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REVIEW ARTICLE

Serum markers in systemic sclerosis with cardiac involvement

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Abstract

Cardiac involvement in systemic sclerosis is a common clinical entity that may range from subclinical to life-threatening complications. The classification of cardiac involvement may be expressed as either primary or secondary involvement. Primary systemic sclerosis heart involvement (SSc-pHI) refers to cardiac pathologies primarily ascribed to systemic sclerosis rather than concomitant conditions like ischemic heart disease and pulmonary hypertension. The timely recognition of cardiac involvement holds significant clinical relevance. Therefore, numerous screening or diagnostic tools have been evaluated to forecast the likelihood of cardiac involvement, particularly in the absence of clinically evident cardiac symptoms. Of these modalities, serum biomarkers are often preferred due to their expeditiousness and non-invasive nature. Hence, the crucial goal of this narrative review is to review serum biomarkers that can be a valuable or promising tool in diagnosing cardiac involvement, especially SSc-pHI, in the early stages or predicting disease prognosis.

Keywords Arrhythmia · Biomarkers · Cardiac involvement · Myocarditis · Systemic sclerosis

Introduction

Cardiac involvement in patients with SSc has been known about since 1926 [1, 2]; however, the deterioration of structural components and the effect of this on disease prognosis and mortality has only recently been better understood [3, 4]. The estimated prevalence of cardiac involvement ranges from 15 to 39%, with rates of up to 80% reported in autopsy studies [5–7]. Heart involvement has been demonstrated in both subsets of SSc, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc). However, there is a stronger association between dcSSc and cardiac involvement, according to the European Scleroderma Trials and Research group (EUSTAR) database [7, 8].

Cardiac involvement is divided into either primary and secondary forms. SSc primary heart involvement (SSc-pHI) represents cardiac complications directly due to the pathological effects of SSc, including inflammation, fibrosis, and vasculopathy. Mostly, SSc-pHI consists of myocardial dysfunction, conduction blocks and arrhythmias, pericardial diseases, and valvular diseases [3, 9]. Other SSc-related conditions, such as pulmonary hypertension (PH), interstitial lung disease, kidney involvement, and non-SSc-specific cardiac conditions, including cardiovascular disorders and ischemic heart diseases, are considered secondary cardiac involvement [6, 7, 10, 11]. Still, it remains challenging to distinguish between these entities [7].

Inflammation, fibrosis, and vasculopathy are the main mechanisms underlying the pathophysiology of heart involvement in SSc. It has been hypothesized that SSc-pHI may be due to cardiac Raynaud's phenomenon, a rare clinical status characterized by recurrent spasms of the coronary arteries, leading to transient ischemia of the heart muscle and inducible myocardial perfusion defects [6]. Besides the vascular hypothesis, heart inflammation also plays an essential role in myocardial damage by inducing patchy or diffuse fibrosis with contraction band necrosis [3, 12]. Fig. 1 summarizes the cellular, molecular, and vascular bases of cardiac involvement and illustrates the types of cardiac complications (Fig. 1). Moreover, the existence of anti-intercalated disk antibodies and anti-heart, which are myocarditis-specific autoantibodies, is strong evidence of an autoimmune path in some SSc patients [13]. Inflammation and immune mechanisms cause not only myocardial fibrosis but also endothelial damage and dysregulation of

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angiogenesis, resulting in irreversible destruction of heart muscle [3]. In conclusion, irreversible myocardial fibrosis leads to decreased ventricular compliance, impaired hemodynamics of the cardiac chambers, and defects in the cardiac conduction system [3, 14].

Cardiac manifestations may vary from asymptomatic to life-threatening complications. In particular, diastolic dysfunction (DD), which is more common than systolic dysfunction and is accepted as an early manifestation of cardiac fibrosis, has been reported to be a common complication with a prevalence of 31.4% [15, 16]. Even though most patients with left ventricular DD identified by echocardiography are usually asymptomatic, the presence of DD is shown to increase mortality by approximately four times [16, 17]. Moreover, decreased left ventricular (LV) ejection fraction (<50%) and LV systolic dysfunction have proven to predict overall survival [18, 19]. Besides DD and systolic dysfunction, arrhythmias and conduction defects can be seen in between 25 and 75% of SSc patients and mainly encompass atrioventricular block (up to 5% and most commonly right bundle branch block), premature ventricular contractions (20–67%), ventricular tachycardia (7–28%), and supraventricular arrhythmias (32–66%) [3, 20]. Arrhythmia is also defined as one of the prognostic factors for mortality [21]. Pericardial involvement (pericardial adhesion, fibrinous pericarditis, and pericardial effusion) has been defined in SSc with prevalence ranging from 33 to 72%. Most patients are asymptomatic but 5–16% of patients have symptomatic pericardial effusion. Fortunately, severe forms of pericardial involvement, including large pericardial effusions and cardiac tamponade, associated with increased mortality (up to 55%) are rare [22]. Valvular diseases are as common as DD and occur in up to 91% of SSc patients [23]. Besides aortic stenosis, mitral and tricuspid valve regurgitations are the most common valve abnormalities [23, 24]. The role of valvular pathologies in disease prognosis and mortality remains obscure, but it is assumed that they may also elevate the risk of death by causing heart failure. All in all, cardiac involvement is closely related to poor prognosis and contributes to an approximately fivefold increase in mortality, accounting for 31% of SSc-related deaths [1, 5, 25, 26].

Given the growing evidence for the impact of cardiac involvement on disease prognosis and mortality, early diagnosis is increasingly important. Besides the general medical examination, many methods (laboratory evaluations, imaging techniques, etc.) are used to investigate and define heart involvement. The comprehensive scope of these diagnostic approaches has been widely examined in numerous excellent reviews and will not be described further in this review [3, 9, 27]. However, there is limited evidence summarizing the utility of serum biomarkers in SSc. Thus, the objective of the present review article is to discuss cardiac biomarkers and to specifically highlight their role in making an early diagnosis and predicting disease prognosis.

Search strategy

This narrative review article followed the search strategy suggested by Gasparyan et al. [28]. The author searched the PubMed/Medline, Scopus, and Web of Science databases for English-language sources, published between January 2017 and March 2023. Randomized control trials, observational studies, and case-control studies focused on cardiac biomarkers in patients with SSc were included. Animal or in vitro studies, case reports, review articles, editorial letters, and conference papers were not selected for further review. The following search terms were used for databases search: ("systemic sclerosis" [MeSH terms] OR "systemic scleroderma" [MeSH terms] OR "scleroderma" [tiab]) AND ("cardiac involvement" [tiab] OR ("heart involvement" [tiab]) AND ("myocarditis" [MeSH terms] OR "myocardial dysfunction" [tiab] OR "myocardial fibrosis" [tiab] OR "diastolic dysfunction" [tiab]) AND ("arrhythmia" [MeSH terms] OR "conduction defect" [tiab] OR "rhythm disturbance" [tiab] OR "cardiac block" [tiab]) AND ("pericarditis" [MeSH terms] OR "pericardial effusion" [MeSH terms] OR "cardiac tamponade" [MeSH terms]) AND ("valvular disease" [tiab] OR "valvular regurgitation" [tiab]) AND ("cardiac markers" [tiab] OR "cardiac biomarkers" [tiab] OR "biomarkers*" [MeSH terms] OR "markers*" [tiab]). The author conducted the searches in February 2023 and evaluated the articles for relevance. Figure 2 shows the screening and selection process.

