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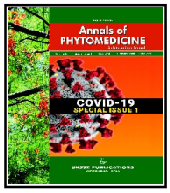

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Special Issue2 (COVID-19)

Effectiveness and outcome of Unani medicine interventions on population at risk of COVID-19

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Abstract

The novel coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The immune response to SARS-CoV-2 can play an important role in disease pathogenesis and clinical manifestations. Considering the antiviral, immuno-modulatory, anxiolytic, anti-inflammatory and antioxidant properties, this open labelled, controlled, interventional, prophylactic study was conducted on individuals at risk in containment zones of different cities of India, *viz.*, Lucknow, Aligarh, New Delhi, Srinagar, Mumbai and Bengaluru. The study focuses on number of patients turning COVID-19 positive, change in ISQ and WHOQOL-BREF scales in both the groups. Apparently, healthy individuals at risk in containment zones were divided into intervention and control groups. The intervention group was further divided into two subgroups. The first subgroup received Unani regimen-I including Unani Joshanda with Khamira Marwareed (KM), the second subgroup received Unani regimen-II including Unani Joshanda with Tiryaq Arba (TA). The control group did not receive any intervention. The duration of intervention was 20 days; follow ups were planned on day 10, day 20 and day 35. A total number of 33021 participants were enrolled in the study, of which 30,931 participants completed the study. It was observed that individuals receiving Unani regimen-I demonstrated lower risk of developing COVID-19 by 74% and those receiving Unani regimen-II by 62% in comparison to the control group. Interventional groups showed highly significant (p<0.001) effect on the quality of life.

1. Introduction

The novel coronavirus disease is caused by severe acute respiratory syndrome coronavirus 2. The immune response of an individual against to SARS-CoV-2 can play a vital role in disease pathogenesis and clinical manifestations (Petrova, 2018; Tan and Hardeland, 2020). Therefore, it is important to utilize any substance that can limit the viral effects. Developing antiviral drugs for COVID-19 is a challenge as viruses can vary in its effects on the immune system. SARS-CoV-2 activates antiviral immune responses and may also cause uncontrolled inflammatory responses, which is characterized by marked pro-inflammatory cytokine release in severe COVID-19 patients, leading to lymphopenia, lymphocyte dysfunction, monocyte and granulocyte abnormalities (Qin *et al.*, 2020). These SARS-CoV-2 induced immune abnormalities may lead to infections by microorganisms, septic shock, and severe multiple organ dysfunction (Meradand Martin, 2020). Therefore, underlying mechanisms for immune abnormalities in with COVID-19 patients must be explained to guide clinical management of the disease. Moreover, rational management of the immune responses to SARS-CoV-2 may be key to successful treatment, which includes enhancing antiviral immunity while inhibiting systemic inflammation (Petrova, 2018; Tanand Hardeland, 2020). Immunomodulators may be promising alternatives to classical treatment of the viral diseases for enhancing host defence responses. In such a scenario, immune modulators better equip the host in defending itself against invading micro-organisms; does not involve the use of organism-specific therapeutics and enhances better host originated mechanisms to participate in the immune response (Tzianabos, 2000).

The preventive measures for such epidemic diseases are mainly aimed towards the prevention of spread of infection by creatinga wareness about hygiene, antiseptic measures and promotion of general health. Major onus of these measures is to improve the host defence (Nikhat, 2020).

Unani medicine has placed great emphasis on the prevention of disease and promotion of health. The system has described six essential factors (*Asbab-e-Sitta Zarooriyah*) for the maintenance of health. Improving immunity is one of the key approaches for prevention of disease and promotion of health in Unani medicine. Therefore, Unani medicine has advocated a strategy to enhance immunity and to provide symptomatic relief in upper respiratory tract infection (Sina, YNM).

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Khamira Marwareed (KM), a classical standardized Unani poly-herbal formulation is a general tonic and is used in neuro-asthenia (*Zof-e-Asab*), cardiac-aesthenia (*Zof-e-Qalb*), palpitation (*Khafkhan*), cerebro-asthenia (*Zof-e-Dimagh*) and polydiypsia (*Atash-e-mufrit*) (Anonymous, 2006; Khan *et al.*, 2011). Another classical standardized Unani polyherbal formulation *Tiryaq Arba* (TA) is classically attributed with antidote (*Tiryaq*), deobsturent (*Mufatteh*), antispasmodic (*Daf-e-tashannuj*) and diuretic (*Mudir*) properties. It is used in the treatment of epilepsy (*Sara*), paralysis (*Falij*), and phlegmatic diseases (*Balghami-amraz*) (Arzani, 2009; Bagli, 2012; Ahsan and Rani, 2019).

