Original Article
Analysis and insights of cardiac amyloidosis: novel perception of rare diseases in cardiology

He Huang[1*], Yanquan Liu[2*], Xiaojun Chen[3], Huidong Guo[4], Yue Yin[5], Mingli Ding[6], Yuan Liu[7*]

[1]Department of Cardiovascular Medicine (Cardiology), The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China; [2]Department of Hematology, The First School of Clinical Medicine, Guangdong Medical University, Dongguan 523808, Guangdong, China; [3]Department of Hematology, The Affiliated Hospital of Putian University, Putian 351100, Fujian, China; [4]Department of Pathology, The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China; [5]Institute of Hematology, Fujian Medical University Union Hospital, Fuzhou 350001, Fujian, China; [6]Department of Nosocomial Infection Management, Ganzhou People's Hospital, Ganzhou 341000, Jiangxi, China; [7]Department of Operating Room, The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi, China. *Equal contributors.

Abstract: Background: Amyloidosis is a rare systemic disease, while cardiac amyloidosis (CA) is nothing more than a chronic disease that causes fatal damage to the structure and function of the heart. The pathogenesis of CA is elusive, the clinical manifestations are diverse and lack of specificity, and the treatment and prognosis of different subtypes vary widely. It is of great practical significance to deepen the understanding of CA. Objective and methods: The clinical data of 39 patients with CA admitted to the First Affiliated Hospital of Gannan Medical University and Fujian Medical University Union Hospital from January 1, 2018 to March 1, 2024 were collected and retrospectively studied, and the clinical features, diagnosis, differentiation, treatment effects and prognosis of CA patients were analyzed. The Kaplan-Meier method was used for survival analysis. Meanwhile, the latest literature from PubMed was retrieved to systematically discuss the research progress in the diagnosis and treatment of CA. This paper is expected to provide novel and valuable references for the clinical and basic research of CA. Results: A total of 39 patients with CA were included in this study, including 23 males (58.97%) and 16 females (41.03%). The average age at diagnosis was 60.51±10.28 years old. In this study, 24 patients (61.54%) had anemia of different degrees, 19 patients (48.72%) were accompanied by abnormal elevation of cardiac troponin T (cTnT), and all patients (100%) had abnormal elevation of N-terminal pro-brain natriuretic peptide (NT-proBNP), and 28 patients (71.79%) had renal impairment. Typical electrocardiogram (ECG) findings in CA patients in this study show low voltage in limb leads, various types of atrioventricular block, various types of tachycardia, atrial fibrillation and poor R-wave progression. The representative results of ultrasonic cardiogram (UCG) showed: 1. Atrium were enlarged, and ventricular wall motion was weakened. 2. Septum and posterior walls of the ventricle were symmetrically thickened, and the myocardium showed speckled strong echo. 3. Mitral regurgitation (moderate to severe) and tricuspid regurgitation. 4. Widening of the pulmonary artery and pulmonary hypertension. Typical results of cardiac magnetic resonance imaging (MRI) of CA patients in this study showed that delayed gadolinium enhancement of the ventricular wall, with ventricular wall thickening to varying degrees and ventricle or atrium enlargement. The pathological manifestations of CA patients in this study were mostly Congo red staining (+) and deposition of eosinophilic amyloid in the affected organs or tissues. All CA patients included in this study received standardized treatment, the median follow-up time was 29.5 (range, 6.5-71) months, and at the latest follow-up, only 12 cases of 39 patients with CA were still alive, and 27 patients died in our study, all of which were due to uncontrollable progression of the disease and failed treatment. Our study showed that there is no statistical significance in the different age groups of the CA patients (*P*>0.05), while it was surprising that male CA patients had significantly worse overall survival (OS) than female patients. Correspondingly, patients who received chemotherapy and were accompanied with renal impairment had a worse prognosis than those who did not receive chemotherapy and had normal renal function (all *P*<0.05). Conclusion: CA is a rare disease caused by systemic amyloidosis, the pivotal points of CA diagnosis and treatment as well as the premise for improving the long-term prognosis of CA patients are clear diagnosis and accurate typing. The treatment of CA also requires targeted individual treatment according to the subtype and etiology of CA patients, so as to maximize the prognosis of CA patients.

Keywords: Cardiac amyloidosis, clinical features, diagnosis and differentiation, treatment, prognosis

Introduction

Amyloidosis is a rare systemic disease. Amyloidosis can be pathologic depositions in various organs or tissues throughout the body, such as skin, gastrointestinal tract, nervous system, and so on. It is called myocardial amyloidosis (CA) when it infiltrates the myocardium and causes damage to cardiac structures and function [1, 2]. CA is a group of pathological protein misfolding and aggregation of specific amyloid fibrin precursors to form insoluble amyloid fibers deposited in the interstitial outside myocardium, resulting in cardiac structure and function abnormalities, clinical manifestations of heart failure and arrhythmia, often accompanied by a variety of systemic amyloidosis extrinsic manifestations [3, 4]. Since CA has been considered a rare disease for many years and is clinically limited by diagnostic techniques and limited knowledge of the disease, no further classification has been performed even when CA is diagnosed. However, the treatment and prognosis of each subtype are quite different. Until now, studies have shown that primary systemic light chain amyloidosis, transthyretin amyloidosis, and secondary amyloidosis are the most common and easily accumulate in the heart [5-7].

Since the pathogenesis of CA is still unclear, the onset is not easy to detect, the early symptoms are not typical, and the clinical manifestations lack specificity, it is often ignored by clinicians, and its diagnosis and treatment are also challenging, resulting in delayed diagnosis and medical treatment of CA patients, and it is easy to be missed and misdiagnosed. Therefore, most patients diagnosed clinically are in the advanced stage of myocardial amyloidosis. At this time, most patients are accompanied by severe heart failure, and the conventional treatment of heart failure drugs have poor effect, which then affects the treatment and prognosis of patients, and the fatality rate is high [8, 9]. In addition, patients with these comorbidities with significant clinical symptoms are often excluded from clinical trials, and this lack of understanding may also lead to poor prognosis and high mortality in CA patients. Up to now, only a few studies have investigated cardiac amyloidosis, and most of them are single-center case reports, and there is a lack of systematic clinical research on CA. Therefore, this study aims to summarize the clinical characteristics, efficacy and prognosis of CA patients, in order to deepen the understanding of cardiologists on this disease, and guide the clinical practice and scientific research of related fields.

Materials and methods

Research subjects

The clinical data of 39 patients with CA admitted to the First Affiliated Hospital of Gannan Medical University and Fujian Medical University Union Hospital from January 1, 2018 to March 1, 2024 were collected and retrospectively studied, and the clinical features, diagnosis and treatment effects and prognosis of CA were analyzed. This study was approved by the medical ethics committee of the First Affiliated Hospital of Gannan Medical University and Fujian Medical University Union Hospital, and all the patients or their families signed informed consent.

Clinical baseline data

Basic clinical data (gender and age), symptoms and signs at admission, past medical history and family medical history (mainly focusing on systemic diseases, autoimmune diseases, multiple myeloma, and so on), routine blood examination indicators (including white blood cell count, platelet count, hemoglobin), biochemical blood examination indicators (including cardiac troponin T (cTnT), N terminal pro B type natriuretic peptide (NT-ProBNP), β_2-microglobulin, creatinine, urea nitrogen, blood calcium, lactate dehydrogenase (LDH), albumin), cardiac instrument examination results (including electrocardiogram, heart color ultrasound, cardiac magnetic resonance imaging), and histopathological analysis of organ involvement in CA patients, treatment modalities (treatment plan and chemotherapy) and clinical data were collected.

