

Management of Heart Failure with Focus on Inflammatory Myocardial Diseases

**A Comparison between Cardiac Sarcoidosis and
Giant Cell Myocarditis**

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Cover illustration: Histopathological examination of cardiac sarcoidosis revealing a non-caseating circumscribed granuloma with giant cells in elastin-van Gieson staining. Figure courtesy of Prof. Anders Oldfors.

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“The people who bind themselves to systems are those who are unable to encompass the whole truth and try to catch it by the tail; a system is like the tail of truth, but truth is like a lizard; it leaves its tail in your fingers and runs away knowing full well that it will grow a new one in a twinkling”.

Reported as being said by IVAN TURGENEV to LEO TOLSTOY
at the Stepping Stones to Freedom International Conclave, St. Petersburg,
Russia in 1856

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ABSTRACT

Background: The prevalence of advanced heart failure (HF) is rising, a condition portrayed by hemodynamic disturbances and poor prognosis. Heart transplantation (HTx) is a valid treatment option once other alternatives have been exhausted. It is crucial to identify the underlying HF etiology to predict prognosis and guide management. Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) are two rare disease entities characterized by myocardial inflammation, leading to ventricular remodelling and advanced HF. We aimed to investigate the relationship between hemodynamic abnormalities and renal function and assess the potential of a multimodal diagnostic approach in improving diagnostic algorithms and developing better treatment options for subjects with CS and GCM.

Methods: Paper I is a nationwide study using information from the Scandiatransplant organ-exchange organization database. Individuals with advanced HF referred for HTx work-up in Sweden were included and data on hemodynamic and renal function were collected retrospectively. In Paper II and IV, information on subjects diagnosed with CS or GCM that had undergone a diagnostic work-up at our institution during the last 30 years was reviewed retrospectively. In Paper III a systematic review and meta-analysis examined the post-HTx outcomes in subjects with CS and GCM.

Results: Paper I found that among all hemodynamic variables, elevated right atrial pressure showed the strongest association with renal dysfunction. Also, elevated renal perfusion pressure was strongly linked to superior kidney

function, regardless of the level of cardiac output. In our studies on inflammatory myocardial diseases, we revealed that GCM is a more aggressive disorder than CS, often developing a fulminant course with severe biventricular failure and a need for advanced treatments. Post-HTx outcomes in people with CS and GCM resemble those in subjects with HF from other etiologies. The differential diagnosis between CS and GCM based solely on cardiac magnetic resonance (CMR) poses challenges since their imaging phenotypes overlap.

Conclusions: Considering the link between hemodynamics and renal function in HF, an approach to manage fluid overload could involve decreasing central venous pressure and/or raising mean arterial pressure to maintain renal perfusion pressure, thereby increasing renal blood flow and improving GFR. CMR features of both CS and GCM exhibit striking similarity, posing a challenge in distinguishing between these two rare conditions using imaging alone. In contrast, differences are observed in their clinical presentation, as subjects with GCM experience more symptoms and have a more fulminant course than individuals with CS. HTx is a safe and effective treatment option for people suffering from advanced HF due to inflammatory myocardial diseases.

Keywords: heart failure, sarcoidosis, myocarditis, heart transplantation, cardiac magnetic resonance, renal function, mortality

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SAMMANFATTNING PÅ SVENSKA

Förekomsten av svår hjärtsvikt ökar, ett tillstånd som kännetecknas av störningar i blodcirkulationen, nedsatt njurfunktion och hög dödlighet. Hjärttransplantation (HTx) är ett bra behandlingsalternativ om inga andra utvägar finns. Vid hjärtsvikt är viktigt att identifiera den underliggande orsaken, inte minst för att kunna skatta prognosen och optimera behandlingen. Hjärtsarkoidos (*cardiac sarcoidosis*, CS) och jättecellsm yokardit (*giant cell myocarditis*, GCM) är två sällsynta tillstånd som präglas av inflammation i hjärtmuskeln medförande hjärtrytmrubbningar, nedsatt kammarfunktion och hjärtsvikt. Syftet med avhandlingen var att undersöka sambandet mellan cirkulationsstörningar och nedsatt njurfunktion vid svår hjärtsvikt, som går under benämningen ”kardio-renala” syndromet. Vi ville även utvärdera om ett multimodalt diagnostiskt förhållningssätt kunde leda till bättre diagnostiska algoritmer och behandlingsstrategier för individer med CS och GCM.

Delarbete I visade att förhöjt ventryck var den hemodynamiska variabel som korrelerade starkast med nedsatt njurfunktionen, oberoende av andra tryck- och flödesmätningar. Därtill uppvisade ett ökat njurperfusionstryck ett starkt samband med bättre njurfunktion, oberoende av hjärtminutvolymens storlek. Avhandlingens övriga studier fann att GCM - i jämförelse med CS – är en mer aggressiv sjukdom, med fulminant förlopp, som ofta leder till biventrikulär svikt och ökat behov av avancerade behandlingar, såsom mekanisk hjärt pump eller HTx. Resultaten efter HTx hos individer med CS eller GCM och de med hjärtsvikt av andra orsaker är likartat. Det kan vara svårt med hjälp av hjärt-MR (cardiac magnetic resonance, CMR) att skilja mellan CS och GCM eftersom deras kontrastmönster vid bildanalys överlappar varandra.

Sammanfattningsvis, så kan njurperfusionen optimeras genom att sänka ventryck och/eller öka artärtryck. Detta kan vara en framkomlig behandlingsväg vid övervätskning hos individer med kardio-renalt syndrom. CS och GCM har liknande utseende vid hjärt-MR, vilket förhindrar differentialdiagnostik med bildanalys och belyser komplexiteten kring utredning av dessa sjukdomar. Till skillnad från bildanalys så förekommer det olikheter vid den kliniska presentationen, där GC, i jämförelse med CS, uppvisar allvarligare sjukdomsbild med snabbare försämring. HTx är säker och effektiv behandling hos individer som lider av svår hjärtsvikt till följd av inflammatorisk hjärtmuskelsjukdom och ger samma resultat som ses hos patienter med hjärtsvikt av andra orsaker.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Association between central haemodynamics and renal function in advanced heart failure: a nationwide study from Sweden

Bobbio E, Bollano E, Polte CL, Ekelund J, Rådegran G, Lundgren J, Haggård C, Gjesdal G, Braun O, Bartfay SE, Bergh N, Dahlberg P, Hjalmarsson C, Esmaily S, Haugen Löfman I, Manouras A, Melin M, Dellgren G, Karason K.
ESC Heart Failure, 2022 Aug;9(4):2654-2663

II. Diagnosis, management, and outcome of cardiac sarcoidosis and giant cell myocarditis: a Swedish single center experience

Bobbio E, Hjalmarsson C, Björkenstam M, Polte CL, Oldfors A, Lindström U, Dahlberg P, Bartfay SE, Szamlewski P, Taha A, Sakiniene E, Karason K, Bergh N, Bollano E.
BMC Cardiovascular Disorders, 2022 Apr 26;22(1):192

III. Short- and long-term outcomes after heart transplantation in cardiac sarcoidosis and giant-cell myocarditis: A systematic review and meta-analysis

Bobbio E, Björkenstam M, Nwaru BI, Giallauria F, Hessman E, Bergh N, Polte CL, Lehtonen J, Karason K, Bollano E.
Clinical Research in Cardiology, 2022 Feb;111(2):125-140

IV. Phenotyping of giant cell myocarditis versus cardiac sarcoidosis using cardiovascular magnetic resonance

Bobbio E, Bollano E, Oldfors A, Hedner H, Björkenstam M, Svedlund S, Karason K, Bergh N, Polte CL.
International Journal of Cardiology, 2023 Sep 15; 387:131143

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ABBREVIATIONS

ACC – American college of cardiology

ACEi – Angiotensin converting enzyme inhibitors

ARBs - Angiotensin receptor blockers

ARNIs - Angiotensin receptor-neprilysin inhibitors

ATG – Anti-thymocyte globulin

AVB - Atrioventricular block

BNP - B-type natriuretic peptide

CI – Cardiac index

CMR – Cardiac magnetic resonance

CO – Cardiac output

CRS - Cardiorenal syndrome

CRT - Cardiac resynchronization therapy

CS – Cardiac sarcoidosis

CT - Computed tomography

CVP – Central venous pressure

ECG – Electrocardiography

EMB – Endomyocardial biopsy

ESC - European society of cardiology

¹⁸F-FDG-PET - ¹⁸F-fluorodeoxyglucose positron emission tomography

GCM – Giant cell myocarditis

HF – Heart failure

HLA - Human leukocyte antigens

HFmrEF – Heart failure with mildly reduced ejection fraction

HFpEF - Heart failure with preserved ejection fraction

HFrEF - Heart failure with reduced ejection fraction

HR – Hazard ratio

HRS - Heart rhythm society

HTx – Heart transplantation

ICD - Implantable cardioverter defibrillators

JCS - Japanese circulation society

LGE - Late gadolinium enhancement

LV – Left ventricular

LVEF – Left ventricular ejection fraction

MAP – Mean arterial pressure

MCS - Mechanical circulatory support

mGFR – Measured glomerular filtration rate

MIDFIN - Myocardial inflammatory diseases in Finland

MPAP - Mean pulmonary arterial pressure

MRAs - Mineralocorticoid receptor antagonists

NOS - Newcastle-Ottawa quality assessment scale

NT-proBNP - N-Terminal prohormone of BNP

NYHA – New York heart association

PAWP - Pulmonary artery wedge pressure

RAP - Right atrial pressure

RHC - Right heart catheterization

RPP – Renal perfusion pressure

RR – Risk ratio

RV – Right ventricular

SCD – Sudden cardiac death

SGLT2 - Sodium-glucose cotransporter-2

sST2 - Soluble suppressor of tumorigenicity-2

TFS - Transplant-free survival

Th-1 cells - T-helper-1 cells

TNF – Tumor necrosis factor

VAs - Ventricular arrhythmias

VAD – Ventricular assist device

VO₂ - Oxygen uptake

1 INTRODUCTION

1.1 Heart Failure

1.1.1 Historical Perspective

The history of heart failure (HF) dates back to ancient times, with evidence found in archaeological discoveries dating over 3,500 years ago in Egypt ¹. Examination of remains revealed signs of pulmonary edema, indicating the presence of HF ². The ancient Egyptians and Chinese documented various aspects of HF, including cardiac hypertrophy and dropsical swellings ². Greek and Roman texts also described symptoms that could be attributed to HF, such as dyspnea and anasarca ^{3,4}.

Throughout history, medical understanding of HF evolved gradually ⁵. In the second century, Galen in the Roman Empire described disorders like atrial fibrillation but failed to recognize the heart's role as a pump ⁶. In the Middle Ages, scholars like Avicenna in the Islamic world discussed therapies for heart diseases ⁷. It wasn't until William Harvey's description of the circulation in 1628 that the understanding of HF began to improve ^{5,8}. During the 19th and early 20th centuries, the management of fluid retention due to HF was treated with Southey's tubes, which were inserted into swollen extremities to facilitate fluid drainage (**Figure 1**). In the 20th century, advancements in cardiac catheterization and surgery allowed for a better characterization of structural heart diseases ⁹. The concept of contractility and the understanding of cardiac function improved, which led to the introduction of drugs for treatment of HF including digitalis and diuretics ⁸.

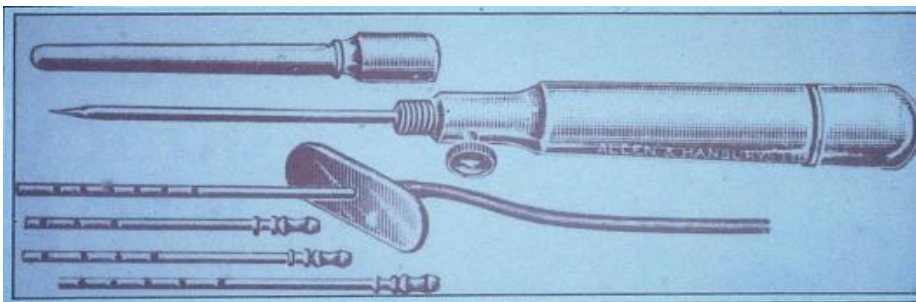


Fig. 1. Southey's tubes were used for removing fluid from edematous peripheries in heart failure patients. *Reproduced with permission of BMJ Publishing Group Ltd from BMJ, ABC of heart failure. History and epidemiology. Davis et al. 2000, Copyright Clearance Center.*

Between the 1940s and 1960s the medical community witnessed significant advancements in HF treatment. However, the understanding of HF pathophysiology remained limited, and treatment mainly focused on symptom management¹⁰. In the 1980s a neuroendocrine disturbance was recognized as an important component of the HF syndrome in addition to ineffective pump function. This led to the development of new treatments targeting HF-induced neurohormonal imbalance including angiotensin converting enzyme inhibitors (ACEi) and beta-blockers¹¹.

In the 1990s treatment with devices emerged including implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT), which helped prevent arrhythmia-related deaths and improved ventricular function¹². In the 2000s, research in molecular biology, genetics, and stem cells offered new avenues for HF treatment. Gene therapy, epigenetics, and stem cell therapy showed promise in regenerating myocardial tissue and improving cardiac function, although obstacles remain in their implementation¹³.

Overall, the understanding and treatment of HF have evolved immensely over the centuries, from ancient times to modern medicine. Although many advancements have been made, individuals with HF still suffer from considerable morbidity and mortality and challenges remain in effectively managing this complex condition.

1.1.2 Definition

HF is a clinical syndrome characterized by key symptoms such as breathlessness, ankle swelling, and fatigue, often accompanied by observable signs like elevated jugular venous pressure, pulmonary crackles, and peripheral edema^{14, 15}. This syndrome stems from structural and/or functional abnormalities of the heart, leading to increased intracardiac pressures and/or inadequate cardiac output, both at rest and during physical activity¹⁴. The identification of the underlying cause of cardiac dysfunction is an essential part of HF work-up, as the specific pathology can guide subsequent treatment decisions.

Traditionally, HF has been categorized based on the level of left ventricular ejection fraction (LVEF)^{14, 15}. This classification stemmed from early treatment trials that showed greater benefit in terms of outcomes in subjects with LVEF \leq 40%, compared to those with levels $>$ 40%^{16, 17}. However, HF encompasses a wide range of LVEF values, and echocardiography measurements can vary significantly. The following

classification was proposed in the most recent guidelines from the European Society of Cardiology (ESC) ¹⁴:

- Reduced LVEF: Defined as LVEF \leq 40%, indicating a significant reduction in left ventricular (LV) systolic function, labeled as HF_rEF.
- Mildly reduced LVEF: Individuals with LVEF between 41% and 49%, denoted as HF_{mr}EF.
- Preserved LVEF: Subjects with symptoms and signs of HF, evidence of cardiac abnormalities, raised natriuretic peptides, and LVEF \geq 50%, classified as HF_pEF.

These classifications are in accordance with the Universal Definition of Heart Failure ¹⁸, offering clarity in sorting subjects with HF according to their LVEF level. It's noteworthy that individuals with non-cardiovascular medical conditions who display symptoms resembling HF in the absence of cardiac dysfunction do not meet HF criteria ¹⁴. Nonetheless, these conditions can co-occur with HF and worsen the HF syndrome.

Additionally, HF can also result from right ventricular (RV) dysfunction, which can be caused by pressure or volume overload ^{14, 19}. While chronic RV failure is often secondary to LV dysfunction-induced pulmonary hypertension, other factors like myocardial infarction, arrhythmogenic right ventricular cardiomyopathy, or valvular disease can contribute to RV dysfunction ²⁰.

1.1.3 Epidemiology

HF affects millions globally, with prevalence rates estimated at 1-2% in developed countries, and over half of these cases involve HF_pEF ²¹⁻²⁴. The likelihood of developing HF over a lifetime is approximately one in five for a 40-year-old man in Europe or North America, and this risk rises with advancing age ²¹. Large-scale studies suggested HF prevalence in the United States at 2.5%, while in Germany it is around 4% ²⁵. In Sweden, the prevalence of HF was estimated to be around 2.2% (**Figure 2**). Incidence rates vary widely ranging between 1 to 9 cases per 1000 person-years, influenced by population demographics and diagnostic criteria ²¹. Notably, incidence rates stabilized between 1970 and 1990 in developed countries and are now possibly decreasing ²¹.

