Influenza A and COVID-19

Subjects: Virology
Contributor: Meilin Jin

Influenza is a highly known contagious viral infection that has been responsible for the death of many people in history with pandemics. These pandemics have been occurring every 10 to 30 years in the last century. The most recent global pandemic prior to COVID-19 was the 2009 influenza A (H1N1) pandemic. A decade ago, the H1N1 virus caused 12,500 deaths in just 19 months globally. Now, again, the world has been challenged with another pandemic. COVID-19 and influenza viruses have very similar signs, and symptoms may explain the similar origin. According to a recent World Health Organization survey, the COVID-19 attack and disease burden in children have been much lower than influenza outbreaks, and the secondary household attack rate has also been low. This is in stark contrast to reports of the virus spreading quickly in enclosed spaces like hospitals or cruise ships, as well as a high prevalence of healthcare-associated infections.

Keywords: COVID-19 ; influenza A ; coronavirus ; pandemic

1. Virology and Structural Characteristics

1.1. Coronavirus (COVID-19)

Coronavirus belongs to the family of Coronaviridae. Coronaviridae is a family of enveloped, positive-strand RNA viruses that infect amphibians, birds, and mammals [1]. The virus's genome size is between 26 to 32 kB, which is considered among the viruses with the most extensive RNA. These viruses have two different surface proteins that are named after their external features [2]. Coronaviridae family is divided into two subfamilies, including Coronavirinae and Torovirinae. The Coronavirinae subfamily is composed of four well-known genera (i.e., alpha coronavirus (α-coronavirus), beta coronavirus (β-coronavirus), gamma coronavirus (γ-coronavirus,) and delta coronavirus (δ-coronavirus)). Human diseases are associated with the genera alpha coronavirus and beta coronavirus, while those belonging to the genera gamma coronavirus and delta coronavirus cause disease in animals. COVID-19 as SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome) belong to the beta coronavirus genus, while HCoV-NL63 and HCoV-229E belong to the alpha coronavirus genus [1]. Coronavirus can infect mammals and birds by triggering various lethal diseases [3].

COVID-19 is the seventh coronavirus known to infect humans, and its clinical symptoms are similar to influenza A, ranging from asymptomatic or mild through severe disease and death. The COVID-19 genome is 50% and 79%, the same as MERS-CoV and SARS-CoV, respectively. The Coronaviruses belong to the enveloped, non-segmented, single-stranded RNA, positive-sense viruses whose genome size is 26–32 kB (nearly 30 kB). Two important ORFs were found in the COVID-19 genome. They are ORF1a and ORF1b, with the potential to encode 16 non-structural proteins (NSP), constituting almost two-thirds of the viral genome.

Moreover, the remaining one-third of the COVID-19 genome encodes structural and accessory proteins. Diverse structural proteins including S (spike), M (membrane), N (nucleocapsid), and E (envelope) were identified in the COVID-19 virion. These structural proteins are critical mediators in cell attachment and entrance, genome replication, and pathogenicity and finally promote infection [3].

The highly glycosylated COVID-19 S protein comprises two subunits called S1 and S2 (Figure 1). S1 with a receptor-binding domain (RBD) plays a crucial role in cell entrance and tissue tropism by binding to ACE2 on the host cell. Furthermore, a polybasic cleavage site (PRRAR) recognized by the prototype proprotein convertase furin was identified at S protein. This pre-processing gives an unusual feature to COVID-19 that significantly increases tissue tropism and transmissibility [3].

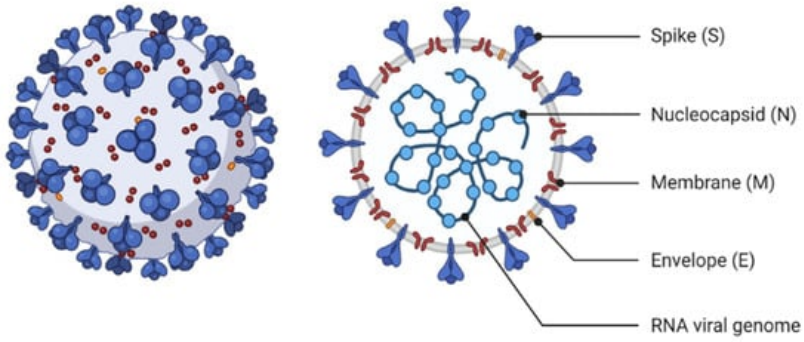


Figure 1. The structural characteristics of Coronavirus.

Moreover, TMPRSS2 is a transmembrane serine protease that facilitates cleavage at the S1-S2 boundary and downstream cell fusion. N protein appears to be directly bound to the RNA genome and involved in ribonucleoprotein construction, which functions in cell fusion and entrance. Furthermore, N protein functioning as a cell cycle inhibitor was determined by cell cycle studies. M protein is involved in ribonucleoproteins formation and is considered a key mediator of inflammatory responses in the host, whereas virion formation and viral pathogenicity are triggered by E protein [4]. COVID-19 genomic RNA has also been demonstrated to contain a 5'-cap structure and a 3'-polyadenylation tail, essential for directing the COVID-19 genomic RNA translation into a structural and non-structural protein. Additionally, stem-loop structures within 5'-UTR and a leader sequence of the COVID-19 genome are essential for transcription and replication. Furthermore, the transcription regulatory sequence (TRS) located throughout the COVID-19 genome is one of the most distinguishing characteristics of COVID-19 and plays a crucial role in transcription regulation (Figure 2) [5].

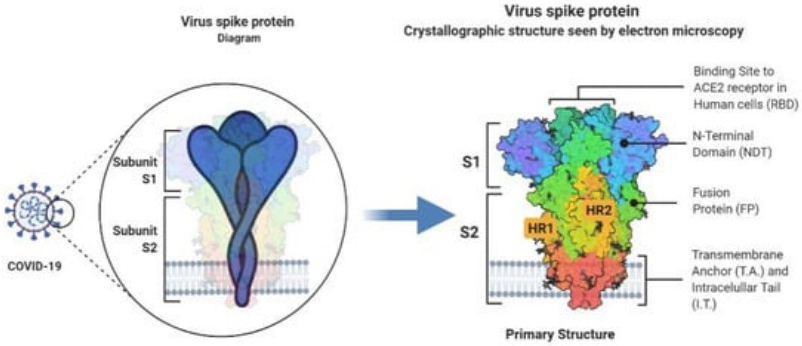


Figure 2. An in-depth look into the structure of the Covid-19 spike glycoprotein.

1.2. Influenza A (H1N1)

The influenza virus has several antigens divided into three types of influenza A, B, C based on the antigenic disparity between nucleoprotein and protein matrix [6]. Based on the surface structure, hemagglutinin and neuraminidase, the B and C types of the influenza virus have merely one serotype [7], while the influenza A virus has 16 serotypes based on hemagglutinin and nine serotypes based on neuraminidase. In this vein, it should be stated that the highest incidence of the flu in humans is caused by the influenza A virus [8]. This virus can infect mammals and birds, including horses, pigs, and various species of poultry as well as humans [6].

