 ± 0.07 × 10^9/L and 5.10 ± 0.98%) compared with the controls (0.35 ± 0.09 × 10^9/L and 6.55 ± 1.43%) or pre-stress (0.34 ± 0.08 × 10^9/L and 6.49 ± 1.35%) (all $P < 0.01$, Table 2). Similarly, stratification analysis based on occupation showed that the post-stress MONO ratio was significantly lower only in nurse subgroup (Table 2).

The BASO count and BASO ratio were significantly lower in post-stress (0.02 ± 0.01 × 10^9/L and 0.44 ± 0.25%) compared with the controls (0.03 ± 0.02 × 10^9/L and 0.60 ± 0.29%) (all $P < 0.01$, Table 2). Stratification analysis based on sex showed that post-stress BASO count was significantly lower only in female subgroup while stratification analysis based on occupation showed that post-stress BASO count and BASO ratio were significantly lower only in nurse subgroup (Table 2).

The NLR and MLR were significantly lower in post-stress (1.45 ± 0.56 and 0.13 ± 0.03) compared with the controls (1.72 ± 0.58 and 0.19 ± 0.05) or pre-stress (1.90 ± 0.65 and 0.20 ± 0.06) (all $P < 0.01$, Table 2). Stratification analysis based on sex and occupation showed that post-stress NLR was significantly lower only in female subgroup and nurse subgroup (Table 2).

The NEUT ratio was significantly lower in post-stress (53.16 ± 8.13%) compared with the controls (56.20 ± 7.41%; $P < 0.05$) or pre-stress (58.56 ± 7.22%; $P < 0.01$, Table 2). Stratification analysis

Table 1

Demographic and clinical characteristics of controls and stress group.

Variable	Controls (n = 152)	Stress (n = 76)	P
Age (years)	35.0 ± 5.0	34.9 ± 5.8	0.906
Sex (M/F)	28/124	15/61	0.858
BMI (kg/m^2)	22.9 ± 3.0	22.8 ± 2.7	0.742
Occupation(Doctor/Nurse)	34/118	17/59	1.000
SBP(mmHg)	116.3 ± 11.2	117.4 ± 12.3	0.505
DBP(mmHg)	75.6 ± 8.3	74.6 ± 9.2	0.408

M = male; F = female; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 2

Comparison of immune factors in controls and stress group.