The Unani Joshanda (decoction) consisting of *Behidana* (seed of *Cydonia oblonga* Mill.; Angiosperms: Rosaceae), *Unnab* (fruit of *Zizyphus jujuba* Mill.; Angiosperms: Rhamnaceae) and *Sapistan* (fruit of *Cordia myxa* Linn.); Angiosperms: Boraginaceae) has evidences of its antiviral, immune modulator, anti-oxidant and broncho-relaxant activity (Al-Bayatyand Al-Tahan, 2008; Hamauzu *et al.*, 2005; Chi *et al.*, 2015). Quality control studies of the Unani Joshanda conducted by the Central Council for Research in Unani Medicine have demonstrated that the preparation is free from any toxic substances. Similarly, *insilico* studies are indicative of its potential to inhibit the S protein and Mpro of SAR-CoV-2 besides, its ability to boost immunity.

Keeping in view, the efficacy of these Unani formulations, the current study was carried out in the identified containment zone/ quarantine facility with at least one confirmed COVID-19 positive case. The objective of the study was to compare number of individuals turning COVID-19 positive receiving Unani regimen-I and II with those receiving no intervention.

2. Materials and Methods

The present study was conducted in the identified containment zone/ quarantine facility in the respective cities through Central Research Institute of Unani Medicine (CRIUM), Lucknow (U.P.), Regional Research Institutes of Unani Medicine (RRIUM), Aligarh (U.P.), Srinagar (J and K), New Delhi and Mumbai (Maharashtra) and National Institute of Unani Medicine (NIUM), Bengaluru (Karnataka) during May to August 2020.The protocol was prepared by a multidisciplinary group of scientists of the CCRUM and vetted by the Interdisciplinary AYUSH Research and Development Task Force setup by Ministry of AYUSH, Government of India.

Subsequent to ethical approval from Central Ethics Committee (CEC) of the CCRUM (Central Council for Research in Unani Medicine) and CTRI registration (CTRI/2020/05/025254), individuals of either gender in the age group of 18-68 years were enrolled in the study after obtaining their written informed consent. Symptomatic or asymptomatic COVID-19 positive patients, pregnant or lactating women, persons exhibiting severe primary respiratory disease or related complications that can be associated with COVID-19, serious critical or mental illness, uncontrolled, unstable co-morbidities, immuno-compromised patients or those on immune-suppressants and steroids, individuals having a past history of allergy to any Unani interventional medicine were excluded. The study was open label, controlled, interventional, non-randomized, community-based clinical study. The sample size was 10,000 in each arm bringing the total sample size of the study to 30,000 complete cases (excluding dropouts).

Table 1: Ingredients of Unani regimen

Unani name	Botanical Name	English name	Quantity
***Khamira Marwareed* (KM)**			
Marwareed	Pearls from *Mytilus margaritiferus*	Pearl	25 g
Tabasheer	Root of *Bambusa ardundinacea* (Retz) Willd.	Common bamboo	25 g
Sandal	Wood of *Santalum album* Linn.	Sandal	25 g
Ambar	Ambra grasea	Ambar	10 g
Arq e Gulab	*Rosa damascena* Mill. distillate	Rose	1L
Arq Baidmushk	*Salix capera* Linn. distillate	Pussy willow	1L
Qand safed		Sugar	1.2 kg
***Tiryaq Arba* (TA)**			
Juntiyana	Root of *Gentiana lutea* Linn.	Yellow gentian	1 part
Zarawand Taweel	Root of *Aristolochia longa* Linn.	Long aristolochia orsarrasine	1 part
Mur Makki	Resin of *Commiphora myrrha* (nees)Engl.	Myrrh	1 part
Habbul Ghar	Leaves of *Laurus nobilis* Linn.	Bay laurel	1 part
Asal/Qand safed		Honey or sugar	Q.S.
Unani Joshanda			
Behidana	Seed of *Cydonia oblonga* Mill.	Quince fruit	5 g
Unnab	Fruit of *Zizyphus jujube* Mill.	Common jujube	5 in number
Sapistan	Fruit of *Cordia myxa* Linn.	Sebsten plum	5 in number

