SCIENCE CHINA PRESS

SCIENCE CHINA Life Sciences
life.scichina.com link.springer.com
https://doi.org/10.1007/s11427-023-2421-0

REVIEW

Chinese Society of Cardiology guidelines on the diagnosis and treatment of adult fulminant myocarditis

Chinese Society of Cardiology, Chinese Medical Association, Writing Group: Jiangang Jiang[1†], Hongyang Shu[1†], Dao Wen Wang[1*], Rutai Hui[2], Chenze Li[3], Xiao Ran[1], Hong Wang[1], Jing Zhang[4], Shaoping Nie[5], Guanglin Cui[1], Dingcheng Xiang[6], Qun Shao[7], Shengyong Xu[8], Discussion experts: Ning Zhou[1], Yuming Li[9], Wei Gao[10], Yuguo Chen[11], Yuan Bian[11], Guoping Wang[1], Liming Xia[1], Yan Wang[1], Chunxia Zhao[1], Zhiren Zhang[7], Yuhua Zhao[12], Jianan Wang[13], Shaoliang Chen[14], Hong Jiang[15], Jing Chen[15], Xianjin Du[15], Mao Chen[16], Yinxian Sun[17], Sheng Li[1], Hu Ding[1], Xueping Ma[18], Hesong Zeng[1], Li Lin[1], Shenghua Zhou[19], Likun Ma[20], Ling Tao[21], Juan Chen[22], Yiwu Zhou[23] & Xiaomei Guo[1]

[1]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China;
[2]Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China;
[3]Zhongnan Hospital of Wuhan University, Wuhan 430062, China;
[4]Fuwai Huazhong Cardiovascular Hospital, Zhengzhou 450003, China;
[5]Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China;
[6]Guangzhou General Hospital of Guangzhou Military Command, Guangzhou 510010, China;
[7]Harbin Medical University Cancer Hospital, Harbin 150081, China;
[8]Union Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China;
[9]Taida Hospital, Tianjin 300457, China;
[10]Peking University Third Hospital, Beijing 100191, China;
[11]Qilu Hospital of Shandong University, Jinan 250012, China;
[12]Kanghua Hospital, Dongguan, Guangzhou 523080, China;
[13]Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou 310003, China;
[14]Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China;
[15]Renmin Hospital of Wuhan University, Wuhan 430060, Wuhan;
[16]West China Hospital, Sichuan University, Chengdu 610044, China;
[17]First Hospital of China Medical University, Shenyang 110002, China;
[18]General Hospital of Ningxia Medical University, Yinchuan 750003, China;
[19]The Second Xiangya Hospital, Central South University, Changsha 410012, China;
[20]The First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei 230002, China;
[21]The First Affiliated Hospital of Air Force Medical University, Xi'an 710032, China;
[22]Central Hospital of Wuhan City, Wuhan 430014, China;
[23]Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

†Contributed equally to this work
*Corresponding author (email: dwwang@tjh.tjmu.edu.cn)

Received 21 March 2023; Accepted 25 July 2023; Published online 7 February 2024

Fulminant myocarditis is an acute diffuse inflammatory disease of myocardium. It is characterized by acute onset, rapid progress and high risk of death. Its pathogenesis involves excessive immune activation of the innate immune system and formation of inflammatory storm. According to China's practical experience, the adoption of the "life support-based comprehensive treatment regimen" (with mechanical circulation support and immunomodulation therapy as the core) can significantly improve the survival rate and long-term prognosis. Special emphasis is placed on very early identification,very early diagnosis,very early prediction and very early treatment.

fulminant myocarditis | guidelines | life support-based comprehensive treatment regimen | diagnosis | treatment | cytokine storm | overactivation of immunity

Introduction

Myocarditis refers to the inflammatory damage of myocardium caused by various reasons, which will eventually lead to the impairment of cardiac function, including decreased systolic and diastolic functions and arrhythmia. Fulminant Myocarditis is the most serious and special type of myocarditis, characterized by rapid onset and rapid progress. Patients will have hemodynamic abnormalities (pump failure and circulatory failure) and severe arrhythmia in a very short time, and may be accompanied by respiratory failure and liver and kidney failure. The early mortality of fulminant myocarditis is very high.

Fulminant myocarditis can be caused by infection, toxin/drug toxicity, and autoimmune diseases. Infection is the most important cause of disease, and viruses are the most common pathogens. Pathogenic mechanisms include direct damage to myocardium caused by viruses or other pathogens, and secondary damage to heart and/or other tissues and organs

caused by excessive activation of innate immune systems and secondary inflammatory storms. Studies have shown that immune overactivation and secondary injury mediated by inflammatory storm play a more important role in the occurrence and development of cardiogenic shock, circulatory dysfunction and multiple organ failure, which are the main pathophysiological links leading to rapid deterioration of the disease and one of the main goals of treatment (Wang and Hui, 2022).

The prodromal symptoms of fulminant myocarditis are mild or lacking specificity. For patients with a recent history of upper respiratory or gastrointestinal virus infection, exposure to or use of cytotoxic drugs with toxic substances, and vaccination history, once they have extreme fatigue, poor appetite, accompanied by chest tightness, dyspnea, palpitations and other manifestations, clinicians need to highly suspect that they may have fulminant myocarditis. The physical examination of the patient indicates that the general condition is poor, the first heart sound is low and dull, the third heart sound or galloping rhythm, or there is a rale in both lungs, especially when there are shock manifestations such as increased heart rate, decreased blood pressure, and wet and cold skin, relevant examinations should be carried out in a timely manner. Once the blood troponin level is increased, ECG is obviously abnormal, and cardiac ultrasound indicates diffuse ventricular wall motion disorder and decreased ejection fraction, the clinical diagnosis of fulminant myocarditis can be proposed.

Previously, due to insufficient understanding of the characteristics and pathophysiological mechanism of the disease, clinical diagnosis was not timely, so the rate of misdiagnosis and missed diagnosis was high. With the promulgation of the Chinese Expert Consensus on the Diagnosis and Treatment of Fulminant Myocarditis in Adults (hereinafter referred to as the Chinese Expert Consensus) in 2017 and its nationwide application (Association PMG of CB of CM et al., 2017) the understanding level and diagnostic efficiency of the majority of medical personnel on fulminant myocarditis have been improved, and it is not uncommon to find fulminant myocarditis. Therefore, it is of great significance to constantly improve the awareness and vigilance of fulminant myocarditis, identify and diagnose it as soon as possible, and quickly carry out standardized treatment to save the lives of patients. With nearly ten years of efforts, Chinese medical workers have formulated a set of treatment regimen for fulminant myocarditis in the acute phase for the first time in the world, reducing the case fatality rate from more than 50% in the past to less than 5%. This program makes China's treatment levels in the leading position in the field of fulminant myocarditis, and Chinese medical workers also published the first expert consensus on fulminant myocarditis in the world. In 2017, Chinese experts summarized the clinical characteristics, diagnosis process and methods of fulminant myocarditis, especially proposed the "life support-based comprehensive treatment regimen", also known as the "Chinese regimen". In the past five years, with the popularization of expert consensus, the level of medical staff's understanding and treatment of fulminant myocarditis has been significantly improved. Chinese experts demonstrated the effectiveness of the "Chinese regimen" in international journals (Li et al., 2019). Subsequently, the *Chinese Journal of Cardiovascular Diseases* published several articles in 2021 and 2022, verifying the effectiveness of the "Chinese regimen" (Jie et al., 2022; Ye et al., 2021; Zhou et al., 2021). With the accumulation of clinical research and treatment experience in China, especially the evidence chain of multicenter clinical research has been fully established, and basic research has made rapid progress, therefore, the Chinese Society of Cardiology believes that it is necessary to upgrade the expert consensus into a guide to better instruct the clinical treatment of fulminant myocarditis in China and save more patients' lives.

In the early expert consensus, a follow-up report published in the *New England Journal of Medicine* earlier believed that the long-term prognosis of patients with fulminant myocarditis after discharge was better (McCarthy et al., 2000). However, the subsequent multicenter large sample follow-up study in Europe proved that the case fatality rate of patients in the acute phase was as high as 28% 60 days after discharge, and the one-year case fatality rate was nearly 40% (Ammirati et al., 2019). Although the follow-up results of patients in our country are significantly better than this result, one quarter of patients have suffered from cardiac function impairment, arrhythmia or myocarditis recurrence one year later (Jiang et al., 2022), indicating that follow-up treatment and long-term prognosis are still an important problem that needs more research to solve.

In addition, although the expert consensus has been promulgated for five years, many medical workers have insufficient understanding and implementation of the expert consensus in practice, resulting in missed diagnosis, misdiagnosis and death of some patients. This guideline emphasizes on strengthening the training of medical personnel, especially on very early identification, very early diagnosis, very early prediction and very early treatment.

Methods

The evidence in this guide is obtained by searching relevant literature in domestic and foreign medical electronic databases (Pubmed and Wanfang Medical Literature Library). The recommendations for diagnosis and treatment methods are divided into three categories of recommendation levels and three levels of evidence according to international general standards. Considering the fact that clinical research of fulminant myocarditis is difficult and there is little few data, the recommended categories in this guideline are as follows:

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.

Class II: The treatment or strategy can be useful or its usefulness is not well established.

Class IIa: Weight of evidence is in favor of usefulness/utility.

Class IIb: Usefulness/efficacy less well established by evidence/opinion.

Class III: Evidence or general agreement that the given treatment of procedure is not useful/effective, and in some cases may be harmful.

The level of evidence sources is expressed as follows:

Level A: data derived from multiple randomized clinical trials or meta-analyses.

Level B: data derived from a single randomized trial or non randomized studies.

Level C: only consensus opinion of experts, case studies, or standard of care.

It should be noted that due to the rapid progress of fulminant myocarditis and the high mortality rate, it is relatively difficult to conduct a randomized double-blind clinical trial, which also does not meet the ethical requirements. However, there are many

https://doi.org/10.1007/s11427-023-2421-0

multi-center observational research results in China. For the research of this kind of critical patients, the international community also adopts historical control research or non inferiority test rather than placebo control. For some clinical routines formed in the daily rescue work, many of them are not supported by published clinical research literature, and can not be given a level of the evidence above B according to internationally recognized standards. However, these diagnosis and treatment methods are clinically effective and have been unanimously recognized by experts. Although they are only rated as level C, it does not mean that the level of evidence is low.

Epidemiology of fulminant myocarditis

Fulminant myocarditis is an acute and severe type of acute myocarditis. patients often suffer from fatal arrhythmia, heart failure, or even sudden death. At present, there is still a lack of epidemiological data directly related to the incidence rate of fulminant myocarditis. This is mainly because fulminant myocarditis is a sporadic disease with extremely rapid disease progression, and some patients often die before the disease is diagnosed. Therefore, it is difficult to directly obtain the incidence rate of the disease through epidemiological investigation of the general population. Up to now, the relevant incidence rate data mainly come from the death cases of myocarditis and acute myocarditis. On this basis, we can preliminarily estimate the incidence rate of fulminant myocarditis.

A Finnish study in 2007 reviewed all death cases due to myocarditis from 1970 to 1988. The study found that the incidence rate of fatal myocarditis after age adjustment was 4.6/1 million person years, and the incidence rate of fatal myocarditis in males (5.1/1 million person years) was slightly higher than that in females (4.2/1 million person years); Children and young adults (<45 years old) are more prone to fatal myocarditis than middle-aged and old people, and with the passage of time, the incidence rate of fatal myocarditis has increased year by year (Kytö et al., 2007). Previous studies have shown that the mortality rate of fulminant myocarditis in the acute phase is about 50% (Lee et al., 2006). Therefore, it can be estimated that the incidence rate of fulminant myocarditis is about 9.2/1 million person years. In addition, the global burden of disease research data from 1990 to 2017 shows that the age standardized incidence rate of myocarditis is about 23.2/100,000 person years. The incidence rate of myocarditis varies in different regions of the world. The incidence rate of myocarditis in the Asia Pacific region is about 45.6/100,000 person years, and the incidence rate of myocarditis in China is about 30–40/100,000 person years. The country with the highest incidence rate of myocarditis is Albania, about 105.6/100,000 person years, while Chile has the lowest incidence rate, about 10.2/100,000 person years (Dai et al., 2021; Vos et al., 2015). Although in different research data, the proportion of fulminant myocarditis in myocarditis varies, according to large multicenter studies, fulminant myocarditis accounts for about 10% of myocarditis (Ammirati et al., 2018a; McCarthy et al., 2000). At the same time, combined with the incidence rate of fatal myocarditis, it can be estimated that the average incidence rate of fulminant myocarditis is about 9–23/1 million person years. According to the proportion of population in China, the annual incidence of fulminant myocarditis among adults over 14 years old is about 30,000 to 50,000.

The mortality of fulminant myocarditis in the acute phase is extremely high. According to previous studies, the case fatality rate of patients with fulminant myocarditis during hospitalization in large hospitals is as high as 45%–55.6% (Hung et al., 2016; Lee et al., 2006; Sawamura et al., 2018). After the expert consensus on fulminant myocarditis in China was published in 2017, the life support-based comprehensive treatment regimen was widely accepted (Wang et al., 2019a). Research results from multiple centers showed that the mortality rate of patients during hospitalization decreased to 3.7%–8.1% (Li et al., 2019; Ye et al., 2021; Zhou et al., 2021). For the long-term prognosis of fulminant myocarditis, the results of international multicenter observational studies show that the incident rate of cardiac death and heart transplantation 60 days after discharge is 27.8%, and the 1-year incident rate is 39.4%. Moreover, the clinical prognosis of fulminant myocarditis is related to histological type. The adverse cardiovascular event rate of giant cell myocarditis is much higher than that of eosinophilic myocarditis and lymphocytic myocarditis. At 60 days of onset, the incidence of cardiac death and heart transplantation in patients with giant cell fulminant myocarditis was 62.5%, while the incidence of cardiac death and heart transplantation in patients with eosinophilic and lymphocytic myocarditis was 26.3% and 21%, respectively. Similarly, during 3-year follow-up, the incidence of cardiac death and heart transplantation in patients with giant cell fulminant myocarditis (81.3%) was significantly higher than that in patients with eosinophilic myocarditis (37.3%) and lymphocytic fulminant myocarditis (39.9%) (Ammirati et al., 2019). In China, 66 patients with fulminant myocarditis were followed up one year after discharge and only one patient died, but 24.2% of them had arrhythmia, cardiac dilatation, heart failure or recurrence of myocarditis (Jiang et al., 2022). To compare and analyze the differences between follow-up studies in China and Europe, we first traced back to the differences in the treatment of patients in the acute phase. China adopted the "Chinese regimen" (see the introduction below), while in Europe, the first reason was insufficient mechanical circulation support (only 69% used mechanical circulation support, of which 55.1% used intra aortic balloon counterpulsation (IABP), and 36.9% used extracorporeal membrane oxygenation (ECMO) or percutaneous cardiac pump IMPELLA in combination with IABP; 50.9% used ECMO or IMPELLA). On the other hand, all patients used norepinephrine, epinephrine, dopamine and/or levosimendan for a long time (median 10 days). At the same time, some patients used cytotoxic drugs, while the use of hormones and gamma globulin was extremely low (Ammirati et al., 2019). In this way, this treatment not only leads to high mortality in hospital, but also may affect long-term prognosis.

In summary, the demographic and clinical characteristics data related to fulminant myocarditis are still very limited at present. We should further establish the registration study of fulminant myocarditis in China, which will help popularize and deepen the understanding of the disease.

Etiology and pathophysiology of fulminant myocarditis

The etiology of fulminant myocarditis is similar to that of acute and non fulminant myocarditis, including infectious and non infectious factors (Table 1). Viral infection is the main cause of myocarditis. 1%–5% of patients with acute viral infection may

have precursor symptoms of myocarditis (Karjalainen and Heikkilä, 1999). However, due to the limitations of detection technology and detection samples, only 10%–20% of patients with viral myocarditis had positive myocardial virological detection (Karjalainen and Heikkilä, 1999). In the 1980s and 1990s, it was found that enterovirus (including coxsackie virus) and adenovirus infection were the main causes of viral myocarditis (Crowell and Landau, 1997). With the rapid development of molecular biology technology, the detection technology of various viruses has been constantly improved. More than viruses, such as parvovirus and human herpesvirus, have also been found to be pathogens causing myocarditis (Schultz et al., 2009). Recently, it was also reported that influenza A virus and human endogenous retrovirus K were detected in myocardial biopsy samples and peripheral blood of patients with fulminant myocarditis (Bratincsák et al., 2010; Heidecker et al., 2020). In the influenza epidemic season, we also found positive cases of influenza B virus IgM antibody clinically. The recent outbreak of the coronavirus disease 2019 (COVID-19) pandemic has also reported cases of fulminant myocarditis caused by the SARS-CoV-2 virus (Chen et al., 2020b). However, no viral antigen or corresponding IgM antibody was detected in most patients either in myocardial biopsy tissues or in peripheral blood. At present, there is no final conclusion on whether the virus type causing myocarditis is regional or epidemic. The difference of these detected virus types may be caused by the nonspecific and different detection schemes of the primers and antibodies used to detect the virus, or by the limited sample size (Schultz et al., 2009). In addition to viruses, fungi and spirochetes may also cause fulminant myocarditis (Semproni et al., 2020) (Table 2).

In recent years, people are more and more aware of fulminant myocarditis caused by non infectious factors, so the diagnosis is increasing year by year. Non infectious factors include allergy, autoimmune diseases and drug toxicity. The eosinophilic fulminant myocarditis can be induced by rapid allergic reactions such as drug allergy caused by penicillin, and some food such as shrimp allergy. Taking aconite, fish gall or snake gall can induce fulminant myocarditis (Lin et al., 2011); patients with autoimmune diseases may suddenly develop fulminant myocarditis; many drugs, especially anti-tumor drugs, have a high probability of causing cardiovascular toxicity, including inducing myocarditis (Moslehi, 2016) (Table 3). Its mechanism may include direct toxicity and immune damage mechanism caused by pattern recognition receptor, especially the latter. It has been found that anthracycline drugs can cause cardiac toxic effects such as

Table 1. Possible factors leading to myocarditis

Infectious factors	
Viral	Adenovirus, Enterovirus (Coxsackie virus, poliovirus, etc.), Arbovirus, Cytomegalovirus, Dengue virus, Eko virus, EB virus, Hepatitis C, Herpesvirus, Human immunodeficiency virus, Influenza virus, Coronavirus, Mumps, Parvovirus, Rabies, Rubella, Rubella, Varicella, Pox, Yellow fever, etc
Bacteria	*Brucella*, *Chlamydia*, *Cholera*, *Clostridium*, *Diphtheria*, *Haemophilus*, *Legionella*, Meningococcus, *Neisseria gonorrhoeae*, Parrot fever, *Salmonella*, Staphylococcus, Tetanus, Tuberculosis, Tularemia
Leptospira	Lyme disease, Relapsing fever, Syphilis
Fungal	Actinomyces, Aspergillus, Blastomycetes, Candida, Coccidiosporosis, Cryptococcosis, Histoplasmosis, Mucor, Nocardia, Sporotrichosis
Rickettsia	Q fever, Rocky Mountain spotted fever, Typhus
Protozoan	African sleeping sickness, Amebiasis, Chagas disease, leishmaniasis, Malaria, Toxoplasmosis
Worm	Ascariasis, Echinococcosis, Filariasis, Paragonimiasis, Schistosomiasis, Roundworm, Trichinellosis
Other	Mycoplasmas
Non infectious factors	
Systemic diseases	Celiac disease, Connective tissue disease, Wegener's granulomatosis, Kawasaki disease, Eosinophilia, Sarcoidosis, Thyrotoxicosis
Hypersensitivity	Antibiotics, Clozapine, Diuretics, Insect bites, Lithium, Snake bites, Tetanus toxoid, Mesalamine
Cardiotoxic substance	Alcohol, Anthracyclines, Arsenic, Carbon monoxide, Catecholamines, Cocaine, Heavy metals

Table 2. Detection methods and positive rates of some myocarditis related viruses

	Test sample	Detection method	Positive proportion	Reference
Enterovirus	Myocardial tissue	PCR	0–33%	(Kindermann et al., 2008; Dennert et al., 2008)
Poliovirus	Peripheral blood	VirCapSeq-VERT	4%	(Heidecker et al., 2020)
Hepatitis C virus	Serum	PCR	0–15%	(Matsumori et al., 2006)
Adenovirus	Myocardial tissue	PCR	0–23%	(Kindermann et al., 2008; Dennert et al., 2008)
Parvovirus B19	Myocardial tissue	PCR	2.5%–60%	(Kindermann et al., 2008; Dennert et al., 2008)
Cytomegalovirus	Myocardial tissue	PCR	0–5%	(Dennert et al., 2008)
Human herpesvirus-6	Myocardial tissue	PCR	8–30%	(Kindermann et al., 2008; Dennert et al., 2008)
EBV	Myocardial tissue/peripheral blood	PCR/VirCapSeq-VERT	0–17%/41%	(Heidecker et al., 2020; Dennert et al., 2008; Veronese et al., 2020)
Endogenous retrovirus K	Peripheral blood	VirCapSeq-VERT	100%	(Heidecker et al., 2020)
Ring virus	Peripheral blood	VirCapSeq-VERT	56%	(Heidecker et al., 2020)
Hemorrhagic fever virus	Myocardial tissue/peripheral blood	PCR	92.86%	(Saggioro et al., 2007)

https://doi.org/10.1007/s11427-023-2421-0

myocarditis pericarditis syndrome (Bristow et al., 1978). Similarly, 5-fluorouracil can also cause fulminant myocarditis (Amraotkar et al., 2016; Çalık et al., 2012; Sasson et al., 1994). In recent 20 years, with the widespread use of new anti-tumor drugs, especially immune checkpoint inhibitors (ICIs), the number of fulminant myocarditis caused by ICIs has increased day by day (Wang et al., 2017). The research shows that the incidence of myocardial injury is about 30%, while that of fulminant myocarditis is 0.5%–1%. With the prolongation of use time or the increase of combined drugs, the incidence is significantly increased (Johnson et al., 2016).

The causes of fulminant myocarditis are diverse, and the histological manifestations of fulminant myocarditis caused by different causes have certain characteristics. The fulminant myocarditis caused by various viruses and ICIs is more manifested as lymphocytic myocarditis, and autoimmune diseases often cause eosinophilic myocarditis (Brambatti et al., 2017). According to the data of more than 100 myocardial biopsies and 50 autopsies from Tongji Hospital of Huazhong University of Science and Technology, the fulminant myocarditis that started in a short time (within a week) was lymphocyte type. The fulminant myocarditis caused by drug or food allergy is basically eosinophilic. There are some differences in the treatment of fulminant myocarditis caused by different causes. Therefore, a clear etiology diagnosis based on clinical diagnosis will help to better formulate treatment strategies and improve the prognosis of patients.