Research criteria

Inclusion criteria: (1) Age >18 years old; (2) All enrolled patients were newly diagnosed, and at least one of the pathological tissues of abdominal fat, kidney, endocardial tissue and others showed positive Congo red staining, and apple green birefringence substance was found under the polarizing microscope; (3) All patients

met at least one of the following conditions (typical heart failure manifestations, New York Heart Association (NYHA) cardiac function grade I-IV, NT-proBNP>332 ng/L, cTnT>0.035 ng/mL); (4) Complete disease course data, laboratory examination results and imaging examination data; (5) Being informed of the study and signed the informed consent, as well as ability to track the survival of patients through the inpatient record system or telephone follow-up.

Exclusion criteria: (1) Patients with severe organ dysfunction; (2) Patients with other hematological diseases or other types of malignant tumors; (3) Pregnant or lactating women; (4) Patients who do not want to be included in this study due to privacy or other reasons; (5) Patients with mental illness or unable to cooperate with the whole process of this study; (6) Patients with serious lack of clinical history data; (7) Patients with amyloidosis without cardiac involvement.

Collection and analysis of instrument parameters

Electrocardiogram (ECG): All CA patients included in this study underwent 12-leads ECG examination, and some of them underwent 24-hour holter ECG examination. ECG data such as arrhythmia and its type, poor R-wave increase in thoracic lead, pseudopathological Q-wave, low voltage in limb lead, and prolonged QT interval were collected.

Ultrasonic electrocardiogram (HCG): The structural and functional parameters of the heart as measured by echocardiography of CA patients were collected, including intraventricular septum thickness (IVS), left ventricular posterior wall thickness (LVPW), internal diameter of both atria, left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), left ventricular stroke volume (SV), ratio of mitral valve filling peak in early diastolic period to late diastolic period, and the presence of pericardial effusion and myocardial echocardiography.

Cardiac MRI (CMR): The contrast agent for late enhanced scanning of CMR is Gadopentetic acid (Gd-DTPA). Some patients in this study underwent cardiacmagnetic resonance late gadolinium enhancement (CMR-LGE), and we collected the methods of LGE reinforcement (focal and diffuse), extent of reinforcement (subendocardial, transmural, and so on) and measured parameters, including cardiac index (CI) and left ventricular mass index (LVMI), stroke volume index (SVI), and so on.

Prognosis follow-up

The electronic inpatient record system was used to follow up the indicators of patients' recent return to the hospital for re-examination and hospitalization status, and the follow-up was conducted by telephone contact. The follow-up date was March 1, 2024. The overall survival (OS) was defined as the interval between the date of diagnosis and the onset of death or loss of follow-up (the end point of follow-up). Subsequently, all patients included in this study were divided into age and gender for comparison grouping according to clinical baseline data. Meanwhile, patients were grouped according to whether chemotherapy was used and whether it was accompanied with renal impairment. We aimed to compare the difference in survival and prognosis between the multiple groups.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. Measurement data conforming to a normal distribution were expressed as mean ± standard deviation, and comparison between the two groups was performed by T-test (or corrected T-test); Measurement data that did not conform to a normal distribution were represented by median (quartile), and Mann-Whitney U test was used for two groups of independent samples. Count data were expressed as cases or cases (%) using χ^2 test (Fisher's precision probability test). The survival curve was plotted by Kaplan-Meier method. *P*<0.05 indicated that the difference was statistically significant.

Results

Baseline data and clinical features

A total of 39 patients with CA were included in this study, including 23 males (58.97%) and 16 females (41.03%). The youngest was 43 years old and the oldest was 81 years old. The average age at diagnosis was 60.51±10.28 years old. CA patients included in this study were admitted with non-specific symptoms and signs of cardiovascular circulatory system (heart dis-

Table 1. Baseline characteristics of patients with CA

Characteristics	Results
Gender	
Male	23 (58.97%)
Female	16 (41.03%)
Age (years)	
≤60	17 (43.59%)
>60	22 (56.41%)
Symptoms of cardiovascular or circulatory system*	
Dyspnea	32 (82.05%)
Weakness or fatigue	25 (64.10%)
Edema of lower limbs	24 (61.54%)
Arrhythmia	23 (58.97%)
Pericardial effusion	23 (58.97%)
Palpitation	21 (53.85%)
Hypotension	19 (48.72%)
Thoracodynia	14 (35.90%)
Syncope	3 (7.69%)
Respiratory symptoms*	
Anhelation	21 (53.85%)
Chest distress	20 (51.28%)
Pleural effusion (hydrothorax)	17 (43.60%)
Cough	15 (38.46%)
Hoarse	5 (12.82%)
Symptoms of the digestive system*	
Abdominal distension	18 (46.15%)
Peritoneal effusion	13 (33.33%)
Hepatosplenomegaly	11 (28.21%)
Manifestations of other organ system diseases*	
Skin, orbital purpura	4 (10.26%)
Tongue hypertrophy	3 (7.69%)
No clinical symptoms or signs (only physical examination found abnormalities)	4 (10.26%)
Previous medical history	
Multiple myeloma	19 (48.72%)
History of cardiovascular diseases	18 (46.15%)
Autoimmune (rheumatic immunity) diseases	11 (28.21%)
History of endocrine diseases	9 (23.08%)
Others	4 (10.26%)

Note: * indicates that some patients may have symptoms or signs of multiple organ systems at the same time, that is, a patient may have several clinical symptoms.

ease), respiratory system disease and digestive system, of which 31 patients (79.49%) were accompanied by underlying disease history. The clinical characteristics and baseline data of all patients with CA are shown in **Table 1**.

Blood laboratory examination results

The 39 cases of CA patients included in this study were accompanied by different degrees of hematology and blood biochemical abnormalities. Among them, 24 patients (61.54%) had anemia of different degrees, 19 patients (48.72%) had abnormal cTnT elevation, and all patients (100%) had abnormal NT-proBNP elevation. Thirty-three patients (84.62%) had hypoproteinemia (albumin <35 g/L), and 28 patients (71.79%) had renal impairment. The specific values of laboratory test results of CA patients in this study are shown in **Table 2**.

Table 2. The blood laboratory examination results of patients with CA

Variables	Actual results	Range of normal value
Blood routine examination		
WBC/(×10^9/L)	11.93±7.52	4-10
HGB/(g·L)	84.64±10.23	Male: 130-170; Female: 120-150
PLT/(×10^9/L)	138.54±13.92	100-300
Blood biochemical examination		
Albumin/(g·L)	24.09±7.61	35-55
Globulin/(g·L)	21.22±9.03	20-30
Creatinine/(μmol/L)	257.23 (49.68, 307.54)	60-130
Urea nitrogen/(mmol/L)	14.53 (5.85, 32.21)	3.2-7.1
Blood β$_2$-microglobulin/(mg·L)	13.28 (0.93, 21.36)	<8
Uric acid/(μmol/L)	554.23±37.69	Male: 150-420; Female: 90-357
NT-proBNP/(pg·mL)	7167.67±89.57	<50 years old: <450 pg/mL; 50-70 years old: <900 pg/mL; >70 years old: <1800 pg/mL
cTnT/(μg/L)	2.51 (0.19, 3.94)	<0.1
Serum calcium/(mmol/L)	2.09±0.65	2.25-2.75
LDH/(U/L)	584.62±26.73	109-245

Note: WBC, white blood cell count; NE, neutrophils; HGB, hemoglobin; PLT, platelet; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnT, cardiac troponin T; LDH, Lactate dehydrogenase.

