



A synopsis of the guidelines for diagnosis and treatment of fulminant myocarditis

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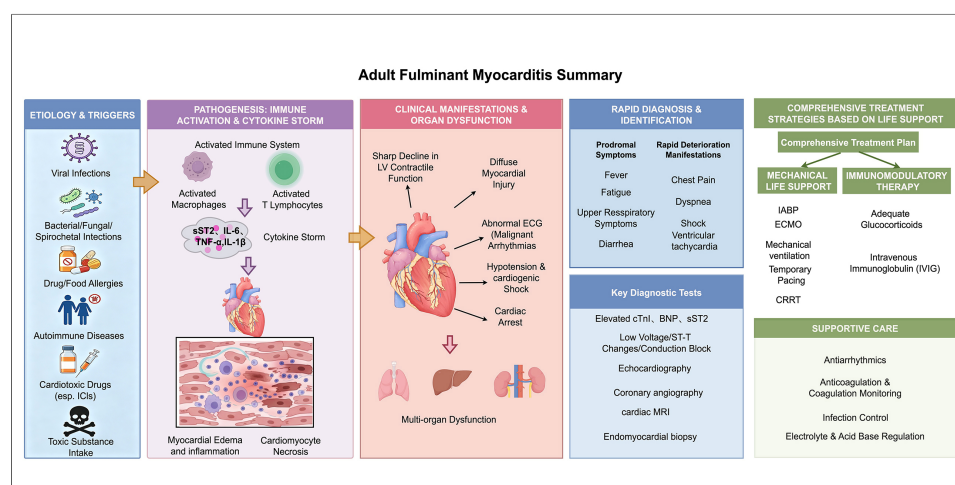
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Abstract

Fulminant myocarditis (FM) represents the most severe subtype of myocarditis, associated with a high in-hospital mortality. For the clinical management of FM, the “life support-based comprehensive treatment regimen” is recommended, which places emphasis on suppressing the core pathophysiological mechanisms underlying FM, namely the excessive activation of innate immune responses and the inflammatory storm. Mechanical circulatory support and immunomodulatory therapy with adequate doses of both glucocorticoids and immunoglobulins constitute the two foundational pillars of this regimen. Notably, the treatment regimen underscores the principle of “ultra-early recognition, ultra-early diagnosis, ultra-early prediction, and ultra-early rescue”. As the first clinical guideline for the diagnosis and treatment of adult FM, this document provides evidence-based and effective therapeutic approaches, which are crucial for significantly reducing mortality and improving long-term prognosis in affected patients.

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INTRODUCTION

Myocarditis refers to inflammatory injury of the myocardium, characterized by inflammatory cell infiltration and cardiac dysfunction. Fulminant myocarditis (FM) represents the most severe phenotype, with acute onset and rapid deterioration. Patients with FM often develop hemodynamic instability, severe arrhythmias, multiple organ failure, and even sudden cardiac death. Authorized by the Chinese Society of Cardiology, the Chinese Expert Consensus on the Diagnosis and Treatment of Fulminant Myocarditis was first published in 2017^[1]. This document has since been updated and formally upgraded into the Chinese Society of Cardiology Guidelines on the Diagnosis and Treatment of Adult Fulminant Myocarditis in 2024 (hereinafter referred to as the “2024 Chinese Guidelines”)^[2,3]. In comparison with its preceding consensus, the 2024 Chinese Guidelines incorporate several novel sections, covering epidemiology, pathological classification, management and follow-up during the convalescent phase, complication mitigation, the establishment of a rapid response team for FM and healthcare system construction. Furthermore, the guidelines integrate the latest advances in the pathophysiological mechanisms of FM and provide a more detailed exposition of diagnostic workup and therapeutic regimens. In line with international standards, recommendations are graded into four classes (I, IIa, IIb and III) and three levels of evidence (A, B, C)^[4,5]. This synopsis presents a condensed version of the guidelines, aiming to help readers rapidly grasp the core contents of the guidelines, especially for popularization of the key clinical concepts in primary healthcare units.

EPIDEMIOLOGY OF FM

Accurate epidemiological data on the incidence of FM remain limited. This is largely because FM is sporadic and progresses extremely rapidly, which frequently results in underdiagnosis or misdiagnosis. Consequently, direct estimation of FM incidence via population-based epidemiological surveys is challenging. To date, available data were primarily derived from fatal cases of acute myocarditis. Based on these estimates, the average incidence of FM is approximately 9–23 per 1 million person-years^[6–9]. When extrapolated to the Chinese population, this corresponds to an estimated annual caseload of 12,600 to 32,200 cases. Nevertheless, this figure is likely to be a marked underestimate due to the underdiagnosis and misdiagnosis of FM, underscoring the urgent need for dedicated epidemiological investigations to ascertain the true disease burden.

Previous studies reported an in-hospital mortality of 45%–55.6% among patients with FM treated in tertiary medical centers^[7,10,11]. FM affects individuals from adolescence to old age. In a cohort of 344 patients with histologically confirmed FM, the median age was 54 years, and older age was associated with poorer 90-day outcomes (death or heart transplantation)^[12]. In another study comprising 220 FM patients, the mean age among non-survivors was 52.63 years, compared with a median age of 35.00 years among survivors^[13], further supporting the prognostic implications of age.

ETIOLOGY, PATHOPHYSIOLOGY AND PATHOLOGY OF FM

The etiology of FM parallels that of acute non-fulminant myocarditis, comprising infectious and non-infectious causes. Viral infection is the primary etiology, while non-infectious factors mainly include autoimmune diseases and drug toxicity.

The pathophysiology of FM is complex. Excessive activation of the innate immune responses and rapid release of inflammatory mediators, which is referred to as “cytokine storm”, are considered the core mechanisms underlying FM. Myocardial injury occurs via two major pathways: direct viral cytotoxicity to cardiomyocytes, and inflammatory damage induced by the cytokine storm [Figure 1]^[14,15].

According to established quantitative immunohistological criteria, myocarditis is defined as ≥ 14 infiltrating leukocytes/mm² on myocardial biopsy^[16]. FM typically demonstrates extensive inflammatory cell infiltration