The selected individuals were divided into two groups, *i.e.*, intervention and control groups. The intervention group was further divided into two subgroups. Both the subgroups received 125 ml of Unani herbal decoction consisting of *Behidana* (seed of *Cydonia oblonga* Mill.), *Unnab* (fruit of *Zizyphus jujuba* Mill.) and *Sapistan* (fruit of *Cordia myxa* L.) in the evening. Additionally, *Unani regimen* -I subgroup received 5 g of *Khamira Marwareed* (KM) in the morning whereas, *Unani regimen*-II subgroup received 5 g of *Tiryaq Arba* (TA) in the morning (Table 1). The control group received no medicine. All participants were asked to follow the general measures/guidelines issued by the Ministry of Health and Family Welfare/Ministry of AYUSH, Govt of India and World Health Organization (WHO)/State government and local health authorities. Any mandatory general measures recommended by Government Health Authorities were given in both arms of study. The drugs of the same batch were dispensed for the complete treatment period at first visit itself. *Khamira Marwareed* bearing batch no. MKM034-35 and *Tiryaq Arba* bearing batch no. IME0099 were provided by CCRUM. The duration of the protocol therapy was 20 days.

The data was collected through door-to-door survey at day 0 (baseline) and day 20 (at the end of the study) and telephonically on day 10 and day 35 for post-trial access. The data was recorded in a Case Record Form (CRF). The objective of the study was to compare number of individuals turning COVID-19 positive receiving *Unani regimen*-I and II with those receiving no intervention. Participants were assessed on the basis of turning COVID-19 positive receiving *Unani regimen*-I and II with those receiving no intervention.

They were also assessed on Immune Status Questionnaire (ISQ) and WHO QOL-BREF Questionnaire. Any adverse events occurring during the period were recorded in the CRF. Participants who developed COVID-19 symptoms with positive RT-PCR were notified to the concerned district authorities for shifting to a COVID-19 treatment facility.

The data was analysed based on per protocol analysis. Objective and subjective parameters were analysed to univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) Ver.25.0.

Table 2: Age-wise distribution of the patients in Intervention and Control group

Age group (Years)	Gender		Total
	Male (%)	Female (%)	
18-28	5445 (31.03%)	4512 (33.72%)	9957
29-39	4365 (24.87%)	3682 (27.52%)	8047
40-50	4472 (25.48%)	3186 (23.81%)	7658
51-60	2287 (13.03%)	1480 (11.06%)	3767
>60	981 (5.59%)	521 (3.89%)	1502
Total	17550	13381	30931
Mean ± SD	**37.70 ± 13.44**	**36.28 ± 12.91**	**37.09 ± 13.23**
Median	**36**	**35**	**35**