Cardiac disease related instrumental examination

All 39 cases of CA patients included in this study had conducted the routine cardiac instrumental examinations, such as ECG and transthoracic UCG. A typical illustration of ECG findings in CA patients can be seen in **Figure 1A-C**. The typical representative findings of UCG results of CA patients can be seen in **Figure 2**. A total of 14 patients in our study underwent cardiac MRI, and the results of cardiac MRI were shown in **Figure 3A-C**. The specific results of cardiac instrument examination for all CA patients in this study are shown in **Table 3**.

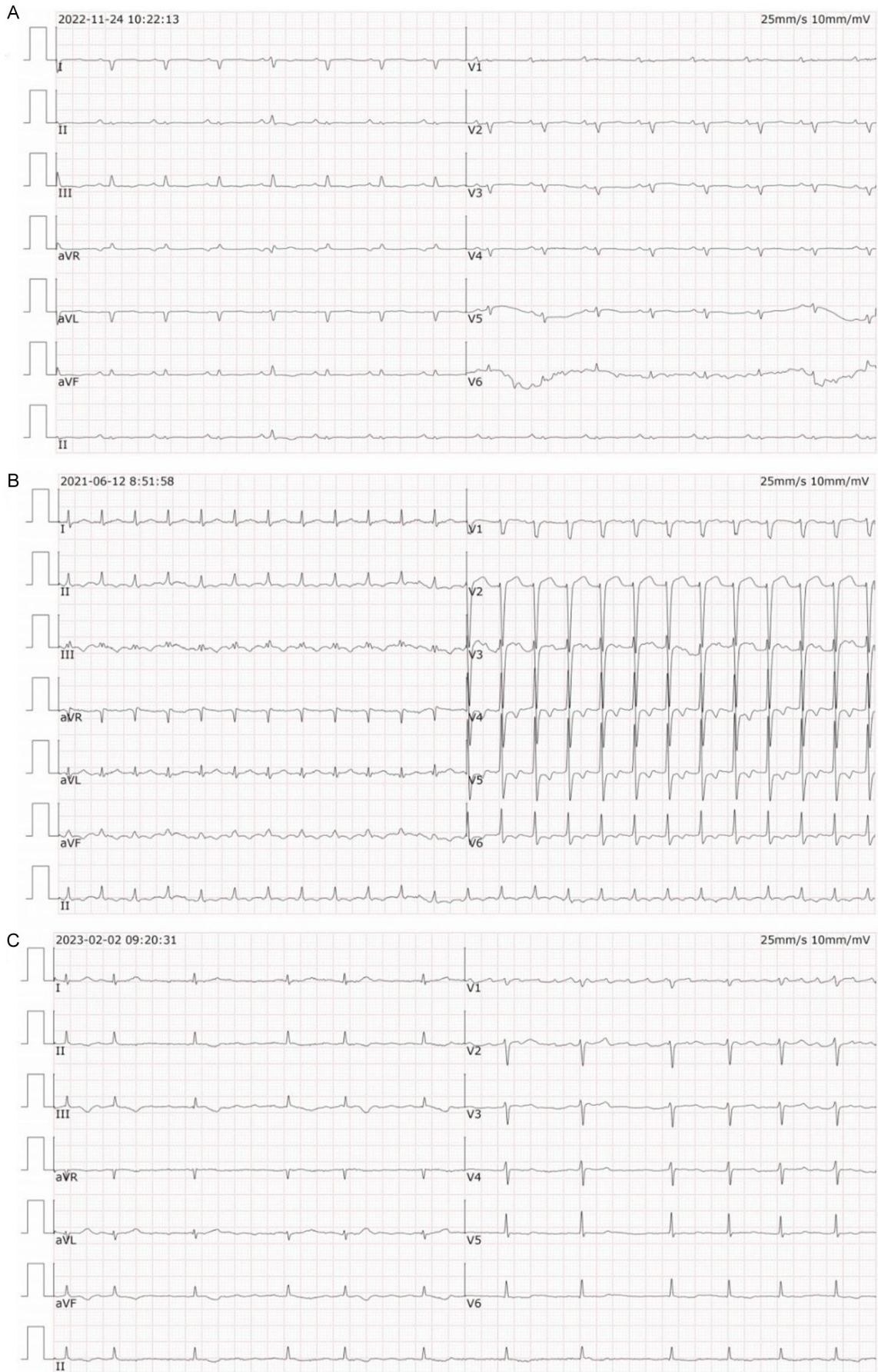*Histological and pathological examination*

Considering that amyloidosis often involves multiple organ systems, the technical requirements of cardiac biopsy are complex, the risk is high, and the CA patients' cooperation is low, the pathological specimens of patients included in this study mainly included bone marrow biopsy, subcutaneous tissue, kidney, and throat tissues. As shown in **Figure 4A-D**, the pathological findings are illustrated as follows: **Figure 4A**: (bone marrow tissue) Focal bone marrow cavity and small blood vessel walls showed homogeneous red staining material (HE staining, ×200). **Figure 4B**: (bone marrow tissue) Congo red staining (+), combined with HE staining (**Figure 4A**), is consistent with amyloidosis. **Figure 4C**: (subcutaneous tissue) Eosinophilic glass-like substance without structure can be seen in the superficial layer of the dermis, which is not distinguishable from the surrounding collagen fibers, and the surrounding inflammatory cells are shown to have circumferential infiltration (HE staining, ×200). **Figure 4D**: (subcutaneous tissue) Congo red staining (+), combined with HE staining (**Figure 4C**), consistent with amyloidosis. **Figure 4E**: (laryngeal tissue) Cloudy, flaky, clumpy powdery material deposition with a small amount of inflammatory cell infiltration (HE staining, ×200). **Figure 4F**: (laryngeal tissue) Congo red staining (+), combined with HE staining (**Figure 4E**), is consistent with amyloidosis. **Figure 4G**, **4H**: (renal needle biopsy tissue) focal deposition of amorphous weak eosinophilic amyloid in renal interstitium (**Figure 4G**: HE staining, ×200; **Figure 4H**: HE staining, ×400).

Treatment regimens

All CA patients included in this study received standardized treatment. Thirty-four patients (87.18%) received furosemide, 29 patients (74.36%) received spirenolactone, 15 patients (38.46%) received β-blockers, and 8 patients (20.51%) received angiotensin-converting en-

Features and prognosis of cardiac amyloidosis

Figure 1. Typical presentation of ECG findings in CA patients. A: 1. Whole lead low voltage; 2. V1-V6 poor R-wave progression. B: 1. Low voltage in limb leads; 2. V1-V3 poor R-wave progression; 3. Supraventricular tachycardia. C: 1. Low voltage in limb leads; 2. V1-V3 poor R-wave progression; 3. Atrial fibrillation.
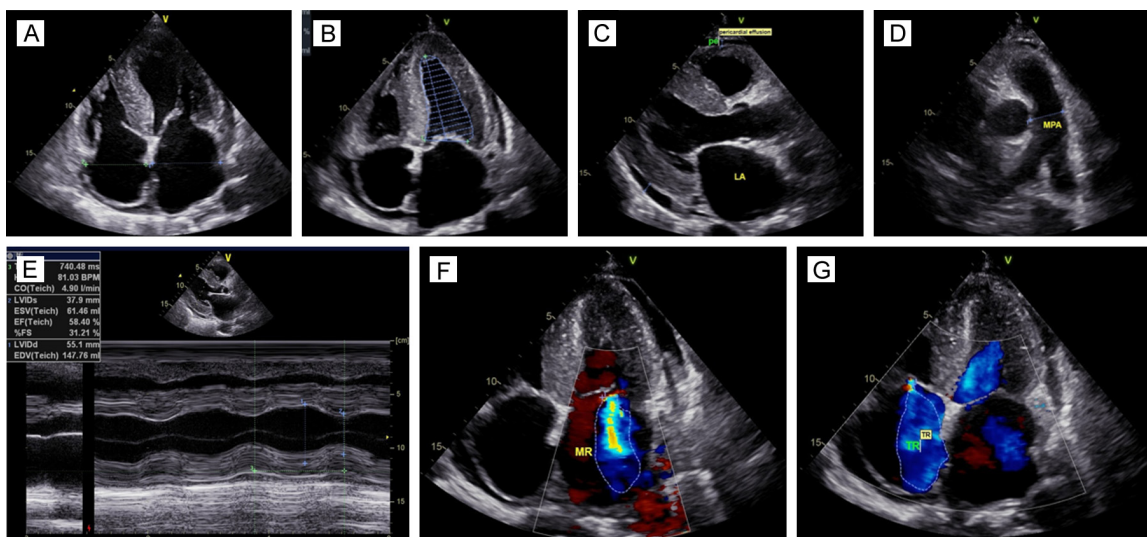