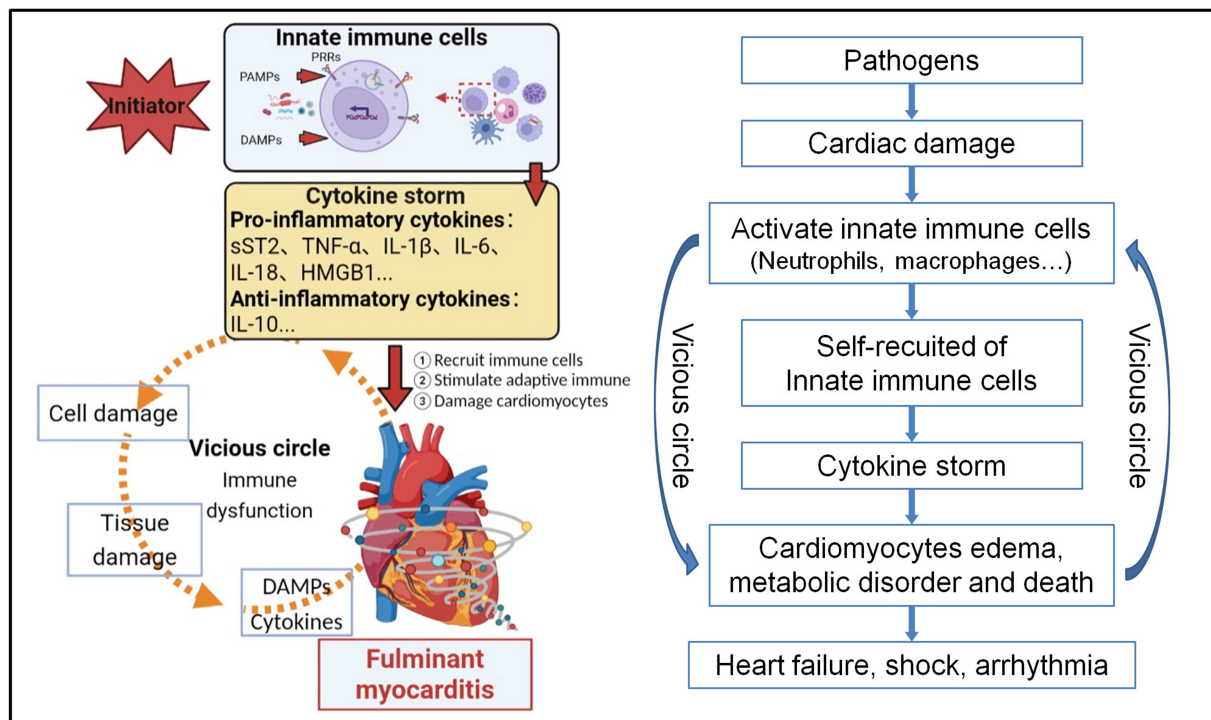


Figure 1. A summary of the pathophysiological mechanisms underlying FM. FM is initiated by viral or other causative agents that invade and damage cardiomyocytes, thereby recruiting neutrophils to the site of injury. The activated neutrophils subsequently promote the infiltration of monocytes and macrophages, which in turn trigger PAMP- or DAMP-mediated activation of innate immune cells. This activation precipitates a robust cytokine storm, inflicting further injury on myocardial tissue. The ensuing tissue destruction amplifies DAMPs-driven immune overactivation, establishing a self-perpetuating vicious cycle that ultimately culminates in the overt clinical syndrome of FM. PAMPs: Pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; PRRs: pattern recognition receptors; sST-2: soluble growth stimulation expressed gene 2; TNF- α : tumor necrosis factor- α ; IL: interleukin; HMGB1: high mobility group box 1; FM: fulminant myocarditis. The drawing part was created with BioRender (<https://biorender.com/6yp4kqp>).

and cardiomyocyte necrosis, with inflammatory cell counts exceeding 50/mm²^[17].

Notably, pathological findings do not always correlate with clinical severity, and some patients diagnosed with FM show only mild histological changes. Therefore, FM remains primarily a clinical diagnosis.

CLINICAL EVALUATION AND DIAGNOSIS OF FM

Early symptoms of FM are usually nonspecific, often presenting as cold-like prodromal symptoms lasting 3-5 days. FM is mainly characterized by hemodynamic instability resulting from severe myocardial injury, and some patients may develop coma or even sudden death due to malignant arrhythmias^[18,19]. Physical signs are also nonspecific, but FM patients typically exhibit hypotension, dyspnea or respiratory depression, and abnormal heart rate or rhythm, indicating hemodynamic collapse^[20-22]. However, fatigue and poor appetite are common.

For patients with suspected FM based on prodromal symptoms, laboratory examinations should be performed [Table 1]. Elevated myocardial injury biomarkers, including high-sensitivity cardiac troponin I (hs-cTnI) or cardiac troponin I or T (cTnI or cTnT), and B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), reflect the presence and severity of myocardial injury^[4,23]. In addition, increased leukocyte count and neutrophil percentage generally indicate infection and systemic inflammation. Liver and renal function tests, electrolyte panels, and acid-base balance help evaluate multiple organ dysfunctions. The severity of hepatic and renal impairment, especially secondary injury, strongly

Table 1. The recommendation for laboratory examinations for patients with FM^[3] (see evidence in Supplementary Table 1)

Recommendations	Class ^a	Level ^b
Blood routine examination is recommended every 1-2 days to track dynamic hematological changes	I	C
Dynamic monitoring of hs-cTnI or cTnI is recommended as the biomarker for the assessment of myocardial injury ^[23,56]	I	B
Serial measurement of plasma NT-proBNP or BNP levels is recommended to assess the severity of cardiac dysfunction and predict outcomes ^[57,58]	I	B
Serial assessments of liver/renal function, arterial blood gases, and blood lactate levels are recommended for disease severity stratification and prognostic evaluation	I	C
Comprehensive coagulation monitoring (including PT, PTA, APTT, TT, INR, FIB, D-dimer, and platelet count) is recommended routinely ^[59,60]	I	A
In patients with suspected FM, dynamic monitoring of inflammatory cytokines is recommended to aid diagnosis and to assess therapeutic response and prognosis ^[61,62]	I	B
Serial measurements of sST2 should be considered in patients with suspected FM ^[26,63,64]	IIa	C
Procalcitonin levels may be considered to guide antibiotic therapy and to evaluate its clinical efficacy ^[65-67]	IIb	A

NT-proBNP: N-terminal pro-B-type natriuretic peptide; hs-cTnI: high-sensitivity cardiac troponin I; PT: prothrombin time; PTA: prothrombin time activity; APTT: activated partial thromboplastin time; TT: thrombin time; INR: international normalized ratio; FIB: fibrinogen; FM: fulminant myocarditis; BNP: B-type natriuretic peptide; sST2: soluble growth stimulation expressed gene 2 protein. ^aclass of recommendation; ^blevel of evidence.

affects the prognosis of patients with FM. Maintenance of electrolyte and acid-base balance, particularly serum potassium, is critical^[24]. Arterial blood gas analysis and blood lactate levels reflect tissue perfusion and oxygenation, and should be dynamically monitored. Coagulation function should also be regularly assessed to identify and correct disseminated intravascular coagulation (DIC), especially in patients receiving intra-aortic balloon pump (IABP) and/or extracorporeal membrane oxygenation (ECMO)^[25].

C-reactive protein is the most widely used marker of systemic inflammation but lacks specificity. High-throughput plasma inflammatory factor profiling in early FM has identified significant alterations in 39 out of 122 factors (28 increased and 11 decreased)^[26]. Notably, the following factors were significantly elevated: soluble ST2 (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). Among these, sST2 level showed particular prominence and correlated well with clinical severity. Conversely, cytotoxic T-lymphocyte-associated protein 4 (CTLA4) was markedly reduced. Levels of these factors gradually tend to normalize with effective treatment and clinical improvement. Classic pro-inflammatory cytokines such as interleukins and tumor necrosis factor (TNF)- α were also increased. Therefore, routine and dynamic monitoring of plasma inflammatory factors is recommended in patients with suspected FM, as it aids in diagnosis, therapeutic evaluation, and prognostic assessment.

