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Review Article

# Clozapine-Induced Myocarditis: A Systematic Review of Case Reports

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**ABSTRACT**

Clozapine-Induced Myocarditis (CIM) is a rare but potentially life-threatening adverse drug reaction linked with the use of clozapine in treatment-resistant. The aim of this systematic review is to recognise the clinical features, diagnostic findings, and clozapine rechallenge outcomes. A systematic literature search was carried out according to the PRISMA 2020 guidelines using PubMed, Scopus, Web of Science and Google Scholar. Case reports published within the past 10 years were screened, and the following data were extracted: demographic details, clinical presentation, diagnostic findings, and outcomes. Using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist, the quality of included case reports was evaluated. Within the first 2 to 4 weeks of clozapine administration, myocarditis development was reported. The most common clinical symptoms included sinus tachycardia, fever, chest pain, and flu-like symptoms. Elevated cardiac troponins and inflammatory markers were the most dependable diagnostic findings, rather than electrocardiographic and echocardiographic, as they were variable. The primary management approach was sudden discontinuation of clozapine and cardiac supportive care. Clozapine rechallenge was attempted in selective cases with critical monitoring but had outcome variations. Clozapine-induced myocarditis is a rare but fatal adverse drug reaction which requires immediate recognition. Timely discontinuation of clozapine and supportive management are important for suitable outcomes. Standard monitoring protocol and more research in predictive biomarkers are critical to improve patient safety and early recognition.

**Keywords:** Adverse drug reaction, Clozapine, Drug-induced cardiotoxicity, Myocarditis.

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## INTRODUCTION

Clozapine is the gold standard pharmacological intervention for the treatment of psychotic disorders, indicating high efficacy in patients who have failed respond to other antipsychotic drugs. Some clinical data has stated that clozapine is more effective in lowering suicidal thoughts and combativeness in this population. These results do not constantly match those of other second-generation antipsychotics (Ronaldson *et al.*, 2012). Regardless of these recognized therapeutic benefits, clozapine has limited utility due to its links with potent life-threatening adverse effects. These adverse effects range from the known risk of agranulocytosis to severe cardiovascular complications such as myocarditis and cardiomyopathy (Higgins *et al.*, 2019). Clozapine-Induced Myocarditis (CIM) is an atypical but major inflammatory disorder of the heart muscle that has a significant risk of mortality. Beyond different geographical regions, reported cases of CIM vary from less than 0.1% in North America and Europe to as high as 3% or more in Australia (Caetano, 2009).

The accurate pathophysiology mechanisms of clozapine-associated myocarditis have not yet been fully determined. In spite of that, many pathways have been put forward. A primary theory conveys an IgE-mediated type 1 hypersensitivity reaction (Jayathilake and Singh, 2009). Drug-induced hypercatecholaminergic state is also observed due to alternative pathophysiological mechanisms in which high amounts of epinephrine and norepinephrine contribute to myocardial inflammation (Markovic *et al.*, 2011). Furthermore, the direct cardiotoxicity involved oxidative stress, which will release the pro-inflammatory cytokines like tumour Necrosis Factor-Alpha (TNF-α), and mitochondrial dysfunction has been engaged in the pathophysiology mechanism of this condition (Yuen *et al.*, 2018).

As per clinical data, CIM occurs early in the course of the therapy. In the majority of the reported cases, it is observed within the first four weeks of the treatment, and the risk increases at the third week. Due to the broad clinical presentation involving tachycardia, fever, fatigue, and flu-like symptoms, making a clear diagnosis is often complicated (Layland *et al.*, 2009). These clinical symptom patterns can be difficult to determine from the small physiological responses that occur commonly during clozapine

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titration. These common responses include sedation and benign sinus tachycardia, or other adverse effects like Clozapine-Induced Pneumonia (CIP) (Wang *et al*., 2008). This results in the delayed or missed diagnosis, as it demands dependence on biomarkers such as C-Reactive Protein (CRP) and troponin, along with imaging methods like echocardiography and Cardiac Magnetic Resonance (CMR), to differentiate CIM from other aetiologies (Yağcıoğlu *et al*., 2019).