N-terminal pro-B-type natriuretic peptide and cardiac troponins

The natriuretic peptide family includes three principal peptides, namely atrial (ANP), B-type (BNP), and C-type natriuretic peptides. ANP secretion is primarily elicited by augmented wall stress within the atria, while B-type natriuretic peptides are released from ventricular tissue concerning cardiomyocyte stretching and are initially synthesized as a 134 amino acid prehormone. This prehormone is then enzymatically divided into two forms: BNP and NT-proBNP. B-type natriuretic peptides have appeared as noteworthy markers for diagnosis and follow-up of heart failure [29–31].

The troponin complex includes three regulatory subunits, namely troponin T, I, and C, and only troponin T and troponin I are recognized as clinically valuable biomarkers for detecting cardiac myocyte injury [30, 31]. Cardiac troponin I (cTnI) is considered a myocardial tissue-specific marker,

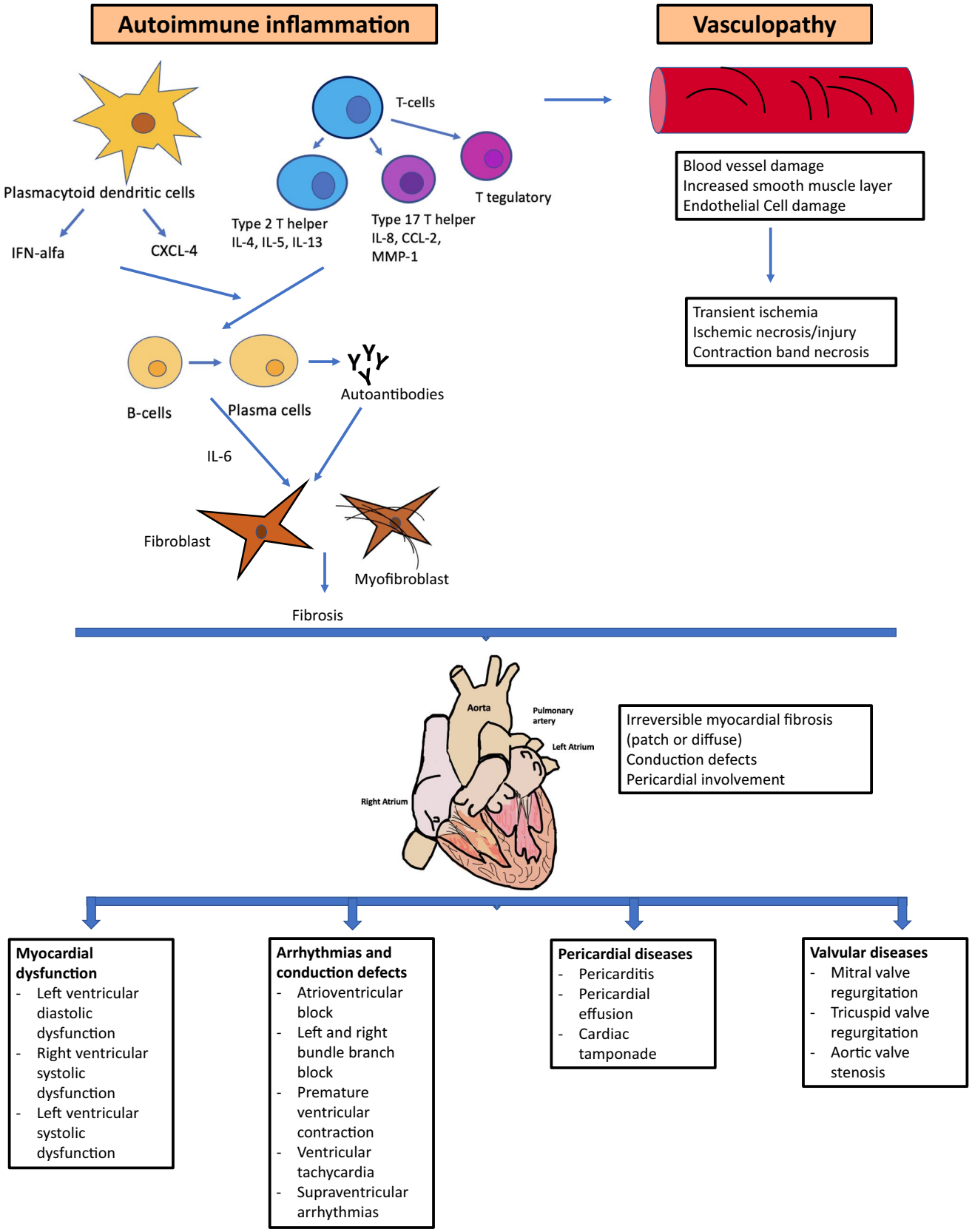

Fig. 1 Pathogenesis of cardiac involvement in systemic sclerosis and associated cardiac complications. Abbreviations: IFN, interferon; CXCL-4, C-X-C motif chemokine ligand-4; IL, interleukin; CCL-2, C–C motif chemokine ligand 2; MMP-1, matrix metalloproteinases-1

while troponin T is detected in both myocardial tissue and regenerating skeletal muscle tissue, making it non-specific [32]. The high-sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI) are newer tests that are more sensitive and able to detect smaller amounts of cardiac troponin T and I (cTnT and cTnI) in the blood [30, 31]. Of these serum biomarkers, NT-proBNP is a valuable biomarker in diagnosing heart failure, predicting its prognosis, and monitoring its treatment. Hs-cTnT and hs-cTnI are commonly used in the diagnosis or management of acute coronary syndrome and heart failure [30, 31]. Thus, numerous studies have evaluated these biomarkers in SSc-pHI, investigated their performance in discerning patients with and without SSc-pHI, and researched the relationship between biomarkers and types of cardiac complications.

NT-proBNP and hs-cTnT may offer diagnostic advantages in detecting subclinical cardiac involvement among SSc patients. Barsotti et al. reported that, as expected, the sensitivity and specificity of hs-cTnT were higher than those of NT-proBNP. However, these biomarkers were not validated and reliable in distinguishing between various types of cardiac involvement, such as DD, pericardial effusion, arrhythmias, and conduction defects [32]. Bosello et al. demonstrated that elevated NT-proBNP and hs-cTnT were closely related to diffuse skin involvement and cardiac complications, such as decreased left ventricular ejection fraction (LVEF), a higher incidence of right bundle branch block, heart failure, and sudden cardiac arrest. Furthermore, the study findings revealed a notably poorer survival rate among SSc patients exhibiting elevations in both cardiac biomarkers, despite already diminished cumulative survival rates observed in patients with increased NT-proBNP and hs-cTnT levels [33]. A recent prospective cohort study aimed to explore the predictive potential of NT-proBNP, hs-cTnT, and C-reactive protein (CRP) in the development of cardiac disease in SSc patients without obvious cardiac manifestations. The study findings indicated a pronounced association between systolic dysfunction and elevated levels of hs-cTnT, whereas increased concentrations of hs-cTnT and NT-proBNP were found to be correlated with the occurrence of arrhythmia [34].