Special investigations for FM include electrocardiography (ECG), echocardiography, chest computed tomography (CT) or X-ray, cardiac magnetic resonance imaging (CMR), and endomyocardial biopsy (EMB). Histopathological analysis based on EMB remains the gold standard for diagnosing myocarditis [Figure 2A and B]. In recent years, with advances in echocardiography and CMR, EMB is less frequently used in uncomplicated myocarditis. Several limitations restrict its broader clinical application: its diagnostic yield is highly dependent on the expertise of the pathologist, and as an invasive procedure, it carries inherent risks, including cardiac perforation with pericardial tamponade, atrioventricular block, chordae tendineae injury, and puncture site bleeding. Nevertheless, EMB is strongly recommended in patients with FM presenting with shock, acute heart failure, or severe arrhythmias, particularly when a specific etiology is suspected, such as immune checkpoint inhibitor (ICI)-associated myocarditis, autoimmune diseases, or peripheral eosinophilia. In such cases, EMB helps clarify the etiology, pathological subtype, and extent of myocardial injury, thereby providing crucial guidance for clinical management^[27].

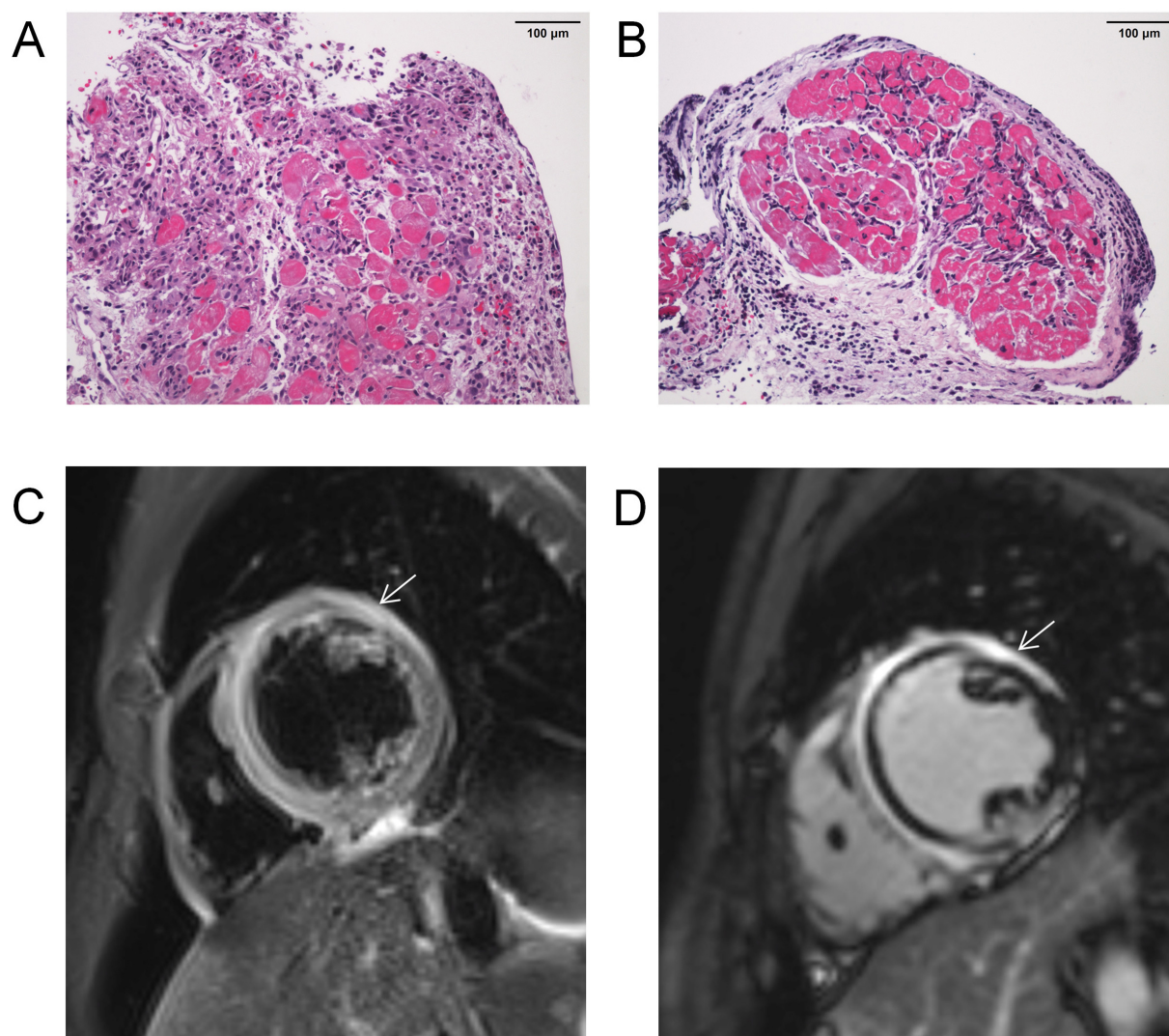


Figure 2. Representative pathological and CMR images from cases with FM. (A and B) Hematoxylin and eosin (H&E) staining of EMB specimens showing cardiac inflammatory infiltration (200×), scale bar = 100 μm; (C) T2-weighted imaging demonstrating marked myocardial edema (white arrow); (D) LGE imaging revealing myocardial injury (white arrow). CMR: Cardiac magnetic resonance imaging; LGE: late gadolinium enhancement; FM: fulminant myocarditis.

ECG shows high sensitivity but low specificity in the diagnosis of FM, and serial examinations are needed to detect dynamic changes^[28]. Echocardiography allows comprehensive evaluation of cardiac structure, function and hemodynamics. Typical findings in FM include significant left ventricular systolic and diastolic dysfunctions, manifested by diffuse left ventricular hypokinesia and regional wall motion abnormalities, which may gradually improve with appropriate treatment^[29,30]. Compared with acute myocarditis, FM demonstrates a more severe reduction in left ventricular longitudinal strain, which may precede overt cardiac dysfunction and thus facilitate early diagnosis^[31].