There are various risk factors that increase the CIM exposure, involving rapid dose titration and the accompanying other psychotropic medications, specifically sodium valproate and selective serotonin reuptake inhibitors (Daniel *et al*., 2023; Li *et al*., 2025). Yet the current treatment strategies prominently need the rapid cessation of clozapine. Currently, there is a lack of standardized guidelines and the crucial urgency to stabilise the cardiotoxicity risks (Mahgoub *et al*., 2025).

The goal of this systematic review is to analyse the prevailing literature, which includes case reports, for better understanding of the clinical presentations, risk factors, and treatment outcomes of clozapine-induced myocarditis.

## METHODOLOGY

### Search Strategy and Study Selection

This systematic review was performed in accordance with the PRISMA 2020 guidelines to assess the clinical features, management outcomes and diagnostic findings of clozapine-induced myocarditis. A systematic and comprehensive literature search was conducted beyond major digital databases involving PubMed, Scopus, Web of Science, and Google Scholar, to obtain and determine the appropriate studies.

Search keywords such as *"clozapine", "myocarditis", "cardiotoxicity", "cardiac inflammation", "myopericarditis", "adverse drug reaction"*, and *"drug-induced cardiomyopathy"* were adapted to identify the applicable studies. To filter the search strategy and optimize understanding while at the same time supporting applicability, Boolean operators (AND, OR) were applied. Specifically, the search strings used in PubMed search were "clozapine AND (myocarditis OR cardiotoxicity OR "cardiac inflammation")". The scopus database search strategy involved "TITLE-ABS-KEY ((clozapine) AND (myocarditis OR myopericarditis OR pericarditis OR cardiotoxicity) AND ("case report*" OR "case series" OR "case study" OR rechallenge))". Filters were utilized to limit results to published case reports within the past 10 years, considering a current evaluation of clozapine-induced cardiac adverse events.

This systematic review focuses on case reports presenting detailed clinical data, permitting in-depth assessment of clinical presentation patterns, approach toward diagnosis, and management outcome linked with clozapine-induced myocarditis.

### Study Inclusion and Screening Process

Titles and abstracts were separately screened for appropriateness to the study aim and background. Articles matching the primary inclusion criteria were consequently examined with the full-text to verify eligibility. Importance was given to case reports and case series which have detailed descriptions about clozapine-induced myocarditis or myopericarditis with proper clinical details.

The case reports that were published in English language were only included for data accuracy and better interpretation as per the search strings. The exclusion criteria for the study were to not include conference abstracts, editorials, commentaries, and review articles.

Dissimilarities about study inclusion were finalised through discussion and common consent. The study selection method was documented using a PRISMA 2020 flow chart diagram, which also ensured clarity and transparency. In which detailed the number of records identified, screened, excluded, and finally included at each stage of the review process were involved (Figure 1).

### Data Extraction

Systematic data extraction was completed from eligible peer-reviewed case reports to ensure reliability in assessing the clinical features of clozapine-induced myocarditis. Extracted data included study details, year of publication, and country of origin.

Demographic details like age, sex, and comorbid conditions were collected to determine potent risk patterns. Data regarding clozapine, including dosage, titration schedule, and duration of therapy, were noted to assess the progressive connection between drug administration and myocarditis development.

Patient-oriented demographic information such as age, sex, and comorbid medical conditions was collected to identify potential risk patterns. Details regarding clozapine exposure, including dosage, titration schedule, and duration of therapy prior to symptom onset, were recorded to evaluate temporal relationships between drug initiation and myocarditis development.

The signs and symptoms extracted included persistent sinus tachycardia, fever, chest pain, dyspnea, flu-like symptoms, gastrointestinal complaints, and other systemic manifestations. To evaluate the accurate diagnosis and condition severity, cardiac biomarkers (troponin, BNP), inflammatory markers (CRP, ESR), electrocardiographic changes, echocardiographic findings, and cardiac magnetic resonance imaging were documented. Clozapine discontinuation and cardiac supportive care therapy were included as the primary management approach. Clozapine rechallenge data has also been extracted.