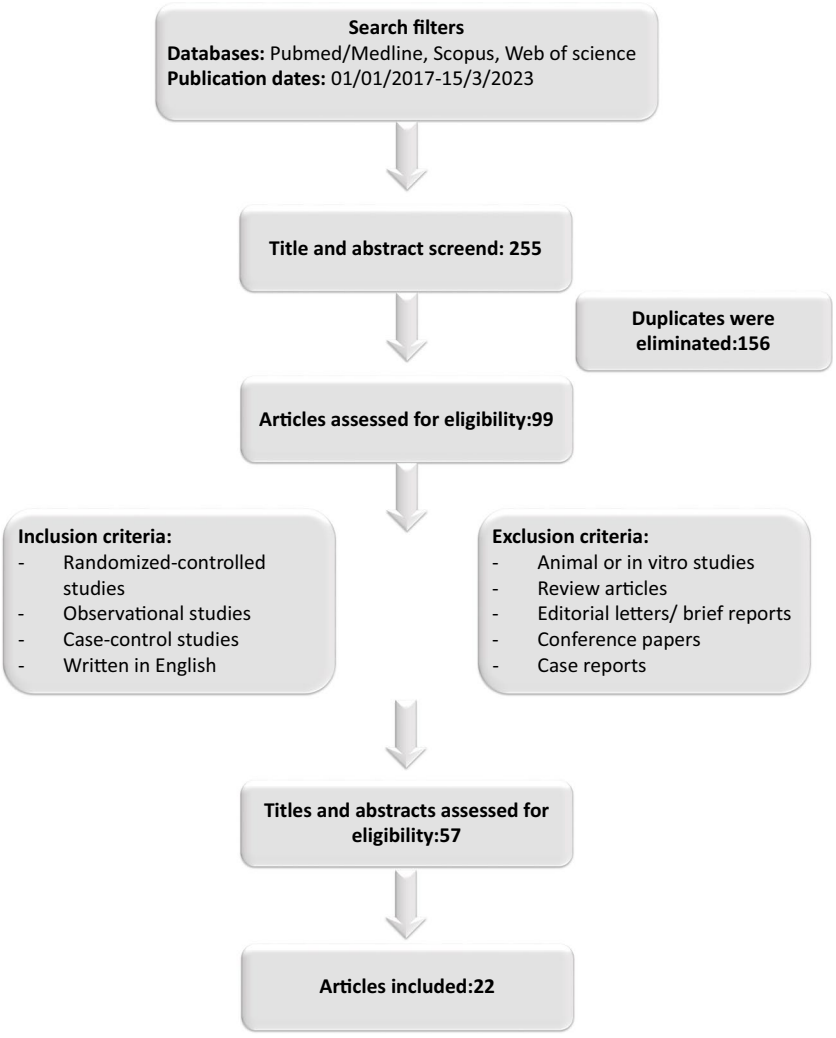

Fig. 2 Flowchart of the narrative review

A retrospective study by Paik et al. aimed to investigate the importance of elevated cTnI in predicting mortality risk in patients with SSc. The authors revealed that patients with elevated cTnI were more likely to be in the dcSSc subset and to have severe cardiopulmonary disease, such as lower LVEF, lower forced vital capacity percent predicted, higher right ventricular systolic pressure, and higher Medsger muscle and heart severity scores. Also, after adjusting for age, gender, disease period, and confounding factors related to cardiopulmonary diseases, SSc patients with increased cTnI had more than double the risk of mortality than those with normal levels of cTnI [35].

Besides hs-cTnT, several lines of evidence show the benefit of hs-cTnI in predicting primary SSc heart disease. In a comparative study, the authors observed an association between elevated levels of NT-proBNP and hs-cTnI with echocardiographic abnormalities, including reduced LVEF, regional hypokinesia, and valve regurgitations [36]. Bissel et al. conducted research screening SSc patients without overt cardiac manifestations to evaluate SSc heart disease-associated arrhythmias with an implantable loop recorder (ILR) and to demonstrate any associations with disease characteristics, soluble biomarkers, and cardiac magnetic resonance imaging (CMR) findings. As expected, this study confirmed that SSc patients with ILR-detected significant arrhythmia had higher hs-cTnI and NT-proBNP levels than those without arrhythmia [37]. A similar study investigated the relationship between disease characteristics, BNP levels, and myocardial abnormalities. The authors found that higher BNP levels were observed in SSc patients with myocardial late gadolinium enhancement, which is a finding suggestive of myocardial fibrosis [38]. In another study, the authors showed significantly higher hs-cTnI and moderately elevated NT-proBNP concentrations in SSc patients with myocardial fibrosis. In particular, this study reported that the utility of hs-cTnI to detect subclinical SSc-pHI was better than that of NT-proBNP [31]. A further investigation by Dumitru et al. revealed that SSc patients with cardiovascular events, including myocarditis and arrhythmias, demonstrated a substantial elevation in NT-proBNP levels and a moderate increase in hs-cTnI levels than those without cardiovascular manifestations. The study established that higher cardiovascular events were likely in patients with elevated NT-proBNP and identified increased NT-proBNP as the only variable predicting cardiovascular events. Consequently, and contrary to the authors' previous study, in this study the superiority of NT-proBNP over hs-cTnI and CMR findings for predicting cardiac involvement in SSc was shown [39].

There are a few studies that contradict the results reported by these earlier studies. Tipparot et al. could not show any connection between cardiac biomarkers and myocardial inflammation [40]. In a prospective observational study conducted by Hromadka et al., no significant association was found between the levels of hs-cTnI and NT-proBNP and subclinical myocardial fibrosis [41]. Luca et al. conducted a comparative histological analysis aimed at delineating the prognostic characteristics of myocarditis in SSc. The authors compared the results among three groups of endomyocardial biopsy-proven virus-negative myocarditis patients (SSc-related myocarditis, isolated myocarditis, and other systemic autoimmune diseases-related myocarditis). Even though patients with SSc had higher degrees of myocardial fibrosis, and thus more common heart failure and dyspnea, and were characterized by worse cardiac prognosis, there were no differences among the groups for cardiac soluble markers, including NT-proBNP and hs-cTnT [42]. Table 1 summarizes the studies discussed above.

Most of the studies described earlier specifically included SSc patients with primary heart involvement and without ischemic heart disease and PH due to interstitial lung disease or PAH, and showed that these soluble biomarkers might have a diagnostic and prognostic benefit for SSc patients with cardiac involvement. Nevertheless, their role in distinguishing cardiac involvement types is unclear. Furthermore, there are no studies demonstrating the role of these cardiac biomarkers to differentiate SSc-pHI from secondary cardiac involvement, including ischemic heart disease and pulmonary hypertension.

Novel soluble biomarkers

The available evidence on new cardiac biomarkers for primary cardiac involvement in SSc is relatively limited. However, it is known that cytokines also contribute to myocardial inflammation, which can lead to cardiac dysfunction. Thus, in addition to other peptides and proteins, cytokines have been investigated as potential biomarkers for heart involvement [12].