Figure 2. Typical representative legend of ultrasonic cardiogram (UCG) examination results of CA patients. The UCG showed: A: Left atrium and right atrium were enlarged, and left ventricular wall motion was weakened. B, C: Septum and posterior wall of left ventricle were symmetrically thickened, and the myocardium showed speckled strong echo. D: Widening of pulmonary artery and pulmonary hypertension. E: M pattern echocardiographic ventricular wave cluster showed significant thickening of the ventricular septum and the posterior wall of the left ventricle. F, G: Mitral regurgitation (moderate to severe) and tricuspid regurgitation.

zyme inhibitor (ACEI)/angiotensin receptor blocker (ARB). Another 21 cases (53.85%) were treated with chemotherapy targeting the primary disease. Among them, the specific chemotherapy regimen for 21 patients included: 10 patients (47.62%) who received bortezomib based chemotherapy, 7 patients (33.33%) received thalidomide/lenalidomide based chemotherapy, 4 patients (19.05%) received cyclophosphamide based chemotherapy, and 3 patients (14.29%) received other chemotherapy regimens.

Follow-up and prognostic analysis

The median follow-up time was 29.5 (range, 6.5-71) months, and at the latest follow-up, only 12 cases of 39 patients with CA were still alive, and 27 patients died in our study, all of which were due to uncontrollable progression of the disease and failed treatment. All patients included in this study were divided into age and gender comparison groups according to clinical baseline data. Meanwhile, patients were grouped according to whether chemotherapy was used and whether they were accompanied

with renal impairment. Our study showed that there is no statistical significance in the different age groups of the CA patients ($P>0.05$), while it was surprising that male CA patients had significantly worse OS than female patients. Correspondingly, patients who received chemotherapy and were accompanied with renal impairment had a worse prognosis than those who did not receive chemotherapy and had a normal renal function (all $P<0.05$). The survival curve of all CA patients in this study is shown in **Figure 5**.

Discussion

Amyloidosis is a kind of disease caused by insoluble filaments with β-like folding structure deposited outside cells by proteins, causing organ dysfunction [10, 11]. Amyloidosis is a systemic disease in which amyloid substances can be pathologically deposited in tissues throughout the body, such as skin, gastrointestinal tract, nervous system, and so on. It is called myocardial amyloidosis when it infiltrates the myocardium and causes damage to cardiac structure and function [12, 13]. Amyloid
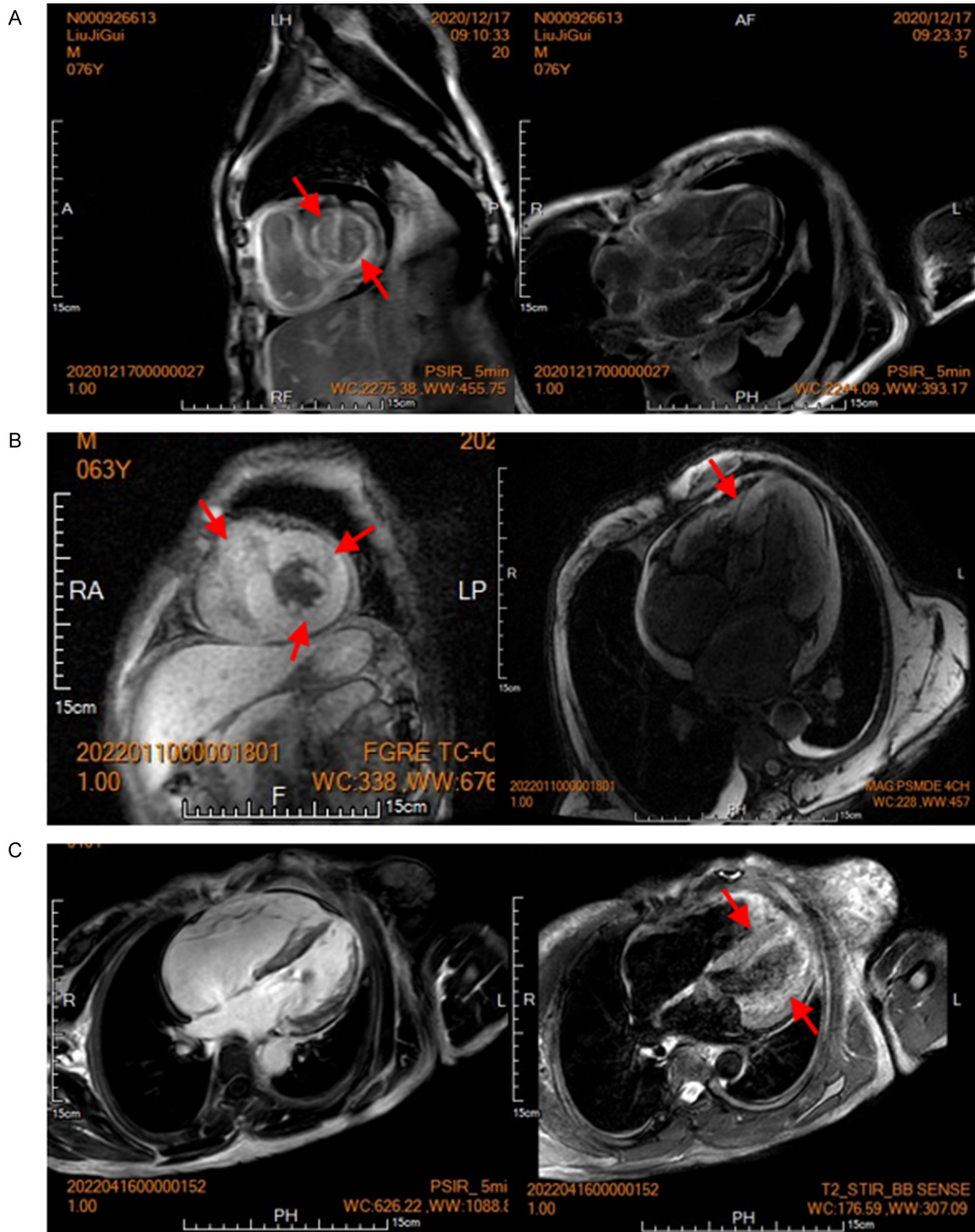
Figure 3. Typical representative legend of cardiac MRI results in CA patients. A: 1. The ventricular septum and the posterior wall of the left ventricle were thickened, and the left and right ventricles and atria were diffused to delay subendocardial enhancement; 2. Enlarged heart, reduced left ventricular systolic and diastolic function, pericardial effusion; 3. Mild regurgitation of mitral and tricuspid valves. B: 1. Left atrium enlargement with atrial muscle thickening, left ventricular wall symmetry thickening; 2. Slight regurgitation of mitral and tricuspid valves. C: 1. The heart is enlarged (especially in the right heart) and the left ventricular systolic and diastolic function is weakened, and the left ventricular wall is delayed and abnormally strengthened; 2. Small amount of pericardial effusion, tricuspid regurgitation. Note: The red arrow represents the site of amyloidosis in cardiac organ.