Recent population-based studies show a 7% decline in HF incidence between 2002 and 2014, primarily among individuals aged 60-84 ²⁶. However, incidence remained stable or increased in younger (<55 years) and older (>85 years) age groups ²¹. This is a concern since these groups have been underrepresented in treatment trials.

The decline in HF incidence is less dramatic than that of myocardial infarction, which is likely due to improved management and survival of the latter. Survivors of myocardial infarction frequently develop ventricular dysfunction due to ischemic sequelae, thus contributing to a higher overall HF burden.

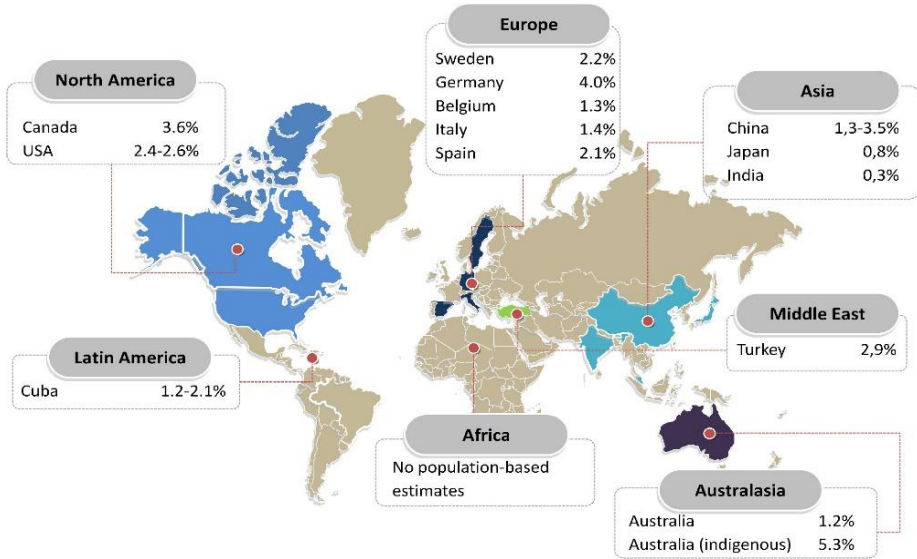


Fig. 2. Prevalence of heart failure in population-based studies around the world, in percentage, per region. *Reproduced with permission of John Wiley and Sons from Eur J Heart Fail, Epidemiology of heart failure. Groenewegen et al. 2020 Copyright Clearance Center.*

1.1.4 Etiology and Pathophysiology

The etiology of HF varies geographically. In developed nations, ischemic heart disease, valvular heart disease, hypertension, and various other factors such as cardiotoxicity from cancer treatments or substance abuse, genetic cardiomyopathies, amyloidosis dominates ¹⁴.

HF manifests through a diverse array of pathophysiological mechanisms, which vary depending on the subtype ^{27, 28}. HFpEF is characterized by structural and cellular alterations, including intercellular fibrosis, inflammation, as well as cardiomyocyte hypertrophy and impaired relaxation ²⁸⁻³⁰. Chronic comorbidities such as type 2 diabetes mellitus, arterial hypertension, and obesity often contribute to HFpEF by promoting the inflammatory processes ³⁰. Endothelial dysfunction, a hallmark of HFpEF, is

implicated early in cardiovascular disease progression and is more prevalent compared to HFrEF^{31, 32}. This dysfunction, influenced by factors like neurohumoral activation and oxidative stress, may precede ventricular diastolic dysfunction, thus acting as a precursor of HFpEF.

In contrast, HFrEF is characterized by myocardial injury, often due to conditions such as coronary artery disease or myocardial infarction that trigger a cascade of events leading to adverse remodeling³³. This remodeling encompasses ventricular dilation, myocyte hypertrophy, and fibrosis, impairing contractility and reducing cardiac output³⁴. Neurohormonal activation, particularly involving the sympathetic nervous system and the renin-angiotensin-aldosterone system, further exacerbates myocardial dysfunction and promotes vasoconstriction and sodium and water retention³⁵.

In HFmrEF, the pathophysiology shares similarities with both HFrEF and HFpEF³³. It often arises from a combination of myocardial injury and structural changes, albeit with less pronounced remodeling than observed in HFrEF. Consequently, subjects with HFmrEF exhibit an intermediate phenotype in terms of symptomatology and prognosis.

Since evidence-based therapies offer symptomatic and prognostic benefits exclusively in HFrEF, an understanding of the nuanced differences between HFrEF and HFpEF is imperative to enable customization of appropriate treatment strategies for each HF category.

1.1.5 Clinical Features

The clinical presentation of HF is heavily influenced by the primary site of dysfunction, whether it is left-sided, right-sided, or involves both ventricles. LV dysfunction, whether due to volume or pressure overload, results in increased pulmonary pressure (backward failure) and subsequent pulmonary congestion, leading to symptoms such as tachypnea and dyspnea (fluid transudation and pulmonary crackles)^{14, 27}. Concurrently, reduced peripheral circulation (forward failure) can lead to peripheral hypoperfusion, impaired renal function, as well as malabsorption of nutrients, often presenting as cardiac cachexia³⁶.

Chronic activation of neurohumoral systems as compensatory mechanisms further exacerbates volume overload, manifesting as ankle or pretibial edema, liver congestion, ascites, and peripheral vasoconstriction (acrocyanosis)³⁷. Anemia, increased pulmonary pressure, and muscle fatigue worsen dyspnea symptoms. Cardiac overload, whether pressure or volume-related, leads to cardiac enlargement, reflected in a leftward shift in palpable cardiac pulsations and an increased cardiothoracic index on chest X-ray. In

volume overload scenarios, ventricular filling volume increases, resulting in characteristic heart sounds like the third or fourth heart sound. Consequently, affecting nearly all organ systems, HF should be considered as a systemic disorder or syndrome with a wide range of clinical manifestations ¹⁴ (**Figure 3**).

In the assessment and classification of HF, two widely utilized systems provide valuable frameworks: the New York Heart Association (NYHA) functional classification and the American College of Cardiology (ACC) staging system ¹⁸. The NYHA class categorizes subjects based on the severity of symptoms and functional limitations, ranging from Class I (no symptoms with ordinary activity) to Class IV (symptoms even at rest) ¹⁸. This classification aids clinicians in gauging the impact of HF on a patient's daily life and guiding treatment decisions. On the other hand, the ACC staging system delineates HF progression based on disease severity and therapeutic interventions, from Stage A (at risk for HF but no structural heart disease or symptoms) to Stage D (refractory HF requiring specialized interventions) ³⁸. This staging system emphasizes the importance of early identification and intervention to prevent disease progression and optimize patient outcomes.

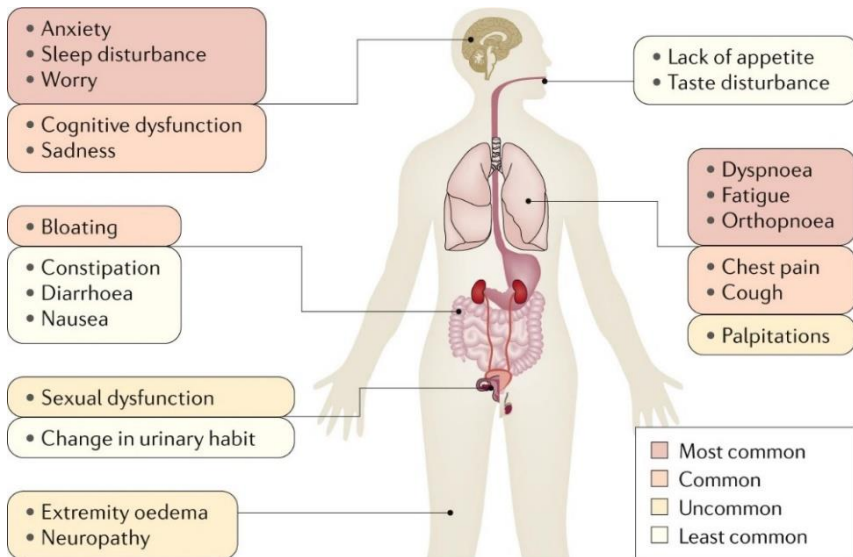


Fig. 3. Signs and symptoms of heart failure. *Reproduced with permission of Springer Nature from Nat Rev Dis Primers, Acute Heart Failure. Arrigo et al. 2020, Copyright Clearance Center.*

1.1.6 Diagnosis and Evaluation

The diagnosis of HF is a multifaceted process that requires a comprehensive evaluation, involving the integration of clinical findings and/or symptoms, and objective evidence of cardiac dysfunction¹⁴. This diagnostic journey typically involves a series of investigations that could be broadly categorized into two main groups: those recommended for the assessment of individuals with suspected HF and those aimed at determining the specific etiology of HF^{14,39}.

Electrocardiography (ECG) is a fundamental tool in screening subjects suspected of having HF, providing valuable information regarding potential personalized treatment options³⁹. Specific ECG abnormalities may offer clues to the etiology of HF, guiding further investigations and treatment strategies. Chest X-rays may support HF diagnosis by revealing pulmonary venous congestion, interstitial edema, or bilateral effusions, although findings must be interpreted cautiously as they lack diagnostic specificity³⁹. Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal prohormone of BNP (NT-proBNP), serve as sensitive markers for HF and are recommended for diagnostic assessment^{14,40}. Elevated concentrations of these peptides reflect increased left ventricular wall stress, aiding in the diagnosis and prognostication of the syndrome⁴¹.

Echocardiography plays a pivotal role in the diagnostic work-up and in phenotyping subjects based on LVEF³⁹. Also, echocardiography provides data on additional parameters, including chamber dimensions, left ventricular hypertrophy, regional wall motion abnormalities, right ventricular function, pulmonary artery pressure, valvular function, and indicators of diastolic function (**Figure 4**)¹⁴.

Cardiac magnetic resonance (CMR) has emerged as a valuable non-invasive modality for diagnosing and prognosticating HF^{14,42,43}. It surpasses echocardiography in evaluating left ventricular volumes, function, wall motion abnormalities, and myocardial tissue characteristics. Myocardial fibrosis, a prevalent pathological feature in HF, exhibits diverse patterns across different etiologies⁴⁴. Late gadolinium enhancement (LGE) CMR facilitates the non-invasive quantification of myocardial fibrosis, serving as a widely adopted technique for identifying etiology and assessing prognosis in individuals with HF^{45,46}. However, CMR primarily detects focal rather than diffuse interstitial fibrosis⁴⁴. Alongside fibrosis, HF entails intracellular abnormalities, myocardial edema, and extra-cellular protein deposition⁴⁵. Myocardial tissue characterization parameters (T1, T2, T2*, and extra-cellular volume) allow for quantification of tissue alterations in HF subjects, encompassing intracellular changes (e.g., fat deposition, iron overload), extra-cellular changes (e.g.,

fibrosis, amyloid protein deposition), or a combination (e.g., myocardial infarction, edema)^{43, 47}. CMR imaging has garnered endorsement in HF guidelines and has demonstrated significant impacts on patient management^{14, 48}.

Computed tomography coronary angiography may be considered in subjects with a low to intermediate pre-test probability of coronary artery disease¹⁴. Coronary angiography is indicated in HF patients experiencing angina pectoris as well as in HFrEF patients with an intermediate to high pre-test probability of coronary artery disease who are deemed potentially suitable for coronary revascularization^{14, 49}.

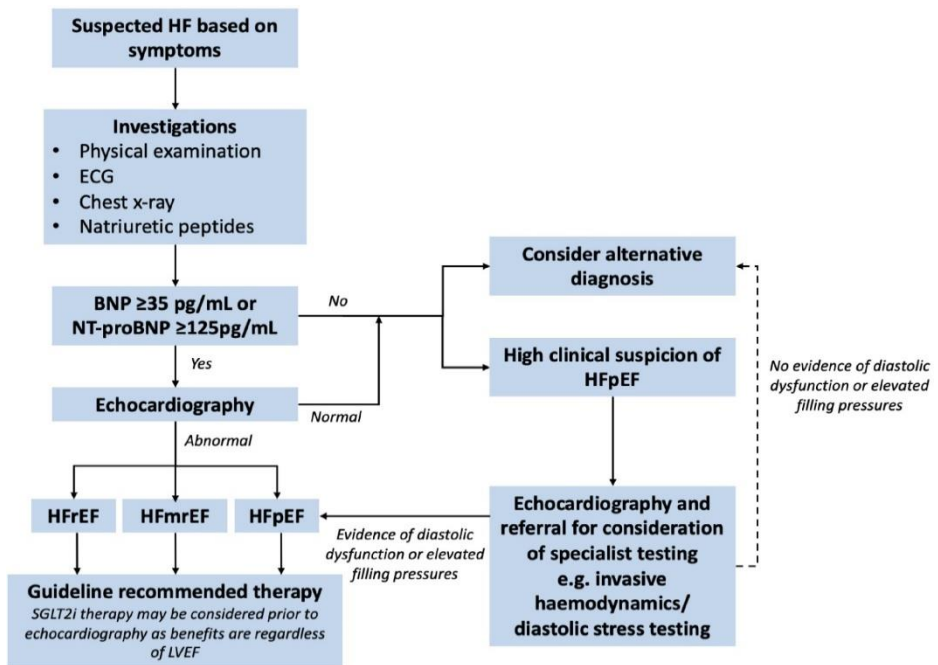


Fig. 4. Diagnostic process in patients with suspected heart failure. *Reproduced with permission of John Wiley and Sons from Eur J Heart Fail, Heart failure diagnosis in the general community – Who, how and when? A clinical consensus statement of the Heart Failure Association of the European Society of Cardiology, Docherty et al. 2023, Copyright Clearance Center*

BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

The HF diagnostic process also encompasses various tests aimed at determining disease severity and potential contributing factors. Exercise testing serves as an objective measure of functional capacity, with both six-minute walk tests and cardiopulmonary exercise tests providing valuable insights^{50, 51}. Cardiopulmonary exercise testing, in particular, allows for quantification of oxygen uptake (VO₂), with lower peak VO₂ values indicating a worse prognosis. Similarly, the six-minute walk test, measuring the distance ambulated in six minutes, correlates well with HF severity.

Right heart catheterization (RHC) is not routinely necessary for diagnosing suspected HF but plays a crucial role in assessing hemodynamics and eligibility for advanced HF therapies^{14, 52}. Persistent elevation in left- and right-sided filling pressures, along with decreased cardiac index despite optimal medical therapy is consistent with advanced HF⁵². However, a diagnosis cannot be solely based on abnormal hemodynamics, which must be interpreted alongside clinical findings⁵².

Furthermore, addressing contributing factors such as severe anemia, thyroid disorders, and sleep-disordered breathing is vital in optimizing HF management and prognosis¹⁴.

1.1.7 Advanced HF

Advanced HF can be delineated as a clinical condition characterized by the persistent presence of severe HF symptoms despite optimal adherence to evidence-based therapies⁵³. It signifies the phase of the condition wherein traditional treatments prove inadequate in managing patient symptoms, necessitating the implementation of advanced therapeutic modalities such as heart transplantation (HTx), implantation of mechanical circulatory support (MCS), intermittent administration of inotropic agents, and occasionally, end-of-life care^{53, 54}.

The term "Refractory HF" is sometimes used interchangeably, albeit it connotes a lack of response to treatment and the irreversibility of cardiac dysfunction and hemodynamic impairment⁵³. However, such conditions are not obligatory for the classification of advanced HF. The most recent ESC guidelines define advanced HF when, despite optimal medical management, the following criteria are met¹⁴:

- a. Clinical evaluation confirms severe HF symptoms (NYHA functional class III or IV) along with episodes of refractory fluid retention, hypoperfusion requiring intravenous inotropes or vasoactive agents, or recurrent malignant ventricular arrhythmias.

- b. Diagnostic testing reveals objective evidence of severe cardiac dysfunction on echocardiogram and/or right heart catheterization, including:
 - LVEF \leq 30% in the context of HFrEF
 - LV diastolic dysfunction with left atrial dilation and/or pulmonary hypertension
 - RV dysfunction
 - Non-operable severe valvular or congenital abnormalities
 - Low cardiac index (\leq 2.2 L/min/m²)
 - High cardiac filling pressures
- c. There is severe impairment of exercise capacity, indicated by low 6-minute walking test distance, or reduced peak oxygen consumption estimated to be of cardiac origin, inability to exercise due to HF.