The pathogenesis of fulminant myocarditis is complex, and may involve the interaction of patients' genetic background, immune status, virus virulence, environment and other factors. Cytokines, as a class of important immunoactive mediators, play a central role in the pathogenesis of fulminant myocarditis. At present, it is believed that the cytokine storm caused by excessive innate immune activation caused by various causes and rapid triggering of immune cells to release a large number of inflammatory factors, also known as "inflammatory storm", is an important reason for the rapid onset, rapid progress, severe illness and high mortality of fulminant myocarditis (Chen et al., 2020a) (Figure 1). In general, the pathophysiological processes of different types of myocarditis are similar. The most thorough research is the enterovirus infection, especially the pathophysiological process of myocarditis caused by coxsackie virus CVB3 (Klingel et al., 2004). The pathophysiological mechanism of myocardial injury caused by the virus includes two aspects (Yajima and Knowlton, 2009): (i) The virus directly damages myocardial cells and other tissue cells and replicates in cells,

Table 3. Drugs that may induce fulminant myocarditis

Drug type	Drug name
Anti tumor drugs	Adalimumab, Irutinib, Ipimab, Navumab, Trastuzumab, Fluorouracil, Anthracycline, Cyclophosphamide
Antibiotics	Penicillin, Amoxicillin, Tetracycline, Sulfonamides, Amphotericin B
Nervous system drugs	Carbamazepine, Clozapine, Amphetamine, Cocaine
Botanical medicine/traditional Chinese medicine	Garcinia grossedentata, Fish gall, Snake gall, Aconite
Other drugs	Allopurinol, Imidazole thiopurine, Isoniazid, Hydrochlorothiazide, Spironolactone, Acetazolamide, Sulfonylurea drugs, Indomethacin, Catecholamine

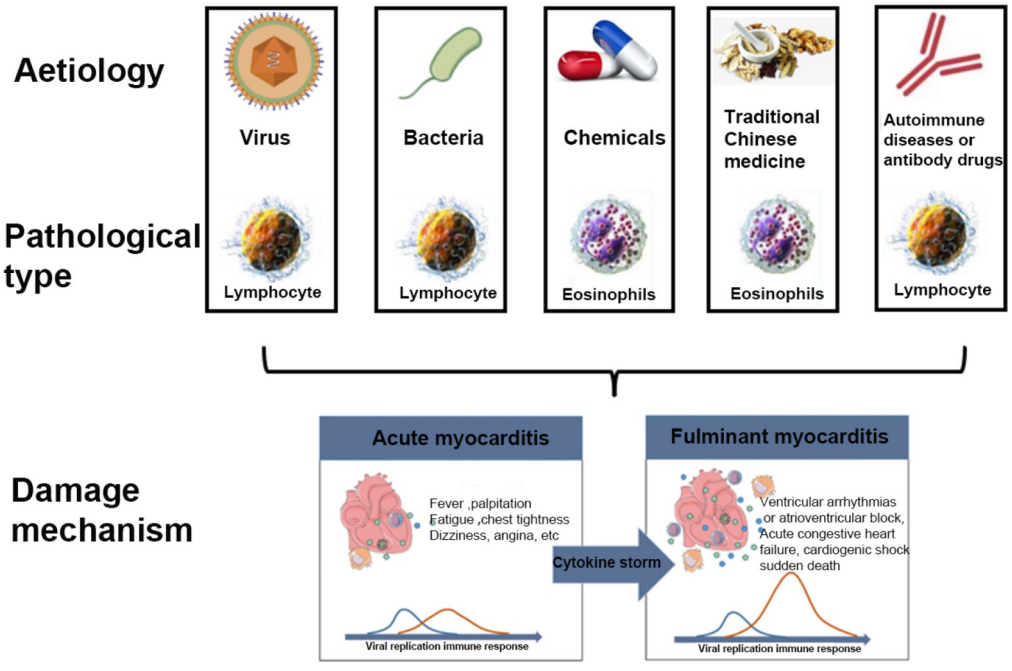

Figure 1. The main etiology, pathology and pathophysiology of fulminant myocarditis. The etiology of fulminant myocarditis includes infectious and non-infectious factors, among which viral infection is the main cause. The over-activated inflammation induced cytokine storm is the main pathophysiology of fulminant myocarditis.

causing degeneration, necrosis and dysfunction of myocardium; viruses released from cell lysis continue to infect other myocardial cells and tissues, and release cytokines to cause damage (Nie et al., 2022; Nie et al., 2021). (ii) Immune mediated injury: cytokines released due to tissue damage caused by virus erosion lead to inflammatory edema, and chemotactic inflammatory cells, including neutrophils, monocytes macrophages, NK cells, T lymphocytes and B lymphocytes, infiltrate in the stroma, and the body's innate and adaptive immune responses are overactivated (Hang et al., 2020). A study has detected the expression level of 122 inflammatory factors in the peripheral blood of patients with fulminant myocarditis at admission, and found that 39 of them had significant changes compared with the normal control population, indicating that the immune system was over activated; The "inflammatory storm" formed by a large number of cytokines and inflammatory mediators, including soluble growth stimulating expression gene 2 protein (sST2), interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF)-α among others, may be the main cause of severe myocardial injury and pump failure (Wang et al., 2022).

In fulminant myocarditis, the "inflammatory storm" caused by excessive innate immune activation mainly causes body damage through the following pathophysiological effects: (i) Some cytokines, including IFN-γ and TNF-α, they can cause nonspecific symptoms such as fever, chills, headache, dizziness and fatigue; (ii) a large number of inflammatory factors have greatly magnified the damage of pathogenic erosion on the heart of patients, resulting in a decrease in myocardial contractility, a sharp decline in cardiac function, and even cardiogenic shock; (iii) various cytokines can induce various types of arrhythmias, including atrial or ventricular tachycardia, atrioventricular block and even cardiac arrest (Ball et al., 2019; Du et al., 2020; Peretto et al., 2019) by prolonging the duration of action potential, affecting L-type Ca^{2+} channels and Kir channels; (iv) a variety of cytokines enter the blood circulation, which can also cause circulatory disorders. In addition, the multiple damage effects of ICIs may be synergetic and jointly affect the cardiac function: (i) ICIs, as monoclonal antibodies, directly combine with antigens on the surface of normal cells (CTLA-4, etc.), leading to T lymphocyte infiltration and complement activation, thus damaging myocardial tissue. (ii) After T lymphocytes recognize the antigen expressed by tumor cells, they can recognize the same tumor antigen or the healthy tissues expressing the same antigen through the circulatory system, leading to the miss target effect. ICIs treatment may enhance the miss target effect by promoting the function of T lymphocytes. (iii) ICIs can increase the expression level of cytokines in circulation and tissues, and promote the infiltration of inflammatory cells in non targeted tissues. (iv) ICIs may promote the production of autoimmunity related antibodies, leading to autoimmunity reaction (Sury et al., 2018).

Although there are relatively few inflammatory cells infiltrated by some non cardiotropic viruses in the heart, other organs (mainly the lungs) are severely damaged due to direct virus attack, and the immune function of the body is low (Uriel et al., 2020). Once the "inflammation storm" occurs and affects the heart, even if there is less inflammatory infiltration in the heart, obvious cardiac dysfunction can occur, which seriously threatens the life of patients (Figure 2). It should be specially pointed out that fulminant myocarditis is not only myocardial damage, but also a systemic disease characterized by myocardial involvement in strict sense. Viral erosion, over activated immune response, and the release of a large number of cytokines ("inflammatory storm") can also lead to multiple organ damage in the whole body. Heart injury is the most serious, and it is the main cause of hemodynamic disorder and patient death. Therefore, the pump dysfunction caused by heart damage is the decisive factor for the severity of patients. The core of the treatment of fulminant myocarditis is to reasonably control the "inflammatory storm" and inhibit the damage of the over activated immune response to the body.

The formation and mechanism of "inflammatory storm" are complex. In general, firstly, special molecules or compounds in pathogens (pathogen related molecular patterns, PAMP) combine with innate immune cells and cardiac cell membranes or intracellular pattern recognition receptors (PRRs) to initiate a series of reactions, especially the activation of NF-κB inflammatory pathway to produce and release inflammatory factors and chemokines, and chemotactic inflammatory cell infiltration. Subsequently, damaged tissue cells release endogenous substances—damage related molecular model (DAMP), which acts on pattern recognition receptors, and continues to stimulate and amplify inflammatory response. At the same time of innate immune initiation, adaptive immune response is initiated through antigen presentation and transmission (Boyd et al., 2006; Gong et al., 2020; Li and Wu, 2021). The root cause of cardiac function damage is the imbalance of the regulation of pro-inflammatory response and anti-inflammatory response of the body, resulting in excessive immune activation and the formation of inflammatory storm. The dysfunctional immune response makes a positive feedback loop between innate immune cells, adaptive immune cells and non immune cells and cytokines, and causes excessive release of cytokines (Li et al., 2023). Therefore, the pathological changes of fulminant myocarditis are mainly myocardial tissue edema, myocardial cell degeneration, necrosis, apoptosis and inflammatory cell infiltration.

Pathology of fulminant myocarditis and its clinical relationship

It is generally believed that the main histopathological evidence of myocarditis is the infiltration of myocytes with the degeneration and necrosis of adjacent myocardial cells. According to the existing quantitative histopathological criteria, myocarditis is defined as more than 14 mononuclear leukocytes ($54/mm^2$) detected in biopsy tissue (Aretz, 1987). Fulminant myocarditis usually shows diffuse infiltration of inflammatory cells with obvious myocardial cell necrosis (more than 50 inflammatory cells/mm^2 under microscope) (Maisch et al., 2014). It is worth noting that the pathological changes do not strictly correspond to the severity of clinical manifestations of myocarditis, and the pathological changes of a few patients with clinically fulminant myocarditis are not serious, so fulminant myocarditis is more a clinical diagnosis.

The general view of the heart in fulminant myocarditis shows that the heart is normal or enlarged, the weight is slightly or significantly increased, and the heart cavity is dilated (especially the left ventricle). The thickness of ventricular wall does not increase significantly, the texture of myocardium is soft and loose, the color of section is light, interstitial edema and gray white or gray yellow spotted lesions can be seen, which can be

https://doi.org/10.1007/s11427-023-2421-0

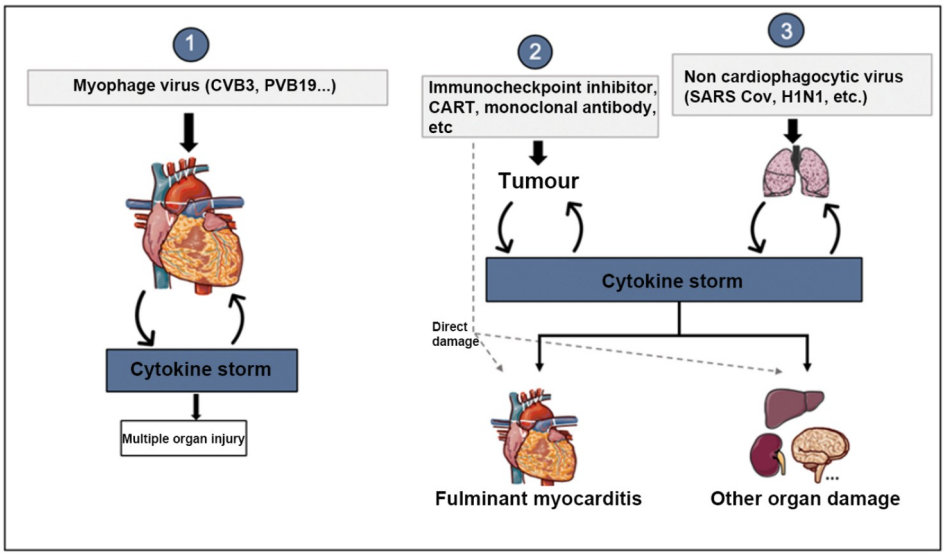

Figure 2. The mechanism underlying common etiologies induced fulminant myocarditis via over-activated inflammation. (1) In clinical practice, myocarditis is mostly caused by cardiotropic viruses, such as CVB3 and PVB19, induced cytokine storms. (2) As for anti-tumor drugs, such as immune checkpoint inhibitors, after contacting with tumor cells, the activated T cells will release large quantities of cytokine. (3) In addition, non-cardiotropic viruses in other organs, especially the lungs, are directly attacked by the virus and usually suffer severe inflammation. Once a cytokine storm is formed, a significant cardiac abnormality can occur, even with few cardiac immune infiltrations.

accompanied by focal hemorrhage or hemorrhagic necrosis. The pathological changes of myocarditis can affect the conduction system, causing arrhythmia and even sudden death in different degrees (Wang, 2021).

Hematoxylin eosin (HE) staining method is routinely used to detect inflammatory changes in the histology of heart biopsy samples. It is recommended that immunohistochemical staining of immune cell markers be performed at the same time to improve the detection sensitivity of immune cells (Ammirati et al., 2020). According to the difference of inflammatory cells infiltrated, it can be divided into the following main pathological types.

(1) Lymphocyte type: this is the most common type, accounting for about 90%. In the acute phase, myocardial cells degenerate and necrosis, and inflammatory cells infiltrate and edema can be seen around myocardial interstitium and small blood vessels. In chronic stage, granulation tissue formation and interstitial fibrosis occur. In fulminant myocarditis, the myocardial cell necrosis is more obvious and extensive, the myocardial interstitium is widened, the tissue is edematous, and there are multiple pieces or diffuse inflammatory cell infiltration. Immunohistochemical staining showed that a large number of macrophages and T lymphocytes were infiltrating the heart tissue, NK cells and neutrophils were seen in some cases, and B cells were rare or absent (Wang, 2021). Lymphocyte type fulminant myocarditis usually has an acute clinical onset, and usually develops to a serious stage within a week. The fulminant myocarditis caused by virus and other pathogens is usually lymphocyte type, and the fulminant myocarditis induced by ICIs also belongs to this type (Sobol et al., 2020).

(2) Eosinophilic granulocyte type: it accounts for a certain proportion of fulminant myocarditis, with an acute onset, mainly caused by drug and food allergy or fulminant myocarditis combined with Kounis syndrome (allergy related ST segment elevation acute coronary syndrome, including allergic angina pectoris and allergic myocardial infarction), among which Kounis syndrome often induces coronary artery spasm (Ravi et al., 2019). In addition, eosinophilia with myocarditis also belongs to this type. The characteristic histopathological features were extensive necrosis of myocardial cells and a large number of eosinophils or eosinophils infiltrating between the myocardium (Wang, 2021).

(3) Giant cell myocarditis: it is a rare type of myocarditis with unknown etiology, severe condition and poor prognosis. About 20% of patients have autoimmune diseases. The characteristic histopathological changes were multinucleated giant cells in the inflammatory infiltrates. Myocardial interstitium showed multiple focal to diffuse inflammatory infiltration, mixed with multinucleated giant cells. The size of multinucleated giant cells can reach 90 μm×20 μm, up to 20 nuclei per cell. The necrosis of myocardial cells was obvious, showing focal, map-like or even extensive necrosis, with fibrosis of varying degrees. The necrotic myocardium was replaced by granulation tissue, and the boundary between viable myocardium and necrotic myocardium was not significant (Wang, 2021).

In addition, sarcoidosis is an inflammatory disease that can affect the whole body, and can also be manifested as isolated cardiac sarcoidosis. The onset of sarcoidosis with fulminant myocarditis is relatively slow. The characteristic histopathological feature was non caseous granuloma, that is, epithelioid cell granuloma with non caseous necrosis as the main form. Granuloma consists of dense macrophages, CD68 positive epithelioid tissue cells, multinucleated giant cells, and T lymphocytes, which are closely packed into round or oval structures. B cells are rare (Wang, 2021).

Clinical evaluation of fulminant myocarditis

Fulminant myocarditis has an acute onset and rapid progress, which will soon lead to severe heart failure, hypotension or cardiogenic shock, malignant arrhythmia, or even sudden death, and may be accompanied by respiratory failure, liver and kidney failure, or systemic multiple organ failure. Vasoactive drugs,

positive inotropic drugs or mechanical circulation support are usually needed to maintain the basic vital signs. The early mortality of fulminant myocarditis is very high (Association PMG of CB of CM et al., 2017; Kociol et al., 2020). Therefore, it is particularly important to make a correct diagnosis and standard treatment as soon as possible.

History taking

Detailed medical history collection and physical examination are very important, which can provide diagnostic clues of fulminant myocarditis to help the diagnosis and differential diagnosis of myocarditis. It is necessary to know the symptoms of upper respiratory tract infection and diarrhea, allergic history of drugs or food, medical history of cardiac toxic drugs (antineoplastic drugs, especially ICIs), and intake history of toxins such as aconite, snake gall and fish gall; infection history, such as COVID-19, tourism history of dengue epidemic area; long time overload and tiredness stress in recent period are important inducing factors; some non cardiac diseases, such as connective tissue disease, bacterial or parasitic infection, diabetes, hyperthyroidism or hypothyroidism, amyloidosis and pheochromocytoma, should also be concerned.

Symptoms: no specificity

Symptoms of prodrome

The prodrome symptoms are usually nonspecific, and can be manifested as fever, fatigue, myalgia, catarrhal symptoms (nasal congestion, runny nose, sore throat, cough), diarrhea, etc. Individual performance varies greatly. Many patients only have low fever, obvious fatigue, no appetite or mild diarrhea in the early stage. These symptoms can last for 3–5 days and are often ignored by patients. They are not the main reason for patients to seek medical advice, but important clues for the diagnosis of myocarditis (Ammirati et al., 2019; Cooper, 2009; Kociol et al., 2020; Pollack et al., 2015; Wang et al., 2019b).

Manifestations of myocardial damage

Hemodynamic disturbance is an important characteristic of fulminant myocarditis. Most patients have dizziness and fatigue, which is caused by hypotension/shock, or even blackness or syncope. Although some patients can lie flat, seemingly stable, but the patient's myocardial damage has been very serious, pump failure will quickly appear; although some patients can lie flat, seemingly stable, but the patient's myocardial damage has been very serious, pump failure will quickly appear; some patients may also have acute left heart failure, manifested as dyspnea, restlessness, sweating, etc; 10%–20% of patients have chest tightness and chest pain, which is related to inflammation involving the pericardium. Some patients may have coronary spasm or even coronary thrombosis due to inflammation; in some patients, malignant arrhythmia (ventricular tachycardia, ventricular fibrillation or high degree of atrioventricular block) is the primary manifestation, and syncope and even sudden death occur repeatedly. When cardiogenic shock occurs, the skin may be cold and wet, pale, cyanosis, piebald changes, or even consciousness disorder (Caforio et al., 2007; Hang et al., 2020; Hufnagel et al., 2000; JCS Joint Working Group, 2011; Mason et al., 1995; Saji et al., 2012; Wang et al., 2019a; Zhou et al., 2021).

Involvement of other tissues and organs

In the early stage of fulminant myocarditis, most patients did not have obvious liver and kidney function damage, but a few patients (about 5%) had obvious liver function damage at the same time of myocardial damage. However, multiple organ function damage or failure is mainly caused by untimely and nonstandard treatment and long-term shock, including liver function damage, renal function damage, abnormal blood coagulation, and even diffuse intravascular coagulation (DIC). A few patients with lung injury caused by pulmonary congestion, inflammatory storm or pulmonary infection may have shortness of breath or even acute respiratory distress syndrome (ARDS). Some patients suffered from severe lung damage, which led to dyspnea and hypoxemia, were diagnosed as severe pneumonia, and the diagnosis of myocarditis was ignored (Hang et al., 2020; Jiang et al., 2022; Zhou et al., 2021).

Physical signs: no specificity

Vital signs

(1) Fever: some patients may have elevated body temperature. The temperature of primary virus infection is generally not too high, and a few patients can reach 39°C.

(2) Hypotension: patients with fulminant myocarditis often suffer from hypotension due to severe cardiac insufficiency and systemic toxic reactions, and their blood pressure cannot be measured in severe cases.

(3) Shortness of breath or respiratory depression: the respiratory rate can be greater than 30 times/min, or it can be reduced. In severe cases, the frequency is less than 10 times/min, and the blood oxygen saturation is less than 90% or lower.

(4) Abnormal heart rate and rhythm: sinus tachycardia is a common manifestation of patients with fulminant myocarditis, but the heart rate of some patients can be basically normal. Although not specific, the increase of heart rate that is not commensurate with the increase of body temperature (the increase of heart rate is greater than 10 times/min for every 10°C increase of body temperature) is an important clinical clue for the diagnosis of fulminant myocarditis. Some patients may have sinus bradycardia and different degrees of conduction block, which is related to myocarditis involving the conduction system. In addition, ventricular or supraventricular premature beats, ventricular or supraventricular tachycardia, and ventricular fibrillation often occur, among which ventricular tachycardia and ventricular fibrillation have the greatest impact on hemodynamics.

Abnormalities of blood pressure, respiration and heart rate indicate unstable hemodynamics, which is a common manifestation of fulminant myocarditis and an indication of the severity of the disease (Bozkurt et al., 2016; Cooper et al., 1997; Jiang et al., 2022; Kociol et al., 2020; Zhou et al., 2021).

Cardiac related signs

The apex beat is weakened, the heart boundary is usually small by percussion, and the heart sound is obviously low and dull by auscultation, and the third heart sound and the galloping rhythm of the third heart sound are often audible. Lung rale and wheezing may occur. The signs of right heart insufficiency are usually not obvious, which is related to the low muscular tension of the whole body and the reduction of returned blood volume. When pericarditis and pericardial effusion are combined, jugular

https://doi.org/10.1007/s11427-023-2421-0

vein filling and liver enlargement may occur, which are often not significant (Association PMG of CB of CM et al., 2017; Caforio et al., 2013; Saji et al., 2012; Zhou et al., 2021).

Other signs

The whole body is cold and damp, the peripheral circulation is poor and the skin is mottled due to shock. Irritation, unresponsiveness, disturbance of consciousness and even coma may occur due to decreased cerebral perfusion and brain injury; jaundice may occur when liver damage is obvious; skin ecchymosis and ecchymosis can be seen when blood coagulation function is abnormal (Jiang et al., 2022; Kociol et al., 2020; Maron et al., 2015).