Table 3. Major results of cardiac instrumental examination in patients with CA

Category of instrumental examination	Results
Electrocardiogram (ECG)*	
Low voltage in limb leads	24 (61.54%)
Various types of atrioventricular block	16 (41.03%)
Atrial fibrillation	13 (33.33%)
Abnormal necrotic Q wave	11 (28.21%)
Various types of tachycardia	8 (20.51%)
V1-V6 poor R-wave progression	4 (10.26%)
Transthoracic ultrasonic cardiogram (UCG)*	
Left ventricular wall thickened	22 (56.41%)
Ventricular septum thickened	13 (33.33%)
Wall of the right ventricle thickened	5 (12.82%)
Diffuse thickening of the left and right ventricles	3 (7.69%)
Atrial enlargement	26 (66.67%)
Mitral regurgitation to varying degrees	17 (43.59%)
Tricuspid valve regurgitation of varying degrees	16 (41.03%)
Pulmonary hypertension	5 (12.82%)
Cardiac MRI	
Delayed gadolinium enhancement of the ventricular wall	11 (78.57%)
Ventricular wall thickens to varying degrees	13 (92.86%)
Ventricle or atrium enlargement	1 (7.14%)

Note: * indicates that the patient has multiple lesions at the same time in results of cardiac instrumental examination, that is, a patient may have several clinico-pathological features.

deposits in the heart eventually lead to cardiac diseases with impaired myocardial diastolic function as the main clinical manifestation. In addition, the clinical understanding and diagnosis of CA are limited, and the early symptoms are not typical, leading to delayed medical treatment. Therefore, most patients diagnosed and treated clinically are in the advanced stage of myocardial amyloidosis. It can eventually develop into angina pectoris, arrhythmia or even congestive heart failure, with a poor prognosis [14, 15].

For many years, CA was considered to be a rare cardiac disease and was clinically limited by diagnostic techniques and limited knowledge of the disease. Even though CA was diagnosed, it was not further classified. However, the treatment and prognosis of each subtype were completely different. At present, 36 precursor proteins have been found to form amyloid deposits, at least 9 of which are related to cardiac amyloidosis, among which primary systemic light chain amyloidosis (AL), transthyretin amy-loidosis (ATTR), secondary amyloidosis and AApoAI amyloidosis are the most common and easily cause cardiac impairment [16, 17].

Amyloidosis causes systemic multi-organ damage, so the symptoms are not typical, which brings great challenges and difficulties to the diagnosis of the disease. Early diagnosis needs to look for the diagnostic clues of CA from the situation of tissue and organ invasion. When CA infiltrates the heart, its early manifestations include heart failure with ejection fraction retention, progressive worsening dyspnea, chest tightness, refractory ascites, pleural effusion, hypotension, and various arrhythmias, which should be timely excluded for diagnosis and disease differentiation [18, 19]. Of course, it should also be noted that when CA is involved with other organs, it can also be manifested as skin ecchymosis and periorbit-al purpura, macroglossia (stiff tongue with teeth marks), hoarseness, right upper abdominal discomfort (hepatosplenomegalysis), proteinuria, and carpal tunnel syndrome, a series of elusive and non-specific clinical symptoms and signs [20-22].

From the perspective of diagnosis and differentiation of CA, histopathological examination, ECG, UCG, CMR, myocardial nuclide imaging and other examination methods could play an essential role in differentiation of CA, which also indicates that the patients included in this study had the above examination methods actively conducted during their hospitalization. It is worth mentioning that endocardial histological biopsy is the gold standard for the diagnosis of CA. Unfortunately, because it is an invasive medical examination means, it is very difficult to implement in clinical practice. If there are typical manifestations of heart involvement, endocardial biopsy can be replaced by abdominal wall fat, small salivary glands and other body tissues. However, the treatment and
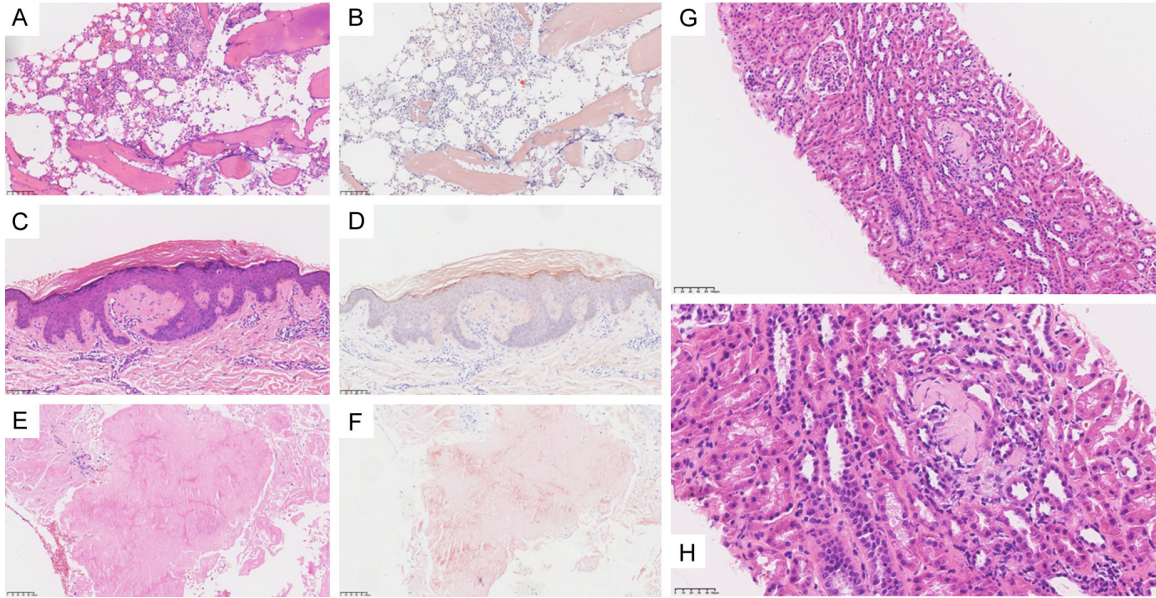
Figure 4. Representative histopathological figures of CA patients. (A, B) Bone marrow tissue. (C, D) Subcutaneous tissue. (E, F) Laryngeal tissue. (G, H) Kidney tissue. Note: (A, C, E) is hematoxylin-eosin (HE) staining, ×20. (B, D, F) is Congo red staining, ×20. (G, H) is HE staining, (G) is ×20, (H) is ×40.
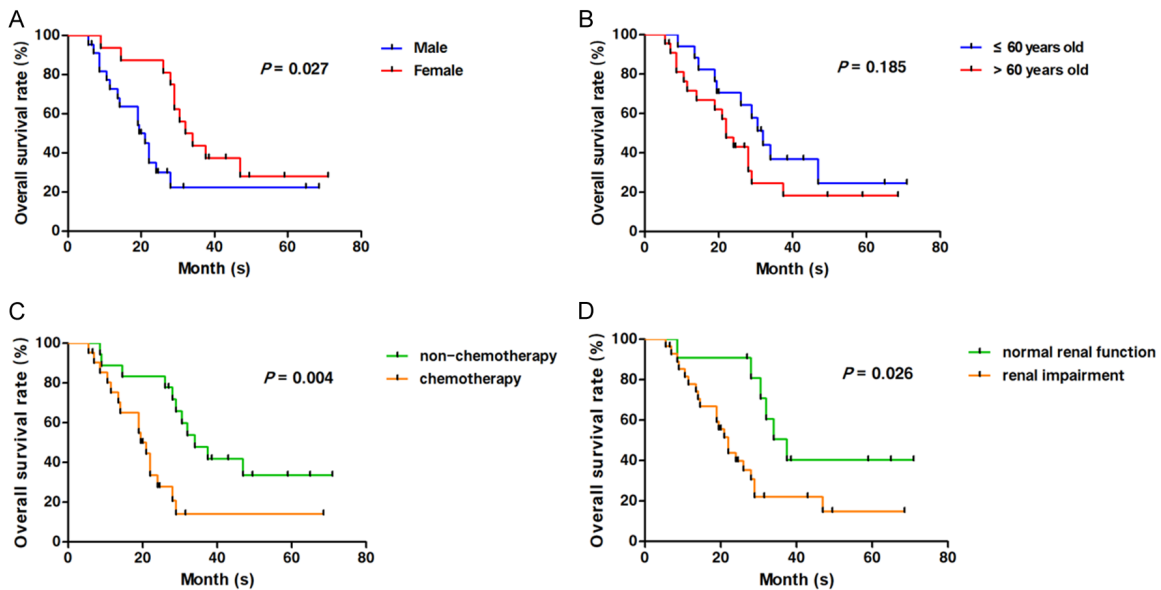