The extracted data were analysed to determine the recurrent therapeutic patterns, diagnostic approaches, and treatment outcomes, with results summarised in Table 1.

## Quality Assessment

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports was been used to maintain the better quality to include and evaluate case reports. This checklist mainly evaluates using key points that are clarity of patient demographics, adequacy of clinical history, diagnostic accuracy, intervention description, and outcome reporting. Case reports which match the JBI checklist standards were only included to increase the credibility and validity of this systematic review. The quality evaluation results were presented in Table 2.

## RESULTS

After appropriate data extraction and quality assessment, 20 case reports and 2 case series were included for final analysis, which described clozapine-induced myocarditis. Within the duration of 2016 and 2025, these cases were published and geographically originated from multiple countries, with the majority from the United States, followed by Europe and Asia.

Using rapid or moderate titrations, clozapine was primarily administered. The daily doses at the time of clinical presentation were varying from 100 mg/day to 350 mg/day.

The cardiac adverse events occurred early, most likely within the first 2-4 weeks of clozapine administration. In between 2-8 days myocarditis developed in several cases; at the same time some cases presented late development during the 3 to 4 weeks of treatment. Prolonged clozapine-associated cardiomyopathy was uncommon.

A lot of variation was observed in clinical manifestations. The common presented symptoms include fever and flu-like symptoms, constant sinus tachycardia, chest pain (pleuritic and substernal), fatigue and dyspnea, and gastrointestinal issues (nausea, vomiting, diarrhoea).

Excluding concealed tachycardia, many patients were primarily asymptomatic. As it highlights the potential for missed or delayed diagnosis. The majority of the cases presented biomarker evidence of myocardial injury and cardiac inflammation. The

