International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 4, 2024

Review Article

# A COMPREHENSIVE REVIEW ON THE MULTIFACETED INTERACTIONS BETWEEN HOST IMMUNITY AND VIRAL PATHOGENESIS IN COVID-19

**MAIREMBAM STELIN SINGH[1,2], SAILU YELLABOINA[3], MAIRAJ AHMED ANSARI[4,5*]**

**[1]Department of Biochemistry, SCLS, Jamia Hamdard, New Delhi, India. [2]Department of Zoology, Rajiv Gandhi University, Arunachal Pradesh, India. [3]All India Institute of Medical Sciences, Bibinagar, Hyderabad, Telangana-508126, India. [4]Department of Biotechnology, SCLS, Jamia Hamdard, New Delhi, India. [5]Centre for Virology, SIST, Jamia Hamdard, New Delhi, India**
**[*]Corresponding author: Mairaj Ahmed Ansari; [*]Email: research_uni@gmail.com**

*Received: 09 Feb 2024, Revised and Accepted: 12 Apr 2024*

**ABSTRACT**

The Corona Virus Disease (COVID-19) pandemic has presented unparalleled challenges, marked by a wide array of clinical presentations spanning from asymptomatic carriage to severe respiratory compromise and multi-organ dysfunction. It is crucial to comprehend the intricate interplay between host immunity and viral pathogenesis to elucidate disease mechanisms and guide therapeutic strategies. This review delves into the multifaceted interactions between host immunity and viral pathogenesis in COVID-19, with a particular focus on the impact of host factors such as age, sex, comorbidities, and genetic predisposition on disease severity. Utilizing state-of-the-art methodologies, including multiomics approaches, has yielded an expansive molecular portrayal of COVID-19, furnishing innovative perspectives on host immune reactions, viral pathogenicity, and disease advancement. Establishing standardized methodologies for data analysis and interpretation while concurrently addressing ethical considerations and promoting interdisciplinary collaboration are crucial steps in advancing our comprehension of COVID-19 pathogenesis. Despite obstacles like complexities in data integration, this review highlights the imperative of persistent endeavors in deciphering the complex interactions between hosts and pathogens to alleviate the global health ramifications of COVID-19.

**Keywords:** COVID-19, HPI, ACE2, Multiomics, Host immunity, Viral proteins


DOI: https://dx.doi.org/10.22159/ijap.2024v16i4.50576 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

## INTRODUCTION

The Corona Virus Disease (COVID-19) pandemic stands as a paramount global health crisis of recent times, profoundly affecting millions worldwide and resulting in substantial morbidity and mortality. This pandemic is attributed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the coronaviridae family [1, 2]. The coronaviridae family encompasses a broad spectrum of viruses capable of inducing respiratory, gastrointestinal, and neurological ailments in both humans and animals. Within the COVID genus, a diverse array of viruses is recognized for eliciting respiratory illnesses in humans, spanning from mild common colds to SARS and Middle East Respiratory Syndrome (MERS). Nonetheless, none have exhibited the extensive global repercussions witnessed by COVID-19, precipitated by SARS-CoV-2 [3, 4]. COVID-19 presents unparalleled challenges to public health due to its high transmissibility and diverse symptomatic spectrum, ranging from asymptomatic cases to severe respiratory distress. The severity of COVID-19 exhibits considerable variation among individuals, influenced by factors such as age, underlying health conditions, and immune status. While some individuals manifest mild symptoms or remain asymptomatic, others progress to severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), and multi-organ failure, resulting in elevated morbidity and mortality rates [5]. The multifactorial mechanisms governing this variability in disease severity entail intricate interactions between the host immune response and viral pathogenesis. Understanding the dynamics of Host-Pathogen Interactions (HPI) is pivotal in elucidating the complexities of COVID-19 and devising effective management strategies [6].

The host possesses an inherent evolutionary capacity to enhance its defense mechanisms against viral intrusion, primarily through innate and adaptive responses. Innate responses encompass swift cytokine production aimed at combating viral infections. Conversely, adaptive responses, including antibody and cell-mediated immune reactions, necessitate time to materialize but are instrumental in eliciting virus-specific immune defenses [7]. These innate and adaptive immune mechanisms have evolved over extensive periods of evolution. By elucidating the intricate molecular underpinnings of HPI, researchers can pinpoint shared targets for therapeutic intervention and devise innovative strategies to modulate the host immune response, thereby constraining viral replication. Comprehending the intricate interplay between host factors and viral pathogenesis is paramount for devising personalized treatments customized to the unique immune profiles and disease progressions of individual patients [6, 8].

The methodology involved conducting a thorough literature search across bibliographic databases, including PubMed, Google Scholar, Web of Science, and Scopus, encompassing both review articles and research papers published between 2019 and 2023. A comprehensive set of keywords, including "Covid," "coronavirus," "host-pathogen interaction (HPI)," "ACE2," and "covid" were utilized for efficient search results. Searches were refined iteratively to ensure coverage, with screening based on titles and abstracts followed by full-text review to select relevant publications.

This review endeavors to delve into the multifaceted interactions between host immunity and viral pathogenesis in the context of COVID-19, exploring the latest advancements in our comprehension of HPI.

### Basic virology of SARS-CoV-2

Coronaviruses represent a category of enveloped, positive-sense, single-stranded RNA viruses recognized for their role in precipitating respiratory ailments in humans. The genome of SARS-CoV-2 spans approximately 30,000 nucleotides and encompasses numerous structural and non-structural proteins pivotal for viral replication and assembly [2, 3]. Grasping the intricacies of the structure, genome arrangement, and replication cycle of SARS-CoV-2 is imperative for unraveling its pathogenesis and formulating efficacious interventions against COVID-19.

### Structure and genome of SARS-CoV-2

SARS-CoV-2, the etiological agent responsible for COVID-19, belongs to the coronaviridae family, a group of enveloped, positive-sense, single-stranded RNA viruses. Its genome spans approximately 30,000 nucleotides and encodes numerous structural and non-structural proteins pivotal for viral replication and assembly. The genome encompasses 14 Open Reading Frames (ORFs), with ORF1a and ORF1b responsible for encoding the viral replicase polyproteins pp1a and pp1ab, respectively. These polyproteins undergo cleavage into individual Non-Structural Proteins (nsps) by viral proteases,

including the Main Protease (Mpro) and Papain-Like Protease (PLpro). Among the structural proteins of SARS-CoV-2 are the Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins. The S protein of SARS-CoV-2 facilitates viral entry into host cells through its binding affinity with the Angiotensin-Converting Enzyme 2 (ACE2) receptor situated on the host cell surface. This interaction is primarily mediated by the Receptor-Binding Domain (RBD) localized within the S1 subunit of the S protein. Subsequently, the S protein undergoes proteolytic cleavage by host cell proteases, including TMPRSS2 and cathepsins, to facilitate membrane fusion and enable viral entry (fig. 1).

**Viral entry mechanism into the host cell**

The initial stage of viral entry entails the binding of the SARS-CoV-2 S protein to the ACE2 receptor present on the surface of host cells. This binding event induces conformational alterations in the S protein, leading to the exposure of the fusion peptide located within the S2 subunit. Following this, host cell proteases, such as TMPRSS2, catalyze the proteolytic cleavage of the S protein, thereby priming the virus for membrane fusion [9]. The fusion peptide then integrates into the host cell membrane, facilitating the fusion between viral and cellular membranes and subsequent release of the viral genome into the cytoplasm of the host cell. Moreover, endocytosis-mediated entry pathways have been implicated in the infection of SARS-CoV-2, whereby the virus is internalized into host cells within endosomal vesicles [9, 10]. This mechanism entails the interaction between the S protein and cell surface receptors, such as ACE2, resulting in the internalization of the virus-receptor complex into endosomes. Subsequent acidification of the endosomal compartment induces conformational alterations in the S protein, facilitating membrane fusion and the subsequent entry of the virus into the cytoplasm of the host cell [10] (fig. 1).