Figure 5. Overall survival (OS) rate of CA patients in this study. A: Patients with CA were divided into gender comparison (male or female) group, and the OS of them was compared. B: Patients with CA were divided into age comparison (≤60 years or >60 years) group, and the OS of them was compared. C: Patients with CA were divided into different treatment options (non-chemotherapy or chemotherapy) group, and the OS was compared. D: Patients with CA were divided into different renal function (normal renal function or renal impairment) groups, and their OS was compared.

prognosis of different types of amyloidosis are completely different, and this method can only diagnose amyloidosis and has limited help for further typing [23]. At the same time, all ECG manifestations in CA patients are not the same, but the most common and most important is QRS low voltage; the more obvious the myocardial infiltration, the lower the voltage, with false

Q waves, atrioventricular block, and bundle branch block are also being more common, where low voltage and ventricular wall hypertrophy contradiction phenomenon are usually an important diagnostic clue of the disease, while ATTR rarely manifests as low voltage [24, 25]. In addition, echocardiography is the most common and simple examination performed in clinical practice, typically showing symmetrical thickening of the left ventricular wall with normal chamber size and scattered flickering granular strong echoes within the myocardium, but most of these manifestations are late manifestations of CA [26, 27]. Late gadoliniumenhancement magnetic resonance imaging (LGE-MRI) is a classic application of CMR in the diagnosis of CA, which is typically characterized by diffuse left ventricular thickening with characteristic subendocardial enhancement, and with the application of phase sensitive inversion recovery sequence (PSIR) technology, the sensitivity and specificity of diagnosis have been significantly improved [28-30]. In addition, measuring cardiomyocyte extracellular volume (ECV) with CMR can further improve the sensitivity of diagnosis. Of course, in recent years, more and more studies have confirmed that Tc-99m-3,3-Diphosphono-1,2-Propanodicarboxylic Acid (Tc-99m DPD) as a tracer of cardiac nuclide imaging can be used for early diagnosis, typing, and identification of other rare and difficult to distinguish types of cardiomyopathy [31-33].

From the perspective of CA treatment, it is mainly the treatment of heart failure, control of arrhythmia and targeted treatment for AL and ATTR. Due to the particularity of CA disease itself and limited technical means, often patients have developed heart failure when they first seek medical treatment, at this time, if the application of conventional heart failure drugs such as beta blockers, ACEI and other drugs often cause patients to have hypotension or even shock, which will aggravate the condition of patients, undoubtedly making the patients' condition and prognosis worse. Therefore, the cornerstone of the treatment of heart failure in CA patients should be the use of salt restriction and diuretics, the careful use of anti-heart failure drugs when tolerable, and the use of vasopressor drugs when necessary [34, 35]. In addition, due to the risk of malnutrition in CA, nutritional support treatment is necessary,

which will help improve the survival rate and quality of life of CA patients [36, 37]. Perhaps it is worth paying attention to that our study found that factors such as the gender, whether accompanied with renal impairment, and whether there is chemotherapy for the primary disease are important aspects that affect the prognosis of CA patients. Hence, it is necessary to attach importance to the personalized treatment of patients, and provide individualized programs for them to fully care for the basic physiological conditions of CA patients in clinical practice.

There is no doubt that the treatment measures and prognosis are quite different for different pathological types of CA, so it is essential to identify the type of CA before starting treatment. For the treatment of AL, targeting plasma cells in the blood system to inhibit their production of monoclonal immunoglobulins and achieve hematological remission is the key. Before treatment, grading should be performed according to the age, blood pressure, cardiac function grade, and the indicators of NT-proBNP, cTnT. High-dose melphalan combined with autologous hematopoietic stem cell transplantation can be applied to mild cases, bortezomib based chemotherapy regimen can be selected for moderately affected patients, including bortezomib + cyclophosphamide + dexamethasone, bortezomib + melphalan + dexamethasone, melphalan + dexamethasone regimen, and the chemotherapy dose can be appropriately increased for severely affected patients [38, 39]. In addition, the immunomodulator thalidomide has also been shown to be effective in patients with AL type of CA [40]. However, when the involvement and organ damage are mild, autologous stem cell transplantation (ASCT) combined with effective chemotherapy can basically achieve the purpose of curing the disease, but unfortunately, once the heart is involved, the indications for ASCT are extremely strict, and there is only a rare chance of transplantation when the heart progresses to CA, so chemotherapy is still the first strategy to be adopted.

Admittedly, for CA patients with ATTR type, current drugs targeting ATTR generally inhibit TTR generation, stabilize TTR tetramer structure and other mechanisms, including Inotersen and Patisiran [41, 42]. *Inotersen* is an anti-

sense oligonucleotide drug, which can bind to the mRNA encoding TTR protein and degrade and inhibit TTR protein generation. While *Patisiran* and *Vutrisiran*, as small interfering RNAs, can silence TTR gene expression and block TTR protein generation, thus producing anti-CA effects, and delay the occurrence of corresponding complications [43, 44]. Nevertheless, immune agents such as prothema (PRX004) can inhibit the promotion of amyloid fibrillary formation and promote clearance through immune-mediated phagocytosis and other related mechanisms, playing a good therapeutic effect [45]. Similarly, epigallocatechin-3-gallate (EGCG), which treats the biological activity of ATTR-type CA by inhibiting the destruction and regulation of oligomers, could also significantly inhibit the formation of TTR amyloid proteins [46]. For CA patients accompanied with heart disfunction and kidney disfunction who are in the stage of failure, multiorgan transplantation can be performed [47]. The orthotopic heart transplantation is definitely an important means in the treatment of CA patients, especially for some patients whose heart function is in the terminal stage and the hematological response reaches CR after chemotherapy, organ transplantation may be the only treatment method, while the reality is that even if they meet the indications for heart transplantation, they are often unable to tolerate surgery because of age, body disease reasons, and so on. Therefore, the novel treatment methods of CA still need to be explored and optimized.