Laboratory examination

Routine blood test

The change of blood routine test in patients with fulminant myocarditis is different according to the difference of pathogen and individual reaction. It was observed clinically that the total number of leukocytes and the proportion of neutrophils in peripheral blood of some patients were not significantly increased, but a considerable number of patients were significantly increased, which may be caused by the release of tissue antigen after severe myocardial injury (similar to acute myocardial infarction). 120 patients with fulminant myocarditis without bacterial infection in the Department of Cardiology of Tongji Hospital affiliated to Huazhong University of Science and Technology were found to have a total number of white blood cells of $(9.91\pm0.42)\times10^9$ L^{-1} and neutrophils of 78.47%±1.09% by blood routine analysis at admission. However, in a small number of patients, the total number of white blood cells decreases, and platelets may also decrease. If the eosinophils in the peripheral blood are elevated, we need to be alert to eosinophilic myocarditis (Brambatti et al., 2017). The increase of neutrophil/lymphocyte ratio and monocyte/lymphocyte ratio indicates the severity of myocarditis (Mirna et al., 2021). In patients with hematological diseases, tumor chemotherapy/targeted drug therapy or autoimmune disease related myocarditis, the changes of blood cells often change with the basic disease status, so it is necessary to monitor the dynamic changes of blood routine examination (Johnson et al., 2016; Savage et al., 2014) (Table 4). The increase of the total number of white blood cells and the proportion of neutrophils requires attention to differentiate septic cardiomyopathy with bacterial infection or severe infection.

Markers of myocardial injury: hs cTnI or cTnI

In most patients with fulminant myocarditis, high-sensitivity troponin I (hs cTnI) or troponin I (cTnI) were significantly increased, even exceeding the upper limit of the laboratory detection range. The change of its level was closely related to disease treatment and prognosis. In the early 1–3 days of the course of disease, it may continue to increase, but it can rapidly decline after reasonable and effective treatment starts very early. The continuous increase of hs cTnI level indicates that the myocardial injury is continuous and aggravated. The absolute value and relative change rate of hs cTnI are predictive factors of hospital death in patients with fulminant myocarditis (Liu et al., 2021a). In addition, there are also cases of fulminant myocarditis with insignificant troponin elevation. Therefore, when troponin elevation is not significant, fulminant myocarditis cannot be absolutely ruled out, especially due to a preference for viruses in the cells of the conduction system, which is manifested as conduction block. It must be judged comprehensively by endocardial biopsy, cardiac nuclear magnetic resonance, or 18 fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) (Bogaty, 2017; Kociol et al., 2020). The increase of creatine kinase and its isoenzyme, lactate dehydrogenase, aspartate aminotransferase and myoglobin suggests that the sensitivity and specificity of myocardial injury are lower than hs cTnI or cTnI. Dynamic monitoring of hs cTnI or cTnI is recommended as a marker for evaluating myocardial injury in fulminant myocarditis (Ammirati et al., 2019; Zhou et al., 2021) (I B) (Table 4).

BNP or NT proBNP

B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT proBNP) is a sensitive index to judge the cardiac function of patients with fulminant myocarditis (McDonagh et al., 2021). The plasma BNP or NT proBNP levels in patients with fulminant myocarditis are usually significantly elevated, reaching more than 10,000 to tens of thousands ng mL^{-1}. The significant increase of NT proBNP level is a predictive factor for adverse prognosis such as cardiac death and heart transplantation in patients with fulminant myocarditis. Reasonable treatment can make it decline rapidly, and the decline rate is also an important reference for predicting the

Table 4. Laboratory examinations of fulminant myocarditis and its level of recommendation

Recommendation	Level of recommendation	Level of evidence
Blood routine monitoring is required every 1–2 days to detect dynamic changes.	I	C
Dynamic monitoring of hs cTnI or cTnI is recommended as a marker for evaluation of myocardial injury in fulminant myocarditis.	I	B
Routine ambulatory monitoring of plasma NT proBNP or BNP levels is used to assess cardiac dysfunction severity and outcome.	I	B
Routine ambulatory monitoring of liver and kidney function, arterial blood gases, and blood lactate levels is recommended for assessment of severity and outcome.	I	C
Routine ambulatory monitoring of patients' coagulation (including Pt, PTA, APTT, TT, INR, FIB, D-dimer, platelet count) is recommended.	I	A
Routine detection and dynamic monitoring of inflammatory factor levels are recommended in patients with suspected fulminant myocarditis for the diagnosis of the disease as well as for the evaluation of therapeutic efficacy and prognosis.	I	B
Routine detection and dynamic monitoring of sST2 is recommended.	IIb	A
The levels of procalcitonin can be consulted to guide the use and effect evaluation of antibiotics.	IIb	A

therapeutic effect and prognosis (Ekström et al., 2016; Ukena et al., 2014). It is suggested that routine dynamic monitoring of plasma NT proBNP level and its changes can be used to judge the severity and outcome of cardiac function injury in patients with fulminant myocarditis (I B) (Ekström et al., 2016; Ukena et al., 2014) (Table 4). Seek expert opinions (Professor Hui Rutai agrees with I B)

Liver and kidney function, electrolyte, acid-base balance

Patients with fulminant myocarditis usually have only severe myocardial damage in the early stage, which can be accompanied by slight increase of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase. Occasionally, patients with severe liver damage had significantly higher liver enzymes in the early stage. However, if the shock is not corrected in time, or if vasoactive drugs such as norepinephrine are used in large doses for a long time, the patient may suffer from severe liver damage, bile enzyme separation and DIC, and may be accompanied by multiple organ function damage such as renal insufficiency (Hang et al., 2020; Veronese et al., 2021). The severity of liver and kidney dysfunction, especially secondary injury, has an important impact on the prognosis of patients with fulminant myocarditis (Colombo et al., 2022; Liu et al., 2021b; Wang et al., 2012). It is recommended that routine dynamic monitoring of liver and kidney function (I C) (Table 4). Seek expert opinions (IIb is recommended, because there is no particularly solid clinical trial and evidence for fulminant myocarditis; Huirutai's personal opinion).

It is important to maintain blood electrolyte and acid-base balance, especially the serum potassium level, which is recommended to be kept at 4.0–5.0 mmol L^{-1} (I A) (Palaka et al., 2020).

Patients with fulminant myocarditis may have hypotension accompanied by pulmonary congestion or even pulmonary edema and hypoxemia (Sasaki et al., 2008; Wang et al., 2012). It is suggested that the blood oxygen saturation of patients with fulminant myocarditis should be monitored regularly and continuously, and the arterial blood gas and blood pH should be monitored dynamically; the blood lactate level was checked regularly to evaluate the treatment of hypoxia and shock; for patients with central venous catheter or Swan Ganz catheter, the blood gas of central vein or mixed vein can be monitored to know the acid-base balance, oxygenation status and tissue metabolism status of patients. The latter has practical significance in judging the severity of shock in patients with fulminant myocarditis (I A) (Jones et al., 2010; Joshi et al., 2014) (Table 4).

Coagulation function test

Shock and inflammatory storm can activate platelets and blood coagulation system, leading to hypercoagulation and consumption of coagulation factors, thus promoting the formation of DIC (Chammas et al., 2021; Hage-Sleiman et al., 2019). Liver damage may promote its occurrence. Timely detection and correction of DIC is extremely important for the prognosis of patients (Tsuboi et al., 1990; Zhao et al., 2021). For patients using IABP and/or ECMO, the blood coagulation function should be monitored in a standardized way (Guglin et al., 2019). Therefore, routine dynamic monitoring of patients' coagulation function is recommended, including prothrombin time (PT), prothrombin activity (PTA), activated partial thromboplastin time (APTT), thrombin time (TT), activated coagulation time (ACT), international standard ratio (INR), fibrinogen (Fib), D-dimer, and platelet count (I A) (Table 4).

Detection of inflammatory factors

C-reactive protein is the most widely used marker of systemic inflammation. Rapid erythrocyte sedimentation rate (except for physiological factors) can also indicate the status of infection and immune response. But it is a non-specific index, and the C-reactive protein of some patients with fulminant myocarditis is increased.

When high-throughput inflammatory factor microarray was used to detect patients with fulminant myocarditis at the early stage of onset, it was found that 39 of the 122 inflammatory factors in plasma had significant changes (28 increased and 11 decreased). Among them, sST2, plasminogen activator inhibitor 1 (PAI-1), sialic acid binding immunoglobulin like lectin 5 (Siglec-5), CD163, interleukin-4 (IL-4), IL-17B and vascular endothelial growth factor-C (VEGF-C) significantly increased, cytotoxic T-lymphocyte associated protein 4 (CTLA4) significantly decreased. After reasonable treatment, the patient's condition improves, the above cytokines will gradually return to normal levels; other cytokines such as interleukin family and TNF-α are also elevated (Chammas et al., 2021; Cooper, 2017; Hang et al., 2020; Rezkalla and Kloner, 2021). In particular, sST2 is even more sensitive than NT proBNP and cTnI for discriminating fulminant myocarditisfrom non fulminant myocarditis (Coronado et al., 2019). Fulminant myocarditis can be diagnosed in patients with clinical symptoms and plasma sST2 greater than 58.39 ng mL^{-1}. Plasma sST2 has a sensitivity of 85.7% and a specificity of 94.7% for diagnosing fulminant myocarditis (Wang et al., 2022). Therefore, routine examination and dynamic monitoring of plasma levels of inflammatory factors are recommended in patients suspected of fulminant myocarditis, which has important implications for diagnosis, therapeutic efficacy, and prognostic evaluation of the disease (I B) (Table 4).

Procalcitonin (PCT) is a glycoprotein of 116 amino acids that is released into the blood by activated inflammatory and tissue cell production following bacterial, fungal and parasitic infections and septic stimuli, and the level of PCT generally varies with the degree of infection (often used as a reference basis for bacterial infections) (Meijers et al., 2021). Bacterial toxins such as lipopolysaccharide (endotoxin) are the most important inducers, and PCT is positively correlated with the severity of the condition and the duration of hospitalization in patients with myocarditis (Grimaud et al., 2020; Mirna et al., 2021). However, PCT can also be produced by the stimulation of inflammatory factors such as IL-1, IL-6, and TNF-α. It has been noted clinically that the majority of patients with fulminant myocarditis have elevated or even significantly elevated PCT that is not due to bacterial infection. As observed in 69 patients with fulminant myocarditis from the Department of Cardiology, Tongji Hospital, Huazhong University of Science and Technology (HUST), the plasma PCT level was (2.917±1.544) ng mL^{-1} on the day of admission, while it reached (21.679±7.564) ng mL^{-1} the next day and was still (3.017±1.446) ng mL^{-1} until discharge, but no evidence of bacterial infection was found. This demonstrates that patients with fulminant myocarditis have elevated PCT, which is associated with myocardial inflammatory cell infiltration, myocardial injury, and inflammatory storm. So, clinical attention should be paid to observation and identification, and other

evidence of infection such as imaging and pathogenetic tests should be combined to determine whether the coinfection was comorbid or not, and the diagnosis of comorbid bacterial infection cannot be made based on PCT alone or elevated peripheral blood leukocytes (IIb). Only when coinfection with bacteria has been clearly established in patients with fulminant myocarditis can the level of PCT be consulted to guide antibiotic use and efficacy evaluation (Daubin et al., 2018; Huang et al., 2018; Kyriazopoulou et al., 2021).

Special examination for fulminant myocarditis

Electrocardiogram

The ECG has high sensitivity but low specificity for the diagnosis of this disease and should be examined multiple times to compare its changes. Sinus tachycardia was most common in patients with fulminant myocarditis, although there were also patients with nonsignificant changes in heart rate. Patients with fulminant myocarditis showed significantly low voltage in all leads on the ECG at admission, and most patients had QRS widening (22.8%), ST segment elevation (19.5%) or ST-T segment changes (37.4%) in extensive leads or some leads, and many had T-wave flattening and/or inversion, which can be accompanied by bundle branch block (22.8%) and other arrhythmias (Ammirati et al., 2017a; Kociol et al., 2020). Most fulminant myocarditis patients can present with ECG changes similar to AMI, presenting with selective or non selective ST segment arched upward elevation in leads, persistent QRS widening, bundle branch block or atrioventricular block, suggesting that myocardial transmural damage is extensive and severe (Sawamura et al., 2018; Ukena et al., 2011). Studies have reported possible arrhythmias in 44% of patients in the acute phase, including atrial fibrillation (approximately 7%), complete atrioventricular block (approximately 17%), paroxysmal ventricular tachycardia or ventricular fibrillation (15%) (Sawamura et al., 2018). The presence of VT, VF, or sinus arrest suggests critical illness, they are also a cause of syncope and sudden death, and hypotension/shock is the most important predisposing factor. Other ECG changes include sinus block, abnormal Q waves, and reduced QRS amplitude (Ammirati et al., 2018a; Dai et al., 2023). Of note, ECG changes can be very rapid in patients with fulminant myocarditis, and they should be kept on continuous ECG monitoring, with routine recording of ECGs when ECGs are changes (Caforio et al., 2013) (I B) (Table 4).

Echocardiography

Echocardiography provides a comprehensive assessment of cardiac structure, function, and flow status. The following changes can be seen in patients with fulminant myocarditis (Ammirati et al., 2018a; Ammirati et al., 2017a; Zuo et al., 2020). (i) Cardiac dysfunction: significant decrease in LV systolic function can be seen. A dramatic decrease in left ventricular ejection fraction over a short period (hours) is one of the important features of fulminant myocarditis, with EF values even as low as 10% in some patients; LV diastolic function was also significantly impaired (decreased E/A′ ratio and increased E/E′ ratio). With reasonable and effective treatment, the patient's cardiac function can improve significantly in the short term, returning to near normal levels soon after a few days. (ii) Diffuse wall hypokinesia of the left ventricle or even peristaltic like beats can be seen. (iii) It is commonly observed that the left ventricle exhibits segmental motion abnormalities on the basis of diffuse hypokinesia, which is characterized by hypokinesia, no motion, paradoxical motion, or even ventricular aneurysm formation and heterogeneous involvement of the systemic myocardial inflammation, usually associated with ST segment elevation on the electrocardiogram. These changes can gradually return to normal within days to 10 days or more of effective treatment. (iv) Change in cardiac chamber size: most patients have normal cardiac chamber size, only a few patients have slightly enlarged cardiac chambers, very few are significantly enlarged, which can recover after effective treatment (Felker et al., 2000). (v) The wall of the chamber is transiently and reversibly thickened, resulting from inflammatory oedema of the mesangium, and is usually 12–13 mm thick and, in severe cases, even 20–30 mm thick, with the thickening of the interventricular septum being the most (Felker et al., 2000). (vi) In comparison with LV long axis strain detection in acute myocarditis, fulminant myocarditis is associated with a significant decline and predates the decline in cardiac function and is thought to be helpful for early diagnosis (Zuo et al., 2021). In addition, detection of vena cava diameter and its rate of change during inspiration can help to judge patient blood volume and guide fluid therapy.

Echocardiography can timely rule out valvular heart disease, hypertrophic or restrictive cardiomyopathy, etc. When combined with the medical history, hs cTnI/cTnI, NT proBNP and ECG examinations, the diagnostic significance of echocardiography was obviously increased. Echocardiography is important in the rapid diagnosis of the disease, determining the severity of the condition, guiding the choice and adjustment of treatment options, the assessment of efficacy and prognosis, and follow-up. Routine workup is recommended for all patients with fulminant myocarditis, especially for those who are hemodynamically unstable and require ambulatory monitoring (I B) (Ammirati et al., 2017a; Ammirati et al., 2016; Caforio et al., 2017; Caforio et al., 2013; Hang et al., 2020).

Chest CT or X-ray

Most patients have little or slightly enlarged heart shadows (Ammirati et al., 2018b). There were signs of pulmonary congestion or pulmonary edema due to left heart insufficiency, such as enhanced hilar vascular shadow, blurred lung fields, etc. Hilar in acute alveolar pulmonary edema is butterfly like, and large confluent shadows are seen in the lung field. Very few patients with combined viral pneumonia can present with severe diffuse lesions plus pulmonary congestion and consolidation in heart failure, which manifests as respiratory distress, ARDS, and, in some patients, pleural effusion and interlobar pleural thickening.

Coronary angiography

Fulminant myocarditis patients have an acute onset, and some patients have inflammation involving the pericardium and pleura, even combined with coronary spasm, thus having chest tightness and shortness of breath or even chest pain, along with significant changes in ECG and myocardial markers, which need to be differentiated from AMI. Therefore, it is recommended to perform coronary angiography as early as possible, regardless of whether the patient has high-risk factors for coronary atherosclerosis (Ammirati et al., 2018b; Caforio et al., 2013), because the treatment and prognosis of the two diseases are completely different. Available literature data and the experience of more

than 200 patients from Tongji Hospital affiliated with Huazhong University of Science and Technology (HUST) have proved that emergency radiography does not increase the mortality of patients with fulminant myocarditis (Zhou et al., 2021). However, care was taken to minimize contrast administration when performing coronary angiography (I A) (Ammirati et al., 2017a; Kociol et al., 2020).

Cardiac magnetic resonance

Cardiac magnetic resonance imaging (CMRI) can provide imaging changes that approximate pathological changes in myocarditis, including myocardial edema, congestion, and capillary exudation, as well as necrosis and fibrosis. Quantitative analysis of myocardial tissue damage is also possible using T1 mapping, T2 mapping techniques and extracellular volume (ECV) parameters (Ferreira et al., 2018; Friedrich et al., 2009). Cardiac magnetic resonance examination combined with troponin elevation has gradually replaced myocardial biopsy as a noninvasive method for the clinical diagnosis of myocarditis and has been used in clinical studies of myocarditis in recent years, especially in low-risk patients (Ammirati et al., 2018a).

The current CMRI diagnostic criteria for myocarditis include the following: (i) T2 imaging suggestive of myocardial edema, including increased T2 signal on T2 weighted imaging or increased T2 mapping; (ii) myocardial inflammation was considered when T1 imaging suggested myocardial injury, including delayed gadolinium enhancement (LGE), increased T1 mapping T1 value or ECV, fulfilling one of the 2 criteria mentioned above (Ferreira et al., 2018). Studies have shown a sensitivity of 87.5% and a specificity of 96.2% for the diagnosis of myocarditis (Luetkens et al., 2019). Moreover, distinguished from ischaemic myocardial injury, myocardial injury in myocarditis is generally marked by epicardial injury, extending from the epicardium to the mid myocardium and endocardium, and the extent of injury is not consistent with the region of coronary distribution (Ammirati et al., 2017a; Ammirati et al., 2017b). CMRI also has obvious limitations, is time-consuming to examine and analyze, and is not suitable for critically ill patients; effective implementation of CMRI requires a high level of post analytical technique, and furthermore, edematous changes in the mid myocardial layers on CMRI are difficult to differentiate from myocardial ischemia; CMRI does not distinguish between inflammatory aetiology and histological type. In addition, CMRI examination has not been universal in county hospitals. Therefore, CMRI has limited diagnostic value in the acute phase of fulminant myocarditis.

Endomyocardial biopsy

Pathological analysis by endomyocardial biopsy (EMB) is the traditional gold standard for the diagnosis of myocarditis. Histological diagnostic criteria for fulminant myocarditis are presented in the pathology section. In recent years, with the development of imaging techniques such as echocardiography and magnetic resonance, EMB has been less applied for common myocarditis. However, for fulminant myocarditis with shock, acute HF or severe arrhythmia as the main manifestations, EMB is recommended to clarify the pathological diagnosis by the current study as well as by the American Heart Association (AHA) and the European Society of Cardiology (ESC) related consensus (Caforio et al., 2013; Cooper et al., 2007; Francis and Lewis, 2018; Heymans et al., 2016).

In addition to providing direct evidence of inflammation in myocardial tissue and thereby establishing a diagnosis of myocarditis, EMB can guide subsequent treatment of myocarditis, although the latter is currently unproven by large-scale clinical studies. EMB can determine the type of pathology, discover pathogens such as viruses and determine its amount, and help to clarify the infiltrating inflammatory cell types in combination with immunohistochemical staining (Bennett et al., 2013; Merken et al., 2018), which is particularly important for the diagnosis of specific types of fulminant myocarditis such as cytomegalovirus myocarditis, eosinophilic myocarditis and sarcoidosis (Ammirati et al., 2021; Tschöpe et al., 2019a). Therefore, EMB is actively recommended for fulminant myocarditis, especially when a specific etiology is clinically suspected, such as the use of ICIS, autoimmune diseases, peripheral blood eosinophilia, etc. to clarify the etiology, pathological type, and status of myocardial injury and to guide clinical treatment (Ammirati et al., 2021; Palaskas et al., 2020; Tschöpe et al., 2019a).

Limitations of this technique limit its clinical use in fulminant myocarditis, including that its diagnostic value relies on the experience of the pathologist; EMB is an invasive procedure with the presence of complications such as cardiac perforation causing pericardial tamponade, atrioventricular block, chordae tendineae injury and bleeding from the puncture site. Complication rates are approximately 1%–2% in experienced centres and up to 8.9% in other centres (Bennett et al., 2013; Singh et al., 2018). There is sampling error, and sampling at low voltage regions under 3D mapping can obviously improve the positive rate (I B) (Casella et al., 2020; Haanschoten et al., 2021).

Diagnosis and differential diagnosis

Diagnostic criteria

Fulminant myocarditis should be suspected in patients with prodromal symptoms such as fever, fatigue, poor appetite or diarrhoea, followed by rapid onset of severe haemodynamic disturbances (including hypotension or shock), severe arrhythmias (atrioventricular block, sinus tachycardia, VT and other malignant arrhythmias); elevated hs cTnI/cTnI and BNP/NT proBNP, and significant ECG changes (low voltage, extensive lead ST segment and T wave changes and conduction block, etc.); patients can be clinically diagnosed with fulminant myocarditis if they present with the following features on echocardiography, such as diffuse wall hypokinesia, markedly decreased left ventricular ejection fraction, decreased left ventricular long axis strain, and markedly increased levels of inflammatory factors, and acute myocardial infarction and stress-induced cardiomyopathy have been excluded. Fulminant myocarditis should also be considered after ruling out acute myocardial infarction in the setting of overt viral infection, history of oncologic ICIS therapy, autoimmune disease, toxicant ingestion, or drug hypersensitivity; In addition, there are rare cases of fulminant myocarditis with viral invasion of the cardiac conduction system, mainly characterized by malignant arrhythmias such as atrioventricular block, frequent VT, and ventricular fibrillation. Hs cTnI/cTnI and BNP/NT proBNP are not significantly elevated at an early stage, and such patients need to be evaluated early for inflammatory factors, echocardiography, EMB, or CMRI, ^{18}FDG-PET to confirm the diagnosis, after excluding electrolyte imbalance, and exclusion of inherited ion channel disorders by history.

