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Influenza and its cardiovascular complications: a comprehensive review

Mohammad Hassan Kalantar Neyestanaki[1], Majid Kalantar Neyestanaki[2]

[1]Department of Medicine, Arak University of Medical Science, Arak, Iran

[2]Department of Animal Science, Qom Agricultural and Natural Resources Research and Education Center, Qom, Iran

Abstract

Influenza is a respiratory illness caused by RNA viruses. These viruses can cause mild to severe illness, and can lead to pandemics and epidemics. Influenza spreads through respiratory droplets produced when an infected person coughs, sneezes, talks, or comes into contact with contaminated surfaces. In some cases, influenza can lead to more serious extrapulmonary complications, such as cardiovascular complications. During influenza virus infection, endothelial cells become activated, evidenced by increased levels of von Willebrand factor, enhanced coagulation, and necrosis. Microcirculatory dysfunction has been linked with adverse outcomes, including increased rates of organ failure and mortality. The most important cardiovascular complications can occur directly, causing myocarditis and pericarditis. They can also occur indirectly, exacerbating underlying cardiovascular conditions such as ischemic heart disease and heart failure. Vaccination and antiviral treatment for influenza can be effective in reducing the risk of these cardiovascular complications. As outlined in the preceding discussion on influenza, its identification and complications have presented a significant challenge in the healthcare domain. However, through enhanced understanding and meticulous research on this virus, we can make informed decisions that will optimize treatment strategies. This article delves into the epidemiological factors, risk factors, and clinical manifestations of influenza and association of influenza with cardiovascular manifestations.

Keywords: influenza, myocarditis, pericarditis, ischemic heart disease, heart failure, vaccination, antiviral treatment

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Introduction

Influenza, caused by different serotypes of influenza viruses, is a respiratory illness ranging from mild to severe, capable of triggering pandemics and epidemics. Transmission occurs through respiratory droplets and contact with contaminated surfaces, with higher prevalence during winter. At-risk groups include older adults, young children, pregnant women, individuals with underlying health conditions, and those overweight. Symptoms manifest 1–4 days post-exposure, encompassing fever, cough, sore throat, and more. Complications may include pneumonia and, rarely, fatalities. Annual vaccination is the primary preventive measure, targeting prevalent influenza strains. Other precautions involve hand hygiene, avoiding sick individuals, and proper cough/sneeze etiquette. The term "influenza" denotes a respiratory illness caused by orthomyxoviruses. These enveloped, negative-sense, single-stranded RNA viruses. Three types (A, B, and C) are recognized, with many subtypes within the type-A virus, cause epidemic acute respiratory disease. Upon inhalation, the virus attaches to respiratory tract cells. Natural defenses, like mucus and antibodies, combat

Address for correspondence: Majid Kalantar, Department of Animal Science, Qom Agricultural and Natural Resources Research and Education Center, Qom, Iran, P.O.Box 195, tel: +982532126495, e-mail: m2332012@gmail.com

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the virus. However, in compromised defenses or absence of specific antibodies, the virus invades epithelial cells, replicating and causing cell death. Retaining critical proteins, infected cells contribute to viral spread [1].

The primary manifestations of influenza infection are respiratory; however, multi-organ involvement is not rare. The relationship between cardiac disease and influenza is intricate. While human influenza typically affects the respiratory tract, numerous observational studies consistently associate influenza with cardiac complications. Robust observational data substantiate the connection between influenza infection and acute myocardial infarction and death [2]. Direct cardiac complications are infrequent, with noted occurrences of pericarditis and myocarditis [3]. The virus can exert both direct and indirect effects on various body systems. The indirect impact of influenza on underlying cardiac issues, such as congestive heart failure and ischemic heart disease, appears to significantly contribute to cardiac morbidity. Our study aims to provide a comprehensive review, focusing on the cardiovascular complications of influenza infection, without omitting any crucial points [4].

Epidemiology

Influenza exhibits seasonal patterns, with peak activity occurring during winter in temperate regions and throughout the year in tropical climates. The virus's ability to undergo antigenic drift and shift, resulting in minor and major changes in its surface proteins, poses a challenge for predicting and combating new strains. Antigenic drift, involving small mutations in hemagglutinin or neuraminidase glycoprotein genes, alters the virus's antigenicity, reducing antibody effectiveness against new strains. This phenomenon drives seasonal influenza epidemics [5]. Antigenic shift, characterized by significant mutations in hemagglutinin or neuraminidase genes, leads to the emergence of novel influenza-A viruses distinct from previously circulating strains. These novel viruses can cause sporadic human infections through contact with infected animals, primarily birds or pigs [6]. Additionally, if the population lacks immunity to the novel virus, it can trigger pandemics. Influenza transmission occurs via the respiratory route through three main mechanisms: inhalation of small-particle aerosols (less than 10 μm in mass diameter) generated during coughing or sneezing, direct contact with larger droplets or particles that settle within 3 meters of the infected individual, and indirect contact with contaminated surfaces harboring viable influenza viruses. Influenza has a substantial global impact, causing millions of cases, hospitalizations, and deaths annually, affecting individuals across all age groups [7].

The association between cardiovascular disease and influenza is longstanding, attributed to a concurrent peak incidence of both diseases in winter months. Epidemiologic studies highlight a rise in cardiovascular deaths during influenza epidemics, underscoring the significance of cardiovascular complications in influenza infection. These complications, including the exacerbation of heart failure, acute ischemic heart disease, and occasionally acute myocarditis, play a crucial role in the heightened morbidity and mortality observed during influenza infections [8, 9].

Risk factors

Particular groups, such as older adults, young children, pregnant women, and individuals with underlying health conditions, are more susceptible to severe influenza complications (Table 1) [10].