Variable		Controls (n = 152)	Pre-stress (n = 76)	Post-stress (n = 76)	P
WBC (10^9/L)		5.47 ± 1.24	5.39 ± 1.17	5.59 ± 1.27	0.594
	M	5.95 ± 1.17	5.74 ± 1.46	6.19 ± 1.27	0.621
	F	5.37 ± 1.23	5.30 ± 1.08	5.44 ± 1.23	0.812
	Doctor	5.66 ± 1.25	5.48 ± 1.28	6.26 ± 1.33	0.165
	Nurse	5.42 ± 1.23	5.37 ± 1.15	5.40 ± 1.19	0.962
NEUT (10^9/L)		3.10 ± 0.92	3.18 ± 0.89	3.00 ± 0.92	0.506
	M	3.17 ± 0.77	3.18 ± 1.02	3.11 ± 0.89	0.965
	F	3.08 ± 0.96	3.18 ± 0.86	2.98 ± 0.93	0.503
	Doctor	3.11 ± 1.00	3.04 ± 0.70	3.24 ± 0.74	0.793
	Nurse	3.09 ± 0.91	3.22 ± 0.94	2.94 ± 0.96	0.259
LYM (10^9/L)		1.89 ± 0.52	1.77 ± 0.50	2.18 ± 0.59**##↑	<0.001
	M	2.19 ± 0.55	2.05 ± 0.68	2.62 ± 0.63#	0.027
	F	1.82 ± 0.49	1.70 ± 0.42	2.07 ± 0.53**##↑	<0.001
	Doctor	2.00 ± 0.50	1.96 ± 0.74	2.54 ± 0.72*#↑	0.009
	Nurse	1.85 ± 0.52	1.71 ± 0.39	2.08 ± 0.51*##↑	<0.001
MONO (10^9/L)		0.35 ± 0.09	0.34 ± 0.08	0.28 ± 0.07**##↓	<0.001
	M	0.40 ± 0.09	0.39 ± 0.12	0.32 ± 0.08*↓	0.049
	F	0.34 ± 0.09	0.33 ± 0.07	0.27 ± 0.07**##↓	<0.001
	Doctor	0.38 ± 0.09	0.36 ± 0.11	0.34 ± 0.08	0.290
	Nurse	0.34 ± 0.09	0.34 ± 0.08	0.27 ± 0.07**##↓	<0.001
EOS (10^9/L)		0.10 ± 0.09	0.09 ± 0.07	0.10 ± 0.07	0.265
	M	0.15 ± 0.13	0.11 ± 0.08	0.11 ± 0.05	0.372
	F	0.09 ± 0.07	0.08 ± 0.06	0.10 ± 0.08	0.340
	Doctor	0.13 ± 0.12	0.10 ± 0.08	0.12 ± 0.05	0.611
	Nurse	0.10 ± 0.07	0.08 ± 0.07	0.10 ± 0.08	0.399
BASO (10^9/L)		0.03 ± 0.02	0.02 ± 0.02	0.02 ± 0.01**↓	<0.001
	M	0.04 ± 0.02	0.02 ± 0.02	0.03 ± 0.02	0.071
	F	0.03 ± 0.01	0.02 ± 0.02	0.02 ± 0.01**↓	<0.001
	Doctor	0.03 ± 0.02	0.02 ± 0.02	0.03 ± 0.02	0.100
	Nurse	0.03 ± 0.01	0.02 ± 0.02	0.02 ± 0.01**↓	<0.001
NLR		1.72 ± 0.58	1.90 ± 0.65	1.45 ± 0.56**##↓	<0.001
	M	1.51 ± 0.45	1.64 ± 0.58	1.22 ± 0.40	0.054
	F	1.77 ± 0.60	1.96 ± 0.65	1.51 ± 0.58##↓	<0.001
	Doctor	1.64 ± 0.64	1.71 ± 0.60	1.32 ± 0.32	0.098
	Nurse	1.75 ± 0.57	1.95 ± 0.65	1.49 ± 0.61*##↓	<0.001
MLR		0.19 ± 0.05	0.20 ± 0.06	0.13 ± 0.03**##↓	<0.001
	M	0.19 ± 0.05			0.001

Table 2 (*continued*)