The influenza A virus is a dangerous virus with a single-stranded, eight-piece RNA genome whose genetic structure lends itself to modification. Genetic mutations may be of minor nature, that may result in a local influenza epidemic in winters due to the widespread viruses, or a more extensive nature, that may give rise to the emergence of a novel virus creating more severe pathogenesis and causing a global epidemic [9]. Antigenic shifts occur only in influenza A and refer to the emergence of a new influenza virus that allows human-to-human transmission. In this context, international travel is a serious global health threat and should be restricted [10]. Influenza A genetic material is packaged into eight negative-sense single-stranded RNA in an enveloped virus. Neuraminidase (NA), hemagglutinin (HA), and less frequently, the matrix 2 (M2) protein are central membrane structural proteins in influenza A. Additionally, the matrix 1 (M1) protein is located beneath the membrane and is surrounded by eight vRNAs that exist as separate viral ribonucleoprotein (vRNP) complexes. In addition, M1 is a key mediator in viral morphology and is important for cell membrane binding. Among other structural proteins, HA is the main contributing factor in influenza A infection. In other words, HA with terminal sialic acid (SA) residues bind to sialylated receptors on the potential host cells [10].

2. Epidemiology

2.1. Epidemiological Prospective of COVID-19

China was the first country to report a case, and it had a higher morbidity and mortality rate than the rest of the world. Furthermore, up to 16 March 2020, Iran, with 14,991 patients, was the third country with the highest reported cases after China and Italy [11]. However, since 28 March, the United States has seen more than 590,000 COVID-19 patients and 24,000 deaths, far above the number of cases reported. COVID-19 cases are rising every day in Brazil, with the number of positive cases expected to exceed [12]. As of February 2021, more than one-hundred million confirmed cases worldwide of COVID-19 had been reported to the World Health Organization [13].

Following the increasing rate of the incidence and the global spread of the virus, the WHO issued a declaration on 30 January 2020, announcing the outbreak of the new coronavirus as the sixth cause of public health emergency of international concern, regarded as a threat not only to China but to all countries. Before this new coronavirus, the WHO had announced the last public health emergency for the outbreak of influenza H1N1 in 2009. The WHO officially named the new coronavirus COVID-19 on 11 February 2020 [14]; on the same day, the International Committee on Virus Taxonomy (ICTV) changed the name of the virus that causes this disease from 2019-nCoV to SARS-COV-2 [15].

2.1.1. Death Rate by Age Group

The death rate and the probability of dying if infected by the virus are highly variable by age in COVID-19. The exploration of mortality rate by age in COVID-19 disclosed age-dependent mortality, and most deaths were recorded in patients older than 50 years. Furthermore, according to a new study conducted by UK researchers using data from mainland China, the average mortality rate of COVID-19 is 0.66%, rising sharply to 7.8% in people over 80 and falling to 0.0016% in children aged nine and younger. They also discovered that about one out of every five people over the age of 80 infected with COVID-19 would likely need hospitalization, compared to only 1% of people under 30 [16]. A study by Eduardo estimated the real-time case rate across different age groups by gender in Latin America (Table 1) [17].

Table 1. Ratio of COVID-19's cases, deaths, and morbidity according to different age groups.

Gender proportion of COVID-19 cases	**Age (Years)**	**10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**
	Male (%)	**47.5**	**50**	**52.8**	**52.3**	**51.8**	**53**	**49.7**	**39.2**
	Female (%)	**52.5**	**50**	**47.2**	**47.7**	**48.2**	**47**	**50.3**	**60.8**
Gender proportion of COVID-19 deaths	**Age (Years)**	**10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**
	Male (%)	**65**	**63.9**	**65.5**	**64.6**	**67.1**	**64.22**	**60.7**	**46.9**
	Female (%)	**35**	**36.1**	**34.5**	**35.4**	**32.9**	**35.8**	**39.3**	**53.1**
Gender proportion of COVID-19 morbidity	**Age (Years)**	**10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**
	Male (%)	**0.94**	**3.17**	**4.16**	**3.38**	**3.32**	**3.02**	**2.55**	**2.85**
	Female (%)	**1.08**	**3.22**	**3.67**	**2.93**	**2.84**	**2.36**	**2.04**	**2.56**

2.1.2. Death Rate by Gender Ratio

A sex bias with males > females was reported for COVID-19 by national case fatality rates (CFRs). Furthermore, SS Bhopal et al. examined the mortality ratio per 100,000 cases and concluded a higher fetal death rate among men than among women [18]. The most likely reasons for the variations found are hypotheses focused on risk factors that vary with sex and age. Differences in the profession, lifestyle (including smoking and alcohol consumption), physical comorbidities, and drugs are all examples. Rather than the science of genders, these theories are based on social and cultural considerations. Age, sex, and the previously listed risk factors, as well as gene expression and epigenetics, would all need to be taken into account when developing genetic bases [18][19]. Male sex is gradually being identified as a risk factor for COVID-19-related disease and death. Male dominance in COVID-19 mortality can be seen in almost all countries with sex-disaggregated records, in which males have a 1.7-fold higher chance of death than females [20]. Gender has a significant effect on immune cell transcriptomes; age affects immune cells or even the immune system differently based on sex. Aging causes a decrease in the proportion of naive T cells, which is more noticeable in males, while B cells decline mainly in males just after the age of 65. Between the ages of 62 and 64, male immune cells undergo abrupt and drastic changes in epigenetic landscape, resulting in an accelerated immunosenescence phenotype characterized by

increased innate proinflammatory gene expression and lower gene expression related to adaptive immunity, which may potentially predispose older males to hyperinflammation and poor adaptive immunity [21].

2.1.3. Death Rate by Health Conditions

Various underlying diseases have also been associated with an increased death rate. According to the Chinese Center for Disease Control and Prevention, respiratory infections, cardiovascular diseases, diabetes, cancers, and hypertension are major contributing factors for the increased death rate by COVID-19. Furthermore, an extensive cohort analysis of over 17 million people was held by EJ Williamson et al. to identify the clinical factors associated with COVID-19 related deaths. They identified hypertension as the most common comorbidity among COVID-19 related deaths. Their result can also be used for developing a predictive model [22].

2.2. Epidemiological Prospective of Influenza A (H1N1)

Influenza strikes at different intensities every year. Its epidemiological trend is influenced by a number of factors, namely the virus's antigenic properties, transmissibility, and community susceptibility [23]. This virus can change the antigen properties of surface glycoproteins, hemagglutinin, and neuraminidase regularly. Major changes in these proteins are called 'antigenic change', and minor changes are called 'antigenic shift'. Epidemics of influenza A are followed by antigenic variations, while local outbreaks are caused by antigenic modifications [24].

The influenza A virus caused several pandemics in the 20th century, so that millions of people have died from this virus in the last century [25]. The influenza A/H1N1 virus was first reported in April 2009 in Mexico and some states of the US. It was then rapidly spread in most countries, so that the WHO announced its pandemic in June 2009 [26][27][28]. Studies in Portugal [29] and Saudi Arabia [30] showed that the influenza A/H1N1 virus spread was 54.40% and 28.4%, respectively. This virus has been created from the simultaneous infection of pigs by the prevailing influenza A subtypes and the simultaneous amplification and shift of its genome, which has caused it to be more pathogenic than the other seasonal subtypes [31][32]

2.2.1. Death Rate by Age Group

COVID-19 and influenza A pandemic differ in the age profile of critically ill patients and patients who die. The age distribution of morbidity during the 1918, 1957, 1968, and 2009 H1N1 pandemics was close to that of seasonal epidemics, with the majority of patients being under 60 years old. However, the percentage of under-60s among influenza deaths was significantly higher during the 2009 pandemic (peak 20 years) than seasonal epidemics [33]. In addition, based on an analysis of 153 influenza-associated deaths younger than five years old, N Bhat et al. suggest that the average influenza-related mortality rate for children was 0.21 deaths per 100,000, with the highest rate for children under the age of six months with a general reduction as they grew older [34].