Pathophysiology

The pathogenesis of disease caused by influenza virus is not completely understood, particularly in molecular terms. Initial viral infection occurs in the upper respiratory columnar epithelium and then spreads distally in airways. Cell damage and death occurs through inhibition of host cell protein synthesis and induction of apoptotic changes in various cell types. Influenza infection may also result in secondary bacterial pneumonia, most commonly with Streptococcus pneumonia or Staphylococcus aureus [11]. Demonstrated defects include diminished forced flow rates, increased total pulmonary resistance, and decreased density-dependent forced flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter, along with increased responses to bronchoprovocation [12, 13]. In addition, abnormalities of carbon monoxide diffusing capacity and increases in the alveolar-arterial oxygen gradient have been seen. Of note, pulmonary function defects can persist for weeks after clinical recovery. Influenza in asthmatics or in patients with chronic obstructive disease may result in acute declines in FVC or FEV1 [14].

Primary viral pneumonia occurs when virus infection reaches the lung either by contiguous spread from the upper respiratory tract or by inhalation. The trachea and bronchi contain bloody fluid, and the mucosa is hyperemic. Tracheitis, bronchitis, and bronchiolitis are seen, with loss of normal ciliated epithelial cells. Submucosal hyperemia, focal hemorrhage, edema, and cellular infiltrate are present. The pathophysiology of bacterial superinfection has been studied intensively, and a number of factors have been identified that could play a role. Uncomplicated influenza is associated with significant

Table 1. Groups at higher risk for influenza complications

Children and adolescents at higher risk for influenza complications	Adults at higher risk for influenza-related complications
• Children younger than 4 years' old	• Individuals aged 65 years or older
• Children with chronic health conditions, including:	• **Pregnant women**
— Pulmonary disorders (such as asthma and **cystic fibrosis**)	• **Smokers**
— Cardiovascular diseases (except hypertension)	• Individuals with chronic health conditions, including:
— Renal disorders (kidney diseases)	— Pulmonary disorders (such as asthma)
— Hepatic disorders (liver diseases)	— Cardiovascular diseases
— Hematologic disorders (**such as severe anemia**)	— Renal disorders (kidney diseases)
— Metabolic disorders (such as diabetes mellitus)	— Hepatic disorders (liver diseases)
• Children with immunosuppression, including:	— Hematologic disorders (blood disorders)
— Children infected with human immunodeficiency virus (HIV)	— Metabolic disorders (such as diabetes mellitus)
— Children taking immunosuppressive medications	• Individuals with immunosuppression, including:
— **Children and adolescents who are receiving long-term salicylate therapy (aspirin)**	— Immunosuppression due to medication
• Children with conditions that compromise respiratory function, respiratory secretions handling, or increase the risk for hypertension, including:	— Immunosuppression due to human immunodeficiency virus (HIV) infection
— Cognitive dysfunction	— Individuals with conditions that compromise respiratory function, respiratory secretions handling, or increase aspiration risk
— Spinal cord injuries	— Individuals with obesity, defined as a body mass index (BMI) greater than 40
— Seizure disorders	— Residents of nursing homes and other chronic-care facilities
— Other neuromuscular disorders	
— Children receiving long-term aspirin therapy, who may be at risk for developing Reye syndrome	
— Children who are residents of chronic-care facilities	
— Pregnant women during the influenza season	

abnormalities in ciliary clearance mechanisms, resulting in reduced clearance of bacteria from epithelial surfaces and The cytokine IL-10 plays an important role in this regard [15, 16].

Influenza infection also reduces clearance by alveolar macrophages and weakens NK cells responses. All of these observations are consistent with the concept that the inflammatory response to influenza infection leads to disruption in the normal host defense against bacterial pathogens, although direct demonstration of this in humans is lacking [17, 18] (Fig. 1).

Virus is first detected just before the onset of illness (within 24 hours), remains elevated for 24 to 48 hours, and then rapidly decreases to low titers. Usually, virus is no longer detectable after 5 to 10 days of virus shedding. However, because of the relative lack of immunity in the young, more prolonged shedding of higher titers of virus is seen in children [19, 20].

There is compelling evidence supporting influenza's role as a trigger for cardiovascular events. The precise mechanism remains unclear, but coagulopathy and inflammation emerge as key factors [21]. Studies indicate an elevated risk of both arterial and venous thromboses following acute infection [22]. Animal studies reveal a coagulopathic state during influenza infection, with increased thrombin generation, fibrin deposition, and fibrinolysis observed in infected mice compared to controls [23]. Coagulation abnormalities, such as excess clotting and consumptive coagulopathy, have been documented in chickens infected with the H5N1 influenza virus [24].

Inflammation plays a role throughout the atherosclerotic process, with systemic inflammation markers like C-reactive protein being linked to increased cardiovascular risk. A study on inflammatory markers in acute myocardial infarction (AMI) showed notably higher levels of cytokines, such as IL-6, in patients with

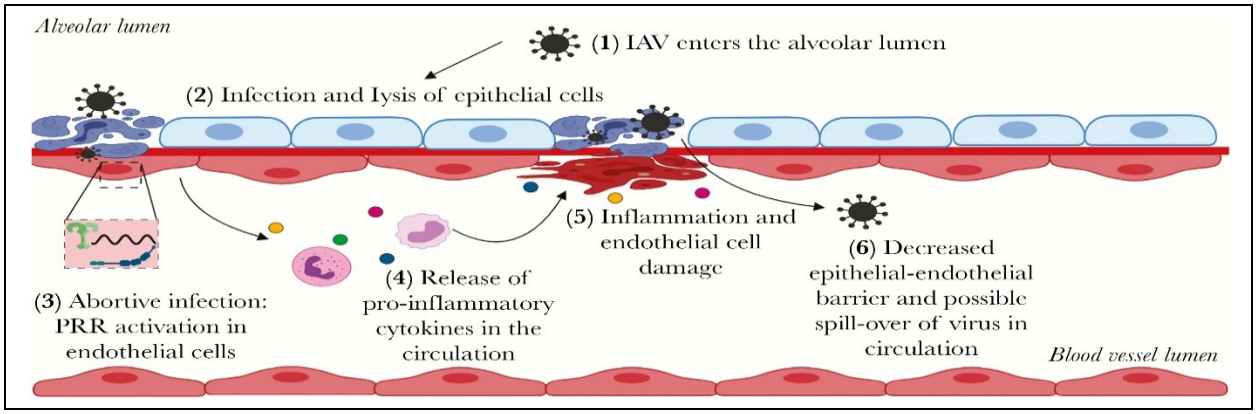

Figure 1. The influenza virus infects alveolar epithelial cells, prompting the release of pro-inflammatory cytokines and chemokines, which induce inflammation and attract immune cells. These activated immune cells infiltrate lung tissue, releasing additional inflammatory mediators, particularly impacting vascular endothelium. Ultimately, this inflammatory cascade can culminate in pneumonia, acute respiratory distress syndrome (ARDS), and significant cardiac complications; IAV — influenza A virus, PRRs — pattern recognition receptors [72]