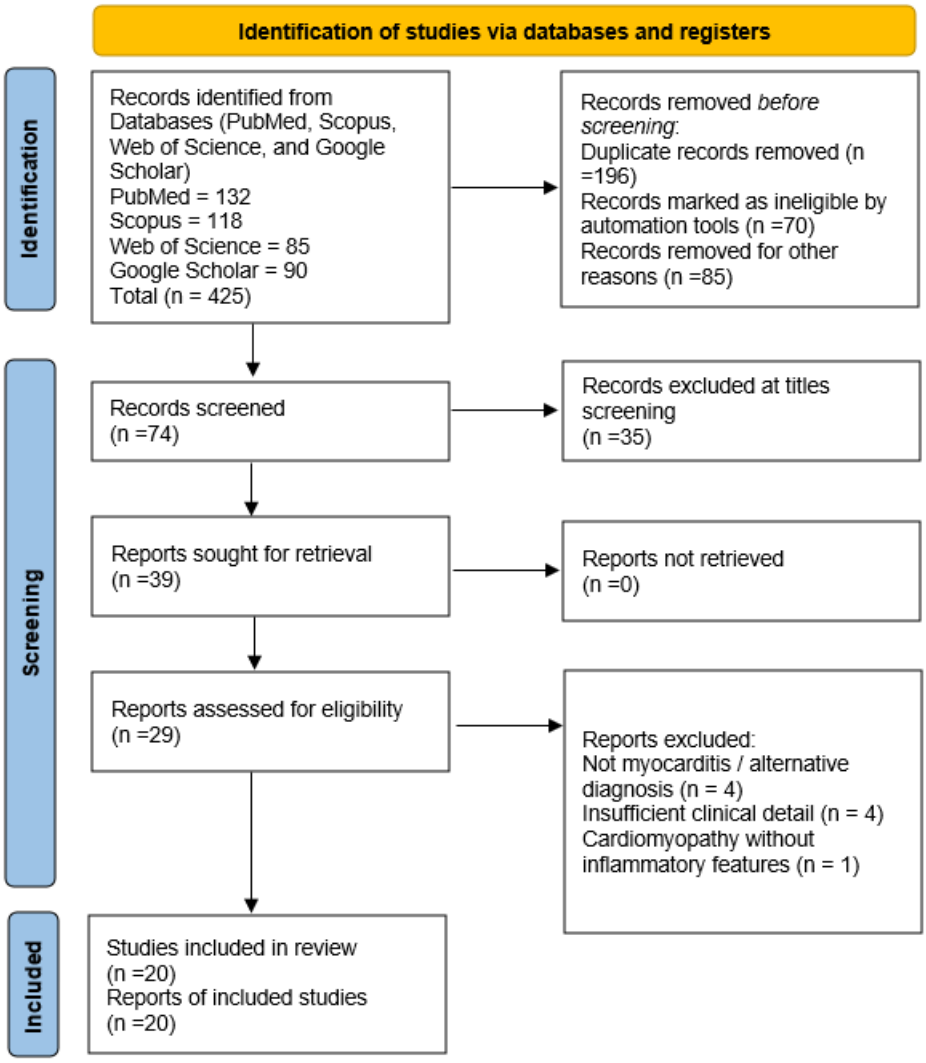


**Figure 1:** The study selection process based on the PRISMA guidelines 2020.

**Table 1: Data Extraction from the Collected Case Report.**

| Author (year) | Country | Age | Sex | Time to onset | Outcome | Rechallenge |
|---|---|---|---|---|---|---|
| Datta and Solomon, 2018 | USA | 40 | Female | 2 days | Full recovery | No |
| Beebani *et al.*, 2021 | USA | 21 | Male | 4 days | Full recovery | No |
| Danilewitz *et al.*, 2021 | Canada | 27 | Male | Initial course: Day 12-16 | Significant recovery. | Yes (successful) |
| Malik *et al.*, 2018 | USA | 19 | Male | Within first weeks of administration | Symptom relieved within 2 days (lost to follow-up). | No |
| Otsuka *et al.*, 2019 | Japan | Late 20s | Male | Day 15 after administration | Recovered; biomarkers normalized. | Yes (successful) |
| Mudra *et al.*, 2018 (Patient A) | Germany | 17 | Male | Day 12-15 | Recovered; biomarkers normalized within two weeks. | No |
| Mudra *et al.*, 2018 (Patient B) | Germany | 15 | Male | Day 14-19 | Recovered; biomarkers normalized. | Yes (failed—recurrence within 4-5 days) |
| Masmoudi *et al.*, 2018 | Tunisia | 24 | Male | Around day 24 (fourth week of therapy) | Recovered; LVEF normalized to 60%. | No |
| Swart *et al.*, 2016 | Netherlands | 22 | Male | ~11 days after administration | Full recovery | No |
| Boscutti *et al.*, 2022 | Italy | 31 | Male | Day 19 after initiation | Full recovery | Yes (successful) |
| Sackey *et al.*, 2018 (Case 1) | USA | 35 | Male | Day 26 | Recovered | No |
| Sackey *et al.*, 2018 (Case 2) | USA | 45 | Male | Day 13 | Recovered | No |
| Mutlu *et al.*, 2024 | Turkey | 13 | Female | Day 15 | Recovered | No |
| Gourisaria *et al.*, 2025 | United Kingdom | 42 | Male | Not clearly mentioned (chronic use) | Significant recovery. | No |
| Hamilton *et al.*, 2022 | USA | 31 | Male | Day 14-16 after initiation | Recovered; rapid improvement within 36-48 hr. | No |
| Im *et al.*, 2021 | USA | 49 | Male | ~3-4 weeks after initiation | Recovery after withdrawal; stabilized and discharged. | No |
| Laws *et al.*, 2021 | USA | 29 | Male | Day 8 after clozapine initiation | Full recovery with normalization of LV function. | No |
| Holden and Begum, 2022 | United Kingdom | 60s | Female | Day 8-18 after initiation | Full recovery. | Yes (successful) |
| Adetiloye *et al.*, 2022 | USA | 29 | Male | Day 20 after initiation | Full recovery; LVEF improved to 55%. | No |
| Brazile *et al.*, 2021 | USA | 25 | Male | ~14 days after initiation | Full recovery; recovery of LV function. | No |

| Author (year) | Country | Age | Sex | Time to onset | Outcome | Rechallenge |
|---|---|---|---|---|---|---|
| Hosseini *et al.*, 2020 | USA | 22 | Male | ~16 days after initiation | Full recovery; Ejection fraction improved to 45-50%, biomarkers normalized. | Yes (successful) |
| Deardorff *et al.*, 2018 | USA | 30 | Male | Day 15-18 after initiation | Became afebrile post-discontinuation with decreasing CRP. | No |

very common abnormalities were observed in some patients, like elevated cardiac troponins, high C-Reactive Protein (CRP), elevated B-type Natriuretic Peptide (BNP), eosinophilia and leukocytosis in some patients.