2.2.2. Death Rate by Sex Ratio

In most nations, males and females have equal case fatality rates for avian influenza. Human A (H7N9) cases, on the other hand, have a high degree of sex inequality, with males over 50 years of age having a slightly higher mortality rate [35]. In this background, T Paskoff et al. studied sex-based variations in mortality during the 1918 influenza pandemic on the island of Newfoundland in 2018 and discovered that mortality rates were generally equivalent in both sexes [36]. Contrary, adult males (15–44 years of age) in the United States and 12 other countries died at greater rates during the 1918 H1N1 pandemic [37].

2.2.3. Death Rate by Health Conditions

C Rodríguez-Rieiro et al. in Spain identified a close association between comorbidity and influenza mortality rate. They also introduced asthma as the most prevalent risk factor among those with pH1N1-related ICU admission [38]. Additionally, N Bhat revealed that underlying diseases, such as neuromuscular disorders and chronic pulmonary disease, could increase childhood mortality from influenza [34].

3. Transmission and Replication

3.1. Transmission and Replication of COVID-19

3.1.1. Transmission

Transmission efficiency was approved as a critical factor in the epidemiology of newly evolved viruses such as influenza A and COVID-19. Transmission modes, including nasal and oral droplets, indirect contacts, and a lesser degree, touching a

surface with the virus on it, are accepted in COVID-19. Pharyngeal shedding is very high during the first week of symptoms and could enhance the risk of transmission. In addition, the presence of COVID-19 in stools and wastewater suggests its fecal-oral transmission. During the incubation cycle, Qun Qian et al. report clear signs of successful COVID-19 replication in a patient's rectum, which may clarify COVID-19's fecal–oral transmission [39].

Asymptomatic and pre-symptomatic transmission, a typical characteristic of infectious diseases, is possible in COVID-19 and contributes to its outbreak. Bai et al. reports a confirmed laboratory COVID-19 case without any clinical sign and suggests that asymptomatic cases could transmit COVID-19 [40]. In addition, Chen Yi et al. indicated that the infection rates of symptomatic and asymptomatic infections among close contacts were 6.30% and 4.11%, respectively [41]. This novel finding suggests the asymptomatic transmission of COVID-19. Growing evidence reveals that due to interaction mechanisms, the transmission and epidemiology of COVID-19 are dependently associated with influenza (Figure 3). ACE-2 overexpression resulting from a viral respiratory infection, in particular, influenza, was identified recently [42]. The study of M Domenech de Cellès et al. with a focus on the impact of influenza on COVID-19 transmission indicated that the transmission of COVID-19 has increased 2–2.5-fold in influenza co-circulating. This novel finding highlights the inevitable effects of influenza vaccination on COVID-19 mortality and transmission [43].

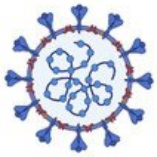
Disease	Flu	COVID-19
Disease Causing Pathogen	 Influenza virus	 SARS-CoV-2
R_0 Basic Reproductive Number	1.3	2.0 - 2.5
CFR Case Fatality Rate	0.05 - 0.1%	2.07%
Incubation Time	1 - 4 days	2 - 14 days
Hospitalization Rate	2%	19%
Community Attack Rate	10 - 20%	30 - 40%
Annual Infected (global)	~ 1 billion	166 Million (ongoing)
Annual Infected (US)	10 - 45 million	33.1 Million (ongoing)
Annual Deaths (US)	10,000 - 61,000	0.5 Million (ongoing)

Figure 3. Epidemiological comparison of Influenza A and COVID-19.

A number of days between virus infection and the onset of clinical manifestation are known as the incubation period. The incubation period is a key element in determining the quarantine period and could necessarily reduce epidemic size. The incubation period is around 14 days for COVID-19, meaning that a 14-day quarantine period is required for the complete absence of disease among healthy individuals exposed to the virus [44].

3.1.2. Replication

Specific coronavirus spike (S) protein binding to the appropriate cellular entry receptors initiates coronavirus infection. Upon cell entrance, ORF1a and ORF1b are immediately translated into non-structural proteins. Here, prior to the replication process explanation, we describe the biological function of each NSP in the context of COVID-19 pathogenesis.

The C-terminal domain of COVID-19 nsp1 triggers translational inhibition by sterically blocking the ribosomal mRNA channel entry site in 43S pre-initiation complex, free 40S subunits non-translating 80S ribosomes. 5′ UTR of COVID-19 with a complex secondary structure efficiently promotes translation under a low ribosome. Therefore, upon COVID-19 infection, host protein production switches to viral protein synthesis [45]. Compared to other NSPs, nsp2 shows maximum sequence variability among coronaviruses, so it was believed that nsp2 protein coevolved in parallel with the hosts to obtain host-specific functions. Nsp2 and nsp3 are involved in RTC formation. Nsp3, through its post-translational activity, affects the host protein's overall structure and; therefore, suppresses the host's innate immune response [46].

A cytoplasmic double-membrane vesicle, required for COVID-19 replication, is induced by the cooperation of nsp4 and nsp3. Nsp5, also called 3C-like protease, or the main protease is thought to engage in synthesizing viral proteins and several nonstructural viral proteins through its protease activity. Moreover, nsp5 prevents interferon I signaling processes through cleavage of STAT 1 transcription factor [47]. By influencing autophagic proteins, including PIK3C3 and ATG5, nsp6 serves as an autophagy-inducing protein. Nsp8, in cooperation with nsp7, forms a heterodimer structure and confers RNA-binding capacity to nsp12. Nsp9 is required for binding coronavirus replication complex to RNA. Nsp10, an essential cofactor for 2′ O-ribose methyltransferase (Nsp16) and guanine-N7 methyltransferase (Nsp14) activation, assists in the methylation of mRNAs guanosine cap to promote transcription, splicing, polyadenylation, and nuclear export of viral mRNA. Nsp11 displays endo-ribonuclease activity that has a major impact on the viral life cycle [48]. Nsp12, an RNA-dependent RNA polymerase (RdRp), functions primarily in COVID-19 genome replication and transcription [49]. Nsp13, Helicase (Hel) or Nucleoside-triphosphatase (NTPase), facilitates RNA folding in the presence of NTPs and plays a crucial role in replication [50]. Nsp14 and nsp16, which stand for N-7- and 2-O′-methyltransferase, respectively, are involved in the viral RNAs capping so that they are required for immune protection against host pattern recognition receptors (PRR), such as IFIT1. Notably, COVID-19 nsp13 (helicase), nsp14 (exonuclease), and nsp15 (endoribonuclease) were found to be highly effective viral interferon antagonists [51]. In conclusion, it is worth mentioning that NSPs are promising therapeutic targets for antiviral drug development.

Viral replication organelles (RO) are generally distinct functional structures indicated to function as ideal platforms for viral RNA synthesis. Double-membrane vesicles (DMVs) are the RO's most abundant component and the central hubs for COVID-19 genome synthesis. By protecting the viral genome from innate immune sensors stimulated by dsRNA, DMVs create an appropriate condition for viral RNA synthesis. Newly synthesized viral RNA translocation from the DMVs to the cytosol is mediated by multiprotein complexes that span both DMV membranes. Therefore, these channels are critical for the COVID-19 life cycle. DMV molecular pores are principally made up of nsp3, nsp4, and nsp6 [52].

