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Mechanism and suggestions of liver damage caused by influenza A virus: a narrative review

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ABSTRACT:

This study aimed to explore the causes and mechanisms of liver damage caused by influenza A virus (IAV), compare the liver damage caused by SARS-CoV-2 and IAV under China's Glasnost, propose treatment and vaccination recommendations for IAV, and provide new ideas for clinical treatment.

With the Chinese government's liberalization of management measures, COVID-19 has gradually faded from people's lives. However, in February and March 2023, a nationwide outbreak of IAV infection immediately followed in China. Numerous patients with H1N1 influenza rushed into hospitals at one time. H1N1 influenza can cause serious illnesses such as high fever and colds, muscle soreness, bronchitis, and severe respiratory distress syndrome. Although decades have passed since the emergence of IAV infection, it is constantly mutating and causing periodic outbreaks. As the number of cases in this nationwide outbreak in China increases, some patients with H1N1 influenza have developed abnormal liver function. Original articles describing H1N1 influenza and liver damage were searched on PubMed, GeenMedical, Wanfang Data, China National Knowledge Infrastructure, and Web of Science, following a review protocol. The latest articles on liver damage related to IAV infection were searched in relevant databases, and the mechanisms of IAV-related liver damage were summarized. Data showed that IAV was closely related to liver damage.

Liver damage was found to be caused by excessive proinflammatory factor production, cytokine disorders and cytokine storms, oxidative stress, ischemia-reperfusion injury, drug therapy, and coinfection with multiple viruses. Moreover, existing liver diseases may worsen liver damage after the infection.

Keywords: Influenza A, H1N1, Liver injury, Systemic inflammatory reaction, Cytokine.

INTRODUCTION

Influenza A viruses (IAVs) are negative-sense RNA viruses that belong to the family *Orthomyxoviridae*. Four pandemics of IAV infection have occurred worldwide, and the first outbreak of influenza A(H1N1) pdm09 in China was in 2009. Since then, A(H1N1) pdm09 has continuously evolved, replicated, and spread in China[1]. According to the latest IAV testing and weekly report released by the National Center of China on February 23rd, the positivity rate for IAV testing in China continues to increase compared with the previous week. Data shows that IAVs account for the highest proportion of test samples, reaching 71%. According to the World Health Organization[2], IAV infection affects approximately 8% of adults and 25% of children annually, resulting in approximately 4 million respiratory-related deaths globally. In China, the

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average annual excess number of influenza-like cases caused by IAV as outpatient and emergency visits is 3 million, 2.34 million inpatients have severe acute respiratory infections, and 90,000 deaths caused by respiratory diseases[3]. Uncontrolled IAV infection will often infect the patient's respiratory system and cause bronchitis and pneumonia. Moreover, it can invade various body organs, causing encephalopathy, liver diseases, and heart diseases, which are even more serious in children and older people.

IAVs are mainly transmitted through respiratory droplets and can be transmitted through direct or indirect contact with mucous membranes such as the mouth, nose, and eyes. In certain places, such as densely populated and enclosed or poorly ventilated rooms, IAVs may be transmitted as aerosols. The main clinical manifestations of IAV infection are fever, sore throat, cough, and difficulty breathing[4].

Many studies in literature have shown a correlation between IAV infection and the liver. Most patients who have contracted H1N1 influenza have respiratory and pulmonary symptoms. According to a survey[5] conducted by German researchers, among 987 children and adults with acute respiratory infections (including patients with H1N1 influenza), 11.1% exhibited increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase activities. Zhang et al[6] investigated the occurrence of hepatitis by establishing three infected mouse models of respiratory IAVs (H1N1, H5N1, and H7N2). The results showed that the levels of serum aminotransferases (ALT and AST) increased, and liver damage significantly occurred a few days later. Carrillo Esper et al[7] reported similar results in liver damage in patients with IAV infection, with high levels of AST, ALT, bilirubin, blood ammonia, and hepatic encephalopathy in one case.

This shows that IAV infection and liver damage are closely related; however, the specific mechanism is not yet clear, which may include changes in liver metabolism and enzyme activity caused by excessive production of proinflammatory cytokines, high liver oxidative stress, decreased antioxidant capacity, and viral antigen damage rather than direct viral invasion[8].

METHODOLOGY

Search Strategy

PubMed, China National Knowledge Infrastructure (CNKI), GeenMedical, and Web of Science databases were searched using the following keywords: "Influenza A virus", "liver damage", "China", "COVID-19", "inflammation", and "treatment of liver damage". If these studies showed overlapping data, only the study with the highest number of participants was included in the analysis.