Hromadka et al. demonstrated that galectin-3 and growth/differentiation factor-15 (GDF-15) levels were correlated with myocardial fibrosis [43]. In 2021, Hromadka et al. designed another study aiming to explore changes evident by CMR in patients with SSc over a 5-year follow-up duration, and to examine the associations between the observed changes and a set of biomarkers, including NT-proBNP, hs-cTnI, GDF-15, galectin-3, and soluble suppression of tumorigenicity 2 (sST2), as well as clinical indicators. The study findings revealed that subclinical myocardial fibrosis was correlated with increased levels of galectin-3 alone. Thus, the authors suggested that serial testing of galectin-3 could be a valuable method for identifying myocardial fibrosis in SSc patients who have not yet developed cardiac symptoms [41]. Similarly, in another study, galectin-3 levels were found to be correlated with mitral regurgitation, and LV systolic and LV diastolic dysfunction. Intriguingly, no significant correlations were identified between galectin-3 and sST2 measurements, nor between either biomarker and the NT-proBNP value. As a

Table 1 Overview of studies investigating N-terminal pro-B-type natriuretic peptide and cardiac troponins in SSc patients with cardiac involvement

Author	Year	Study population	Diagnostic tool	Cardiac complications	Markers	Results
Barsotti S et al. [32]	2017	65 SSc pts (12 pts with cardiac involvement)	ECG ECHO	Diastolic dysfunction Pericardial effusion Arrhythmias Conduction defects	NT-proBNP Hs-cTnT	Sensitivity and specificity in predicting cardiac involvement Hs-cTnT>NT-proBNP. An elevated hs-cTnT was observed in all SSc patients with cardiac involvement. However, only some of these patients had elevated NT-proBNP.
Nordin A et al. [36]	2017	110 SSc pts 105 age- and gender-matched HC	ECHO	Decreased LVEF Regional hypokinesia Valve regurgitations	NT-proBNP Hs-cTnI	Elevated levels of NT-proBNP and hs-cTnI were associated with echocardiographic abnormalities. Even after adjusting for renal disease and estimated glomerular filtration rate, NT-proBNP remained linked with all three echocardiographic pathologies. However, while hs-cTnI continued to be associated with lower LVEF<50%/hypokinesia and higher estimated pulmonary artery pressure, its correlation with valvular regurgitation disappeared.
Bosello S et al. [33]	2018	195 SSc pts 30 age- and gender-matched HC	ECG ECHO	Decreased LVEF Higher incidence of RBBB Heart failure Sudden cardiac arrest	NT-proBNP Hs-cTnT	NT-proBNP and hs-cTnT were closely related to diffuse skin involvement and cardiac complications. This study showed the potential utility of these markers in prognosticating the risk of cardiac death.
Bissel LA et al. [37]	2019	19 SSc pts	ILR CMR	Arrhythmias	Creatine kinase NT-proBNP Hs-cTnI	Pts with arrhythmias had higher hs-cTnI and NT-proBNP levels. Nevertheless, creatine kinase levels between the pts with and without arrhythmias were similar.
Sugiyama K et al. [38]	2019	49 SSc pts (female)	ECG CMR	LGE	BNP	LGE-positive pts had higher BNP levels (myocardial LGE was associated with myocardial fibrosis).
Tipparot T et al. [40]	2019	30 SSc pts	CMR	Myocardial inflammation	CK-MB NT-proBNP Hs-cTnT	Early disease onset and higher skin scores at diagnosis were associated with elevated myocardial inflammation. No relationship was found between cardiac biomarkers and myocardial inflammation.
De Luca G et al. [42]	2020	12 SSc-VNM pts 12 i-VNM pts 10 a-VNM pts	ECG 24-h Holter ECG CMR Endomyocardial biopsy	SSc-VNM i-VNM a-VNM	NT-proBNP Hs-cTnT	NT-proBNP and hs-cTnT were not different among the groups.

Table 1 (continued)

Author	Year	Study population	Diagnostic tool	Cardiac complications	Markers	Results
Hromadka M et al. [41]	2021	25 SSc pts	CMR	Myocardial fibrosis	NT-proBNP Hs-cTnI Gal-3 sST2 GDF-15	NT-proBNP and hs-cTnI were not found to be associated with myocardial fibrosis in patients with SSc who had no documented history of heart disease throughout a five-year follow-up period. However, sub-clinical myocardial fibrosis was correlated with elevated gal-3 concentrations. Disease severity progression was associated with GDF-15 values.
Dumitru RB et al. [31]	2021	83 SSc pts	CMR	Myocardial fibrosis Myocardial perfusion defects LV dysfunction	Creatine kinase NT-proBNP Hs-cTnI	This study showed higher hs-cTnI and moderately elevated NT-proBNP levels in SSc patients with focal and diffuse myocardial fibrosis. Hs-cTnI was a better marker than NT-proBNP in detecting subclinical SSc-pHI.
Dumitru RB et al. [39]	2021	74 SSc pts	ECG 24-h Holter ECG Stress ECG ILR CMR	Arrhythmias Myocarditis	NT-proBNP Hs-cTnI	NT-proBNP and hs-cTnI levels were higher in pts with myocarditis and arrhythmias. Elevated NT-proBNP (>125 pg/mL) was a crucial biomarker in predicting cardiovascular events (OR=5.335, p=0.040). NT-proBNP was a better marker than hs-cTnI in predicting cardiac involvement.
Jha M et al. [34]	2022	675 SSc pts	ECHO	Systolic dysfunction Arrhythmias PAH PH	NT-proBNP Hs-cTnT CRP	Systolic dysfunction was associated with elevated hs-cTnT. Arrhythmia was associated with elevated hs-cTnT and NT-proBNP levels. The study found significantly higher CRP, hs-cTnT, and NT-proBNP levels in SSc patients with PH and PAH. The findings revealed that increased levels of these three biomarkers were indicative of patients at increased risk of mortality.
Paik JJ et al. [35]	2022	272 SSc pts	ECG ECHO CMR (if necessary)	Lower LV ejection fraction Higher right ventricular systolic pressure	cTnI	Elevated cTnI was found to be associated with severe cardiopulmonary disease and increased mortality.

Pts, patients; *HC*, healthy controls; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *Hs-cTnT*, high sensitivity cardiac troponin T; *Hs-cTnI*, high sensitivity cardiac troponin I; *Gal-3*, galectin-3; *GDF-15*, growth/differentiation factor-15; *sST2*, suppression of tumorigenicity-2; *CK-MB*, creatine kinase-myocardial band; *LVEF*, left ventricular ejection fraction; *RBBB*, right bundle branch block; *PH*, pulmonary hypertension; *PAH*, pulmonary arterial hypertension; *ECG*, electrocardiography; *ECHO*, echocardiography; *ILR*, implantable loop recorder; *CMR*, cardiac magnetic resonance imaging; *LGE*, late gadolinium enhancement; *SSc-VNM*, SSc-related myocarditis; *i-VNM*, isolated myocarditis; *a-VNM*, other systemic autoimmune disease-related myocarditis

result, the authors suggested that galectin-3 might be a valuable marker for the purpose of screening and facilitating early diagnosis of cardiac involvement in SSc [44].