**Replication cycle of the virus**

Upon entry into the host cell, the viral genomic RNA functions as a template for the translation of viral replicase proteins, which include nsps originating from ORF1a and ORF1b. These nsps assemble into the viral Replicase Complex (RC), which is responsible for catalyzing the replication and transcription of the viral genome [11]. This process results in the production of full-length genomic RNA and a series of subgenomic RNAs (sgRNAs). The sgRNAs encode viral structural and accessory proteins crucial for viral assembly and release. Notably, viral RNA synthesis occurs within double-membrane vesicles (DMVs) derived from host cell membranes during replication [12]. These double-membrane vesicles (DMVs) act as replication compartments, providing a protected environment where viral RNA synthesis occurs without interference from the host cell's innate immune responses.

The newly synthesized viral genomic RNA and sgRNAs are subsequently encapsulated into virion particles by the viral nucleocapsid protein (N) and assembled at the Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC). Ultimately, mature virions are released from the host cell either through exocytosis or budding from the plasma membrane, facilitating the dissemination of infection to adjacent cells and tissues [13].

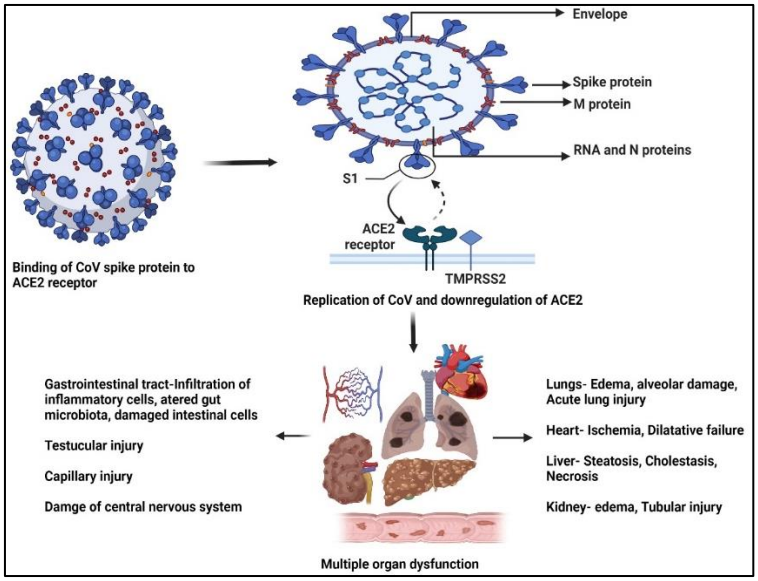


**Fig. 1: Schematic representation of SARS-CoV and its binding on ACE2 receptors**

The replication of the CoV begins with the attachment to the host through receptor-mediated endocytosis, followed by penetration into the host cells, genomic replication, assemblage, formation of virion and release. The S proteins from the CoV bind to host ACE2 and invade the host, which is mediated by TMPRSS211 serine protease. (Image has been created using biorender).

**Host immune response**

**Innate immune response to SARS-CoV-2**

The innate immune response acts as the primary defense mechanism against viral infections, including those caused by SARS-CoV-2. Upon viral entry, Pattern Recognition Receptors (PRRs) such as Toll-Like Receptors (TLRs) and Retinoic acid-inducible Gene I (RIG-I)-Like Receptors (RLRs) detect viral Pathogen-Associated Molecular Patterns (PAMPs), initiating the production of proinflammatory cytokines and type I interferons (IFNs) [14]. Type I IFNs play a pivotal role in inhibiting viral replication and dissemination by inducing an antiviral state in neighboring cells. Additionally, innate immune cells such as macrophages, dendritic cells, and Natural Killer (NK) cells are recruited to the infection site, where they contribute to viral clearance through phagocytosis and cytotoxicity [15]. Macrophages produce inflammatory cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α), which coordinate the recruitment and activation of other immune cells. NK cells recognize and eliminate virus-infected cells through the release of cytotoxic granules containing perforin and granzymes [16] (fig. 2).

Nonetheless, SARS-CoV-2 has evolved mechanisms to evade and manipulate the innate immune response. The virus hampers the production of IFNs by disrupting the activation of transcription factors, including Interferon Regulatory Factors (IRFs) And Nuclear Factor-Kappa B (NF-κB). Additionally, certain SARS-CoV-2 proteins, such as Nsp1 and Nsp3, counteract the host's antiviral defenses by

targeting critical signaling pathways associated with innate immunity [14, 15].

**Adaptive immune response to the virus**

The adaptive immune response against SARS-CoV-2 involves the orchestrated activation of B cells and T cells, pivotal in eradicating the virus and conferring long-lasting immunity. B cells are responsible for generating antibodies that target and neutralize viral antigens, notably the SARS-CoV-2 spike protein [15]. These antibodies hinder viral entry into host cells by impeding the interaction between the virus and its cellular receptor, ACE2. Concurrently, T cells play a crucial role in eliminating virus-infected cells and regulating immune responses. CD4+T helper cells coordinate the adaptive immune reaction by stimulating B cells and cytotoxic CD8+T cells (fig. 2) [16].

A robust adaptive immune response is crucial for effectively combating SARS-CoV-2 infection and resolving COVID-19. However, certain individuals may encounter dysregulated immune responses characterized by excessive inflammation and tissue damage, which can lead to severe disease manifestations like ARDS and multi-organ failure. Remarkably, SARS-CoV-2 has evolved strategies to evade detection and elimination by the adaptive immune system [17]. The virus diminishes the expression of Major Histocompatibility Complex (MHC) molecules on infected cells, thereby hindering antigen presentation and T-cell recognition (fig. 2). Furthermore, specific SARS-CoV-2 proteins, such as the nucleocapsid protein (N), hinder the activity of T cells and impede their effector functions, thus fostering viral persistence and immune evasion [15].

**Immune evasion strategies employed by the virus**

SARS-CoV-2 employs diverse immune evasion strategies to circumvent detection and elimination by the host immune system. One notable strategy involves the suppression of IFN signaling, a pivotal step in initiating an antiviral response [18]. Certain SARS-CoV-2 proteins, such as Nsp1 and Nsp3, hinder the production of type I IFNs by impeding the activation of crucial signaling pathways, including the IRF3 pathway (fig. 2) [19]. Furthermore, SARS-CoV-2 has been observed to disrupt antigen presentation and T-cell recognition by reducing the expression of MHC molecules on infected cells. This downregulation of MHC molecules impedes the ability of infected cells to display viral antigens to T cells, thereby hindering effective immune surveillance and response. This impedes the capacity of infected cells to present viral antigens to T cells, enabling the virus to evade immune surveillance and establish persistent infection [20]. Additionally, certain SARS-CoV-2 proteins, like the nucleocapsid protein (N), have been identified to directly hinder the activity of T cells and compromise their effector functions. This encompasses the suppression of T cell proliferation and cytokine production alongside the induction of T cell apoptosis. Through its interaction with T cells, SARS-CoV-2 can dampen the adaptive immune response, thereby promoting viral persistence [21].

**Host factors influencing disease severity**

Numerous host factors contribute to the spectrum of COVID-19 severity, encompassing demographic features like age and sex, as well as underlying health conditions and genetic susceptibilities. Comprehending these factors holds paramount importance for risk assessment, tailoring treatment modalities, and crafting precise interventions aimed at ameliorating disease severity and enhancing clinical prognosis [22]. Through deciphering the intricate dynamics between host factors and disease trajectory, scientists strive to unveil innovative therapeutic targets and approaches for addressing severe manifestations of COVID-19.

