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REVIEW

Interpretation of Cardiac Magnetic Resonance Post-Contrast Sequences and Late Gadolinium Enhancement in Takotsubo Syndrome

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Abstract

Purpose of Review To analyze the diagnostic utility of cardiac magnetic resonance (CMR) images, including post-contrast sequences and late gadolinium enhancement (LGE) findings in Takotsubo syndrome (TTS).

Recent Findings TTS usually mimics acute coronary syndrome, making differential diagnosis challenging. CMR plays a key role in TTS diagnosis, particularly through T2 weighted/T2 mapping and LGE sequences. While TTS is not characterized by fibrosis replacement, LGE is detected in approximately 25% of cases, raising questions about its interpretation and prognostic relevance.

Summary This perspective article aims to critically analyze the challenges in LGE interpretation, including patterns, timing, imaging protocols, and pathophysiological mechanisms in TTS. Standardization of CMR protocols and artificial intelligence-based techniques may improve accuracy. Further research is needed to explore the LGE's impact on TTS prognosis and clinical management.

Keywords Cardiac magnetic resonance · Artificial intelligence · Late gadolinium enhancement · Fibrosis · Takotsubo syndrome · Stress cardiomyopathy

Introduction

Stress cardiomyopathy, also referred as Takotsubo syndrome (TTS) is an acute, transient, and reversible left ventricular dysfunction often challenging to distinguish from an acute coronary syndrome [1]. Cardiac magnetic resonance (CMR) imaging has become a cornerstone in TTS diagnosis, providing superior myocardial tissue characterization and diagnostic yield compared to echocardiography and coronary angiography, leading to an accurate differential diagnosis [2]. Among CMR sequences, the T2 and post-contrast gadolinium-based sequences provide valuable insights into myocardial injury occurring during TTS, yet late gadolinium enhancement interpretation in TTS remains challenging. This perspective article discusses the interpretation and limitations of late gadolinium-enhanced CMR sequences in the setting of TTS.

Takotsubo Features and Cardiac Magnetic Resonance

TTS patients present with impaired myocardial contractility due to regional wall motion abnormalities extending beyond one single coronary distribution [1]. The ventricular dysfunction results in acute heart failure without evidence of obstructive epicardial coronary artery disease. TTS can manifest in various clinical presentations, and multiple echocardiographic patterns [3], and is typically triggered by emotional or physical stress, including comorbidities and severe physical illness [4–7]. Diagnosis is made according to either Mayo Clinic or InterTak criteria [8, 9]. The heightened sympathetic nervous system activation with catecholamine overproduction, which characterizes TTS pathophysiology [10], induces chest pain, myocardial stunning, and microvascular dysfunction, eventually leading to overt acute heart failure and arrhythmias. Although the pathophysiology is not fully understood, catecholamines play an essential role. The mechanism by which catecholamines

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cause TTS includes irreversible cellular calcium overload, mitochondrial dysfunction, and reactive oxidative species over-expression [4].

Although initially considered benign, emerging evidence highlights its potential for adverse outcomes [11–13]. Accordingly, an accurate diagnosis and prognostication is necessary. CMR has been shown to play a crucial role in distinguishing TTS from acute myocardial infarction and myocarditis, monitoring its resolution over time [14]. Unlike ischemic cardiomyopathy and myocarditis, which are associated with necrosis leading to irreversible fibrosis replacement, the myocardial dysfunction in TTS is the expression of stunning myocardium secondary to microvascular dysfunction, catecholamine-induced toxicity, and myocardial edema without significant fibrosis.

Late Gadolinium-Enhancement Interpretation in Takotsubo Syndrome

Typical cardiac magnetic resonance (CMR) features of Takotsubo syndrome (TTS) include myocardial edema, which is detectable via T2-weighted imaging and T2 mapping. A key distinguishing feature from myocardial infarction is the absence of ischemic-pattern late gadolinium enhancement (LGE). In some cases, atypical or diffuse LGE patterns may be observed. Although TTS is not characterized by replacement fibrosis—and the absence of LGE is often used to support its diagnosis based on consensus and clinical experience—a notable proportion of patients (approximately 25%) do present with LGE on CMR [15]. Figure 1 provides a point-by-point guide for LGE interpretation.