CMR reveals imaging features closely resembling pathological changes in myocarditis, including myocardial edema, hyperemia, capillary leakage, necrosis, and fibrosis^[32,33]. Quantitative assessment of myocardial injury can be achieved using T1 mapping, T2 mapping, and extracellular volume (ECV). The combination of CMR with elevated troponin levels has gradually emerged as a non-invasive tool for the clinical diagnosis of myocarditis, especially in low-risk patients^[30]. According to current diagnostic criteria, CMR-based diagnosis of myocarditis requires at least one of the following: (i) Evidence of myocardial edema on T2 imaging,

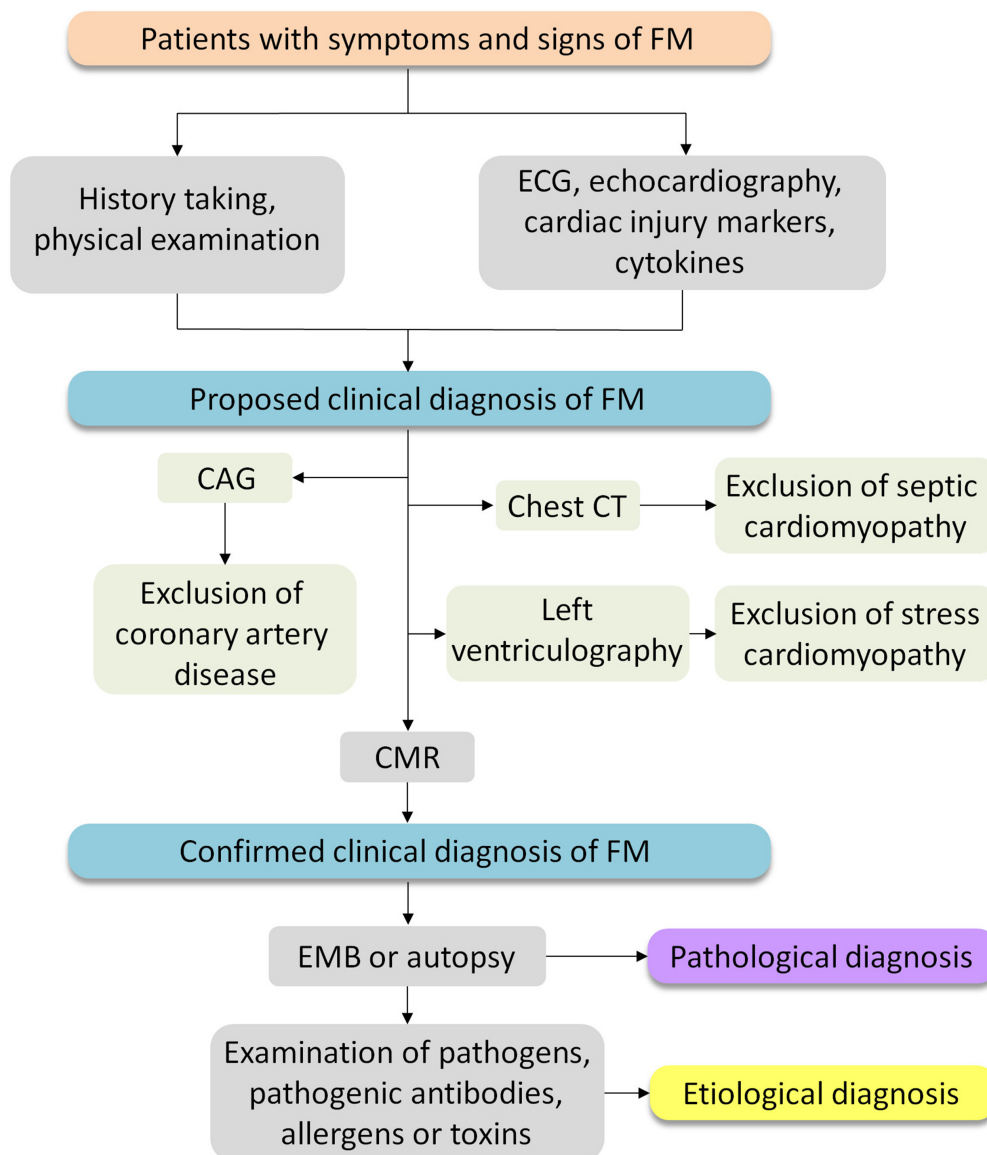


Figure 3. Diagnostic algorithm for FM^[3]. Electrocardiography (ECG), echocardiography, cardiac troponin I (cTnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and blood cytokine testing should be performed immediately; coronary angiography (CAG) is required to rule out coronary artery disease. Left ventriculography may be used to exclude stress cardiomyopathy, and chest computed tomography (CT) to rule out septic cardiomyopathy due to severe infection, when clinically indicated. Cardiac magnetic resonance imaging (CMR) should be scheduled at an appropriate time based on the patient's clinical status. EMB: Endomyocardial biopsy; FM: fulminant myocarditis.

including increased T2 signal on T2-weighted imaging or elevated T2 mapping values; (ii) Evidence of myocardial injury on T1 imaging, including late gadolinium enhancement (LGE), increased T1 mapping values, or elevated ECV^[32] [Figure 2C and D]. In addition, fluorodeoxyglucose uptake reflects metabolically active inflammatory cells in acute myocarditis, and fluorodeoxyglucose positron emission tomography (FDG-PET) is useful to detect disease activity when clinically indicated^[34,35].

Based on the above-mentioned clinical evaluations, the diagnosis of FM is established at three levels: clinical diagnosis, pathological diagnosis, and etiological diagnosis [Figure 3]. Patients with prodromal symptoms, abnormal ECG, elevated biomarkers of myocardial injury and inflammation, and abnormal echocardiographic findings are considered to have a clinical diagnosis of FM. After exclusion of myocardial infarction by coronary angiography (CAG), CMR or EMB should be performed as early as possible to confirm the diagnosis. Finally, etiological investigations include pathogenic microorganism detection, autoimmune antibody testing, and toxicology screening.