Despite limited epidemiological data, it is estimated that 1–10% of the HF population experiences advanced HF ⁵⁴. A study in Minnesota found that, among residents aged \geq 45 years, the prevalence of advanced HF was 0.2% of the total population, equivalent to 10% of the HF population ⁵⁵. Importantly, individuals with advanced HF face a significantly reduced life expectancy ⁵⁶. In one cohort study, subjects with stage D, HF had an alarming 80% mortality rate at 5 years ⁵⁷. Individuals with advanced HF experience dysfunction in multiple organs as consequence of the disease's progression ⁵³. Heart failure is a systemic syndrome characterized by progressive involvement of multiple organs. Chronic low cardiac output and the inflammatory response induced by HF affect organs including the kidneys, lungs, liver, and brain ^{53, 55}. Consequently, the severity of multiorgan failure correlates with the degree of cardiac impairment.

1.1.8 Cardiorenal Syndrome

HF and renal dysfunction often coexist, creating a bidirectional relationship where dysfunction in one organ exacerbates dysfunction in the other⁵⁸. This intricate interplay, termed cardiorenal syndrome (CRS), presents significant clinical challenges and underscores the importance of understanding the multifaceted interactions between the heart and kidneys. At the core of CRS lies a complex network of pathophysiological mechanisms⁵⁸ (**Figure 5**).

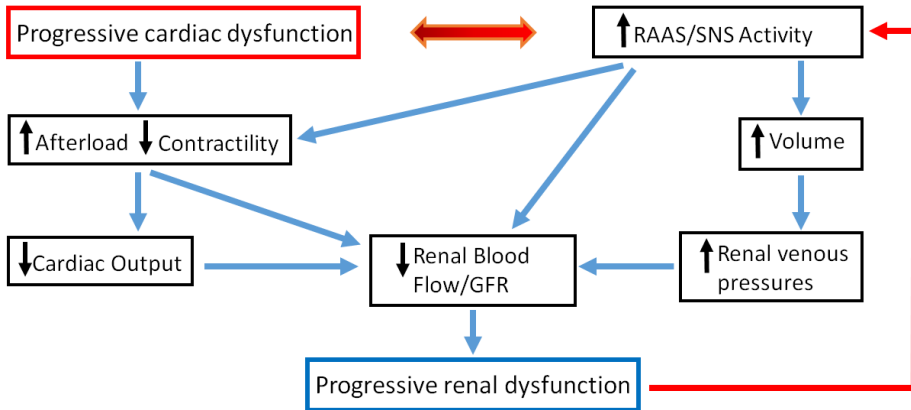


Fig. 5. Pathophysiological connections in cardiorenal syndrome.

GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system

Neurohumoral adaptations, such as activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, play a pivotal role in HF-induced renal dysfunction⁵⁸. These adaptations, triggered by hemodynamic derangements in HF, lead to salt and water retention, systemic vasoconstriction, and impaired renal perfusion. Despite compensatory mechanisms aimed at preserving perfusion to vital organs, including the brain and heart, the maladaptive nature of these adaptations ultimately contributes to renal impairment⁵⁹. Reduced renal perfusion, resulting from decreased cardiac output and elevated venous pressures, further compounds renal dysfunction.

The kidneys, reliant on adequate perfusion for optimal function, are particularly vulnerable to hemodynamic alterations characteristic of HF. Increased renal venous pressure, stemming from congestive HF states, exerts additional stress on renal function, impairing glomerular filtration and exacerbating renal dysfunction⁶⁰. Right ventricular dysfunction, commonly observed in HF, further complicates the cardiorenal relationship. Right ventricular dilation and dysfunction not only contribute to elevated venous pressures but also impair left ventricular filling. This will further stimulate neurohumoral activation leading to increased systemic congestion and additional impairment of renal perfusion^{58, 60, 61}.

The prevalence of renal impairment in HF subjects underscores the clinical significance of CRS. Moderate to severe kidney dysfunction is observed in a substantial proportion of HF patients, further complicating management and outcomes⁶². Acute HF exacerbations, frequently necessitating aggressive diuretic therapy, may precipitate transient renal dysfunction, blurring the lines between intrinsic renal disease and CRS^{59, 63}. Distinguishing between underlying renal pathology and CRS is paramount for implementing appropriate management strategies and optimizing outcomes in HF subjects with renal impairment.

Diagnosis of CRS relies on meticulous evaluation of renal function in the context of HF⁵⁸. Serum creatinine levels and estimated glomerular filtration rate serve as primary indicators of renal function, aiding in the identification of CRS in HF patients. However, challenges arise in differentiating between CRS and underlying renal disease, particularly in the setting of acute HF exacerbations. Ancillary tests, such as urine sodium concentration and blood urea nitrogen/creatinine ratio, may provide additional insights into the underlying pathophysiology of renal dysfunction in CRS.

Despite advances in our understanding of CRS, therapeutic strategies remain limited. Targeted interventions aimed at mitigating neurohumoral activation, optimizing renal perfusion, and alleviating venous congestion hold promise in ameliorating renal dysfunction in HF⁵⁹. However, the heterogeneity of CRS presentations and the multifactorial nature of its pathogenesis underscore the need for individualized treatment approaches tailored to the specific needs of each patient.

1.2 Cardiac Sarcoidosis and Giant Cell Myocarditis

1.2.1 Introduction

Cardiac sarcoidosis (CS) and giant cell myocarditis (GCM) are rare and serious types of inflammatory myocardial diseases with diverse clinical presentations and outcomes⁶⁴. Despite extensive research efforts, their exact causes and pathophysiological mechanisms remain largely unknown. The diagnosis typically relies on the pathological examination of an endomyocardial biopsy (EMB), although distinguishing between the two conditions can be arduous due to overlapping features^{65,66}.

Initial symptoms may include HF, serious ventricular arrhythmias (VAs), and conduction abnormalities⁶⁶. GCM tends to present more aggressively and carries a poorer prognosis if not promptly identified and managed⁶⁷. The debate continues whether CS and GCM represent distinct diseases or different manifestations of the same disorder. The notion that these two disorders are linked and part of a single disease continuum has persisted for decades and continues to spark discussions^{67,68}.

Sarcoidosis was first described in 1869, with its name and histological definition established in the late 19th and early 20th centuries^{69,70}. Cardiac involvement was documented in the late 1920s and further confirmed through autopsy studies in the mid-20th century^{71,72}. Prior to the availability of EMB, the CS diagnoses were primarily made post-mortem⁷³.

The earliest case report of GCM dates back to 1905, characterizing it as a fatal myocarditis with distinctive histopathological features^{74,75,66}. Although initially interchangeably used with terms like granulomatous myocarditis, GCM has been recognized as a separate entity since the mid-20th century⁶⁶. Despite advancements in diagnostic techniques such as EMB in the 1980s, it is still arduous to accurately diagnose and manage these two clinical conditions due to the lack of consensus on clinical work-up and treatment strategies⁷⁶.

In recent years, advancements in imaging, electrophysiology, and genomic studies have increased recognition and research interest in CS. However, the heterogeneity of these myocardial diseases continues to challenge physicians, highlighting the ongoing need for better diagnostic and management strategies.

1.2.2 Epidemiology

The epidemiology of both CS and GCM is characterized by obscurity, which reflects diverse population demographics and inconsistent diagnostic methods. Sarcoidosis incidence and prevalence data are arduous to ascertain due to sampling biases and diagnostic uncertainties. Reported incidence rates vary widely across different populations, with estimates ranging from 5.0 per 100,000 person-years in the United Kingdom and United States to 19 per 100,000 in Scandinavia^{77, 78}. Prevalence rates also vary, with Finland reporting 28.2 per 100,000 individuals⁷⁹. There are no comparable figures available from other sources specifically related to CS. The disease commonly affects individuals between 20 to 40 years old, with a secondary peak in women over 60 years old⁷⁸. Female sex is associated with a slightly higher incidence^{80, 81}.

Cardiac involvement is believed to occur in around 5% of subjects with sarcoidosis, but prevalence estimates vary depending on study type⁸¹. Clinical studies have reported CS in approximately 2-11% of subjects with systemic sarcoidosis^{82, 83, 84}. Autopsy studies have revealed higher rates of CS, with up to 67.8% of Japanese sarcoidosis patients showing signs of cardiac involvement post-mortem⁸⁵. Modern imaging techniques indicate silent cardiac involvement in 3.7-49% of sarcoidosis patients, suggesting a higher prevalence than reported in previous clinical studies^{86, 87}.

GCM is rarer than CS, with limited epidemiological data available. Autopsy studies suggest a prevalence of 6.6-23.4 per 100,000 individuals, while clinical studies have documented GCM in 0.2-3% of subjects with suspected myocarditis or idiopathic dilated cardiomyopathy^{75, 88}. GCM typically occurs in adults aged 16 to 69 years, with worse outcomes reported in younger subjects⁷⁶. Sex distribution in GCM varies across studies, with some showing equal distribution between men and women^{65 89}.

Overall, the epidemiology of sarcoidosis, CS, and GCM underscores the complexity of these conditions and the need for further research to better understand their prevalence, risk factors, and clinical outcomes.

1.2.3 Pathophysiology

The pathogenesis of CS and GCM involves intricate immune-mediated mechanisms influenced by genetic, infectious, and environmental factors⁹⁰⁻⁹². Both conditions are characterized by complex immune responses leading to myocardial tissue damage and dysfunction.

Sarcoidosis manifests as inflammatory granulomas in multiple organs, primarily affecting the lungs^{93, 94}. While its exact cause remains elusive, it is believed to stem from an immune response to antigen exposure in genetically susceptible individuals^{91, 95}. The granulomas, comprising macrophages, T-lymphocytes, and other immune cells, aim to contain the causative agents but can disrupt tissue integrity^{93, 96, 97}. Although not a classic autoimmune disease, sarcoidosis does share some autoimmune characteristics⁹⁸.

Immunologically, sarcoidosis triggers an exaggerated response driven by T-helper-1 (Th-1) cells, culminating in granuloma formation (**Figure 6**)^{99, 100}. Upregulated cytokines like interferon gamma and tumor necrosis factor alpha contribute to tissue inflammation and injury^{101, 102}. However, the mechanisms underlying fibrosis or resolution remain unclear. Genetic predisposition significantly influences sarcoidosis susceptibility and organ involvement, with certain human leukocyte antigens (HLA) class II genes implicated in disease risk¹⁰³. Epigenetic mechanisms also contribute to immune dysregulation. Infectious agents, particularly mycobacteria and propionibacteria, are thought to initiate the immune cascade in sarcoidosis⁹⁶. Environmental and occupational exposures to microbial bioaerosols, insecticides, and dust particles have also been linked to the disease⁹⁴.

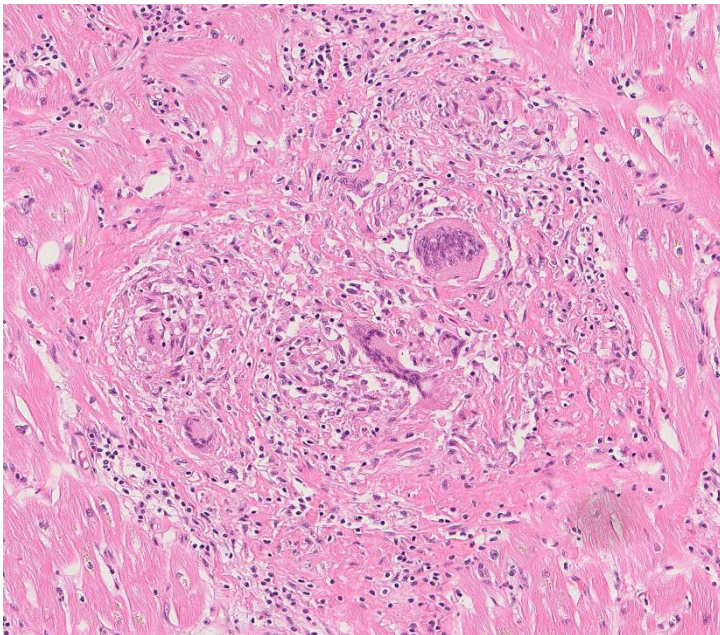


Fig. 6. Typical “stamped” sarcoid granuloma. Hematoxylin and eosin stain.

On the other hand, less is known about GCM's pathogenesis. Histologically, GCM presents with multinucleated giant cells, necrosis, and inflammatory cell infiltration, albeit without well-formed granulomas¹⁰⁴. Autoimmunity, particularly involving CD4-positive T-lymphocytes, plays a pivotal role in GCM, similar to CS^{65, 76}. Both conditions exhibit Th-1/2 imbalance and dysregulated cytokine production, indicating robust inflammatory responses^{65, 101}. Experimental models suggest that GCM can be induced in animals via autoimmunization with myosin, with cyclosporine therapy showing preventive effects^{105, 106}. However, specific autoantigens in humans remain poorly defined. Plakoglobin expression studies hint at potential links between GCM, CS, and other cardiomyopathies, necessitating further investigation^{107, 108}. Viral infections and drug reactions are potential triggers for GCM, while recruitment and activation of eosinophils may distinguish it from CS in terms of pathogenesis. Understanding these nuances is critical for enhancing diagnosis and treatment approaches for GCM.

1.2.4 Clinical Manifestations

Lung sarcoidosis often resolves spontaneously in about two-thirds of patients, contrasting with the potentially unfavorable prognosis in subjects with cardiac involvement¹⁰⁹. CS may precede, follow, or coexist with pulmonary or extra-pulmonary manifestations, with no clear correlation between the extent of extra-cardiac involvement and cardiac outcomes¹¹⁰. Clinical presentations vary depending on the extent and location of granulomatous infiltration within the heart, primarily affecting the myocardium and epicardium.

Manifestations of CS vary from asymptomatic electrocardiographic or imaging abnormalities to HF, life-threatening arrhythmias and sudden cardiac death (SCD)⁹⁰. Common complaints include palpitations, presyncope or syncope, and symptoms related to ventricular dysfunction⁹². Conduction abnormalities are frequent due to granulomatous infiltration of the atrioventricular septum, often presenting as heart block. Ventricular arrhythmias are significant concerns, ranging from premature beats to life-threatening ventricular fibrillation, often associated with electrical storms¹¹¹. HF in CS results from myocardial inflammation and fibrosis, leading to systolic or diastolic dysfunction. Structural abnormalities predispose to re-entry mechanisms, with ventricular tachycardia originating from scarred regions. Despite advancements in treatment, VAs remain common, contributing to a high risk of SCD rates^{90,111}. Other manifestations of CS include valve dysfunction, pericardial involvement, and coronary artery involvement. A timely detection of CS requires a high level of suspicion, especially in subjects with systemic sarcoidosis, new onset cardiomyopathy, heart block or unexplained ventricular arrhythmias. This is important, since early diagnosis and intervention may significantly improve outcome⁹⁰.

GCM is characterized by acute onset, progressive HF, and without treatment leads to death¹¹². Symptoms can vary widely, ranging from HF to VAs or symptoms mimicking acute myocardial infarction^{92,112}. Distinguishing between CS and GCM based on clinical presentation alone is challenging, emphasizing the importance of histological evaluation of EMB and advanced imaging modalities.

Optimal management of both conditions requires a multidisciplinary approach that gives specific attention to early recognition and intervention to mitigate disease progression and improve outcomes.

1.2.5 Diagnostic Work-up

Diagnosis of CS

Diagnosing CS presents significant difficulties, with an unequivocal diagnosis relying on a clinical presentation suggestive of myocardial disease alongside histological evidence of non-caseating granulomatous inflammation in myocardial tissue^{113, 114}. However, identifying CS, especially in cases of isolated cardiac involvement, remains difficult and often hinges on a high index of suspicion. Consequently, CS can be overlooked as the cause of advanced HF leading to HTx, with the diagnosis only revealed upon examination of the explanted heart¹¹⁵.