The LGE pattern in ischemic cardiomyopathy is either sub-endocardial or transmural, reflecting coronary distributions, while it might be either sub-epicardial, mid-wall, or patchy in myocarditis. Both ischemic cardiomyopathy and myocarditis exhibit high signal intensity LGE. Conversely, TTS is characterized by either a transmural or patchy pattern with a lower signal intensity (Fig. 2) [16].

Second, the timing of CMR acquisition has been shown to significantly influence LGE detection. Studies have consistently shown that the earlier the scan is performed, the higher the likelihood of identifying LGE. Specifically, a comparison between studies that performed CMR within three days of symptom onset and those conducted later revealed a significant difference [15]. While late imaging (beyond three days) detected LGE only in a small fraction of cases [17, 18], , early imaging within the first three days showed a markedly higher detection rate [19–21]. This finding likely explains the low prevalence of LGE in routine clinical practice and supports the hypothesis that LGE in TTS primarily reflects transient myocardial extracellular expansion secondary to myocardial edema a concept that will be explored further below. Consequently, the interpretation of LGE patterns may vary significantly depending on whether the scan is conducted within the first few days of symptom onset or later in the disease course.

Third, the technical protocol applied might influence LGE detection. Different protocols exist, varying in their sensitivity to LGE, and they employ either qualitative or quantitative approaches. The former method relies on visual interpretation, classifying myocardial enhancement simply as present or absent. Conversely, the latter requires operators to manually delineate the endocardial and epicardial borders, allowing for a semi-automated calculation of the LGE percentage [22]. Sensitivity thresholds often expressed as standard deviations above the mean signal intensity, also impact detection rates. Studies utilizing higher-sensitivity protocols consistently report greater LGE detection compared to those employing lower-sensitivity techniques [21, 23, 24]. These observations underscore the critical role of the imaging protocol, which must be carefully considered when interpreting LGE findings.

Finally, the underlying mechanisms of LGE in TTS differ from those observed in ischemic cardiomyopathy and myocarditis (Table 1). In the former, myocardial necrosis results from an oxygen supply-demand mismatch, whereas in the latter, it arises from a cytotoxic inflammatory response.

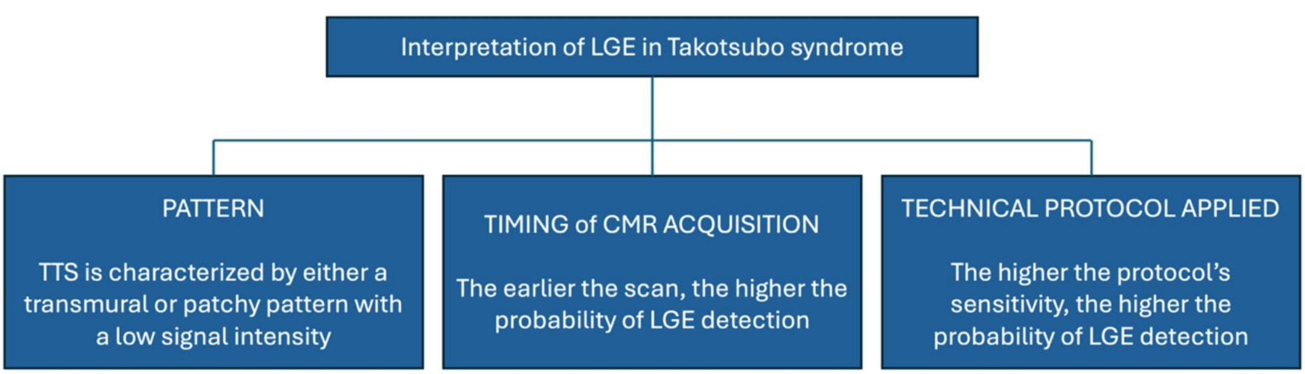

Fig. 1 Aspects to be considered when interpreting LGE in takotsubo syndrome. LGE: late gadolinium enhancement; TTS: takotsubo syndrome