**Demographic and health factors influencing COVID-19 severity**

Age, sex, and underlying health conditions, often referred to as comorbidities, are pivotal determinants of COVID-19 severity. Advanced age consistently emerges as a notable risk factor for severe disease outcomes and mortality [23]. Elderly individuals frequently exhibit compromised immune systems and a higher prevalence of comorbidities such as hypertension, diabetes, and cardiovascular disorders, which collectively contribute to adverse clinical trajectories [24]. Furthermore, sex-based distinctions in COVID-19 severity are evident, with males exhibiting a propensity towards more severe disease manifestations and heightened mortality rates compared to females. The underlying reasons for this divergence are multifaceted, potentially encompassing variations in immune responses, hormonal influences, and lifestyle elements [25].

Comorbidities, encompassing conditions like obesity [26], chronic lung disease [27], kidney disorders [28], and immunosuppression [29], correlate with heightened susceptibility to severe COVID-19 manifestations. These underlying health ailments impede both immune and respiratory functionalities, rendering individuals more prone to complications such as ARDS and multi-organ dysfunction [30]. Moreover, socio-economic determinants, inclusive of healthcare accessibility, living standards, and occupation, exert notable influence on disease severity. Individuals hailing from marginalized communities and economically disadvantaged backgrounds often encounter obstacles in accessing healthcare services and exhibit elevated prevalence rates of comorbidities, thereby amplifying disparities in COVID-19 outcomes [31, 32].

**Genetic susceptibility to severe COVID-19**

Genetic factors significantly influence an individual's susceptibility to severe COVID-19. Through Genome-Wide Association Studies (GWAS), numerous genetic variants linked to heightened risk of severe disease outcomes have been identified, particularly within genes governing immune regulation and host-viral interactions [33, 34]. Notably, variants within the gene encoding the ACE2 receptor, pivotal for SARS-CoV-2 entry, have emerged as relevant determinants. Variants affecting ACE2 expression or function may modulate viral entry and replication kinetics, thereby impacting disease severity [35].

Similarly, genetic variations in genes encoding components of the immune system, including cytokines and Human leukocyte Antigen (HLA) genes, can influence immune responses to SARS-CoV-2 and contribute to disease severity [36]. Variants associated with dysregulated cytokine responses, such as elevated levels of proinflammatory cytokines like IL-6, are correlated with an increased risk of cytokine storm and severe respiratory complications. Moreover, host genetic factors may affect vaccine efficacy and the occurrence of adverse reactions to COVID-19 vaccines [37]. Understanding the genetic determinants of COVID-19 severity can facilitate risk stratification and personalized treatment approaches, thus enhancing disease management.

**Immunological factors affecting disease outcomes**

Immunological factors play a pivotal role in determining disease outcomes in COVID-19. Dysregulated immune responses, characterized by excessive inflammation and cytokine release, contribute to the pathogenesis of severe manifestations such as ARDS and multi-organ failure [38, 39]. Severe COVID-19 cases often exhibit an exaggerated immune response known as a cytokine storm, marked by elevated levels of proinflammatory cytokines, including IL-6, TNF-α, and Interleukin-1β (IL-1β), which cause tissue damage and systemic complications. Conversely, impaired immune responses, such as T cell dysfunction and lymphopenia (reduced lymphocyte count), are also linked to severe COVID-19 (fig. 2) [40]. Dysfunction of cytotoxic CD8+T cells, critical for viral clearance, can lead to prolonged viral replication and disease progression [41].

Moreover, pre-existing immune dysregulation, encompassing autoimmune conditions and immunodeficiency disorders, can predispose individuals to severe COVID-19. Patients with autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus may experience exacerbations of their underlying conditions during COVID-19 infection, potentially resulting in worse clinical outcomes [42].

**Viral factors influencing disease severity**

The severity of COVID-19 is influenced by several viral factors, encompassing viral load dynamics, the emergence of Variants of

Concern (VOCs), and specific viral elements contributing to cytokine storm and hyperinflammation [43]. Understanding the intricacies of these viral factors is imperative for anticipating disease outcomes, informing clinical management decisions, and devising targeted interventions to alleviate disease severity.

**Viral load concern**

The viral load, referring to the amount of virus present in an infected individual, plays a pivotal role in determining the severity of COVID-19. Elevated viral loads consistently correlate with more severe clinical outcomes, including an increased likelihood of respiratory failure and mortality [44]. The initial viral load upon exposure, along with the subsequent kinetics of viral replication within the host, significantly influence the progression of the disease. Research indicates that individuals with severe COVID-19 typically exhibit higher viral loads in respiratory specimens, such as nasopharyngeal swabs and bronchoalveolar lavage fluid, compared to those with mild or asymptomatic disease [45]. Furthermore, prolonged viral shedding, characterized by persistent detection of viral RNA in respiratory samples, is more prevalent among patients with severe disease and is associated with prolonged symptom duration and higher mortality rates [46].

The association between viral load and disease severity highlights the critical need for early detection and monitoring of viral replication in individuals with COVID-19 [44]. Quantitative assessments of viral load, such as determining Reverse Transcription Polymerase Chain Reaction (RT-PCR) cycle threshold values, hold significant prognostic value and can inform clinical management strategies, including the initiation of antiviral treatments and the timing of hospital discharge. Moreover, individuals with higher viral loads pose a greater risk of transmitting the virus to others, underscoring the importance of promptly identifying and isolating infectious individuals to curb the spread of COVID-19 within communities [47].

**Variants of concern and their impact on pathogenesis**

The emergence of VOCs has sparked apprehension regarding their potential impact on the pathogenesis and severity of COVID-19 [48]. VOCs, characterized by distinct mutations in the viral genome, may display altered transmissibility, virulence, and immune evasion capabilities compared to the original strain of SARS-CoV-2. Notably, several VOCs, including the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants, have been linked to heightened disease severity and increased mortality rates in specific demographics [49]. These variants harbour mutations primarily within the spike protein, particularly in the Receptor-Binding Domain (RBD), potentially enhancing viral affinity for the ACE2 receptor and facilitating cellular entry. Furthermore, VOCs may demonstrate resistance to neutralization by antibodies generated post-natural infection or vaccination, thereby diminishing the efficacy of existing therapeutics and vaccines [50]. Of note, the Delta variant, in particular, has been associated with breakthrough infections in vaccinated individuals, prompting the development of booster doses to bolster immunity against emerging variants [51].

**Viral contributions to cytokine storm**

The phenomenon known as cytokine storm, characterized by the dysregulated and excessive release of proinflammatory cytokines, is a hallmark of severe COVID-19, contributing significantly to tissue damage, multi-organ failure, and unfavorable clinical outcomes. Viral factors, encompassing specific viral proteins and genetic variations, play a pivotal role in instigating and perpetuating cytokine storms and hyperinflammation among COVID-19 patients [52]. Notably, the SARS-CoV-2 spike protein, particularly the S1 subunit housing the RBD, possesses the capacity to directly stimulate immune cells and provoke the production of proinflammatory cytokines such as IL-6 and TNF-α. Moreover, viral proteins like the nucleocapsid protein (N) and Nsp1 have been implicated in modulating host immune responses and fostering the release of cytokines [53] (fig. 2).

Genetic variations within the viral genome, particularly mutations found in the ORF3a and ORF7a genes, have been linked to heightened cytokine production and increased disease severity among COVID-19 patients. These genetic alterations have the potential to bolster viral replication and intensify host immune responses, thereby triggering exaggerated inflammatory reactions and the onset of cytokine storm [54, 55]. Moreover, viral elements implicated in immune evasions, such as the inhibition of IFN signaling, can compromise host antiviral defenses and foster hyperinflammation. Notably, proteins encoded by SARS-CoV-2, such as Nsp1 and Nsp3, disrupt crucial signaling pathways integral to innate immunity, thus resulting in dysregulated cytokine responses and exacerbating inflammatory pathology [56].