ST-elevated myocardial infarction (STEMI) compared to those with non-ST-elevated myocardial infarction (NSTEMI). Mice studies have demonstrated increased inflammatory cytokines, including TNF-α and IL-6, in the context of influenza infection. Experimental studies in healthy individuals reveal transient endothelial dysfunction mediated by various inflammatory cytokines, whose circulating levels surge during acute inflammation [25, 26].

The endothelium functions as an essential endocrine organ crucial for maintaining overall body homeostasis. Healthy endothelial cells play roles in regulating antioxidants, exert anti-inflammatory and anticoagulant actions, and control vascular relaxation, contraction, thrombogenesis, fibrinolysis, and platelet activation and inhibition. Endothelial dysfunction (ED) can lead to the loss of these crucial homeostatic functions, resulting in various pathologies. Endothelial injury can occur due to hemodynamic factors (e.g., wall shear stress), chemical factors (e.g., LDL cholesterol or glucose), or bacterial and viral infections (e.g., influenza). The loss of endothelial integrity permits lipid infiltration, leading to the formation of atheromatous plaques [27].

During influenza virus infection, endothelial cells become activated, evidenced by increased levels of von Willebrand factor, enhanced coagulation, and necrosis [28–30]. In mice and ferrets infected with influenza virus, endothelial cells produce various pro-inflammatory cytokines, with the observation that this effect may be specific to the virus subtype [31]. Highly pathogenic influenza viruses such as H7N9 and H5N1 can significantly impact endothelium, replicating efficiently in human pulmonary microvascular endothelial cells. Thus, infection of endothelial cells by these viruses may contribute to the virus's pathogenicity and dissemination beyond the respiratory tract, particularly affecting the cardiovascular system [32].

In the lower respiratory tract's alveoli, endothelial cells are closely situated to alveolar epithelial cells, which are susceptible to influenza virus infection. The infection of alveolar epithelial cells may expose endothelial cells to virus particles, either through basolateral release from infected epithelial cells or due to alveolar wall damage caused by infection, necrosis, and inflammation [33].

Furthermore, patients infected with SARS-CoV-2 exhibit elevated cytokine levels and inflammation biomarkers, leading to a cytokine storm and multi-organ involvement, including cardiovascular complications [34]. SARS-CoV-2 spike proteins can provoke a pro-inflammatory response in brain endothelial cells, potentially compromising blood-brain barrier integrity and function [35, 36]. Therefore, similar to other respiratory viruses like SARS-CoV-2 and RSV, influenza viruses interact primarily with endothelial cells in various blood vessels and the heart, leading to diverse pathological manifestations (Fig. 2).

Influenza clinical symptoms

In uncomplicated influenza, the incubation period is typically one to four days, with systemic symptoms initially prevailing, including fever, chills, headaches, myalgia, malaise, and anorexia. Severe cases may exhibit prostration. Myalgia or headache, often linked to fever height, are usually the most bothersome symptoms. Fever ranges from 37.8 to 40.0°C (100 to 104°F) and can peak at 41.1°C (106°F). Myalgia may affect limbs