Inclusion and Exclusion Criteria for Citations

The inclusion criteria are as follows: (1) studies assessing the correlation between IAV and liver disease risk assessment, (2) studies conducting clinical research on IAV-related liver damage, and (3) studies evaluating IAV-related damage and diseases of other body organs. The exclusion criteria are as follows: (1) the study focused on IAV but did not involve IAV-induced damage to the liver and other body parts, (2) the article content is too simple to allow further analysis, and (3) the study was published before 2016.

Our focus was on studies that (1) assess the correlation between the influenza A virus and liver disease risks, (2) conduct clinical research on IAV-related liver damage, (3) evaluate IAV-related damages and diseases in other body organs.

STRUCTURAL CHARACTERISTICS OF IAV

IAV is a member of the *Orthomyxoviridae* family consisting of single-stranded RNA viruses and can experience periodic changes in the antigenic characteristics of its envelope[9] (Figure 1). These antigenic changes are the reason for the different outbreaks annually. IAV has two different glycoproteins, namely, H protein (hemagglutinin) and N protein (neuraminidase). Hemagglutinin has three main subtypes (H1, H2, and H3), and neuraminidase has two subtypes (N1 and N2). Major changes in these glycoproteins are referred to as antigenic shifts, whereas minor changes are called antigenic drifts; antigenic shifts are associated with epidemics and pandemics[10]. The low proofreading activity of their polymerases and the genomic reassortment among IAV subtypes allow them to evolve continuously, constituting a constant threat to human and animal health[11].

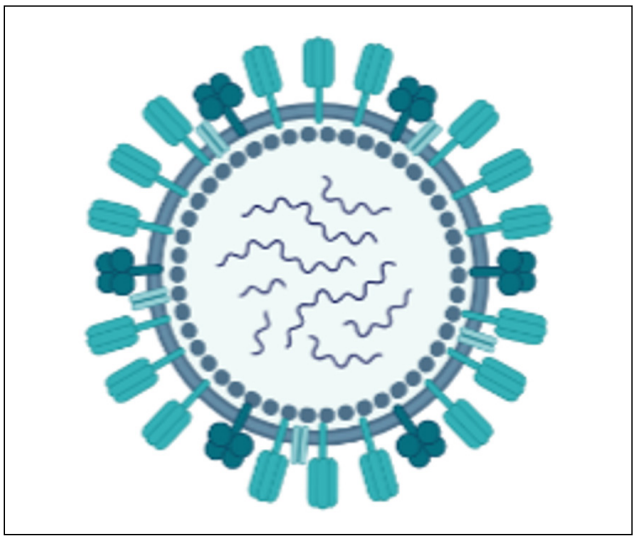

Figure 1. Structural diagram of Influenza A virus.

MECHANISM OF IAV-INDUCED LIVER DAMAGE

Systemic Inflammation

The excessive production of proinflammatory factors causes damage to the liver. IAV infection can cause high cell death rates in the upper respiratory tract, lower respiratory tract, and lung parenchyma. In severe infections, high cell death rates can exacerbate inflammation[12]. Macrophages are large phagocytes that play a major role in immunity and can phagocytose foreign body particles and aging-damaged cells[13]. However, some Brazilian scholars[14] have discovered that IAV or its surface glycoprotein hemagglutinin triggers inflammatory programmed cell death in human and murine macrophages in a Toll-like receptor-4 (TLR4) and tumor necrosis factor (TNF)-dependent manner. The reduction in macrophage abundance causes the persistent presence of apoptotic cells that have not been cleared, which may lead to plasma membrane rupture and release of proinflammatory cell contents through secondary necrosis[15]. In the case of necrosis and plasma membrane rupture, molecules related to intracellular damage leak out from the damaged cells. These released molecules send tissue damage signals to the immune system through different receptors (TLR2, TLR4, TLR9, and RAGE) and induce inflammatory responses[16]. This leads to the polarization of the inflammatory response, which is initiated differently from the top and basal outer sides of the airway epithelium. The integrity of the epithelial barrier is also impaired, accompanied by significant epithelial damage and basal stem cell infection[17]. Local barrier damage causes the IAV to spread to the liver through the bloodstream, causing liver inflammation and damage (Figure 2).

Liver-Induced Cytokine Disorders and Cytokine Storms

Cytokine storm is a phenomenon where various cytokines (such as TNF-α, interleukin [IL-1], IL-6, IL-12, interferon [IFN]-α, IFN-β, and IFN-γ) are rapidly produced in large quantities in body fluids after an infection. The inflammatory response pathways caused by IAV infection include Kupffer cell activation and IFN pathway. Macrophages exhibit high plasticity and diversity, which are crucial for maintaining liver homeostasis and responding to injuries or infections[18]. Kupffer cells are macrophages resident in the liver hepatic sinusoid, which participate as the main intravascular phagocyte and form an immunosuppressive microenvironment in the liver to stabilize the liver[19]. They release pro-inflammatory factors through the activation of the endotoxin lipopolysaccharide (LPS) signaling system and mediate liver damage through interactions with other liver cells[20]. IAV infection activates liver Kupffer cells and promotes the large-scale release of proinflammatory factors, particularly IL-6, TNF-α, and IFN-γ[21]. These cytokines gradually diffuse throughout the body and induce excessive immune responses, leading to cytokine storms. These inflammatory mediators activate the immune system and lead to uncontrolled life-threatening inflamma-