Diagnostic process

The diagnosis of fulminant myocarditis was made from three aspects: proposed diagnosis (clinical presentation, ECG, cardiac markers, cardiac ultrasound and screening for inflammatory factors), confirmation of diagnosis (coronary angiography, EMB or CMRI), and etiological diagnosis (etiology and toxicant testing help to search for the etiology). It is critical to make a clinical diagnosis very early, so these three aspects are not strictly performed in a step-wise fashion. In particular, coronary angiography should be performed as early as possible to exclude acute myocardial infarction, while EMB and detection of inflammatory factors help confirm the diagnosis. The diagnostic strategy and flow are shown in Figure 3.

(1) Proposed diagnosis: patients suspected of fulminant myocarditis by the presence of prodromal symptoms, clinical manifestations and signs of upper respiratory or digestive tract infection as well as elevated ECG and troponin should undergo echocardiography as soon as possible to clarify the possibility of fulminant myocarditis.

(2) Confirmation of diagnosis: fulminant myocarditis can be diagnosed clinically in patients who are proposed to have fulminant myocarditis after coronary angiography has been performed to exclude acute myocardial infarction. EMB can be performed as early as possible to clarify the pathological diagnosis if the patient can tolerate testing.

(3) Etiological diagnosis: patients with fulminant myocarditis can be searched for the etiological factors by using pathogen microorganism detection, autoimmune related antibody and poison detection.

Differential diagnosis

Fulminant myocarditis involves multiple organs and systems, has a severe and variable clinical presentation, and often requires the above tests and examinations early in the course of the disease to exclude the following diseases:

(1) AMI: a massive AMI presenting with pulmonary congestion leading to circulatory collapse, shock, electrocardiographic changes and marked elevation of the cardiac markers hs cTnI/cTnI and BNP/NT proBNP, is the most desirable condition to differentiate from fulminant myocarditis. Identification is made primarily by coronary angiography and cannot be made solely on empirical judgment.

(2) Septic cardiomyopathy: in patients with shock due to severe bacterial infection, toxic and immunological insults can also lead to myocardial damage, with a significant decrease in cardiac systolic function and a significant increase in hs cTnI/cTnI and BNP/NT proBNP in severe cases, resembling fulminant myocarditis. Their early presence of significant bacterial infection, significant elevation of blood leukocytes, and other systemic manifestations are helpful for identification.

(3) Ordinary acute myocarditis: ordinary acute myocarditis usually also has a history of previous infection, chest tightness, palpitations and other symptoms and myocardial damage, but the acute myocarditis has a significantly milder impairment of cardiac function, a milder clinical condition than fulminant myocarditis, no obvious hemodynamic disturbance and conduction abnormalities, and the condition can extend over a long period to become chronic myocarditis or cardiomyopathy changes.

(4) Stress cardiomyopathy: also known as left ventricular apical ballooning syndrome or octobasket heart, with severe impairment of cardiac function and significant increases in hs cTnI and NT proBNP, needs to be differentiated from fulminant myocarditis. The syndrome has the following salient features: It has a female predominance and there is strong psychological stress as a predisposing factor; It closely resembles AMI but without fixed stenosis on coronary angiography and can quickly recover after reasonable treatment. Stress induced cardiomyopathy can also be induced by intense stress mimicked during pheochromocytoma sympathetic crises (Y-Hassan and Falhammar, 2020). In addition, very few patients with fulminant myocarditis also show ballooning changes in the heart, which can be identified by a clear history and features of inflammatory storm, and myocardial biopsy can finally lead to a definite diagnosis.

In addition to the diseases mentioned above, fulminant myocarditis is also differentiated from diseases such as viral pneumonia.

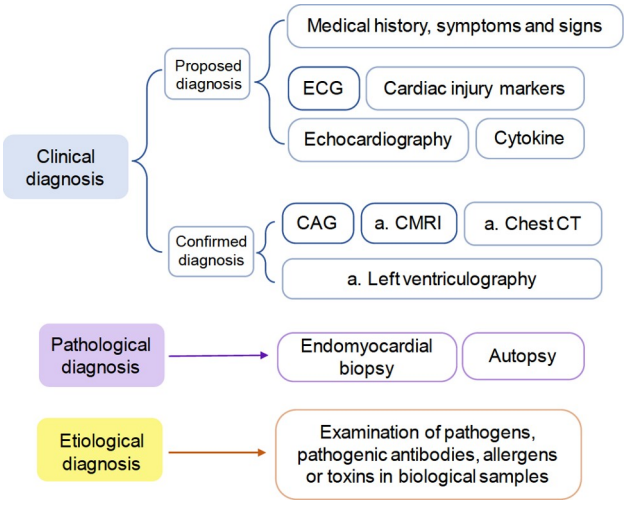

Figure 3. Flow chart of myocarditis diagnosis. ECG, echocardiography, cTnI, NTpro-BNP, CAG (coronary angiography) and blood cytokine detection need to be completed immediately. a, It means that it should be performed when necessary. Left ventriculography is to exclude stress cardiomyopathy, and chest CT is to exclude septic cardiomyopathy caused by severe infection. Select an appropriate time for CMRI (cardiac magnetic resonance imaging) according to the situation.

Acute phase treatment of fulminant myocarditis

Because patients with fulminant myocarditis have a rapid onset, rapid changes in condition and high mortality, it is recommended that hospitals establish a rapid response team and a standardized, concise and easy to master practice path for the treatment of fulminant myocarditis according to the actual situation, so as to ensure the standardized implementation of the "life support-based comprehensive treatment regimen" and improve the success rate of rescue of fulminant myocarditis.

Establishment of rapid response team for treatment of fulminant myocarditis

(1) The cardiology team is the core, and is fully responsible for the diagnosis (including coronary angiography, myocardial biopsy), risk assessment, establishment of life support system, operation and management, implementation of comprehensive treatment plan, and long-term follow-up of patients with fulminant

myocarditis in the hospital. Superior treatment center and basic level hospitals have established information exchange. Once the patients with suspected fulminant myocarditis need to be referred, they can be directly referred by the basic level hospital or assisted by the rapid response team members with life support equipment according to the practical conditions and the patient's condition.

(2) Pre hospital first aid/emergency intensive care medical team: this team is in charge of the whole process of identification, transfer and pre hospital first aid of outpatient and emergency patients, and completes patient referral and pre hospital treatment together with the cardiology team.

(3) Imaging and pathology department team: the physicians of cardiac ultrasound department are responsible for the evaluation of cardiac function of patients in the hospital during the treatment and long-term follow-up; cardiac MRI physicians are responsible for the diagnosis, differential diagnosis and follow-up of myocarditis through CMRI; pathologists are responsible for making accurate pathological diagnosis on tissue samples from myocardial biopsy/autopsy or heart transplantation.

(4) Backup support for cardiovascular surgery: for patients with difficulties in percutaneous insertion or removal of mechanical circulatory support devices, vascular surgery backup support is required for vascular incision, catheter insertion and withdrawal; very few patients with severe cardiac function impairment and difficulty in recovery can be transferred to cardiac surgery for bridging left ventricular assist device implantation or heart transplantation.

(5) MDT support team: patients with fulminant myocarditis often suffer from multiple organ dysfunction. When organ disorders occur except for heart and treatment is difficult, appropriate treatment plans can be formulated after consultation with multiple specialties.

The above teams are composed of 3–5 people. The cardiology team is responsible for regularly conducting theoretical training on the treatment scheme, mechanical support practice and work flow drill for the above team members, so that patients with fulminant myocarditis can be treated quickly, normatively and effectively.

Practice path

(1) The basic level hospital and the superior treatment center shall establish information exchange and open a green channel for the treatment of fulminant myocarditis. If the patients or their families agree and the hospital conditions are available, they can consider timely referral for treatment.

(2) It is necessary to take the cardiology department as the leading department and cooperate with multiple departments to complete the treatment of patients with acute and critical diseases.

(3) Once the superior treatment center assists the primary hospital for diagnosis, the primary hospital should immediately start drug treatment to maintain vital signs and quickly transfer the patient to the superior treatment center.

(4) After receiving the referral information, the superior treatment center immediately started the "green channel". The cardiology doctors and nurses prepared life support auxiliary equipment, emergency angiography, etc., and the ultrasound doctors prepared bedside ultrasound.

(5) The members of the treatment center evaluate the patients' condition, establish the corresponding life support auxiliary system, and start a comprehensive treatment plan.

(6) Members of the treatment center evaluate the condition of the patient according to the laboratory examination and special examination results every day, and adjust the treatment plan at any time.

(7) All discharged patients were followed up for 6 months by members of the treatment center, and then the local hospital doctors could be instructed to follow up the patients.

Patient bedside monitoring

ECG blood pressure oxygen saturation monitoring

Patients with fulminant myocarditis can develop severe hemodynamic disorders, arrhythmias, respiratory failure, and other critical conditions, so close monitoring of temperature, blood pressure, heart rate, cardiac rhythm, respiratory rate, oxygen saturation, and daily water output and intake are required, with daily assessment of symptom and sign changes. ECG monitoring can timely detect arrhythmias, such as supraventricular arrhythmias, ventricular arrhythmias, and atrioventricular block, in patients with fulminant myocarditis. Blood pressure monitoring includes noninvasive blood pressure and invasive blood pressure and is able to accurately determine shock. Oxygen saturation is mainly monitored by finger pulse oxygen and arterial blood gas analysis. In patients with poor peripheral circulation, arterial blood gas analysis to monitor partial pressure of oxygen and oxygen saturation is more accurate (I, A) (Jensen et al., 1998). In fulminant myocarditis patients undergoing VA ECMO assisted, oxygen saturation of the right upper extremity more closely reflect the patient's systemic oxygenation profile (I, B) (Lee et al., 2020).

Invasive blood pressure monitoring

Relative to noninvasive blood pressure, invasive blood pressure monitoring has high accuracy and is suitable for patients with unstable hemodynamic status who are severely ill (I, A) (Kim et al., 2014). Systolic blood pressure less than 90 mmHg or mean arterial pressure less than 60 mmHg for more than 30 min was considered a common hemodynamic indicator of shock. Invasive blood pressure is usually measured by puncture catheterization of the radial, brachial, femoral, dorsal foot arteries, and other sites. Stable invasive BP waveforms are important for IABP, and the supportive effects of IABP can be effectively assessed by monitoring of aortic systolic, diastolic, and counterpulsation pressures. Whereas patients receiving veno arterial extracorporeal membrane oxygenation (VA-ECMO) assistance have a smaller pulse pressure difference due to increased left ventricular afterload, invasive blood pressure can indirectly assess cardiac function and aortic valve patency in patients. Raising ECMO flow increases patient mean arterial pressure (map) and it is reasonable to keep Map >60 mmHg (I, C) (Du et al., 2018).

Central venous pressure

Central venous pressure (CVP) is the pressure of the right atrium and intrathoracic great veins, measured through the superior and inferior vena cava or the right atrial internal canal, which reflects the right atrial pressure and is one of the main indicators of hemodynamics observed clinically. A central venous pressure of more than 15 mmHg in patients with shock suggests possible right heart dysfunction or volume overload, and central venous

https://doi.org/10.1007/s11427-023-2421-0

pressure is an important hemodynamic indicator (II, B) (Heidenreich et al., 2022). Patients receiving mechanical ventilation will have increased central venous pressure due to increased intrathoracic pressure. While in patients receiving VA-ECMO support, the central venous pressure will significantly decrease due to the loss of blood return caused by vena cava drainage. The impact of these factors needs to be considered when using central venous pressure to assess volume status.

PICCO hemodynamic monitoring

Pulse wave indicating continuous cardiac output (PICCO) integrates a large number of static and dynamic hemodynamic parameters, including cardiac output (CO), whole heart end diastolic volume (GEDV), extravascular lung water (EVLW), stroke variability (SVV), and so on, by combining transcardial thermodilution and pulse contour analysis. Hemodynamic indices obtained by PICCO improve the accuracy of bedside assessment and can guide clinical decision making, especially in hypotensive patients (I, B) (Li et al., 2021a). However, the accuracy of PICCO is also affected by multifaceted factors. Common critical care techniques such as continuous renal replacement therapy (CRRT), IABP, ECMO affect the thermodilution process and need careful consideration when using PICCO to monitor hemodynamics.

Principles of rescue

"Life support-based comprehensive treatment regimen", emphasizes "very early recognition, very early diagnosis, very early prediction and very early rescue".

Although fulminant myocarditis has an acute onset and rapid disease progression with a high early case fatality rate, patients once they go through the dangerous period and the long-term prognosis is mostly good, so great attention should be paid to the treatment of fulminant myocarditis, which can save the patient's life as soon as a clinical diagnosis is made and treatment is initiated as soon as possible. The key problem in patients with fulminant myocarditis is acute circulatory failure and cardiogenic shock, the main pathophysiological mechanism of which is "excessive immune activation and inflammatory storm formation". Based on the mature experience of our multicenter trial and the clinical practice of multiple hospitals, this guideline recommends "life support-based comprehensive treatment regimen" for patients with fulminant myocarditis. Its core content includes: (i) mechanical circulatory support: maintaining circulatory stability and ensuring organ perfusion with a mechanical circulatory device, allowing the failing heart to rest, rather than raising blood pressure with cardiotonic and vasoactive drugs; (ii) immunomodulatory therapy: the use of adequate doses of glucocorticoids and adequate doses of immunoglobulins to modulate immunity, which is the fundamental measure; (iii) use of neuraminidase inhibitors to attenuate myocardial injury; (iv) other treatments: ventilator assisted breathing if necessary, temporary pacemaker implantation and blood purification therapy, etc (Figure 4).

Rescue methods

Life support therapy is at the highest priority of all treatments for fulminant myocarditis and is the central link of "life support-based comprehensive treatment regimen". Life support therapy includes mechanical circulatory support and respiratory support, etc.

Mechanical circulatory support

The myocardium is damaged by diffuse inflammation in

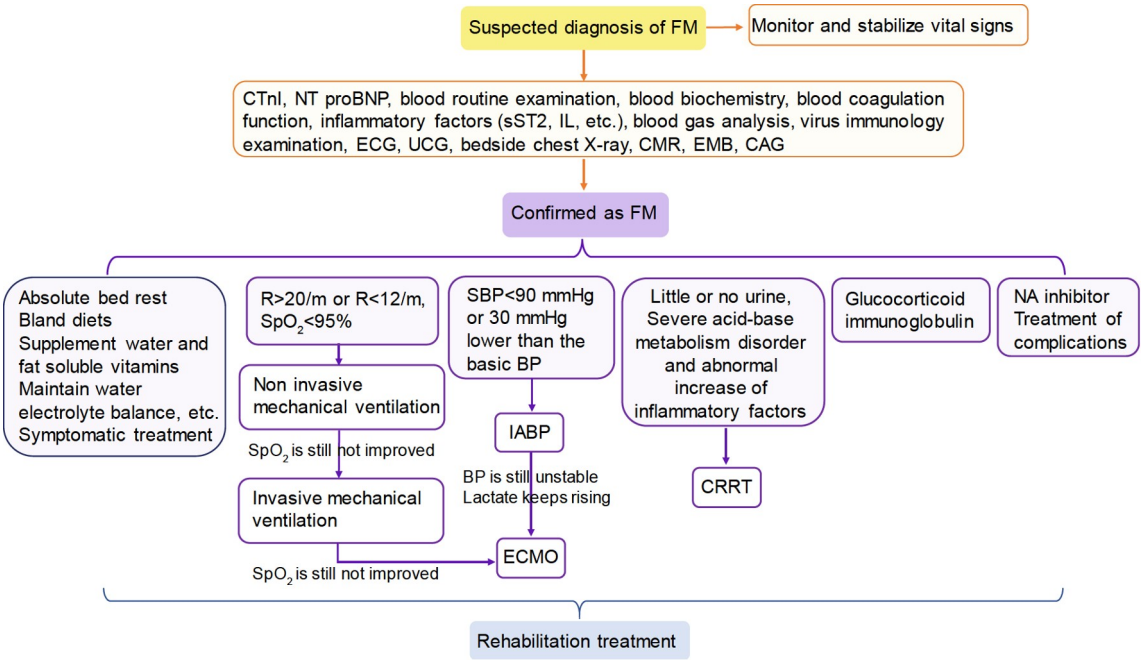

Figure 4. Treatment flow chart of patients with myocarditis in the acute phase. cTnI, cardiac troponin I; sST2, soluble growth stimulating expression gene 2 protein; IL, interleukin; ECG, electrocardiogram; UCG, echocardiography; CMRI, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; SpO_2, blood oxygen partial pressure; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; IABP, intra aortic balloon counterpulsation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; NA, neuraminidase.

fulminant myocarditis, and pump failure, hypotension, or cardiogenic shock occur, which, combined with pulmonary congestion and lung inflammatory injury, severely hamper systemic blood and oxygen supply. Mechanical circulatory support actively reduces cardiac work and restores cardiac function under systemic therapy and is the preferred treatment and one of the central links. Vasoactive drugs and cardiotonics will aggravate the burden on the damaged heart, aggravate organ ischemia and promote myocardial inflammatory injury, resulting in serious consequences. So vasoactive drugs and cardiotonics are used only in the absence of mechanical circulatory support. Mechanical circulatory support is employed once available (Gustafsson, 2018; Kociol et al., 2020). Mechanical circulatory support include the following:

(1) Intra-aortic balloon pump (IABP). The balloon of the IABP is rapidly inflated (varying from 30–60 mL) in early diastole and the balloon occupies the intra-aortic (distal to the left subclavian artery opening to proximal to the left renal artery opening) space, which elevates aortic pressure, drives blood flow, and increases perfusion in organs such as the heart and brain and kidneys. Rapid deflation of the balloon of the IABP before systole, resulting in reduced intra-aortic pressure, reduces afterload during systole and reduces cardiac work, whereas it increases stroke volume and forward blood perfusion (Gustafsson, 2018; Kociol et al., 2020). A recent retrospective study of IABP use in a large sample of patients with cardiogenic shock demonstrated that IABP use in fulminant myocarditis patients significantly reduced in-hospital death (Chu et al., 2021). In addition, multicenter studies and empirical reports have confirmed that the early administration of IABP in fulminant myocarditis patients significantly increases systolic blood pressure above 20 mmHg, decreases the faster sinus rate by approximately 10 beats/min, reduces the use of vasoactive drugs, and improves the short- and long-term prognosis (Jie et al., 2022; Li et al., 2019; Maisch et al., 2014; Zhou et al., 2021). If IABP is used extremely early, more than 70% of patients do not require the addition of other mechanical circulatory devices such as ECMO to maintain circulatory stability. Therefore, immediate IABP use is recommended in patients with fulminant myocarditis who present with early manifestations of shock such as hypotension and increased heart rate (I, A) (Chu et al., 2021; Jie et al., 2022; Kociol et al., 2020; Li et al., 2019; Maisch et al., 2014; Ye et al., 2021; Zhou et al., 2021) (Table 5)

(2) ECMO. VA-ECMO, which directly drains blood from the level of the right atrium to extracorporeal oxygenation and reinfusion to the aorta (1–6 L min^{-1}), is able to completely or partially replace cardiopulmonary function and rapidly stabilize the circulation. The application of VA-ECMO for fulminant myocarditis treatment has been supported by numerous clinical data (Albert et al., 2020; Ammirati et al., 2017a; Ammirati et al., 2019; Chong et al., 2018). (i) With IABP support, shock still cannot be completely corrected, fulminant myocarditis patients still have peripheral hypoperfusion, and ECMO needs to be used; (ii) patients with sudden cardiac arrest in fulminant myocarditis, especially if standard cardiopulmonary resuscitation (CPR) is performed for more than 10 min without restoration of effective spontaneous circulation or interrupted by a short period of return of spontaneous circulation, during which time there are repeated episodes of cardiac arrest, or recurrent episodes of ventricular tachycardia; (iii) no contraindications to ECMO assisted (Kociol et al., 2020; Yannopoulos et al., 2020). Median treatment duration with ECMO has been reported to range from 5 to 9 days, with discharge rates ranging from 55% to 81.8% (Asaumi et al., 2005; Ammirati et al., 2017a; Chong et al., 2018; Kondo et al., 2022; Lorusso et al., 2016). However, in recent years, following Chinese expert consensus, multiple centers have recommended that IABP should be applied first and, when IABP is insufficient to correct shock, ECMO should be reintroduced (i.e., combining IABP and ECMO) along with immunomodulatory therapy to reduce the in-hospital mortality of fulminant myocarditis to less than 5% (Li et al., 2019; Zhou et al., 2021). Limitations of VA ECMO assisted circulation are the increased risk of left ventricular afterload and pulmonary edema, the possibility of a slow recovery of LV function with difficulty in aortic valve opening, and the difficulty in ECMO removal. Combined IABP can compensate for its limitation (Combes et al., 2020; Henry et al., 2021; Hu et al., 2020; Mehrpour et al., 2019). In conclusion, immediate addition of ECMO is recommended when IABP is insufficient to correct circulatory disturbance. When patients have severe circulatory dysfunction, severe LV dysmotility, or cardiac arrest, a combination of ECMO and IABP should be performed immediately (I, A) (Albert et al., 2020; Ammirati et al., 2019; Ammirati et al., 2017a; Chong et al., 2018; Wang et al., 2019a) (Table 5).

(3) Impella and other cardiac assist devices. In addition to IABP and ECMO, mechanical circulatory assist techniques have Impella and tandem heart (Combes et al., 2020). Temporary circulatory support for cardiogenic shock. Temporary circulatory support for cardiogenic shock (Combes et al., 2020). The Impella system works by pumping oxygenated blood from the left ventricle transcatheter across the aortic valve directly into the ascending aorta via a built-in micro axial flow pump at the leading edge of the catheter, establishing a left ventricle ascending aorta drainage pathway and thereby partially replacing left ventricular function (Gao et al., 2020). Recently, the application of Impella alone or in combination with VA-ECMO in circulatory support in patients with fulminant myocarditis extends the support time and improves long-term prognosis, which has been supported by clinical evidence (I, B) (Annamalai et al., 2018; Kennel et al., 2021; Kondo et al., 2022; Tschöpe et al., 2019b). Tandem heart as a biventricular assist system has also been reported in case reports of circulatory support in fulminant myocarditis (IIa, C) (Pahuja et al., 2019) (Table 5).

