Original Research Article (Clinical)

Immune status determined as per guidelines of Ayurveda found associated with clinical outcomes of COVID-19 disease — Results of a cross-sectional pilot study

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A B S T R A C T

Background: A key public health priority during the emergence of a novel pathogen is probing the factors contributing in clinical severity of the disease COVID-19. Moreover, analysis of the determined clinical outcomes is required and thus, modifiable predictor values need to be identified. In Ayurveda, outcome of a disease is a multivariate function and this exploratory work is an attempt to identify one such factor “Vyadhiksamatwa” (immune status).

Materials and methods: A questionnaire-based, cross-sectional study was conducted in fifty diagnosed cases of COVID-19. Study participants were subjected to a questionnaire to assess relationship between the three determinants of the disease - exposure, clinical severity, and Vyadhiksamatwa.

Results: Clinical severity was found strongly correlated with Vyadhiksamatwa with the value of Pearson Correlation - 0.740 significant at the 0.01 level (2-tailed).

Conclusion: In the determination of clinical severity of disease, there are two epidemiological factors responsible – extrinsic (exposure) and intrinsic (Vyadhiksamatwa). It has been observed that higher the value of Vyadhiksamatwa of an individual, lesser will be the clinical severity of the disease in that individual. Vyadhiksamatwa can alter the host response to infections.

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1. Introduction

The World Health Organization declared the outbreak of the coronavirus disease 2019 (COVID-19), caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a public health emergency of international concern in the year 2020 [1]. The disease is spreading globally despite multiple efforts done worldwide to contain it [2]. Initially, the clinical severity of COVID-19 disease was categorized under mild, moderate, and severe illness. However, with the global outbreak, asymptomatic category is also observed that has no symptoms but can transmit the virus to others [3]. The percentage of asymptomatic infection in an electronic meta-analysis was found to be 15.6% (95% CI, 10.1%-23.0) [4]. There is variable presentation of the disease among different age groups and serious manifestations can be commonly observed in immunocompromised, old-aged, and comorbid conditions and less severe in the pediatric age group, implying the role of immunity in pathogenesis of COVID-19 [5–7]. Studies revealed that the immune system plays a crucial role in response to SARS-CoV-2 with significant difference among severe and non-severe patients [8]. The outcome of clinical infection majorly depends on the capacity in mounting effective anti-viral immune responses of an individual in time, so as to control the viral spread, preventing multiple organ injuries and speed-up recovery from infection [9]. Therefore, it is necessary to understand basic pathological and immunological process responsible for COVID-19 for formulating the therapeutic guidelines on a rational basis [10]. In Ayurveda, the concept of Vikaravighatabhava (disease inhibiting factors) and Vikaravighatabhavabhava (absence of disease inhibiting factors)
determines the manifestation and progression of the disease. Based on the amalgamation of the three factors, (Nidana, Dosa, and Dushya), as well as Vyadhiksamatwa Bala (immunity) of an individual, the progression of disease can be mapped [11, Nidana Sthana; Prameha Nidana, Chapter 4/4]. Acharya Charka has mentioned that even unwelcome food does not produce disease in all individuals, suggesting that one’s immune system is instrumental in manifestation of the disease. This can be implicated further as Vyabhibalavrodhitrata (resistance against disease) and Vyadhutrpadaka Pratibandhakatwa (resistance against agents causing the disease) [11, Sutra Sthana; Vidhishonitiya Adhyaaya, Chapter 28/7]. When the external etiological factors vitiate the Doshas, the morbid Doshas further vitiate Dusyas (body tissues) leading to Dhatu Vaishyamaya i.e., disease. Dosa and Dusya are the fundamental factors responsible for the occurrence of disease. Vyadhiksamatwa Bala also acts as an antagonist for pathogenesis. “Bala” is the term employed for Kapha [11], Sutra Sthana; Kiyanta Shiraseeya Adhyaaya, Chapter 17/117; Rukta Dhatu [11, Sutra Sthana; Vidhishonitiya Adhyaaya, Chapter 24/4]; Vayu [11, Chikitsa Sthana; Satamya Sevana Sthana; Vidvatayadi Chikitsa, Chapter 28/3.]; Agni [11, Chikitsa Sthana; Vidvatayadi Chikitsa, Chapter 15/3–4.] [12, Chikitsa Sthana; Grahanti Chikitsa, Chapter 12/31, and Oja [13, Sutra Sthana; Doshadhatu, malakshayavriddhi Viganyaniya, Chapter 15/19] in classical texts. Vyadhiksamatwa refers to the biological defense potential to fight against the onset of disease and arrest further progression of the disease so as to maintain the homeostasis. Roga Bala (strength of the disease) is assessed by the strength of Nidana, as there is major role of Pradhanika Hetu (major etiological factor) i.e., SARS-CoV-2 in the manifestation of the disease COVID-19 which is a non-modifiable entity, while Rogi Bala (strength of patient) can be interpreted by six factors - Satamya Sevana (antigen in low dose and with respect to adhikaran tantrayukti intake of wholesome diet), Agni (power of digestion, assimilation, and metabolism), Vayu (age), Snigdha diet (unctuous food), Vayamamashakti (exercise power) and Bala (strength) of the individual, and except age all other factors are modifiable [11, Sutra Sthana; Atreyabhadrakapiya Adhyaaya: Chapter 26/106].