In summary, amyloidosis can occur in any organ of the body through the deposition of amyloid fibrils, and when these accumulate in the heart, it causes cardiac amyloidosis, and it is undoubtedly a life-threatening progressive malignant disease. CA is an increasingly recognized cause of heart failure with poor prognosis. However, the pathophysiology of CA is multifactorial, including increased oxidative stress, mitochondrial damage, apoptosis, impaired metabolism, and altered intracellular calcium balance [48]. Although CA is regarded as a rare disease, with the innovation and development of diagnosis and treatment technology, current studies have found that CA may be hereditary or a result of the aging process, but regardless of the type of CA, patients will experience a heavy burden of clinical symptoms and economic pressure [49]. To date, gratifying progress has

been made in the clinical management of conservative drug therapy for CA. Surgical treatment, such as mechanical circulatory support and heart transplantation, should be considered for suitable patients. The use of AI-driven algorithms for early diagnosis and treatment and the development of newer genetic engineering technologies will drive improvements in diagnosis, treatment and prognosis for CA patients in the future [50].

Conclusion

To sum up, CA is a disease caused by systemic amyloidosis involving the heart. Therefore, the key and difficult points of CA diagnosis and treatment as well as the premise and basis for improving the long-term prognosis of CA patients are clear diagnosis and accurate typing. With the improvement of various medical examination techniques, new non-invasive methods are expected to replace traumatic myocardial biopsy for definitive diagnosis. In daily clinical practice, electrocardiogram, echocardiography, and cardiac MRI are effective means for the diagnosis of CA, but myocardial biopsy is still the "gold standard" for the diagnosis of CA, and blood biochemical items such as NT-proBNP, cTnT or renal globulin filtration rate can also stratify the risk of CA patients, this will provide strong help for subsequent treatment. There is no doubt that in addition to treating heart failure and arrhythmia, the treatment of CA also requires targeted individual treatment according to the subtype and etiology of CA patients, so as to maximize the prognosis of CA patients.

Acknowledgements

Written informed consent was obtained from the patient or the patient's family.

References

[1] Porcari A, Fontana M and Gillmore JD. Transthyretin cardiac amyloidosis. Cardiovasc Res 2023; 118: 3517-3535.

[2] Rubin J and Maurer MS. Cardiac amyloidosis: overlooked, underappreciated, and treatable. Annu Rev Med 2020; 71: 203-219.

[3] Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, Roger VL, Gertz MA, Dispenzieri A, Zeldenrust SR and Redfield MM. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Heart Fail 2014; 2: 113-122.

[4] Bloom MW and Gorevic PD. Cardiac amyloidosis. Ann Intern Med 2023; 176: 33-48.

[5] de Marneffe N, Dulgheru R, Ancion A, Moonen M and Lancellotti P. Cardiac amyloidosis: a review of the literature. Acta Cardiol 2022; 77: 683-692.

[6] Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, Pantazis A, Pankuweit S, Rigopoulos AG and Linhart A. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur J Heart Fail 2021; 23: 512-526.

[7] Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J and Ruberg FL; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation 2020; 142: e7-e22.

[8] Gertz MA. Immunoglobulin light chain amyloidosis: 2022 update on diagnosis, prognosis, and treatment. Am J Hematol 2022; 97: 818-829.

[9] Martinez-Naharro A, Hawkins PN and Fontana M. Cardiac amyloidosis. Clin Med (Lond) 2018; 18 Suppl 2: s30-s35.

[10] Vaxman I and Gertz M. When to suspect a diagnosis of amyloidosis. Acta Haematol 2020; 143: 304-311.

[11] Saito Y, Nakamura K and Ito H. Molecular mechanisms of cardiac amyloidosis. Int J Mol Sci 2021; 23: 25.

[12] Tuzovic M, Yang EH, Baas AS, Depasquale EC, Deng MC, Cruz D and Vorobiof G. Cardiac amyloidosis: diagnosis and treatment strategies. Curr Oncol Rep 2017; 19: 46.

[13] McVeigh T and Tennyson C. Understanding and recognizing cardiac amyloidosis. JAAPA 2020; 33: 16-20.

[14] Griffin JM and Maurer MS. Transthyretin cardiac amyloidosis: a treatable form of heart failure with a preserved ejection fraction. Trends Cardiovasc Med 2021; 31: 59-66.

[15] Michels da Silva D, Langer H and Graf T. Inflammatory and molecular pathways in heart failure-ischemia, HFpEF and transthyretin cardiac amyloidosis. Int J Mol Sci 2019; 20: 2322.

[16] Hagen CE, Dasari S, Theis JD, Rech KL, Dao LN, Howard MT, Dispenzieri A, Chiu A, Dalland JC, Kurtin PJ, Gertz MA, Kourelis TV, Muchtar E, Vrana JA and McPhail ED. Gastrointestinal amyloidosis: an often unexpected finding with systemic implications. Hum Pathol 2023; 139: 27-36.

[17] Muchtar E, Dispenzieri A, Magen H, Grogan M, Mauermann M, McPhail ED, Kurtin PJ, Leung N, Buadi FK, Dingli D, Kumar SK and Gertz MA. Systemic amyloidosis from A (AA) to T (ATTR): a review. J Intern Med 2021; 289: 268-292.

[18] Kaiser ME and Lewis TJ. Heart of the matter: decoding the underdiagnosed cardiac amyloidosis. Cureus 2023; 15: e50527.

[19] Decotto S, Corna G, Villanueva E, Arenaza DP, Seropian I, Falconi M, Oberti P, Aguirre MA, Posadas-Martínez ML, Carretero M, Agatiello CR and Pizarro R. Prevalence of moderate-severe aortic stenosis in patients with cardiac amyloidosis in a referral center. Arch Cardiol Mex 2024; 94: 71-78.

[20] Lacouture Fierro JA, Ribero Vargas DA, Sánchez Cano J, Gaviria Jaramillo LM, Perilla Suarez OG, Galvez Cárdenas KM and Ospina Ospina S. Clinical characterization and outcomes of a cohort of colombian patients with AL Amyloidosis. Colomb Med (Cali) 2023; 54: e2025667.

[21] De Carli G, Mandoli GE, Salvatici C, Biagioni G, Marallo C, Turchini F, Ghionzoli N, Melani A, Pastore MC, Gozzetti A, D'Ascenzi F, Cavigli L, Giacomin E, Cameli M and Focardi M. Speckle tracking echocardiography in plasma cell disorders: the role of advanced imaging in the

early diagnosis of AL systemic cardiac amyloidosis. Int J Cardiol 2024; 398: 131599.

[22] Schmidt EK, Mustonen T, Kiuru-Enari S, Kivelä TT and Atula S. Finnish gelsolin amyloidosis causes significant disease burden but does not affect survival: FIN-GAR phase II study. Orphanet J Rare Dis 2020; 15: 19.

[23] Gertz MA. Cardiac amyloidosis. Heart Fail Clin 2022; 18: 479-488.

[24] Konishi T and Hamabe A. Serial electrocardiographic and echocardiographic assessments of cardiac amyloidosis presenting with myocardial ischemia. Cardiol J 2023; 30: 1059-1060.

[25] Duca F, Rettl R, Kronberger C, Poledniczek M, Binder C, Dalos D, Koschutnik M, Donà C, Beitzke D, Loewe C, Nitsche C, Hengstenberg C, Badr-Eslam R, Kastner J, Bergler-Klein J and Kammerlander AA. Amyloid burden correlates with electrocardiographic findings in patients with cardiac amyloidosis-insights from histology and cardiac magnetic resonance imaging. J Clin Med 2024; 13: 368.

[26] Vereckei A, Katona G, Szénási G, Vidács LD, Földeák D, Takács H, Nagy V and Sepp R. Novel electrocardiographic criteria may render possible the more accurate recognition of cardiac amyloidosis. ESC Heart Fail 2024; 11: 1030-1038.