A recent study demonstrated that reduced tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) levels, elevated Angiopoietin 2 concentrations, and higher Osteopontin levels were closely associated with both right ventricular (RV) systolic dysfunction and LV systolic dysfunction. Moreover, the study further revealed low TRAIL levels were closely associated with LV diastolic dysfunction [45]. Another study by Iannazzo et al. found higher sST2 and IL-33 levels in SSc patients than in healthy controls. In particular, this study showed that SSc patients with DD had elevated levels of sST2 than those without DD [46].

Peptides and proteins play a significant role in the pathogenesis of fibrosis. As such, a few studies have been conducted to detect cardiac involvement by measuring the levels of these fibrosis-related peptides and proteins in SSc patients with or without overt cardiac manifestations [45, 47]. In a study, SSc patients with abnormal echocardiographic measurements had higher serum periostin levels. This study also demonstrated higher periostin expression in vivo in heart samples of patients with higher circulating periostin levels. Furthermore, periostin expression was detected in not only collagen type I deposition areas but also areas unaffected by fibrosis, indicating that periostin deposition may be an early event in fibroblast activation in SSc-associated cardiomyopathy. Therefore, elevated periostin expression, correlated with circulating periostin levels, may serve as a promising biomarker for detecting myocardial fibrosis [47]. Table 2 summarizes the studies mentioned above.

Autoantibodies related to cardiac involvement

Anti-centromere, anti-topoisomerase I (anti-Scl-70), anti-RNA polymerase III (anti-RNAP III), and anti-Th/To and anti-fibrillarin (anti-U3-RNP) are SSc-specific antibodies, three of which are included in the 2013 classification criteria for SSc [48, 49]. Indeed, the association between some autoantibodies, namely anti-Scl-70 and anti-fibrillarin, and cardiac involvement is proven in the literature. Consistent with previous studies, Nihtyanova et al. showed an increased frequency of cardiac involvement in patients diagnosed with dcSSc than those with lcSSc. Notably, the study found that the highest and second-highest incidences of cardiac involvement were observed in SSc patients with anti-fibrillarin (anti-U3-RNP) and anti-Scl-70 antibodies, respectively [50]. Tieu et al. aimed to evaluate clinical features and mortality results among patients diagnosed with SSc exhibiting inverted phenotypes. Specifically, this study explored the comparison of results between lcSSc patients with anti-Scl-70 positivity and dcSSc patients with anti-centromere positivity. The findings indicated that cardiac involvement was more prevalent in dcSSc with anti-centromere positivity and dcSSc with anti-Scl-70 positivity than in lcSSc with either anti-centromere or anti-Scl-70 antibodies [51]. Keppeke et al. aimed to develop a reliable anti-fibrillarin assay for clinical use. Besides that, the authors investigated the association between specific SSc phenotypes and anti-fibrillarin antibodies and found that SSc patients with higher anti-fibrillarin antibodies were characterized by a higher frequency of the dcSSc phenotype, more cardiac involvement, and scleroderma renal crisis [52].

There is not enough published evidence concerning the relationship between non-SSc-specific antibodies (such as anti-SSA/Ro60, anti-Ro/TRIM2, organ-specific antibodies) and cardiac involvement. A recent study by Caforio et al. showed that serum anti-heart (AHA) and anti-intercalated disk autoantibodies (AIDA), defined as new autoimmune markers, were significantly higher in SSc patients with heart involvement when compared to control groups, including ischemic heart failure, non-inflammatory cardiac disease, and healthy participants. The rate of AHA and AIDA positivity in SSc was higher in past and/or current smokers and female patients. Furthermore, the frequency of AHA positivity was notably higher in SSc patients with interstitial lung disease (ILD) and those receiving immunosuppressive and prostanoid therapies. A trend was also identified for an association between AHA positivity and anti-Scl-70 positivity. Moreover, AHAs were significantly connected with a history of chest pain, elevated hs-cTnI level, AIDA, and pericardial edema detected on CMR. Non-cardiac associations for the presence of AIDA positivity were also found. Thus, AIDA positivity was closely related to the SSc pattern in nailfold video capillaroscopy and digital ulcers. Prognostically, AHA positivity was additionally linked to diminished survival rates regardless of cardiac deterioration, while AIDA positivity was found to lack any significant association with prognostic outcomes [13].

Conclusion

Cardiac involvement is actually as common as any other well-known organ involvement in SSc and is associated with poor prognosis and high mortality [3, 6]. Therefore, early detection of cardiac involvement, especially SSc-pHI, has a vital role in the quality of life and life expectancy of affected patients. For this purpose, several studies have been conducted to determine and clarify screening/diagnostic approaches [53]. Laboratory tests and imaging techniques are the most commonly studied methods. As a

non-invasive and rapid method, serum biomarkers, such as soluble peptides and proteins, cytokines, and autoantibodies, have been evaluated and commonly compared with cardiac abnormalities detected by echocardiography and CMR [3, 6, 30].

Based on the existing body of literature, it has been demonstrated that the employment of NT-proBNP, hs-cTnT, and hs-cTnI biomarkers can be of significant value in the diagnosis of myocardial fibrosis [32–34]. Such fibrosis is known to result in diastolic and systolic dysfunction, and consequently heart failure, in clinical practice. The elevated levels of these biomarkers are also associated with valve regurgitation and arrhythmias [37]. However, these three biomarkers are not SSc-specific

Table 2 Characteristics of studies investigating novel biomarkers in systemic sclerosis patients with cardiac involvement

Author	Year	Study population	Diagnostic tool	Cardiac complications	Markers	Results
Hromadka M et al. [43]	2017	33 SSc pts 20 HC	ECHO CMR	Myocardial fibrosis	NT-proBNP Hs-cTnI Gal-3 GDF-15 PIIINP	GDF-15 and galectin-3 were positively correlated with myocardial fibrosis parameters.
Hromadka M et al. [41]	2021	25 SSc pts	CMR	Myocardial fibrosis	NT-proBNP Hs-cTnI Gal-3 sST2 GDF-15	NT-proBNP and hs-cTnI were not found to be associated with myocardial fibrosis in patients with SSc who had no documented history of heart disease throughout a five-year follow-up period. However, sub-clinical myocardial fibrosis was correlated with elevated gal-3 concentrations. GDF-15 was found to be closely associated with disease activity.
Vertes V et al. [44]	2022	40 SSc pts	ECHO	Mitral regurgitation LV systolic and LV diastolic dysfunction	NT-proBNP Gal-3 sST2	Gal-3 levels were found to be correlated with mitral regurgitation, and LV systolic and LV diastolic dysfunction. Gal-3 might be a valuable marker in enabling early diagnosis of cardiac involvement.
Tennoe AH et al. [45]	2022	371 SSc pts 100 HC	ECHO	RV systolic dysfunction LV systolic dysfunction LV diastolic dysfunction	TRAIL ANG-2 OPN	Low TRAIL levels were related to RV systolic, LV systolic, and LV diastolic dysfunction. Elevated ANG-2 and OPN levels were closely connected with RV systolic and LV systolic dysfunction. These three markers were also independently associated with mortality.
Iannazzo F et al. [46]	2022	50 SSc pts	ECHO	Diastolic dysfunction	IL-33 sST2	sST2 and IL-33 levels were higher in SSc patients than in healthy controls. In addition, SSc patients with DD had elevated sST2 levels than those without DD.
El-Adili F et al. [47]	2023	106 SSc pts 22 HC	ECHO	Myocardial fibrosis	Periostin BNP	SSc patients with abnormal echocardiographic measurements of LV dimensions, LV posterior wall thickness, and LV mass, had higher periostin expression in heart samples and higher serum periostin levels.