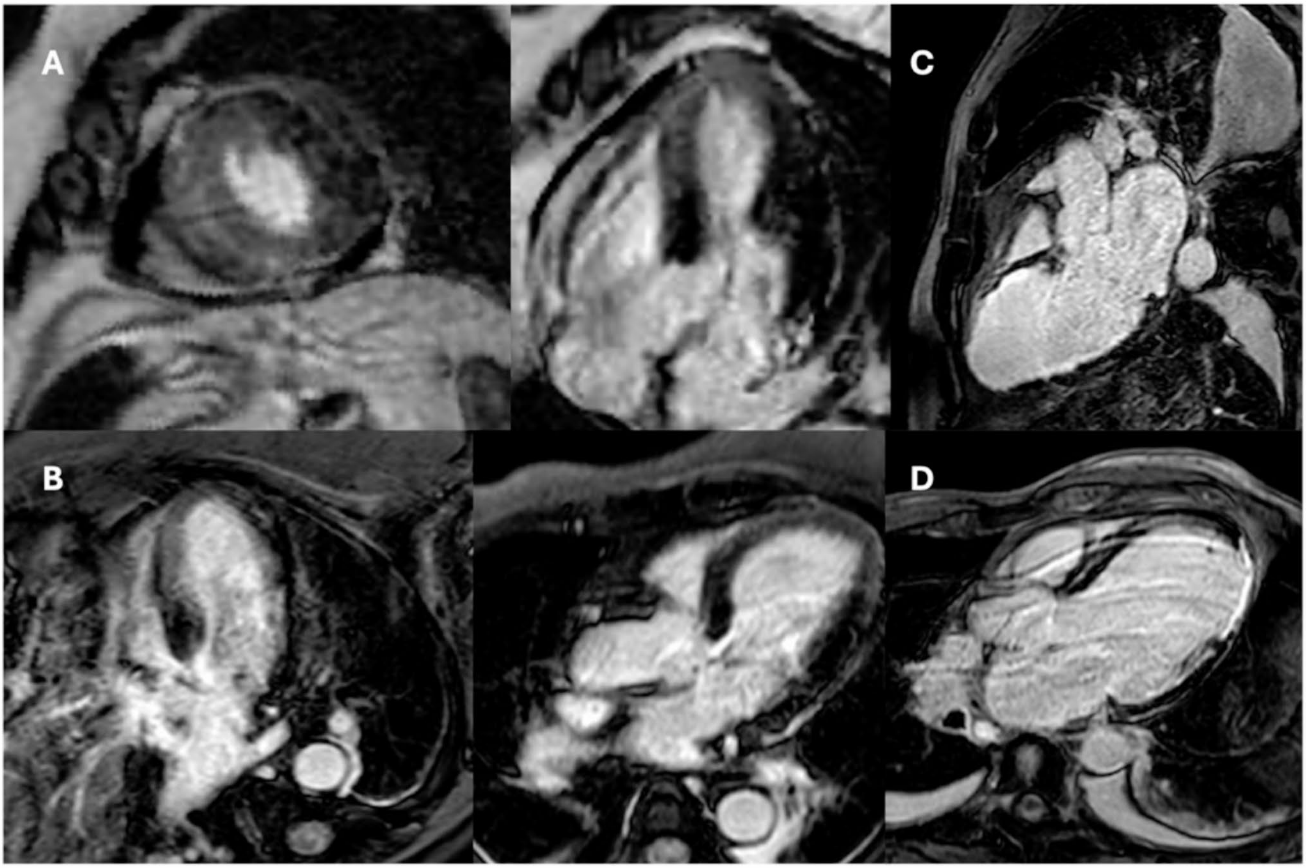

Fig. 2 Post-contrast cardiac magnetic resonance sequences showing transmural late gadolinium enhancement with low signal intensity in takotsubo syndrome (Panel **A** and **B**), and subendocardial/transmural late gadolinium enhancement with high signal intensity in ischemic cardiomyopathy (Panel **C** and **D**), acquired according to the same sensitivity protocol