Immunomodulatory therapy

Excessive immune activation and inflammatory storm lead to severe injury of myocardium in fulminant myocarditis. Targeting this pathophysiological basis, "immunomodulatory" therapy, comprising adequate doses of glucocorticoids and adequate doses of immunoglobulins, rather than "immunosuppressive" therapy using cytotoxic drugs, is able to block the pathogenetic link, reduce inflammation and edema, fight shock, relieve clinical symptoms, save patients' lives and improve outcomes.

(1) Very early use of adequate doses of glucocorticoids. There is good reason for the use of glucocorticoids in patients with fulminant myocarditis, which have potent anti shock, anti myocardial inflammation, edema and injury effects by inhibiting nuclear transcription factor NF-κB activity while suppressing inflammatory factor production and inflammatory storm, stabilizing intracellular lysosomal membranes, attenuating toxin damage, reducing myocardial depressor release function and protecting myocardium through non nuclear receptor mechan-

Table 5. Treatment of fulminant myocarditis in acute stage and its level of recommendation

Recommend	Level of recommendation	Level of evidence
Early use of IABP for circulatory support is recommended in those with hemodynamic instability.	I	A
Immediate initiation of ECMO or direct initiation of ECMO therapy is recommended when an IABP is insufficient to improve circulation in those with hemodynamic instability.	I	A
Impella alone or in combination with ECMO can be used for circulatory support therapy in patients with fulminant myocarditis.	IIa	C
Tandem heart as a biventricular assist system can be used for circulatory support in fulminant myocarditis. A right heart assist device (Impella RP) may also be considered when combined with or predominant right heart dysfunction.	IIa	C
After admission, intravenous methylprednisolone infusion at 3–8 mg kg^{-1} per day is recommended to be started as early as possible, halved after 3–5 consecutive days, and maintained at 20–40 mg d^{-1} for 1–3 months.	I	A
It is recommended to start intravenous gamma-globulin at 10–20 g per day as early as possible after admission and halve after 3–5 days to 5–10 g for 3 days for a total amount of about 2 g kg^{-1}.	I	A
Oseltamivir phosphate capsules (75 mg orally, 2 times/day) are recommended, and peramivir can be used as an alternative for 3–5 days.	IIa	C
Maintenance of mean arterial pressure at 60–65 mmHg is recommended to minimize the amount and timing of vasoactive drugs, and early referral of patients for mechanical circulatory support.	I	A
Inotropic agents (levosimendan, milrinone, and cediranib) increase cardiac contractility, reduce LV filling pressure to improve LV function, and improve withdrawal from mechanical circulatory assist devices in patients with fulminant myocarditis.	IIa	C
CRRT: early application of CRRT is recommended in fulminant myocarditis combined with organ dysfunction, especially renal function injury.	IIa	C
Mechanical ventilation: ventilators can be used as an adjunct in acute left heart failure, improving pulmonary function and reducing the patient's exertional load and cardiac work.	IIa	C
Treatment of arrhythmia: (1) Those with tachyarrhythmias (ventricular fibrillation) should be defibrillated or synchronized with electrical cardioversion immediately. Early use of extracorporeal life support therapy is recommended when arrhythmias cannot be terminated.	IIa	C
(2) Those who are relatively hemodynamically stable and should not be used negative inotropic, negative frequency antiarrhythmic drugs such as β receptor blockers or non dihydropyridine calcium antagonists.	III	C
(3) Placement of a temporary pacemaker is recommended for those with bradycardia. it can be treated with drugs that raise heart rate such as isoproterenol or atropine if unavailable.	IIa	C
(4) In patients with bradycardia, implantation of a permanent pacemaker is not recommended in the acute phase. ICDs are not recommended in patients with VT, in the acute phase and after recovery from disease (Evans et al., 2021; Prochnau et al., 2010).	III	C
(5) Those with stable disease for more than 2 weeks, but in whom the conduction block remained unrecovered, were considered for implantation of a permanent pacemaker.	IIa	C
Proton pump inhibitors: fulminant myocarditis patients are mostly under acute stress, and high-dose hormone therapy is used in some patients, especially in critically ill patients using mechanical circulatory support. Proton pump inhibitors are recommended for stress ulcer and gastrointestinal bleeding prevention.	IIa	C
Prevention of infection: fulminant myocarditis patients are mostly complicated by various degrees of infection, so anti infective treatment is recommended from the beginning.	IIa	C
Routine use of antifungals is not recommended.	III	C

isms (Hafezi-Moghadam et al., 2002). Glucocorticoid use during fulminant myocarditis not only failed to promote viral spread but also reduced myocardial viral titers, which was found to be associated with a significant increase in interferon production. Therefore, glucocorticoids are part of immunomodulatory therapy and are recommended to be started immediately after diagnosis. Methylprednisolone 200–500 Mg (or 3–8 mg kg^{-1}) was administered intravenously daily (can be reinvigorated with methylprednisolone on the basis of intravenous dexamethasone 10–20 mg as an emergency). It is gradually reduced depending on the condition (usually starting at a left ventricular EF value greater than 40%) after 3–5 consecutive days of treatment. Patients with fulminant myocarditis are recommended to be treated very early with adequate doses of glucocorticoids (Chen et al., 2013; Cooper et al., 1997; Jiang et al., 2022; Kociol et al., 2020; Li et al., 2019; Schultheiss et al., 2011; Wang et al., 2019a; Zhou et al., 2021). Patients were changed to oral prednisone 20–40 mg d^{-1} before discharge and was maintained for 1–3 months. Treatment discontinuation and adjustment of therapy were considered during follow-up based on patient symptoms, cardiac function, cTnI level, inflammatory factor levels, the degree of myocardial inflammation and edema revealed by CMRI or myocardial biopsy, and the degree of tolerance to medications (I, A) (Table 5).

(2) Very early intravenous use of adequate doses of immunoglobulin. Intravenous immunoglobulins are obtained from the plasma of multiple healthy individuals and have multiple effects including antiviral, anti-inflammatory and modulating immunity. Studies have shown that Fc fragments of immunoglobulins bind to immune cell Fc receptors especially macrophages. The Fc fragment of immunoglobulins binds the high affinity Fc receptor FCγRI, promoting the expression of inflammation inhibitory FcγRIIB, thereby producing marked anti-inflammatory therapeutic effects (Samuelsson et al., 2001). Binding of immunoglo-

bulins to Fc receptors on macrophages produces a marked polarizing effect, such that M1 macrophages are markedly decreased, whereas M2 macrophages are markedly increased, thereby suppressing myocardial inflammatory factor transcription and translation in myocarditis, while immunoglobulin treatment markedly reduces inflammatory cell infiltration such as monocytes/macrophages and the number of dendritic like cells in the myocardium and suppresses myocardial inflammation (Shioji et al., 2001). Experimental studies from Tongji Hospital of Wuhan found that treatment with immunoglobulins was highly effective against fulminant myocarditis in different model animals. It is recommended to start intravenous gammaglobulin at 10–20 g daily as early as possible after admission, and the dose of gammaglobulin is reduced to 5–10 g after 3–5 days and continued for another 3–5 days, with a total amount of about 2 g kg^{-1} (I, A) (Albert et al., 2020; Jiang et al., 2022; McNamara et al., 2001; McNamara et al., 1997; Moulik et al., 2010; Schultheiss et al., 2011; Tschöpe et al., 2021; Zhou et al., 2021) (Table 5).

Although there is a lack of large controlled studies using glucocorticoids or immunoglobulins alone for fulminant myocarditis, small controlled studies have confirmed that intravenous immunoglobulin use is highly effective in the treatment of patients with fulminant myocarditis, especially in our country, the combination of adequate doses of glucocorticoids and adequate doses of immunoglobulins has achieved significant success in the treatment of fulminant myocarditis, A new concept of "immunomodulatory therapy" combined with the results of basic research is proposed.

Antiviral therapy

Although viral infection is still thought to be the most common initiating factor in myocarditis on the basis of clinical prodromal symptoms, a large proportion of patients do not have direct evidence of viral infection. And most of the antiviral drugs, except influenza virus, are nonspecific and the effect is uncertain, so no special recommendation should be made at this time.

The neuraminidase inhibitors oseltamivir and peramivir have become the mainstay of guideline recommended treatments for influenza A and B by inhibiting their release from infected cells, preventing aggregation after release of progeny virus from host cells, and facilitating virus inactivation to reduce the release and spread of nascent virus (Laborda et al., 2016). Recently, it was shown that the expression level of neuraminidase is significantly higher after myocardial injury, leading to aggravation of myocardial injury by desialylation on the cardiomyocyte surface. Neuraminidase inhibitors might have synergistic therapeutic effects through effects other than antiviral (Li et al., 2021b; Li et al., 2019; Savage et al., 2014). Oseltamivir phosphate capsules (75 mg orally, 2 times/day) are recommended routinely in patients with fulminant myocarditis, or peramivir intravenously (IIa, C) (Wang et al., 2019a) (Table 5).

Other mechanical support treatment

(1) Mechanical ventilation treatment. Mechanical ventilation: ventilators can be used as an adjunct to medical therapy in acute left heart failure and can improve pulmonary function, especially significantly reduces the patient's exertional load and cardiac work. According to the principle that every effort is made to reduce the load on the heart, it is recommended that positive pressure ventilation be given to patients with shortness of breath/distress, rapid respiratory rate, or respiratory depression (abnormal respiratory rhythm) with or without oxygen desaturation (Association SMB of CM, 2007; Cardenas and Lynch, 2006).

Common modes of mechanical ventilation include the following:

(i) Noninvasive mechanical ventilation: noninvasive mechanical ventilation is recommended for patients with dyspnea/distress or respiratory rate>20 BPM, who can fully cooperate and adapt to ventilator ventilation, and who are expected to achieve short-term remission (Sevransky et al., 2004). Non invasive mechanical ventilation is contraindicated in patients with unclear consciousness and impaired airway self-cleaning capacity (Antonelli et al., 2000; Hilbert et al., 2001). Patients should be closely monitored for vital signs and treatment response when non-invasive mechanical ventilation treatment is applied, and immediately changed to invasive mechanical ventilation if necessary.

(ii) Invasive mechanical ventilation: patients unable to adapt to noninvasive mechanical ventilation, patients requiring cardiopulmonary resuscitation, and patients with shortness of breath or distress should be decisively placed on invasive mechanical ventilation. Invasive mechanical ventilation should be used as early as possible for respiratory failure and the appearance of respiratory and metabolic acidosis (Association SMB of CM, 2007; Marini et al., 1988; Tasaka et al., 2022). Therefore, the indication for invasive mechanical ventilation is significantly looser for fulminant myocarditis than for other diseases. Although there is currently a lack of RCT studies evaluating the therapeutic significance of early invasive mechanical ventilation for fulminant myocarditis with respiratory failure, the experience in China has proved that invasive mechanical ventilation is more effective in improving hypoxemia, reducing the work of breathing, alleviating respiratory distress, and helping cardiac function recovery (I, a) (Table 5).

(2) CRRT. As an adjuvant therapeutic measure, the main purpose of CRRT is to continuously clear toxins and inflammatory factors to alleviate damage caused by inflammatory storm, while helping regulate body fluid and acid-base balance and stabilize the internal environment. It should be used early when combined with renal impairment or acute left heart failure.

Patients with fulminant myocarditis often present with disturbed hemodynamics and fluid retention due to capillary leak, so CRRT is recommended in critically ill patients; When combined with systemic infection, CRRT can significantly improve hemodynamics in patients with septic shock by clearing inflammatory mediators and help improve survival (IIa, C) (Chu et al., 2021; Kopterides et al., 2012; Tzartos et al., 2008) (Table 5).

Immunoadsorption may help effectively clear inflammatory factors. Although there is no evidence from large-scale clinical trials, results from clinical studies with small samples (Felix et al., 2015; Jensen and Marchant, 2016) suggest that immunoadsorbent therapy may improve clinical symptoms and cardiac function in patients (IIa, B) (Bulut et al., 2010; Bygren et al., 1985; Felix et al., 2000; Mobini et al., 2003; Palmer et al., 1988) (Table 5). Immunosorbent can be tried when available.

Use of vasoactive and inotropic agents

Vasoactive drugs excite β1 receptors of the myocardium, increasing myocardial contractility, elevating heart rate and

https://doi.org/10.1007/s11427-023-2421-0

increasing cardiac output; some vasoactive agents excite peripheral vascular receptors, which constrict blood vessels, thereby maintaining blood pressure and ensuring blood supply to important organs. However, prolonged application of vasoactive drugs at large doses increases myocardial oxygen consumption, myocardial ischemia, and induces arrhythmias, and its strong peripheral vasoconstrictor effect may lead to ischemic injury or even necrosis in organs such as the kidney, liver, and gastrointestinal tract, forming irreversible damage. Commonly used vasoactive agents include dopamine, norepinephrine, m-hydroxylamine, and pituitrin, etc. This class of drugs is not recommended in principle for patients with fulminant myocarditis. However, in the absence of mechanical circulatory support conditions, vasoactive drugs should be administered temporarily to maintain the patient's mean arterial pressure at 60–65 mmHg in the absence of minimal perfusion to vital organs (Kędziora et al., 2021; Morkane et al., 2022). Early institution of mechanical circulatory support or referral of the patient to a center with mechanical circulatory support should be undertaken to minimize the dose and timing of vasoactive drug use in patients with (I, A) (Chu et al., 2021; Li et al., 2019; Rajagopal et al., 2010) (Table 5).

Inotropic agents increase cardiac contractility and decrease LV filling pressure to improve LV function. Levosimendan, as a calcium sensitizer, has selective sensitizing effects on systolic Ca^{2+}, thereby increasing cardiac contractility and improving diastolic function (Bouchez et al., 2018; Farmakis et al., 2016). But levosimendan still increases myocardial oxygen consumption and is not recommended but may be considered in the recovery period (Apostolopoulou et al., 2018; Busani et al., 2012; Latva-Hirvelä et al., 2009; Parissis and Filippatos, 2009; Schweigmann et al., 2011). The administration of levosimendan increases the success rate of device weaning from ECMO in patients on mechanical circulatory support with ECMO alone (IIa, C) (Affronti et al., 2013; Cholley et al., 2019; Vally et al., 2019) (Table 5).

Digitalis is the most commonly used inotropic agent in our country, with a small number of individual case reports, but it should be used with caution (IIa, C) (Caforio and McKenna, 1996; Dehtiar et al., 2001; Roubille et al., 2013) (Table 5).

Other treatments

General supportive care should be aggressively administered, and the main contents include: (i) the patient should definitely lie in bed for rest, reduce the visitation and interference with the patient, avoid patient emotional irritation and fluctuation. (ii) Patients should be given a light taste, digestible and nutrient rich diet with few meals or by nasogastric feeding tube nutrition. (iii) Nasal cannulae, face mask oxygen, or positive pressure oxygen should be administered. (iv) Drugs that improve myocardial energy metabolism should be administered (Chen et al., 2016). (v) Supplementation with water-soluble and fat soluble vitamins, will help prevent DIC. (vi) Fluid supplementation: the amount of water intake is decided based on urine. Rapid intake of water and rapid discharge of water are strictly prohibited. (vii) Trimetazidine may favour myocardial metabolism (Chen et al., 2016; Chen et al., 2018). (viii) Application of proton pump inhibitors prevent stress ulcers and gastrointestinal bleeding. (ix) Physical cooling, or treatment with glucocorticoids may be used in case of hyperthermia, and nonsteroidal anti-inflammatory drugs are not recommended.

Common complications of fulminant myocarditis and its management

Prevention and treatment of arrhythmias

20%–30% of patients with fulminant myocarditis have comorbid arrhythmias. Such as severe arrhythmia will cause or aggravate hemodynamic disorders, threatening the patient's life. In addition to myocardial inflammation, the most important risk factors that trigger arrhythmias include severe hypotension, hypoxia, and the use of vasoactive drugs such as dopamine, etc. Preventive measures: first, the above triggers need to be eliminated, including: (i) intravenous dexamethasone 10–20 mg immediately after diagnosis; (ii) maintain an appropriate blood pressure, and maintain a map of 60–65 mmHg (not to be overestimated) with small amounts of dopamine and m-hydroxylamine/or norepinephrine when mechanical circulatory support conditions are not available, such as on the way to referral; (iii) mechanical ventilation was given when the patient had shortness of breath; (iv) Reduce dopamine dosage. Treatment of comorbid arrhythmias should follow existing arrhythmia guidelines, and patients' cardiac function and blood pressure levels should also be considered fully to select appropriate drugs or management strategies (Camm et al., 2012; Camm et al., 2010; Dickstein et al., 2010; Hsu et al., 2011; Vardas et al., 2007; Zipes et al., 2006).

(1) Prediction of malignant arrhythmias. The presence of sinus bradycardia, widened QRS, dynamic changes on ECG, worsening left ventricular function on echocardiography, persistently elevated or fluctuating cardiac troponin levels, or the presence of non sustained VT often heralds the development of malignant arrhythmias (Chen et al., 2020c).

(2) Treatment of tachyarrhythmias. (i) Tachyarrhythmias that affect hemodynamics, such as AF, atrial flutter, and tachypacing, VT, and VF, should be rapidly identified and managed to correct the hemodynamic disturbances. In those with hemodynamic impairment due to above arrhythmias, electrical cardioversion should be administered immediately, along with drugs to prevent recurrence such as intravenous amiodarone; Those who do not correct or recur after electrical cardioversion should be offered early treatment with extracorporeal mechanical circulatory support with the goal of stabilizing hemodynamics and improving symptoms (IIa, C).

(ii) For hemodynamically relatively stable arrhythmias such as frequent ventricular extrasystoles, appropriate treatment strategies and anti arrhythmic drugs are selected based on clinical symptoms, cardiac functional status, and the nature of the arrhythmia; Myocarditis patients are often complicated by cardiac dysfunction, and patients with tachyarrhythmias are not suitable for antiarrhythmic drugs with negative inotropic properties, such as nondihydropyridine calcium channel blockers and others; Rapid and short acting β-blocker therapy may be tried intravenously in case of tachycardia or VT, ventricular fibrillation, suspected sympathetic hyperactivation or sympathetic storm (IIa, C).

(3) Treatment of bradyarrhythmias. Temporary pacemakers should be installed immediately in patients with marked bradycardia or conduction block, if temporary pacemaker for placement are not available, slow intravenous pumping with isoproterenol should be used temporarily, but dose control is required to prevent induction of tachyarrhythmia (JCS Joint

Working Group, 2011). Slow type arrhythmias can recover in the vast majority of myocarditis patients, and implantation of a permanent pacemaker is not recommended in the acute phase (III, C). In rare patients in whom conduction block has not recovered after 2 weeks of stable disease, implantation of a permanent pacemaker should be considered; In patients who develop ventricular fibrillation during the acute phase, an implantable cardioverter defibrillator (ICD) is not recommended.

Prevention and treatment of DIC

Patients are highly prone to severe coagulopathy due to shock, inflammatory storm and combined liver injury. So fulminant myocarditis combined with DIC is common, and it is a common cause of patient death. Clinically, it has been observed that delayed diagnosis and treatment of fulminant myocarditis, prolonged shock, recurrent cardiac arrest, and prolonged use of blood pressure medications such as norepinephrine are all risk factors for DIC. Effective preventive measures include: (i) early diagnosis and prompt treatment to effectively correct cardiogenic shock and curb inflammatory storm; (ii) early daily monitoring of coagulation, and timely detection of DIC aura; (iii) DIC is associated with recurrent cardiac arrest, circulatory instability, sympathoexcitation and should be corrected; (iv) try to avoid prolonged and high-dose use of blood pressure increasing drugs such as norepinephrine, m-hydroxylamine and pituitrin, which aggravate hepatic ischemia and inflammation and promote hepatic necrosis and irreversible DIC; (v) all patients with DIC are recommended to be treated immediately with fresh plasma, cryoprecipitate and platelet transfusion, or artificial liver in addition to glucocorticoids and immunoglobulins (Hu and Mei, 2017).

Prevention and treatment of systemic capillary leak syndrome

Systemic capillary leak syndrome (SCLS) is also known as hyperleak syndrome, multisystem inflammatory syndrome. SCLS is a relatively common fatal complication in hematological disorders and their targeted therapies and in septic cardiomyopathy, but occurs sporadically in fulminant myocarditis. The mechanism of SCLS is associated with an inflammatory storm, in which damage to the vascular endothelium by cytokines leads to leakage of plasma and proteins into the interstitial space and body cavity, whereupon hypovolemic shock, tissue and organ edema, hemoconcentration, and refractory hypoalbuminemia occur, and severe edema can occur in the myocardium, and its occurrence is associated with a severe inflammatory storm that fails to be recognized and treated promptly. Therefore, effective preventive measures are early detection and diagnosis of fulminant myocarditis, and timely treatment according to the treatment regimen introduced in this guideline, suppressing the inflammatory storm. SCLS can be corrected in the vast majority of patients, after effective treatment, whereas patients with severe forms of SCLS require special attention. On the basis of mechanical support and immunomodulatory therapy, glucocorticoids and immunoglobulins need to be increased, plasma needs to be supplemented, and high molecular weight hydroxyethyl starch injection needs to be used to help restore blood volume (Heradstveit et al., 2010); in addition, treatments such as Anti-IL-6 monoclonal antibodies (such as tocilizumab) may be helpful.

Prevention of infection: use of antibiotics

In principle, antibiotics are not used in patients with fulminant myocarditis, but larger doses of glucocorticoids are used, and some patients have significant pulmonary congestion or endotracheal intubation and endovascular intervention (IABP or IABP+ECMO), etc., therefore, broad-spectrum antibiotics are recommended for infection prevention. However, ongoing evaluation is recommended, and if not complicated by infection, discontinuation of antibiotics is required after removal of the circulatory support system.

If an infection has already occurred, it should be treated aggressively with respect to pathogen culture and susceptibility test results, at which point early and adequate administration of antibiotics and empirical medication should be followed by the principle of "step-down" to mitigate the infection from damage to the microcirculatory system as early as possible; Ideally, antibiotics should be administered within 1 h. During the course of anti infection, dynamic evaluation should be continued, and the source of infection should be sought quickly and the focus of infection should be controlled so that the treatment strategy can be adjusted at any time (Association PMG of CB of CM et al., 2017).