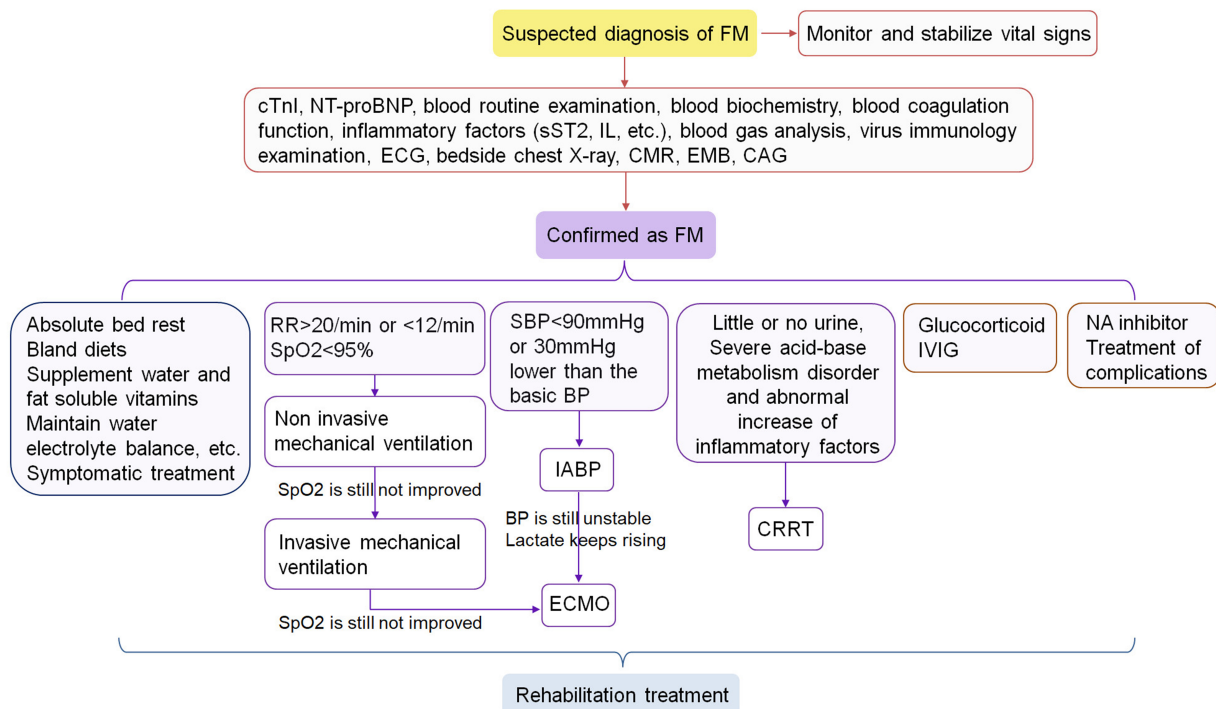


Figure 4. The treatment of FM in the acute phase^[3]. NT-proBNP: N-terminal pro-B-type natriuretic peptide; cTnl: cardiac troponin I; sST2: soluble growth stimulating expression gene 2 protein; IL: interleukin; ECG: electrocardiogram; CMR: cardiac magnetic resonance imaging; EMB: endomyocardial biopsy; CAG: coronary angiography; RR: respiratory rate; SpO2: blood oxygen saturation; SBP: systolic blood pressure; BP: blood pressure; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; CRRT: continuous renal replacement therapy; IVIG: intravenous immunoglobulin; NA: neuraminidase; FM: fulminant myocarditis.

TREATMENT OF FM IN THE ACUTE PHASE

Once FM is diagnosed or suspected, it is recommended to start standardized treatment immediately, known as “life support-based comprehensive treatment regimen” (hereafter referred to as the “comprehensive treatment regimen”; [Figure 4](#)). To facilitate efficient implementation, hospitals are advised to establish a rapid response team and a standardized, concise, and practical clinical pathway led by the cardiovascular team. Pre-hospital emergency care, emergency intensive care, imaging and pathology services, cardiovascular surgery, and a multidisciplinary treatment support team should be integrated into the rapid response system to ensure standardized delivery of the regimen and to improve the outcomes of patients with FM^[3].

The comprehensive treatment regimen is guided by the principle of “ultra-early recognition, ultra-early diagnosis, ultra-early prediction, and ultra-early rescue”. The primary therapeutic goal in FM is to promptly reverse acute circulatory failure and cardiogenic shock. Key recommendations of treatment are summarized in [Table 2](#).

The core components of the comprehensive treatment regimen include: (i) mechanical circulatory support (MCS). This strategy prioritizes “resting the failing heart” over elevating blood pressure with inotropes or vasoactive agents. Accordingly, MCS devices such as IABP, ECMO and Impella are recommended to maintain hemodynamic stability and adequate organ perfusion. Vasoactive drugs are generally not recommended unless MCS is unavailable. Inotropic agents are also not recommended except for temporary use during MCS; (ii) Immunomodulatory therapy. It primarily consists of early, combined, and sufficient doses of glucocorticoids and intravenous immunoglobulin (IVIG). Immunosuppressive therapy with cytotoxic agents is not recommended; (iii) Antiviral therapy. For patients with influenza virus infection, neuraminidase inhibitors are recommended. Emerging evidence suggests that neuraminidase inhibitors may

Table 2. Treatment of FM in the acute phase^[3] (see evidence in Supplementary Table 2)

Recommendations	Class ^a	Level ^b
MCS		
For patients with hemodynamic instability, early initiation of IABP is recommended ^[68-70]	I	A
Immediate initiation of ECMO is recommended when an IABP is insufficient to rectify the hemodynamic instability ^[71-73]	I	A
The Impella device, either alone or in combination with ECMO, should be considered for circulatory support in patients with FM ^[47,74]	IIa	C
Tandem heart, as a biventricular assist device, should be considered for circulatory support. In patients with predominant or concurrent right heart dysfunction, Impella RP (right heart assist device) should also be considered	IIa	C
Immunomodulatory Therapy		
After admission, intravenous methylprednisolone at a dosage of 3-8 mg/kg per day is recommended to be started as early as possible. After 3-5 consecutive days, the dose should be reduced by half, and subsequently maintained at 20-40 mg per day for 1-3 months ^[75-77]	I	A
Early administration of IVIG at a dose of 10-20 g per day is recommended. After 3-5 days, the dose should be halved to 5-10 g per day for additional 3 days, with a total cumulative dose of approximately 2 g/kg ^[78-80]	I	A
Other pharmacotherapy		
Oseltamivir phosphate capsule (75 mg orally, twice daily) should be considered, and peramivir may be used as an alternative. The course of treatment is typically 3-5 days ^[37,81]	IIa	C
Maintenance of mean arterial pressure within 60-65 mmHg is recommended to minimize the dosage and duration of vasoactive drugs, and to facilitate early referral of patients for MCS ^[82-84]	I	A
In patients on MCS, inotropic agents (levosimendan, milrinone, and cedilanid) should be considered to assist in weaning from the support devices ^[85,86]	IIa	C
Proton pump inhibitors should be considered to prevent stress ulcer and gastrointestinal bleeding ^[87,88]	IIa	C
Broad spectrum antibiotics should be considered for infection prophylaxis during and after MCS ^[41,42]	IIa	C
Routine use of antifungals is not recommended ^[89]	III	C
Other supportive treatment		
Mechanical ventilation should be considered as an adjunct in acute left heart failure to improve pulmonary function, reduce the patient's work of breathing, and decrease cardiac workload ^[4]	IIa	C
Early application of CRRT should be considered in patients with FM complicated by organ dysfunction, particularly when renal dysfunction is present ^[4,90]	IIa	C
Treatment of arrhythmia ^[91]		
In patients with tachyarrhythmia complicated by hemodynamic instability, immediate defibrillation or synchronized electrical cardioversion should be considered. Early use of extracorporeal life support therapy should be considered when arrhythmia cannot be terminated	IIa	C
In patients who are relatively hemodynamically stable, antiarrhythmic drugs with negative inotropic and negative chronotropic effects (such as adrenergic β -receptor blockers or non-dihydropyridine calcium channel antagonists) are not recommended	III	C
In patients with bradycardia, temporary pacemaker implantation should be considered. If temporary pacing is unavailable, drugs that raise heart rate, such as isoproterenol or atropine, may be considered as an alternative ^[92]	IIa	C
In patients with bradycardia, implantation of a permanent pacemaker is not recommended in the acute phase. ICD is not recommended in patients with ventricular tachycardia in the acute phase or following disease recovery	III	C
In patients whose clinical condition has been stable for more than 2 weeks but in whom conduction block persists without recovery, implantation of a permanent pacemaker should be considered	IIa	C

IABP: Intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; IVIG: intravenous immunoglobulin; CRRT: continuous renal replacement therapy; ICD: implantable cardioverter defibrillator; MCS: mechanical circulatory support; FM: fulminant myocarditis; Impella RP: Impella right pump. ^aclass of recommendation; ^blevel of evidence.

also attenuate myocardial injury through mechanisms beyond direct antiviral effects^[36,37]; (iv) Other supportive treatment. It includes mechanical ventilation, continuous renal replacement therapy (CRRT), and temporary pacemaker implantation when clinically indicated.