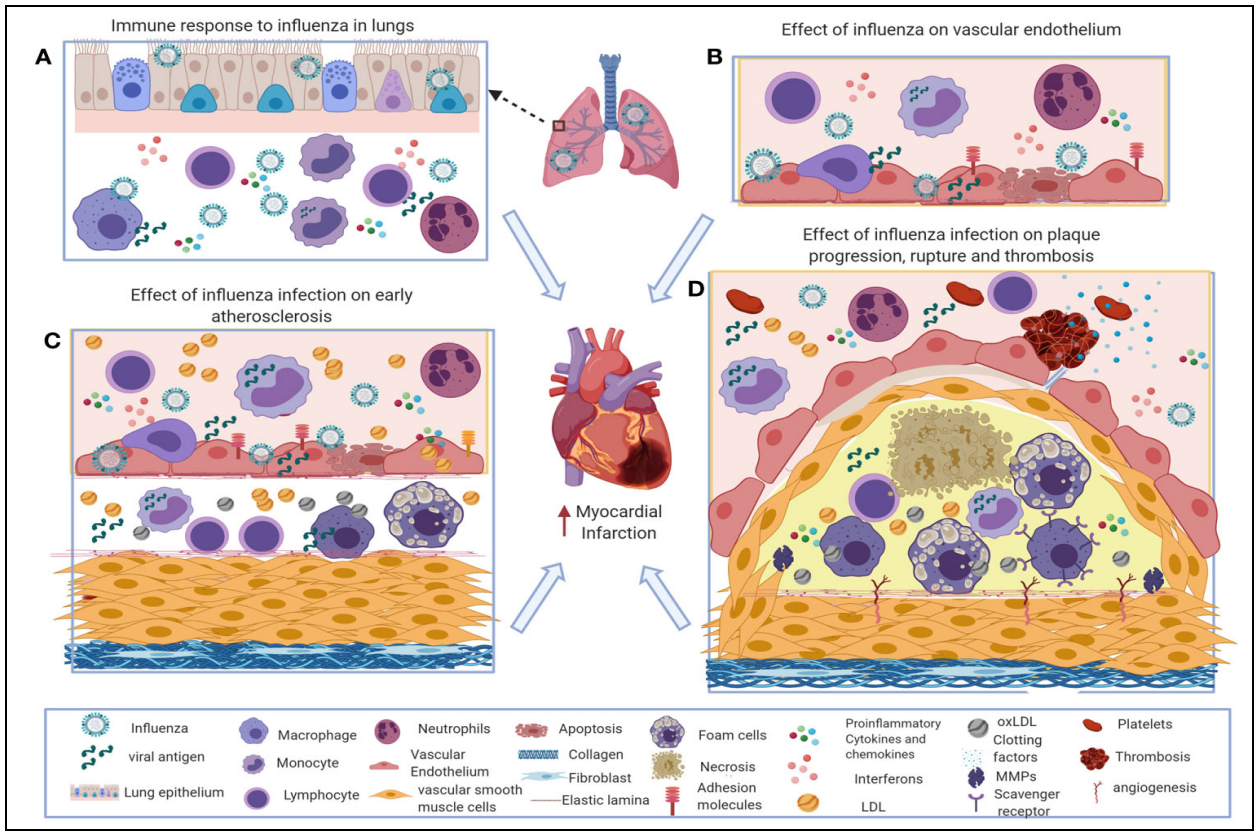

Figure 2. Influenza infection initiates immune responses that recruit macrophages, neutrophils, and NK cells to combat the virus. However, dysregulation leads to excessive inflammation, enhancing chemotactic factors and adhesion molecules on endothelial cells, promoting inflammatory cell recruitment to atherosclerotic plaques. Inflammatory mediators also directly promote atherogenesis, worsening atherosclerosis and potentially leading to cardiac complications like acute myocardial infarction [73]

or back muscles, with prominent calf muscle pain in children. Severe eye muscle pain and arthralgia, but not arthritis, can occur [37].

Systemic symptoms persist for about 3 days, matching the typical fever duration. Respiratory symptoms, like a dry cough, severe pharyngeal pain, and nasal obstruction, accompany onset but are overshadowed initially. In early stages, patients seem toxic with a flushed face, hot and moist skin, watery and reddened eyes, and a clear nasal discharge. Gastrointestinal symptoms are rare in adults but can affect 10 to 20 percent of children. Uncommon presentations include afebrile respiratory illness or systemic signs without respiratory involvement [38].

Pulmonary complications are more common in older adults and immunosuppressed individuals. Signs in complications differ; for instance, pulmonary complications exhibit cough, dyspnea, tachypnea, hypoxia, and fever [39]. Other complications encompass cardiac (myocardial infarction, heart failure, myocarditis, and pericarditis) [40], musculoskeletal (myositis and rhabdomyolysis) [41], and central nervous system involvement (seizures, encephalopathy, encephalitis, cerebrovascular accident, acute disseminated encephalomyelitis, and Guillain-Barré syndrome) [42]. Additionally, individuals who had an influenza infection within one year before contracting COVID-19 were more likely to experience severe illness from SARS-CoV-2 infection [43]. Vaccinated individuals may show similar but less severe manifestations.

Cardiovascular complications

Influenza, despite being a virus primarily associated with respiratory symptoms, also can leads to extra-pulmonary manifestations. One of the most significant among these is cardiac involvement, which carries high morbidity and mortality rates. The following elaborates on the most important cardiac complications.

Ischemic heart disease (IHD)

Numerous extensive epidemiological investigations have demonstrated a temporal correlation between the prevalence of influenza viruses and a rise in hospitalizations and fatalities attributed to ischemic heart disease (IHD). The hypothesis posits that influenza-

-associated IHD is instigated by inflammation, a known contributor to acute coronary syndrome development [44]. Moreover, a noteworthy surge in the incidence of IHD-related deaths has been identified during epidemic periods. Previous studies have indicated that the rates of a first myocardial infarction (MI) were most pronounced within the initial 3 days following an acute respiratory infection, with a diminishing effect observed over time [8, 45].

Myocarditis

Myocarditis is characterized by diffuse inflammation of the myocardium, accompanied by focal myocyte necrosis, with viral infection being the primary cause. The incidence of influenza-associated myocarditis has been documented to reach up to 10% [46]. Viral myocarditis exhibits a spectrum of clinical manifestations influenced by presentation timing, myocardial involvement extent, and individual factors, ranging from subclinical cases to sudden death.

Clinically diagnosed myocarditis, identified through a combination of symptoms, elevated cardiac enzymes, and echocardiographic findings, has been reported in approximately 0.4–13% of hospitalized adult patients with documented influenza [47]. The clinical course varies, with severity spanning from asymptomatic cases to severe disease. Most patients experience acute cardiac dysfunction symptoms, such as chest pain, dyspnea, syncope, hypotension, and arrhythmia, typically occurring between days 4 and 7 after the initial viral infection symptoms [48, 49].

Electrocardiogram (ECG) changes, documented in several studies, include sinus tachycardia, partial right bundle branch block (RBBB), ST depression, and deep T-wave inversion in the anterior precordial leads. Notably, there is a consistent regression of ECG changes, with normalization occurring within a week. Recent studies examining cardiac enzymes in influenza patients report elevated CKMB levels in 0–5%, while TnT and TnI remain within normal ranges. Regarding echocardiography, the majority of studies show no ejection fraction (EF) or wall motion abnormalities, with no significant changes in EF observed during the study period [50, 51].

Pericarditis

Viral infection, particularly influenza, stands out as the primary cause of pericarditis [52]. The viral etiologies of myocarditis and pericarditis often overlap. While many cases of influenza-associated pericarditis are clinically insignificant, occasional complications of significance may arise. Pericardial effusions, varying in size and clinical impact, commonly complicate influenza-related myocarditis. Electrocardiography and echocardiography play crucial roles in monitoring and detecting complications associated with pericarditis [53].

Heart failure

Congestive heart failure, identified through regional or global hypokinesis on echo/MRI, emerges as the predominant complication, affecting 84% of individuals with influenza-associated myocarditis. A significant proportion of those with heart failure necessitate advanced cardiac support therapies [54]. Additionally, heart failure independent of myocarditis has been documented during influenza infection. Notably, right ventricular dysfunction (48%) surpasses left ventricular dysfunction (17%) in prevalence, exceeding what is typically reported in patients with acute respiratory distress syndrome (ARDS) [52].