Table 1 Main LGE differences among takotsubo syndrome, myocarditis, and ischemic cardiomyopathy

LGE	Takotsubo syndrome	Myocarditis	Ischemic cardiomyopathy
Pattern	Transmural or patchy	Mid-wall or subepicardial	Subendocardial or transmural
Signal intensity	+/-	++	++
High T2 associated	++	++	+/-
Follow-up	Absent	May be still present, progressed, or reduced	Present and irreversible

Interestingly, post-mortem studies in TTS have documented inflammatory cell infiltration, contraction band necrosis, and interstitial fibrosis [25]. However, while myocardial necrosis has been reported in TTS, significant fibrosis replacement, as seen in ischemic cardiomyopathy and myocarditis, is rare. This is further supported by the observation that only a very small proportion of patients (approximately 2%) exhibit LGE during follow-up (Fig. 3) [15]. This low proportion further supports that LGE in TTS is mainly determined by edema (Fig. 4), which usually resolves quickly. Yet, when LGE is detected on follow-up scans, potential explanations might be hypothesized, including a previously unrecognized myocardial infarction or coexisting pathology that may have contributed to persistent LGE findings [26, 27].

Diagnostic Challenges and Misinterpretation Risks

According to the points previously discussed, interpreting gadolinium-enhanced CMR in TTS presents several diagnostic challenges that must be carefully addressed to avoid misclassification. One of the primary difficulties lies in the overlapping imaging features shared with conditions such as myocarditis and myocardial infarction with non-obstructive coronary arteries (MINOCA). Distinguishing TTS from these entities requires an appropriate understanding of imaging patterns and clinical context. A collaborative team effort between clinicians, radiologists, and imager cardiologists would be desirable. Additionally, as previously discussed, the timing of imaging plays a crucial role, as LGE and myocardial edema can evolve over days to weeks,