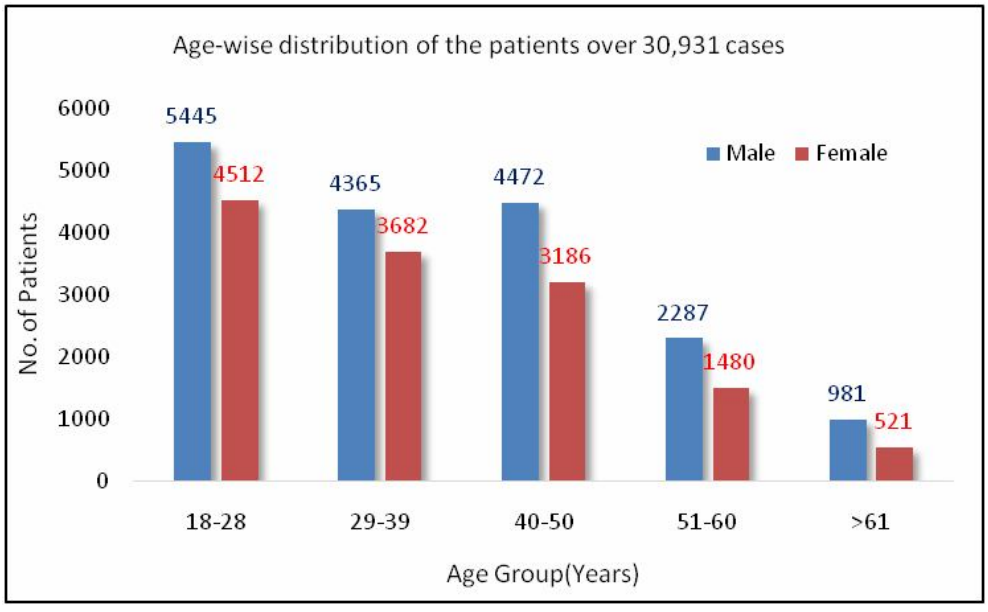

Figure 1: Age-wise distribution of the patients in Intervention and Control group.

Table 3: Distribution of Temperament according to Age and Gender

Age (in Years)	Temperament								Total	
	Damvi		Saudavi		Safravi		Balghami			
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
18-28	2661	1964	569	526	940	814	1275	1208	**5445**	**4512**
29-39	1782	1343	600	443	686	691	1197	1205	**4365**	**3682**
40-50	1437	820	694	478	837	588	1504	1300	**4472**	**3186**
51-60	581	306	456	282	408	238	842	654	**2287**	**1480**
>60	236	120	207	119	165	73	373	209	**981**	**521**
Total	6697	4553	2526	1848	3036	2404	5191	4576	17550	13381

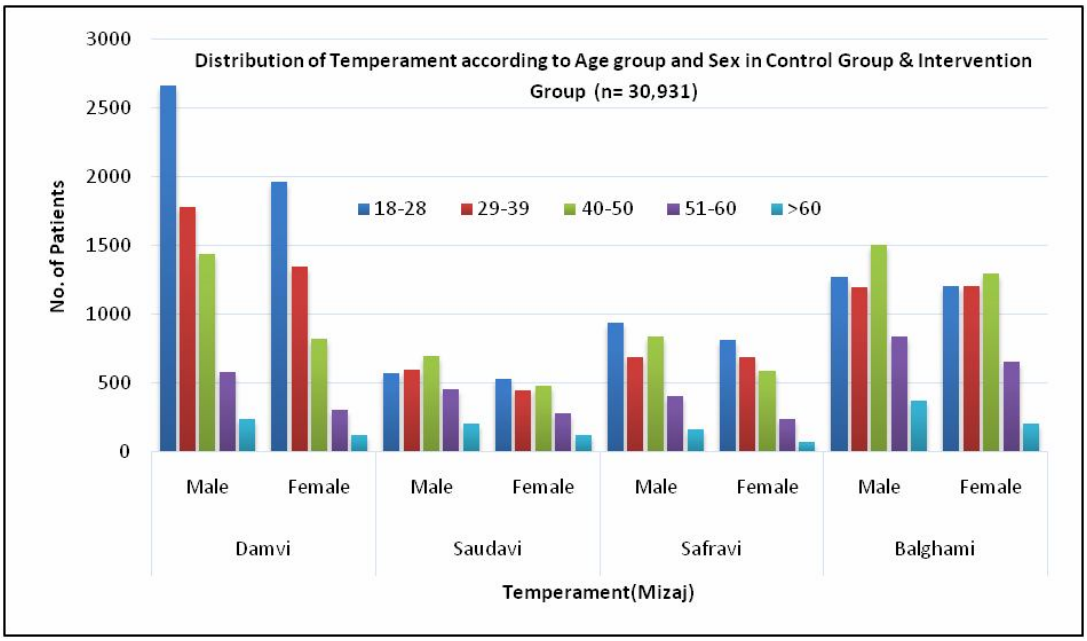

Figure 2: Distribution of Temperament according to Age and Gender in Intervention group.

3. Results

In the present study, a total no of 33021 participants were enrolled in the study from the identified containment zones. Out of these, 30931 (93.67%) participants completed the study. A total of 1673 (5.07%) dropped out because of non-compliance or lost to follow up whereas, 417 (1.26%) developed symptoms associated with COVID-19 like fever, headache, muscle pain, cough.