Suspicion for CS should arise primarily in individuals with established extra-cardiac sarcoidosis who display cardiac symptoms or signs, as well as in those experiencing unexplained high degree atrioventricular block (AVB), sustained VAs, or HF⁹⁰. Elevated cardiac troponins, raised natriuretic peptides, and newly identified anti-heart and anti-intercalated disk antibodies further bolster suspicions of CS in individuals with pre-existing extra-cardiac sarcoidosis^{116, 117}. For individuals without a prior diagnosis of sarcoidosis, elevated levels of angiotensin-converting enzyme, circulating lysozyme, and soluble interleukin-2 receptor may assist in determining a diagnosis⁹⁰.

While echocardiography offers limited sensitivity, it can furnish supporting evidence of CS. Notably, both cardiac ultrasound and standard ECG readings may appear normal in CS cases¹¹⁸. Chest computed tomography (CT) can suggest intrathoracic sarcoidosis, but definitive evaluation typically requires advanced imaging modalities such as CMR and/or ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET)^{119, 120}. The rationale for utilizing ¹⁸F-FDG-PET in suspected CS stems from the active uptake of glucose and its analogs by inflammatory cells within sarcoid granulomas¹¹⁹. Abnormal cardiac PET findings, characterized by increased ¹⁸F-FDG uptake, are especially useful for the diagnosis of CS. Frequently, this imaging modality may reveal one or more areas of heightened ¹⁸F-FDG uptake consistent with inflammation, which contrasts to a suppressed physiologic uptake by cardiac myocytes forming the background. Additionally, PET enables quantification of ¹⁸F-FDG uptake using standardized values, providing insight into the intensity and heterogeneity of the inflammatory process (**Figure 7**).

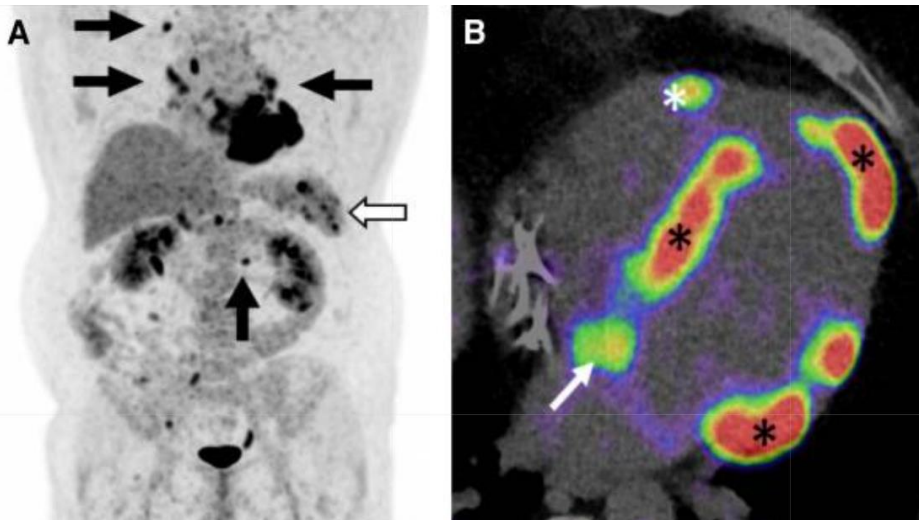


Fig. 7. Whole-body PET revealing positive ^{18}F -FDG uptake in lymph nodes (arrows) and spleen (hollow arrow) (A). A 4-chamber PET/CT image displaying ^{18}F -FDG accumulation at various cardiac sites, including the LV septum, apex, and basal lateral wall (asterisks), the right ventricular free wall (arrow), and the interatrial septum (arrow) (B). *Adapted with permission of Oxford University Press from Eur Heart J, Cardiac sarcoidosis: phenotypes, diagnosis, treatment, and prognosis, Lehtonen et al. 2023, Copyright Clearance Center.*

In suspected CS, CMR serves as an important non-invasive diagnostic tool. The appearance of CS on CMR varies significantly depending on the stage of the disease, displaying diverse patterns of LGE that may involve all layers of the myocardium and affect both ventricles (**Figure 8**)^{90, 121}. Moreover, research demonstrates that combining CMR with ^{18}F -FDG-PET/CT provides complementary insights, enhancing the assessment of risk and prognosis in this heterogeneous patient cohort¹²². The presence of myocardial scar identified by CMR correlates with the development of ventricular arrhythmias and sudden cardiac death¹²³.

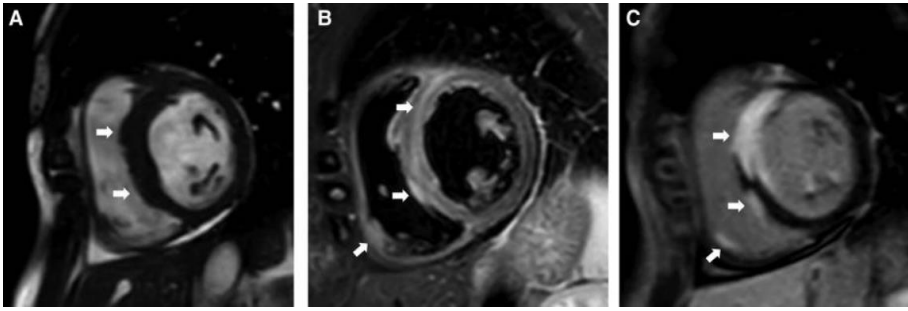


Fig. 8. Magnetic resonance imaging scans of a patient diagnosed with cardiac sarcoidosis. A short-axis cardiac cine image displays a thickened ventricular septum (A). A T2-weighted image reveals edema in the septum and localized inflammation in the right ventricle (B). In the late gadolinium enhancement image, there is evidence of transmurular involvement in the septum, papillary muscles, and localized inflammation in the right ventricular free wall (C). *Reproduced with permission of Oxford University Press from Eur Heart J, Cardiac sarcoidosis: phenotypes, diagnosis, treatment, and prognosis, Lehtonen et al. 2023, Copyright Clearance Center.*

There are currently three sets of diagnostic criteria for CS. The criteria provided by the World Association for Sarcoidosis and Other Granulomatous Disorders and the Heart Rhythm Society (HRS) are quite similar^{113, 124}. On the other hand, the updated criteria from the Japanese Circulation Society (JCS) are more intricate but do not mandate histological proof like the former two¹¹⁴. The HRS criteria are outlined in **Table 1**. While probable CS is often considered sufficient for clinical decision-making, the level of diagnostic certainty matters, as studies have shown that a definite diagnosis is generally associated with a poorer prognosis, although this is not always the case¹²⁵⁻¹²⁷. Discrepancies among these guidelines have led to non-uniform CS cohorts across different regions and institutions¹²⁸.

<p>1. Histological diagnosis from myocardial tissue, definite cardiac sarcoidosis requires presence of non-necrotizing granulomas with no alternative cause</p>
<p>2. Clinical diagnosis from noninvasive and invasive studies, probable cardiac sarcoidosis requires histologic diagnosis of extracardiac sarcoidosis and presence of one or more of the following:</p>
<p>–cardiomyopathy or atrioventricular block responsive to immunosuppression</p>
<p>–unexplained reduced left ventricular ejection fraction (<40%)</p>
<p>–unexplained sustained ventricular tachycardia (spontaneous or induced)</p>
<p>–2nd degree (Mobitz type II) or 3rd degree heart block</p>
<p>–patchy uptake on dedicated cardiac 18-F fluorodeoxyglucose PET^a</p>
<p>–late gadolinium enhancement on CMR^a</p>
<p>–positive gallium uptake^a</p>
<p>and exclusion of other causes for the cardiac manifestations</p>

Table 1. The heart rhythm society’s criteria for the diagnosis of cardiac sarcoidosis. *Reproduced with permission of Oxford University Press from Eur Heart J, Cardiac sarcoidosis: phenotypes, diagnosis, treatment, and prognosis, Lehtonen et al. 2023, Copyright Clearance Center.*

CMR, cardiac magnetic resonance; PET, positron emission tomography.

The HRS criteria recommend, and many centers favor, extra-cardiac biopsies over EMB with due to perceived advantages in sensitivity and safety¹¹³. Even so, the long-standing criticism about EMB's lack of sensitivity are mostly stemmed from obsolete techniques and can be considered outdated¹²⁹. Targeting specific myocardial areas aided by cardiac imaging and/or intracardiac voltage mapping enhances EMB's sensitivity¹³⁰. One advantage of EMB is that it allows for immunohistochemical studies of myocardial tissue and also studies of transcriptomics, which enhances the capability to differentiate CS from other cardiomyopathies^{131, 132}. The risks for serious complications in association with EMB are minimal.

Diagnosis of GCM

The diagnosis GCM can pose challenges and is frequently overlooked until autopsy or examination of the explanted heart in connection with cardiac transplantation. GCM should be included in the list of potential diagnoses for all subjects presenting with new-onset cardiomyopathy, especially when accompanied by rapidly progressive HF despite guideline-directed medical therapy, or associated with serious VAs, and/or high-degree heart block ^{64, 112}. Biomarkers indicating myocardial injury, such as troponin, are not useful for the diagnosis GCM ¹¹⁷. Although elevated BNP levels, suggestive of HF, are not specific for GCM, they consistently predict adverse outcomes including cardiac death and heart transplantation ¹¹⁷.

While most patients present with ECG abnormalities (such as sinus tachycardia, ST-segment elevation, T-wave inversion, VAs), a normal ECG does not exclude GCM ^{66, 133}. Information regarding the specific contribution of imaging biomarkers in GCM remains scarce. Echocardiography typically shows LV dysfunction, but fails to reveal pathognomonic patterns. The effect of GCM on LV systolic function may vary from a severe impairment to a more mild reduction and in some cases EF is preserved. Additional findings may include increased wall thickness, LV dilation and the presence of an aneurysm sometimes filled with thrombus. RV involvement can also be observed. Sometimes, echocardiography yields unremarkable results. CMR findings in GCM closely resemble those of CS, displaying diverse LGE patterns affecting all myocardial layers and both ventricles, including the right ventricular insertion points (**Figure 9**).

In the differentiation between GCM and CS, ¹⁸F-FDG-PET/CT may assist, especially when extra-cardiac sarcoidosis is evident, strongly suggesting CS ¹¹². However, the utility of ¹⁸F-FDG-PET/CT in suspected GCM remains controversial.

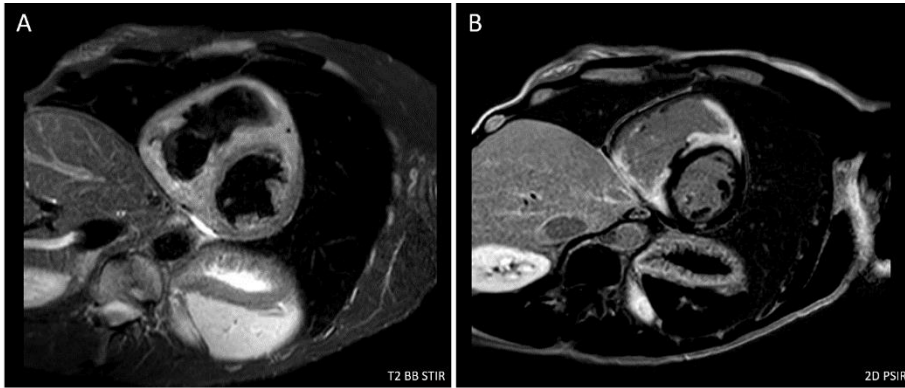


Fig. 9. Magnetic resonance imaging scans of a patient diagnosed with giant cell myocarditis showing signs of edema (A), and extensive biventricular late gadolinium enhancement (B).

2D PSIR, 2-dimensional phase-sensitive inversion recovery; T2 BB STIR, T2-weighted black blood short tau inversion recovery

Histological Diagnosis

A confirmed diagnosis of CS and GCM necessitates histological verification from myocardial tissue. Sarcoidosis is characterized histologically by the presence of non-caseating granulomas⁶⁵. These granulomas consist of a core containing mononuclear phagocytes (macrophages, epithelioid cells, and giant cells), encircled by T-lymphocytes, plasma cells, and mast cells, all surrounded by a fibrous ring^{65, 90} (**Figure 10**).

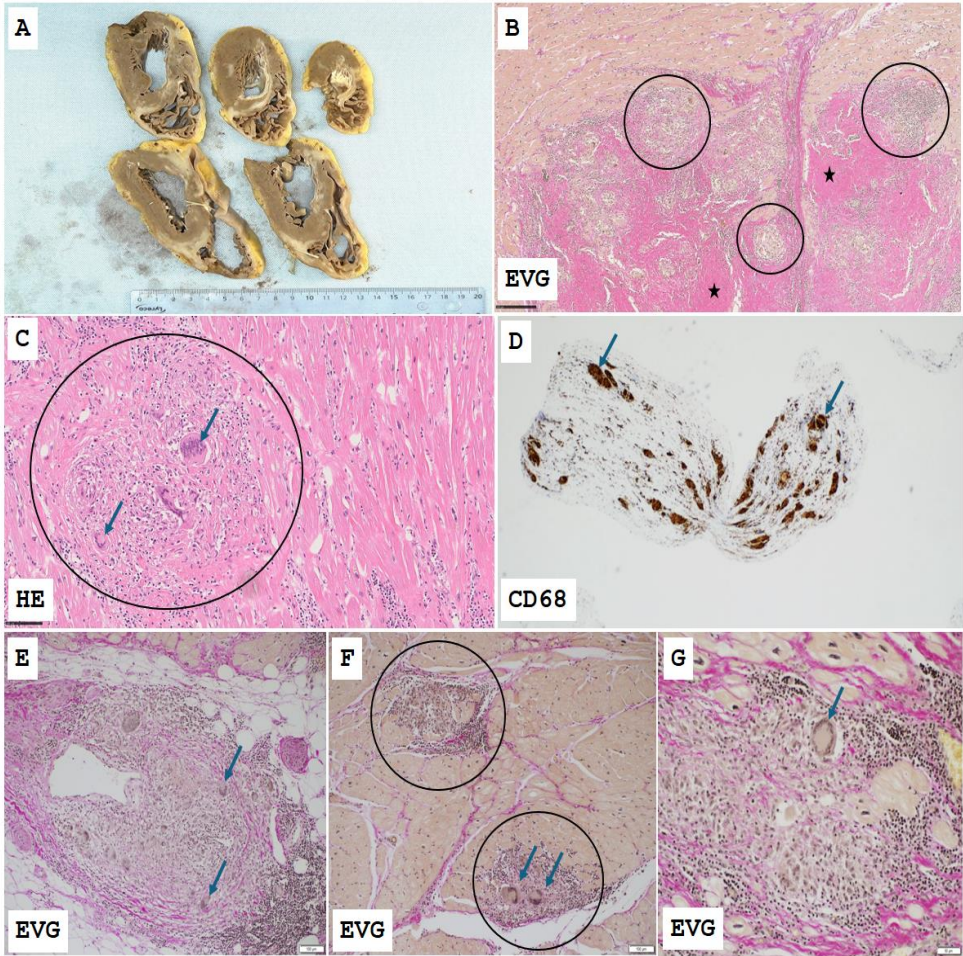


Fig. 10. Histopathological examination of cardiac sarcoidosis reveals well-defined fibrotic lesions evident in a photograph of an explanted heart (Panel A). Non-caseating granulomas (circles) and confluent fibrosis (stars) are marked in panel B (elastin-van Gieson stain, EVG). Panel C shows a non-caseating circumscribed granuloma (circle) with giant cells (arrows) in the myocardium in high-magnification hematoxylin-eosin (HE) staining. Macrophages and giant cells (arrows) can also be highlighted with CD68 antibody immunohistochemical staining (panel D). In panels (E–G), arrows mark multinuclear giant cells and circles encompass non-caseating granulomas.

In GCM, at least in the fulminant form of the disease, the diagnostic sensitivity of EMB is 80-85%, which is higher than that observed for CS¹³⁴. Pathognomonic histological features of GCM include diffuse or multifocal inflammatory infiltrates in the myocardium comprising lymphocytes, macrophages and multinucleated giant cells, accompanied by myocardial damage⁶⁵ (**Figure 11**). These giant cells are often surrounded by intact or degranulated eosinophils and typically extend to the inflammation's borders⁶⁵. Fibrosis, if present, is usually mild at the acute stage of disease. While poorly formed granulomas may be observed in GCM, the presence of well-organized follicular granulomas sometimes containing central giant cells are more characteristic for sarcoidosis and excludes the presence of GCM¹¹². Special stains for non-viral organisms should yield negative results.