RTC contains nsp12-nsp7-nsp8 function in COVID-19 genome replication and transcription. COVID-19 replication is a complex process that involves RNA synthesis, proofreading, and capping. The COVID-19 genomic replication begins with the full-length negative-sense genomic synthesis that serves as a template to make a new positive-sense genomic RNA. In this context, the negative-strand synthesis is initiated by RdRp protein binding to the 3' end of the genome in a process stimulated by 3' end RNA secondary structures and sequences. Then, RdRp selects and binds to an appropriate nucleoside triphosphate (NTP) via the formation of phosphodiester bonds, so nucleotide incorporation results in the 3' end of the nascent RNA extension. Processivity is critical for successful COVID-19 genome replication. Nsp7/nsp8 protein through interaction with the RNA backbone bestows high processivity on RdRp. The increased mutation rate in RNA virus replication is correlated with enhancing diversity in viral genomic sequence. Nsp14 provides a 3′–5′ exonuclease activity that assists RNA synthesis with a unique RNA proofreading function. Following replication, COVID-19 genomes need to undergo capping at their 5' end and polyadenylation at their 3' end. This process is similar to those that take place in eukaryotic cells, but COVID-19 genome capping and polyadenylation occur in the cytoplasm. Several momentous biological activities, including host immune response evasion, mRNA translation, and stability, have been reported for the final viral RNA cap [53].

3.2. Transmission and Replication of Influenza A

3.2.1. Transmission

Several possible routes, including nasal and oral droplets and indirect contact, have been approved for Influenza A transmission. Indirect contact refers to transmission via a fomite, an object like a doorknob or toy, contaminated with the infectious virus. Additionally, airborne virus transport on microscopic particles, or the so-called aerosolized fomites, is also considered for Influenza A transmission [54]. Unlike COVID-19, effective transmission of influenza has not been observed in truly asymptomatic people. The incubation period is around 1.4 days for Influenza A, meaning that a 1.4 day quarantine period is required for the complete absence of disease among healthy exposed individuals [55]. Additionally, reproduction number (R0), an epidemiological transmission index in infectious diseases, is around 1.5 and 3 for influenza A and COVID-19, respectively [56].

This finding indicates that COVID-19 is more transmissible than influenza A. Indeed, different policies are required to control these diseases.

3.2.2. Replication

Each vRNP comprises viral RNA (vRNA), viral polymerase, and a number of nucleoproteins (NP) molecules in influenza A. Two distinct conserved regions in 5′ and 3′ UTRs mediate the helical hairpin formation and allow RNA-dependent RNA polymerase (RdRp) to bind to vRNA. Contrary to most RNA-containing viruses, influenza viruses are transcribed and

replicate in the nucleus. In this context, following the cytoplasmic appearance of the vRNA, the nucleocytoplasmic transport system, including importin-α and importin-β, detects nuclear localization signal (NLS) and transport vRNA into the nucleus. RdRp, as a heterotrimeric enzyme with three subunits, including PB1, PB2, and PA, plays a central role in replication and transcription. It is worth noting that many viruses exploit the perturbation of cell cycle progression to create a favorable condition for virus replication. RhoA kinase can potentially promote G1/S phase transition through pRb phosphorylation. By binding to and inhibiting NS1, H1N1 non-structural protein 1 (NS1) induces cell cycle arrest and favors cell condition for virus replication [57].

Two-step replication of influenza is initiated by complementary RNA synthesis (cRNA). In other words, prior to vRNA replication, vRNA is transcribed to cRNA. Following cRNA synthesis, newly synthesized nucleoprotein (NP) molecules and a single copy of the viral polymerase bind to cRNA to assemble into a cRNP. In a similar manner to cRNA synthesis, cRNA in cRNP acts as a template for vRNA production. In a sequence identical to cRNP formation, newly synthesized vRNA binds to accessory proteins, forming vRNP. Then, the influenza virus NS2 mediates vRNP nuclear export [58]. H1C as a member of the histone H1 family mediates intra-chromosome compaction. Besides, H1C promotes IFN-β production through IRF3 nuclear transportation. It was ascertained that H1C affects influenza virus replication by interaction with NS2. An extensive study by M Jin et al. demonstrated better replication of the H1N1 influenza virus in H1C knockout A549 cells than the wild-type A549 cells. As such, H1C plays a key role in H1N1 influenza host adaptation [59][60]

Notably, recent exploration by Liping Song et al. disclosed the relationship between miRNA and H1N1 influenza replication. Using a 3'-UTR reporter assay and virus proliferation analysis in MDCK cells, they identified putative miRNA complementary sequence in the influenza virus genome. They found that miR-323, miR-491, and miR-654 play a crucial role against influenza A infection via binding to the PB1 gene and, subsequently, inhibiting influenza A replication [61].

4. Clinical Manifestation

4.1. Clinical Manifestation of COVID-19

Twelve surface receptors of COVID-19, including ACE2, were determined by Gu et al. Among them, ASGR1 and KREMEN1 govern COVID-19 infection independently, so they may be specific receptors COVID-19 infection. These multiple host cell surface receptors enable COVID-19 to infect numerous body organs. Hence, COVID-19 patients present highly variable clinical symptoms in the clinic. Notably, no specific clinical signs that could reliably distinguish between COVID-19 and other viral respiratory infections have been reported. Most COVID-19 patients are mildly ill and experience flu-like upper respiratory symptoms, such as cough, shortness of breath, fever, dryness, fatigue, and so on. However, some patients may progress to acute respiratory distress syndrome, metabolic acidosis, or coagulation dysfunction and should receive mechanical ventilation and support in an intensive care unit (ICU) [62][63][5][10]. In addition, COVID-19 is associated with gastrointestinal symptoms, such as diarrhea, vomiting, or abdominal pain during the early phases of the disease (see Table 2 for a list of main symptoms). In the following section, we clarify the pathogenesis of COVID-19 in several organs.

Table 2. A comparative analysis of the principal features in COVID-19 and Influenza A(H1N1).

Feature		COVID-19	Influenza A(H1N1)	References
Epidemiology and Transmission	Fecal-oral transmission	Proved	Not proved	[39][50]
	Age composition	Most patients were older than 50	Most patients were younger than 60	
	Transmission mode	Asymptomatic/ symptomatic	Symptomatic	[64]
	Reproduction number	3	1.5	[52]
	Incubation period	4.9	1.4	[51]
Treatment	Anti-viral drug	N3/ebselen/Remdesivir	Oseltamivir and zanamivir	[60][65][66]
	CP therapy	*	*	[67][68]
	Vitamin D	*	*	[57][58]
	MSC therapy	*	Not effective	[69]

Feature			COVID-19	Influenza A(H1N1)	References
Diagnosis	CRISPR-based SHERLOCK technique		*	Not develop	[70]
	qPCR		*	*	[71]
	Gut microbiome		*	*	[72]
	Lymphopenia		*	*	[73]
	CT scan		Ground-glass opacities have frequently been placed in the periphery of lower lobes	Ground-glass opacities has a central, peripheral, or random distribution	[74]
Clinical manifestation	Acute lung injury		*	*	[44]
	Cardiovascular		*	*	[38]
	Gastrointestinal	diarrhea	*	*	[75]
		nausea	*	*	
		vomiting	*	*	
Molecular biology	Receptor for virus-cell entrance		ACE2	Sialic acid receptor	[76][77]
	Genetic material		Just one positive-sense single-stranded RNA	Eight negative-sense single-stranded RNA	[78]
	Location of replication		DMV (cytoplasm)	Nucleus	[19]

* These things are ongoing as it's a current issue and now these are usable.