3.1 Demographic findings

Maximum number of participants 7931 (25.64%) were from Mumbai (Maharashtra), followed by 7588 (24.53%) participants from New Delhi, 4699 (15.20%) participants from Lucknow, 4617 (14.93%) participants from Srinagar (Jammu and Kashmir), 3048 (9.85%) participants from Aligarh (Uttar Pradesh) and 3048 (9.85%) participants from Bengaluru (Karnataka). This depicts the pan Indian expression of the data from various ethnic groups.

The mean age of the participants was 37.09 ± 13.23. Of these, 9957 (32.19%) participants were within the age group of 18-28 years. 56.74% of the participants were male with a mean age of 37.70 ± 13.44, while the mean age for females was 36.28 ± 12.91 (Table 2, Figure 1).

A total number of 6697 (21.65%) males with *Damvi* (sanguineous) temperament participated in the study. This was followed by 5191 (16.78%) males with *Balghami* (phlegmatic) temperament (Table 3, Figure 2).

3.2 Relative risk of developing COVID-19

The study showed that 0.92% and 1.32% participants in Intervention group receiving *Unani regimen*-I and *Unani regimen*-II, respectively developed COVID-19 or COVID like symptoms in comparison to 3.49% participants in control group. Individuals receiving *Unani regimen*-I had 74% (relative risk ratio 0.26) where as those receiving *Unani regimen*-II had a 62% (relative risk ratio 0.38) lower risk of developing COVID-19 (Table 4 A, B).

3.3 Immunity status as assessed with Immunity Status Questionnaire (ISQ)

The study showed that the mean change in total ISQ score of *Unani regimen*-I group over control group is 0.622 and that of *Unani regimen*-II group over control group is 0.79 (Table 5).

3.4 Quality of life as measured with WHO QOL BREF

The study showed that the mean change in quality of life of participants in Intervention group receiving *Unani regimen*-I and Unani *regimen*-II over control group is 0.32 and 0.95 in the physical domain, 0.56 and 1.11 in psychological domain, 0.05 and 0.3 in social domain and 0.31 and 0.29 in environmental domain, respectively (Table 6, Figure 3).

Table 4A: Relative Risk Ratio in the *Unani regime*-I and Control group

Treatment group	COVID-19 suspected cases (positive)	Negative cases	Total	Cumulative incidence
Intervention group	95	10,207	10,302	95/10302 = 0.0092
Control group	358	9,882	10,240	358/10240 = 0.0349
Risk ratio = $\frac{0.0092}{0.0349}$ = 0.26				
Percentage Relative Effect (1-RR)*100 = 74%				

Table 4B: Relative Risk Ratio in the *Unani regime*-II and Control group

Treatment group	COVID-19 suspected cases (positive)	Negative cases	Total	Cumulative incidence
Intervention group	137	10,252	10,389	137/10389 = 0.0132
Control group	358	9,882	10,240	358/10240 = 0.0349
Risk ratio = $\frac{0.0132}{0.0349}$ = 0.38				
Percentage Relative Effect (1-RR)*100 = 62%				