The primary objective of the study was to evaluate the factors contributing to the clinical severity of COVID-19 illness along with determining the relationship among these factors. Additionally, the second objective was to assess the modifiability of their components.

2. Material and methods

2.1. Study design

A cross-sectional, observational study using the survey strategy to collect data was conducted in COVID Testing Centre at All India Institute of Ayurveda (AIIA), New Delhi from August 22, 2020 to September 9, 2020.

2.2. Setting

The study was conducted among the population visiting the COVID Testing Centre, AIIA, New Delhi and individuals who were found to be positive by Rapid Antigen test (RAT) for SARS-CoV-2 were included in the study.

2.3. Study population

The pilot study employed 50 patients diagnosed with COVID-19 illness through RAT. Individuals aged 18–60 years of either sex, willing to participate in the study were included. A written informed consent was obtained from them at the time of testing in the COVID Testing Centre, AIIA, New Delhi. All eligible participants were informed regarding arrangement of a scheduled phone call interview on the same day of their testing. The purpose of the survey and time required to complete the survey questionnaire was informed to them. The patients were interviewed through questionnaires via telephonic conversation.

2.4. Data collection

2.4.1. Development of survey questionnaire (ref: Annexure 1)

An electronic, structured questionnaire was used by the interviewers to conduct the telephonic interview with the study participants. To reduce interviewer bias, all the interviews were conducted by the same researcher. Collected information covered the following: demographic characteristics and epidemiological variables including exposure, vyadhiksamatwa, and clinical severity were measured. The purpose of the questionnaire was to assess the prevalence of three variables in the study participants. For preparation of the questionnaire, literature was searched with respect to these factors. The methodology included the following steps - a) Review of literature – Classical texts of Ayurveda and contemporary science b) Extraction of relevant material c) Translation of concepts in questionnaire format as mentioned in Table 1. d) Scoring and data management. The data that was captured using the data collection form.

Exposure factor or risk assessment is a product of individual exposures and individual behavioral elements [14]. Thus, was categorized under the domains of behavior, contact history, and social policy. Behavioral domain included practices of adherence to infection prevention and control (IPC) during interactions, following social-distancing norms, and following government guidelines. Direct/indirect contact history included residential factor, occupation, travel history, and mass gatherings. Data from the Arogya Setu app, an application that notifies the users if they are in vicinity of a diagnosed positive patient, was also incorporated [15]. Clinical severity of the illness was assessed, based on the grading system of symptoms [16]. Vyadhiksamatwa factor was assessed through factors stated as above in introduction. Though