**Interplay between host and pathogen**

**Immunopathology**

The dysregulated production of proinflammatory cytokines, known as cytokine responses, is pivotal in the immunopathology associated with severe COVID-19 [38]. Upon viral invasion, the host immune system initiates a response characterized by the release of cytokines, including IL-6, TNF-α, and IL-1β, among others [40, 41]. In severe cases, this dysregulation can culminate in a hyperinflammatory condition termed cytokine storm. This excessive immune activation contributes to tissue damage, multi-organ dysfunction, and unfavorable clinical outcomes. Moreover, cytokine storm is closely linked to the development of ARDS, a severe complication characterized by extensive lung inflammation in COVID-19 patients [52]. The dysregulated cytokine responses observed in severe cases of COVID-19 are believed to arise from a combination of viral factors and host immune dysregulation. SARS-CoV-2 infection triggers the activation of innate immune sensors, such as TLRs and RLRs, leading to the production of proinflammatory cytokines. Additionally, viral proteins such as the nucleocapsid protein (N) and Nsp1 have been implicated in modulating host immune responses and promoting cytokine release [57] (fig. 2).

**Role of renin-angiotensin system (RAS)**

The Renin-Angiotensin System (RAS) is a fundamental regulatory pathway crucial for maintaining blood pressure, fluid balance, and inflammatory responses. ACE2, a pivotal component of the RAS, acts as the cellular receptor facilitating the entry of SARS-CoV-2 into host cells [58]. Upon binding to ACE2, SARS-CoV-2 leads to the downregulation of ACE2 expression, resulting in disrupted RAS signaling and imbalanced levels of angiotensin II (Ang II). This dysregulation in COVID-19 is characterized by heightened production of Ang II and activation of the Angiotensin Type 1 Receptor (AT1R), ultimately culminating in increased vascular permeability, inflammation, and tissue damage (fig. 2). The inflammation mediated by Ang II is intricately linked to the development of acute lung injury and ARDS, severe complications often observed in COVID-19 patients [59]. Furthermore, dysregulated RAS signaling may exacerbate endothelial dysfunction, thrombosis, and cardiovascular complications in individuals affected by COVID-19 [60]. Understanding the intricate interplay of the renin-angiotensin system in COVID-19 pathogenesis is pivotal for devising targeted therapeutic interventions to mitigate severe outcomes associated with the disease.

**Impact of host genetics**

Host genetics significantly influence individual susceptibility to viral infections and the severity of diseases like COVID-19. Genetic variations in crucial host factors, including genes encoding viral receptors, immune response pathways, and antiviral defence mechanisms, play pivotal roles in determining the outcome of viral encounters. For instance, genetic alterations within the ACE2 gene, responsible for encoding the cellular receptor utilized by SARS-CoV-2, may impact the virus's ability to bind and enter cells, thereby shaping an individual's vulnerability to infection [61]. Similarly, gene variations governing innate and adaptive immune responses, such as TLRs, cytokines, and HLA genes, can significantly influence immune reactions to SARS-CoV-2 and affect disease severity. Additionally, host genetic factors can also affect how individuals respond to therapeutic interventions, including antiviral medications and vaccines. Understanding these genetic

predispositions is essential for developing personalized approaches to combat COVID-19 effectively [62]. Comprehending the impact of host genetics on both susceptibility to COVID-19 and the severity of its associated outcomes is paramount for identifying individuals at heightened risk and devising personalized treatment regimens. Incorporating host genetic data into clinical protocols holds promise for enhancing risk assessment and refining therapeutic strategies for COVID-19 patients.

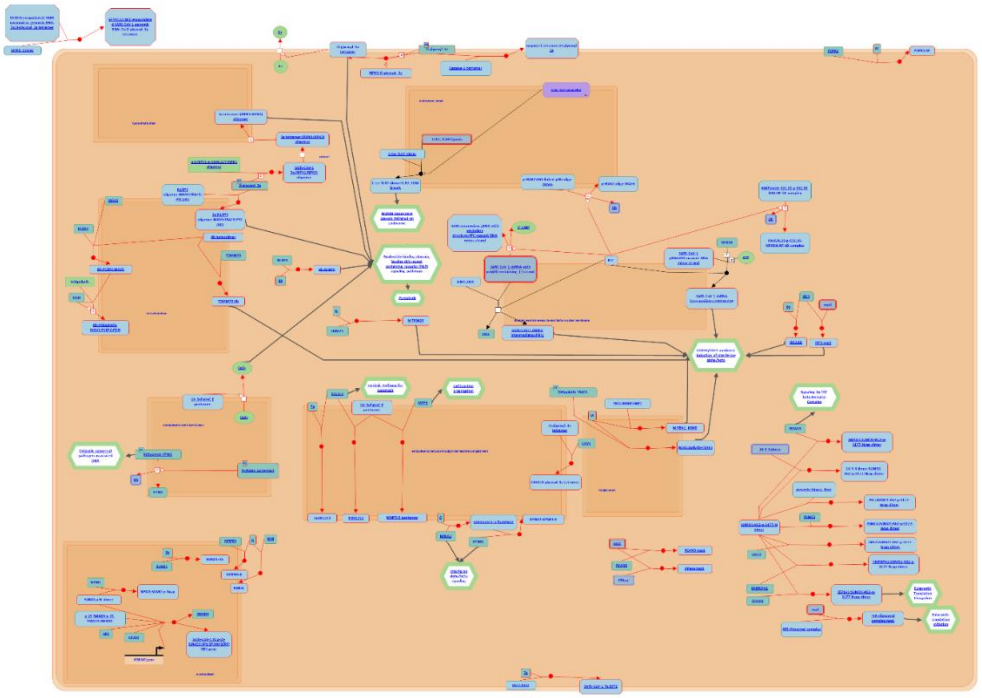

**Fig. 2: Interaction of coronavirus with host proteins**

Each stage of viral replication, including attachment and entry, translation of viral replicase, genome transcription and replication, translation of structural proteins, and virion assembly and release, relies on host factors. These interactions may induce changes in cellular structure and function, triggering host stress responses, autophagy, cell death, and innate immune processes. This illustration elucidates the molecular mechanisms through which SARS-CoV manipulates host cell death pathways, innate immune responses, translation, intracellular signalling, regulatory pathways, and cell-cell junctions. (Image has been generated with Reactome Pathway)

**Vaccines and their impact on hpis**

Gaining insight into the influence of vaccines on host-pathogen interactions is imperative for comprehending immune protection mechanisms and formulating robust vaccination strategies. Vaccines stimulate a comprehensive immune response, activating both innate and adaptive immunity to confer durable protection against pathogens [63]. Incorporating an understanding of host-pathogen interactions into vaccine design and development holds substantial promise for bolstering vaccine effectiveness and tackling the obstacles presented by emerging variants of concern [64].