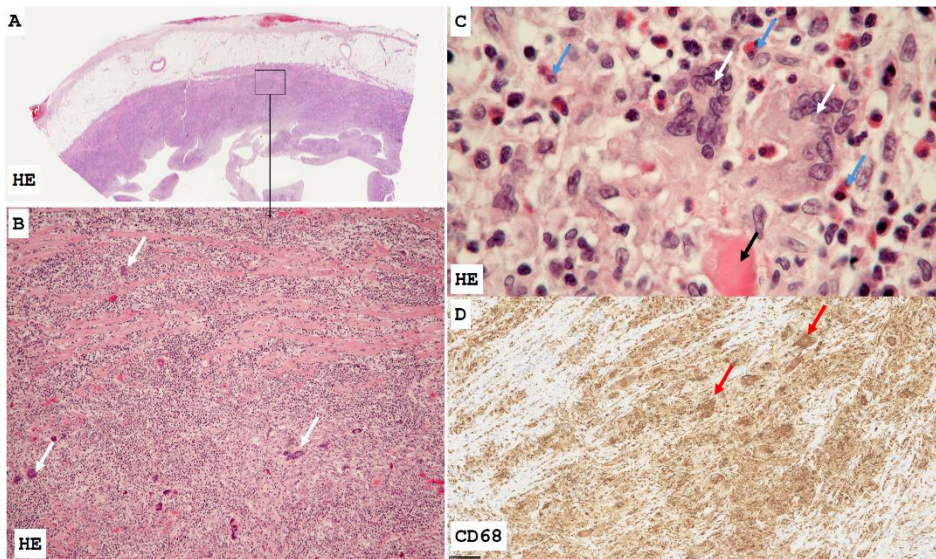


Fig. 11. Histopathology of giant cell myocarditis. Cardiac myocytes impacted by giant cell myocarditis in low-magnification hematoxylin-eosin (HE) staining (Panel A). In Panels B and C, there are visible multifocal inflammatory infiltrates characterized by lymphocytes alongside multinucleated giant cells (indicated by white arrows), eosinophils (blue arrows) as well as areas of coagulative necrosis (black arrow). Giant cells can also be highlighted with CD68 antibody staining (panel D).

1.3 Treatment Strategies and Prognosis

1.3.1 Management of Heart Failure

HF management involves a multifaceted approach aimed at alleviating symptoms, improving quality of life, and reducing morbidity and mortality¹⁴. Pharmacological interventions form the cornerstone of treatment for HF patients. Management is multifaceted and tailored to the individual's condition, often categorized by ejection fraction. In HFrEF, pharmacotherapy focuses on four main pillars^{14, 15}. ACEIs, angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs) play a crucial role in HF management. These medications counteract the deleterious effects of the renin-angiotensin-aldosterone system, leading to vasodilation, improved cardiac remodeling, and reduced fluid retention.

Beta-blockers, such as carvedilol and metoprolol succinate, are another class of medications frequently employed in HF management. These agents block the effects of catecholamines on the heart and, thereby, reduce heart rate, lower myocardial oxygen demand, counteract adverse remodeling, and ultimately improve cardiac function and prognosis¹³⁵. Mineralocorticoid receptor antagonists (MRAs) like spironolactone and eplerenone are often added to the treatment regimen in subjects with HFrEF. MRAs antagonize the effects of aldosterone, increasing diuresis, lowering blood pressure control, and slowing down myocardial fibrosis¹⁴. Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, originally developed for diabetes management, have shown remarkable benefits in HF management regardless of diabetes status^{15, 136}. These drugs, including empagliflozin, dapagliflozin, and canagliflozin, reduce the risk of HF hospitalization, cardiovascular death, and renal events¹³⁷. They exert their effects by promoting diuresis, reducing cardiac workload, and improving myocardial energetics¹³⁷. Another important goal in managing HF is to optimize fluid balance and reduce symptoms of congestion. Diuretics, such as loop diuretics (e.g., furosemide) and thiazides, are commonly used to achieve this by promoting diuresis and relieving fluid overload, thereby alleviating symptoms like dyspnea and edema¹⁴.

For subjects with HFpEF, management focuses on controlling comorbidities such as hypertension, diabetes, and obesity, as well as symptom relief with diuretics and other supportive measures¹⁴. Notably, SGLT2 inhibitors have recently been added to international guidelines for treatment of HFpEF after clinical drug trials showed improved outcome in this patient population with reduced risk of cardiovascular death and less hospitalization for HF¹³⁶.

Regular monitoring, patient education, lifestyle modifications (e.g., sodium restriction, regular exercise), and close follow-up provided by healthcare personnel are essential components of HF management to optimize therapeutic efficacy, prevent exacerbations, and improve long-term outcomes¹⁴.

1.3.2 Corticosteroids

In CS, clinical symptoms together with evidence of active inflammation, confirmed by EMB or PET, impose the initiation of immunosuppression⁹⁰. However, in cases with subclinical disease and no left ventricular dysfunction, the benefit of immunosuppression is uncertain, raising the need for an individualized treatment plan tailored for the specific patient.

Corticosteroids are the primary treatment, with evidence suggesting improvement in atrioventricular conduction and potential prevention of left ventricular function deterioration⁹⁰. However, their effects on arrhythmias and mortality are unclear^{126, 138, 139}. Usually, treatment begins with prednisone alone, adjusted according to disease severity¹⁴⁰. Severe cases may require additional immunomodulators or intravenous methylprednisolone pulses. Typically, the start dose for prednisone is 0.5 mg/kg/day and, for the most part, the dose is titrated down every 4 weeks in decrements of 5–10 mg until a maintenance dose of 5–10 mg/day is reached¹⁴⁰. Monitoring treatment response involves regular assessments of symptoms, left ventricular function, arrhythmia burden, and cardiac biomarkers. Decreasing systolic function, new wall-motion abnormalities, and increasing mitral regurgitation on echocardiography indicate persistent disease activity⁹⁰. Follow-up with imaging by means of CMR can be problematic due to artifacts from intra-cardiac devices¹⁴¹. Instead, repeated PET scans are often used to monitor CS activity and guide tailoring of treatment. However, routine PET scanning has not shown clear benefits in improving quality of life or event-free survival and may expose patients to unnecessary radiation⁹⁰.

There are no international guidelines available for the treatment of GCM, and studies on the therapy of this condition are scarce. One landmark study involving 11 patients outlined a treatment strategy based on an immunosuppression protocol¹⁴². Combining immunosuppressive therapy with guideline-directed HF and arrhythmia management has notably improved GCM prognosis. Typical immunosuppressive therapy involves corticosteroids and 1 or 2 additional agents^{112, 140}. A standard regimen includes intravenous methylprednisolone (10 mg/kg/day up to 1 g/day) for 3 days, followed by a prednisone taper, starting at 40 to 60 mg/day and reducing to 5 to 10 mg/day over 6 to 8 weeks¹¹².

1.3.3 Other Immunosuppressants

In CS, second-line immunosuppressive agents, such as methotrexate, azathioprine, mycophenolate mofetil, leflunomide, and cyclophosphamide, are utilized when corticosteroids prove ineffective or their dosage requires reduction to mitigate side effects of toxicity⁹⁰. Methotrexate (10–20 mg weekly) and azathioprine (1–2 mg/kg daily) are commonly used, necessitating careful monitoring for adverse effects such as hepatotoxicity and leukopenia⁹⁰. Biologic anti-tumor necrosis factor (TNF) agents, such as infliximab and adalimumab, are considered third-line options, particularly when other treatments fail^{143, 144}. Infliximab is administered at a dose of 5 mg/kg during weeks 0, 2, and 4, followed by subsequent administrations every 8 weeks for one year or until signs of inflammation persist, along with supplementary therapy (low-dose azathioprine or methotrexate) to lower the production of neutralizing antibodies⁹⁰. Rituximab, targeting B lymphocytes, shows promise but lacks sufficient evidence¹⁴⁵. Ongoing trials aim to assess various treatment strategies, including prednisone-methotrexate combination therapy (CHASM-CS trial), interleukin-1 receptor antagonist influence (MAGIC-ART trial), and comparing corticosteroids with antibiotics (J-ACNES trial)¹⁴⁶⁻¹⁴⁸. Additionally, the RESOLVE-Heart trial investigates the safety of namilumab, a monoclonal antibody targeting granulocyte-macrophage colony stimulating factor, in active CS (<https://clinicaltrials.gov/study/NCT05351554>). These trials aim to enhance treatment efficacy and safety in the management of corticosteroid-resistant or dependent cases.

Historically, subjects with GCM faced detrimental outcomes, with a 100% mortality rate or need for heart transplantation within one year of diagnosis if not treated with immunosuppressive drugs, and a median transplant-free survival (TFS) of less than three months after symptom onset⁷⁶. Treatment with corticosteroids alone showed similar TFS compared to no

immunosuppressive therapy ⁷⁶. However, combination immunosuppressive therapy incorporating cyclosporine significantly improved median TFS from 3.0 to 12.4 months ^{67, 92, 112}. Studies involving cyclosporine demonstrated a trend towards lower rates of cardiac transplantation or death. Additional immunosuppressive agents such as Muromonab-CD3 antibody, anti-thymocyte globulin (ATG), or Alemtuzumab (a monoclonal CD52 T-cell surface protein antagonist), in combination with cyclosporine, have shown promising results, most likely due to their targeting of T cells implicated in GCM's pathogenesis ^{112, 140}.

Notably, combination immunosuppression improved overall survival rates, with TFS rates reaching 69% at one year, 58% at two years, and 52% at five years ⁶⁷. Biopsy specimens taken after immunosuppressive treatment revealed significant reductions in eosinophilic infiltration, giant cells, lymphocytic myocarditis foci, and necrosis ¹⁴². Additionally, LVEF appeared to stabilize after immunosuppression, indicating potential preservation of cardiac function ¹⁴². The standard regimen for GCM typically involves intravenous methylprednisolone combined with ATG or Alemtuzumab and cyclosporine ¹¹². Alternative regimens incorporating high-dose corticosteroids with cyclosporine and azathioprine have also shown favorable outcomes, with a 91% one-year survival rate ¹¹².

1.3.4 Device Therapy and Mechanical Circulatory Support

A significant number of deaths in HF patients, particularly those with mild symptoms, occur suddenly and unexpectedly, often due to electrical disturbances including ventricular arrhythmias, bradycardia, or asystole, as well as acute vascular events¹⁴⁹. While treatments that mitigate cardiovascular disease progression can lower the annual rate of sudden death, they don't address arrhythmic events as they happen¹⁴⁹. ICDs effectively correct potentially lethal ventricular arrhythmias and, in transvenous systems, prevent bradycardia. Some antiarrhythmic drugs may decrease tachyarrhythmias and rates of SCD rates, but they don't reduce overall mortality and might even increase the risk of death¹⁵⁰. For secondary prevention, ICDs are recommended to lower sudden death risk and overall mortality in patients recovering from a ventricular arrhythmia causing hemodynamic instability, expecting to live more than one year with good functional status, unless the arrhythmia follows a recent myocardial infarction or other reversible causes^{14, 149}. In primary prevention, ICDs are advised to reduce sudden death and all-cause mortality risks in symptomatic HF patients (NYHA class II-III) of ischemic origin, with a LVEF $\leq 35\%$ despite optimal medical therapy for over three months, provided they are expected to have good functional status for more than a year¹⁴.

In advanced HF, patients may require pharmacological therapy and short-term MCS until long-term MCS or heart transplantation becomes necessary^{151, 152}. MCS improves survival and symptoms in advanced HF^{53, 54}. Short-term MCS aims to reverse critical organ hypoperfusion and hypoxia, supporting the central nervous system and organ function until the patient's prognosis becomes clearer¹⁵³. It is utilized as a bridge to decision, recovery, or transition to long-term MCS or transplantation. Long-term MCS extends life, improves quality of life, and serves as a bridge to transplantation or as destination therapy¹⁵⁴⁻¹⁵⁶. Heart transplantation remains the gold standard for treatment of advanced heart failure, significantly improving quality of life and physical functioning⁵³. Despite challenges such as organ donor shortage and post-transplant complications, careful recipient selection based on life expectancy and comorbidities is crucial. The decision pathway for transplantation or MCS is complex and individualized, and must take into account several aspects including patient conditions and external factors like waiting list time and center resources.

Management of symptomatic VAs and prevention of SCD in CS pose challenges. While the effects of immunosuppression on VAs remain uncertain, corticosteroids are recommended if inflammation is present^{90, 113, 146}. Antiarrhythmic drugs like amiodarone or sotalol are commonly used, and if unsuccessful, catheter ablation may be considered^{113, 138, 157}. Studies show variable success rates with ablation, and in cases of active inflammation intravenous methylprednisolone may be beneficial before ablation^{157, 158}. In refractory cases, cardiac sympathectomy could be an option^{113, 159}. Subjects with clinically manifest CS face a 10% risk of SCD over 5 years, necessitating careful consideration of ICD placement¹¹³. Guidelines recommend ICDs based on certain criteria, including reduced ejection fraction (LVEF<35%) or permanent pacing needs¹⁴⁹. Syncope history as an indication for ICD placement is debated^{160, 161}. Advanced cardiac imaging may guide decision-making, but whether pathological LGE patterns on CMR can be considered to be a surrogate for arrhythmia substrate is controversial. A substantial proportion of CS patients may not meet standard ICD criteria yet remain at significant risk, warranting long-term arrhythmia monitoring¹⁶². The decision to implant an ICD should be made by a multidisciplinary team after careful risk assessment, taking into account both advantages and disadvantages and involving the patient in the process. Complications associated with ICDs in CS patients are relatively common, underlining the importance of starting immunosuppression post-implantation in order to mitigate infection risks¹⁶³.

Many subjects with GCM experience ventricular tachycardia or high-degree heart block⁶⁷. Managing arrhythmias in GCM resembles treatment approaches applied in other cardiomyopathies. Advanced conduction issues may necessitate temporary pacing, often followed by a permanent pacemaker insertion despite immunosuppression¹¹². A Finnish registry showed that 17% of GCM patients received permanent pacemakers⁶⁷. Ventricular fibrillation or unstable ventricular tachycardia may demand antiarrhythmic drugs like amiodarone and/or ICDs for secondary prevention, especially if survival beyond one year is expected^{149, 161}. ICDs for primary prevention are recommended for those with low ejection fraction (<35%) despite optimal medical therapy. Guidelines advise ICDs in CS patients that fulfill specific criteria, but corresponding recommendations for GCM are not available due to lack of evidence. Yet, considering extensive LGE on CMR and refractory arrhythmias, case-specific ICD consideration in GCM is suggested. The Finnish registry reported 57% of GCM patients receiving ICDs, with appropriate therapies delivered to 55%, and no device infections despite treatment with immunosuppression¹⁶⁴.

LV assist devices can be considered for CS-related terminal HF¹⁶⁵. GCM may cause hemodynamic instability necessitating inotropic support or temporary MCS¹⁶⁶. Refractory shock may require various temporary MCS options¹⁶⁶. In a multicenter study, up to 78% of GCM patients were successfully bridged to transplantation with MCS¹⁶⁷. GCM subjects require biventricular MCS before transplantation more frequently than those with idiopathic dilated cardiomyopathy^{168, 169}. However, pre-transplant treatment with a ventricular assist device (VAD) in GCM may elevate the risk for recurrence of the disease post-transplant for unknown reasons.

1.3.5 Role of Heart Transplantation

HTx remains the preferred treatment for advanced HF when there are no contraindications⁵³. With a 1-year survival rate of approximately 90% and a median survival period of 12.5 years, HTx significantly enhances quality of life and functional capacity^{53, 170}. Following transplantation, the main challenges revolve around the effectiveness and potential side effects of immunosuppressive therapy, including issues such as rejection, infection, cardiac allograft vasculopathy, late graft dysfunction, malignancy, renal failure, hypertension, and diabetes mellitus, besides primary graft failure^{53, 170}. HTx emerges as a viable option for terminal HF associated with CS. Registry data suggested that post-transplant survival for CS patients were similar to those of non-CS recipients^{171, 172}. However, the number of individuals with CS that have undergone HTx is small and little is known about post-transplant long-term morbidity and mortality in this patient population.