Management of complications is also critical to optimizing therapeutic efficacy and improving prognosis in patients with FM. Arrhythmias occur in 20%-30% of FM patients. The therapeutic objective is to prevent and correct hemodynamic instability caused by arrhythmias. For tachyarrhythmias, electrical cardioversion may

Table 3. Convalescent management for patients with FM^[3] (see evidence in Supplementary Table 3)

Recommendations	Class ^a	Level ^b
Follow-up assessment		
Patients with FM require regular and comprehensive evaluation after discharge, encompassing clinical manifestations, biomarkers, resting ECG, 24-hour Holter, echocardiography and CMR, as clinically indicated	I	C
Exercise and cardiac rehabilitation		
Moderate-to-high intensity exercise is not recommended in all patients with FM within 3-6 months following discharge ^[93-95]	III	B
Patients categorized as having “healing myocarditis” and “healed myocarditis” may benefit from cardiac exercise rehabilitation training ^[44]	I	C
Exercise training for cardiac rehabilitation is not recommended in patients with active myocarditis in the acute phase, defined by the presence of typical symptoms, elevated biomarker levels, and abnormal echocardiographic findings ^[46]	III	C
Immunomodulatory therapy in the convalescent phase		
In patients with GCM, EM, cardiac sarcoidosis, or ICI-associated myocarditis, corticosteroids or other immunosuppressive agents are recommended after discharge ^[96-98]	I	B
In patients with chronic lymphocytic myocarditis without evidence of viral infection as suggested by EMB, corticosteroid and immunosuppressive therapy are recommended to improve cardiac function ^[99]	I	B
In patients with persistently elevated myocardial injury biomarkers or CMR suggestive myocardial edema after discharge, corticosteroid therapy should be considered, as it may ameliorate myocardial inflammation ^[100,101]	IIa	C

ECG: Electrocardiography; CMR: cardiac magnetic resonance imaging; GCM: giant cell myocarditis; EM: eosinophilic myocarditis; ICI: immune checkpoint inhibitor; EMB: endomyocardial biopsy; FM: fulminant myocarditis. ^aclass of recommendation; ^blevel of evidence.

be used; for severe bradycardia or high-grade conduction block, temporary pacing is indicated^[38]. Lethal complications such as DIC and systemic capillary leak syndrome (SCLS) should be prevented through early recognition and prompt intervention to reverse cardiogenic shock and control the cytokine storm^[39,40].

It is important to note that FM is not primarily caused by bacterial infection; therefore, antibiotics are not indicated for the treatment of the underlying disease. However, broad-spectrum antibiotics are recommended for infection prophylaxis during and after MCS. If infection develops, aggressive and adequate antimicrobial therapy should be initiated promptly, followed by step-down de-escalation as early as possible to minimize microcirculatory injury^[41,42].

CONVALESCENT MANAGEMENT AND LONG-TERM FOLLOW-UP OF FM

Following standardized acute-phase treatment, the majority of patients with FM achieve clinical recovery. However, some patients may exhibit persistent myocardial inflammation and edema of varying degrees, which can lead to left ventricular dilation, arrhythmias, cardiac dysfunction, or even inflammatory cardiomyopathy^[43]. Therefore, rigorous and systematic clinical assessment is mandatory both before discharge and during long-term follow-up.

Post-discharge patients can be stratified into three categories: healed myocarditis, healing myocarditis, and persistent myocarditis^[44]. Oral corticosteroids are effective for patients with chronic inflammatory edema and persistently elevated myocardial injury biomarkers. For patients with pathologically confirmed giant cell myocarditis (GCM), eosinophilic myocarditis (EM), cardiac sarcoidosis, or ICI-associated myocarditis, corticosteroids or other immunosuppressive agents may be administered^[45].

All patients in the convalescent phase are recommended to receive angiotensin-converting enzyme inhibitors (ACEI), β -blockers, and trimetazidine^[4]. Moderate-to-severe physical activity is contraindicated within the first 3-6 months after discharge. Prior to initiating cardiac rehabilitation, a comprehensive clinical re-evaluation is essential. For patients with healed myocarditis, exercise-based cardiac rehabilitation may be initiated no earlier than 6 months after the acute onset, starting with low-intensity training^[44,46] [Table 3].

CONCLUSION

Multiple international societies have issued guidance documents on the management of myocarditis and/or FM. Table 4 summarizes key recommendations from the 2024 Chinese Guidelines^[3], the 2020 American Heart Association (AHA) Scientific Statement^[19], the 2024 American College of Cardiology (ACC) Expert Consensus^[47], and the 2025 European Society of Cardiology (ESC) Guidelines^[48]. These guidance documents demonstrate general consensus on the definition of FM, pathological diagnostic criteria, laboratory markers, diagnostic workflows, and the role of MCS. A previous review on the diagnosis and management of FM similarly aligns with these guidelines on the aforementioned aspects^[49]. However, that review places particular emphasis on the life-saving role of MCS in FM management and elaborates on the efficacy, advantages and limitations of various life-support devices including Impella, VA-ECMO, ECMELLA (VA-ECMO + Impella), PROPELLA (prolonged Impella support), BIPELLA [left-sided Impella circulatory pump (CP) combined with right-sided Impella right pump (RP)], and device escalation strategies in deteriorating myocarditis cases, thereby supplementing the current guidelines with detailed MCS-related insights. By contrast, the guidelines offer more comprehensive and systematic coverage. Notably, substantial controversies persist regarding pharmacotherapy between the Chinese Guidelines and other international guidance documents.

Previous guidelines generally recommended managing acute heart failure in FM in accordance with standard heart failure guidelines, utilizing vasoactive or inotropic agents^[19,47,48]. In contrast, the Chinese Guidelines exercise extreme restraint in the use of these drugs. Vasoactive agents are generally not recommended; they may be used only temporarily to maintain mean arterial pressure when MCS is unavailable, and should be discontinued once MCS is initiated. Inotropic agents are likewise not recommended, except as short-term adjunctive therapy to facilitate successful weaning from devices in patients receiving MCS^[3].

The Chinese Guidelines emphasize that the cornerstone of pharmacological therapy for improving heart failure lies in controlling overactivated inflammation through the combination of glucocorticoids and IVIG, irrespective of pathological subtypes. Other guidelines, however, hold that immunomodulatory therapy should be primarily reserved for specific subtypes of myocarditis (e.g., GCM or ICI-associated myocarditis). Historically, the use of glucocorticoids in infectious myocarditis has been controversial, primarily due to concerns regarding potential exacerbation of viral infection. However, research findings have revealed that dexamethasone administration in a mouse model of viral myocarditis reduced myocardial viral titers rather than promoting viral replication, which may result from a significant increase in interferon production^[37,50]. Thus, glucocorticoids exert immunomodulatory effects alongside multiple protective roles, including anti-shock activity, stabilization of lysosomal membrane structure, mitigation of toxin-induced damage, and reduction of myocardial depressant factor release. The early initiation of adequate glucocorticoid therapy is therefore deemed essential for the management of FM.