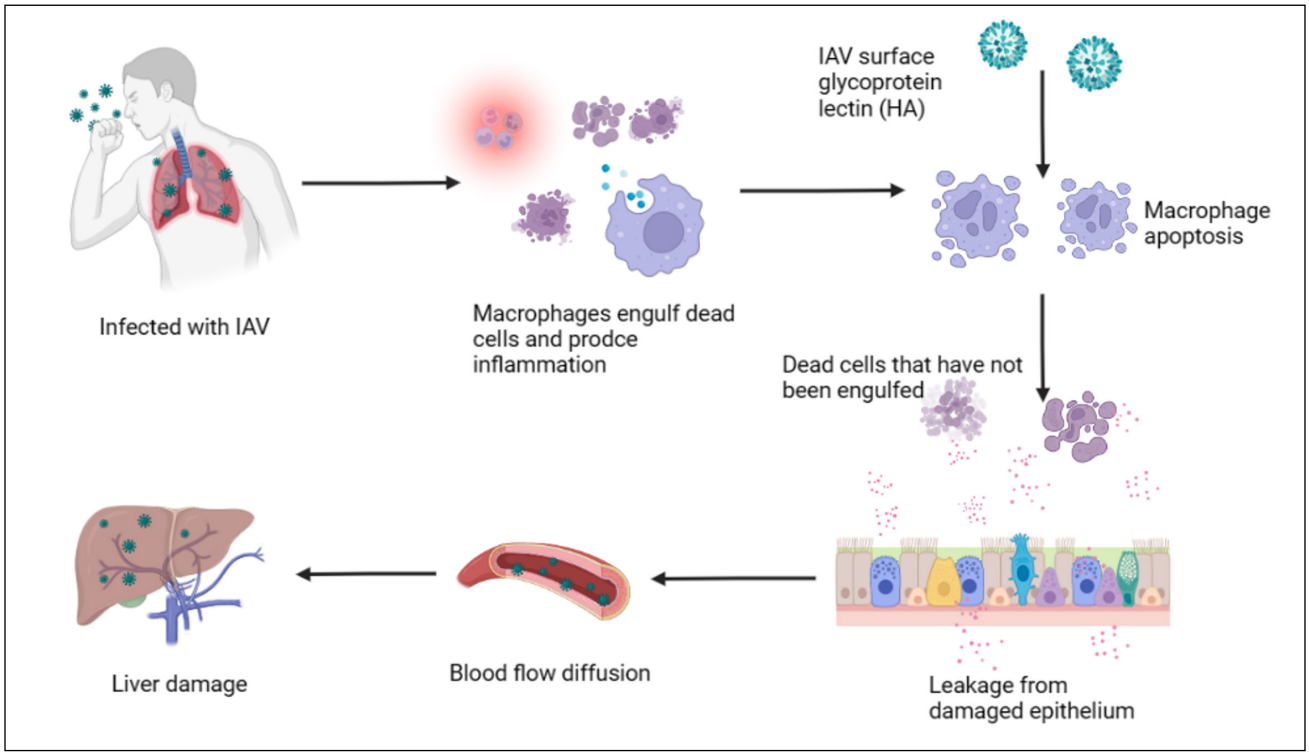

Figure 2. The mechanism of excessive inflammation leading to liver injury.