Do not rely solely on procalcitonin levels to decide whether to initiate antibiotics in patients with fulminant myocarditis, particularly when suspected of having comorbid sepsis, septic shock, or rely on clinical assessment alone; In cases where the patient has sufficient evidence of infection, but the optimal course of antibiotics cannot be clearly defined, reference to the procalcitonin level and the clinical situation is recommended to decide on antibiotic administration rather than relying on the clinical situation alone. For patients without high risk of multi drug resistance (MDR), combination therapy is not recommended; When the pathogenic bacteria are clear, drug susceptibility is clear, and combination medication is not recommended; Routine use of antifungals is not recommended (IIa, C) (Evans et al., 2021).

Treatment and follow-up of the convalescent phase of fulminant myocarditis

Patients with fulminant myocarditis recover before and after discharge from hospital, and the myocardium remains inflamed and edematous to varying degrees, which can present with left ventricular enlargement, arrhythmias and cardiac dysfunction, even progressing to inflammatory cardiomyopathy (Schultheiss et al., 2019; Tschöpe et al., 2021). After patients with fulminant myocarditis are discharged from the hospital, rehabilitation period treatment and long-term follow-up are needed to help cardiac function recover and prevent the occurrence of complications.

Rehabilitation period treatment

Assessment and classification

Patients with fulminant myocarditis require a regular and adequate assessment before and after discharge (e.g., Table 6) regarding clinical presentation, biomarkers, resting ECG, 24h Holter, cardiac ultrasound, EMB if necessary, or cardiac magnetic resonance, etc (Ammirati et al., 2018a; Schwaab et al., 2022). Based on the evaluation contents, patients discharged from the

https://doi.org/10.1007/s11427-023-2421-0

Table 6. Evaluation content of fulminant myocarditis

Evaluation methods	Evaluation contents	Evaluation purposes
Clinical presentation and physical examination	NYHA cardiac function grade, chest pain, clinical manifestations of infection, fatigue, palpitations, peripheral edema, pulmonary rales, blood pressure, heart rate, temperature, respiratory rate	Assessment of the signs or symptoms of HF
Resting ECG	Arrhythmia, conduction or repolarization abnormalities	Assessment of cardiac electrophysiology
24 h Holter ECG	Sinus tachycardia or bradycardia, paroxysmal atrial fibrillation, frequent premature atrial or ventricular complexes, intermittent bundle branch block, high degree atrioventricular block, and heart rate variability	Assessment of cardiac electrophysiology
Biomarkers	Troponin, CK-MB, C-reactive protein, BNP, or NT proBNP	Assessment of myocardial injury, HF, inflammation
Cardiac ultrasound	Ventricle size, atrium size, interventricular septum thickness, left ventricular systolic function, left ventricular diastolic function, global longitudinal strain, pericardial effusion	Assessment of cardiac structure and ejection function

hospital can be classified as healed myocarditis, healing myocarditis, and persistence myocarditis (Ammirati et al., 2020; Schwaab et al., 2022). Evaluation parameters were largely normal in patients with healed myocarditis; some of the indices assessed in the patients with healing myocarditis were not normal but had improved significantly; there was no significant improvement in cardiac structure and function in patients with persistence myocarditis. EMB and cardiac magnetic resonance can reflect myocardial edema, inflammation, necrosis, fibrosis, and guide the treatment of patients in the rehabilitation period (Aquaro et al., 2019; Greulich et al., 2020; Li et al., 2021c).

Pharmacotherapy

Treatment options should be determined based on the type of myocarditis pathology. For patients with giant cell myocarditis, eosinophilic myocarditis, sarcoidosis myocarditis and immune checkpoint inhibitor related myocarditis, hormones or immunosuppressive agents can improve the patient's symptoms after discharge (Brambatti et al., 2017; Ekström et al., 2016; Ganesan et al., 2020) (I, B). Hormone therapy improves cardiac function in chronic lymphocytic myocarditis without viral infection as suggested by EMB (Frustaci et al., 2009; Merken et al., 2018; Torre-Amione et al., 2008) (I, B). Oral hormones improve myocardial inflammatory edema in patients with discharge myocardial injury markers persistently above normal values or cardiac magnetic resonance suggestive of myocardial inflammatory edema (IIa, C) (Ammirati et al., 2021; Liu et al., 2021a). Oral treatment with angiotensin-converting enzyme inhibitors, β receptor blockers, and trimetazidine is recommended for all patients; for patients presenting with signs and symptoms of arrhythmia, normative pharmacotherapy may be administered according to the relevant guidelines (I, C) (Al-Khatib et al., 2018; Caforio et al., 2013; Ponikowski et al., 2016). Patients with myocarditis who have received standard anti HF therapy, but whose heart failure symptoms persist, require an EMB to gain further insight into the type of myocarditis pathology (I, C) and to decide whether immunosuppressive therapy is added (Figure 5).

Nonpharmacologic interventions

Patients with giant cell myocarditis have a high risk of ventricular tachycardia (Cooper et al., 1997), and ICD implantation is recommended to prevent sudden death (Al-Khatib et al., 2018) (I, C). Patients with chronic myocarditis in whom medications fail to improve cardiac function should undergo long-term mechanical circulatory assistance or heart transplantation (Kociol et al., 2020) (I, C).

Exercise based cardiac rehabilitation

Moderate to high intensity exercise is not recommended for all fulminant myocarditis patients within 3–6 months of discharge (III, B) (Caforio et al., 2013; Kociol et al., 2020). Before undergoing cardiac rehabilitation, all patients should be evaluated again with comprehensive examinations, including cardiac magnetic resonance, Holter, exercise stress test, for exercise related sudden death risk assessment (I, B). In patients with inflammation and scarring of the myocardium and persistent LV dysfunction suggested by cardiac magnetic resonance, moderate- to high-intensity exercise is not recommended (Caforio et al., 2013). In patients with healed myocarditis, exercise based cardiac rehabilitation is acceptable after 6 months of the acute phase (IIa, B) (Schwaab et al., 2022). Exercise intensity should begin at low intensity, and assessments of clinical manifestations, electrocardiograms, biomarkers, as well as echocardiography should be performed regularly during cardiac rehabilitation (I, C) (Schwaab et al., 2022).

Long term follow up

Patients with fulminant myocarditis can fully recover after discharge and can also develop persistent cardiac dysfunction and even progress to inflammatory cardiomyopathy. All patients with fulminant myocarditis should be followed up long-term after discharge (I, C) (Schwaab et al., 2022) (Table 7). The follow-up contents included clinical symptoms and signs, cardiac ultrasound, electrocardiogram, cTnI, NT proBNP, inflammatory indicators such as cytokines, CMRI, and EMB if necessary in order to promptly detect abnormalities of cardiac structure and function and prevent the occurrence of complications.

Unresolved issues need further researches in future: although the treatment regimen recommended in the guidelines is greatly achieved, small proportion of patients (approximately 5%) have poor response to the treatments, and we need to develop new drugs and methods to treat them. Approximately a quarter of discharged patients under this regimen have cardiac dilation, heart failure or arrhythmias during one year follow-up and we have no good way to improve them though long-term outcome is much better than that by traditional treatments. Most importantly, we are lack of understanding of detaled pathophisiologic mechanisms of the lethal disease, such as how it triggers, what key molecule(s) play and then we may block it or eraly diagnose based on the early biomarker, and which cytokines play key roles during development of cytokine storm and then we may target it to miligate inflammation; we need to understand mechanism of

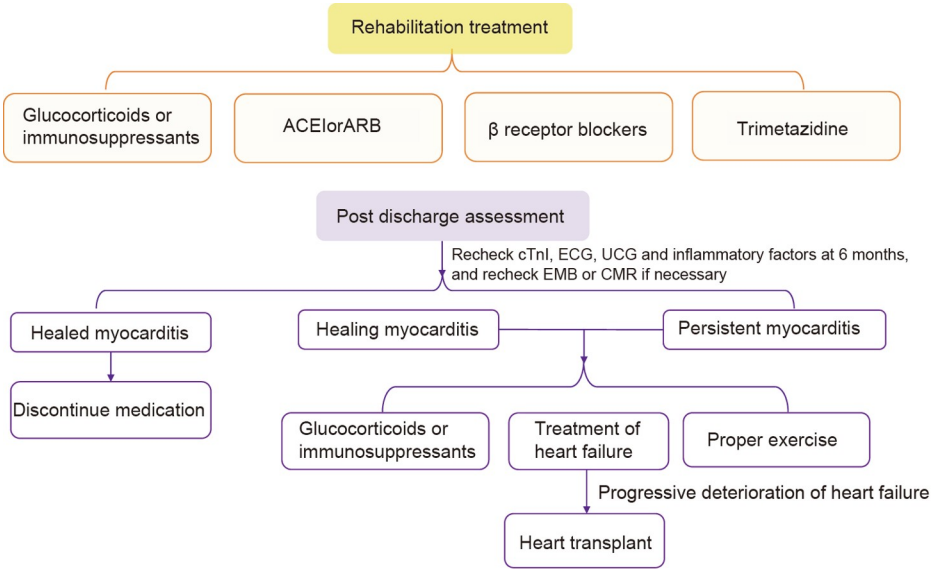

Figure 5. Flow chart of rehabilitation treatment for patients with myocarditis. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor antagonist; cTnI, cardiac troponin I; ECG, electrocardiogram; UCG, echocardiography; CMRI, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy. All patients with myocarditis need to rest 3–6 months after onset, avoid exercise, treat as chronic heart failure, and take glucocorticoid, ACEI/ARB, β receptor blockers, and trimetazidine orally. At the 6th month after discharge, the changes of myocardial enzymes, electrocardiogram, color Doppler ultrasound and inflammatory factors were comprehensively evaluated. If necessary, cardiac magnetic resonance imaging and percutaneous endomyocardial biopsy were rechecked to investigate the cardiac structure, myocardial edema and fibrosis. If the patient recovers, it is recommended to stop taking the medicine; patients with high cTnI levels need to continue to take glucocorticoids or immunosuppressants. If the patient's symptoms or test results continue to not recover, endocardial biopsy may be considered to further clarify the pathological changes of the heart. For patients with decreased cardiac function, it is recommended to refer to the treatment of chronic heart failure for cardiac rehabilitation; patients with progressive heart failure were treated with heart transplantation.

Table 7. Long term follow-up of fulminant myocarditis

Recommend	Level of recommendation	Level of evidence
Patients with fulminant myocarditis require a regular and adequate evaluation (e.g., Table 6) after discharge for clinical manifestations, biomarkers, resting ECG, 24 h Holter, cardiac ultrasound Doppler, cardiac magnetic resonance, etc (Schwaab et al., 2022).	I	C
Moderate to high intensity exercise should be avoided in all patients with fulminant myocarditis within 3–6 months of hospital discharge (Kociol et al., 2020).	III	B
Patients with "healing myocarditis" and "healed myocarditis", who may benefit from cardiac exercise rehabilitation training (Schwaab et al., 2022).	I	C
Patients with myocarditis who are in the acute phase (typical symptoms, increased levels of markers, and abnormal cardiac ultrasound findings) are contraindicated for exercise training for cardiac rehabilitation (Schwaab et al., 2022).	III	C
Hormones or immunosuppressive agents can improve symptoms in patients with giant cell myocarditis, eosinophilic myocarditis, and nodular myocarditis and in patients with immune checkpoint inhibitor associated myocarditis after discharge (Kandolin et al., 2013; Birnie et al., 2016; Esfahani et al., 2019; Brambatti et al., 2017; Chen et al., 2020a; Sury et al., 2018; Basso, 2022; Ammirati and Moslehi, 2023).	I	B
Hormone and immunosuppressant therapy improves cardiac function in patients with chronic lymphocytic myocarditis without viral infection as suggested by EMB (Frustaci et al., 2009).	I	B
Hormone therapy improves myocardial inflammation in patients with endomyocardial biopsy confirmed or clinically suspected viral infective myocarditis, and markers of myocardial injury persist above normal values after hospital discharge or in patients with inflammation suggestive of myocardial oedema on cardiac magnetic resonance (Liu et al., 2021a).	IIa	C

chronicity of this disease. All these issues require further research in recent future.

Compliance and ethics

The formulation of this guideline was entrusted and assigned by the Chinese Society of Cardiology, undertaken by the Emergency and Critical Care Group of the Chinese Society of Cardiology, and written and discussed by senior experts and clinical front-line experts from multiple medical centers and disciplines across the country, including the Department of Cardiology, Department of Critical Care Medicine, Department of Pathology, Department of Rehabilitation, and Department of Imaging. The preparation of this guideline is supported by the Chinese Medical Association and the National Natural Science Foundation of China, and there is no commercial conflict of interest.

Acknowledgement

This work was supported in part by the National Natural Science Foundation of China (81790624, 81630010) and Top-Notch Talent Program of Hubei Province and Tongji Hospital (2021YBJRC005). We thank all the menbers of secretary group for their hard work: Zheng Wen, Luyun Wang, Houjuan Zuo, Kun Miao, Hongyang Shu, Jiahui Fan.

References

Affronti, A., di Bella, I., Carino, D., and Ragni, T. (2013). Levosimendan may improve weaning outcomesin venoarterial ECMO patients. ASAIO J 59, 554–557.

Al-Khatib, S.M., Stevenson, W.G., Ackerman, M.J., Bryant, W.J., Callans, D.J., Curtis, A.B., Deal, B.J., Dickfeld, T., Field, M.E., Fonarow, G.C., et al. (2018). 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Heart Rhythm 15, e73–e189.

Albert, C.L., Carmona-Rubio, A.E., Weiss, A.J., Procop, G.G., Starling, R.C., and Rodriguez, E.R. (2020). The enemy within: sudden-onset reversible cardiogenic shock with biopsy-proven cardiac myocyte infection by severe acute respiratory syndrome coronavirus 2. Circulation 142, 1865–1870.

Ammirati, E., Cipriani, M., Lilliu, M., Sormani, P., Varrenti, M., Raineri, C., Petrella, D., Garascia, A., Pedrotti, P., Roghi, A., et al. (2017a). Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. Circulation 136, 529–545.

Ammirati, E., Cipriani, M., Moro, C., Raineri, C., Pini, D., Sormani, P., Mantovani, R., Varrenti, M., Pedrotti, P., Conca, C., et al. (2018a). Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis. Circulation 138, 1088–1099.

Ammirati, E., Frigerio, M., Adler, E.D., Basso, C., Birnie, D.H., Brambatti, M., Friedrich, M.G., Klingel, K., Lehtonen, J., Moslehi, J.J., et al. (2020). Management of acute myocarditis and chronic inflammatory cardiomyopathy. Circ Heart Fail 13, e007405.

Ammirati, E., Moroni, F., Sormani, P., Peritore, A., Milazzo, A., Quattrocchi, G., Cipriani, M., Oliva, F., Giannattasio, C., Frigerio, M., et al. (2017b). Quantitative changes in late gadolinium enhancement at cardiac magnetic resonance in the early phase of acute myocarditis. Int J Cardiol 231, 216–221.

Ammirati, E., and Moslehi, J.J. (2023). Diagnosis and treatment of acute myocarditis. JAMA 329, 1098–1113.

Ammirati, E., Pedrotti, P., and Roghi, A. (2016). Nondilated left ventricle as an adding clue helping discrimination between acute myocarditis from other cardiomyopathies. J Am Coll Cardiol 68, 1817–1818.

Ammirati, E., Veronese, G., Bottiroli, M., Wang, D.W., Cipriani, M., Garascia, A., Pedrotti, P., Adler, E.D., and Frigerio, M. (2021). Update on acute myocarditis. Trends Cardiovasc Med 31, 370–379.

Ammirati, E., Veronese, G., Brambatti, M., Merlo, M., Cipriani, M., Potena, L., Sormani, P., Aoki, T., Sugimura, K., Sawamura, A., et al. (2019). Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 74, 299–311.

Ammirati, E., Veronese, G., Cipriani, M., Moroni, F., Garascia, A., Brambatti, M., Adler, E.D., and Frigerio, M. (2018b). Acute and fulminant myocarditis: a pragmatic clinical approach to diagnosis and treatment. Curr Cardiol Rep 20, 114.

Amraotkar, A.R., Pachika, A., Grubb, K.J., and DeFilippis, A.P. (2016). Rapid extracorporeal membrane oxygenation overcomes fulminant myocarditis induced by 5-fluorouracil. Texas Heart Inst J 43, 178–182.

Annamalai, S.K., Esposito, M.L., Jorde, L., Schreiber, T., A. Hall, S., O'Neill, W.W., and Kapur, N.K. (2018). The impella microaxial flow catheter is safe and effective for treatment of myocarditis complicated by cardiogenic shock: an analysis from the Global cVAD Registry. J Cardiac Fail 24, 706–710.

Antonelli, M., Conti, G., Bufi, M., Costa, M.G., Lappa, A., Rocco, M., Gasparetto, A., and Meduri, G.U. (2000). Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation. JAMA 283, 235–241.

Apostolopoulou, S.C., Vagenakis, G.A., Tsoutsinos, A., Kakava, F., and Rammos, S. (2018). Ambulatory intravenous inotropic support and or levosimendan in pediatric and congenital heart failure: safety, survival, improvement, or transplantation. Pediatr Cardiol 39, 1315–1322.

Aquaro, G.D., Ghebru Habtemicael, Y., Camastra, G., Monti, L., Dellegrottaglie, S., Moro, C., Lanzillo, C., Scatteia, A., Di Roma, M., Pontone, G., et al. (2019). Prognostic value of repeating cardiac magnetic resonance in patients with acute myocarditis. J Am Coll Cardiol 74, 2439–2448.

Aretz, H.T. (1987). Myocarditis: The Dallas criteria. Hum Pathol 18, 619–624.

Asaumi, Y., Yasuda, S., Morii, I., Kakuchi, H., Otsuka, Y., Kawamura, A., Sasako, Y., Nakatani, T., Nonogi, H., and Miyazaki, S. (2005). Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. Eur Heart J 26, 2185–2192.

Association PMG of CB of CM, Cardiology EC of CJ, and Cardiomyositis WG of AO. (2017). Chinese expert consensus on diagnosis and treatment of adult fulminant myocarditis (in Chinese). Chin J Cardiovasc Dis 45, 742–752.

Association SMB of CM. (2007). Guidelines for the diagnosis and treatment of acute lung injury/acute respiratory distress syndrome (2006) (in Chinese). Chin J Emerg Med 16, 343–349.

Ball, S., Ghosh, R.K., Wongsaengsak, S., Bandyopadhyay, D., Ghosh, G.C., Aronow, W.S., Fonarow, G.C., Lenihan, D.J., and Bhatt, D.L. (2019). Cardiovascular toxicities of immune checkpoint inhibitors. J Am Coll Cardiol 74, 1714–1727.

Basso, C. (2022). Myocarditis. N Engl J Med 387, 1488–1500.

Bennett, M.K., Gilotra, N.A., Harrington, C., Rao, S., Dunn, J.M., Freitag, T.B., Halushka, M.K., and Russell, S.D. (2013). Evaluation of the role of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000–2009. Circ Heart Fail 6, 676–684.

Birnie, D.H., Nery, P.B., Ha, A.C., and Beanlands, R.S.B. (2016). Cardiac sarcoidosis. J Am Coll Cardiol 68, 411–421.

Bogaty, P. (2017) Beating, fast and slow. N Engl J Med 377, 1305.

Bouchez, S., Fedele, F., Giannakoulas, G., Gustafsson, F., Harjola, V.P., Karason, K., Kivikko, M., von Lewinski, D., Oliva, F., Papp, Z., et al. (2018). Levosimendan in acute and advanced heart failure: an expert perspective on posology and therapeutic application. Cardiovasc Drugs Ther 32, 617–624.

Boyd, J., Mathur, S., Wang, Y., Bateman, R., and Walley, K. (2006). Toll-like receptor stimulation in cardiomyoctes decreases contractility and initiates an NF-κB dependent inflammatory response. Cardiovasc Res 72, 384–393.

Bozkurt, B., Colvin, M., Cook, J., Cooper, L.T., Deswal, A., Fonarow, G.C., Francis, G.S., Lenihan, D., Lewis, E.F., McNamara, D.M., et al. (2016). Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. Circulation 134.

Brambatti, M., Matassini, M.V., Adler, E.D., Klingel, K., Camici, P.G., and Ammirati, E. (2017). Eosinophilic myocarditis. J Am Coll Cardiol 70, 2363–2375.

Bratincsák, A., El-Said, H.G., Bradley, J.S., Shayan, K., Grossfeld, P.D., and Cannavino, C.R. (2010). Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. J Am Coll Cardiol 55, 928–929.

Bristow, M.R., Thompson, P.D., Martin, R.P., Mason, J.W., Billingham, M.E., and Harrison, D.C. (1978). Early anthracycline cardiotoxicity. Am J Med 65, 823–832.

Bulut, D., Scheeler, M., Wichmann, T., Börgel, J., Miebach, T., and Mügge, A. (2010). Effect of protein A immunoadsorption on T cell activation in patients with inflammatory dilated cardiomyopathy. Clin Res Cardiol 99, 633–638.

Busani, S., Pasetto, A., Ligabue, G., Malavasi, V., Lugli, R., and Girardis, M. (2012). Levosimendan in a case of severe peri-myocarditis associated with influenza A/H1N1 virus. Br J Anaesthesia 109, 1011–1013.

Bygren, P., Freiburghaus, C., Lindholm, T., Simonsen, O., Thysell, H., and Wieslander, J. (1985). Goodpasture's syndrome treated with staphylococcal protein a immunoadsorption. Lancet 326, 1295–1296.

Caforio, A.L.P., and McKenna, W.J. (1996). Recognition and optimum management of myocarditis. Drugs 52, 515–525.

Caforio, A.L.P., Adler, Y., Agostini, C., Allanore, Y., Anastasakis, A., Arad, M., Böhm, M., Charron, P., Elliott, P.M., Eriksson, U., et al. (2017). Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Eur Heart J 38, 2649–2662.

Caforio, A.L.P., Calabrese, F., Angelini, A., Tona, F., Vinci, A., Bottaro, S., Ramondo, A., Carturan, E., Iliceto, S., Thiene, G., et al. (2007). A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J 28, 1326–1333.

Caforio, A.L.P., Pankuweit, S., Arbustini, E., Basso, C., Gimeno-Blanes, J., Felix, S.B., Fu, M., Helio, T., Heymans, S., Jahns, R., et al. (2013). Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 34, 2636–2648.

Çalık, A.N., Çeliker, E., Velibey, Y.ı., Çağdaş, M., and Güzelburç, Ö. (2012). Initial dose effect of 5-fluorouracil: rapidly improving severe, acute toxic myopericarditis. Am J Emerg Med 30, 257.e1–257.e3.