Vaccines are meticulously engineered to emulate the presence of a pathogen, such as a virus or bacterium, while avoiding disease manifestation, prompting the immune system to recognize and memorize the pathogen's characteristics. This recognition enables the immune system to mount a swift and vigorous response upon subsequent encounters with the actual pathogen. For instance, in the context of SARS-CoV-2, the virus responsible for COVID-19, vaccines like the Pfizer-BioNTech and Moderna mRNA vaccines [65], as well as the Johnson and Johnson viral vector vaccine [66], have been developed to target the virus's spike protein, a crucial component for viral entry into host cells. By focusing on the spike protein, these vaccines trigger the production of neutralizing antibodies and activate T cells, furnishing protection against SARS-CoV-2 infection. The influence of vaccines on host-pathogen interactions has been thoroughly examined across different experimental models, including murine models of pulmonary tuberculosis induced by *Mycobacterium tuberculosis* [67]. Studies have indicated that vaccination can impact the prevalence of more virulent strains within the lungs of vaccinated subjects, underscoring the intricate dynamics between the host's immune response and the pathogen. Furthermore, the impact of vaccinated hosts on the population structure of microorganisms has been elucidated, particularly in the context of "*imperfect vaccines,*" which function by attenuating the growth rate of a microorganism rather than entirely preventing infection and transmission to new hosts [67]. Transcriptomics, a field of study focusing on the analysis of RNA transcripts, has proven invaluable in elucidating the intricate dynamics of host-pathogen interactions. By examining the gene expression profiles of host cells during severe SARS-CoV-2 infection and following vaccination, researchers have gained crucial insights into the human body's immune response [68, 69]. This comprehensive understanding is pivotal for tracking the evolution of viruses like SARS-CoV-2 and evaluating the implications of emerging variants of concern. Armed with this knowledge, scientists can tailor next-generation vaccines and vaccination strategies to effectively combat the evolving landscape of infectious diseases.

**Multi-omics in studying hpis**

The amalgamation of multi-omics data has enabled the discernment of prospective therapeutic targets, the formulation of diagnostic markers, and the elucidation of the intricate interactions between the virus and the host. These advanced technologies, characterized by their high-throughput nature, have furnished a holistic comprehension of the molecular terrain of SARS-CoV-2 infection, the host's immune reaction, and the pathophysiological underpinnings of COVID-19 [70].

**Genomics and transcriptomics in COVID-19**

Metagenome sequencing stands as a pivotal high-throughput genomics methodology for swiftly identifying emerging pathogens and accurately diagnosing COVID-19. This approach directly extracts

genetic information from environmental samples, laying the groundwork for comprehensive microbiota sequencing. For instance, in a study conducted by lin *et al.*, 310 clinical samples from 248 COVID-19 patients underwent metagenome sequencing, revealing the presence of SARS-CoV-2 in 98.7% of the samples. Moreover, a multiomics investigation integrated proteomics, acetylomics, phosphoproteomics, and exometabolome analyses to thoroughly delineate the host responses provoked by SARS-CoV-2 infection in human lung epithelial cells [71]. The research delineated the activation of the Hippo signaling pathway, perturbations in metabolic pathways, and immune pathways in reaction to SARS-CoV-2 infection. Furthermore, it pinpointed various prospective therapeutic targets, encompassing the Hippo signaling pathway [71, 72], the interferon signaling pathway [73], and the NF-kB pathway [74].

The COVID-19 Host Genetics Initiative has convened the human genetics community to collate, exchange, and scrutinize data aimed at unraveling the genetic underpinnings of COVID-19 susceptibility, severity, and prognosis [75]. By amalgamating genomics data, investigators have pinpointed potential genetic predisposing factors linked to severe COVID-19, including variants in the human leukocyte antigen (HLA) genes [76] and the IFN-induced transmembrane protein-3 gene [77].

**Proteomic and metabolomics**

The exploration of proteomics and metabolomics has proven pivotal in delineating the intricate proteomic and metabolic shifts elicited by SARS-CoV-2 infection. These investigations have unveiled a comprehensive spectrum of alterations, shedding light on changes in immune responses, fatty acid metabolism, amino acid metabolism, and other critical pathways. For instance, in a study conducted by Wang *et al.*, the proteomic and metabolomic profiles associated with the immune response were scrutinized in individuals vaccinated with an inactivated SARS-CoV-2 vaccine. The findings underscored the impact of COVID-19 infection on pathways linked to arginine biosynthesis, alanine, aspartate, and glutamate metabolism, as well as glycine, serine, and threonine metabolism. Furthermore, the investigation demonstrated notable alterations in various pathways after vaccination with the inactivated SARS-CoV-2 vaccine, encompassing vitamin B6 metabolism, biosynthesis of unsaturated fatty acids, and phenylalanine metabolism, among others [78]. Proteomic analysis has unveiled aberrations in the extracellular matrix [79], immunity [80], and homeostasis [81] among COVID-19 survivors in comparison to healthy individuals. Elevated levels of specific proteins associated with inflammation and immune response, such as IL-6, CRP, and ferritin, were observed in COVID-19 patients [82].

Additionally, metabolomic investigations have delineated notable changes in the immune response [83], fatty acid metabolism [84], and amino acid metabolism [81] among individuals afflicted with COVID-19. The altered biomolecular profile offers insights into the dysregulated biological pathways, contributing valuable understanding to the pathogenesis of COVID-19. For instance, a study by Valdes *et al.* highlighted specific metabolites, such as cytosine and indole-3-acetic acid, which exhibited differential expression, predominantly distinguishing between COVID-19-positive and-negative patients alongside other metabolites. Another study delved into the potential utility of saliva and plasma metabolomic profiles as a means of risk stratification among COVID-19 patients. The investigation revealed that severe cases of COVID-19 correlate with dysregulated innate immunity, lymphocytopenia, cytokine storm, and altered metabolite profiles [85]. These observations hold substantial importance in tailoring personalized diagnostic and therapeutic interventions, ultimately enhancing patient prognosis. Through the analysis of multiomics data across various infection stages, researchers can pinpoint disease progression biomarkers, prognosticate patient outcomes, and customize treatment approaches. The integration of multi-omics data harbors the potential to drive the advancement of personalized diagnostic and therapeutic methodologies, thereby fostering enhanced patient outcomes.

## CONCLUSION

The COVID-19 pandemic has posed a significant challenge, manifesting across a spectrum of clinical presentations from asymptomatic cases to severe respiratory compromise and multi-organ dysfunction. Host-related variables such as age, gender, underlying health conditions, and genetic predisposition contribute to the diverse severity observed in patients, underscoring the necessity for personalized medicine strategies in patient care. The integration of advanced methodologies such as multiomics has yielded a holistic understanding of the molecular dynamics of the disease, unveiling novel insights into host immune reactions, viral pathogenesis, and disease evolution. Moving forward, the future of COVID-19 research entails integrating longitudinal multiomics data to capture the temporal dynamics of host responses, establishing standardized methodologies for data analysis and interpretation, and exploring novel therapeutic strategies targeting host-pathogen interactions. Nevertheless, challenges such as complexities in data integration, ethical considerations, and the imperative for interdisciplinary collaboration persist as obstacles to furthering our comprehension of COVID-19 pathogenesis.

## ACKNOWLEDGEMENT

Nil

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

Mairembam Stelin Singh has performed all the experiments throughout the study. Sailu Yellaboina has designed the whole study for experimental research. Mairaj Ahmed Ansari has supervised and proof read the manuscript.