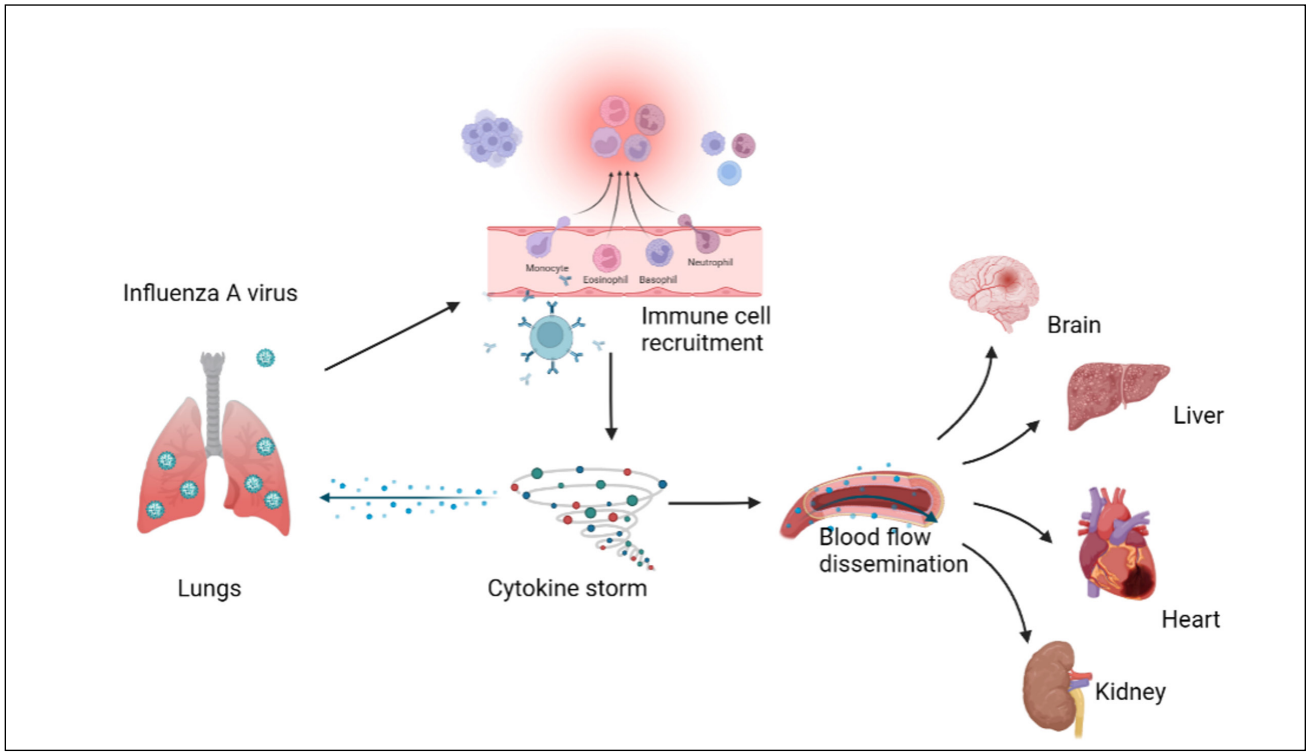

Figure 3. The mechanism of liver injury caused by cytokine disorders.

tion[22]. The immune system cannot control excessive levels of cytokines, and these cytokines attack all cells in the body, leading to systemic inflammation, failure, and death (Figure 3). The cyclic GMP-AMP synthase-(cGAS-) stimulator of the IFN gene (STING) pathway is a key mediator of inflammation[23]. The DNA or cGAMP of IAV-invaded cells and apoptotic necrosis can be phagocytosed or transferred to the cytoplasm of dendritic cells and phagocytes, further activating the cGAS-STING signal transduction, promoting the secretion of proinflammatory cytokines and chemokines, and leading to the increased production of immune cells[24]. This further promotes the occurrence of cytokine storms and damages the liver and other organs.

Oxidative Stress-Induced Liver Damage

IAV-infected host cells produce reactive oxygen species (ROS). Moderate increases in ROS levels can promote cell proliferation and differentiation[25]; however, IAV infection can lead to excessive ROS production, overloading the antioxidant defense system, increasing oxidative stress[26], and disrupting the redox balance of the immune system[27]. Excessive ROS production can also increase mitochondrial damage, leading to apoptosis and cell death[28]. ROS are mainly produced as byproducts of mitochondrial respiration, and they are very susceptible to oxidative damage, which is conducive to increased ROS production, forming a vicious cycle[29]. Mitochondria, as the main energy producers and biosynthetic centers of cells, are at the center of various immune pathways through oxidative stress reactions and cellular signaling[30]. They are extensively damaged during IAV infection, leading to severe liver damage. Mitochondria can also coordinate liver fat metabolism (FFA can enter the mitochondria for oxidation)[31]. If mitochondria are extensively damaged, liver fat accumulation occurs, leading to the development of fatty liver.

Moreover, oxidative stress can mediate ferroptosis in liver cells. Organ damage and degenerative diseases are driven by iron death, and excessive or deficiency in iron death can lead to tissue damage and tumor development[32]. Iron death of liver cells can promote the activation of STING signaling in macrophages, promoting spontaneous liver damage[33] (Figure 4).

Liver-Related Ischemia–Hypoxia–Reperfusion Injury

IAVs mainly attack airway and alveolar epithelial cells, leading to epithelial damage[34]. The influenza virus matrix 1 (M1) protein is released from virus-infected cells and triggers apoptotic cell death in lung epithelial and immune cells by activating TLR4[35]. Fluid and protein leak into the airway and alveolar spaces, threatening gas exchange and making the body hypoxic. It affects the return of hepatic venous blood and increases the pressure in the hepatic portal vein, making the liver ischemic and hypoxic[36]. Under low circulation and hypoxic conditions, insufficient blood supply to the liver affects nutrient transport and accumulation of metabolic byproducts, leading to liver tissue damage.