Pts, patients; *HC*, healthy controls; *BNP*, brain natriuretic peptide; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *Hs-cTnT*, high sensitivity cardiac troponin T; *Hs-cTnI*, high sensitivity cardiac troponin I; *Gal-3*, galectin-3; *GDF-15*, growth/differentiation factor-15; *sST2*, suppression of tumorigenicity-2; *TRAIL*, tumor necrosis factor-related apoptosis-inducing ligand; *ANG-2*, angiopoietin-2; *OPN*, osteopontin; *PIIINP*, procolagen III N terminal propeptide; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *RV*, right ventricular; *DD*, diastolic dysfunction; *ECHO*, echocardiography; *CMR*, cardiac magnetic resonance imaging

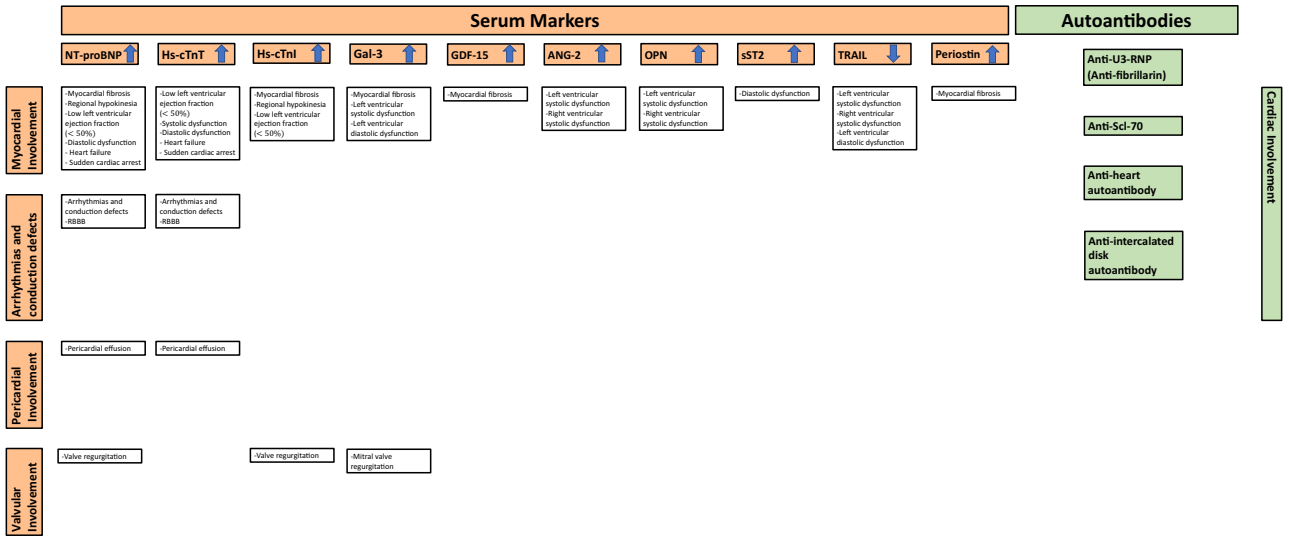

Fig. 3 Clinical associations of serum biomarkers and autoantibodies in systemic sclerosis patients with cardiac involvement. Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; Hs-cTnT, high sensitivity cardiac troponin T; Hs-cTnI, high sensitivity cardiac troponin I; Gal-3, galectin-3; GDF-15, growth/differentiation factor-15; ANG-2, angiopoietin-2; OPN, osteopontin; sST2, suppression of tumorigenicity-2; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; RBBB, right bundle branch block

markers and have been observed to be increased in comorbidities, including ischemic heart disease, heart failure, kidney impairment, and other SSc-related diseases, like PH. Therefore, further studies are needed to clarify the role of NT-proBNP, hs-cTnT, and hs-cTnI in SSc patients with cardiovascular involvement and to define novel sensitive and specific cardiac biomarkers for SSc-pHI [6, 7].

The lack of specific markers has encouraged studies evaluating novel biomarkers. Results regarding new biomarkers are also favorable. Among these biomarkers, galectin-3 appears to be a promising marker in which elevated concentrations are related to myocardial fibrosis, mitral regurgitation, and LV systolic and diastolic dysfunction [41, 44]. Elevated angiopoietin-2 and osteopontin levels and decreased TRAIL concentrations have been shown to be linked with both LV and RV systolic dysfunction [45]. The studies evaluating autoantibodies show that anti-Scl-70 and anti-fibrillarin, namely anti-U3-RNP, antibodies are closely related to cardiac involvement in SSc [51, 52]. Figure 3 illustrates serum markers that could potentially be useful in detecting cardiac involvement.

In conclusion, the assessment of serum biomarkers represents a valuable, non-invasive means of screening patients with SSc for cardiac involvement. However, there are currently no established guidelines for diagnosing or defining the prognosis of these patients. In addition, the role of these biomarkers in predicting the type of cardiac complications and responsiveness to therapeutic intervention is still unknown. Therefore, further studies are needed to identify more sensitive and specific cardiac biomarkers and to elucidate their role in diagnosis, prognosis, and treatment follow-up.

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Compliance with ethical standards

Disclosures None.

References

1. Volkmann ER, Andréasson K, Smith V (2023) Systemic sclerosis. Lancet 401(10373):304–318. https://doi.org/10.1016/S0140-6736(22)01692-0
2. Deswal A, Follansbee WP (1996) Cardiac involvement in scleroderma. Rheum Dis Clin North Am 22(4):841–860. https://doi.org/10.1016/s0889-857x(05)70304-5
3. Moysidou GS, Dara A, Arvanitaki A, Skalkou A, Pagkopoulou E, Daoussis D et al (2023) Understanding and managing cardiac involvement in systemic sclerosis. Expert Rev Clin Immunol 19(3):293–304. https://doi.org/10.1080/1744666X.2023.2171988
4. Caetano J, Batista F, Amaral MC, Oliveira S, Alves JD (2022) Acute hospitalization in a cohort of patients with systemic