Camm, A.J., Kirchhof, P., Lip, G.Y.H., Schotten, U., Savelieva, I., Ernst, S., Van Gelder, I.C., Al-Attar, N., Hindricks, G., Prendergast, B., et al. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 31, 2369–2429.

Camm, A.J., Lip, G.Y.H., De Caterina, R., Savelieva, I., Atar, D., Hohnloser, S.H., Hindricks, G., Kirchhof, P., Bax, J.J., Baumgartner, H., et al. (2012). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 33, 2719–2747.

Cardenas, V.J., and Lynch, J.E. (2006). Mechanical ventilation and acute respiratory distress syndrome. Semin Thorac Cardiovasc Surg 18, 8–12.

Casella, M., Dello Russo, A., Bergonti, M., Catto, V., Conte, E., Sommariva, E., Gasperetti, A., Vettor, G., Tundo, F., Sicuso, R., et al. (2020). Diagnostic yield of electroanatomic voltage mapping in guiding endomyocardial biopsies. Circulation 142, 1249–1260.

Chammas, J., Delaney, D., Chabaytah, N., Abdulkarim, S., and Schwertani, A. (2021). COVID-19 and the cardiovascular system: insights into effects and treatments. Can J Physiol Pharmacol 99, 1119–1127.

Chen, C., Li, H., Hang, W., and Wang, D.W. (2020a). Cardiac injuries in coronavirus disease 2019 (COVID-19). J Mol Cell Cardiol 145, 25–29.

Chen, C., Zhou, Y., and Wang, D.W. (2020b). SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz 45, 230–232.

Chen, H.S., Wang, W., Wu, S.N., and Liu, J.P. (2013). Corticosteroids for viral myocarditis. Cochrane Database Syst Rev 2013, CD004471.

Chen, J., Chen, S., Li, Z., Zhou, P., Huang, W., Wang, H., Shi, J., Ni, Y., Lin, L., and Lei, Y. (2020c). Role of electrocardiograms in assessment of severity and analysis of the characteristics of ST elevation in acute myocarditis: A two-centre study. Exp Ther Med 20, 1.

Chen, J., Lai, J., Yang, L., Ruan, G., Chaugai, S., Ning, Q., Chen, C., and Wang, D.W. (2016). Trimetazidine prevents macrophage-mediated septic myocardial dysfunc-

tion via activation of the histone deacetylase sirtuin 1. Br J Pharmacol 173, 545–561.
Chen, J., Wang, B., Lai, J., Braunstein, Z., He, M., Ruan, G., Yin, Z., Wang, J., Cianflone, K., Ning, Q., et al. (2018). Trimetazidine attenuates cardiac dysfunction in endotoxemia and sepsis by promoting neutrophil migration. Front Immunol 9, 2015.
Cholley, B., Levy, B., Fellahi, J.L., Longrois, D., Amour, J., Ouattara, A., and Mebazaa, A. (2019). Levosimendan in the light of the results of the recent randomized controlled trials: an expert opinion paper. Crit Care 23, 385.
Chong, S.Z., Fang, C.Y., Fang, H.Y., Chen, H.C., Chen, C.J., Yang, C.H., Hang, C.L., Yip, H.K., Wu, C.J., and Lee, W.C. (2018). Associations with the in-hospital survival following extracorporeal membrane oxygenation in adult acute fulminant myocarditis. J Clin Med 7, 452.
Chu, S., Sun, P., Zhang, Y., Li, J., Liu, L., Shi, Y., Wang, H., Chen, H., Fu, M., and Huo, Y. (2021). Intra-aortic balloon pump on in-hospital outcomes of cardiogenic shock: findings from a nationwide registry, China. ESC Heart Fail 8, 3286–3294.
Colombo, D., Albore, M., Del Nonno, F., Bolino, G., D'Ambrosio, M., Salvi, A., Cecannecchia, C., and Falasca, L. (2022). Fatal fulminant HSV-2 myocarditis: A complicated presentation. Int J Infect Dis 114, 124–127.
Combes, A., Price, S., Slutsky, A.S., and Brodie, D. (2020). Temporary circulatory support for cardiogenic shock. Lancet 396, 199–212.
Cooper, L.T., Baughman, K.L., Feldman, A.M., Frustaci, A., Jessup, M., Kuhl, U., Levine, G.N., Narula, J., Starling, R.C., Towbin, J., et al. (2007). The role of endomyocardial biopsy in the management of cardiovascular disease: A Scientific Statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. Eur Heart J 28, 3076–3093.
Cooper, L.T. (2009). Myocarditis. N Engl J Med 360, 1526–1538.
Cooper, L.T. (2017). When lightning strikes. Circulation 136, 546–548.
Cooper, L.T., Berry, G.J., and Shabetai, R. (1997). Idiopathic giant-cell myocarditis—natural history and treatment. N Engl J Med 336, 1860–1866.
Coronado, M.J., Bruno, K.A., Blauwet, L.A., Tschöpe, C., Cunningham, M.W., Pankuweit, S., van Linthout, S., Jeon, E., McNamara, D.M., Krejčí, J., et al. (2019). Elevated sera sST2 is associated with heart failure in men ≤50 years old with myocarditis. J Am Heart Assoc 8, e008968.
Crowell, R.L., and Landau, B.J. (1997). A short history and introductory background on the coxsackieviruses of group B. Curr Top Microbiol Immunol 223, 1–11.
Dai, H., Lotan, D., Much, A.A., Younis, A., Lu, Y., Bragazzi, N.L., and Wu, J. (2021). Global, regional, and national burden of myocarditis and cardiomyopathy, 1990–2017. Front Cardiovasc Med 8, 610989.
Dai, M.Y., Yan, Y.C., Wang, L.Y., Zhao, C.X., Wang, D.W., and Jiang, J.G. (2023). Characteristics of electrocardiogram findings in fulminant myocarditis. J Cardiovasc Dev Dis 10, 280.
Daubin, C., Valette, X., Thiollière, F., Mira, J.P., Hazera, P., Annane, D., Labbe, V., Floccard, B., Fournel, F., Terzi, N., et al. (2018). Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. Intensive Care Med 44, 428–437.
Dehtiar, N., Eherlichman, M., Picard, E., Kleid, D., Glaser, J., Raveh, D., and Schlesinger, Y. (2001). Cytomegalovirus myocarditis in a healthy infant: Complete recovery after ganciclovir treatment. Pediatr Crit Care Med 2, 271–273.
Dennert, R., Crijns, H.J., and Heymans, S. (2008). Acute viral myocarditis. Eur Heart J 29, 2073–2082.
Dickstein, K., Vardas, P.E., Auricchio, A., Daubert, J.C., Linde, C., McMurray, J., Ponikowski, P., Priori, S.G., Sutton, R., van Veldhuisen, D.J., et al. (2010). 2010 Focused Update of ESC Guidelines on device therapy in heart failure: An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J 31, 2677–2687.
Du, Y., Tu, L., Zhu, P., Mu, M., Wang, R., Yang, P., Wang, X., Hu, C., Ping, R., Hu, P., et al. (2020). Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med 201, 1372–1379.
Du, Z., Jia, Z., Wang, J., Xing, Z., Jiang, C., Xu, B., Yang, X., Yang, F., Miao, N., Xing, J., et al. (2018). Effect of increasing mean arterial blood pressure on microcirculation in patients with cardiogenic shock supported by extracorporeal membrane oxygenation. Clin Hemorheol Microcirc 70, 27–37.
Ekström, K., Lehtonen, J., Kandolin, R., Räisänen-Sokolowski, A., Salmenkivi, K., and Kupari, M. (2016). Long-term outcome and its predictors in giant cell myocarditis. Eur J Heart Fail 18, 1452–1458.
Esfahani, K., Buhlaiga, N., Thébault, P., Lapointe, R., Johnson, N.A., and Miller, W.H. (2019). Alemtuzumab for immune-related myocarditis due to PD-1 therapy. N Engl J Med 380, 2375–2376.
Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C.M., French, C., Machado, F.R., Mcintyre, L., Ostermann, M., Prescott, H.C., et al. (2021). Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 47, 1181–1247.
Farmakis, D., Alvarez, J., Gal, T.B., Brito, D., Fedele, F., Fonseca, C., Gordon, A.C., Gotsman, I., Grossini, E., Guarracino, F., et al. (2016). Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper. Int J Cardiol 222, 303–312.
Felix, S.B., Beug, D., and Dörr, M. (2015). Immunoadsorption therapy in dilated cardiomyopathy. Expert Rev Cardiovasc Ther 13, 145–152.
Felix, S.B., Staudt, A., Dörffel, W.V., Stangl, V., Merkel, K., Pohl, M., Döcke, W.D., Morgera, S., Neumayer, H.H., Wernecke, K.D., et al. (2000). Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy. J Am Coll Cardiol 35, 1590–1598.
Felker, G.M., Boehmer, J.P., Hruban, R.H., Hutchins, G.M., Kasper, E.K., Baughman, K.L., and Hare, J.M. (2000). Echocardiographic findings in fulminant and acute myocarditis. J Am Coll Cardiol 36, 227–232.
Ferreira, V.M., Schulz-Menger, J., Holmvang, G., Kramer, C.M., Carbone, I., Sechtem, U., Kindermann, I., Gutberlet, M., Cooper, L.T., Liu, P., et al. (2018). Cardiovascular magnetic resonance in nonischemic myocardial inflammation. J Am Coll Cardiol 72, 3158–3176.
Francis, R., and Lewis, C. (2018). Myocardial biopsy: techniques and indications. Heart 104, 950–958.
Friedrich, M.G., Sechtem, U., Schulz-Menger, J., Holmvang, G., Alakija, P., Cooper, L. T., White, J.A., Abdel-Aty, H., Gutberlet, M., Prasad, S., et al. (2009). Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 53, 1475–1487.
Frustaci, A., Russo, M.A., and Chimenti, C. (2009). Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J 30, 1995–2002.
Ganesan, S.K., Venkatratnam, P., Mahendra, J., and Devarajan, N. (2020). Increased mortality of COVID-19 infected diabetes patients: role of furin proteases. Int J Obes 44, 2486–2488.
Gao, C.Y., Zhang, J., Bhat, R.A., and Zhang, J. (2020). Research progress in the application of Impella as a percutaneous mechanical circulatory support (in Chinese). Chin J Hear Fail Cardiomyopathy 4, 217–221.
Gong, T., Liu, L., Jiang, W., and Zhou, R. (2020). DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat Rev Immunol 20, 95–112.
Greulich, S., Seitz, A., Müller, K.A.L., Grün, S., Ong, P., Ebadi, N., Kreisselmeier, K.P., Seizer, P., Bekeredjian, R., Zwadlo, C., et al. (2020). Predictors of mortality in patients with biopsy-proven viral myocarditis: 10-year outcome data. J Am Heart Assoc 9, e015351.
Grimaud, M., Starck, J., Levy, M., Marais, C., Chareyre, J., Khraiche, D., Leruez-Ville, M., Quartier, P., Léger, P.L., Geslain, G., et al. (2020). Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 10, 69.
Guglin, M., Zucker, M.J., Bazan, V.M., Bozkurt, B., El Banayosy, A., Estep, J.D., Gurley, J., Nelson, K., Malyala, R., Panjrath, G.S., et al. (2019). Venoarterial ECMO for adults. J Am Coll Cardiol 73, 698–716.
Gustafsson, F. (2018). Management of patients with cardiogenic shock on temporary mechanical circulatory support: urgent transplantation or on to the next pump? Eur J Heart Fail 20, 187–189.
Haanschoten, D.M., Adiyaman, A., 't Hart, N.A., Jager, P.L., and Elvan, A. (2021). Value of 3D mapping-guided endomyocardial biopsy in cardiac sarcoidosis. Eur J Clin Invest 51, e13497.
Hafezi-Moghadam, A., Simoncini, T., Yang, Z., Limbourg, F.P., Plumier, J.C., Rebsamen, M.C., Hsieh, C.M., Chui, D.S., Thomas, K.L., Prorock, A.J., et al. (2002). Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. Nat Med 8, 473–479.
Hage-Sleiman, M., Derre, N., Verdet, C., Pialoux, G., Gaudin, O., Senet, P., Fartoukh, M., Boissan, M., and Garnier, M. (2019). Meningococcal purpura fulminans and severe myocarditis with clinical meningitis but no meningeal inflammation: a case report. BMC Infect Dis 19, 252.
Hang, W., Chen, C., Seubert, J.M., and Wang, D.W. (2020). Fulminant myocarditis: a comprehensive review from etiology to treatments and outcomes. Sig Transduct Target Ther 5, 287.
Heidecker, B., Williams, S.H., Jain, K., Oleynik, A., Patriki, D., Kottwitz, J., Berg, J., Garcia, J.A., Baltensperger, N., Lovrinovic, M., et al. (2020). Virome sequencing in patients with myocarditis. Circ Heart Fail 13, e007103.
Heidenreich, P.A., Bozkurt, B., Aguilar, D., Allen, L.A., Byun, J.J., Colvin, M.M., Deswal, A., Drazner, M.H., Dunlay, S.M., Evers, L.R., et al. (2022). 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. Circulation 145.

Henry, T.D., Tomey, M.I., Tamis-Holland, J.E., Thiele, H., Rao, S.V., Menon, V., Klein, D.G., Naka, Y., Piña, I.L., Kapur, N.K., et al. (2021). Invasive management of acute myocardial infarction complicated by cardiogenic shock: a scientific statement from the american heart association. Circulation 143, e815.
Heradstveit, B.E., Guttormsen, A., Langørgen, J., Hammersborg, S.M., Wentzel-Larsen, T., Fanebust, R., Larsson, E.M., and Heltne, J.K. (2010). Capillary leakage in post-cardiac arrest survivors during therapeutic hypothermia—a prospective, randomised study. Scand J Trauma Resusc Emerg Med 18, 29.
Heymans, S., Eriksson, U., Lehtonen, J., and Cooper Jr., L.T. (2016). The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol 68, 2348–2364.
Hilbert, G., Gruson, D., Vargas, F., Valentino, R., Gbikpi-Benissan, G., Dupon, M., Reiffers, J., and Cardinaud, J.P. (2001). Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 344, 481–487.
Hsu, K.H., Chi, N.H., Yu, H.Y., Wang, C.H., Huang, S.C., Wang, S.S., Ko, W.J., and Chen, Y.S. (2011). Extracorporeal membranous oxygenation support for acute fulminant myocarditis: analysis of a single center's experience. Eur J Cardio Thoracic Surg doi: 10.1016/j.ejcts.2010.12.050.
Hu, W., Zhou, J., Chen, L., Huang, J., Hu, W., Zhu, Y., and Yuan, T. (2020). Insufficient left ventricular unloading after extracorporeal membrane oxygenation. Herz 45, 186–191.
Hu, Y., and Mei, H. (2017). Consensus of Chinese experts on the diagnosis of disseminated intravascular coagulation (2017 edition) (in Chinese). Chin J Hematol 38, 361–363.
Huang, D.T., Yealy, D.M., Filbin, M.R., Brown, A.M., Chang, C.C.H., Doi, Y., Donnino, M.W., Fine, J., Fine, M.J., Fischer, M.A., et al. (2018). Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med 379, 236–249.
Hufnagel, G., Pankuweit, S., Richter, A., Schönian, U., and Maisch, B. (2000). The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID). Herz 25, 279–285.
Hung, Y., Lin, W.H., Lin, C.S., Cheng, S.M., Tsai, T.N., Yang, S.P., and Lin, W.Y. (2016). The prognostic role of QTc interval in acute myocarditis. Acta Cardiol Sin 32, 223–230.
JCS Joint Working Group (2011). Guidelines for diagnosis and treatment of myocarditis (JCS 2009). Circ J 75, 734–743.
Jensen, L.A., Onyskiw, J.E., and Prasad, N.G.N. (1998). Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. Heart Lung 27, 387–408.
Jensen, L.D., and Marchant, D.J. (2016). Emerging pharmacologic targets and treatments for myocarditis. Pharmacol Ther 161, 40–51.
Jiang, J.G., Liu, C., Cui, G.L., Chen, C., Zuo, H.J., Li, R., and Wang, D.W. (2022). Long term prognosis of fulminant myocarditis and predictors related to impaired cardiac function post discharge (in Chinese). Chin J Cardiovasc 50, 263–269.
Jie, Y.C., Jiang, Y.W., Liang, K.J., Zhou, X.O., Zhang, C.T., Fu, Z., and Zhao, Y.H. (2022). A single center real world study of mechanical circulatory support combined with immunomodulation in the treatment of fulminant myocarditis (in Chinese). Chin J Cardiovasc Dis 50, 277–281.
Johnson, D.B., Balko, J.M., Compton, M.L., Chalkias, S., Gorham, J., Xu, Y., Hicks, M., Puzanov, I., Alexander, M.R., Bloomer, T.L., et al. (2016). Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 375, 1749–1755.
Jones, A.E., Shapiro, N.I., Trzeciak, S., Arnold, R.C., Claremont, H.A., and Kline, J.A. (2010). Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 303, 739–746.
Joshi, R., de Witt, B., and Mosier, J.M. (2014). Optimizing oxygen delivery in the critically Ill: the utility of lactate and central venous oxygen saturation (ScvO2) as a roadmap of resuscitation in shock. J Emerg Med 47, 493–500.
Kandolin, R., Lehtonen, J., Salmenkivi, K., Räisänen-Sokolowski, A., Lommi, J., and Kupari, M. (2013). Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ Heart Fail 6, 15–22.
Karjalainen, J., and Heikkilä, J. (1999). Incidence of three presentations of acute myocarditis in young men in military service. A 20-year experience. Eur Heart J 20, 1120–1125.
Kędziora, A., Piątek, J., Hymczak, H., Wasilewski, G., Guzik, B., Drwiła, R., Kapelak, B., Sobczyk, D., Konstanty-Kalandyk, J., and Wierzbicki, K. (2021). Early postoperative hemodynamic instability after heart transplantation – incidence and metabolic indicators. BMC Anesthesiol 21, 236.
Kennel, P.J., Lumish, H., Kaku, Y., Fried, J., Kirtane, A.J., Karmpaliotis, D., Takayama, H., Naka, Y., Sayer, G., Uriel, N., et al. (2021). A case series analysis on the clinical experience of Impella 5.5® at a large tertiary care centre. ESC Heart Fail 8, 3720–3725.
Kim, S.H., Lilot, M., Sidhu, K.S., Rinehart, J., Yu, Z., Canales, C., and Cannesson, M. (2014). Accuracy and precision of continuous noninvasive arterial pressure monitoring compared with invasive arterial pressure. Anesthesiology 120, 1080–1097.
Kindermann, I., Kindermann, M., Kandolf, R., Klingel, K., Bültmann, B., Müller, T., Lindinger, A., and Böhm, M. (2008). Predictors of outcome in patients with suspected myocarditis. Circulation 118, 639–648.
Klingel, K., Sauter, M., Bock, C.T., Szalay, G., Schnorr, J.J., and Kandolf, R. (2004). Molecular pathology of inflammatory cardiomyopathy. Med Microbiol Immunol 193, 101–107.
Kociol, R.D., Cooper, L.T., Fang, J.C., Moslehi, J.J., Pang, P.S., Sabe, M.A., Shah, R.V., Sims, D.B., Thiene, G., and Vardeny, O. (2020). Recognition and initial management of fulminant myocarditis. Circulation 141, e69.
Kondo, T., Okumura, T., Shibata, N., Imaizumi, T., Dohi, K., Izawa, H., Ohte, N., Amano, T., and Murohara, T. (2022). Differences in prognosis and cardiac function according to required percutaneous mechanical circulatory support and histological findings in patients with fulminant myocarditis: insights from the CHANGE PUMP 2 study. J Am Heart Assoc 11, e023719.
Kopterides, P., Theodorakopoulou, M., Ilias, I., Nikitas, N., Frantzeskaki, F., Vassiliadi, D.A., Armaganidis, A., and Dimopoulou, I. (2012). Interrelationship between blood and tissue lactate in a general intensive care unit: a subcutaneous adipose tissue microdialysis study on 162 critically ill patients. J Crit Care 27, 742.e9–742.e18.
Kyriazopoulou, E., Liaskou-Antoniou, L., Adamis, G., Panagaki, A., Melachroinopoulos, N., Drakou, E., Marousis, K., Chrysos, G., Spyrou, A., Alexiou, N., et al. (2021). Procalcitonin to reduce long-term infection-associated adverse events in Sepsis. A randomized trial. Am J Respir Crit Care Med 203, 202–210.
Kytö, V., Saraste, A., Voipio-Pulkki, L.M., and Saukko, P. (2007). Incidence of fatal myocarditis: a population-based study in finland. Am J Epidemiol 165, 570–574.
Laborda, P., Wang, S.Y., and Voglmeir, J. (2016). Influenza neuraminidase inhibitors: synthetic approaches, derivatives and biological activity. Molecules 21, 1513.
Latva-Hirvelä, J., Kytö, V., Saraste, A., Vuorinen, T., Levijoki, J., and Saukko, P. (2009). Effects of levosimendan in experimental acute coxsackievirus myocarditis. Eur J Clin Invest 39, 876–882.
Lee, C.H., Tsai, W.C., Hsu, C.H., Liu, P.Y., Lin, L.J., and Chen, J.H. (2006). Predictive factors of a fulminant course in acute myocarditis. Int J Cardiol 109, 142–145.
Lee, J.G., Kim, N., Narm, K.S., Suh, J.W., Hwang, J., Paik, H.C., and Yoo, Y.C. (2020). The effect of additional stepwise venous inflow on differential hypoxia of veno-arterial extracorporeal membrane oxygenation. ASAIO J 66, 803–808.
Li, C., Wang, S., Wang, H., Wu, Y., Ma, J., Li, W., and Duan, J. (2021a). The effects of hemodynamic monitoring using the PiCCO system on critically ill patients. Am J Transl Res 13, 10578–10585.
Li, C., Zhao, M., Xiao, L., Wei, H., Wen, Z., Hu, D., Yu, B., Sun, Y., Gao, J., Shen, X., et al. (2021b). Prognostic value of elevated levels of plasma N-acetylneuraminic acid in patients with heart failure. Circ Heart Fail 14.
Li, D., and Wu, M. (2021). Pattern recognition receptors in health and diseases. Sig Transduct Target Ther 6, 291.
Li, H., Zhang, M., Zhao, Q., Zhao, W., Zhuang, Y., Wang, J., Hang, W., Wen, Z., Wang, L., Chen, C., et al. (2023). Self-recruited neutrophils trigger over-activated innate immune response and phenotypic change of cardiomyocytes in fulminant viral myocarditis. Cell Discov 9, 103.
Li, H., Zhu, H., Yang, Z., Tang, D., Huang, L., and Xia, L. (2021c). Application of multiparametric quantitative cardiac magnetic resonance for detection and monitoring of myocardial injury in patients with fulminant myocarditis. Acad Radiol 28, e35–e43.
Li, S., Xu, S., Li, C., Ran, X., Cui, G., He, M., Miao, K., Zhao, C., Yan, J., Hui, R., et al. (2019). A life support-based comprehensive treatment regimen dramatically lowers the in-hospital mortality of patients with fulminant myocarditis: a multiple center study. Sci China Life Sci 62, 369–380.
Lin, C.C., Phua, D.H., Deng, J.F., and Yang, C.C. (2011). Aconitine intoxication mimicking acute myocardial infarction. Hum Exp Toxicol 30, 782–785.
Liu, C., Wang, Z., Chen, K., Cui, G., Chen, C., Wang, L., and Jiang, J. (2021a). The absolute and relative changes in high-sensitivity cardiac troponin I are associated with the in-hospital mortality of patients with fulminant myocarditis. BMC Cardiovasc Disord 21, 571.
Liu, L., Yang, X., Gu, Y., Jiang, T., Xu, J., and Xu, M. (2021b). Predictive value of the age, creatinine, and ejection fraction (ACEF) score in patients with acute fulminant myocarditis. Front Physiol 12, 596548.
Lorusso, R., Centofanti, P., Gelsomino, S., Barili, F., Di Mauro, M., Orlando, P., Botta, L., Milazzo, F., Actis Dato, G., Casabona, R., et al. (2016). Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: A 5-year multi-institutional experience. Ann Thorac Surg 101, 919–926.
Luetkens, J.A., Faron, A., Isaak, A., Dabir, D., Kuetting, D., Feisst, A., Schmeel, F.C., Sprinkart, A.M., and Thomas, D. (2019). Comparison of Original and 2018 Lake Louise Criteria for diagnosis of acute myocarditis: results of a validation cohort. Radiol-Cardiothoracic Imag 1, e190010.
Maisch, B., Ruppert, V., and Pankuweit, S. (2014). Management of fulminant myocarditis: A diagnosis in search of its etiology but with therapeutic options. Curr