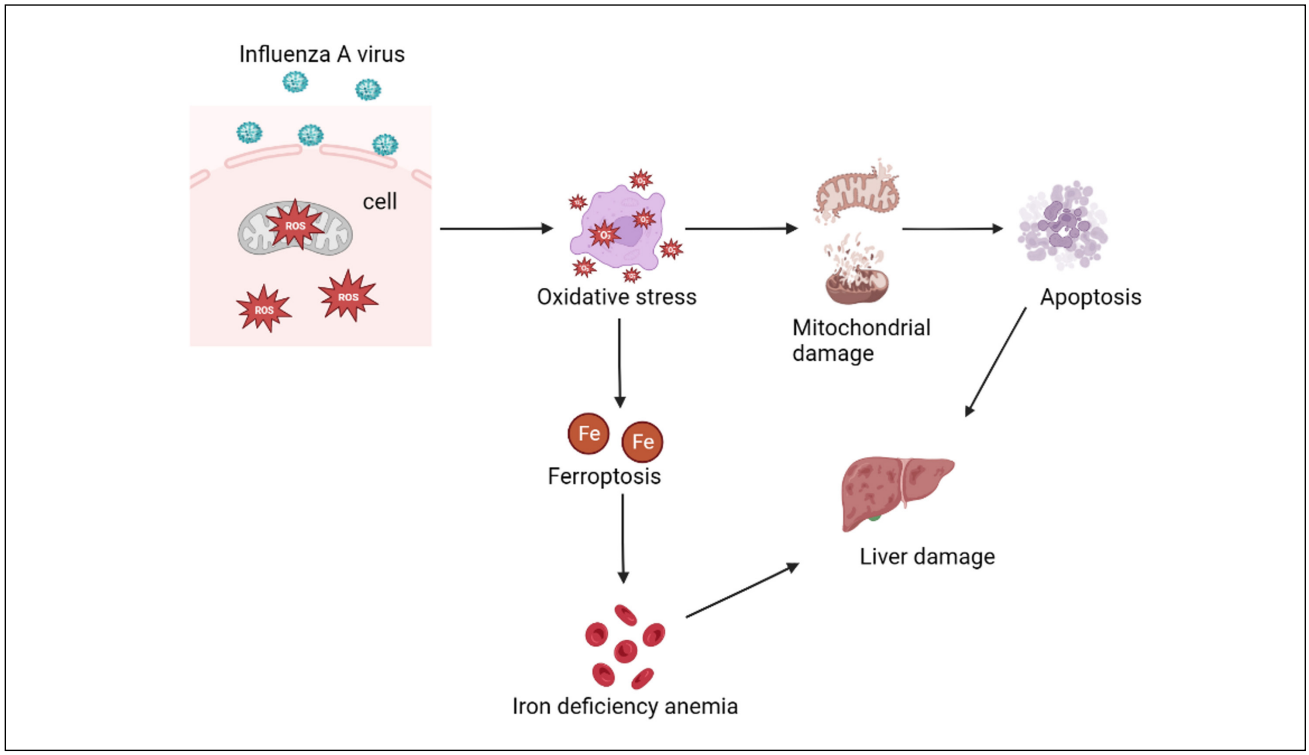

Figure 4. The mechanism of oxidative stress leading to liver injury.

Temporary interruption of liver blood flow leads to ischemia-reperfusion injury in the liver[37]. Shortly after reperfusion, an inflammatory cascade coordinated by Kupffer cells occurs, exacerbating ROS and cytokine production. Subsequently, neutrophils, macrophages, and various effector CD3+T cells migrate to the liver parenchyma, enhancing the validation response and causing liver damage[38]. Excessive neutrophil recruitment can also exacerbate liver damage by promoting the inflammatory cascade induced by neutrophil extracellular traps[39]. Subsequently, inflammatory signals from the damaged tissue activate neutrophils[40], which recruit more neutrophils into the liver by releasing inflammatory and chemotactic factors, forming a positive feedback loop[41].