sclerosis: a 10-year retrospective cohort study. Rheumatol Int 42(8):1393–1402. https://doi.org/10.1007/s00296-021-04983-4
5. Agoston Coldea L, Zlibut A, Revnic R, Florea M, Muntean L (2021) Current advances in cardiac magnetic resonance imaging in systemic sclerosis. Eur Rev Med Pharmacol Sci 25(10):3718–3736. https://doi.org/10.26355/eurrev_202105_25940
6. Bruni C, Ross L (2021) Cardiac involvement in systemic sclerosis: Getting to the heart of the matter. Best Pract Res Clin Rheumatol 35(3):101668. https://doi.org/10.1016/j.berh.2021.101668
7. Bruni C, Buch MH, Furst DE, De Luca G, Djokovic A, Dumitru RB et al (2022) Primary systemic sclerosis heart involvement: A systematic literature review and preliminary data-driven, consensus-based WSF/HFA definition. J Scleroderma Relat Disord 7(1):24–32. https://doi.org/10.1177/23971983211053246
8. EUSTAR co-authors, Allanore Y, Meune C, Vonk MC, Airo P, Hachulla E, Caramaschi P et al (2010) Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 69(1):218–221. https://doi.org/10.1136/ard.2008.103382
9. Nie LY, Wang XD, Zhang T, Xue J (2019) Cardiac complications in systemic sclerosis: early diagnosis and treatment. Chin Med J (Engl) 132(23):2865–2871. https://doi.org/10.1097/CM9.0000000000000535
10. Afifi N, Khalifa MMM, Al Anany AAMMM, Hassan HGEMA (2022) Cardiac calcium score in systemic sclerosis. Clin Rheumatol 41(1):105–114. https://doi.org/10.1007/s10067-021-05887-1
11. Ferlito A, Campochiaro C, Tomelleri A, Dagna L, De Luca G (2022) Primary heart involvement in systemic sclerosis, from conventional to innovative targeted therapeutic strategies. J Scleroderma Relat Disord 7(3):179–188. https://doi.org/10.1177/23971983221083772
12. De Luca G, Cavalli G, Campochiaro C, Bruni C, Tomelleri A, Dagna L, Matucci-Cerinic M (2021) Interleukin-1 and systemic sclerosis: getting to the heart of cardiac involvement. Front Immunol 12:653950. https://doi.org/10.3389/fimmu.2021.653950
13. Caforio ALP, De Luca G, Baritussio A, Seguso M, Gallo N, Bison E et al (2021) Serum organ-specific anti-heart and anti-intercalated disk autoantibodies as new autoimmune markers of cardiac involvement in systemic sclerosis: frequency, clinical and prognostic correlates. Diagnostics (Basel) 11(11):2165. https://doi.org/10.3390/diagnostics11112165
14. RESCLE Investigators, Systemic Autoimmune Diseases Study Group (GEAS), González García A, Fabregate M, Manzano L, Guillén Del Castillo A, Rubio Rivas M, Argibay A et al (2022) Left ventricular diastolic dysfunction in systemic sclerosis: clinical, immunological and survival differences in the Spanish RESCLE registry. Semin Arthritis Rheum 55:152033. https://doi.org/10.1016/j.semarthrit.2022.152033
15. Hui M, Zhou J, Zhang L, Duan X, Li M, Wang Q et al (2021) Prevalence and risk factors for left ventricular diastolic dysfunction in systemic sclerosis: a multi-center study of CRDC cohort in China. Clin Rheumatol 40(11):4589–4596. https://doi.org/10.1007/s10067-021-05804-6 Epub 2021 Jun 17
16. Varga J, Lee DC (2019) Getting to the heart of the matter: detecting and managing cardiac complications in systemic sclerosis. Ann Rheum Dis 78(11):1452–1453. https://doi.org/10.1136/annrheumdis-2019-216115
17. Hinze AM, Perin J, Woods A, Hummers LK, Wigley FM, Mukherjee M, Shah AA (2022) Diastolic dysfunction in systemic sclerosis: risk factors and impact on mortality. Arthritis Rheumatol 74(5):849–859. https://doi.org/10.1002/art.42054
18. EUSTAR group, Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A et al (2017) Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 76(11):1897–1905. https://doi.org/10.1136/annrheumdis-2017-211448
19. Feher A, Miller EJ, Peters DC, Mojibian HR, Sinusas AJ, Hinchcliff M, Baldassarre LA (2023) Impaired left-ventricular global longitudinal strain by feature-tracking cardiac MRI predicts mortality in systemic sclerosis. Rheumatol Int 43(5):849–858. https://doi.org/10.1007/s00296-023-05294-6
20. Gawałko M, Balsam P, Lodziński P, Grabowski M, Krzowski B, Opolski G, Kosiuk J (2020) Cardiac Arrhythmias in Autoimmune Diseases. Circ J 84(5):685–694. https://doi.org/10.1253/circj.CJ-19-0705
21. Hu S, Hou Y, Wang Q, Li M, Xu D, Zeng X (2018) Prognostic profile of systemic sclerosis: analysis of the clinical EUSTAR cohort in China. Arthritis Res Ther 20(1):235. https://doi.org/10.1186/s13075-018-1735-4
22. Hosoya H, Derk CT (2018) Clinically symptomatic pericardial effusions in hospitalized systemic sclerosis patients: demographics and management. Biomed Res Int 2018:6812082. https://doi.org/10.1155/2018/6812082
23. Colaci M, Schinocca C, Bosco YD, Ronsivalle G, Guggino G, de Andres I et al (2022) Heart valve abnormalities in systemic sclerosis patients: a multicenter cohort study and review of the literature. J Clin Rheumatol 28(1):e95–e101. https://doi.org/10.1097/RHU.0000000000001638
24. Kurmann RD, El-Am EA, Radwan YA, Sandhu AS, Crowson CS, Matteson EL et al (2021) Increased risk of valvular heart disease in systemic sclerosis: an underrecognized cardiac complication. J Rheumatol 48(7):1047–1052. https://doi.org/10.3899/jrheum.201005
25. Pokeerbux MR, Giovannelli J, Dauchet L, Mouthon L, Agard C, Lega JC et al (2019) Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. Arthritis Res Ther 21(1):86. https://doi.org/10.1186/s13075-019-1867-1
26. Li X, Qian YQ, Liu N, Mu R, Zuo Y, Wang GC, Jia Y, Li ZG (2018) Survival rate, causes of death, and risk factors in systemic sclerosis: a large cohort study. Clin Rheumatol 37(11):3051–3056. https://doi.org/10.1007/s10067-018-4291-z
27. Abignano G, Del Galdo F (2020) Biomarkers as an opportunity to stratify for outcome in systemic sclerosis. Eur J Rheumatol 7(Suppl 3):S193–S202. https://doi.org/10.5152/eurjrheum.2020.19065
28. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31(11):1409–1417. https://doi.org/10.1007/s00296-011-1999-3
29. Romaniello A, Rubattu S, Gigante A, Simonelli F, Grimaldi MC, D'Angelo A et al (2019) Atrial natriuretic peptide predicts disease progression and digital ulcers development in systemic sclerosis patients. J Cardiovasc Med (Hagerstown) 20(11):771–779. https://doi.org/10.2459/JCM.0000000000000852
30. Ross L, Moxey J, Nikpour M (2021) Are troponin and B-type natriuretic peptides useful biomarkers for the diagnosis of systemic sclerosis heart involvement? A systematic literature review. Semin Arthritis Rheum 51(1):299–309. https://doi.org/10.1016/j.semarthrit.2020.10.016
31. Dumitru RB, Bissell LA, Erhayiem B, Fent G, Kidambi A, Swoboda P et al (2021) Predictors of subclinical systemic sclerosis primary heart involvement characterised by microvasculopathy and myocardial fibrosis. Rheumatology (Oxford) 60(6):2934–2945. https://doi.org/10.1093/rheumatology/keaa742
32. Barsotti S, Stagnaro C, d'Ascanio A, Parma A, Emdin M, Conti U et al (2017) High sensitivity troponin might be a marker of subclinical scleroderma heart involvement: a preliminary study. J Scleroderma Relat Disord 2(3):183–187
33. Bosello S, De Luca G, Berardi G, Canestrari G, de Waure C, Gabrielli FA et al (2019) Cardiac troponin T and NT-proBNP as diagnostic and prognostic biomarkers of primary cardiac