4.1.1. Cardiovascular

ACE2 is a membrane-bound aminopeptidase that plays a crucial role in the cardiovascular and immune systems [79]. ACE2 mediates COVID-19 entrance into specific host cells by binding to COVID-19 spike protein [65]. It was recently disclosed that people who suffer from cardiovascular disease experience a more severe disease than normal individuals due to ACE2 upregulation [66]. Thus, cardiovascular comorbidity contributes to elevated COVID-19 mortality. Furthermore, there is accumulating evidence that COVID-19 itself could trigger cardiovascular disorders, including venous thromboembolism, myocardial injury, and acute coronary syndrome (ACS). Cardiac troponin I is a cardiac regulatory protein that signals myocardial necrosis. Qing Deng et al. recognized elevated expression of Cardiac troponin I in COVID-19 patients during hospitalization.

Additionally, cardiac troponin I level was significantly higher in severe cases than in non-severe cases. In this manner, COVID-19 could function as a potential contributing factor to the development of myocardial damage [80]. Together, these data support bidirectional causation between COVID-19 and the cardiovascular system.

4.1.2. Gastrointestinal (GI)

ACE2 expression is greatly more abundant in the human and mouse small intestine than all other organs, such as lungs. In addition, coordinated action of TMPRSS2 and TMPRSS4 significantly increases COVID-19 infection in human small intestinal enterocytes. GI symptoms, including diarrhea, nausea, and vomiting, occur in COVID-19 patients, but the most frequent symptom is the lack of appetite. The incidence of gastrointestinal complaints was greater in 19 patients hospitalized in medical units and intensive care units (ICU) than in patients observed solely in the emergency care unit [81]. Besides, M. Aziz et al. investigated the role of GI symptoms in predicting the severity of COVID-19. They indicated that GI symptoms, especially diarrhea, is associated with worse outcome [82]. All these findings suggest that COVID-19 is actively involved in GI tract infection.

4.1.3. Lung

Ling Leng et al. used a comprehensive proteome study and bioinformatics analysis to discover proteomic profiles of COVID-19-infected human lung tissues. In the COVID-19 lung tissue, ferroxidase ceruloplasmin (CP), which is associated with the peroxidation of Fe (II) transferrin to Fe (III) transferrin, was significantly elevated resulting in increased oxygen intake, which affected normal relaxed breathing. Increased SLC4A1 expression was also found in COVID-19 lung tissue, which resulted in a malfunction of gas exchange in the lungs as well as urinary acidification. SFTPB is associated with the

development of lamellar bodies in the alveoli as well as the removal of surface tension. The COVID-19 lung tissue displayed a significant decrease in SFTPB. In addition, COVID-19 lung tissues have a high level of activation of the non-canonical NF-B/NFKB2 pathway, which is a central mediator in cytokine and chemokine synthesis. It is worth noting that the non-canonical NF-B/NFKB2 pathway has never been confirmed to be activated during cytokine storms caused by other respiratory viruses, including influenza [83].

4.2. Clinical Manifestation of Influenza A (H1N1)

Influenza A has been recognized as a major contributing factor in acute respiratory tract infection. Additionally, pharyngitis, dyspnea, diarrhea, nausea/vomiting, headache, shortness of breath, runny nose/rhinorrhea, Sore throat, and myalgia are also frequently seen in influenza A patients [68]. On the other hand, high detection of influenza A (H1N1) in myocardial and pericardial tissues and fluid implies a causal relationship between influenza A (H1N1) and myocarditis [84]. It has been confirmed that influenza A (H1N1) viruses infect and subsequently induce GI cell death via sialic acid (SA)–α 2, 6–galactose (Gal)-terminated saccharides [85]. A Riquelme et al. retrospectively conducted a study on the prevalence of GI clinical symptoms in Chilean influenza A (H1N1) patients. They observed 72 patients with vomiting (14.3%), 147 patients with diarrhea (29.4%), and 182 patients (36.4%) with nausea. Besides, gastrointestinal symptoms were observed in one out of four influenza A (H1N1) patients in a similar study in North America [69].

Notably, a significant accumulation of viral replicative intermediate agents such as dsRNAs after infection with influenza A (H1N1) were noticed, which were recognized by innate immune receptors such as membrane-bound TLR3 and cytosolic RIG1-like receptors (MDA5, RIG-1, and LGP2). MDA5 appears to be a Runx3 inducer, which is intriguing. Cell apoptosis is thought to be a cellular process that effectively clears virus-infected cells, thereby acting as a powerful tool for the prevention of virus spreading. An excessive amount of uncontrolled apoptosis can trigger pulmonary tissue damage and lung dysfunction, which would increase morbidity and mortality. Runx3 is known to modulate the H1N1 influenza-induced host airway epithelial cell apoptosis. Runx3 overexpression in airway somatic cells, induced by H1N1 influenza infection, aggravates the disease severity by promoting host cell apoptosis and tissue injury [86].

We finally investigate two important questions as to viral infection as follows:

4.2.1. How Obesity Impacts Viral Infections?

COVID-19 has a greater effect on ACE2 expression in adipose tissue than in lung tissue, which is a significant target tissue. Obese people have more adipose tissue, which means they have more ACE2-expressing cells and, as a result, obesity can increase infection susceptibility and a risk factor for COVID-19-related mortality [71]. In a systematic review of the literature, J Siqueira et al. determined a close association between increasing BMI and deterioration in clinical outcome. They concluded that obesity led to higher levels of hospitalization, poor outcomes, and increased mortality in COVID-19 infected patients [87].

Additionally, a close correlation was recently found between obesity and the risk of intensive care unit (ICU) admission and hospitalized patients with influenza A (H1N1) infection. L. Fezeu indicated that severely obese influenza A (H1N1) patients had a twofold higher risk of mortality and ICU admission compared with influenza A (H1N1) patients who were not severely obese [70].

4.2.2. Why Women Have Less Tendency to Be Affected by Viral Infections?

A growing body of evidence suggests that many variations exist between men and women in the immune response to infection. Data from hospitals worldwide disclosed that respiratory system diseases, such as those triggered by acute viral infections, are more prevalent in men (25%) than in women. The presence of two X chromosomes in women affects the immune system even if one is inactive. Several immune system components, including TLR7, FOXP3, CD40L, TLR8, and CXCR3, are affected by the X chromosome and can be upregulated in women and impact the response to viral infections. It has been proposed that the X chromosome encodes several immune regulatory genes, and they could trigger lower viral load levels, inflammation, and death after viral infection in females than in males. The TLR7 gene located on the X chromosome is expressed in numerous immune system cells, such as B cells, macrophages, dendritic cells, and circulating monocytes. TLR7 plays a critical role in single-strand RNA virus recognition via inducing anti-COVID-19 antibodies and generating pro-inflammatory cytokines, including IL-1 and IL-6 family members. As such, the TLR7 overexpression in women is associated with enhanced resistance to viral infections [88].

Furthermore, plasma levels of ACE2 were compared in 1485 men and 537 women with heart disease from two different cohorts. It was discovered that men had higher plasma ACE2 levels than women. The study indicates that the variation in plasma ACE2 can explain the intensity of COVID-19 in men [89].