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| Table 1: Exposure, Host factor and Clinical Outcomes assessed in the subjects. |
|-----------------------------------------------|
| Exposure | Host factor | Clinical Outcomes (Grading) |
| Health impact assessment (Locality/Community) | Incompatible items (satmyato/pataya va’) | Pyrexia |
| Ventilation associated event (VAE) | Strong digestive power (Diptagni) | Cough |
| Housing (Room Density) | Age (vaya) | Fatigue |
| Personal Protective Equipment (mask/hand hygiene/social distancing) | Dietary patterns favouring unctuous food (Snigdha ahara) | Aches/Pains |
| Contact tracing | Physical exercise (Vyáyama) | Anorexia |
| Occupational history | Strength (bala) | Sore throat |
| | | Conjunctivitis |
| | | Headache |
| | | Nausea & Vomiting |
| | | Ageusia |
| | | Dyspnoea |
there are varying definitions of Vyadhiksamatwa, the purpose of the study was to understand the dynamic nature of this factor. Thus, this aspect was selected as it also had a rational value in applied science. Exposure to an exogenous entity can be considered viruddha ahara (incompatible food). This type antagonism reaction is neutralized through Vyadhiksamatwa. This is further a function of suitability to that antigen, exposure in small quantity/mild exposure, strong digestive power, age-dependent, and in persons having function, physical exercise, and strength. The exogenous factor i.e., exposure was already assessed, so as to avoid repetition; only un-wholesome dietary part was considered and thus enquired. All the items were scored on the scale of frequency.

2.5. Bias

The questionnaire was administered on the very same day when the patient was diagnosed with COVID-19 illness so as to mitigate the effect of amnesic bias.

2.6. Statistical methods

Descriptive statistics (n, mean, and standard deviation) of the demographic and other participant characteristics were calculated. Every analysis was performed on observed data (no imputation was used to the replace missing values). A cross-tabulation with Chi-square test was used to assess the association between the three variables mentioned. All statistical analyses were performed using SPSS-v.26 for Windows.

2.7. Ethical considerations

This study was approved by the institutional review boards of AIHA, New Delhi. Permission from Institutional Ethics Committee was obtained (IEC-AIHA/2020-P 48) and Clinical Trial Registry of India was done (CTRI/2020/08/027,494). A written informed consent was obtained from the participants on the day of testing.

3. Results

3.1. Descriptive data

Fifty diagnosed cases of COVID-19 were included in the study. The mean age of the patients enrolled in the study was 35.5 years. Thirty-two participants were male and 18 were female. Of the total number of participants, 58% had positive contact history and 56% of the population was found to have an education level above graduate. The mean age of the patients enrolled in the study was 35.5 years. Of the total participants, 8% were health workers per-

3.2. Outcome data (assessment of variables in the population)

3.2.1. Exposure

Mean value of this variable was found to be 17.52. Exposure score was calculated by measuring factors such as host behavior (personal hygiene practices), contact history, social distancing, population density, and ventilation. Each of the variable was scored between 0 (Nil) to 3 (Severe) and 0.76% of them were localized in an area of high-room density (more than 2). Most of the times and 84% of them were regularly wearing mask. Social distancing was maintained properly by only 70% of the population and 44% had poor ventilation in their houses. Only 6% of them were following immunity booster measures suggested by Government of India.

3.2.2. Clinical severity

During the emergence of a completely novel pathogen, the most critical health question pertains to the spectrum of illness presentation or severity profile. The mean value of clinical score was found to be 5.3. It was determined through gradations of symptoms. Of the total population, 18% were asymptomatic. Among the symptomatic ones, the most common presenting complaint was fever (56%), followed by cough (52%). Only 1% of them had nausea and vomiting. 4% of the patients had breathing difficulty, and 9% complained of headache. Anosmia was present in 12% of the population, and dysgeusia in 14%.

3.2.3. Vyadhikshamata - immune status

The mean value for this variable was found to be 14.52. The score can be assessed through the functional outcome of multiple and definite factors contributing to this entity, mentioned by Acharya Charaka. 58% of the population was in Madhyamvaya (middle-age group) category. 58% of the cases had a normal built or body type. Assessment of Agni was done on two parameters — Abhyavaharana shakti (capacity of food intake) and Jarana Shakti (capacity to digest). It was found that 60% of them had above average Abhyavaharana Shakti and only 22% of them had good Jarana Shakti. 40% of them gave a history of consumption of unctuous food on regular basis. Vyuymana (exercise) was a regular activity present in only 14% of Cases.

3.3. Assessment of relationship between the variables

Median value for clinical score, Vyadhikshamata and exposure factor are 3.5,15.0 and 17.5 respectively as shown in Fig. 1. The correlation between clinical score and Vyadhikshamata was found to highly significant ($r = -0.74$, $p < 0.001$), indicating that higher value of Vyadhikshamata enforces lower clinical manifestation of the disease. However, exposure factors (like use of mask, social distancing, and others) could not reveal any significant relationship.