involvement and disease severity in systemic sclerosis: a prospective study. Eur J Intern Med 60:46–53. https://doi.org/10.1016/j.ejim.2018.10.013
34. Jha M, Wang M, Steele R, Baron M, Fritzler MJ, Canadian Scleroderma Research Group, Hudson M (2022) NT-proBNP, hs-cTnT, and CRP predict the risk of cardiopulmonary outcomes in systemic sclerosis: Findings from the Canadian Scleroderma Research Group. J Scleroderma Relat Disord 7(1):62–70. https://doi.org/10.1177/23971983211040608
35. Paik JJ, Choi DY, Mukherjee M, Hsu S, Wigley F, Shah AA, Hummers LK (2022) Troponin elevation independently associates with mortality in systemic sclerosis. Clin Exp Rheumatol 40(10):1933–1940. https://doi.org/10.55563/clinexprheumatol/fytfmy
36. Nordin A, Svenungsson E, Björnådal L, Elvin K, Larsson A, Jensen-Urstad K (2017) Troponin I and echocardiography in patients with systemic sclerosis and matched population controls. Scand J Rheumatol 46(3):226–235. https://doi.org/10.1080/03009742.2016.1192217
37. Bissell LA, Dumitru RB, Erhayiem B, Abignano G, Fent G, Kidambi A et al (2019) Incidental significant arrhythmia in scleroderma associates with cardiac magnetic resonance measure of fibrosis and hs-TnI and NT-proBNP. Rheumatology (Oxford) 58(7):1221–1226. https://doi.org/10.1093/rheumatology/key430
38. Sugiyama K, Kobayashi H, Kobayashi Y, Yokoe I, Takei M, Kitamura N (2019) Association of cardiac magnetic resonance-detected myocardial abnormalities with disease characteristics and brain natriuretic peptide levels in systemic sclerosis without cardiac symptoms. Int J Rheum Dis 22(6):1016–1022. https://doi.org/10.1111/1756-185X.13540
39. Dumitru RB, Bissell LA, Erhayiem B, Kidambi A, Dumitru AH, Fent G et al (2021) Cardiovascular outcomes in systemic sclerosis with abnormal cardiovascular MRI and serum cardiac biomarkers. RMD Open 7(3):e001689. https://doi.org/10.1136/rmdopen-2021-001689
40. Tipparot T, Foocharoen C, Mahakkanukrauh A, Suwannaroj S, Nanagara R, Pussadhamma B, Chaosuwannakit N (2019) Clinical and laboratory predictions of myocardial inflammation as detected by cardiac magnetic resonance imaging in patients with systemic sclerosis: A pilot study. Int J Rheum Dis 22(12):2125–2133. https://doi.org/10.1111/1756-185X.13727
41. Hromadka M, Baxa J, Seidlerova J, Miklik R, Rajdl D, Sudova V et al (2021) Myocardial involvement detected using cardiac magnetic resonance imaging in patients with systemic sclerosis: A Prospective observational study. J Clin Med 10(22):5364. https://doi.org/10.3390/jcm10225364
42. De Luca G, Campochiaro C, De Santis M, Sartorelli S, Peretto G, Sala S et al (2020) Systemic sclerosis myocarditis has unique clinical, histological and prognostic features: a comparative histological analysis. Rheumatology (Oxford) 59(9):2523–2533. https://doi.org/10.1093/rheumatology/kez658
43. Hromadka M, Seidlerova J, Suchy D, Rajdl D, Lhotsky J, Ludvik J et al (2017) Myocardial fibrosis detected by magnetic resonance in systemic sclerosis patients- relationship with biochemical and echocardiography parameters. Int J Cardiol 249:448–453. https://doi.org/10.1016/j.ijcard.2017.08.072
44. Vertes V, Porpaczy A, Nogradi A, Tokes-Fuzesi M, Hajdu M, Czirjak L et al (2022) Galectin-3 and sST2: associations to the echocardiographic markers of the myocardial mechanics in systemic sclerosis - a pilot study. Cardiovasc Ultrasound 20(1):1. https://doi.org/10.1186/s12947-022-00272-7
45. Tennoe AH, Murbræch K, Didriksen H, Ueland T, Palchevskiy V, Weigt SS et al (2022) Serum markers of cardiac complications in a systemic sclerosis cohort. Sci Rep 12(1):4661. https://doi.org/10.1038/s41598-022-08815-8
46. Iannazzo F, Pellicano C, Colalillo A, Ramaccini C, Romaniello A, Gigante A, Rosato E (2022) Interleukin-33 and soluble suppression of tumorigenicity 2 in scleroderma cardiac involvement. Clin Exp Med. https://doi.org/10.1007/s10238-022-00864-7
47. El-Adili F, Lui JK, Najem M, Farina G, Trojanowska M, Sam F, Bujor AM (2023) Periostin overexpression in scleroderma cardiac tissue and its utility as a marker for disease complications. Arthritis Res Ther 25(1):11. https://doi.org/10.1186/s13075-022-02943-2
48. Leclair V, D'Aoust J, Gyger G, Landon-Cardinal O, Meyer A, O'Ferrall E et al (2022) Autoantibody profiles delineate distinct subsets of scleromyositis. Rheumatology (Oxford) 61(3):1148–1157. https://doi.org/10.1093/rheumatology/keab492
49. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al (2013) 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 72(11):1747–1755. https://doi.org/10.1136/annrheumdis-2013-204424
50. Nihtyanova SI, Sari A, Harvey JC, Leslie A, Derrett-Smith EC, Fonseca C et al (2020) Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol 72(3):465–476. https://doi.org/10.1002/art.41153
51. Tieu A, Chaigne B, Dunogue B, Dion J, Regent A, Casadevall M et al (2022) Autoantibodies versus skin fibrosis extent in systemic sclerosis: a case-control study of inverted phenotypes. Diagnostics (Basel) 12(5):1067. https://doi.org/10.3390/diagnostics12051067
52. Keppeke GD, Satoh M, Kayser C, Matos P, Hasegawa T, Tanaka S et al (2022) A cell-based assay for detection of anti-fibrillarin autoantibodies with performance equivalent to immunoprecipitation. Front Immunol 13:1011110. https://doi.org/10.3389/fimmu.2022.1011110
53. Psarras A, Soulaidopoulos S, Garyfallos A, Kitas G, Dimitroulas T (2017) A critical view on cardiovascular risk in systemic sclerosis. Rheumatol Int 37(1):85–95. https://doi.org/10.1007/s00296-016-3530-3