References

1. Payne, S. Family Coronaviridae. Viruses 2017, 149–158.
2. Chen, Y.; Liu, Q.; Guo, D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J. Med. Virol. 2020, 92, 418–423.
3. Hoffmann, M.; Kleine-Weber, H.; Pöhlmann, S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol. Cell 2020, 78, 779–784.
4. Satarker, S.; Nampoothiri, M. Structural proteins in severe acute respiratory syndrome coronavirus-2. Arch. Med. Res. 2020, 51, 482–491.
5. Mohammadi-Dehcheshmeh, M.; Moghbeli, S.M.; Rahimirad, S.; Alanazi, I.; Al Shehri, Z.S.; Ebrahimie, E. Achilles' heel of SARS-CoV-2: Transcription regulatory sequence and leader sequence in 5'untranslated region have unique evolutionary patterns and are vital for virus replication in infected human cells. Preprints 2020.
6. Christman, M.C.; Kedwaii, A.; Xu, J.; Donis, R.O.; Lu, G. Pandemic (H1N1) 2009 virus revisited: An evolutionary retrospective. Infect. Genet. Evol. 2011, 11, 803–811.
7. Taubenberger, J.K.; Morens, D.M. The pathology of influenza virus infections. Annu. Rev. Pathol. Mech. Dis. 2008, 3, 499–522.
8. Fouchier, R.A.M.; Munster, V.; Wallensten, A.; Bestebroer, T.M.; Herfst, S.; Smith, D.; Rimmelzwaan, G.F.; Olsen, B.; Osterhaus, A.D.M.E. Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls. J. Virol. 2005, 79, 2814–2822.
9. Roxas, M.; Jurenka, J. Colds and influenza: A review of diagnosis and conventional, botanical, and nutritional considerations. Altern. Med. Rev. 2007, 12, 25–48.
10. Hamilton, B.S.; Whittaker, G.R.; Daniel, S. Influenza virus-mediated membrane fusion: Determinants of hemagglutinin fusogenic activity and experimental approaches for assessing virus fusion. Viruses 2012, 4, 1144–1168.
11. Arab-Mazar, Z.; Sah, R.; Rabaan, A.A.; Dhama, K.; Rodriguez-Morales, A.J. Mapping the incidence of the COVID-19 hotspot in Iran–Implications for Travellers. Travel Med. Infect. Dis. 2020, 34, 101630.
12. Marson, F.A.L.; Ortega, M.M. COVID-19 in Brazil. Pulmonology 2020, 26, 241–244.
13. Betancourt, W.Q.; Schmitz, B.W.; Innes, G.K.; Prasek, S.M.; Brown, K.M.P.; Stark, E.R.; Foster, A.R.; Sprissler, R.S.; Harris, D.T.; Sherchan, S.P.; et al. COVID-19 containment on a college campus via wastewater-based epidemiology, targeted clinical testing and an intervention. Sci. Total Environ. 2021, 779, 146408.
14. Lai, C.-C.; Shih, T.-P.; Ko, W.-C.; Tang, H.-J.; Hsueh, P.-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int. J. Antimicrob. Agents 2020, 55, 105924.
15. Gorbalenya, A.E.; Baker, S.C.; Baric, R.; de Groot, R.J.; Drosten, C.; Gulyaeva, A.A.; Haagmans, B.L.; Lauber, C.; Leontovich, A.M.; Neuman, B.W.; et al. Severe acute respiratory syndrome-related coronavirus: The species and its viruses—A statement of the Coronavirus Study Group. bioRxiv 2020.
16. Verity, R.; Okell, L.C.; Dorigatti, I.; Winskill, P.; Whittaker, C.; Imai, N.; Cuomo-Dannenburg, G.; Thompson, H.; Walker, P.G.T.; Fu, H.; et al. Estimates of the severity of coronavirus disease 2019: A model-based analysis. Lancet Infect. Dis. 2020, 20, 669–677.
17. Undurraga, E.A.; Chowell, G.; Mizumoto, K. COVID-19 case fatality risk by age and gender in a high testing setting in Latin America: Chile, March–August 2020. Infect. Dis. Poverty 2021, 10, 11.
18. Bhopal, S.S.; Bhopal, R. Sex differential in COVID-19 mortality varies markedly by age. Lancet 2020, 396, 532–533.
19. Guilmoto, C.Z.Z. COVID-19 death rates by age and sex and the resulting mortality vulnerability of countries and regions in the world. medRxiv 2020.
20. Scully, E.P.; Schumock, G.; Fu, M.; Massaccesi, G.; Muschelli, J.; Betz, J.; Klein, E.Y.; West, N.E.; Robinson, M.; Garibaldi, B.T.; et al. Sex and gender differences in COVID testing, hospital admission, presentation, and drivers of severe outcomes in the DC/Maryland region. medRxiv 2021.
21. Takahashi, T.; Iwasaki, A. Sex differences in immune responses: Biological sex differences in immunity potentially underlie male bias for severe COVID-19. Science 2021, 371, 347–348.
22. Williamson, E.J.; Walker, A.J.; Bhaskaran, K.; Bacon, S.; Bates, C.; Morton, C.E.; Curtis, H.J.; Mehrkar, A.; Evans, D.; Inglesby, P.; et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020, 584, 430–436.

23. Moghadami, M.; Moattari, A.; Tabatabaee, H.R.; Mirahmadizadeh, A.; Rezaianzadeh, A.; Hasanzadeh, J.; Ebrahimi, M.; Zamiri, N.; Alborzi, A.; Bagheri Lankarani, K. High titers of hemagglutination inhibition antibodies against 2009 H1N1 influenza virus in Southern Iran. Iran. J. Immunol. 2010, 7, 39–48.

24. Webster, R.G.; Kendal, A.P.; Gerhard, W. Analysis of antigenic drift in recently isolated influenza A (H1N1) viruses using monoclonal antibody preparations. Virology 1979, 96, 258–264.

25. Kilbourne, E.D. Influenza pandemics of the 20th century. Emerg. Infect. Dis. 2006, 12, 9–14.

26. Neumann, G.; Noda, T.; Kawaoka, Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature 2009, 459, 931–939.

27. Balish, A.; Warnes, C.M.; Wu, K.; Barnes, N.; Emery, S.; Berman, L.; Shu, B.; Lindstrom, S.; Xu, X.; Uyeki, T.; et al. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus-United States, 2009. Morb. Mortal. Wkly. Rep. 2009, 58, 826–829.

28. Lange, E.; Kalthoff, D.; Blohm, U.; Teifke, J.P.; Breithaupt, A.; Maresch, C.; Starick, E.; Fereidouni, S.; Hoffmann, B.; Mettenleiter, T.C.; et al. Pathogenesis and transmission of the novel swine-origin influenza virus A/H1N1 after experimental infection of pigs. J. Gen. Virol. 2009, 90, 2119–2123.

29. Malveiro, D.; Flores, P.; Sousa, E.; Guimarães, J.C. The 2009 pandemic influenza A (H1N1) virus infection: Experience of a paediatric service at a third-level hospital in Lisbon, Portugal. Rev. Port. Pneumol. Engl. Ed. 2012, 18, 175–181.

30. Al-Tawfiq, J.A.; Abed, M.; Saadeh, B.M.; Ghandour, J.; Shaltaf, M.; Babiker, M.M. Pandemic influenza A (2009 H1N1) in hospitalized patients in a Saudi Arabian hospital: Epidemiology and clinical comparison with H1N1-negative patients. J. Infect. Public Health 2011, 4, 228–234.

31. Brockwell-Staats, C.; Webster, R.G.; Webby, R.J. Diversity of influenza viruses in swine and the emergence of a novel human pandemic influenza A (H1N1). Influenza Respir. Viruses 2009, 3, 207–213.

32. Hillyard, R.D. Novel swine-origin influenza A (H1N1) virus investigation team emergence of a novel swime origin-inf A (H1N1) virus in humans. N. Engl. J. Med. 2009, 360, 2605–2615.

33. Lemaitre, M.; Carrat, F. Comparative age distribution of influenza morbidity and mortality during seasonal influenza epidemics and the 2009 H1N1 pandemic. BMC Infect. Dis. 2010, 10, 162.

