



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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ABSTRACT

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 Vikaravighatabhavaabhava (absence of disease inhibiting factors)

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determines the manifestation and progression of the disease. Based on the amalgamation of the three factors, (*Nidana*, *Dosha*, 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 unwholesome food does not produce disease in all individuals, suggesting that one's immune system is instrumental in manifestation of disease. This can be implicated further as *Vyadhibalavirodhitwa* (resistance against disease) and *Vyadhyutpadaka Pratibandhakatwa* (resistance against agents causing the disease) [11, *Sutra Sthana*; *Vividhashitapitiya Adhyaya*, Chapter 28/7]. When the external etiological factors vitiate the *Doshas*, the morbid *Doshas* further vitiate *Dusyas* (body tissues) leading to *Dhatu Vaishyama* i.e., disease. *Dosha* and *Dushya* 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 Adhyaya*, Chapter 17/117], *Rakta Dhatu* [11, *Sutra Sthana*; *Vidhishonitiya Adhyaya*, Chapter 24/4], *Vayu* [11, *Chikitsa Sthana*; *Vatavyadhi Chikitsa*, Chapter 28/3.], *Agni* [[11], *Chikitsa Sthana*; *Grahani Chikitsa*, Chapter 15/3–4.], [[12], *Chikitsa Sthana*; *Grahani Chikitsa*, Chapter 12/31], and *Oja* [[13], *Sutra sthana*; *Doshadhatumalakshayavridhi 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 - *Satamy Sevana* (antigen in low dose and with respect to *adhikaran tantrayukti* intake of wholesome diet), *Agni* (power of digestion, assimilation, and metabolism), *Vaya* (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 Adhyaay*: 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

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 (sātmyatō'lpatayā vā')	Pyrexia Cold
Ventilation associated event (VAE)	Strong digestive power (Diptāgnē)	Cough Fatigue
Housing (Room Density)	Age (vaya)	Aches/Pains
Personal Protective Equipment (mask/hand hygiene/social distancing)	Dietary patterns favouring unctuous food (Snigdha ahara)	Anorexia Sore throat Conjunctivitis
Contact tracing	Physical exercise (Vyāyama)	Anosmia
Occupational history	Strength (bala)	Ageusia Headache Nausea & Vomiting 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 *virudhha 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 unctious, physical exercise, and strength. The exogenous factor i.e., exposure was already assessed, so as to avoid repetition; only unwholesome 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 AIIA, New Delhi. Permission from Institutional Ethics Committee was obtained (IEC-AIIA/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 graduation. Number of participants with missing data for each variable of interest was zero.

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 urban area. Of the total participants, 8% were health workers performing regular duties and 62% were non-health workers, not going out for regular duties. It was observed that 20% of the population was residing in an area of high-room density (more than 2) and 54% of the infected persons had visited a high-risk area within a span of 1–6 days. 8% of the population had a close contact history i.e., more than 20 COVID-19 infected individuals were within their circumference of 500 m. 72% of them were maintaining personal hygiene

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 – *Abhyavharana shakti* (capacity of food intake) and *Jarana Shakti* (capacity to digest). It was found that 60% of them had above average *Abhayavaharana Shakti* and only 22% of them had good *Jarana Shakti*. 40% of them gave a history of consumption of unctuous food on regular basis. *Vyayama* (exercise) was a regular activity present in only 14% of cases.

3.3. Assessment of relationship between the variables

Median value for clinical score, *Vyadhiksamatwa* and exposure factor are 3.5,15.0 and 17.5 respectively as shown in Fig. 1. The correlation between clinical score and *Vyadhiksamatwa* was found to highly significant ($r = -0.74, p < 0.001$), indicating that higher value of *Vyadhiksamatwa* 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 *Vyadhiksamatwa*

An urgent need for effective therapeutics in matters of public health concern, require a gross understanding of the epidemiology

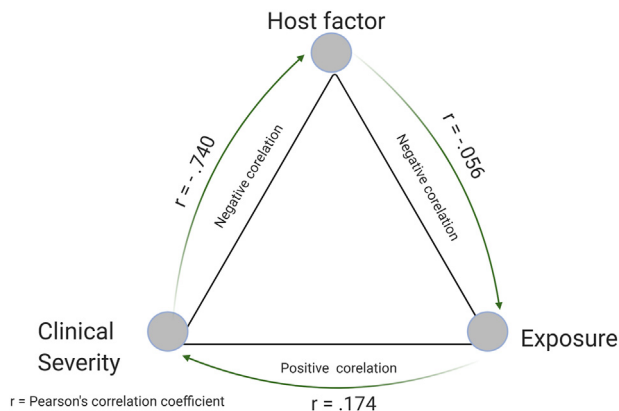


Fig. 1. Inter - relationship between the three variables (Exposure Host factor Clinical Outcomes) evaluated in the study.