## CONFLICT OF INTERESTS

Declared none

## REFERENCES

1. Mallah SI, Ghorab OK, Al-Salmi S, Abdellatif OS, Tharmaratnam T, Iskandar MA. COVID-19: breaking down a global health crisis. Ann Clin Microbiol Antimicrob. 2021;20(1):35. doi: 10.1186/s12941-021-00438-7, PMID 34006330, PMCID PMC8129964.
2. Peng M. Outbreak of COVID-19: an emerging global pandemic threat. Biomed Pharmacother. 2020;129:(110499). doi: 10.1016/j.biopha.2020.110499, PMID 32768974, PMCID PMC7334916.
3. Hassan SA, Sheikh FN, Jamal S, Ezeh JK, Akhtar A. Coronavirus (COVID-19): a review of clinical features, diagnosis, and treatment. Cureus. 2020;12(3):e7355. doi: 10.7759/cureus.7355, PMID 32328367, PMCID PMC7170025.
4. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). StatPearls Publishing; 2023.
5. Lake MA. What we know so far: COVID-19 current clinical knowledge and research. Clin Med (Lond). 2020;20(2):124-7. doi: 10.7861/clinmed.2019-coron, PMID 32139372, PMCID PMC7081812.
6. Fung TS, liu DX. Human coronavirus: host-pathogen interaction. Annu Rev Microbiol. 2019;73(1):529-57. doi: 10.1146/annurev-micro-020518-115759, PMID 31226023.
7. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses. 2020;12(4):372. doi: 10.3390/v12040372.
8. Li C, He Q, Qian H, liu J. Overview of the pathogenesis of COVID-19 (Review). Exp Ther Med. 2021;22(3):1011. doi: 10.3892/etm.2021.10444, PMID 34345293.
9. Wu F, Zhao S, Yu B, Chen YM, Wang W, Hu Y. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. bioRxiv; 2020. doi: 10.1101/2020.01.24.919183.
10. Mehta S, Sharma N, Jain S. Impact of COVID-19 pandemic on maternal mortality ratio in a tertiary care hospital of Rajasthan: a retrospective analysis. Asian J Pharm Clin Res. 2022;15(10):39-41. doi: 10.22159/ajpcr.2022.v15i10.45535.
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.

Lancet. 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5, PMID 31986264, PMCID PMC7159299.

12. Li C, He Q, Qian H, liu J. Overview of the pathogenesis of COVID-19 (Review). Exp Ther Med. 2021;22(3):1011. doi: 10.3892/etm.2021.10444, PMID 34345293, PMCID PMC8311250.
13. Skariyachan S, Challapilli SB, Packirisamy S, Kumargowda ST, Sridhar VS. Recent aspects on the pathogenesis mechanism, animal models and novel therapeutic interventions for middle East Respiratory Syndrome coronavirus infections. Front Microbiol. 2019;10:569. doi: 10.3389/fmicb.2019.00569, PMID 30984127, PMCID PMC6448012.
14. Park SH. An impaired inflammatory and innate immune response in COVID-19. Mol Cells. 2021;44(6):384-91. doi: 10.14348/molcells.2021.0068, PMID 34098591, PMCID PMC8245320.
15. Hosseini A, Hashemi V, Shomali N, Asghari F, Gharibi T, Akbari M. Innate and adaptive immune responses against coronavirus. Biomed Pharmacother. 2020;132:(110859). doi: 10.1016/j.biopha.2020.110859, PMID 33120236, PMCID PMC7580677.
16. Taefehshokr N, Taefehshokr S, Hemmat N, Heit B. COVID-19: perspectives on innate immune evasion. Front Immunol. 2020;11:580641. doi: 10.3389/fimmu.2020.580641, PMID 33101306, PMCID PMC7554241.
17. Ahmadpoor P, Rostaing L. Why the immune system fails to mount an adaptive immune response to a COVID-19 infection. Transpl Int. 2020;33(7):824-5. doi: 10.1111/tri.13611, PMID 32236983.
18. Lopez L, Sang PC, Tian Y, Sang Y. Dysregulated interferon response underlying severe COVID-19. Viruses. 2020;12(12):1433. doi: 10.3390/v12121433, PMID 33322160, PMCID PMC7764122.
19. Uday Srikar VS, Naga Swarna YV, Yugandhar G. The loss of smell (anosmia) in COVID 19 patients-to what extent it helps in the diagnosis of COVID 19 and factors influencing its recovery-a clinical study. Asian J Pharm Clin Res. 2022;15(2):135-7. doi: 10.22159/ajpcr.2022.v15i2.43872.
20. Farzi R, Aghbash PS, Eslami N, Azadi A, Shamekh A, Hemmat N. The role of antigen-presenting cells in the pathogenesis of COVID-19. Pathol Res Pract. 2022;233:(153848). doi: 10.1016/j.prp.2022.153848, PMID 35338971, PMCID PMC8941975.
21. Oliveira DS, Medeiros NI, Gomes JA. Immune response in COVID-19: what do we currently know? Microb Pathog. 2020;148:104484. doi: 10.1016/j.micpath.2020.104484, PMID 32916246, PMCID PMC7480770.
22. Nikhra V. The agent and host factors in COVID-19: exploring pathogenesis and therapeutic implications. Biomed J Sci Techn Res. 2020;27:20669-81.
23. Nepomuceno MR, Acosta E, Alburez Gutierrez D, Aburto JM, Gagnon A, Turra CM. Besides population age structure, health and other demographic factors can contribute to understanding the COVID-19 burden. Proc Natl Acad Sci USA. 2020;117(25):13881-3. doi: 10.1073/pnas.2008760117, PMID 32576710, PMCID PMC7322063.
24. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. J Infect. 2020;80(6):e14-8. doi: 10.1016/j.jinf.2020.03.005, PMID 32171866.
25. Mukherjee S, Pahan K. Is COVID-19 gender-sensitive? J Neuroimmune Pharmacol. 2021;16(1):38-47. doi: 10.1007/s11481-020-09974-z, PMID 33405098, PMCID PMC7786186.
26. Yang J, Tian C, Chen Y, Zhu C, Chi H, Li J. Obesity aggravates COVID-19: an updated systematic review and meta-analysis. J Med Virol. 2021;93(5):2662-74. doi: 10.1002/jmv.26677, PMID 33200825, PMCID PMC7753795.
27. Gülsen A, König IR, Jappe U, Dromann D. Effect of comorbid pulmonary disease on the severity of COVID-19: a systematic review and meta-analysis. Respirology. 2021;26(6):552-65. doi: 10.1111/resp.14049, PMID 33955623, PMCID PMC8207055.
28. Singh J, Malik P, Patel N, Pothuru S, Israni A, Chakinala RC. Kidney disease and COVID-19 disease severity-systematic review and meta-analysis. Clin Exp Med. 2022;22(1):125-35. doi: 10.1007/s10238-021-00715-x, PMID 33891214, PMCID PMC8063780.
29. Tassone D, Thompson A, Connell W, lee T, Ungaro R, An P, Ding Y, Ding NS. Immunosuppression as a risk factor for COVID-19: a meta-analysis. Intern Med J. 2021;51(2):199–205. doi: 10.1111/imj.15142, PMCID: PMC8014211.
30. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. Med J Aust. 2020;213(2):54-56.e1. doi: 10.5694/mja2.50674, PMID 32572965, PMCID PMC7361309.
31. Qiu Y, Chen X, Shi W. Impacts of social and economic factors on the transmission of coronavirus disease 2019 (COVID-19) in China. J Popul Econ. 2020;33(4):1127-72. doi: 10.1007/s00148-020-00778-2, PMID 32395017, PMCID PMC7210464.
32. Hawkins RB, Charles EJ, Mehaffey JH. Socio-economic status and COVID-19-related cases and fatalities. Public Health. 2020;189:129-34. doi: 10.1016/j.puhe.2020.09.016, PMID 33227595, PMCID PMC7568122.
33. Hu J, Li C, Wang S, Li T, Zhang H. Genetic variants are identified to increase risk of COVID-19 related mortality from UK Biobank data. Hum Genomics. 2021;15(1):10. doi: 10.1186/s40246-021-00306-7, PMID 33536081, PMCID PMC7856608.
34. Pairo Castineira E, Rawlik K, Bretherick AD, Qi T, Wu Y, Nassiri I. GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19. Nature. 2023;617(7962):764–8. doi: 10.1038/s41586-023-06034-3, PMCID: PMC10208981.
35. Horowitz JE, Kosmicki JA, Damask A, Sharma D, Roberts GH, Justice AE. Genome-wide analysis provides genetic evidence that ACE2 influences COVID-19 risk and yields risk scores associated with severe disease. Nat Genet. 2022;54(4):382–92. doi: 10.1038/s41588-021-01006-7, PMCID: PMC9005345.
36. Langton DJ, Bourke SC, Lie BA, Reiff G, Natu S, Darlay R. The influence of HLA genotype on the severity of COVID-19 infection. HLA. 2021;98(1):14-22. doi: 10.1111/tan.14284, PMID 33896121, PMCID PMC8251294.
37. Araujo A, Sgorlon G, Aguiar LE, Cidrao MH, Teixeira KS, Villalobos Salcedo JM. Influence of polymorphic variations of IFNL, HLA, and IL-6 genes in severe cases of COVID-19. Exp Biol Med (Maywood). 2023;248(9):787-97. doi: 10.1177/15353702231181343, PMID 37452704, PMCID PMC10350587.
38. Davitt E, Davitt C, Mazer MB, Areti SS, Hotchkiss RS, Remy KE. COVID-19 disease and immune dysregulation. Best Pract Res Clin Haematol. 2022;35(3):101401. doi: 10.1016/j.beha.2022.101401, PMID 36494149, PMCID PMC9568269.
39. Jamal M, Bangash HI, Habiba M, lei Y, Xie T, Sun J, Wei Z, Hong Z, Shao l, Zhang Q. Immune dysregulation and system pathology in COVID-19. Virulence. 2021;12(1):918-36. doi: 10.1080/21505594.2021.1898790, PMCID: PMC7993139.
40. Lagunas Rangel FA, Chavez Valencia V. High IL-6/IFN-γ ratio could be associated with severe disease in COVID-19 patients. J Med Virol. 2020;92(10):1789-90. doi: 10.1002/jmv.25900, PMID 32297995, PMCID PMC7262117.
41. Ganji A, Farahani I, Khansarinejad B, Ghazavi A, Mosayebi G. Increased expression of CD8 marker on T-cells in COVID-19 patients. Blood Cells Mol Dis. 2020;83:(102437). doi: 10.1016/j.bcmd.2020.102437, PMID 32325421, PMCID PMC7194879.
42. Mohammed N, Kamal Saeed AS. COVID-19 disease and autoimmune disorders: A mutual pathway. World J Methodol. 2022 Jul 20;12(4):200-23. doi: 10.5662/wjm.v12.i4.200, PMID 36159097, PMCID: PMC9350728.
43. Lim YX, Ng YL, Tam JP, liu DX. Human coronaviruses: a review of virus-host interactions. Diseases. 2016;4(3):26. doi: 10.3390/diseases4030026, PMID 28933406, PMCID PMC5456285.
44. Tsukagoshi H, Shinoda D, Saito M, Okayama K, Sada M, Kimura H. Relationships between viral load and the clinical course of COVID-19. Viruses. 2021;13(2):304. doi: 10.3390/v13020304, PMID 33672005, PMCID PMC7919281.
45. Dadras O, Afsahi AM, Pashaei Z, Mojdeganlou H, Karimi A, Habibi P. The relationship between COVID-19 viral load and disease