4. Discussion

4.1. Stratification of host responses based on Vyadhikshamata

An urgent need for effective therapeutics in matters of public health concern, require a gross understanding of the epidemiology...
and pathogenesis of the disease. The determinants of a disease severity seem to stem from host factors rather than viral genetic variations [17]. Host factors instrumental in the outcome can be classified as extrinsic and intrinsic. Two types of factors were measured through interviewing the subjects. It has been clinically correlated with other physiological forms like Bala and Oja (essence of all seven dhatu). Factors attributing to Bala can be constitutional, temporal or even acquired [18]. The study deals with the application of a descriptive model of pathogenesis mentioned in Ayurveda “Vikrati vighata bhava abhava”.

Based on the research model, stratification of exposed population can be done on the basis of host defense potential. The subjects having the Vyadhiksamatwa score of more than the median value (15.00) had a better clinical outcome (i.e., lesser clinical score) than those subjects who had a score of less than the median value. Fig. 2 shows this distribution.

4.2. An empirical equation of clinical outcome

The results of the study have provided an empirical equation of outcome. It is a function of three variables - clinical score, exposure score, and Vyadhiksamatwa. In this study, severity of disease was found positively co-related with exposure and negatively related with Vyadhiksamatwa. Thus, this relationship can be represented through the equation. Clinical severity has been found directly proportional to exposure and inversely proportional to Vyadhiksamatwa.

4.3. Determinants of the three variables - Exposure, Clinical Outcomes and Vyadhiksamatwa

The assessment of grade of exposure has been done, based on temporal factors, occupational history, living conditions, and contact history. Exposure score was above the median value in health care workers and patients who lived in urban areas and higher room density (indicator of overcrowding). This is further supported by a study conducted in the UK and the USA which reported that the risk of reporting a positive test for COVID-19 was increased among front-line health-care workers [18]. Impact of room-density has also been investigated in this respect and the relationship between urban area and COVID-19 virus has been observed [19]. Host behavior and number of contacts is also one of the contributing factors [20] since the pandemic can be spread by aerosol transmission from person-to-person, with direct or indirect contact [21]. Social distancing is a type of non-pharmaceutical counter-measures (NPCs). The intervention is aimed to minimize physical contact between individuals thereby reducing the possibility for new infections [22]. Age is another important factor that determines the clinical severity as it has been reported that the disease is more fatal in older patients [23]. Closed areas with low airflow and ventilation increase the risk of COVID 19 infection [24]. The relationship between high population density and spread of epidemics has been reported in earlier studies [23]. Personal hygiene practices such as hand-sanitization are mandatory to limit the community spread of viral diseases, especially SARS-CoV-2 [24].

The determination of variables was done based on all these variables.

4.3.1. Vyadhiksamatwa

Virus antigens can be considered as Dehadhatu-pratyankha Dravyas (substances with properties opposing body tissues) which enter the body and elicit varying individual responses, depending on multiple factors. Relationship of individual factors that determine Vyadhiksamatwa were also assessed with respect to clinical severity. Jarana Shakti had the strongest negative co-relation (−0.735) with the clinical severity at the p-value of 0.0001. It was followed by Abhayavarharana Shakti with a negative co-relation (−0.747) at the p-value of 0.001. Along with Abhayavarharana Shakti, vyayama (exercise), daily intake of unctuous food, and body—build. Acharya Charaka has mentioned the importance of Dehagni (all the entities in the body that are responsible for digestion and metabolism). It has been stated that it is the fundamental causative agent for longevity, complexion, strength, health, motivation, growth, luster, Oja, body temperature, and various other forms of Agni. It has been mentioned that the existence of an individual is dependent on Agni [11, Chikitsa Sthana; Grahani Chikitsa, Chapter 15/2]. Every exogenous particle in Koshta (large anatomical body cavities) is first subjected to the action of Jatharagni (metabolic factors located in digestive tract). Jatharagni digests the food materials and transforms it for utilization by the respective Dhatus Paramamus (tissues). Moreover, action of Bhutagni (agni from five basic elements) is to convert Vajra (heterogenous to body) substances into Sajata (homogenous to body). If this conversion of Dehadhatu-pratyankha Dravyas (virus antigens) is not facilitated, then these may lead to a disease. Assessment of Agnibala can be done through Abhayavarharana and Jarana Shakti. Both the parameters of Agni were found closely related to the clinical score. Therefore, Bala of Agni was found closely related to clinical severity, in the inverse direction. Vyayama has been mentioned under different contexts - Dincharya (daily regimen), Anagatabadhapratisedha (prevention of future diseases), Balavriddhikarabhava (factors enhancing immunity), and Dashavridhahatraparisaka (ten-fold examination of patient). Physical exercise provides strength and stability to the body along with endurance toward distress and mitigation of doshas and stimulation of Agni [11, Sutra Sthana; Naveganadharaniya Adhyaya; Chapter 7/32]. Elderly not only have compromise immunity and self-defense making them more vulnerable to infectious diseases and acute respiratory distress syndrome but are also more likely to have health conditions such as coronary, lung or kidney diseases, diabetes which can contribute to their low immunity levels.