Electrocardiogram (ECG) findings were unspecific and mostly presented sinus tachycardia, ST-segment changes, or QTc prolongation. Decreased Left Ventricular Ejection Fraction (LVEF) was observed in several patients. Even though some patients showed preserved systolic function in spite of notable biomarker elevation. In some cases, cardiac magnetic resonance imaging was performed, which reported myocardial edema and late gadolinium enhancement.

Most of the cases were diagnosed as acute myocarditis, while several demonstrated myopericarditis or perimyocarditis. A minor set of patients presented with myocarditis associated with acute cardiomyopathy, and one case reported chronic non-dilated cardiomyopathy followed by long-term clozapine use.

As soon as myocarditis was suspected or determined, clozapine was stopped in all the cases. The treatment which was administered for cardiac supportive care includes beta-blockers and ACE inhibitors, diuretics, nonsteroidal anti-inflammatory drugs or colchicine and critical care monitoring in very severe cases. Routine endomyocardial biopsy was not performed on any of the patients.

After the immediate clozapine withdrawal, patients observed symptomatic relief and biochemical improvements with normal inflammatory markers.

A zero-mortality rate resulted in all included cases. In many cases, patients showed complete recovery of left ventricular function on follow-up echocardiography.

As per the included cases, clozapine rechallenge was performed in six patients. As a result, using very slow titration and close monitoring, five rechallenges were successful. Only one rechallenge resulted in relapse of myocarditis, warranting permanent discontinuation. Successful rechallenge was reported more prominently when the myocarditis episode was mild and promptly reversible.

## DISCUSSION

This systematic review gathers the published case reports with detailed descriptions of clozapine-induced myocarditis. It is mainly highlighting the early onset effect of clozapine and its general outcomes. In some cases, it also appears that rather than a dose-dependent toxic effect, it represents an immune-mediated inflammation.

In several cases, myocarditis generally developed in the first month of clozapine administration, with many cases presenting within the first 2-3 weeks (Datta *et al.*, 2018; Beebani *et al.*, 2021; Malik *et al.*, 2018). Some reports documented very early onset, that is, within the first week (Datta *et al.*, 2018; Laws *et al.*, 2021). These findings suggest that myocarditis can develop rapidly and aggressively with early onset.

In some cases, a hypersensitivity-mediated mechanism is also interconnected between clozapine initiation and symptom onset, rapid improvement following drug discontinuation, frequent elevation of inflammatory markers, and the presence of eosinophilia (Masmoudi *et al.*, 2018; Mudra *et al.*, 2018).

As per the included reports, the clinical presentations of CIM were highly variable. There are certain common clinical features present, including fever, persistent sinus tachycardia, chest pain, dyspnea, and flu-like symptoms (Beebani *et al.*, 2021; Sackey *et al.*, 2018; Boscutti *et al.*, 2022). Especially, some patients were initially asymptomatic, with inexplicable tachycardia as the only early abnormal symptom (Masmoudi *et al.*, 2018; Otsuka *et al.*, 2019).

Laboratory findings were more constant than clinical symptoms. Elevated cardiac troponins and C-reactive protein levels were reported in almost every case and often followed imaging abnormalities (Datta *et al.*, 2018; Adetiloye *et al.*, 2022). Electrocardiographic findings were usually unclear; echocardiographic reports varied from preserved systolic function to severe left ventricular dysfunction (Swart *et al.*, 2016; Hosseini *et al.*, 2020). Magnetic resonance imaging impressions also supported the evidence of myocardial inflammation (Brazile *et al.*, 2021; Laws *et al.*, 2021). All of the above findings significantly suggest myocarditis development.