Cardiac arrhythmia

In influenza, cardiac arrhythmias take center stage. The prevalent reported arrhythmias include atrioventricular conduction block [55] and ventricular fibrillation [56]. These arrhythmias are predominantly attributed to underlying fulminant myocarditis in the context of influenza infection. A recent study, highlighting that 15.4% of deaths attributed to pH1N1 in the United States occurred at home, suggests a potential association between influenza infection, arrhythmias, and cardiac arrest [53].

Microcirculatory dysfunction

The alterations in microcirculatory function observed in individuals infected with influenza viruses are not well comprehended. The microcirculation plays a pivotal role in the regulation of organ perfusion. Microcirculatory dysfunction has been linked with adverse outcomes, including increased rates of organ failure and mortality, in various studies involving different shock conditions [57, 58]. Blood flow resistance is primarily influenced by blood vessel diameter and is modulated by endothelium-derived factors such as nitric oxide and prostaglandins [59, 60]. Inflammatory cytokines and other alarmin mediators contribute to the vasodilatory response of blood vessels during inflammation, causing significant alterations in tissue blood flow, potentially leading to tissue hypoxia. This dysregulation of blood flow is considered a major factor contributing to severe hypoxemia in influenza patients [61]. Notably, a reduction in the speed of pulmonary microcirculation was observed concurrently with the presence of virus-infected cells in the lung [62].

Patients severely affected by influenza, particularly Influenza A (H1N1) with acute respiratory distress syndrome (ARDS), exhibit clinically significant microcirculatory abnormalities. Recent evidence indicates that

microcirculatory abnormalities are present in patients with acute lung injury associated with severe influenza A (H1N1) infection, independent of bacterial co-infection [63]. Animal studies suggest that acute severe respiratory dysfunction in cigarette-smoke-exposed and flu-infected mice is associated with the accumulation of platelet-rich neutrophil-platelet aggregates (NPAs) in the lung microcirculation within 2 days post-flu infection, suggesting increased susceptibility to influenza and its microcirculatory complications among smokers [64].

Management

Vaccination

Available vaccines formulations include various inactivated influenza vaccines (IIVs), such as egg-based vaccines for individuals ≥ 18 years of age and cell culture-based vaccines for those ≥ 6 months of age. Given the association between peak influenza activity and cardiovascular events, studies have evaluated the effect of influenza vaccination on the reduction of multiple cardiovascular end points. a large prospective randomized double-blinded placebo controlled study of 658 patients with coronary artery disease (CAD) found a significant reduction in coronary ischemic events, specifically cardiovascular death, MI, cardiac revascularization, or hospitalization with myocardial ischemia, in the 12 months following influenza vaccination with the inactivated influenza vaccine [54, 65].

Antiviral treatment

Two classes of antivirals are available for influenza treatment: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (rimantadine and amantadine) [66]. Neuraminidase and hemagglutinin, surface glycoproteins on Influenza A viruses, play critical roles in viral replication. Hemagglutinin binds to sialic acid compounds on cell surfaces, facilitating viral entry into target cells. While essential for this initial step, hemagglutinin's presence also impedes the release of newly formed virions after budding from infected cells. Neuraminidase, on the other hand, is an enzyme that cleaves sialic acid residues from glycan structures on infected cells, allowing for the release of progeny viruses and their spread to uninfected cells in the surrounding environment [67]. A retrospective study evaluated the impact of neuraminidase inhibitors on the recurrence of cardiovascular disease after influenza infection. The study found that patients with a history of cardiovascular disease and acute influenza who were prescribed oseltamivir within two days experienced fewer cardiac events (MI, angina, stroke, heart failure, sudden cardiac death) within 30 days of influenza diagnosis. This finding highlights the potential for neuraminidase inhibitors to reduce the cardiovascular complications associated with influenza [68].

Other medications

Influenza virus infections are linked to increased levels of proinflammatory cytokines, often described as a cytokine storm. While antiviral therapy, if initiated early, may prevent this reaction [69], three classes of drugs with anti-inflammatory properties — statins, peroxisome proliferator-activated receptors-α agonists (fibrates), and peroxisome proliferator-activated receptors-γ agonists (glitazones) — individually or in combination, have the potential to prevent influenza-associated acute lung injury [70, 71].

Conclusions

Influenza, a subgroup of RNA viruses within the orthomyxoviridae family, is a respiratory illness with a significant global impact, causing millions of cases, hospitalizations, and deaths annually. Elderly individuals, young children, pregnant women, and individuals with underlying health conditions, including chronic pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders, obesity, and immunocompromised individuals, are considered high-risk groups. However, the burden of influenza is often underestimated due to the focus on well-recognized respiratory-related manifestations. A comprehensive literature review suggests that influenza can also cause extra-pulmonary complications, including pneumonia, cardiac involvement, musculoskeletal complications, and central nervous system involvement. Influenza can affect the cardiovascular system through various mechanisms, including coagulopathy and inflammation. Cardiovascular involvement in acute influenza infection can manifest as direct effects on the myocardium (myocarditis and pericarditis) or as an exacerbation of pre-existing cardiovascular conditions (heart failure, ischemic heart disease). The clinical presentation can range from asymptomatic to fulminant myocarditis, leading to cardiogenic shock and death. Influenza-specific prevention through vaccination or treatment with antiviral agents has been shown to reduce the risk and/or severity of certain complications, but further research is needed. Early recognition of the extra-pulmonary manifestations of influenza infection is crucial to initiate timely therapeutic interventions and organ-specific supportive care.

In conclusion, a deeper understanding of this virus through ongoing research is essential to make informed decisions and optimize treatment strategies. Additionally, a comprehensive understanding of the cardiovascular manifestations associated with influenza

infection remains a challenge and warrants ongoing research endeavors.