Pre-Existing Liver Damage

MTS and crystal violet analysis showed that the selective cytotoxicity of the IAV is higher in hepatocellular carcinoma cells than in normal liver cells[42]. Therefore, compared with normal individuals, patients with liver cancer are more susceptible to severe damage in the presence of IAV infection. Some researchers[43] compared the incidence rate of swine flu between liver transplant recipients and normal people and found that the cumulative incidence of liver transplant recipients was higher, and more serious complications were noted. Compared with the general population, the detection rates of laboratory-confirmed IAV infection in kidney transplant recipients have increased five times, and the risk of hospitalization for IAV infection has increased by more than four times[43]. The recent use of large doses of corticosteroids and recent rejection reactions are considered risk factors related to IAV infection complications in liver transplant recipients[44]. According to Li et al[45], IAV exacerbated the development of autoimmune hepatitis. A 68-year-old woman who had a history of unexplained hepatitis before IAV infection was diagnosed with autoimmune hepatitis accompanied by severe liver damage during the infection. A 48-year-old woman with autoimmune hepatitis, despite receiving immunosuppressive therapy (using glucocorticoids), still had a recurrence of liver damage after an IAV infection. Therefore, early isolation, strengthened observation, and timely diagnosis are crucial for patients with existing liver diseases.

Drug Damage

Therapeutic drugs induced liver damage. Some patients who lack medical knowledge become overly anxious after being infected with IAV and purchase various antiviral drugs, antibiotics, antipyretics, and painkillers on their own. Some patients even take multiple antiviral drugs simultaneously. Oseltamivir is the most commonly used antiviral agent for IAV infection treatment and prevention. These drugs can cause liver damage. Oseltamivir is an effective inhibitor of IAV particle ceramidase. Mastroianni et al[46] found that an 18-year-old patient with H1N1 influenza who had no previous history of liver disease sustained mixed liver cell and cholestatic liver damage 4 days after taking oseltamivir, with high liver disease-relat-

ed indicators. After discontinuing oseltamivir for 2 weeks, liver damage was alleviated. In the clinical trials of oseltamivir, 2% of the treated patients have high serum aminotransferase levels; however, no study has reported liver damage with jaundice clinically so far. Antipyretic and analgesic drugs such as aspirin and acetaminophen are also medications that patients with H1N1 influenza will purchase independently. Aspirin is a causative factor of Rayleigh's syndrome, and warnings against the use of aspirin in children were issued as early as 1980[47]. Paracetamol is a nonsteroidal anti-inflammatory drug, mainly composed of acetaminophen. When taken, a small part of the paracetamol will be converted into the hepatotoxic substance N-acetyl-para-benzoquinone through hepatic cytochrome P450 isoenzymes[48]. The intake of high doses can lead to liver toxicity, causing extensive central lobular liver necrosis[49] and even requiring liver transplantation. Therefore, in the presence of an IAV infection, patients should not panic and overdose themselves. For patients with underlying liver diseases, the dosage of medication must be considered to avoid increasing the burden on the liver.

Multiple Virus Infection

By the end of 2022, China had fully liberalized its management policy regarding COVID-19. In the following two months, China's national infection rate reached 80%, and the number of infected people exceeded 1.1 billion. IAV and COVID-19 have many similarities, being the main pathogens that mainly infect the human respiratory tract and can cause respiratory symptoms ranging from mild respiratory disease to respiratory failure[50]. Hoy et al[51] revealed that the COVID-19 pandemic and subsequent interruption of IAV transmission reduced the population's immunity to IAV infection and increased the frequency of severe IAV infection in 2022. In the analysis of IAV infection and COVID-19 coinfection cases by the United Kingdom national surveillance[52], patients with coinfection had a 5.9 times greater risk of death. Researchers[53] at the University of Hong Kong have demonstrated through a mixed infection model of Syrian hamsters with SARS-CoV-2 and influenza A(H1N1)pdm09 that simultaneous or sequential mixed infections can induce more severe tissue damage than a single infection. Of the 95 patients with COVID-19 investigated by Wuhan Tongji Hospital, 50.5% also had IAV infection. In these patients, a study[54] found that coinfection of COVID-19 and IAV infection may further enhance the activation of neutrophils, leading to the development of viral over-immune response and cytokine storms. Thus, the acute massive outbreak of COVID-19 in China has led to numerous people gathering in hospitals, exacerbating the spread of IAV and other respiratory viruses. Therefore, the current outbreak of IAV infection in China is bound to cause more severe liver damage.

COMPARISON OF IAV INFECTION AND COVID-19

With the wide restriction of COVID-19, the IAV and COVID-19 spread together. COVID-19 also inflicts serious damage to the liver. Clinicians compared liver dysfunction caused by COVID-19 and IAV (Table 1), and 45.2% of patients with COVID-19 and 45.3% with H1N1 influenza reported liver dysfunction[55]. The IAV-induced liver damage is similar to that caused by COVID-19, both of which will cause liver damage because of the imbalance in cytokines and activation of immune cells. Ritter et al[56] analyzed 1,624 patients with COVID-19 and 2,056 patients with IAV infection and found that cholestasis injury was more severe in patients with COVID-19 than in patients with IAV infection (24% and 17%, respectively). Shafran et al[57] studied 865 patients with IAV infection and 872 patients with COVID-19 and found that most patients with IAV infection had transaminase peak earlier during hospitalization. ALT was significantly reduced in patients with COVID-19, with an average difference of 26 U/L[58]. Clinical deterioration of the liver in patients with COVID-19 is usually delayed 7-10 days after symptom onset. Moreover, the decrease in the lymphocyte count in patients with COVID-19 was much greater than that in patients with H1N1, with data from researchers showing a decrease of nearly eight times[59].