In all the included case reports, discontinuation of clozapine was the initial management approach and resulted in rapid clinical

**Table 2: Quality Assessment of the Collected Case Reports by Using JBI Scale.**

| Study (Author, Year) | Demographics | Patient History | Clinical Condition | Diagnostics | Intervention | Post-Intervention Outcome | Adverse Event Identified | Takeaway Lessons | Included |
|---|---|---|---|---|---|---|---|---|---|
| Datta and Solomon, 2018 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Beebani *et al.*, 2021 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Danilewitz *et al.*, 2021 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Malik *et al.*, 2018 | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Included |
| Otsuka *et al.*, 2019 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Mudra *et al.*, 2018 (Case A) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Mudra *et al.*, 2018 (Case B) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Masmoudi *et al.*, 2018 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Swart *et al.*, 2016 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Boscutti *et al.*, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Sackey *et al.*, 2018 (Case 1) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Sackey *et al.*, 2018 (Case 2) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Mutlu *et al.*, 2024 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Gourisaria *et al.*, 2025 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Hamilton *et al.*, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Im *et al.*, 2021 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Laws *et al.*, 2021 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Holden and Begum, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Adetiloye *et al.*, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| Hosseini *et al.*, 2020 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |

improvement in most of the patients (Datta *et al.*, 2018; Hamilton *et al.*, 2022). For cardiac supportive therapy, beta-blockers, ACE inhibitors, diuretics, and anti-inflammatory agents were included, especially in patients with reports of reduced left ventricular ejection fraction (Adetiloye *et al.*, 2022; Hosseini *et al.*, 2020).

As per these findings, overall outcomes were promising with complete cardiac function recovery. The mortality rate was zero among all the included cases. According to our findings, it is crucial to understand the importance of early recognition and rapid drug withdrawal.

As myocarditis is considered a life-threatening adverse drug reaction, clozapine rechallenge has a high risk. Clozapine rechallenge was attempted in a limited number of patients. In most of the cases, rechallenge was successful when performed with very slow titration and prominent cardiac function monitoring (Otsuka *et al.*, 2019; Danilewitz *et al.*, 2021; Holden and Begum, 2022). Although, in one adolescent patient, a rechallenge attempt resulted in recurrence of myocarditis (Mudra *et al.*, 2018). As per the results and findings, rechallenge may be carefully considered in selected patients with resistance.

## LIMITATIONS

This systematic review has certain limitations that are to be considered. The evidence for the study was mainly obtained from published case reports. As case reports are basically subjective to publication and as reporting bias. It also does not allow the establishment of causality or estimation or incidence of the diseases. Secondly, a very significant heterogeneity also exists among the case reports included like patient characteristics, diagnostic approaches, treatment strategies, and outcome reporting, limiting direct comparisons between cases. Thirdly, the studies that were only published in English were included that makes the study in language bias. It also avoids the relevant cases published in other languages.

## CONCLUSION

Clozapine-induced myocarditis is one of the most potentially life-threatening conditions but is very rare. It commonly develops within the first month of clozapine therapy and presents with unclear symptoms. Elevated levels of cardiac troponins and inflammatory markers are more dependable indicators than electrocardiogram or echocardiography. To significantly improve recovery outcomes, sudden discontinuation of clozapine and prompt cardiac supportive care are important. Clozapine rechallenge should be attempted only in selective cases under strict cardiac function monitoring due to the high risk of recurrence.

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## ABBREVIATIONS

**ACE:** Angiotensin-Converting Enzyme; **BNP:** B-type Natriuretic Peptide; **CIM:** Clozapine-Induced Myocarditis; **CIP:** Clozapine-Induced Pericarditis; **CMR:** Cardiac Magnetic Resonance Imaging; **CRP:** C-Reactive Protein; **ECG:** Electrocardiogram; **ESR:** Erythrocyte Sedimentation Rate; **JBI:** Joanna Briggs Institute; **LV:** Left Ventricle / Left Ventricular; **LVEF:** Left Ventricular Ejection Fraction; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **TNF:** Tumor Necrosis Factor.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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