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References

1. Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's principles of internal medicine. 21st edition ed: McGraw Hill Press 2022.
2. Warren-Gash C, Hayward AC, Hemingway H, et al. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. Lancet Infect Dis. 2009; 9(10): 601–610, doi: 10.1016/S1473-3099(09)70233-6, indexed in Pubmed: 19778762.
3. Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol. 2008; 130(3): 304–309, doi: 10.1016/j.ijcard.2008.04.044, indexed in Pubmed: 18625525.
4. Jeyanathan T, Overgaard C, McGeer A. Cardiac complications of influenza infection in 3 adults. CMAJ. 2013; 185(7): 581–584, doi: 10.1503/cmaj.110807, indexed in Pubmed: 23549966.
5. Berkhoff EGM, de Wit E, Geelhoed-Mieras MM, et al. Fitness costs limit escape from cytotoxic T lymphocytes by influenza A viruses. Vaccine. 2006; 24(44-46): 6594–6596, doi: 10.1016/j.vaccine.2006.05.051, indexed in Pubmed: 16837112.
6. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. Clin Infect Dis. 2003; 37(8): 1094–1101, doi: 10.1086/378292, indexed in Pubmed: 14523774.
7. Kalil AC, Thomas PG. Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care. 2019; 23(1): 258, doi: 10.1186/s13054-019-2539-x, indexed in Pubmed: 31324202.
8. Warren-Gash C, Hayward AC, Hemingway H, et al. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. J Infect Dis. 2012; 206(11): 1652–1659, doi: 10.1093/infdis/jis597, indexed in Pubmed: 23048170.
9. Warren-Gash C, Bhaskaran K, Hayward A, et al. Circulating influenza virus, climatic factors, and acute myocardial infarction: a time series study in England and Wales and Hong Kong. J Infect Dis. 2011; 203(12): 1710–1718, doi: 10.1093/infdis/jir171, indexed in Pubmed: 21606529.
10. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases: Elsevier Inc.; 2014.
11. Treanor J. Influenza viruses, including avian influenza and swine influenza. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2010: 2265–2288, doi: 10.1016/b978-0-443-06839-3.00165-x.
12. Johanson WG, Pierce AK, Sanford JP. Pulmonary function in uncomplicated influenza. Am Rev Respir Dis. 1969; 100(2): 141–146, doi: 10.1164/arrd.1969.100.2.141, indexed in Pubmed: 5805258.
13. Kondo S, Abe K. The effects of influenza virus infection on FEV1 in asthmatic children. The time-course study. Chest. 1991; 100(5): 1235–1238, doi: 10.1378/chest.100.5.1235, indexed in Pubmed: 1935277.
14. Qian M-M, Wu W. Dong K-X. Clinical features and TCM syndromes of infectious AECOPD caused by influenza virus. Journal of Hainan Medical College. 2021; 27(24).
15. Levandowski RA, Gerrity TR, Garrard CS. Modifications of lung clearance mechanisms by acute influenza A infection. J Lab Clin Med. 1985; 106(4): 428–432, indexed in Pubmed: 4045299.
16. Pittet LA, Hall-Stoodley L, Rutkowski MR, et al. Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae. Am J Respir Cell Mol Biol. 2010; 42(4): 450–460, doi: 10.1165/rcmb.2007-0417OC, indexed in Pubmed: 19520922.
17. van der Sluijs KF, van Elden LJR, Nijhuis M, et al. IL-10 is an important mediator of the enhanced susceptibility to pneumococcal pneumonia after influenza infection. J Immunol. 2004; 172(12): 7603–7609, doi: 10.4049/jimmunol.172.12.7603, indexed in Pubmed: 15187140.
18. Sun K, Metzger DW. Influenza infection suppresses NADPH oxidase-dependent phagocytic bacterial clearance and enhances susceptibility to secondary methicillin-resistant Staphylococcus aureus infection. J Immunol. 2014; 192(7): 3301–3307, doi: 10.4049/jimmunol.1303049, indexed in Pubmed: 24563256.
19. Small CL, Shaler CR, McCormick S, et al. Influenza infection leads to increased susceptibility to subsequent bacterial superinfection by impairing NK cell responses in the lung. J Immunol. 2010; 184(4): 2048–2056, doi: 10.4049/jimmunol.0902772, indexed in Pubmed: 20083661.
20. Hayden FG, Fritz R, Lobo MC, et al. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. J Clin Invest. 1998; 101(3): 643–649, doi: 10.1172/JCI1355, indexed in Pubmed: 9449698.
21. Marsden PA. Inflammation and coagulation in the cardiovascular system: the contribution of influenza. Circ Res. 2006; 99(11): 1152–1153, doi: 10.1161/01.RES.0000251962.44753.7f, indexed in Pubmed: 17122443.
22. Smeeth L, Cook C, Thomas S, et al. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet. 2006; 367(9516): 1075–1079, doi: 10.1016/S0140-6736(06)68474-2, indexed in Pubmed: 16581406.
23. Keller TT, van der Sluijs KF, de Kruif MD, et al. Effects on coagulation and fibrinolysis induced by influenza in mice with a reduced capacity to generate activated protein C and a deficiency in plasminogen activator inhibitor type 1. Circ Res. 2006; 99(11): 1261–1269, doi: 10.1161/01.RES.0000250834.29108.1a, indexed in Pubmed: 17068293.