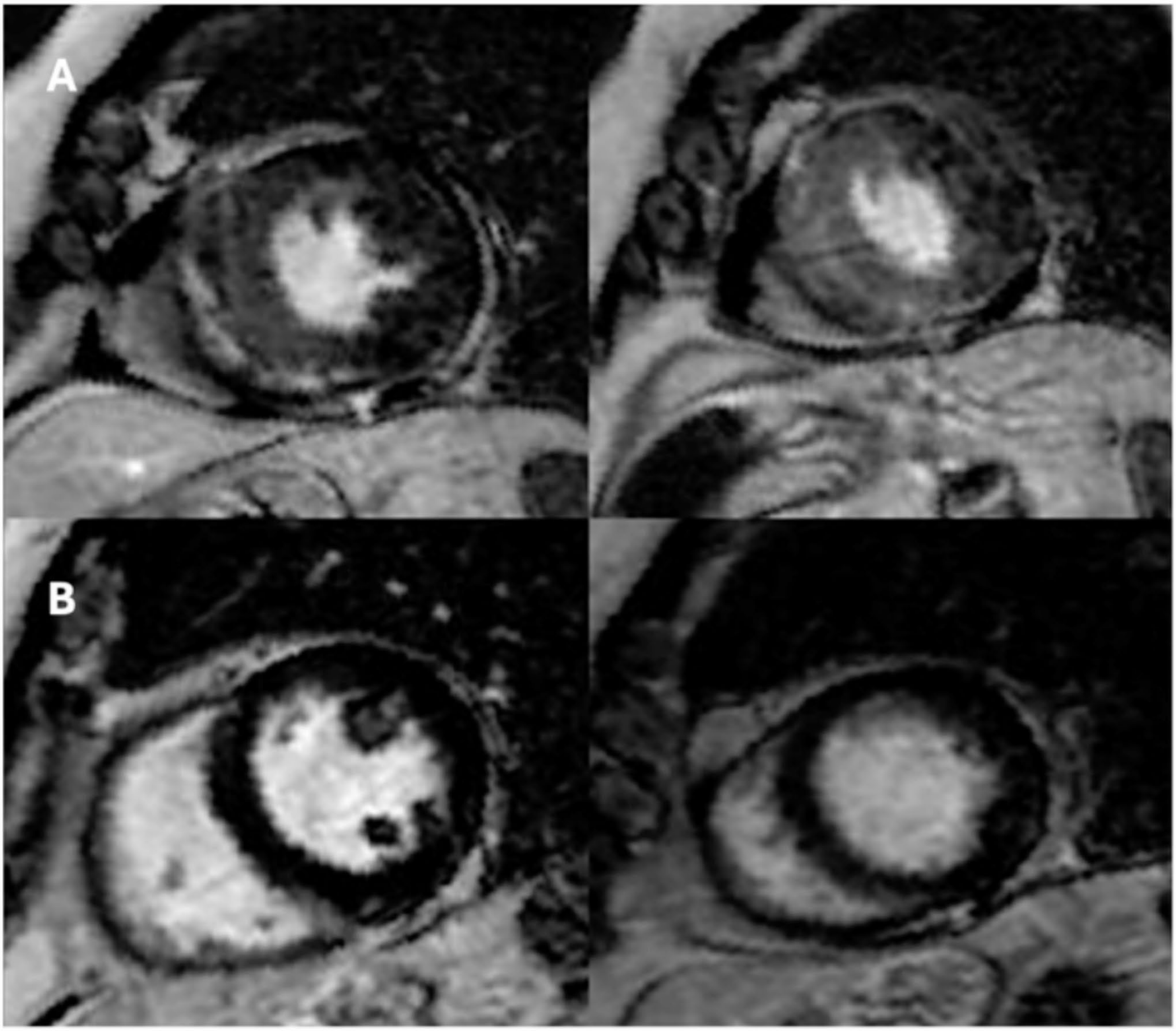

Fig. 3 Post-contrast cardiac magnetic resonance sequences showing late gadolinium enhancement in takotsubo syndrome (Panel **A**), which was not detected at subsequent follow-up (Panel **B**)

influencing the accuracy of findings depending on when the scan is performed. Another potential pitfall is the variability in LGE detection, which depends on the chosen thresholding technique and acquisition parameters, sometimes leading to inconsistencies in interpretation. Addressing these challenges is essential to improving the reliability of CMR in TTS and ensuring its proper integration into clinical decision-making.

LGE and Prognosis

Although some CMR features may offer prognostic insights [14], the prognostic significance of LGE in TTS remains unclear and has yet to be deeply investigated. Specifically, no significant differences in either major adverse cardiovascular events, heart failure incidence, or ejection fraction based on the presence of LGE were reported [23, 28]. Similarly, a study examined the LGE clinical implications using different sensitivity thresholding methods but found no association with clinical presentation, mortality, ECG patterns, or triggering factors [29]. Given the low prevalence of LGE over time, these findings suggest that its presence in TTS may not indicate a worse prognosis. However, further prospective studies, particularly focusing on short-term outcomes, such as ventricular arrhythmias, which have been identified as clinically significant despite lacking CMR features [30], are required to clarify its prognostic value in TTS.