Despite potential allograft recurrence risks, transplantation remains a reasonable recourse for medically unmanageable GCM⁹². A multicenter registry revealed that approximately half of GCM patients underwent HTx, with a significant post-transplant mortality rate, possible attributed to less aggressive immunosuppression initially^{76, 112}. The necessity for HTx was notably lower in studies implementing more intense upfront immunosuppression¹⁴². GCM has been linked to heightened risks of early rejection, encompassing both cellular and humoral rejection, with a recurrence rate of the disease in 20-25% of patients throughout long-term post-HTx monitoring^{76, 142, 173}. Despite reports of enhanced survival in more recent eras, the outcomes of subjects with GCM who have undergone HTx remains uncertain^{169, 173}.

Surveillance EMB post-HTx lacks standard guidelines for asymptomatic patients, though consideration is warranted for those exhibiting new-onset heart block, ventricular arrhythmias, or declining left ventricular systolic function ¹¹². Asymptomatic recurrent GCM with preserved left ventricular function typically involves steroid pulse therapy followed by tapering. In refractory cases, higher-dose corticosteroids and ATG are commonly employed, with alemtuzumab being a potential option due to its CD52-mediated effects on T cells ¹⁷⁴⁻¹⁷⁶. Still, post-HTx outcomes in patients with both CS and GCM have been poorly investigated.

2 AIMS

2.1 Overall Aim

The cardiorenal syndrome is characterized by an ill-defined reciprocal pathophysiological process that leads to deterioration of both the heart and kidneys. We sought to study how various heart failure-induced hemodynamic aberrations were related to impaired renal function. Cardiac sarcoidosis and giant cell myocarditis are both rare inflammatory myocardial diseases that have overlapping features and promote heart failure. We aimed to explore the similarities and differences between these disorders in terms of demographics, clinical presentation, and outcomes. Also, we wanted to examine whether the use of advanced imaging could improve diagnostic algorithms as well as management strategies in patients with these diseases. Ultimately, our objective was to assess the potential of heart transplantation as a safe and effective treatment for patients with advanced HF due to inflammatory myocardial diseases.

2.2 Specific Aims

The specific aims of the thesis were:

- To assess the relationship between invasive central hemodynamic variables and renal function in patients with advanced HF in a large, multicenter, nationwide study (**Paper I**);
- To compare the demographics, clinical presentation, and outcomes of patients diagnosed with CS or GCM (**Paper II**);
- To collate information from single-center and registry studies in order to perform a systematic review and meta-analysis of post-HTx outcomes in patients with CS and GCM and compare them with transplant recipients with other HF etiologies (**Paper III**);
- To systematically analyze and compare the CMR findings in patients with biopsy-proven GCM and CS and to assess the capability of CMR in differentiating between these two rare conditions (**Paper IV**).

3 MATERIALS AND METHODS

3.1 Study Population and Study Design

An overview of the studies included in this thesis is shown in **Table 2**.

Paper I:

All individuals referred for HTx evaluation in Sweden between 1988 and 2019 were identified via a search in the Scandiatransplant database. Scandiatransplant is an organ-exchange organization for five Nordic countries¹⁷⁷. The Scandiatransplant organization manages a registry that collects pre- and post-HTx information on patients from the Nordic nations. During the period of interest, three centers in Sweden conducted HTx procedures: Sahlgrenska University Hospital in Gothenburg, Lund University Hospital in Lund, and Karolinska University Hospital in Stockholm.

In this retrospective cohort study, we enrolled individuals aged 18 years or older with advanced HF who underwent RHC at a Swedish HTx center. Patients also had to have undergone a measurement of glomerular filtration rate (mGFR) within a month of RHC. Exclusion criteria consisted of ongoing renal replacement therapy, treatment with MCS, or evaluation for re-transplantation. The diagnosis of advanced HF was determined based on ESC guidelines.

Paper II:

We retrospectively identified all adult patients diagnosed with CS or GCM at Sahlgrenska University Hospital in Gothenburg, Sweden, between 1991 and 2020. As recommended by the HRS and JCS, histological diagnosis of CS required a positive myocardial biopsy or, when unavailable, evidence of extra-cardiac sarcoidosis along with clinical and imaging findings consistent with CS. Diagnostic imaging techniques could include ¹⁸F-FDG-PET/CT, CMR, or echocardiography. Clinical diagnosis of CS was permitted when positive biopsy results were lacking in other organs, aligning with JCS guidelines. The diagnosis of GCM required histological confirmation of widespread inflammatory infiltrates with multinucleated giant cells and myocyte damage. All myocardial samples underwent reassessment by an experienced cardiac pathologist to mitigate the risk of misdiagnosis due to overlapping histological characteristics of CS and GCM.

Paper III:

Following the PRISMA guidelines, our systematic review employed a comprehensive search strategy utilizing relevant keywords, Medical Subject Headings terms, and commonly used terminology related to *cardiac sarcoidosis*, *giant-cell myocarditis*, and *heart transplantation*. We systematically searched multiple electronic databases (PubMed, Scopus, Science Citation Index, and EMBASE) from their inception dates to December 2019. Additional searches were conducted in Google Scholar, with screening limited to the first 200 results per search. Two authors independently screened titles and/or abstracts for eligibility, with discrepancies resolved through group discussion. Grey literature, conference abstracts, trial registries, and communication with researchers were also utilized to identify relevant information. Additionally, a manual search of reference lists from included studies was conducted to ensure thorough coverage of the literature. All identified articles were assessed against predefined inclusion and exclusion criteria.

Paper IV:

The study included patients evaluated at Sahlgrenska University Hospital between 2005 and 2022. Inclusion criteria were availability of CMR examination at clinical presentation, while exclusion criteria comprised initiation of immunosuppressive treatment before CMR, poor image quality, or an incomplete CMR examination. All patients had their diagnosis of CS or GCM confirmed through histopathological examination of EMB. A skilled cardiac pathologist re-evaluated all samples to minimize the risk of misdiagnosis. A re-analysis of CMR images was blinded with respect to diagnosis and conducted by an experienced expert. Clinical outcomes, including HTx or all-cause death, were used as internal controls to validate diagnoses. Follow-up commenced on the date of initial presentation and concluded on the date the endpoint was reached or on November 30, 2022.

Table 2. Overview of the studies included in this thesis

	Paper I	Paper II	Paper III	Paper IV
Study period	1988-2019	1991-2020	From database inception to December 2019	2005-2022
Subjects (no.)	1001 subjects with advanced HF	CS: 71 GCM: 21	CS: 499 non-CS: 145,891 GCM: 69 non-GCM: 16,297	EMB-proven CS:26 EMB-proven GCM:14
Outcomes studied	Relationship between invasive central hemodynamic variables and renal function	Demographics, clinical presentation, and outcomes in CS vs GCM	Mortality, acute cellular rejection and disease recurrence in CS and GCM post-HTx	CMR features of CS and GCM. Ability of CMR in distinguishing between CS and GCM
Study design	Retrospective, multicenter, nationwide study	Retrospective, single center study	Systematic review and meta-analysis	Retrospective, single center study
Results	Elevated RAP and RPP were strongly associated with renal function	GCM displayed higher NT-proBNP levels, more often biventricular failure and worse outcomes	Post-HTx outcomes in CS and GCM resembled those in HF due to other etiologies	CMR alone was not able to differentiate between CS and GCM
Conclusions	Decreasing CVP and/or raising MAP could be considered a valid approach to ensure adequate RPP	GCM appears to have more severe symptoms and a fulminant course than CS	When needed, HTx is a valid therapeutic option in CS and GCM	CMR features of both CS and GCM are overlapping, making the differentiation based solely on CMR challenging

Abbreviations: CMR, Cardiac Magnetic Resonance; CS, Cardiac Sarcoidosis; CVP, Central Venous Pressure; GCM, Giant Cell Myocarditis; HTx, Heart Transplantation; MAP, Mean Arterial Pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; RPP, Renal Perfusion Pressure.

3.2 Data Collection

Paper I:

The hemodynamic parameters collected during RHC included heart rate, mean right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), pulmonary artery wedge pressure (PAWP), and mean arterial pressure (MAP). Cardiac output (CO) was assessed via thermodilution, while cardiac index (CI) was computed as CO divided by body surface area. Transpulmonary gradient was defined as PAWP minus MPAP, and pulmonary vascular resistance was determined as the transpulmonary gradient divided by CO and expressed in Wood units. Renal perfusion pressure (RPP) was calculated as the difference between MAP and RAP. GFR was measured directly using plasma clearance of ^{51}Cr -ethylenediaminetetraacetic acid or iohexol and expressed as mL/min/1.73m², or estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.

Paper II:

ECG was interpreted at clinical presentation, noting heart rhythm and rate, PQ interval, presence of atrioventricular blocks as well as bundle branch blocks, Q waves, or premature ventricular complexes. Echocardiography, performed at presentation, was re-analyzed offline for left ventricular systolic function and volumes, and left ventricular diastolic function. RV dysfunction was diagnosed based on a multiparametric approach. CMR images were re-analyzed by experienced cardiologists who measured LV volumes, calculated ejection fraction, and assessed LGE.

Paper III:

Literature search and data extraction for the meta-analysis were performed by two authors independently, and a third reviewer checked for accuracy. Primary outcomes focused on 1-, 5-, and 10-year mortality post-HTx, while secondary outcomes included acute cellular rejection and disease recurrence. We extracted the most comprehensive risk ratio (RR) or hazard ratio (HR) with corresponding 95% confidence intervals from each study. Additional numerical data from graphical presentations in published works were obtained from authors, and unpublished data were provided by one of our co-authors. In cases of overlapping data, only publications with the largest patient cohort

were included in the meta-analysis, with all related publications documented. Any discrepancies were resolved through discussion with the contributing statistician.

Paper IV:

The study collected clinical data from medical records, covering symptoms, treatments, complications, laboratory results, and other relevant information. Baseline data were recorded before starting disease-modifying immunosuppressive therapy. CMR image analysis was performed in a blinded manner by an experienced imaging expert.

3.3 Ethical Aspects

Paper I is covered by Ethical and Amendment approvals with Reg Num. 728-12 and 2020-04281. Paper II and IV are covered by Ethical and Amendment approvals with Reg Num. 286-18 and 2023-02475-02. The systematic review presented in Paper III was solely based on previously reported data and did not involve any contact with patients. Hence, ethical vetting was not required for this study.

3.4 Statistical Methods

Paper I:

Descriptive statistics were presented as mean \pm standard deviation for continuous variables and as numbers with percentages for categorical variables. Missing data were handled using both complete case analysis and multiple imputation. Multiple imputation involved generating 100 replicas of the dataset with imputed values using predictive mean matching. Penalized spline regression was used to evaluate the relationship between hemodynamic variables and mGFR. Multivariable analyses were performed adjusting for age, sex, and center. Absolute standardized coefficients were obtained to compare how different hemodynamic variables contributed to mGFR. Additionally, subgroup analyses were conducted based on HF etiology and work-up period. Statistical tests were two-tailed with significance set at $p < 0.05$, without adjustments for multiplicity.

Paper II:

Descriptive statistics were utilized to describe demographic and clinical characteristics, with data presented as median (Interquartile Range) or numbers (percentages). Mann–Whitney U test and Fisher’s exact test were carried out to compare baseline data between CS and GCM patients. Baseline was established at the first manifestation/symptom indicative of CS or GCM diagnosis. The primary outcome was a composite of death or HTx. The Kaplan–Meier estimates were used to generate survival curves and the log-rank test applied for group comparison. Univariate and multivariate Cox regression was used to assess the prognostic impact of CS vs GCM on outcome and also to evaluate the predictive potential of preselected patient characteristics. Multivariate models were adjusted for variables significant at $p \leq 0.005$ in univariate analysis. Six CS and 2 GCM patients were excluded from survival analysis due to insufficient follow-up time; they were diagnosed either at the time of transplantation, implantation of MCS, or autopsy. Poisson regression was used to assess trends over time. Statistical significance was set at $p < 0.05$ for all tests.

Paper III:

The study protocol adhered to the guidelines outlined in the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P). It was registered in PROSPERO (Reg Num: CRD42019140574) and published prior to commencing the systematic review¹⁷⁸. Eligible studies and conference abstracts included those reporting clinical outcomes (such as survival, acute cellular rejection, and disease recurrence) of patients who underwent HTx due to CS or GCM.

Given the prognostic nature of our clinical question, observational research was the primary focus, encompassing cross-sectional, case-control, and cohort studies. In addition, we considered interventional and population-based studies, including randomized controlled trials, community studies, and field research,. We only included data from adult cardiac recipients who were 18 years or older, while excluding sources that did not allow for the calculation of outcome rates being excluded. There were no restrictions in terms of language, date, or publication status.

Risk of bias within the included studies was evaluated by two reviewers using the Newcastle-Ottawa Quality Assessment Scale (NOS), which assesses three domains: selection of study groups, comparability of study groups, and ascertainment of exposure or outcome. Discrepancies between reviewers were

resolved through consensus among a broader group of co-authors. Three studies were not assessed for bias due to their abstract format and unsuccessful attempts to contact the authors.

Random-effects meta-analysis was employed to determine pooled effect estimates for clinically, methodologically, and statistically homogeneous studies. Heterogeneity between studies was assessed using the I^2 statistic, accompanied by a p value to indicate significance. The I^2 statistic estimates the percentage of variability in effect estimates due to heterogeneity rather than chance. Results of the meta-analysis were visually depicted using forest plots. Effect estimates from all studies were presented as RRs, except for those in Madan et al.'s study, which reported HRs. HRs were converted to approximate RRs using formulae proposed by Van der Weele et al ¹⁷⁹.

Paper IV:

Statistical analysis included Mann-Whitney U test for continuous variables, Pearson's chi-square or Fisher's exact tests for categorical variables. Kaplan-Meier estimates and the log rank test were used for event rates. Significance was set at $p < 0.05$.

3.5 Methodological Considerations

In **Paper I**, we aimed to study how various central hemodynamic aberrations impact renal function in advanced HF secondary to various cardiac diseases. This paper offers valuable insights into the relationship between hemodynamics and renal function in this group of patients with severe cardiac failure, leveraging a nationwide sample and direct GFR measurement. Limitations encompass its retrospective design, which prevented the retrieval and control of confounding variables such as comorbidities and medications. While most patients exhibited stable chronic HF, the discrepancy in timing between GFR measurements and RHC may have introduced bias. Additionally, a notable portion of initially eligible patients were excluded due to missing mGFR values. Nonetheless, we believe our study yields robust and valuable insights into the relationship between central hemodynamics and renal insufficiency, supporting the implementation of goal-directed hemodynamic treatment strategies for managing worsening renal function across various HF conditions.

In **Paper II**, we focused on two subgroups of patients with inflammatory myocardial diseases. Both CS and GCM are rare conditions that typically lead to advanced HF. Our study aimed to determine if CS and GCM, despite sharing

clinical similarities, are distinct disease entities with different trajectories and outcomes, and if management for these disorders differs. This paper benefits from a robust dataset and rigorous diagnostics, particularly for GCM, through histological examination by an experienced cardiac pathologist. Thorough follow-up with no missing cases provides a complete picture of patient outcomes. However, a retrospective design and a single-center origin may limit generalizability. Additionally, incomplete data on CMR and ^{18}F -FDG-PET scans may affect the completeness of the findings.

Paper III provided valuable insights into post-HTx outcomes in patients with inflammatory myocardial diseases. Most of the current knowledge on HTx in CS and GCM has arisen from single-center studies, which are susceptible to bias due to small sample sizes as well as potential over- or underestimation of outcome measures. Additionally, the few registry studies examining post-HTx outcomes for patients with these conditions often suffer from incomplete data. The objective of the present study was to address these shortcomings by collecting data from single-center and registry studies for a systematic review and meta-analysis. A potential bias that may reduce the credibility of a meta-analysis involves the inclusion of overlapping studies, leading to double counting of patients. To mitigate this, we selectively included publications with the largest patient cohorts for outcomes of interest. One limitation of the present study is the small sample size for each outcome, which undermined the power of the meta-analysis and hindered the assessment of potential publication bias. Strategies adopted to reduce this risk, included a thorough literature search and contacting authors to relevant papers, which strengthened the comprehensiveness of the study.