24. Muramoto Y, Ozaki H, Takada A, et al. Highly pathogenic H5N1 influenza virus causes coagulopathy in chickens. Microbiol Immunol. 2006; 50(1): 73–81, doi: 10.1111/j.1348-0421.2006.tb03764.x, indexed in Pubmed: 16428877.
25. Szretter KJ, Gangappa S, Belser JA, et al. Role of host cytokine responses in the pathogenesis of avian H5N1 influenza viruses in mice. J Virol. 2007; 81(6): 2736–2744, doi: 10.1128/JVI.02336-06, indexed in Pubmed: 17182684.
26. Di Stefano R, Di Bello V, Barsotti MC, et al. Inflammatory markers and cardiac function in acute coronary syndrome: difference in ST-segment elevation myocardial infarction (STEMI) and in non-STEMI models. Biomed Pharmacother. 2009; 63(10): 773–780, doi: 10.1016/j.biopha.2009.06.004, indexed in Pubmed: 19906505.
27. Stanek A, Fazeli B, Bartuś S, et al. The role of endothelium in physiological and pathological states: new data. Biomed Res Int. 2018; 2018: 1098039, doi: 10.1155/2018/1098039, indexed in Pubmed: 30581842.
28. Goeijenbier M, van Gorp ECM, Van den Brand JMA, et al. Activation of coagulation and tissue fibrin deposition in experimental influenza in ferrets. BMC Microbiol. 2014; 14: 134, doi: 10.1186/1471-2180-14-134, indexed in Pubmed: 24884666.
29. Short KR, Kasper J, van der Aa S, et al. Influenza virus damages the alveolar barrier by disrupting epithelial cell tight junctions. Eur Respir J. 2016; 47(3): 954–966, doi: 10.1183/13993003.01282-2015, indexed in Pubmed: 26743480.
30. Ashar HK, Mueller NC, Rudd JM, et al. The role of extracellular histones in influenza virus pathogenesis. Am J Pathol. 2018; 188(1): 135–148, doi: 10.1016/j.ajpath.2017.09.014, indexed in Pubmed: 29107075.
31. Chan LLY, Hui KPY, Kuok DIT, et al. Risk assessment of the tropism and pathogenesis of the highly pathogenic avian influenza A/H7N9 virus using ex vivo and in vitro cultures of human respiratory tract. J Infect Dis. 2019; 220(4): 578–588, doi: 10.1093/infdis/jiz165, indexed in Pubmed: 31001638.
32. Short K, Kroeze EV, Reperant L, et al. Influenza virus and endothelial cells: a species specific relationship. Frontiers in Microbiology. 2014; 5, doi: 10.3389/fmicb.2014.00653.
33. Short KR, Kuiken T, Van Riel D. Role of endothelial cells in the pathogenesis of influenza in humans. J Infect Dis. 2019; 220(11): 1859–1860, doi: 10.1093/infdis/jiz349, indexed in Pubmed: 31283821.
34. Perisetti A, Goyal H, Gajendran M, et al. Prevalence, mechanisms, and implications of gastrointestinal symptoms in COVID-19. Front Med (Lausanne). 2020; 7: 588711, doi: 10.3389/fmed.2020.588711, indexed in Pubmed: 33195352.
35. Rahban M, Stanek A, Hooshmand A, et al. Infection of human cells by SARS-CoV-2 and molecular overview of gastrointestinal, neurological, and hepatic problems in COVID-19 patients. J Clin Med. 2021; 10(21), doi: 10.3390/jcm10214802, indexed in Pubmed: 34768321.
36. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS--CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood-brain barrier. Neurobiol Dis. 2020; 146: 105131, doi: 10.1016/j.nbd.2020.105131, indexed in Pubmed: 33053430.
37. Javanian M, Barary M, Ghebrehewet S, et al. A brief review of influenza virus infection. J Med Virol. 2021; 93(8): 4638–4646, doi: 10.1002/jmv.26990, indexed in Pubmed: 33792930.
38. Liu WD, Yeh CY, Shih MC, et al. Clinical manifestations and risk factors for mortality of patients with severe influenza during the 2016-2018 season. Int J Infect Dis. 2020; 95: 347–351, doi: 10.1016/j.ijid.2020.04.013, indexed in Pubmed: 32289562.
39. Daoud A, Laktineh A, Macrander C, et al. Pulmonary complications of influenza infection: a targeted narrative review. Postgrad Med. 2019; 131(5): 299–308, doi: 10.1080/00325481.2019.1592400, indexed in Pubmed: 30845866.
40. Radovanovic M, Petrovic M, Barsoum MK, et al. Influenza myopericarditis and pericarditis: a literature review. J Clin Med. 2022; 11(14), doi: 10.3390/jcm11144123, indexed in Pubmed: 35887887.
41. Kietaibl AT, Fangmeyer-Binder M, Göndör G, et al. Acute viral myositis: profound rhabdomyolysis without acute kidney injury. Wien Klin Wochenschr. 2021; 133(15-16): 847–850, doi: 10.1007/s00508-021-01866-3, indexed in Pubmed: 33905028.
42. Robinson CP, Busl KM. Neurologic manifestations of severe respiratory viral contagions. Crit Care Explor. 2020; 2(4): e0107, doi: 10.1097/CCE.0000000000000107, indexed in Pubmed: 32426749.
43. Hwang JH, You YS, Yeom SW, et al. Influenza viral infection is a risk factor for severe illness in COVID-19 patients: a nationwide population-based cohort study. Emerg Microbes Infect. 2023; 12(1): 2164215, doi: 10.1080/22221751.2022.2164215, indexed in Pubmed: 36580041.
44. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis. 2010; 10(2): 83–92, doi: 10.1016/S1473-3099(09)70331-7, indexed in Pubmed: 20113977.
45. Lichenstein R, Magder LS, King RE, et al. The relationship between influenza outbreaks and acute ischemic heart disease in Maryland residents over a 7-year period. J Infect Dis. 2012; 206(6): 821–827, doi: 10.1093/infdis/jis435, indexed in Pubmed: 22798684.
46. Nicholson KG, Webster RG, Hay AJ. Textbook of influenza: Blackwell Science Ltd. ; 1998.
47. Kodama M. Influenza myocarditis. Circ J. 2010; 74(10): 2060–2061, doi: 10.1253/circj.cj-10-0833, indexed in Pubmed: 20838004.
48. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis. 2005; 11(2): 201–209, doi: 10.3201/eid1102.041061, indexed in Pubmed: 15752436.
49. Onitsuka H, Imamura T, Miyamoto N, et al. Clinical manifestations of influenza a myocarditis during the influenza epidemic of winter 1998-1999. J Cardiol. 2001; 37(6): 315–323, indexed in Pubmed: 11433807.
50. Erden I, Erden EC, Ozhan H, et al. Echocardiographic manifestations of pandemic 2009 (H1N1) influenza a virus infection. J Infect. 2010; 61(1): 60–65, doi: 10.1016/j.jinf.2010.04.006, indexed in Pubmed: 20430056.
51. Verel D, Warrack AJ, Potter CW, et al. Observations on the A2 England influenza epidemic: a clinicopathological study. Am Heart J. 1976; 92(3): 290–296, doi: 10.1016/s0002-8703(76)80109-3, indexed in Pubmed: 949023.