4.4. Modifying the host defense response

The determinants of Vyadhiksamatwa among three variables are modifiable as well as non-modifiable. For instance, Bala of an individual is itself a functional entity which can be derived from three axial components; out of them only one “Yuktikiritabala” (artificial immunity) can be a controlled [11, Sutra Sthana; Tristraiishaniya Adhyaya; Chapter 11/36]. Vyadhiksamatwa is a function of bala (strength), Agni (metabolism), snigdha ahara (dietary factors), and vyayama (lifestyle modifications). Bala is dependent on modifiable as well as non-modifiable factors. Non-modifiable determinants include birth in a geographical region where people are naturally strong, in a race of strong people, at a time when people naturally gain strength, i.e., favorable disposition of time, excellence of beeja (sperm and ovum) and kshetra (uterus) qualities, and age [11, Sharir Sthana; Khuddika Garbhavakranti Sharira, Chapter 3/6–13]. Modifiable factors include physique, ingested food, satmya (wholesome), satva (psychological strength), and exercise. Agni is dependent on age, temporal factors, dietary regimen, lifestyle, and psychological factors.

4.5. Modulation of host response and possible role of epigenetics

Researches have identified epigenetic mechanism as the silent modulators of host defenses [25]. Epigenetics can be defined as the dynamic relationship between the environment and gene expression. The modifications control gene expression through factors such as diet, obesity, physical activity, tobacco smoking, alcohol
consumption, environmental pollutants, and psychological stress [26]. This can be further interpreted as the underlying mechanism behind factors modifying Vyadhiksamatwa as well.

Immunological studies indicate that the clinical severity of COVID-19 is consistently correlated with cell-mediated immunity in SARS-CoV-2 infection [27–29]. SARS-CoV-2 breaks down antiviral immunity mediated by NK cells at an early stage of infection and evades and/or antagonizes different arms of the innate immune system. Cellular immune responses to COVID-19 are being evaluated for their role in control of infection and progression of disease. These approaches can accelerate the development of immune therapies in therapeutic and preventive care.

4.6. Limitations

This pilot study was a basic attempt to assess the role of a host factor responsible in progression of a disease; similar and more extensive work can be done to assess its role in the occurrence of the disease with a longitudinal study design. In this study, as exposures and outcomes are being assessed simultaneously, there is a probability of recall bias and information bias with respect to confounding factors given the dynamic nature of host responses to infections and particularly when studying samples from human patients with an unknown time retrospectively. Longitudinal monitoring is critical in order to reveal the relationships.

Measurement of variables is the most fundamental component of research methodology exposure, clinical severity, and host factor. Future work can be done to develop objective parameters for measuring variables such as host factor. During the study, role of hyper-immune response with respect to the measure assessed could not be elicited as the researchers did not encounter any patient with severe clinical staging in the participants. Our exploratory results do not define the particular biological mechanism by which the host factor alters the clinical severity.

5. Conclusion

In this observational study Vyadhiksamatwa was found to be a determinant of clinical outcome in diagnosed cases of COVID-19. An inverse association between the clinical severity and immune status was found. The host factor is a multivariate function of modifiable and non-modifiable attributes. The varying host responses can be considered for the development of clinical guidelines in the prevention and management of COVID-19 illness. Epidemiological research to investigate the relationship between host responses and severity of infection can be carried out to understand the mechanics of the immune response’s translation of the fundamentals to practical guidelines can accelerate the development of immune therapies.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2021.03.007.

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