Heart Fail Rep 11, 166–177.
Marini, J.J., Smith, T.C., and Lamb, V.J. (1988). External work output and force generation during synchronized intermittent mechanical ventilation: effect of machine assistance on breathing effort. Am Rev Respir Dis 138, 1169–1179.
Maron, B.J., Levine, B.D., Washington, R.L., Baggish, A.L., Kovacs, R.J., and Maron, M.S. (2015). Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 2: preparticipation screening for cardiovascular disease in competitive athletes. Circulation 132.
Mason, J.W., O''Connell, J.B., Herskowitz, A., Rose, N.R., McManus, B.M., Billingham, M.E., and Moon, T.E. (1995). A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 333, 269–275.
Matsumori, A., Shimada, T., Chapman, N.M., Tracy, S.M., and Mason, J.W. (2006). Myocarditis and heart failure associated with hepatitis C virus infection. J Cardiac Fail 12, 293–298.
McCarthy, R.E., Boehmer, J.P., Hruban, R.H., Hutchins, G.M., Kasper, E.K., Hare, J.M., and Baughman, K.L. (2000). Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 342, 690–695.
McDonagh, T.A., Metra, M., Adamo, M., Gardner, R.S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., et al. (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 42, 3599–3726.
McNamara, D.M., Holubkov, R., Starling, R.C., Dec, G.W., Loh, E., Torre-Amione, G., Gass, A., Janosko, K., Tokarczyk, T., Kessler, P., et al. (2001). Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 103, 2254–2259.
McNamara, D.M., Rosenblum, W.D., Janosko, K.M., Trost, M.K., Villaneuva, F.S., Demetris, A.J., Murali, S., and Feldman, A.M. (1997). Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. Circulation 95, 2476–2478.
Mehrpour, O., Asadi, S., Yaghoubi, M.A., Azdaki, N., Mahmoodabadi, N., and Javadmoosavi, S.Y. (2019). Cardiogenic shock due to aluminum phosphide poisoning treated with intra-aortic balloon pump: a report of two cases. Cardiovasc Toxicol 19, 474–481.
Meijers, W.C., Bayes-Genis, A., Mebazaa, A., Bauersachs, J., Cleland, J.G.F., Coats, A.J.S., Januzzi, J.L., Maisel, A.S., McDonald, K., Mueller, T., et al. (2021). Circulating heart failure biomarkers beyond natriuretic peptides: review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). Eur J Heart Fail 23, 1610–1632.
Merken, J., Hazebroek, M., Van Paassen, P., Verdonschot, J., Van Empel, V., Knackstedt, C., Abdul Hamid, M., Seiler, M., Kolb, J., Hoermann, P., et al. (2018). Immunosuppressive therapy improves both short- and long-term prognosis in patients with virus-negative nonfulminant inflammatory cardiomyopathy. Circ Heart Fail 11, e004228.
Mirna, M., Schmutzler, L., Topf, A., Hoppe, U.C., and Lichtenauer, M. (2021). Neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio predict length of hospital stay in myocarditis. Sci Rep 11, 18101.
Mobini, R., Staudt, A., Felix, S.B., Baumann, G., Wallukat, G., Deinum, J., Svensson, H., Hjalmarson, Å., and Fu, M. (2003). Hemodynamic improvement and removal of autoantibodies against β1-adrenergic receptor by immunoadsorption therapy in dilated cardiomyopathy. J Autoimmun 20, 345–350.
Morkane, C.M., Sapisochin, G., Mukhtar, A.M., Reyntjens, K.M.E.M., Wagener, G., Spiro, M., Raptis, D.A., and Klinck, J.R. (2022). Perioperative fluid management and outcomes in adult deceased donor liver transplantation—A systematic review of the literature and expert panel recommendations. Clin Transplant 36, e14651.
Moslehi, J.J. (2016) Cardiovascular toxic effects of targeted cancer therapies. N Engl J Med 375, 1457–1467.
Moulik, M., Breinholt, J.P., Dreyer, W.J., Kearney, D.L., Price, J.F., Clunie, S.K., Moffett, B.S., Kim, J.J., Rossano, J.W., Jefferies, J.L., et al. (2010). Viral endomyocardial infection is an independent predictor and potentially treatable risk factor for graft loss and coronary vasculopathy in pediatric cardiac transplant recipients. J Am Coll Cardiol 56, 582–592.
Nie, X., Fan, J., Li, H., Wang, J., Xie, R., Chen, C., and Wang, D.W. (2022). Identification of cardiac circRNAs in mice with CVB3-induced myocarditis. Front Cell Dev Biol 10, 760509.
Nie, X., Li, H., Wang, J., Cai, Y., Fan, J., Dai, B., Chen, C., and Wang, D.W. (2021). Expression profiles and potential functions of long non-coding RNAs in the heart of mice with coxsackie B3 virus-induced myocarditis. Front Cell Infect Microbiol 11, 704919.
Pahuja, M., Adegbala, O., Mishra, T., Akintoye, E., Chehab, O., Mony, S., Singh, M., Ando, T., Abubaker, H., Yassin, A., et al. (2019). Trends in the incidence of in-hospital mortality, cardiogenic shock, and utilization of mechanical circulatory support devices in myocarditis (analysis of national inpatient sample data, 2005–2014). J Cardiac Fail 25, 457–467.
Palaka, E., Grandy, S., Darlington, O., McEwan, P., and Doornewaard, A. (2020). Associations between serum potassium and adverse clinical outcomes: A systematic literature review. Int J Clin Pract 74, e13421.
Palaskas, N., Lopez-Mattei, J., Durand, J.B., Iliescu, C., and Deswal, A. (2020). Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. J Am Heart Assoc 9, e013757.
Palmer, A., Gjorstrup, P., Severn, A., Welsh, K., and Taube, D. (1988). Treatment of systemic lupus erythematosus by extracorporeal immunoadsorption. Lancet 332, 272.
Parissis, J.T., and Filippatos, G. (2009). Levosimendan in viral myocarditis: not only an inodilator but also a cardioprotector? Eur J Clin Invest 39, 839–840.
Peretto, G., Sala, S., Rizzo, S., De Luca, G., Campochiaro, C., Sartorelli, S., Benedetti, G., Palmisano, A., Esposito, A., Tresoldi, M., et al. (2019). Arrhythmias in myocarditis: State of the art. Heart Rhythm 16, 793–801.
Pollack, A., Kontorovich, A.R., Fuster, V., and Dec, G.W. (2015). Viral myocarditis—diagnosis, treatment options, and current controversies. Nat Rev Cardiol 12, 670–680.
Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S., Falk, V., González-Juanatey, J.R., Harjola, V., Jankowska, E.A., et al. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail 18, 891–975.
Prochnau, D., Surber, R., Kuehnert, H., Heinke, M., Klein, H.U., and Figulla, H.R. (2010). Successful use of a wearable cardioverter-defibrillator in myocarditis with normal ejection fraction. Clin Res Cardiol 99, 129–131.
Rajagopal, S.K., Almond, C.S., Laussen, P.C., Rycus, P.T., Wypij, D., and Thiagarajan, R.R. (2010). Extracorporeal membrane oxygenation for the support of infants, children, and young adults with acute myocarditis: A review of the Extracorporeal Life Support Organization registry. Crit Care Med 38, 382–387.
Ravi, V., Ayub, M.T., Suboc, T., Alyousef, T., and Gomez, J. (2019). A curious case of coronary vasospasm with cardiogenic shock: type 1 kounis syndrome complicated by eosinophilic myocarditis. Cureus 11, e4522.
Rezkalla, S.H., and Kloner, R.A. (2021). Viral myocarditis: 1917–2020: From the Influenza A to the COVID-19 pandemics. Trends Cardiovasc Med 31, 163–169.
Roubille, F., Tournoux, F., Roubille, C., Merlet, N., Davy, J.M., Rhéaume, E., Busseuil, D., and Tardif, J.C. (2013). Management of pericarditis and myocarditis: Could heart-rate-reducing drugs hold a promise? Arch Cardiovasc Dis 106, 672–679.
Saggioro, F.P., Rossi, M.A., Duarte, M.I.S., Martin, C.C.S., Alves, V.A.F., Moreli, M.L., Figueiredo, L.T.M., Moreira, J.E., Borges, A.A., and Neder, L. (2007). Hantavirus infection induces a typical myocarditis that may be responsible for myocardial depression and shock in hantavirus pulmonary syndrome. J Infect Dis 195, 1541–1549.
Saji, T., Matsuura, H., Hasegawa, K., Nishikawa, T., Yamamoto, E., Ohki, H., Yasukochi, S., Arakaki, Y., Joo, K., and Nakazawa, M. (2012). Comparison of the clinical presentation, treatment, and outcome of fulminant and acute myocarditis in children. Circ J 76, 1222–1228.
Samuelsson, A., Towers, T.L., and Ravetch, J.V. (2001). Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 291, 484–486.
Sasaki, H., Kawai, A., and Kurosawa, H. (2008). Mechanical support for patients with fulminant acute myocarditis: strategy for biventricular failure and respiratory failure. J Cardiac Surg 23, 526–527.
Sasson, Z., Morgan, C.D., Wang, B., Thomas, G., MacKenzie, B., and Platts, M.E. (1994). 5-Fluorouracil related toxic myocarditis: case reports and pathological confirmation. Can J Cardiol 10, 861–864.
Savage, E., Wazir, T., Drake, M., Cuthbert, R., and Wright, G. (2014). Fulminant myocarditis and macrophage activation syndrome secondary to adult-onset Still's disease successfully treated with tocilizumab. Rheumatology 53, 1352–1353.
Sawamura, A., Okumura, T., Ito, M., Ozaki, Y., Ohte, N., Amano, T., and Murohara, T. (2018). Prognostic value of electrocardiography in patients with fulminant myocarditis supported by percutaneous venoarterial extracorporeal membrane oxygenation—analysis from the CHANGE PUMP study. Circ J 82, 2089–2095.
Schultheiss, H.P., Fairweather, D.L., Caforio, A.L.P., Escher, F., Hershberger, R.E., Lipshultz, S.E., Liu, P.P., Matsumori, A., Mazzanti, A., McMurray, J., et al. (2019). Dilated cardiomyopathy. Nat Rev Dis Primers 5, 32.
Schultheiss, H.P., Kuhl, U., and Cooper, L.T. (2011). The management of myocarditis. Eur Heart J 32, 2616–2625.
Schultz, J.C., Hilliard, A.A., Cooper Jr, L.T., and Rihal, C.S. (2009). Diagnosis and treatment of viral myocarditis. Mayo Clinic Proc 84, 1001–1009.
Schwaab, B., Kindermann, I., Bjarnason-Wehrens, B., Preßler, A., Niebauer, J., Rauch, B., Völler, H., and Reibis, R. (2022). Viral myocarditis: a forbidden indication for cardiac rehabilitation? Eur J Prev Cardiol 29, 2064–2068.
Schweigmann, U., Velik-Salchner, C., Kilo, J., and Schermer, E. (2011). How mechanical circulatory support helps not to need it-new strategies in pediatric heart failure. Artif Organs 35, 1105–1109.
Semproni, M., Rusk, R., and Wuerz, T. (2020). Fatal Lyme carditis presenting as fluctuating high-grade atrioventricular block. CMAJ 192, E574–E577.

Sevransky, J.E., Levy, M.M., and Marini, J.J. (2004). Mechanical ventilation in sepsis-induced acute lung injury/acute respiratory distress syndrome: An evidence-based review. Crit Care Med 32, S548–S553.
Shioji, K., Kishimoto, C., and Sasayama, S. (2001). Fc receptor-mediated inhibitory effect of immunoglobulin therapy on autoimmune giant cell myocarditis. Circ Res 89, 540–546.
Singh, V., Mendirichaga, R., Savani, G.T., Rodriguez, A., Blumer, V., Elmariah, S., Inglessis-Azuaje, I., and Palacios, I. (2018). Comparison of utilization trends, indications, and complications of endomyocardial biopsy in native versus donor hearts (from the nationwide inpatient sample 2002 to 2014). Am J Cardiol 121, 356–363.
Sobol, I., Chen, C.L., Mahmood, S.S., and Borczuk, A.C. (2020). Histopathologic characterization of myocarditis associated with immune checkpoint inhibitor therapy. Arch Pathol Lab Med 144, 1392–1396.
Sury, K., Perazella, M.A., and Shirali, A.C. (2018). Cardiorenal complications of immune checkpoint inhibitors. Nat Rev Nephrol 14, 571–588.
Tasaka, S., Ohshimo, S., Takeuchi, M., Yasuda, H., Ichikado, K., Tsushima, K., Egi, M., Hashimoto, S., Shime, N., Saito, O., et al. (2022). ARDS Clinical Practice Guideline 2021. J Intensive Care 10, 32.
Torre-Amione, G., Anker, S.D., Bourge, R.C., Colucci, W.S., Greenberg, B.H., Hildebrandt, P., Keren, A., Motro, M., Moyé, L.A., Otterstad, J.E., et al. (2008). Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): a placebo-controlled randomised trial. Lancet 371, 228–236.
Tschöpe, C., Ammirati, E., Bozkurt, B., Caforio, A.L.P., Cooper, L.T., Felix, S.B., Hare, J. M., Heidecker, B., Heymans, S., Hübner, N., et al. (2021). Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol 18, 169–193.
Tschöpe, C., Cooper, L.T., Torre-Amione, G., and Van Linthout, S. (2019a). Management of myocarditis-related cardiomyopathy in adults. Circ Res 124, 1568–1583.
Tschöpe, C., Van Linthout, S., Klein, O., Mairinger, T., Krackhardt, F., Potapov, E.V., Schmidt, G., Burkhoff, D., Pieske, B., and Spillmann, F. (2019b). Mechanical unloading by fulminant myocarditis: LV-IMPELLA, ECMELLA, BI-PELLA, and PROPELLA concepts. J Cardiovasc Trans Res 12, 116–123.
Tsuboi, H., Sone, T., Sassa, H., Itoh, T., Koyama, T., Takasu, A., and Minakuchi, K. (1990). Rescue of a patient with fulminant myocarditis by percutaneous extracorporeal bypass. Jpn J Med 29, 519–522.
Tzartos, S.J., Bitzopoulou, K., Gavra, I., Kordas, G., Jacobson, L., Kostelidou, K., Lagoumintzis, G., Lazos, O., Poulas, K., Sideris, S., et al. (2008). Antigen-specific apheresis of pathogenic autoantibodies from myasthenia gravis sera. Ann N Y Acad Sci 1132, 291–299.
Ukena, C., Kindermann, M., Mahfoud, F., Geisel, J., Lepper, P.M., Kandolf, R., Böhm, M., and Kindermann, I. (2014). Diagnostic and prognostic validity of different biomarkers in patients with suspected myocarditis. Clin Res Cardiol 103, 743–751.
Ukena, C., Mahfoud, F., Kindermann, I., Kandolf, R., Kindermann, M., and Böhm, M. (2011). Prognostic electrocardiographic parameters in patients with suspected myocarditis. Eur J Heart Fail 13, 398–405.
Uriel, N., Sayer, G., and Clerkin, K.J. (2020). Myocardial injury in COVID-19 patients. J Am Coll Cardiol 76, 547–549.
Vally, S., Ferdynus, C., Persichini, R., Bouchet, B., Braunberger, E., Lo Pinto, H., Martinet, O., Vandroux, D., Aujoulat, T., Allyn, J., et al. (2019). Impact of levosimendan on weaning from peripheral venoarterial extracorporeal membrane oxygenation in intensive care unit. Ann Intensive Care 9, 24.
Vardas, P.E., Auricchio, A., Blanc, J.J., Daubert, J.C., Drexler, H., Ector, H., Gasparini, M., Linde, C., Morgado, F.B., Oto, A., et al. (2007). Guidelines for cardiac pacing and cardiac resynchronization therapy: the task force for cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Eur Heart J 28, 2256–2295.
Veronese, G., Ammirati, E., Brambatti, M., Merlo, M., Cipriani, M., Potena, L., Sormani, P., Aoki, T., Sugimura, K., Sawamura, A., et al. (2020). Viral genome search in myocardium of patients with fulminant myocarditis. Eur J Heart Fail 22, 1277–1280.
Veronese, G., Ammirati, E., Chen, C., Klingel, K., Suzuki, M., Okumura, T., Maisch, B., Zuo, H., Ni, L., Jiang, J., et al. (2021). Management perspectives from the 2019 Wuhan international workshop on fulminant myocarditis. Int J Cardiol 324, 131–138.
Vos, T., Barber, R.M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., et al. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386, 743–800.
Wang, D., Li, S., Jiang, J., Yan, J., Zhao, C., Wang, Y., Ma, Y., Zeng, H., Guo, X., Wang, H., et al. (2019a). Chinese society of cardiology expert consensus statement on the diagnosis and treatment of adult fulminant myocarditis. Sci China Life Sci 62, 187–202.
Wang, D.W. (2021). Diagnosis and Treatment of Fulminant Myocarditis (in Chinese). Beijing: Science Press.
Wang, D.W., and Hui, R.T. (2022). Implement the Chinese program for the treatment of fulminant myocarditis to save more lives (in Chinese). Chin J Cardiovasc Dis 50, 212–218.
Wang, D.Y., Okoye, G.D., Neilan, T.G., Johnson, D.B., and Moslehi, J.J. (2017). Cardiovascular toxicities associated with cancer immunotherapies. Curr Cardiol Rep 19, 21.
Wang, J., He, M., Li, H., Chen, Y., Nie, X., Cai, Y., Xie, R., Li, L., Chen, P., Sun, Y., et al. (2022). Soluble ST2 is a sensitive and specific biomarker for fulminant myocarditis. J Am Heart Assoc 11, e024417.
Wang, Q., Pan, W., Shen, L., Wang, X., Xu, S., Chen, R., and Ge, J. (2012). Clinical features and prognosis in Chinese patients with acute fulminant myocarditis. Acta Cardiol 67, 571–576.
Wang, Z., Wang, Y., Lin, H., Wang, S., Cai, X., and Gao, D. (2019b). Early characteristics of fulminant myocarditis vs non-fulminant myocarditis. Medicine 98, e14697.
Y-Hassan, S., and Falhammar, H. (2020). Cardiovascular manifestations and complications of pheochromocytomas and paragangliomas. J Clin Med 9, 2435.
Yajima, T., and Knowlton, K.U. (2009). Viral myocarditis. Circulation 119, 2615–2624.
Yannopoulos, D., Bartos, J., Raveendran, G., Walser, E., Connett, J., Murray, T.A., Collins, G., Zhang, L., Kalra, R., Kosmopoulos, M., et al. (2020). Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet 396, 1807–1816.
Ye, F.M., Zhang, J.J., Wang, B.L., and Zhang, J. (2021). Analysis of the effect of mechanical circulation support and immune regulation on fulminant myocarditis with cardiogenic shock (in Chinese). Chin J Cardiovasc Dis Med 49, 894–899.
Zhao, F., Shi, G., Wu, Z., and Guo, Z. (2021). A successful rescue of juvenile fulminant myocarditis by extracorporeal membrane oxygenation combined with intra-aortic balloon pump: a case report. Ann Transl Med 9, 1355.
Zhou, N., Zhao, Y., Jiang, J., Shen, L., Li, J., Wan, J., Ma, X., Zhang, J., Ammirati, E., and Wang, D.W. (2021). Impact of mechanical circulatory support and immunomodulation therapy on outcome of patients with fulminant myocarditis: Chinese registry of fulminant myocarditis. Sig Transduct Target Ther 6, 350.
Zipes, D.P., Camm, A.J., Borggrefe, M., Buxton, A.E., Chaitman, B., Fromer, M., Gregoratos, G., Klein, G., Moss, A.J., Myerburg, R.J., et al., (2006). ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death–executive summary: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Eur Heart J 27, 2099–2140.
Zuo, H., Li, H., Li, R., Ma, F., Jiang, J., Li, C., Xia, L., Wang, H., and Wang, D.W. (2021). Myocardial strain features by 2D-STE during the course of fulminant myocarditis. Medicine 100, e25050.
Zuo, H., Li, R., Ma, F., Jiang, J., Miao, K., Li, H., Nagel, E., Tadic, M., Wang, H., and Wang, D.W. (2020). Temporal echocardiography findings in patients with fulminant myocarditis: beyond ejection fraction decline. Front Med 14, 284–292.