52. Zanettini MT, Zanettini JO, Zanettini JP. Pericarditis. Series of 84 consecutive cases. Arq Bras Cardiol. 2004; 82(4): 360–369, doi: 10.1590/s0066-782x2004000400007, indexed in Pubmed: 15320556.
53. Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza: a systematic review. Int J Cardiol. 2013; 167(6): 2397–2403, doi: 10.1016/j.ijcard.2013.01.274, indexed in Pubmed: 23474244.
54. Sellers SA, Hagan RS, Hayden FG, et al. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. Influenza Other Respir Viruses. 2017; 11(5): 372–393, doi: 10.1111/irv.12470, indexed in Pubmed: 28745014.
55. Gokhroo R, Barjaty H, Bhawna K. Cardiac conduction system affection in a case of swine flu. J Assoc Physicians India. 2011; 59: 51–2, indexed in Pubmed: 21751667.
56. Wiegand JA, Torgersen C, Bloechlinger S, et al. Influenza A(H1N1) infection and severe cardiac dysfunction in adults: A case series. Wien Klin Wochenschr. 2011; 123(3-4): 120–123, doi: 10.1007/s00508-010-1520-0, indexed in Pubmed: 21240687.
57. Machiedo GW, Zaets SB, Berezina TL, et al. Trauma-hemorrhagic shock-induced red blood cell damage leads to decreased microcirculatory blood flow. Crit Care Med. 2009;37(3):1000-10. doi: 10.1097/CCM.0b013e3181962d39. PubMed PMID. ; 19237910, doi: 10.1097/CCM.0b013e3181962d39.
58. Trzeciak S, McCoy JV, Phillip Dellinger R, et al. Microcirculatory Alterations in Resuscitation and Shock (MARS) investigators. Early increases in microcirculatory perfusion during protocol--directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med. 2008; 34(12): 2210–2217, doi: 10.1007/s00134-008-1193-6, indexed in Pubmed: 18594793.
59. Granger DN, Rodrigues SF, Yildirim A, et al. Microvascular responses to cardiovascular risk factors. Microcirculation. 2010; 17(3): 192–205, doi: 10.1111/j.1549-8719.2009.00015.x, indexed in Pubmed: 20374483.
60. Feletou M, Tang EHC, Vanhoutte PM. Nitric oxide the gatekeeper of endothelial vasomotor control. Front Biosci. 2008; 13: 4198–4217, doi: 10.2741/3000, indexed in Pubmed: 18508506.
61. Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Critical Care. 2009; 13(5): R148, doi: 10.1186/cc8044.
62. Ueki H, Wang IH, Fukuyama S, et al. In vivo imaging of the pathophysiological changes and neutrophil dynamics in influenza virus-infected mouse lungs. Proc Natl Acad Sci U S A. 2018; 115(28): E6622–E6629, doi: 10.1073/pnas.1806265115, indexed in Pubmed: 29941581.
63. Salgado DR, Ortiz JA, Favory R, et al. Microcirculatory abnormalities in patients with severe influenza A (H1N1) infection. Can J Anaesth. 2010; 57(10): 940–946, doi: 10.1007/s12630-010-9365-6, indexed in Pubmed: 20661679.
64. Kaminski TW, Brzoska T, Li X, et al. Lung microvascular occlusion by platelet-rich neutrophil-platelet aggregates promotes cigarette smoke-induced severe flu. JCI Insight. 2024; 9(2), doi: 10.1172/jci.insight.167299, indexed in Pubmed: 38060312.
65. Brydak LB, Romanowska M, Nowak I, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. Eur Heart J. 2008; 29(11): 1350–1358, doi: 10.1093/eurheartj/ehm581, indexed in Pubmed: 18187561.
66. Holmes EC, Hurt AC, Dobbie Z, et al. Understanding the impact of resistance to influenza antivirals. Clin Microbiol Rev. 2021; 34(2), doi: 10.1128/CMR.00224-20, indexed in Pubmed: 33568554.
67. Heneghan CJ, Onakpoya I, Jones MA, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016; 20(42): 1–242, doi: 10.3310/hta20420, indexed in Pubmed: 27246259.
68. Casscells SW, Granger E, Kress AM, et al. Use of oseltamivir after influenza infection is associated with reduced incidence of recurrent adverse cardiovascular outcomes among military health system beneficiaries with prior cardiovascular diseases. Circ Cardiovasc Qual Outcomes. 2009; 2(2): 108–115, doi: 10.1161/CIRCOUTCOMES.108.820357, indexed in Pubmed: 20031822.
69. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat Med. 2006; 12(10): 1203–1207, doi: 10.1038/nm1477, indexed in Pubmed: 16964257.
70. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med. 2010; 38(4 Suppl): e91–e97, doi: 10.1097/CCM.0b013e3181c92eeb, indexed in Pubmed: 19935413.
71. Fedson DS. Confronting the next influenza pandemic with anti-inflammatory and immunomodulatory agents: why they are needed and how they might work. Influenza Other Respir Viruses. 2009; 3(4): 129–142, doi: 10.1111/j.1750--2659.2009.00090.x, indexed in Pubmed: 19627370.
72. Short KR, Kuiken T, Van Riel D. Role of endothelial cells in the pathogenesis of influenza in humans. J Infect Dis. 2019; 220(11): 1859–1860, doi: 10.1093/infdis/jiz349, indexed in Pubmed: 31283821.
73. Gopal R, Marinelli MA, Alcorn JF. Immune Mechanisms in Cardiovascular Diseases Associated With Viral Infection. Front Immunol. 2020; 11: 570681, doi: 10.3389/fimmu.2020.570681, indexed in Pubmed: 33193350.