severity: a systematic review. Immun Inflamm Dis. 2022;10(3):e580. doi: 10.1002/iid3.580, PMID 34904379, PMCID PMC8926507.

46. Biju P, Pallavi RV, Dsouza S, Asif Iqbal M, Ahmed G. A review on the impact of the COVID-19 pandemic on the health care sector. Int J Pharm Pharm Sci. 2021;13(10):1-6. doi: 10.22159/ijpps.2021v13i10.42566.
47. Rabaan AA, Tirupathi R, Sule AA, Aldali J, Mutair AA, Alhumaid S. Viral dynamics and real-time RT-PCR Ct values correlation with disease severity in COVID-19. Diagnostics (Basel). 2021;11(6):1091. doi: 10.3390/diagnostics11061091, PMID 34203738, PMCID PMC8232180.
48. Hadj Hassine I. COVID-19 vaccines and variants of concern: a review. Rev Med Virol. 2022;32(4). doi: 10.1002/rmv.2313.
49. Zahmatkesh S. Review of concerned SARS-CoV-2 variants like Alpha (B. 1.1. 7). Beta (B. 1.351), Gamma (P. 1). Delta (B. 1.617. 2), and Omicron (B. 1.1. 529), as well as novel methods for reducing and inactivating SARS-CoV-2 mutants in wastewater treatment facilities. Journal of Hazardous Materials Advances. 2022;7:100140. doi: 10.1016/j.hazadv.2022.100140, PMID: 37520798.
50. Hajizadeh F, Khanizadeh S, Khodadadi H, Mokhayeri Y, Ajorloo M, Malekshahi A. SARS-COV-2 RBD (Receptor binding domain) mutations and variants (A sectional-analytical study). Microb Pathog. 2022;168:(105595). doi: 10.1016/j.micpath.2022.105595, PMID 35597364, PMCID PMC9116045.
51. He X, He C, Hong W, Zhang K, Wei X. The challenges of COVID-19 delta variant: prevention and vaccine development. Med. 2021;2(4):846-54. doi: 10.1002/mco2.95, PMID 34909755, PMCID PMC8661803.
52. Tang Y, liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol. 2020;11:1708. doi: 10.3389/fimmu.2020.01708, PMID 32754163, PMCID PMC7365923.
53. Attiq A, Yao LJ, Afzal S, Khan MA. The triumvirate of NF-κB, inflammation and cytokine storm in COVID-19. Int Immunopharmacol. 2021;101(B):108255. doi: 10.1016/j.intimp.2021.108255, PMID 34688149, PMCID PMC8516728.
54. Su CM, Wang L, Yoo D. Activation of NF-κB and induction of proinflammatory cytokine expressions mediated by ORF7a protein of SARS-CoV-2. Sci Rep. 2021;11(1):13464. doi: 10.1038/s41598-021-92941-2, PMID 34188167, PMCID PMC8242070.
55. Zhang J, Ejikemeuwa A, Gerzanich V, Nasr M, Tang Q, Simard JM. Understanding the role of SARS-CoV-2 ORF3a in viral pathogenesis and COVID-19. Front Microbiol. 2022;13:854567. doi: 10.3389/fmicb.2022.854567, PMID 35356515, PMCID PMC8959714.
56. Ramasamy S, Subbian S. Critical determinants of cytokine storm and type I interferon response in COVID-19 pathogenesis. Clin Microbiol Rev. 2021;34(3). doi: 10.1128/CMR.00299-20, PMID 33980688, PMCID PMC8142516.
57. Kouwaki T, Nishimura T, Wang G, Oshiumi H. RIG-I-like receptor-mediated recognition of viral genomic RNA of severe acute respiratory syndrome Coronavirus-2 and viral escape from the host innate immune responses. Front Immunol. 2021;12:700926. doi: 10.3389/fimmu.2021.700926, PMID 34249006, PMCID PMC8267574.
58. Lanza K, Perez lG, Costa lB, Cordeiro TM, Palmeira VA, Ribeiro VT, Simoes E Silva AC. COVID-19: the renin-angiotensin system imbalance hypothesis. Clin Sci (Lond). 2020;134(11):1259-64. doi: 10.1042/CS20200492, PMCID: PMC7276636.
59. Silhol F, Sarlon G, Deharo JC, Vaisse B. Downregulation of ACE2 induces overstimulation of the renin-angiotensin system in COVID-19: should we block the renin-angiotensin system? Hypertens Res. 2020;43(8):854-6. doi: 10.1038/s41440-020-0476-3, PMID 32439915, PMCID PMC7242178.
60. Lumbers ER, Head R, Smith GR, Delforce SJ, Jarrott B, H Martin J. The interacting physiology of COVID-19 and the renin-angiotensin-aldosterone system: key agents for treatment. Pharmacol Res Perspect. 2022;10(1):e00917. doi: 10.1002/prp2.917, PMID 35106954, PMCID PMC8929333.
61. Elhabyan A, Elyaacoub S, Sanad E, Abukhadra A, Elhabyan A, Dinu V. The role of host genetics in susceptibility to severe viral infections in humans and insights into host genetics of severe COVID-19: a systematic review. Virus Res. 2020;289:198163. doi: 10.1016/j.virusres.2020.198163, PMID 32918943, PMCID PMC7480444.
62. Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA, Kennedy RB. The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. Immunol Rev. 2020;296(1):205-19. doi: 10.1111/imr.12897, PMID 32658335, PMCID PMC7404857.
63. Jordan SC. Innate and adaptive immune responses to SARS-CoV-2 in humans: relevance to acquired immunity and vaccine responses. Clin Exp Immunol. 2021;204(3):310-20. doi: 10.1111/cei.13582, PMID 33534923, PMCID PMC8013613.
64. Varghese PM, Tsolaki AG, Yasmin H, Shastri A, Ferluga J, Vatish M. Host-pathogen interaction in COVID-19: pathogenesis, potential therapeutics and vaccination strategies. Immunobiology. 2020;225(6):152008. doi: 10.1016/j.imbio.2020.152008, PMID 33130519, PMCID PMC7434692.
65. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and moderna vaccines. Eur Rev Med Pharmacol Sci. 2021;25(3):1663-9. doi: 10.26355/eurrev_202102_24877, PMID 33629336.
66. Livingston EH, Malani PN, Creech CB. The Johnson and Johnson vaccine for COVID-19. JAMA. 2021;325(15):1575. doi: 10.1001/jama.2021.2927, PMID 33646285.
67. Zatarain Barron ZL, Ramos Espinosa O, Marquina Castillo B, Barrios Payan J, Cornejo Granados F, Maya Lucas O. Evidence for the effect of vaccination on host-pathogen interactions in a murine model of pulmonary tuberculosis by mycobacterium tuberculosis. Front Immunol. 2020;11:930. doi: 10.3389/fimmu.2020.00930, PMID 32508826.
68. Mehta P, Swaminathan A, Yadav A, Chattopadhyay P, Shamim U, Pandey R. Integrative genomics important to understand host-pathogen interactions. Brief Funct Genomics. 2024;23(1):1-14. doi: 10.1093/bfgp/elac021, PMID 35909219.
69. Butler D, Mozsary C, Meydan C, Foox J, Rosiene J, Shaiber A. Shotgun transcriptome, spatial omics, and isothermal profiling of SARS-CoV-2 infection reveals unique host responses, viral diversification, and drug interactions. Nat Commun. 2021;12(1):1660. doi: 10.1038/s41467-021-21361-7, PMCID: PMC7954844.
70. Aggarwal S, Acharjee A, Mukherjee A, Baker MS, Srivastava S. Role of multiomics data to understand host-pathogen interactions in COVID-19 pathogenesis. J Proteome Res. 2021;20(2):1107-32. doi: 10.1021/acs.jproteome.0c00771, PMID 33426872, PMCID PMC7805606.
71. Zhou P, Yang XL, Wang XG, Hu B, Zhang l, Zhang W. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. doi: 10.1038/s41586-020-2012-7, PMCID: PMC7095418.
72. Meng F. SARS-CoV-2 NSP13 suppresses the hippo pathway downstream effector YAP. bioRxiv. 2023:2023-34. doi: 10.1101.2023.11.30.569413.
73. Soltani Zangbar MS, Parhizkar F, Ghaedi E, Tarbiat A, Motavalli R, Alizadegan A. A comprehensive evaluation of the immune system response and type-I interferon signaling pathway in hospitalized COVID-19 patients. Cell Commun Signal. 2022;20(1):106. doi: 10.1186/s12964-022-00903-6, PMID 35842705, PMCID PMC9287826.
74. Kircheis R, Haasbach E, Lueftenegger D, Heyken WT, Ocker M, Planz O. NF-κB pathway as a potential target for the treatment of critical stage COVID-19 patients. Front Immunol. 2020;11:598444. doi: 10.3389/fimmu.2020.598444, PMID 33362782, PMCID PMC7759159.
75. Butler Laporte G, Povysil G, Kosmicki JA, Cirulli ET, Drivas T, Furini S. Exome-wide association study to identify rare variants influencing COVID-19 outcomes: results from the Host Genetics Initiative. PLOS Genet. 2022;18(11):e1010367. doi: 10.1371/journal.pgen.1010367, PMID 36327219.