Table 5: ISQ Scores parameter wise distribution of subjects

ISQ Scores	Intervention group (TA) (n = 10389)		Intervention group (KM) (n = 10302)		Control group (n = 10240)		Intervention group (TA)		Intervention group (KM)		Control group	
	Follow-up Period		Follow-up Period		Follow-up Period		Improvement (Mean changes)					
	Base Line	End of the study	Base Line	End of the study	Base Line	End of the study	Base Line vs End of the study		Base Line vs End of the study		Base Line vs End of the study	
Sudden high fever	0.54 ± 0.69	0.28±0.49	0.62±0.61	0.37±0.54	0.38±0.55	0.33±0.68	-0.259	↓	-0.256	↓	-0.053	↓
Diarrhoea	0.65 ± 0.67	0.48±0.63	0.71±0.59	0.54±0.58	0.37±0.56	0.27±0.52	-0.177	↓	-0.173	↓	-0.096	↓
Headache	1.26±0.80	1.10±0.90	1.07±0.64	0.91±0.64	0.71±0.79	0.56±0.79	-0.166	↓	-0.162	↓	-0.145	↓
Skin problems (e. g. acne&eczema)	0.81±0.94	0.64±0.84	0.64±0.81	0.56±0.77	0.46±0.74	0.43±0.73	-0.164	↓	-0.073	↓	-0.038	↓
Muscle and joint pain	1.86±1.22	1.69±1.34	1.08±0.95	0.96±0.90	0.78±0.87	0.68±0.87	-0.170	↓	-0.122	↓	-0.096	↓
Common Cold	1.17±0.74	0.83±0.83	1.06±0.55	0.69±0.66	0.81±0.75	0.58±0.77	-0.348	↓	-0.370	↓	-0.229	↓
Coughing	0.82±0.66	0.53±0.61	0.86±0.58	0.59±0.64	0.68±0.76	0.49±0.77	-0.293	↓	-0.268	↓	-0.192	↓
I score my general health	7.82±2.03	8.61±1.64	4.17±3.43	4.26±3.68	7.28±1.44	7.58±1.32	0.788	↑	0.095	↑	0.294	↑
I Score my immune functioning	7.91±1.97	8.70±1.53	4.36±3.59	4.38±3.77	7.31±1.40	7.62±1.27	0.785	↑	0.020	↑	0.311	↑
ISQ Scores Final Score	**6.13±1.91**	**7.34±2.17**	**7.02±1.82**	**8.06±1.65**	**8.06±1.33**	**8.48±1.44**	**1.207**	**↑**	**1.039**	**↑**	**0.417**	**↑**

Table 6: WHO-QOL-BREF questionnaire wise distribution of subjects

WHO-QOL-BREF domains	Intervention group (TA) (n = 10389)		Intervention group (KM) (n=10302)		Control group (n = 10240)		Intervention group (TA)	Intervention group (KM)	Control group
	Mean ± SD						Improvement (Mean changes)		
	Base line	End of the study	Base line	End of the study	Base line	End of the study	Base line vs End of the study	Base line vs End of the study	Base Line vs End of the study
Domain 1 (Physical)	21.75± 2.71	23.14± 3.30	22.95± 3.67	23.72± 3.60	21.61±2.76	22.05± 2.82	1.39	0.76	0.44
Domain 2 (Psychological)	18.81± 2.58	20.10± 2.67	18.82± 3.23	19.56± 2.96	18.45± 2.79	18.63± 2.45	1.29	0.73	0.18
Domain 3 (Social)	9.51± 1.71	10.06± 1.68	9.21± 1.74	9.51± 1.59	9.15± 1.67	9.40± 1.68	0.55	0.30	0.25
Domain 4 (Environmental)	24.18± 3.96	24.62± 3.10	22.64± 4.60	23.10± 4.10	23.66± 4.37	23.81± 3.96	0.44	0.45	0.15