Table 1. Comparison of symptoms between influenza A and COVID-19.

	Influenza A Virus	COVID-19
Onset of symptom	Sudden onset	Gradual onset
Loss of taste or smell	Less occurrence	Sometimes
Tachypnea or dyspnea	Less occurrence	Common
Early transaminase expression	Early peak occurrence	Early mild or moderate elevation
Decreased number of lymphocytes	Relatively few	Relatively more

The abscissa of the table describes two different viruses, Influenza A Virus, and COVID-19, and the ordinate describes the symptoms of infection.

TREATMENT AND VACCINATION RECOMMENDATIONS FOR IAV INFECTION IN PATIENTS WITH LIVER DISEASE

The IAV has caused multiple pandemics in human history, placing a great burden on the global healthcare system. The recent IAV infection outbreak in China just followed the COVID-19 outbreak in the whole country. Most people are infected with COVID-19 or recovering from COVID-19. The overall immunity of the whole population is relatively low, and the number of hospitalized patients is in an oversaturated state, resulting in the overloaded operation of the medical system. In this situation, patients with liver diseases are more prone to infection and new liver damage. Compared with the general population, patients with liver disease should be more cautious in dealing with the spread of IAV in such situations. We recommend the following for the treatment and vaccination of patients with liver disease infected with IAV:

1. During the outbreaks of COVID-19 and IAV, all patients with liver disease should reduce their visits to personnel gathering places, wash their hands frequently, wear masks when going out, and avoid being infected with multiple viruses simultaneously.
2. Patients with liver diseases should not panic excessively after infection or take multiple medications. They should consult a doctor in advance.
3. Patients with chronic hepatitis who had IAV infection should pay sufficient attention to the early detection of various liver indicators to prevent further liver damage.
4. Patients with liver disease taking immunosuppressants should not stop the treatment during IAV infection outbreaks and should consider receiving IAV vaccines. IAV vaccines can reduce the risk of infection-related complications and death in these patients[60].
5. Inactivated vaccines are used for attenuated live vaccines, particularly for liver transplant recipients who are contraindicated from using attenuated live vaccines[61].
6. Patients with liver cirrhosis (including those receiving treatment) and liver transplant recipients benefit from IAV vaccination and can safely receive it[62].
7. Liver transplant recipients must receive timely IAV vaccination annually. Although researchers have not found evidence of reduced IAV infection complications among recipients receiving the same season's vaccine, vaccination can reduce the risk of hospitalization and death in recipients after IAV infection[63].

DISCUSSION

IAV infection has existed for many years worldwide. The recent spread after the outbreak of COVID-19 in China has caused many new problems and public health challenges.

IAV infection can be accompanied by varying degrees of liver dysfunction. Liver enzymes are important parameters for evaluating general liver damage; thus, serum levels of ALT, AST, and ALP, which are biomarkers of liver damage, must be measured[64]. The abnormal increase in transaminase levels, which is usually temporary and mild, is the most noticeable result. However, among individuals with underlying liver diseases, the incidence rate of liver failure and death after an IAV infection is higher. Moreover, the incidence of liver damage in patients with severe infection is significantly higher than that in patients with mild infection. The literature search on IAV-related liver damage revealed that IAV infection is closely related to liver damage. The possible mechanisms of IAV-related liver damage include the following: IAV infection causes excessive production of proinflammatory factors, cytokine disorders, and cytokine storms, oxidative stress caused by IAV infection, hepatic ischemia and hypoxia caused by IAV infection, hepatic diseases are already present because of stimulation or addition of IAV infection, liver damage caused by excessive medication used to treat IAV infection, and multiple infections of swine flu and COVID-19 caused by the newly liberalized domestic epidemic policy (Figure 5). This article focuses on evaluating the effect and possible mechanisms of IAV infection on liver damage and proposes recommendations for treatment and vaccination, aiming to strengthen the importance of IAV monitoring.