[27] Cotella J, Randazzo M, Maurer MS, Helmke S, Scherrer-Crosbie M, Soltani M, Goyal A, Zareba K, Cheng R, Kirkpatrick JN, Yogeswaran V, Kitano T, Takeuchi M, Fernandes F, Hotta VT, Campos Vieira ML, Elissamburu P, Ronderos R, Prado A, Koutroumpakis E, Deswal A, Pursnani A, Sarswat N, Addetia K, Mor-Avi V, Asch FM, Slivnick JA and Lang RM. Limitations of apical sparing pattern in cardiac amyloidosis: a multicentre echocardiographic study. Eur Heart J Cardiovasc Imaging 2024; 25: 754-761.

[28] Zheng Y, Liu X, Yang K, Chen X, Wang J, Zhao K, Dong W, Yin G, Yu S, Yang S, Lu M, Su G and Zhao S. Cardiac MRI feature-tracking-derived torsion mechanics in systolic and diastolic dysfunction in systemic light-chain cardiac amyloidosis. Clin Radiol 2024; 79: e692-e701.

[29] Hou W, Wang Z, Huang J, Fan F, Yang F, Qiu L, Zhao K, Qiu J, Yang Y, Ma W, Gong Y and Hong T. Early diagnostic and prognostic value of myocardial strain derived from cardiovascular magnetic resonance in patients with cardiac amyloidosis. Cardiovasc Diagn Ther 2023; 13: 979-993.

[30] Boretto P, Patel NH, Patel K, Rana M, Saglietto A, Soni M, Ahmad M, Sin Ying Ho J, De Filippo O, Providencia RA, Hyett Bray JJ and D'Ascenzo F. Prognosis prediction in cardiac amyloidosis by cardiac magnetic resonance imaging: a systematic review with meta-analysis. Eur Heart J Open 2023; 3: oead092.

[31] Rischpler C, Kersting D, Kessler L, Varasteh Z, Luedike P, Carpinteiro A, Rassaf T, Herrmann K and Papathanasiou M. Reply: recent evidence on cardiac (99m)Tc-DPD uptake after therapy with tafamidis may reveal the road to an ultra-early diagnosis in patients with ATTR amyloidosis. J Nucl Med 2024; 65: 330.

[32] Caobelli F. Recent evidence on cardiac (99m)Tc-DPD uptake after therapy with tafamidis may reveal the road to an ultra-early diagnosis in patients with ATTR amyloidosis. J Nucl Med 2024; 65: 329.

[33] Nunes ARP and Alves VM. Mitral annular calcification as a potential false-positive for cardiac amyloidosis in 99m Tc-DPD scintigraphy accurately identified by SPECT/CT. Clin Nucl Med 2024; 49: e179-e181.

[34] Maraj D, Ramanan S, Patel PM, Memon M and Hawes E. Persistent heart failure despite medical therapy leading to a diagnosis of cardiac amyloidosis. Cureus 2023; 15: e43547.

[35] Medarametla GD, Kahlon RS, Mahitha L, Shariff S, Vakkalagadda NP, Chopra H, Kamal MA, Patel N, Sethi Y and Kaka N. Cardiac amyloidosis: evolving pathogenesis, multimodal diagnostics, and principles of treatment. EXCLI J 2023; 22: 781-808.

[36] Driggin E, Helmke S, De Los Santos J, Teruya S, Guadalupe S, Goldsmith J and Maurer MS. Markers of nutritional status and inflammation in transthyretin cardiac amyloidosis: association with outcomes and the clinical phenotype. Amyloid 2020; 27: 73-80.

[37] Russo M, Vita GL, Stancanelli C, Mazzeo A, Vita G and Messina S. Parenteral nutrition improves nutritional status, autonomic symptoms and quality of life in transthyretin amyloid polyneuropathy. Neuromuscul Disord 2016; 26: 374-377.

[38] Carretero M, Villanueva E, Brulc EB, Faelo FM, Aguirre MA, Pérez-de-Arenaza D, Belziti CA, Arbelbide JA, Nucifora EM and Posadas-Martinez ML. Cardiac and autologous stem cell transplantation hematopoietic in patients with AL amyloidosis. Arch Cardiol Mex 2023; 93: 435-441.

[39] Brennan X, Withers B, Jabbour A, Milliken S, Kotlyar E, Fay K, Ma D, Muthiah K, Hamad N, Dodds A, Bart N, Keogh A, Hayward C, Macdonald P and Moore J. Efficacy of bortezomib, cyclophosphamide and dexamethasone in cardiac AL amyloidosis. Intern Med J 2022; 52: 1826-1830.

[40] Ravichandran S, Hall A, Jenner M, Garg M, Kishore B, Lachmann H, Gillmore J, Pitchford A, Oughton JB, Mahmood S, Sachchithantham S, Hawkins P, Brown S and Wechalekar A. A phase 1b dose-escalation study of carfilzomib in combination with thalidomide and dexa-

methasone in patients with relapsed/refractory systemic immunoglobulin light chain amyloidosis. Amyloid 2023; 30: 290-296.

[41] Robinson C, Pham C, Zamarripa AM, Dugay CS, Lee CA, Berger AA, Landman A, Cornett EM, Kassem H, Kaye AD, Urits I, Viswanath O and Ganti L. Inotersen to treat polyneuropathy associated with hereditary transthyretin (hATTR) amyloidosis. Health Psychol Res 2023; 10: 67910.

[42] Campbell CM, Baiyee CAMT, Almaani S, Bumma N, Sharma N, LoRusso S, Redder E, Bittengle J, Pfund K, Friemer M, Tong M, Kahwash R, Efebera Y, Parikh S and Vallakati A. Targeted therapeutics for transthyretin amyloid cardiomyopathy. Am J Ther 2023; 30: e447-e453.

[43] Argon A, Nart D and Yilmazbarbet F. Cardiac amyloidosis: clinical features, pathogenesis, diagnosis, and treatment. Turk Patoloji Derg 2024; 40: 1-9.

[44] Chen H, Chandrashekar P, Fischer K, Carlson D, Narayan U, Chen J and Masri A. Navigating the complex web of prescribing amyloidosis therapeutics: a primer. J Am Heart Assoc 2022; 11: e023895.

[45] Zhang W, Ding J, Wang W, Wang D, Pan Y and Xu D. Status and future directions of therapeutics and prognosis of cardiac amyloidosis. Ther Clin Risk Manag 2023; 19: 581-597.

[46] Alexander KM, Singh A and Falk RH. Novel pharmacotherapies for cardiac amyloidosis. Pharmacol Ther 2017; 180: 129-138.

[47] Brubaker AL, Urey MA, Taj R, Parekh JR, Berumen J, Kearns M, Shah M, Khan A, Kono Y, Ajmera V, Barman P, Tran H, Adler ED, Silva Enciso J, Asimakopoulos F, Costello C, Bower R, Sanchez R, Pretorius V and Schnickel GT. Heart-liver-kidney transplantation for AL amyloidosis using normothermic recovery and storage from a donor following circulatory death: short-term outcome in a first-in-world experience. Am J Transplant 2023; 23: 291-293.

[48] Morfino P, Aimo A, Franzini M, Vergaro G, Castiglione V, Panichella G, Limongelli G and Emdin M. Pathophysiology of cardiac amyloidosis. Heart Fail Clin 2024; 20: 261-270.

[49] Tavares S and Dirksen A. Cardiac amyloidosis at a glance. Br J Nurs 2024; 33: 424-429.

[50] Brownell D, Pillai AJ and Nair N. Cardiac amyloidosis: a contemporary review of medical and surgical therapy. Curr Cardiol Rev 2024; 20: 72-81.