FM is predominantly a clinical diagnosis. The disease progresses rapidly during the acute phase, and pathological diagnosis is usually not obtainable in a timely manner. Circulating levels of inflammatory factors and sST2 can identify whether patients are in a state of excessive immune activation and cytokine storm, which is of great guiding significance for the initiation of immunomodulatory therapy. Notably, sST2 exhibits high sensitivity for distinguishing FM from non-FM conditions, surpassing that of NT-proBNP and cTnI. Through quantitative analysis, it was determined that patients presenting with relevant clinical manifestations and an sST2 level $> 58.39 \text{ ng}\cdot\text{mL}^{-1}$ should be considered for a suspected diagnosis of FM^[26]. Additionally, dynamic changes in plasma inflammatory factors and sST2 levels serve as reliable indicators of therapeutic response and clinical improvement, and are also important for guiding dose adjustments of immunomodulatory agents. Therefore, these guidelines recommend dynamic monitoring of inflammatory factors and sST2 in FM patients. Given variations in local healthcare systems, technical and cost-related

Table 4. Comparison of recommendations between current guidelines on myocarditis and FM

	2024 Chinese guidelines^[3]	2020 AHA scientific statement^[19]	2024 ACC expert consensus^[47]	2025 ESC guidelines^[48]
The subject	FM	FM	Myocarditis	Myocarditis and pericarditis
Definition of FM	FM refers to acute diffuse inflammatory damage of myocardium with hemodynamic abnormalities	FM is defined a sudden and severe inflammation of the myocardium resulting in myocyte necrosis, edema, and cardiogenic shock	A 4-stage classification of myocarditis is proposed FM is comparable with stage D, which is defined as advanced myocarditis as evidenced by hemodynamic instability requiring inotropes/vasopressors or TCS, or electrical instability requiring intervention	FM is defined as myocarditis with acute onset (≤ 4 weeks) and hemodynamically unstable patients requiring inotropes or MCS
Recommendations of EMB	EMB is actively recommended for FM, especially when a specific etiology is clinically suspected, such as the use of ICLs, autoimmune diseases, peripheral blood eosinophilia, to clarify the etiology, the pathological type, the status of myocardial injury and the guidance to clinical treatment	EMB is recommended for most patients presenting with FM	Most stage D patients should undergo EMB	EMB is recommended in patients with high-risk myocarditis, and/or hemodynamic instability, and/or in patients with intermediate-risk myocarditis not responding to conventional therapy in order to detect a specific histologic subtype and to assess the presence of viral genome for treatment
CAG	Depending on the clinical manifestations, it is recommended to perform CAG as early as possible to rule out acute myocardial infarction, regardless of whether the patient has high-risk factors for coronary atherosclerosis	No specific recommendation for CAG	Under the circumstances of an acute rise in troponin, myocardial infarction needs to be excluded by CAG or absence of ischemic LGE on CMR	Depending on the initial clinical assessment, ACS should be ruled out by coronary CT or invasive CAG depending on likelihood of obstructive coronary artery disease
MCS	MCS is the preferred therapeutic strategy in patients with a diagnosis of FM Immediate use of IABP is recommended in patients with FM who present with early manifestations of shock. Addition of ECMO is recommended when IABP is insufficient to correct circulatory disturbance. In patients with severe circulatory dysfunction, severe LV dysmotility or cardiac arrest, a combination of ECMO and IABP should be performed immediately	Nearly all patients with FM will require temporary MCS	Stage D patients who develop electrical or hemodynamic instability and require TCS or advanced therapies The TCS devices used most often include IABP, intravascular axial flow device (Impella), or VA-ECMO	Temporary MCS should be performed early and in a timely manner in patients with FM with refractory cardiogenic shock Among temporary MCS, ECMO represents the most frequently applied or recommended approach

Immunomodulatory therapy	The immunomodulatory therapy for FM comprises very early use of adequate doses of glucocorticoids and adequate doses of immunoglobulins. Cytotoxic immunosuppressant is not recommended in the treatment of FM.	Immunomodulatory therapy is considered according to the type of myocarditis: · Lymphocytic myocarditis: steroids may be helpful but still controversial · GCM: high-dose steroids combined with immunosuppressants (such as cyclosporine or azathioprine) · EM: high-dose corticosteroids · ICI-associated myocarditis: high-dose corticosteroids. Antithymocyte globulin or IVIG for unstable patients who do not respond to corticosteroids. Tacrolimus or mycophenolate mofetil for stable patients who do not respond to corticosteroids	Immunosuppressive therapy is used in these conditions: · EM · GCM · Granulomatous myocarditis (sarcoid) · ICI-associated myocarditis · Other autoimmune-related conditions Immunosuppressive therapy typically includes high-dose steroids. For GCM, cyclosporine or tacrolimus should be added. IVIG can be considered in the setting of inflammatory, antibody-mediated, or autoimmune disorders	Corticosteroids should be considered in patients with fulminant, non-infectious forms of myocarditis to stabilize the patients. For GCM, immunosuppressive therapy typically involves corticosteroids and one or two additional immunosuppressive agents (cyclosporine, azathioprine or mycophenolate mofetil)
Vasoactive drugs	The use of vasoactive drugs is not recommended for patients with FM. Only when MCS is unavailable, vasoactive drugs may be administered temporarily to maintain the mean arterial pressure in patients with FM. The referral of patients to a tertiary center and early use of MCS is recommended to minimize the dose and duration of vasoactive drug.	It mentioned nearly all patients with FM will require vasoactive drug support, and no detail was discussed	No specific description	It mentioned FM is a cause of cardiogenic shock, and should be treated accordingly with inotropic or vasopressor support, and no detail was discussed
Inotropic drugs	The use of inotropic drugs is not recommended in the acute phase of FM. In patients on MCS, inotropic agents should be considered to assist in weaning from the support devices	No specific description	Intravenous inotropic agents may be administered for evidence of inadequate cardiac output	It mentioned FM is a cause of cardiogenic shock, and should be treated accordingly with inotropic or vasopressor support, and no detail was discussed
Management of arrhythmias	For tachyarrhythmias that affect hemodynamics, cardioversion should be administered immediately, along with drugs to prevent recurrence. For hemodynamically stable arrhythmias, appropriate treatment and anti-arrhythmic drugs are selected based on clinical symptoms, cardiac functional status, and the nature of the arrhythmia. Temporary pacemakers should be installed immediately in patients with marked bradycardia or conduction block.	No specific description	The treatment of arrhythmia in myocarditis should be in keeping with current guidelines for arrhythmia, and the detail was not discussed in this expert consensus	Temporary transvenous external pacing should be considered in patients with high-degree conduction disorders. GCM is associated with a high risk of life-threatening VA and ICD implantation can be considered.
Advanced HF referral	The patients with FM should be handled in a medical center with a rapid response team for FM. Once the diagnosis of FM is made in an institution without processing capability, the treatment with drugs should be immediately started to maintain vital signs, allowing quick referral of patients to the tertiary centers.	For institutions without advanced HF surgical and medical management capabilities, consideration for transfer of patients with FM from the emergency department directly to a tertiary referral hospital is warranted	The patients with any of the following should be referred to an advanced HF center with a multidisciplinary myocarditis team: severe ventricular dysfunction; life-threatening arrhythmia; cardiogenic shock; refractory HF; fulminant onset; and most cases of HF/DCM with associated systemic immune-mediated disease; or suspected giant cell, eosinophilic, or sarcoid myocarditis	It is crucial to be aware of the severe condition and, when needed, to refer patients with FM to tertiary referral centers that can institute temporary MCS and perform early EMB.