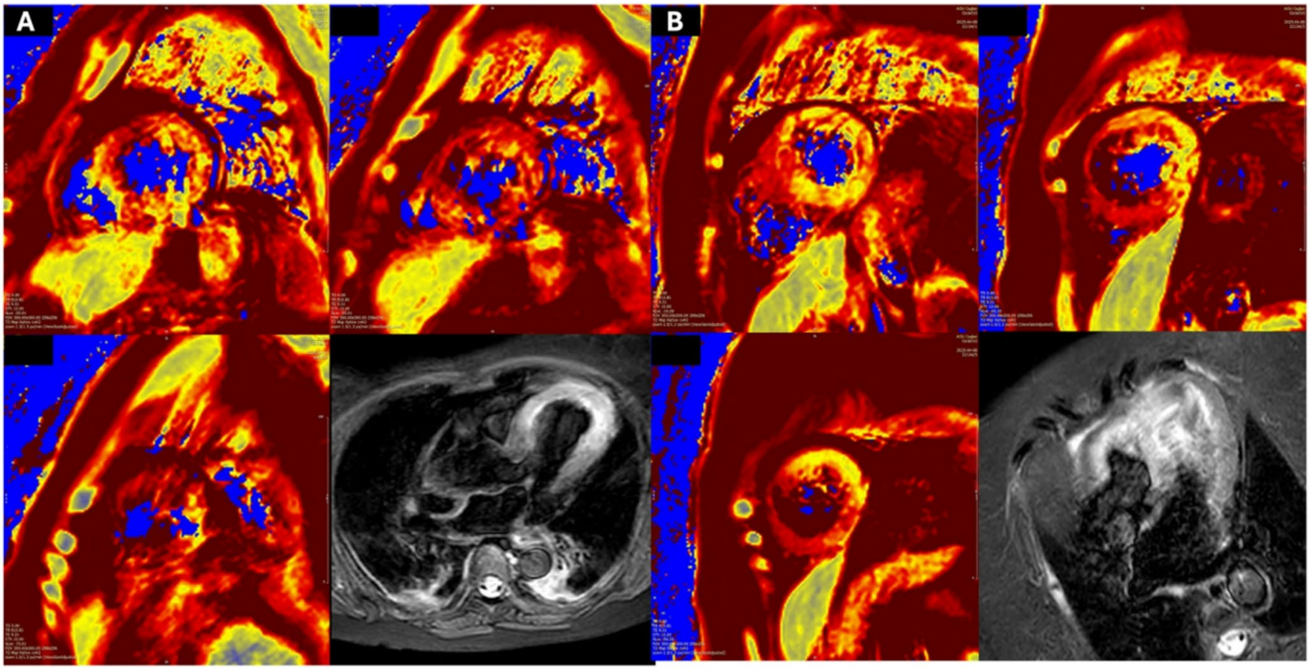

Fig. 4 T2-weighted and T2 mapping cardiac magnetic resonance sequences showing myocardial edema in classical apical-ballooning (Panel **A**) and mid-ventricular takotsubo syndrome (Panel **B**)

Future Directions

Future research should aim to refine the diagnostic accuracy of LGE CMR in TTS by addressing several key areas. A major priority is the standardization of imaging protocols and interpretation criteria to ensure greater reproducibility across institutions. The exploration of novel contrast agents with enhanced myocardial uptake and clearance properties could further improve tissue characterization. Additionally, the integration of artificial intelligence-assisted analysis is promising for reducing interobserver variability, supporting CMR interpretation standardization. Another point of investigation is the implementation of multiparametric imaging [31], combining techniques such as echocardiography and CMR, including LGE, T1/T2 mapping, strain imaging, and perfusion studies to provide higher specificity in differentiating TTS from other myocardial diseases and prognostic refinement.

Conclusion

LGE sequences are widely used in CMR to assess myocardial fibrosis and necrosis. Gadolinium-enhanced CMR remains a valuable tool in the assessment of TTS, yet its interpretation requires careful consideration of myocardial injury mechanisms, imaging timing, and technical limitations. While the absence of ischemic-pattern LGE is a hallmark feature, the presence of atypical enhancement patterns needs to be further investigated. In TTS, the expected findings include the absence of significant LGE in most cases; shaded patchy or transmural LGE in selected cases, likely due to necrosis, edema, and interstitial expansion; rare LGE detection at the CMR follow-up reflecting the reversible nature of the disease. Standardization of imaging protocols and emerging artificial intelligence-driven analysis tools may improve diagnostic yield. Further studies are needed to clarify the implications of LGE in TTS and its potential role in risk stratification.

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This article highlighted the role of CMR in Takotsubo syndrome diagnosis and prognosis.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests The authors declare no competing interests.

Conflict of Interest The authors have no conflicts of interest to disclose.

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