34. Bhat, N.; Wright, J.G.; Broder, K.R.; Murray, E.L.; Greenberg, M.E.; Glover, M.J.; Likos, A.M.; Posey, D.L.; Klimov, A.; Lindstrom, S.E.; et al. Influenza-associated deaths among children in the United States, 2003–2004. N. Engl. J. Med. 2005, 353, 2559–2567.

35. Dudley, J.P.; Mackay, I.M. Age-specific and sex-specific morbidity and mortality from avian influenza A (H7N9). J. Clin. Virol. 2013, 58, 568–570.

36. Paskoff, T.; Sattenspiel, L. Sex-and age-based differences in mortality during the 1918 influenza pandemic on the island of Newfoundland. Am. J. Hum. Biol. 2019, 31, e23198.

37. Noymer, A.; Garenne, M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Popul. Dev. Rev. 2000, 26, 565–581.

38. Rodríguez-Rieiro, C.; Carrasco-Garrido, P.; Hernández-Barrera, V.; de Andres, A.; Jimenez-Trujillo, I.; de Miguel, A.; Jiménez-García, R. Pandemic influenza hospitalization in Spain (2009): Incidence, in-hospital mortality, comorbidities and costs. Hum. Vaccines Immunother. 2012, 8, 443–447.

39. Qian, Q.; Fan, L.; Liu, W.; Li, J.; Yue, J.; Wang, M.; Ke, X.; Yin, Y.; Chen, Q.; Jiang, C. Direct evidence of active SARS-CoV-2 replication in the intestine. Clin. Infect. Dis. 2020.

40. Bai, Y.; Yao, L.; Wei, T.; Tian, F.; Jin, D.-Y.; Chen, L.; Wang, M. Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020, 323, 1406–1407.

41. Chen, Y.; Wang, A.; Yi, B.; Ding, K.; Wang, H.; Wang, J.; Shi, H.; Wang, S.; Xu, G. The epidemiological characteristics of infection in close contacts of COVID-19 in Ningbo city. Chin. J. Epidemiol. 2020, 41, 668–672.

42. Smith, J.C.; Sausville, E.L.; Girish, V.; Yuan, M.L.; Vasudevan, A.; John, K.M.; Sheltzer, J.M. Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. Dev. Cell 2020, 53, 514–529.

43. de Celles, M.D.; Casalegno, J.-S.; Lina, B.; Opatowski, L. Influenza may facilitate the spread of SARS-CoV-2. medRxiv 2020.

44. Linton, N.M.; Kobayashi, T.; Yang, Y.; Hayashi, K.; Akhmetzhanov, A.R.; Jung, S.; Yuan, B.; Kinoshita, R.; Nishiura, H. Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: A statistical analysis of publicly available case data. J. Clin. Med. 2020, 9, 538.

45. Schubert, K.; Karousis, E.D.; Jomaa, A.; Scaiola, A.; Echeverria, B.; Gurzeler, L.-A.; Leibundgut, M.; Thiel, V.; Mühlemann, O.; Ban, N. SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat. Struct. Mol. Biol. 2020, 27, 959–966.

46. Asghari, A.; Naseri, M.; Safari, H.; Saboory, E.; Parsamanesh, N. The Novel Insight of SARS-CoV-2 Molecular Biology and Pathogenesis and Therapeutic Options. DNA Cell Biol. 2020, 39, 1741–1753.

47. Zhu, X.; Wang, D.; Zhou, J.; Pan, T.; Chen, J.; Yang, Y.; Lv, M.; Ye, X.; Peng, G.; Fang, L.; et al. Porcine deltacoronavirus nsp5 antagonizes type I interferon signaling by cleaving STAT2. J. Virol. 2017, 91, e00003-17.

48. Li, Y.; Zhou, L.; Zhang, J.; Ge, X.; Zhou, R.; Zheng, H.; Geng, G.; Guo, X.; Yang, H. Nsp9 and Nsp10 contribute to the fatal virulence of highly pathogenic porcine reproductive and respiratory syndrome virus emerging in China. PLoS Pathog. 2014, 10, e1004216.

49. Kirchdoerfer, R.N.; Ward, A.B. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. Nat. Commun. 2019, 10, 2342.

50. Shu, T.; Huang, M.; Wu, D.; Ren, Y.; Zhang, X.; Han, Y.; Mu, J.; Wang, R.; Qiu, Y.; Zhang, D.-Y.; et al. SARS-Coronavirus-2 Nsp13 possesses NTPase and RNA helicase activities that can be inhibited by bismuth salts. Virol. Sin. 2020, 35, 321–329.

51. Yuen, C.-K.; Lam, J.-Y.; Wong, W.-M.; Mak, L.-F.; Wang, X.; Chu, H.; Cai, J.-P.; Jin, D.-Y.; To, K.K.-W.; Chan, J.F.-W.; et al. SARS-CoV-2 nsp13, nsp14, nsp15 and orf6 function as potent interferon antagonists. Emerg. Microbes Infect. 2020, 9, 1418–1428.

52. Wolff, G.; Limpens, R.W.A.L.; Zevenhoven-Dobbe, J.C.; Laugks, U.; Zheng, S.; de Jong, A.W.M.; Koning, R.I.; Agard, D.A.; Grünewald, K.; Koster, A.J.; et al. A molecular pore spans the double membrane of the coronavirus replication organelle. Science 2020, 369, 1395–1398.

53. Robson, F.; Khan, K.S.; Le, T.K.; Paris, C.; Demirbag, S.; Barfuss, P.; Rocchi, P.; Ng, W.-L. Coronavirus RNA proofreading: Molecular basis and therapeutic targeting. Mol. Cell 2020, 79, 710–727.

54. Asadi, S.; ben Hnia, N.G.; Barre, R.S.; Wexler, A.S.; Ristenpart, W.D.; Bouvier, N.M. Influenza A virus is transmissible via aerosolized fomites. Nat. Commun. 2020, 11, 4062.

55. Wu, Z.; Harrich, D.; Li, Z.; Hu, D.; Li, D. The unique features of SARS-CoV-2 transmission: Comparison with SARS-CoV, MERS-CoV and 2009 H1N1 pandemic influenza virus. Rev. Med. Virol. 2021, 31, e2171.

56. Liu, Y.; Gayle, A.A.; Wilder-Smith, A.; Rocklöv, J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J. Travel Med. 2020, 27, taaa021.

57. Jiang, W.; Wang, Q.; Chen, S.; Gao, S.; Song, L.; Liu, P.; Huang, W. Influenza A virus NS1 induces G0/G1 cell cycle arrest by inhibiting the expression and activity of RhoA protein. J. Virol. 2013, 87, 3039–3052.

58. Dou, D.; Revol, R.; Östbye, H.; Wang, H.; Daniels, R. Influenza A virus cell entry, replication, virion assembly and movement. Front. Immunol. 2018, 9, 1581.

59. Liu, X.; Yang, C.; Hu, Y.; Lei, E.; Lin, X.; Zhao, L.; Zou, Z.; Zhang, A.; Zhou, H.; Chen, H.; et al. hisT1h1c regulates interferon-$β$ and inhibits influenza Virus replication by interacting with irF3. Front. Immunol. 2017, 8, 350.

60. Liu, X.; Yang, C.; Sun, X.; Lin, X.; Zhao, L.; Chen, H.; Jin, M. Evidence for a novel mechanism of influenza A virus host adaptation modulated by PB 2-627. FEBS J. 2019, 286, 3389–3400.

61. Song, L.; Liu, H.; Gao, S.; Jiang, W.; Huang, W. Cellular microRNAs inhibit replication of the H1N1 influenza A virus in infected cells. J. Virol. 2010, 84, 8849–8860.