Follow-up	Long-term follow-up should be conducted in all patients with FM after discharge. The follow-up contents include clinical symptoms and signs, echocardiography, ECG, cTnI, NT-proBNP, inflammatory indicators such as cytokines, CMR, and EMB if necessary in order to promptly detect abnormalities of cardiac structure and function and to prevent the occurrence of complications	No specific description	Longitudinal follow-up for stage D patients are typically conducted in 2 time points after discharge: 2-4 weeks: echocardiogram, biomarkers (hs-troponin, BNP and CRP) and ECG 6 months: CMR	Follow-up is recommended in all patients with myocarditis, with clinical assessment, ECG, Holter-ECG registration, exercise test (if no signs of ongoing inflammation), echocardiography, and CMR within at least 6 months after the index hospitalization
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AHA: American Heart Association; ACC: American College of Cardiology; ESC: European Society of Cardiology; MCS: mechanical circulatory support; TCS: temporary circulatory support; EMB: endomyocardial biopsy; ICI: immune checkpoint inhibitor; CAG: coronary angiography; CMR: cardiac magnetic resonance imaging; LGE: late gadolinium enhancement; ACS: acute coronary syndrome; CT: computed tomography; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; LV: left ventricle; GCM: giant cell myocarditis; EM: eosinophilic myocarditis; IVIG: intravenous immunoglobulin; VA: ventricular arrhythmias; ICD: implantable cardioverter defibrillator; HF: heart failure; DCM: dilated cardiomyopathy; ECG: electrocardiography; cTnI: cardiac troponin I; NT-proBNP: N-terminal pro-B-type natriuretic peptide; BNP: B-type natriuretic peptide; FM: fulminant myocarditis; CRP: C-reactive protein.

feasibility issues may affect the implementation of dynamic monitoring for these biomarkers. Regions may reasonably set the frequency and intervals of monitoring to strike an optimal balance between cost control and therapeutic management.

In previous reports, the in-hospital mortality rate among patients with FM ranged from 45%-55.6%^[7,10,11]. Two multicenter studies have evaluated the treatment regimen recommended by the Chinese Guidelines. Among 169 FM patients, 81 receiving the “life support-based comprehensive regimen” had an in-hospital mortality of 3.7%, compared with 46.6% in those not receiving this regimen^[37]. In another study comprising 138 FM patients, 96 treated with the recommended protocol showed an in-hospital mortality of 4.2%, versus 52.4% in patients not treated with the protocol^[20]. These findings demonstrate the efficacy of the comprehensive treatment regimen. Nevertheless, both studies were retrospective in design, and all enrolled patients were diagnosed clinically without pathological confirmation. Therefore, further clinical trials on FM based on pathological or CMR-confirmed diagnoses are essential to verify therapeutic efficacy.

Notably, the therapies specified in this regimen are primarily delivered in qualified medical centers. In clinical practice, timely access of FM patients to such centers is critical for effective rescue. The healthcare system for FM management consists of three core components: referral centers, primary-care units, and connecting networks. Referral centers should establish rapid response teams for FM and be equipped with life-support devices to admit patients and deliver standardized treatment per the protocol. Primary-care units should prioritize capabilities in recognizing, diagnosing, and providing emergency management for FM, so as to stabilize patients and secure opportunities for timely referral. The connecting networks focus on regular training for primary-care providers; when FM patients present, they enable information exchange and online guidance between referral centers and local units, and allow prompt initiation of referral to minimize transit-related delays. Given regional disparities in healthcare system models and available resources, the number, distribution, and density of referral centers, primary-care units, and supporting networks vary across regions, leading to divergent response efficiencies. Provided that each region maintains the integrity of these three components according to local conditions and ensures unobstructed referral pathways, patients can be transferred to qualified centers as early as possible to maximize their chances of receiving standardized treatment.

The regimen proposed in the Chinese Guidelines still has limitations. Notably, for acute-phase management, the regimen is not stratified according to pathological subtypes, and no dedicated strategies have been established for special subtypes such as GCM and ICI-associated myocarditis. Given the abrupt onset and rapid progression of FM, most existing clinical studies focus on myocarditis in general, with FM included merely as a subgroup. There are few clinical trials specifically targeting FM, featuring small sample sizes, and substantial practical obstacles remain to the design and implementation of randomized controlled trials. Continuous accumulation of clinical evidence will therefore be required going forward. Notably, there are substantial discrepancies between the Chinese Guidelines and other international guidelines regarding the scope of application for immunomodulatory therapy, and further clinical evidence is needed to underpin the respective recommendations.

Current immunomodulatory therapies exert broad-spectrum effects through non-selective interference with inflammation. Developing targeted therapeutic approaches based on specific inflammatory pathways and molecules may represent a novel strategy for precise immunomodulation in the future (e.g., sST2-neutralizing antibodies^[51]). Elevated levels of S100A8/A9 have also been associated with cardiac dysfunction and disease severity in FM patients^[52], and nanoparticles delivering S100A9-targeting siRNA have been shown to block neutrophil infiltration and improve cardiac function in a mouse model^[53]. Among FM patients who survive the acute phase, follow-up data indicate that approximately one-quarter of patients still present symptoms such as cardiac enlargement, heart failure, and arrhythmias one year after discharge^[54]. To date, limited interventions have been established to improve the long-term outcomes of these patients, highlighting the need to advance our understanding of the chronic disease trajectory of FM. It was reported that hydroxychloroquine combined with prednisolone therapy significantly improved the prognosis and heart function in patients with chronic inflammatory cardiomyopathy^[55]. In summary, these issues require further investigation, and the life support regimen will be refined and updated in light of future research findings.

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Authors' contributions

Designed the review and revised the manuscript: Wang DW
Wrote the manuscript: Wen Z, Shu H, Jiang J, Li C, Fan J, Ran X
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Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

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Conflicts of interest

Wang DW is a Consulting Editor of *The Journal of Cardiovascular Aging* and a Guest Editor of the Special Issue "Fulminant Myocarditis: Mechanisms, Diagnostics, and Life Support Strategies". Wang DW was not involved in any stage of the editorial process for this manuscript, including reviewer selection, manuscript

handling, or decision-making. The other authors declare that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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