According to Ru et al[65], virus particles can be found in multiple areas of the patient's bronchial mucosa, lungs, myocardium, and liver after an IAV infection, thereby confirming the hypothesis that the virus invades different organ cells. Undoubtedly, the lungs are the most susceptible organs to contracting the H1N1 virus. After an IAV infection, numerous cells die, and the glycoprotein hemagglutinin on the surface of the virus can cause programmed macrophage death and reduce the phagocytosis of dead cells. Inflammatory reactions polarize and disrupt the integrity of the epithelial barrier, spreading IAV through the bloodstream to the liver and other organs. In addition, cytokine storms and hypoxia caused by pulmonary dysfunction will lead to damage in the organogenesis in various tissues. Severe IAV infection can cause damage to multiple organ functions. At the beginning of this year, in the presence of successive outbreaks of COVID-19 and IAV in China, we should be more alert to the serious damage caused by multi-virus infections. For multiple organ damage caused by the IAV, real-time monitoring of biological indicators such as lung, heart, kidney, and liver functions should be carried out, and timely treatment and vaccination should be carried out to prevent further IAV-induced damage to the body.

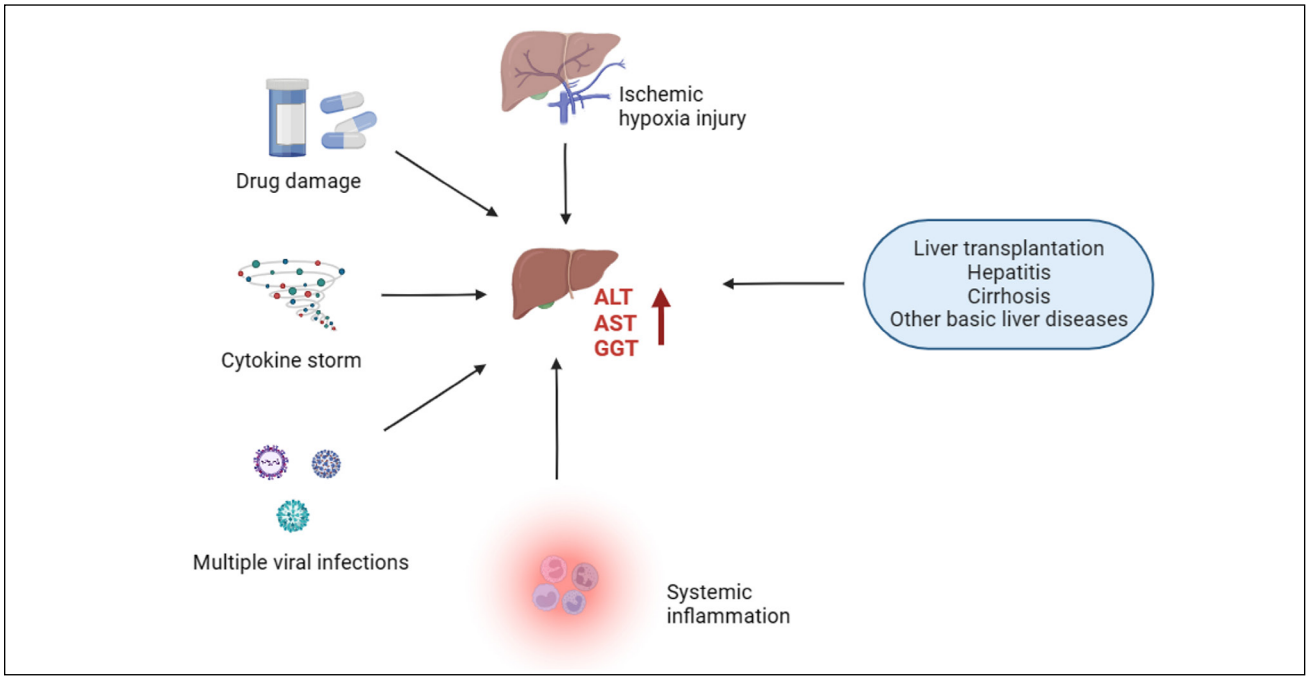

Figure 5. Possible mechanisms leading to liver injury.

CONCLUSIONS

We suggest the following possible pathogenesis of IAV-induced liver damage: (1) IAV infection increases proinflammatory factors and causes cytokine storms, (2) IAV causes hepatic ischemia and hypoxia, (3) IAV stimulates or exacerbates existing underlying liver diseases, and (4) multiple infections with COVID-19 and IAV aggravates liver damage. In addition to viruses, drug-induced liver damage is considered to be a causative factor of liver damage. Systemic validation reactions, oxidative stress, and ischemia-hypoxia-reperfusion injury factors may be the main causes. Therefore, timely treatment and vaccination are very necessary.

Conflict of Interest:

The author reports no conflict of interest in this argument.

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Ethics Approval and Informed Consent:

Not applicable.

Availability of Data and Materials:

Data sharing is not applicable to this paper, as no new data were created in this study.

Authors' Contributions:

Y-Z. Yin was involved in data collection, analysis, and writing the manuscript; S.-Q. Li was involved in project management and quality evaluation; R.-L. Luo and R.-F. Li were involved in data collection and graph production. All authors read, edited, and approved the manuscript.

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