62. Shao, W.; Li, X.; Goraya, M.U.; Wang, S.; Chen, J.-L. Evolution of influenza a virus by mutation and re-assortment. Int. J. Mol. Sci. 2017, 18, 1650.

63. Huang, S.S.H.; Banner, D.; Fang, Y.; Ng, D.C.K.; Kanagasabai, T.; Kelvin, D.J.; Kelvin, A.A. Comparative analyses of pandemic H1N1 and seasonal H1N1, H3N2, and influenza B infections depict distinct clinical pictures in ferrets. PLoS ONE 2011, 6, e27512.

64. Bolsen, T.; Palm, R.; Kingsland, J.T. Framing the Origins of COVID-19. Sci. Commun. 2020, 42, 562–585.

65. Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020, 581, 215–220.

66. Zheng, Y.-Y.; Ma, Y.-T.; Zhang, J.-Y.; Xie, X. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 2020, 17, 259–260.

67. Leng, Z.; Zhu, R.; Hou, W.; Feng, Y.; Yang, Y.; Han, Q.; Shan, G.; Meng, F.; Du, D.; Wang, S.; et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis. 2020, 11, 216–228.

68. Chaiwarith, R.; Prommee, N.; Liwsrisakun, C.; Oberdorfer, P.; Nuntachit, N.; Pothirat, C. A novel influenza A H1N1 clinical manifestations in patients at Chiang Mai University Hospital. J. Med. Assoc. Thail. 2011, 94, 908–915.

69. Riquelme, A.; Alvarez-Lobos, M.; Pavez, C.; Hasbun, P.; Dabanch, J.; Cofre, C.; Jimenez, J.; Calvo, M. Gastrointestinal manifestations among Chilean patients infected with novel influenza A (H1N1) 2009 virus. Gut 2009, 58, 1567–1568.

70. Fezeu, L.; Julia, C.; Henegar, A.; Bitu, J.; Hu, F.B.; Grobbee, D.E.; Kengne, A.-P.; Hercberg, S.; Czernichow, S. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: A systematic review and meta-analysis. Obes. Rev. 2011, 12, 653–659.

71. Kassir, R. Risk of COVID-19 for patients with obesity. Obes. Rev. 2020, 21, e13034.

72. Long, C.; Xu, H.; Shen, Q.; Zhang, X.; Fan, B.; Wang, C.; Zeng, B.; Li, Z.; Li, X.; Li, H. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur. J. Radiol. 2020, 126, 108961.

73. Dara, M.; Talebzadeh, M. CRISPR/Cas as a potential diagnosis technique for COVID-19. Avicenna J. Med. Biotechnol. 2020, 12, 201–202.

74. Panning, M.; Eickmann, M.; Landt, O.; Monazahian, M.; Ölschläger, S.; Baumgarte, S.; Reischl, U.; Wenzel, J.J.; Niller, H.H.; Günther, S.; et al. Detection of influenza A (H1N1) v virus by real-time RT-PCR. Eurosurveillance 2009, 14, 19329.

75. Huang, I.; Pranata, R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): Systematic review and meta-analysis. J. Intensive Care 2020, 8, 36.

76. Cheng, Y.; Zhao, H.; Song, P.; Zhang, Z.; Chen, J.; Zhou, Y.-H. Dynamic changes of lymphocyte counts in adult patients with severe pandemic H1N1 influenza A. J. Infect. Public Health 2019, 12, 878–883.

77. Gu, S.; Chen, Y.; Wu, Z.; Chen, Y.; Gao, H.; Lv, L.; Guo, F.; Zhang, X.; Luo, R.; Huang, C.; et al. Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza. Clin. Infect. Dis. 2020, 71, 2669–2678.

78. Deriu, E.; Boxx, G.M.; He, X.; Pan, C.; Benavidez, S.D.; Cen, L.; Rozengurt, N.; Shi, W.; Cheng, G. Influenza virus affects intestinal microbiota and secondary salmonella infection in the gut through type I interferons. PLoS Pathog. 2016, 12, e1005572.

79. Smart, L.; Fawkes, N.; Goggin, P.; Pennick, G.; Rainsford, K.D.; Charlesworth, B.; Shah, N. A narrative review of the potential pharmacological influence and safety of ibuprofen on coronavirus disease 19 (COVID-19), ACE2, and the immune system: A dichotomy of expectation and reality. Inflammopharmacology 2020, 28, 1141–1152.

80. Deng, Q.; Hu, B.; Zhang, Y.; Wang, H.; Zhou, X.; Hu, W.; Cheng, Y.; Yan, J.; Ping, H.; Zhou, Q. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. Int. J. Cardiol. 2020, 311, 116–121.

81. Zhong, P.; Xu, J.; Yang, D.; Shen, Y.; Wang, L.; Feng, Y.; Du, C.; Song, Y.; Wu, C.; Hu, X.; et al. COVID-19-associated gastrointestinal and liver injury: Clinical features and potential mechanisms. Signal Transduct. Target. Ther. 2020, 5, 256.

82. Aziz, M.; Haghbin, H.; Lee-Smith, W.; Goyal, H.; Nawras, A.; Adler, D.G. Gastrointestinal predictors of severe COVID-19: Systematic review and meta-analysis. Ann. Gastroenterol. 2020, 33, 615–630.

83. Leng, L.; Cao, R.; Ma, J.; Mou, D.; Zhu, Y.; Li, W.; Lv, L.; Gao, D.; Zhang, S.; Gong, F.; et al. Pathological features of COVID-19-associated lung injury: A preliminary proteomics report based on clinical samples. Signal Transduct. Target. Ther. 2020, 5, 240.

84. Puzelli, S.; Buonaguro, F.M.; Facchini, M.; Palmieri, A.; Calzoletti, L.; De Marco, M.A.; Arace, P.; De Campora, E.; Esposito, C.; Cassone, A.; et al. Cardiac tamponade and heart failure due to myopericarditis as a presentation of infection with the pandemic H1N1 2009 influenza A virus. J. Clin. Microbiol. 2010, 48, 2298–2300.

85. Maines, T.R.; Jayaraman, A.; Belser, J.A.; Wadford, D.A.; Pappas, C.; Zeng, H.; Gustin, K.M.; Pearce, M.B.; Viswanathan, K.; Shriver, Z.H.; et al. Transmission and pathogenesis of swine-origin 2009 A (H1N1) influenza viruses in ferrets and mice. Science 2009, 325, 484–487.

86. Gan, H.; Hao, Q.; Idell, S.; Tang, H. Transcription factor Runx3 is induced by influenza A virus and double-strand RNA and mediates airway epithelial cell apoptosis. Sci. Rep. 2015, 5, 17916.

87. de Siqueira, J.V.V.; Almeida, L.G.; Zica, B.O.; Brum, I.B.; Barceló, A.; de Siqueira Galil, A.G. Impact of obesity on hospitalizations and mortality, due to COVID-19: A systematic review. Obes. Res. Clin. Pract. 2020, 14, 398–403.

88. Conti, P.; Younes, A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: Clinical response to viral infection. J. Biol. Regul. Homeost. Agents 2020, 34, 339–343.

89. Sama, I.E.; Ravera, A.; Santema, B.T.; van Goor, H.; ter Maaten, J.M.; Cleland, J.G.F.; Rienstra, M.; Friedrich, A.W.; Samani, N.J.; Ng, L.L.; et al. Circulating plasma concentrations of ACE2 in men and women with heart failure and

effects of renin-angiotensin-aldosterone-inhibitors. Eur. Heart J. 2020, 41, 1810–1817.