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-pratyanka 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 *Abhayavharana Shakti* with a negative co-relation (−0.747) at the p-value of 0.001. Along with *Abhayavharana Shakti*, *vyayama* (exercise), daily intake of unctuous food, and body–built. *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 *Koshtha* (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 *Dhatu Paramanus* (tissues). Moreover, action of *Bhutagni* (*agni* from five basic elements) is to convert *Vijatiya* (heterogenous to body) substances into *Sajatya* (homogenous to body). If this conversion of *Dehadhatu-pratyanka Dravyas* (virus antigens) is not facilitated, then these may lead to a disease. Assessment of *Agnibala* can be done through *Abhayavharana* 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), *Balavid-dhikarabhava* (factors enhancing immunity), and *Dashavidhaaturapariksa* (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 “*Yuktikritabala*” (artificial immunity) can be a controlled [11, Sutra Sthana; Tistraishaniya 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

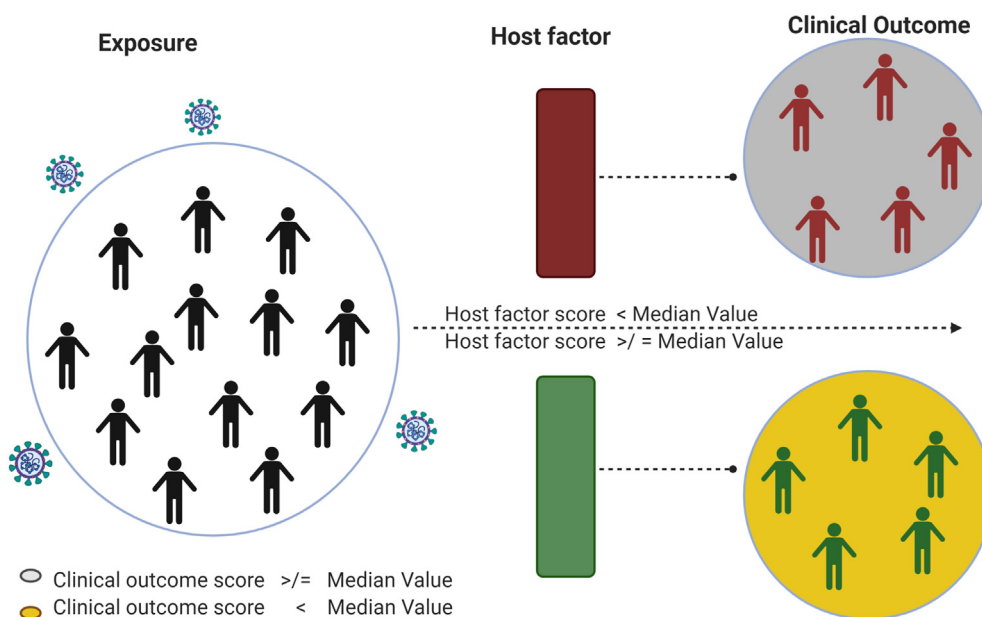


Fig. 2. Stratification of host responses in cases of COVID-19 disease based on Vyadhikshamatwa.

consumption, environmental pollutants, and psychological stress [26]. This can be further interpreted as the underlying mechanism behind factors modifying Vyadhikshamatwa 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 Vyadhikshamatwa 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>.

References

[1] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
 [2] Xu B, Gutierrez B, Mekaru S, Sewalk K, Goodwin L, Loskill A, et al. Epidemiological data from the covid-19 outbreak, real-time case information. Scientific Data 2020;7:106. <https://doi.org/10.1038/s41597-020-0448-0>.