Variable		Controls (n = 152)	Pre-stress (n = 76)	Post-stress (n = 76)	P
			0.20 ± 0.07	0.13 ± 0.04**##↓	
	F	0.20 ± 0.06	0.21 ± 0.06	0.13 ± 0.03**##↓	<0.001
	Doctor	0.20 ± 0.05	0.20 ± 0.07	0.14 ± 0.04**##↓	0.001
	Nurse	0.19 ± 0.06	0.21 ± 0.06	0.13 ± 0.03**##↓	<0.001
NEUT ratio (%)		56.20 ± 7.41	58.56 ± 7.22	53.16 ± 8.13*##↓	<0.001
	M	53.16 ± 6.56	55.15 ± 7.62	49.60 ± 7.61	0.103
	F	56.88 ± 7.45	59.40 ± 6.93	54.04 ± 8.07*##↓	0.001
	Doctor	54.45 ± 8.13	55.84 ± 7.72	51.70 ± 4.97	0.232
	Nurse	56.70 ± 7.15	59.30 ± 6.96	53.58 ± 8.83*##↓	<0.001
LYM ratio (%)		34.77 ± 6.80	32.98 ± 6.77	39.46 ± 7.90**##↑	<0.001
	M	36.94 ± 6.22	35.92 ± 7.45	42.92 ± 8.14*#↑	0.015
	F	34.28 ± 6.85	32.17 ± 6.46	38.61 ± 7.67**##↑	<0.001
	Doctor	35.84 ± 7.49	35.22 ± 7.61	40.45 ± 5.97	0.061
	Nurse	34.46 ± 6.59	32.25 ± 6.43	39.17 ± 8.40**##↑	<0.001
MONO ratio (%)		6.55 ± 1.43	6.49 ± 1.35	5.10 ± 0.98**##↓	<0.001
	M	6.84 ± 1.45	6.81 ± 1.67	5.27 ± 0.95**#↓	0.002
	F	6.48 ± 1.42	6.41 ± 1.27	5.06 ± 0.99**#↓	<0.001
	Doctor	6.83 ± 1.41	6.65 ± 1.50	5.45 ± 1.08**#↓	0.004
	Nurse	6.47 ± 1.43	6.44 ± 1.32	5.00 ± 0.94**##↓	<0.001
EOS ratio (%)		1.89 ± 1.48	1.60 ± 1.20	1.96 ± 1.37	0.302
	M	2.43 ± 1.96	1.85 ± 1.28	1.83 ± 0.76	0.358
	F	1.76 ± 1.33	1.53 ± 1.18	1.86 ± 0.42	0.361
	Doctor	2.29 ± 1.91	1.87 ± 1.21	1.95 ± 0.73	0.593
	Nurse	1.77 ± 1.32	1.52 ± 1.19	1.83 ± 1.44	0.376
BASO ratio (%)		0.60 ± 0.29	0.47 ± 0.33	0.44 ± 0.25**↓	<0.001
	M	0.63 ± 0.28	0.43 ± 0.33	0.40 ± 0.32*↓	0.011
	F	0.59 ± 0.29	0.48 ± 0.34	0.44 ± 0.26**↓	<0.001
	Doctor	0.59 ± 0.27	0.46 ± 0.33	0.44 ± 0.33	0.153
	Nurse	0.60 ± 0.29	0.48 ± 0.34	0.43 ± 0.23**↓	<0.001

Pre-stress = blood test data of medical workers before providing medical service for Wuhan COVID-19 patients; Post-stress = blood test data of medical workers after providing medical service for Wuhan COVID-19 patients; M = male; F = female; WBC = white blood cell; NEUT = neutrophil; LYM = lymphocyte; MONO = monocyte; EOS = eosinophil; BASO = basophilic granulocyte; NEUT = neutrophil; NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio.

Continuous variables were analyzed using one-way ANOVA test. *p < 0.05, **p < 0.01 *vs* controls; #p < 0.05, ##p < 0.01 *vs* pre-press. The symbols ↑ and ↓ represented significantly higher or lower.

based on sex and occupation showed that the post-stress NEUT ratio was significantly lower only in female subgroup and nurse subgroup (Table 2). However, there was no difference in WBC count, NEUT count, EOS count and EOS ratio between post-stress and controls or pre-stress.

4. Discussion

This study enrolled 76 frontline medical workers and 152 controls, and revealed changes in some immune cells of frontline medical workers after providing medical support for patients with COVID-19 in Wuhan. We found that post-stress medical workers had higher LYM count and LYM ratio, lower MONO count, MONO ratio, NLR, MLR and NEUT ratio than controls and pre-stress, especially in females and nurses. The post-stress medical workers had lower BASO count and BASO ratio than controls. However, WBC count, NEUT count, EOS count and EOS ratio, did not change after providing medical support for Wuhan COVID-19 patients and were not significantly different between two groups.