Our objective in **Paper IV** was to systematically compare the CMR characteristics in patients with CS and GCM and determine the ability of CMR to distinguish between these rare entities. The differential diagnosis between CS and GCM is still challenging and little is known about the CMR appearance of GCM as well as the ability of the method to distinguish between GCM and CS. Despite its strengths, especially the high level of diagnostic certainty, our retrospective imaging study is also constrained by several limitations. The primary limitation lies in the study design, which involved a relatively small number of included patients. Nevertheless, this number is noteworthy given the rarity of the studied conditions. Secondly, our study is susceptible to selection bias due to the chosen design, as patients undergoing EMB typically present with greater disease severity. The limited availability of T2-weighted sequences in patients with CS is an additional constraint, necessitating careful interpretation of the results. Furthermore, it should be noted that technological advancements during the extended inclusion period may have influenced our

findings through improved image quality among other factors. Lastly, incorporating newer CMR imaging parameters such as T1 and T2 mapping, along with results from ^{18}F -FDG-PET/CT, would have been advantageous, but these data were only partially accessible.

4 RESULTS

4.1 Paper I

Patient characteristics

In this study, 1001 patients with advanced HF were included¹⁷⁷. Dilated cardiomyopathy was the most common diagnosis, followed by ischemic heart disease and other non-ischemic cardiac conditions. The mean age was 48.8 ± 12.9 years, and 24% were women. Nearly all patients exhibited NYHA class III or IV symptoms, with a mean LVEF of $23.2 \pm 11\%$. mGFR was moderately impaired (60.4 ± 18 mL/min/1.73m²), as was estimated GFR. Hemodynamic profiles showed elevated filling pressures, reduced CO, and lower mixed venous oxygen saturation, particularly in patients with mGFR < 60 mL/min/1.73m².

Hemodynamics and renal function

In univariate analyses, mGFR exhibited a negative correlation with RAP and a positive correlation with MAP and CI, while no significant relationship was found with HR or PAWP.

In multivariable analysis, RAP, MAP, and CI remained independently associated with mGFR, with PAWP showing a positive independent association. High RAP and low MAP were associated with worse mGFR, while high renal perfusion pressure (RPP= MAP - RAP) was associated with better mGFR. These relationships were consistent across different HF etiologies and over time.

Figure 12 illustrates absolute standardized coefficients, allowing for a comparison of the influence of various hemodynamic variables on mGFR¹⁷⁷. In **Figure 12A**, it is observed that RAP exhibited the most substantial negative impact on mGFR, followed by MAP and CI, which had a positive impact. In **Figure 12B**, RPP (MAP - RAP) displayed the most significant positive impact on mGFR, followed by CI.

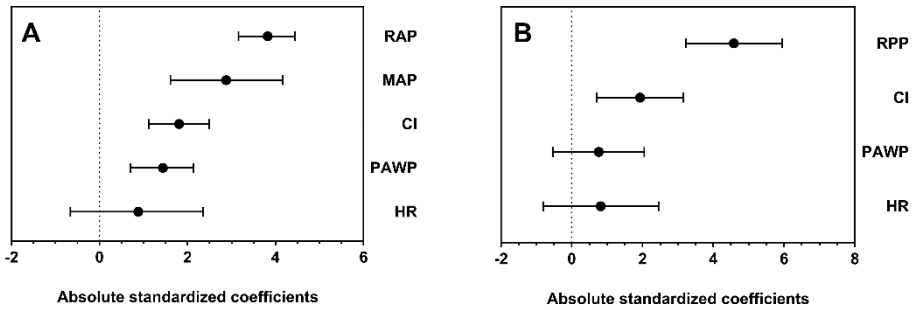


Fig. 12. Analysis of covariance with absolute standardized (dimensionless) coefficients enabling comparison of the impact of different haemodynamic variables on measured glomerular filtration rate. *Reproduced with permission of John Wiley and Sons from ESC Heart Failure, Association between central haemodynamics and renal function in advanced heart failure: a nationwide study from Sweden, Bobbio et al. 2022, Copyright Clearance Center*

CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; RPP, renal perfusion pressure.

Figure 13A demonstrates that the combination of high RAP and low MAP correlated with notably poorer mGFR compared to any other RAP/MAP profile. Similarly, **Figure 13B** indicates that patients with high RPP had higher mGFR compared to those with low RPP, regardless of whether CI was high or low.

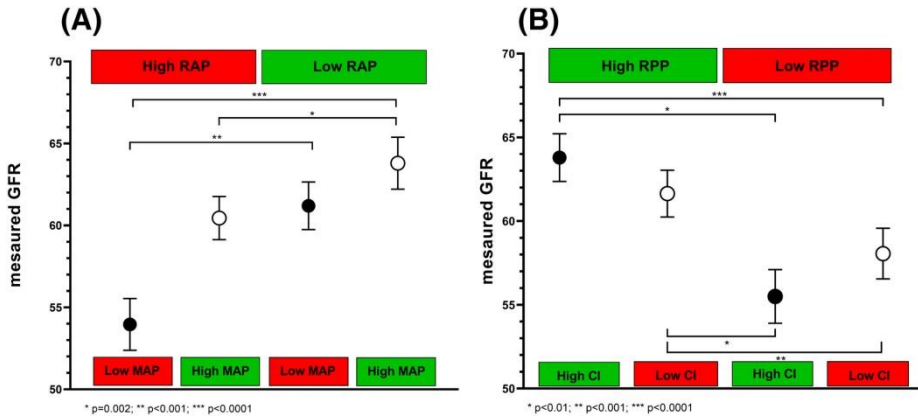


Fig.13. Effects of (A) high or low RAP (\geq or $<$ 10 mmHg) on mGFR in participants with high or low MAP (\geq or $<$ 73.5 mmHg) and (B) high or low RPP (\geq or $<$ 64 mmHg) on mGFR in participants with high or low CI (\geq or $<$ 1.9 L/min/m²). *Reproduced with permission of John Wiley and Sons from ESC Heart Failure, Association between central haemodynamics and renal function in advanced heart failure: a nationwide study from Sweden, Bobbio et al. 2022, Copyright Clearance Center*

CI, cardiac index; MAP, mean arterial pressure; mGFR, measured glomerular filtration rate; RAP, right atrial pressure; RPP, renal perfusion pressure.

4.2 Paper II

Patient characteristics and clinical presentation

This study included 71 patients with CS and 21 patients with GCM¹⁸⁰. CS was confirmed in 46% of patients through myocardial samples, while 32% had extra-cardiac biopsies indicative of sarcoidosis. Most patients with CS had extra-cardiac sarcoidosis, predominantly affecting the lungs. Patients with CS were older and had a higher body mass index compared to GCM patients. Cardiac manifestations at presentation were similar between the two groups, with heart failure being the most common.

All patients, except those diagnosed post-HTx, received immunosuppressive therapy. Steroids were the primary treatment for CS, with additional medications used in some cases. Patients with GCM received steroids in combination with other immunosuppressants.

Imaging findings and diagnosis

Echocardiography and CMR at presentation revealed more severe LV and RV dysfunction in GCM patients compared to CS patients. GCM patients also had a higher prevalence of LV diastolic dysfunction and mild pulmonary hypertension.

Outcomes

During follow-up, 25% of CS patients reached the composite endpoint of HTx or death, with the majority undergoing HTx (n=11). For GCM patients, 71% reached the endpoint, most of them undergoing HTx as well (n=11). Male sex, GCM diagnosis, and certain clinical and imaging features were associated with worse outcomes in univariate and multivariate analyses.

The Kaplan-Meier curves illustrated a rapid divergence in event-free survival between CS and GCM patients who displayed a poorer outcome (**Figure 14**). A few patients (n=13 CS and n=2 GCM) receive an ICD implantation due to sustained VAs, but this was not included in outcome analyses.

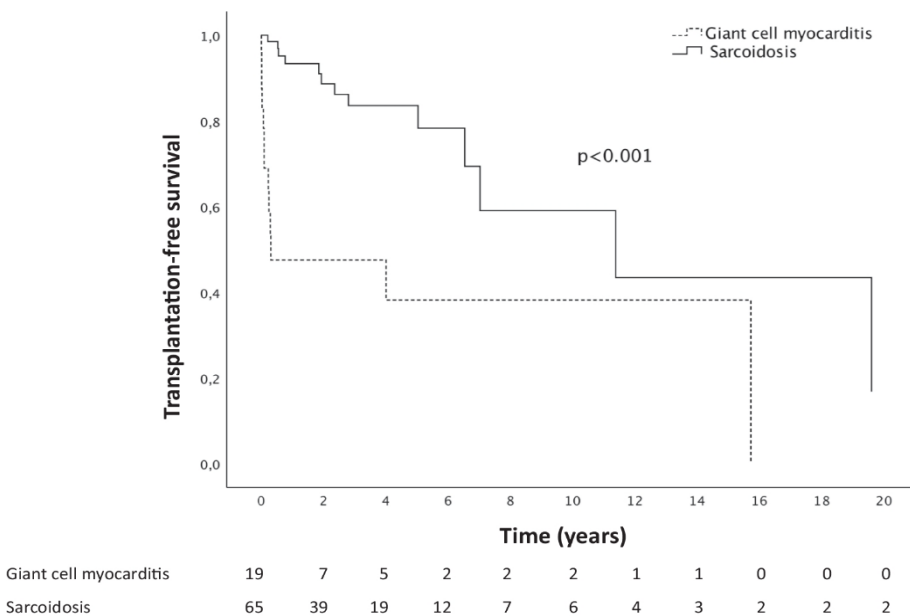


Fig. 14. Kaplan–Meier curves for transplantation-free survival in patients with cardiac sarcoidosis and giant cell myocarditis. *Reproduced with permission of Springer Nature from BMC Cardiovasc Disord, Diagnosis, management, and outcome of cardiac sarcoidosis and giant cell myocarditis: a Swedish single center experience, Bobbio et al. 2022, Creative Commons Attribution 4.0 International License.*

4.3 Paper III

Literature Search and Risk of Bias

Nine articles and five peer-reviewed abstracts were included, comprising data from 499 CS, 69 GCM, 145,891 non-CS, and 16,297 non-GCM patients¹⁸¹. Ten studies were conducted in North America, three in Europe, and one in East Asia. Survival rates and outcomes post-HTx were reported in various publications, along with histopathological findings and immunosuppressive regimens. Based on the NOS, the overall quality of the 11 selected studies was ranked as moderate, (with lower) but with ratings classified as low in the domains of outcome assessment and confounding.

Outcomes: Post-Transplant Survival, Acute Cellular Rejection Rate and Disease Recurrence

Patients with CS exhibited higher 1-, 5-, and 10-year post-HTx survival rates compared to non-CS individuals. At 5-year follow-up, the difference was statistically significant. GCM patients did not show any differences in survival compared to controls at 1- or 5-year follow-up.

In patients with CS, the risk for acute cellular rejection was higher within the first year after HTx and lower after 5 years of follow-up, when compared to controls. GCM patients did not differ from controls in terms of acute rejection rates.

Recurrence rates varied, with some studies reporting CS recurrence in 4%-18% of HTx patients and GCM recurrence in 15% of cases.

Overall, the analysis provides insights into survival rates, rejection risks, and disease recurrence post-HTx in CS and GCM patients, but variations in reported outcomes and study quality warrant careful interpretation of our findings.

4.4 Paper IV

Patient Characteristics

This retrospective imaging study embraced 26 patients with EMB-proven CS and 14 with EMB-proven GCM¹⁸². Baseline demographic and clinical features showed similar ages and a male predominance in patients with GCM and CS. GCM patients exhibited a higher NYHA class upon presentation compared to those with CS. High-grade AVBs and HF were common presentations in CS, while ventricular tachycardia/cardiac arrest and HF were predominant in GCM. Troponin T and N-terminal prohormone of brain natriuretic peptide levels were higher in the GCM population, indicating a more severe clinical course in these patients.

Basic CMR Characteristics

CMR findings demonstrated similar pathological features in left ventricular and right ventricular dimensions and function in both CS and GCM. Thinned LV myocardium and RV wall motion abnormalities were less prevalent in CS. RV segments with an increased T2 signal were less frequently encountered in CS. LV LGE characteristics were similar in both groups, but the number of RV segments with LGE was lower in CS.

Detailed Late Gadolinium Enhancement Characteristics

The distribution patterns of LGE in both ventricles were comparable in CS and GCM, with no significant differences between groups. Patchy and confluent LV and RV LGE patterns were observed in both groups, with no significant variations in terms of involvement of insertion points, papillary muscles, or the "hook sign" (**Figure 15**).

Medical Treatment and Clinical Outcome

All CS and GCM patients received disease-modifying immunosuppressive treatment, with different dosages and combinations based on the nature and severity of their condition. Over a median follow-up of 38 months for CS and 19 months for GCM, a significant difference in event-free survival was observed, with better outcomes in CS patients.

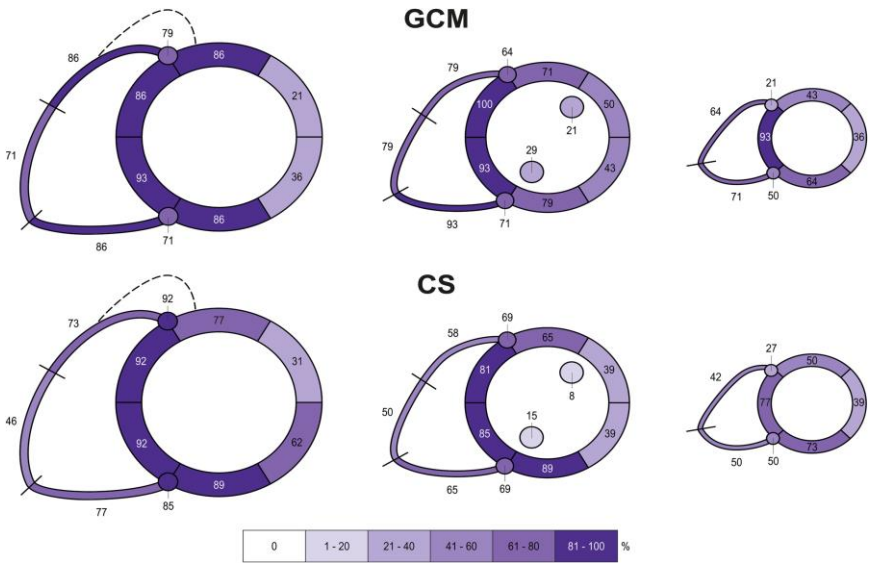


Fig. 15. The distribution of late gadolinium enhancement in giant cell myocarditis (GCM) and cardiac sarcoidosis (CS) is examined. Left ventricular assessment follows a 16-segment model, while right ventricular evaluation follows an 8-segment model (with circles denoting anteroseptal and inferoseptal insertion points of the right ventricle). Prevalence percentages are indicated by numbers and color scale. *Reproduced with permission of Elsevier from Int J Cardiol, Phenotyping of giant cell myocarditis versus cardiac sarcoidosis using cardiovascular magnetic resonance, Bobbio et al. 2023, Creative Commons Attribution 4.0 International License.*

5 DISCUSSION

The aim of this thesis was to improve the clinical understanding of the association between central hemodynamic aberrations and renal function in advanced HF secondary to various cardiac diseases. By focusing on a specific subgroup of HF patients, we sought to determine whether CS and GCM, despite known clinical similarities, are distinct disease entities, with different outcomes and therapeutic approaches, and investigate how imaging can improve diagnostic algorithms.

This thesis has demonstrated that: 1) Among patients with advanced HF, elevated RAP had a greater impact on impaired GFR compared to decreased MAP, while higher RPP showed a stronger correlation with improved GFR than elevated CI; 2) GCM displayed a more aggressive clinical progression than CS, characterized by severe biventricular failure, elevated levels of circulating biomarkers, and a greater need for HTx; 3) Following HTx, HF patients due to CS and GCM experience similar outcomes as those with HF from other etiologies; 4) Distinguishing between CS and GCM solely based in CMR is challenging due to the overlap in their imaging phenotypes.