76. Mentzer AJ, O'Connor D, Bibi S, Chelysheva I, Clutterbuck EA, Demissie T. Human leukocyte antigen alleles associate with COVID-19 vaccine immunogenicity and risk of breakthrough infection. Nat Med. 2023;29(1):147-57. doi: 10.1038/s41591-022-02078-6, PMID 36228659, PMCID PMC9873562.
77. Quarleri J, Delpino MV. Type I and III IFN-mediated antiviral actions counteracted by SARS-CoV-2 proteins and host inherited factors. Cytokine Growth Factor Rev. 2021;58:55-65. doi: 10.1016/j.cytogfr.2021.01.003, PMID 33608189, PMCID PMC7871890.
78. Wang Y, Wang X, luu lDW, Chen S, Jin F, Wang S, Huang X, Wang l, Zhou X, Chen X, Cui X, li J, Tai J, Zhu X. Proteomic and metabolomic signatures associated with the immune response in healthy individuals immunized with an inactivated SARS-CoV-2 vaccine. Front Immunol. 2022;13. doi: 10.3389/fimmu.2022.848961.
79. Mao K, Tan Q, Ma Y, Wang S, Zhong H, liao Y. Proteomics of extracellular vesicles in plasma reveals the characteristics and residual traces of COVID-19 patients without underlying diseases after 3 mo of recovery. Cell Death Dis. 2021;12(6):541. doi: 10.1038/s41419-021-03816-3, PMID 34035220, PMCID PMC8146187.
80. Russell CD, Valanciute A, Gachanja NN, Stephen J, Penrice Randal R, Armstrong SD. Tissue proteomic analysis identifies mechanisms and stages of immunopathology in fatal COVID-19. Am J Respir Cell Mol Biol. 2022;66(2):196-205. doi: 10.1165/rcmb.2021-0358OC, PMID 34710339, PMCID PMC8845132.
81. Jose C. Metabolomics analysis reveals a modified amino acid metabolism that correlates with altered oxygen homeostasis in COVID-19 patients. Sci Rep. 2021;11.
82. di Flora DC, Dionizio A, Pereira HA, Garbieri TF, Grizzo lT, Dionisio TJ, Leite A de l. Analysis of plasma proteins involved in inflammation, immune response/complement system, and blood coagulation upon admission of COVID-19 patients to hospital May help to predict the prognosis of the disease. Cells. 2023;12(12):1661. doi: 10.3390/cells12121601, PMCID: PMC10297236.
83. Bi X, Liu W, Ding X, Liang S, Zheng Y, Zhu X. Proteomic and metabolomic profiling of urine uncovers immune responses in patients with COVID-19. Cell Rep. 2022;38(3):110271. doi: 10.1016/j.celrep.2021.110271, PMID 35026155.
84. Wu D, Shu T, Yang X, Song JX, Zhang M, Yao C. Plasma metabolomic and lipidomic alterations associated with COVID-19. Natl Sci Rev. 2020;7(7):1157-68. doi: 10.1093/nsr/nwaa086, PMID 34676128, PMCID PMC7197563.
85. Valdes A, Moreno LO, Rello SR, Orduna A, Bernardo D. Metabolomics study of COVID-19 patients in four different clinical stages. Sci Rep. 2022;12(1):1650. doi: 10.1038/s41598-022-05667-0, PMID 35102215, PMID: 35102215.