In this study, some immune cells of frontline doctors and nurses had significant changes after providing medical support for patients with COVID-19 in Wuhan. Infectious disease outbreaks have psychological stress on healthcare workers. Previous studies reported that SARS outbreak has created psychological stress on healthcare workers [4,5]. Recent studies revealed that COVID-19 puts a lot of stress on medical staff and they suffered from psychological burden [6,14]. Stress response is a complex process, in which environmental factors and mental factors are involved to modulate the immune system by activating nervous system [15,16]. Previous studies showed that psychological stress regulates immune response and influences the redistribution of leukocytes through stress responses by activating the sympathetic nervous system (SNS) and hypothalamus–pituitary-adrenal cortex (HPA) axis, which release catecholaminergic neurotransmitters and corticosterone [9,17–19]. Thus, the changes of immune cells of the frontline medical workers may be caused by psychological stress. Moreover, stress has been shown to be immunosuppressive in several viral infections [20]. For example, chronic stressor could down-regulate the immune response to influenza virus vaccination [21]. On the one hand, the changes of immune cells of the frontline medical workers may make them more susceptible to COVID-19. On the other hand, the changes of immune cells of the frontline medical workers indicated them suffered from psychological stress. We think more attentions should be paid to mental health and immune response of frontline medical workers, and provide appropriate psychological interventions for them.

Considerable evidences demonstrated that stress affected males and females potentially to different extents by distinct mechanisms [22,23]. Numerous studies conducted that the sex differences in stress response caused by adrenal and gonadal [24]. For example, testosterone is negatively correlated with adrenocorticotropic hormone and corticosterone or cortisol while estrogen acts on both the hypothalamus and the adrenal gland to stimulate the output of the HPA axis [25,26]. Previous study indicated that women responded to acute stressors in a more pro-inflammatory fashion with increased mobilization of various immune cells than men [24]. Recent study indicated that higher IL-6 and MCP-1 stress response was associated with cardiovascular events among women only [27]. Those results indicated female were more sensitive to psychological stress. In current study, 77.2% of frontline medical workers in stress group were female. Our study further indicated that the changes of immune cells of frontline medical workers were more significant in females.

In this study, 77.6% of frontline medical workers in stress group were nurses. Another findings in our study was that, compared with doctors, nurses had significant changes in immune cells after treating and caring patients with COVID-19. Previous study indicated that that nurses in emergency departments were more likely to develop distress than doctors during the SARS outbreak [28]. The reasons might be that the nurses maintained close and frequent contact with patients, and worked longer than usual. On the other hand, 94.9% of nurses were female and the changes of immune cells of frontline medical workers were more significant in females.

This study has several limitations. Firstly, our study did not perform a self-administered questionnaire to investigate physical symptoms and psychological outcomes, such as depression, anxiety, stress, and post-traumatic stress disorder (PTSD), among frontline doctors and nurses. Secondly, as mentioned above, psychological stress regulates immune response through stress hormones. Our study did not detect the levels of stress hormones, such as adrenaline, noradrenaline and glucocorticoid, among frontline doctors and nurses. Thirdly, the immune system includes the number of immune cells, the level of cytokines and the function of immune cells. Psychological stress regulates immune response and is immunosuppressive in viral infections. Lymphocytes, especially the function of CD8$^+$ cytotoxic T lymphocytes, are important for antiviral. However, our study made some observation on changes of immune cell numbers and their overall composition in the peripheral blood. It would be more complete if the functions of some immune cells, such as T cells, and common cytokine levels in the blood could be assessed. This aspect will be studied in our prospective research. Due to the persistence of the epidemic, the long-term immune response and psychological effects of healthcare workers in more regions deserve further study.

5. Conclusion

In summary, our data indicated that changes of immune cells were found in frontline medical workers providing medical support for Wuhan COVID-19 patients, especially in females and nurses. Those maybe caused by psychological stress and we recommend to pay more attention to mental health of frontline medical workers, and provide appropriate psychological interventions for them.

Author contributions

Conceived and designed the study: Wei Jiang and Zongfang Li. Collected the clinical data: Juanjuan Yang, Qian Wang, Shuqun Zhang and Wei Jiang. Analyzed the clinical data: Juanjuan Yang, Wei Jiang and Qian Wang. Wrote the paper: Juanjuan Yang, Wei Jiang and Zongfang Li.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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