Hemodynamics and renal function in advanced heart failure

The perception that decreased renal function in HF is primarily attributed to impaired CO and intravascular volume depletion following diuretic treatment persists¹⁸³. However, in Paper I focusing on advanced HF subjects, we found that elevated RAP is strongly associated with impaired GFR. Although the cross-sectional design of our study limits our ability to establish causal relationships, there is a compelling inclination to propose that renal congestion, rather than impaired forward flow or hypovolemia, is the main contributor to renal insufficiency in HF. This proposition is physiologically plausible, as an increase in RAP retrogradely transmitted into the venous system is expected to elevate renal interstitial pressure due to the encapsulated nature of the organ. Consequently, elevated renal interstitial pressure diminishes renal blood flow, leading to a progressive decline in GFR secondary to nephron collapse^{184, 185}. Supporting evidence includes early experimental studies demonstrating that elevated central venous pressure (CVP) induces renal congestion and exacerbates renal dysfunction¹⁸⁴. Clinical studies have also shown a reverse correlation between venous pressure and renal plasma flow in chronic HF patients, indicating an association between increased CVP and renal

dysfunction, especially in right-sided HF secondary to pulmonary hypertension¹⁸⁶. Moreover, a retrospective analysis involving 178 HF patients revealed that the progression of renal dysfunction was more closely linked to venous congestion than impairment of CI¹⁸⁷, which is in line with our findings. Additionally, elevated CVP has been implicated in significantly reducing estimated GFR in acute HF, along with low systolic blood pressure¹⁸⁸.

A MAP below 65 mmHg is typically considered insufficient for organ perfusion including the kidney^{189, 190}. In Paper I we observed that reduced MAP is independently linked to impaired renal function regardless of RAP levels. Still, elevated RAP exerts a more pronounced negative effect on measured GFR compared to decreased MAP. Similar conclusions were reached in experimental models where heightened CVP hampers renal blood flow to a greater extent than equivalent reductions in systemic blood pressure^{184, 185}. Renal blood flow is regulated by multiple factors and can be maintained amid declining forward flow and arterial blood pressure by local autoregulatory mechanisms. Heightened CVP, on the other hand, disrupts renal autoregulation, resulting in impaired kidney perfusion and ultimately in progressive renal damage^{185, 191, 192}. Additionally, neurohormonal activation in HF exacerbates reduced GFR through constriction of pre-glomerular arterioles^{185, 191}.

In Paper I, we also showed that elevated RPP levels correlated with improved renal function, irrespective of CI. In situations of severely reduced MAP, an increase in CVP may interfere with the kidney's local blood flow regulation, rendering it dependent on RPP¹⁹³. Thus, enhancing forward flow doesn't necessarily alleviate renal dysfunction, as increased CO may benefit other organs than the kidneys. Findings from other previous multicenter studies support this notion, showing that improvements in CI did not correlate with better renal outcomes, re-hospitalization prevention, or enhanced survival rates^{194, 195}.

CS and GCM: two sides of the same coin?

Distinguishing between CS and GCM can be challenging due to shared clinical and histopathological characteristics⁶⁷. Both conditions may present with HF, ventricular arrhythmias and conduction abnormalities, with GCM often displaying a more aggressive course¹⁹⁶. Histologically, CS is characterized by fibrosis and non-necrotizing myocardial granulomas, while GCM is identified by multinucleated giant cells and eosinophils as well as necrosis^{65, 196, 197}. The underlying reasons for clinical differences in the clinical courses of CS and

GCM remain unclear, with speculation about diverse environmental exposures or variations in host genetic and immunological factors ¹⁹⁶.

Debates persist regarding whether these two entities are distinct diseases or merely different manifestations of a single underlying disorder ¹⁹⁸. Instances of patients exhibiting features of both conditions have been reported ^{199, 200}, with extra-cardiac sarcoidosis detected in a subset of individuals undergoing cardiac biopsy for suspected GCM ¹⁹⁸. Hence, it was suggested that GCM might represent a specific subtype of sarcoidosis primarily affecting the heart ^{67, 198}. Our results in Paper II suggests that CS and GCM are distinct clinical and pathological entities, each with its own unique disease trajectory often requiring tailored immunosuppressive treatments. In our study cohort, GCM patients exhibited a more aggressive disease course characterized by diastolic dysfunction, severe RV dysfunction, and mild pulmonary hypertension. GCM patients also experienced worse outcomes. A recent study from Finland corroborated these findings, highlighting the greater severity of cardiac injury severity and more fulminant progression in GCM compared with CS ⁶⁷.

Notably, our research population from Papers II and IV exhibited a higher prevalence of men in both GCM and CS cohorts, consistent with previous report from Japan and the United States ⁶⁵. In Paper II, male sex emerged as a robust independent predictor of worse outcomes, despite no significant difference in age or comorbidity between the sexes. This disparity in outcomes may partly stem from differences in testosterone levels. Previous studies suggest that testosterone, acting through the soluble suppressor of tumorigenicity-2 (sST2) pathway, can exacerbate myocarditis, including GCM ²⁰¹. Additionally, elevated sST2 levels correlate with a heightened risk of HF in men with clinically suspected or biopsy-confirmed myocarditis ²⁰².

Role of imaging in the differential diagnosis between CS and GCM

Diagnosing inflammatory myocardial diseases like CS and GCM is still challenging, even with the availability of advanced imaging methods, and the use of EMB, which despite its limitations is considered the gold standard ^{203, 204}. Echocardiography serves as the primary diagnostic tool for suspected CS and GCM, revealing varied findings including changes in wall thickness, regional wall motion abnormalities, and impaired systolic and diastolic function ²⁰⁵⁻²⁰⁸. A recent publication from our research group confirmed the echocardiographic diversity of CS and GCM, and demonstrated how this variability can be used to differentiate between acute (non-fulminant) and fulminant forms of these inflammatory myocardial diseases ²⁰⁹. Still, distinguishing between CS and GCM is demanding due to the overlap between

these conditions and the limitation of echocardiography in tissue characterization²⁰⁹. Nonetheless, echocardiography's effectiveness as an initial diagnostic tool lies in its capacity to exclude diagnoses other than myocarditis and reinforce the initial suspicion of potentially severe inflammatory heart disease. Several studies have highlighted that LV and/or RV dysfunction serve as prominent indicators of severe myocarditis, necessitating prompt application of advanced imaging modalities as well as other complementary diagnostic techniques.

In the diagnostic work-up of patients with clinically suspected inflammatory myocardial diseases, CMR has assumed a pivotal role, owing to its multifaceted tissue characterization capabilities^{121, 203}. Its applications extend to the challenging diagnostic evaluation of CS, often complemented by ¹⁸F-FDG-PET/CT¹¹³. However, relying solely on CMR-features like multifocal LGE and “hook sign” for the diagnosis CS has been questioned by our study. In Paper IV, we found similar CMR features in both CS and GCM, complicating the differentiation between the two and emphasizing the necessity of supplementary imaging modalities.

In Paper IV, disease involvement of the RV was also extensively examined for the first time in this group of patients, revealing that CS patients had a lesser extent of RV engagement. Simultaneous LV and RV dysfunction has been found to be related to poor outcomes in patients with inflammatory myocardial diseases^{210, 211}. Our findings suggest a more severe form of biventricular myocardial inflammation in GCM individuals, which probably contributes to their worse outcome when compared to CS patients.

The clinical significance of the striking CMR similarity between CS and GCM underscores the need for supplementary imaging techniques such as ¹⁸F-FDG-PET/CT and/or EMB. This is particularly relevant in suspected cases of isolated CS, where a diagnostic EMB plays a pivotal role. Cardiac ¹⁸F-FDG PET/CT is a highly sensitive imaging modality for detecting inflammatory myocardial diseases and of value in cases of suspected myocarditis with inconclusive EMB findings. Although the methods ability to distinguish between GCM and CS remains debatable, the detection of extra-cardiac inflammatory activity strongly favors the diagnosis of CS. These insights highlight the intricate nature of inflammatory myocardial diseases and emphasize the importance of continued research to refine diagnostic strategies and optimize patient management protocols.

Outcomes in CS and GCM

In Paper II and IV, GCM patients displayed worse outcomes than CS patients, including a higher likelihood of requiring HTx and an increased mortality risk. This aligns with findings from the Multicenter Idiopathic GCM Registry, where CS patients demonstrated a 5-year transplant-free survival rate of 61%, contrasting the 10% observed among GCM cases, indicative of GCM's more aggressive and fulminant nature⁶⁵. Similarly, the Myocardial Inflammatory Diseases in Finland (MIDFIN) Study by Nordenswan et al. reported a 5-year event-free survival estimate of 77% in CS subjects, contrasting sharply with the considerably lower 27% found in individuals with GCM⁶⁷. These findings underscore the distinct clinical trajectories and prognostic implications of GCM and CS, emphasizing the importance of accurate diagnosis and tailored management to optimize outcomes for patients with these challenging conditions.

Post-heart transplantation outcomes in CS and GCM

The long-term outcome for CS patients treated with HTx remains unclear due to small sample sizes in previous studies. Concerns exist regarding the development of extra-cardiac sarcoidosis and its impact on prognosis, particularly the potential for pulmonary hypertension leading to RV dysfunction and graft failure. Pulmonary hypertension in patients with lung sarcoidosis may stem from various pathways, including granulomatous angiitis and altered vascular mechanics due to CS^{212, 213}.

The meta-analysis outlined in Paper III, found that individuals with CS experienced lower post-HTx mortality than control subjects after 1, 5, and 10 years. While the lower relative mortality risk after 1 year was not significant, the 28% reduction in the risk of death after 5 years was statistically evident. One database-driven study presented as a conference abstract reported significantly higher post-HTx survival among patients with CS compared with controls during a maximum 10-year follow-up²¹⁴. Additionally, patients with CS displayed a lower risk of acute cellular rejection at the 5-year mark compared with controls. Despite these favorable outcomes, it remains crucial to accurately diagnose CS and GCM and carefully select patients for HTx. Pre-transplant assessments should thoroughly determine HF etiology and evaluate systemic involvement in case of inflammatory myocardial diseases^{113, 215}. Many centers implement a more aggressive immunosuppression strategy after HTx in CS patients, including induction therapy and long-term low-dose prednisolone treatment^{144, 216}.

Despite positive outcomes, some centers remain cautious about conducting transplant in CS individuals due to concerns regarding disease recurrence¹⁴⁴. While early post-transplant immunosuppression usually keeps cardiac sarcoidosis dormant, recurrence has been observed after tapering medications to maintenance levels²¹⁷. In this context it has been suggested that treatment of emerging rejections with high doses of corticosteroids may prevent reactivation of CS²¹⁸. In Paper III, post-HTx recurrence of sarcoidosis in the allograft was observed in about 5% of patients, warranting prolonged surveillance and continued use of low-dose prednisolone for prevention.

When conventional HF treatments fail, HTx is the primary therapeutic option for GCM subjects. Nonetheless, concerns persist regarding heightened risks of early rejection and disease recurrence in the allograft, leaving the prognosis uncertain^{76, 219}. The results of Paper III showed that survival rates did not differ between patients with GCM and the control group at 1 and 5 years post-HTx. Furthermore, there were no differences in the frequency of acute cellular rejections between GCM and non-GCM patients, consistent with previous reports²²⁰. Elamm et al. reported comparable post-HTx survival rates between GCM patients and subjects with idiopathic dilated cardiomyopathy²²⁰.

In our study, we found that about 8% of patients in the GCM group experienced disease recurrence. In our study, we found that roughly 8% of individuals in the GCM group experienced disease recurrence in the allograft, highlighting the necessity for optimal immunosuppressive regimens. Although a standard immunosuppressive protocol may suffice to prevent GCM recurrence, the use of antithymocyte globulin in the post-operative phase and cautious corticosteroid tapering have been proposed to mitigate recurrence risk^{221, 222}. Despite these challenges, a beneficial response to immunosuppressive treatment and a favorable survival rate demonstrate that HTx is a safe option for patients with GCM resulting in excellent long-term graft-survival.

6 CONCLUSION

This thesis advances our understanding of the intricate relationships between central hemodynamic aberrations, renal function, and clinical outcomes in advanced HF caused by various cardiac diseases. Moreover, it delves into the nuanced differences and similarities between CS and GCM, shedding light on their clinical manifestations, imaging features and outcomes.

The adverse interplay between the heart and kidney in HF causing deterioration of both organs is known as the cardiorenal syndrome. The condition lacks a clear definition and effective treatment options are scarce. Paper I identified the key hemodynamic abnormalities associated with declining renal function in subjects with HF. Our results showed that elevated RAP correlated more strongly with impaired kidney function than reduced MAP, and a decrease in RPP was more closely linked to renal insufficiency than reduced CO. Consequently, when managing fluid overload in subjects with the cardiorenal syndrome, focusing on lowering CVP and/or maintaining adequate MAP to optimize RPP could prove to be beneficial treatment strategies, provided that intravascular hypovolemia is avoided.

Papers II and IV focused on investigating GCM and CS, two rare inflammatory myocardial diseases associated with advanced HF. Individuals with GCM typically endure a more aggressive disease trajectory compared with those with CS, leading to worse short- and long-term prognoses. Clinical indicators that should raise a suspicion of GCM include markedly elevated levels of circulating natriuretic peptides, severe biventricular failure and pulmonary hypertension. The findings in Paper IV revealed similarities in CMR features between GCM and CS, presenting a challenge in distinguishing between these conditions based solely on CMR assessments. This underscores the necessity for additional diagnostic modalities, such as imaging techniques like ^{18}F -FDG-PET/CT and/or an invasive EMB, to ensure accurate diagnosis, particularly when isolated CS is suspected. Although the role of ^{18}F -FDG-PET/CT in distinguishing between GCM and CS remains debatable, the detection of patterns typical for extra-cardiac sarcoidosis strongly supports a diagnosis of CS.

Paper III showed that subjects with CS who underwent HTx experienced superior short- and long-term survival rates and lower rates of primary graft failure compared to those with non-CS. Individuals with and without GCM have similar survival rates following HTx. Neither people with CS nor those with GCM exhibit heightened susceptibility to acute cellular rejection after HTx compared to other transplant recipients. These findings endorse the

utilization of HTx for individuals with advanced heart failure caused by inflammatory myocardial diseases, provided that emphasis is maintained on accurate diagnosis, careful patient selection, and diligent post-transplant management.

7 FUTURE DIRECTIONS

Over the last decade, there has been a global progress in enhancing the multidisciplinary approach to cardiorenal medicine. This advancement includes establishing mutual terminology and clear disease definitions, deepening our understanding of the bidirectional relationship between heart failure and renal impairment, developing innovative biomarkers for early detection and prognosis, and introducing novel imaging techniques. However, despite these advancements, patients with both heart and kidney disease still face high symptom burden, frequent hospitalizations and excess mortality. There is a pressing need for early identification and prevention of CRS deterioration. Establishing dedicated cardiorenal interdisciplinary teams to identify and manage decompensated CRS, along with cross-training among nephrology and cardiology professionals, is crucial. Guidelines and best practice models from major professional societies, specifically tailored to cardiorenal management are needed, alongside research funding aimed at future therapies.

The prevailing challenges posed by CS and GCM underscore the pressing need for better understanding of these inflammatory disorders and standardized approaches to diagnosis and management. In the case of CS, uncertainties persist regarding its genetic and molecular etiology, along with the potential impact such knowledge would have on diagnosis and treatment. This includes determining the most effective methods for cardiac screening, understanding the prognostic implications of subclinical cardiac involvement, and assessing the safety of watchful waiting strategies. Furthermore, questions remain regarding the optimal approach to definitively diagnose CS, tailoring immunosuppressive treatments, and evaluation of SCD risk to identify suitable candidates for ICD therapy. Similarly, in GCM, significant gaps in knowledge persist regarding predictors of response to immunosuppressive treatment, optimal medication choices and combinations, and the role of ventricular unloading devices such as intra-aortic balloon pumps and axial flow pumps.

Addressing these uncertainties in both conditions requires the adoption of universal diagnostic criteria to facilitate larger prospective clinical trials aimed at tackling these critical issues and ultimately improving patient outcomes.

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