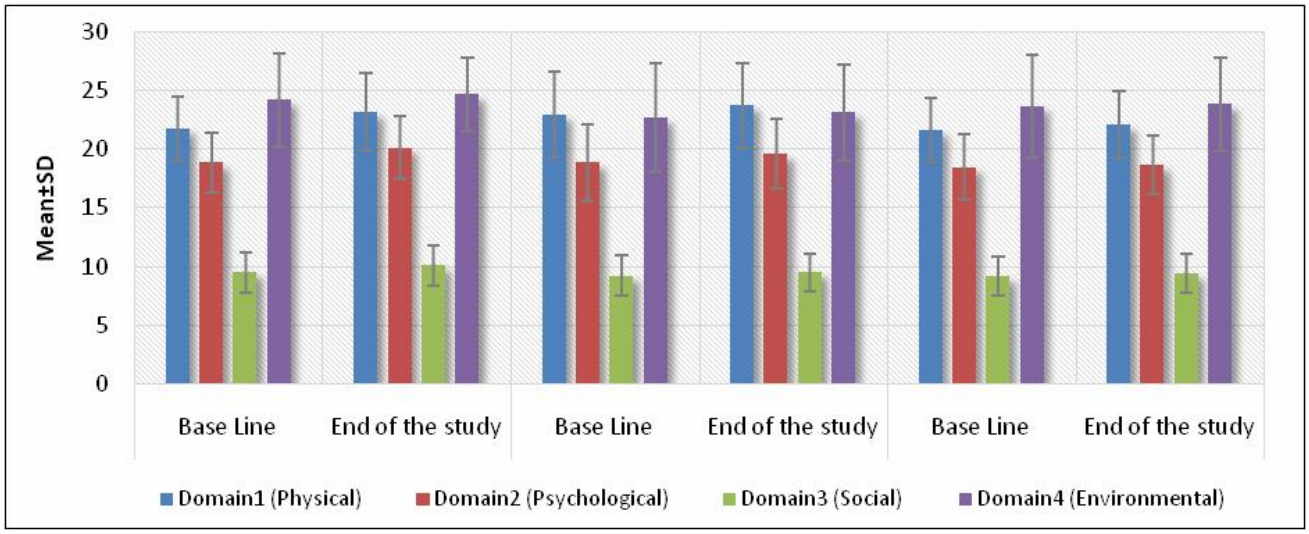

Figure 3: Distribution of patients according to WHO-QOL-BREF questionnaire.

4. Discussion

In the present study, a total no of 30931 participants completed the study. It was observed that male participation was higher with 4169 more males participating in the study bringing the male to female ratio to 1.3: 1. The mean age difference between the male and female is 1.42 ± 0.53 years.

Mizaj (Temperament) is a unique characteristic of an individual developed due to interaction between different elements in the body affecting the normal physical and emotional state/reaction and defining morphological, physiological and psychological features of the individual (Mojahedi *et al.*, 2014). *Damvi* (sanguineous) temperament participants out numbered other *Mizaj* (temperament) as *Damvi* (sanguineous) temperament individuals are attributed with optimistic attitude and probably that is why we have maximum number of participants from that temperament (Itrat, 2014).

It was observed that majority of the symptoms were present in all the groups between 10-20 days. This decreased susceptibility in the intervention group may be attributed to the immune-modulating effect of the *Unani regimen*-I and II. Interventional formulations, *i.e.*, KM modulates the cell mediated immuno responses *via* cytokine modulation within 10-14 days (Khan *et al.*, 2009) and TA increase CD3, CD4 and CD8 cells (Bagli, 2012). The immune modulatory effect of the ingredients of *Unani Joshanda* (decoction) may have attributed to the effect in the intervention group (Al-Bayaty and Al-Tahan, 2008; Hamauzu, 2005; Chi *et al.*, 2015).

It is observed that there was an improvement in the immunity status of the participants in intervention and control groups. However, in the intervention group, the final ISQ scores in *Unani regimen*-II subgroup are marginally 0.168 (Mean changes) better than the *Unani regimen*-I subgroup. This could be because ingredients of KM and TA possess immunestimulatory and anti-oxidant activity (Mahboubi, 2016; Ansari, 2020).

The quality of life of the participants was assessed on WHO QOL BREF. The questions in physical domain were pertaining to activities of daily life, dependence on medical substances and aids, agility, mobility, pain, sleep, rest and work capacity. Under the psychological domain perception towards body image, feelings, self-esteem, believes, thinking, learning, memory and concentration were analysed.The social and environmental domains cannot be altered therapeutically, however, when the body is agile and the mind at peace, resilience increases.

The improvement in quality of life in the intervention group may be attributed to the immune-stimulatory, anti-inflammatory and anti-oxidant effect of the *Unani regimen*-I and II (Gadir, 2014; Mahboubi, 2016; Ansari, 2020). It was also observed that none of the participants have reported any adverse events during the study.

5. Conclusion

It is concluded that out of the 33021 participants enrolled in the study from the identified containment zones, 30931 (93.67%) participants completed the study. The study provides evidences of relative improvement in the quality of life in all domains including physical, psychological, social and environmental.

An improvement in the immunity status of the participants in intervention and control groups was observed. However, in the intervention group, the final ISQ scores in *Unani regimen*-II subgroup are marginally better than the *Unani regimen*-I subgroup. *Khamira Marwareed* (KM) an immune-modulator and general tonic offered 74% prophylactic protection against COVID-19; whereas TA an antidote provided 62% prophylactic protection against COVID-19.

It is concluded that *Unani regimen*-I and Unani *regimen*-II were found effective in decreasing the susceptibility of developing COVID-19 or COVID like symptoms among the participants. The *Unani regimens* also improved the immunity status and quality of life. No adverse events were reported during the study.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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