- [3] National Health Commission of People's Republic of China. Diagnostic and treatment plan of Coronavirus disease 2019. 7th ed. 2020. tentative <http://www.nhc.gov.cn/yzygj/s7653p/202003/>.
- [4] He J, Guo Y, Mao R, Zhang J. Proportion of asymptomatic coronavirus disease 2019: a systematic review and meta-analysis. *J Med Virol* 2021 Feb;93(2): 820–30. <https://doi.org/10.1002/jmv.26326>. Epub 2020 Aug 13. PMID: 32691881; PMCID: PMC7404334.
- [5] Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics* 2020 Jun;145(6):e20200834. <https://doi.org/10.1542/peds.2020-0834>. Epub 2020 Mar 16. PMID: 32179659.
- [6] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199e207. <https://doi.org/10.1056/NEJMoa2001316>.
- [7] Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Trav Med* 2020;27. <https://doi.org/10.1093/jtm/taaa021> 46c9294 a7dfe4cef80dc7f5912eb1989.shtml.
- [8] Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020;27:1451–4. <https://doi.org/10.1038/s41418-020-0530-3>.
- [9] Chang F, Chen H, Chen P, Ho M, Hsieh S, Lin J, et al. Immunologic aspects of characteristics, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *J Biomed Sci* 2020;27:72. <https://doi.org/10.1186/s12929-020-00663-w>.
- [10] Tay MZ, Poh CM, Rénia L, MacAry P, Ng L. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363–74. <https://doi.org/10.1038/s41577-020-0311-8>.
- [11] Acharya Yadavji Trikamji, editor. CharakaSamhita of agnivesha, Nidana sthana; Prameha Nidana; chapter 4 Verse4. Varanasi: Chaukhambha Surabharati prakashan; 2018. p. 212.
- [12] Tripathi Brahmanand, editor. Ashtanga samgraha of Vagbhata, Chikitsa Sthana; Grahani Chikitsa; Chapter 12 Verse31. Varanasi: Chaukhambha Surabharati prakashan; 2015.
- [13] Vaidya Ambikadutta Shastri. In: Sushruta samhita of sushruta with ayurved tattvasandipika, Sutra sthana: Doshadhatumalakshayavridhhi Viganyaniya; chapter 15 Verse19. Varanasi: Chaukhambha Sanskrit publication; 2016.
- [14] Chatterjee R, Bajwa S, Dwivedi D, Kanji R, Ahammed M, Shaw R. COVID-19 Risk Assessment Tool: dual application of risk communication and risk governance. *Progress in Disaster Science* 2020;7:100109.
- [15] Chaturvedi A. Top 10 popular smartphone apps to track COVID-19. Available from Geospatial World, <https://www.geospatialworld.net/blogs/popular-apps-COVID-19/>. [Accessed 24 August 2020].
- [16] CDC. Novel coronavirus, wuhan, China: symptoms CDC. January 26, 2020 accessed on, <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>. [Accessed 20 August 2020].
- [17] Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill* 2020;25(4).
- [18] Nguyen LH, Drew DA, Joshi AD, Guo C, Ma W, Mehta R, et al. Risk of COVID-19 among frontline healthcare workers and the general community: a prospective cohort study. Preprint MedRxiv 2020:2020. <https://doi.org/10.1101/2020.04.29.20084111>. 04.29.20084111. Published 2020 May 25.
- [19] LUMC-COVID-19 Research Group, Chen Q, Toorop MMA, de Boer MGJ, Rosendaal FR, Lijfering WM. Why crowding matters in the time of COVID-19 pandemic? - a lesson from the carnival effect on the 2017/2018 influenza epidemic in The Netherlands. *BMC Publ Health* 2020;20(1):1516. <https://doi.org/10.1186/s12889-020-09612-6>. Published 2020 Oct 6.
- [20] Mishra Swasti, Gayen Amiya, Haque Sk Mafizul. COVID-19 and urban vulnerability in India. *Habitat Int* 2020;103:102230. <https://doi.org/10.1016/j.habitatint.2020.102230>.
- [21] ECDC (European Centre for Disease Prevention and Control). COVID- 19 2020. 2020 [cited 2020 March 30].
- [22] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *J Am Med Assoc* 2020;323(18): 1775–6.
- [23] Mangen MJ, Nielen M, Burrell AM. Simulated effect of pig-population density on epidemic size and choice of control strategy for classical swine fever epidemics in The Netherlands. *Prev Vet Med* 2002;56(2):141–63.
- [24] Mathai E, Allegranzi B, Kilpatrick C, Pittet D. Prevention and control of health care-associated infections through improved hand hygiene. *Indian J Med Microbiol* 2010;28(2).
- [25] Morandini AC, Santos CF, Yilmaz Ö. Role of epigenetics in modulation of immune response at the junction of host-pathogen interaction and danger molecule signaling. *Pathog Dis* 2016;74(7).
- [26] Epigenetics and lifestyle. *Alegria-Torres JA, Baccarelli A. Bollati VE* *Epigenomics* 2011 Jun;3(3):267–77.
- [27] To K-K-W, Tsang O-T-Y, Leung W-S, Tam AR, Wu T-C, Lung DC. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020;20:565–74.
- [28] Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis* 2020;71(16): 2027–34.
- [29] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130:2620–9.