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DISSERTATION

Multiscale phenoTYPing in Heart Failure
Multiskalen PhenoTYPing bei Herzinsuffizienz
(TYPE-HF)

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Xiaodan Gong

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Abbreviations

CHF	Chronic heart failure
EF	Ejection fraction
6MWT	6-minute walking test
ECG	Electrocardiogram
BP	Blood pressure
NYHA	New York Heart Association
ICM	Ischemic cardiomyopathy
DCM	Dilated cardiomyopathy
HF	Heart failure
ROC	Receiver operating characteristic
AUC	Area under ROC Curve
CI	Confidence interval
BSA	Body surface area
BMI	Body mass index
HR	Heart rate
PND	Paroxysmal nocturnal dyspnea
COPD	Chronic obstructive pulmonary disease
PPH	Primary pulmonary hypertension
ACE	Angiotensin converting enzyme
AT1	Angiotensin II receptor type 1
DPP	Dipeptidyl peptidase
GLP	Glucagon like peptide
RAAS	Rennin angiotensin aldosterone system
6MWD	6-minute walk distance
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
VO2	Oxygen consumption
CRF	Case report form
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
RDW-CV	Red cell distribution width - coefficient of variation
NLR	Neutrophil-to-lymphocyte ratio
RLC	Relative lymphocyte counts
eGFR	Estimated glomerular filtration rate
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
NT-proBNP	N-terminal pro-B-type natriuretic peptide
MR-proANP	Mid-regional pro-atrial natriuretic peptide

LDH	Lactate dehydrogenase
HbA1c	Glycated hemoglobin
INR	International normalized ratio
FT3	Free triiodothyronine
FT4	Free thyroxine
TSH	Thyroid stimulating hormone
MCHC	Mean corpuscular hemoglobin concentration
MPV	Mean platelet volume
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CK-MB	Creatine kinase-myoglobin binding
LDH	Lactate dehydrogenase
CRP	C-reactive protein
QTc interval	Corrected QT interval
LBBB	Left bundle branch block
RBBB	Right bundle branch block

Zusammenfassung

Einführung

Chronices Herzversagen (CHF) ist keine eigenständige Krankheit, sondern eine Reihe klinischer Syndrome, die auf strukturellen und funktionellen Abnormalitäten des Herzens beruhen und das Endstadium verschiedener Herz-Kreislauf-Erkrankungen darstellen [1]. Die Behandlung von Patienten mit CHF bleibt eine der grundlegendsten und herausforderndsten Aufgaben auf dem Gebiet der kardiovaskulären Erkrankungen. Aufgrund der zunehmenden Alterung der Weltbevölkerung, Fortschritten bei der Behandlung von Herz-Kreislauf-Erkrankungen und wirksamer sekundärer Prävention hat sich CHF zunehmend verbreitet. Daher ist es von entscheidender Bedeutung, CHF genau zu bewerten und effektiv zu behandeln, um Remission zu erreichen. Eine Vielzahl von Untersuchungsmethoden wurde vorgeschlagen und in der klinischen Praxis zur Bewertung von Patienten mit CHF angewendet. Einige Ansätze sind jedoch schwierig und riskant für Patienten mit CHF oder erfordern spezialisierte Techniker, was ihre klinische Anwendung in gewissem Maße einschränkt [2, 3]. Daher ist es immer nützlich und notwendig, umfassende Ansätze zur Bewertung von CHF zu suchen und das Risiko zu stratifizieren, insbesondere nichtinvasive, sichere, kostengünstige und wiederholbare Methoden. Baseline-Charakteristika und Medikamente, der 6-Minuten-Gehtest (6MWT), Laboruntersuchungen und Elektrokardiogramm (EKG) gehören zu den am häufigsten verwendeten Methoden zur klinischen Bewertung und Überwachung von Patienten mit CHF. Sie werden jedoch oft in der Routine klinischer Arbeit unterbewertet und untergenutzt und verdienen weitere Untersuchungen [3, 4].

Ziel

Das Ziel meiner Dissertation war es, zuvor übersehene Trends in diesen vier Bereichen bei gesunden Kontrollpersonen und Patienten mit CHF zu identifizieren. Das zugrunde liegende Ziel besteht darin, diese nichtinvasiven, sicheren, kostengünstigen und wiederholbaren Tests in der Routine klinischer Arbeit besser und umfassender zu nutzen. Um diese Aspekte besser und umfassender nutzen zu können, wurden sie ausgewählt, um sie weiter zu untersuchen und wertvolle Bereiche zu identifizieren, die zuvor übersehen wurden.

Methoden und Ergebnisse

In unserer Studie wurden insgesamt 108 Teilnehmer eingeschlossen (gesunde Kontrollpersonen: n=15, Patienten mit CHF: n=93). Das Durchschnittsalter betrug 59,24 ± 11,78 Jahre und 77,8% der Teilnehmer waren männlich. Patienten mit CHF wurden basierend auf der NYHA-Klassifikation in zwei verschiedene Kategorien eingeteilt, einschließlich NYHA I bis III (NYHA I: n=16, NYHA II: n=43, NYHA III: n=34) und den

beiden Myokardiopathien, einschließlich ICM und DCM (ICM: n=37, DCM: n=56).
In Bezug auf den ersten Teil, die Baseline-Charakteristika und Medikamente, wurden signifikante Unterschiede zwischen den Kontrollgruppen und den CHF-Gruppen festgestellt. Das Alter der Kontrollgruppe war signifikant jünger als das der NYHA I bis III-Gruppen (p=0,030, p<0,001, P<0,001) und das der ICM- und DCM-Gruppen (p<0,001 bzw. p=0,002). Die Prävalenz von Vorhofflimmern in der Kontrollgruppe war signifikant niedriger als in den NYHA I bis III-Gruppen (p=0,007, 0,003 bzw. p=0,002) und den ICM- und DCM-Gruppen (p=0,001 bzw. p=0,002). Der Anteil der Teilnehmer mit Hypertonie in der Kontrollgruppe war signifikant niedriger als in den NYHA II und III-Gruppen (p=0,011 bzw. P=0,001) und in den ICM- und DCM-Gruppen (p<0,001 bzw. p=0,024), und in der DCM-Gruppe war er signifikant niedriger als in der ICM-Gruppe (p=0,027). CHF-Symptome korrelierten eng mit der NYHA-Klassifikation, und es wurden keine signifikanten Unterschiede zwischen den ICM- und DCM-Gruppen festgestellt. ACE-Hemmer und/oder AT1-Antagonisten wurden häufig bei Patienten mit CHF verwendet, insbesondere bei milden bis mittelschweren Gruppen. Betablocker und Aldosteronantagonisten wurden häufig bei Patienten mit CHF verschrieben, und es wurden keine deutlichen Unterschiede zwischen den verschiedenen NYHA-Klassen und zwischen den ICM- und DCM-Gruppen festgestellt. Schleifendiuretika, Sacubitril/Valsartan und Amiodaron wurden häufiger bei Patienten mit fortgeschrittenem CHF verabreicht, und es wurden nur wenige Unterschiede zwischen den ICM- und DCM-Gruppen festgestellt. Statine, Aspirin und P2Y12-Inhibitoren wurden häufiger in der ICM-Gruppe verschrieben. SGLT2-Inhibitoren wurden hauptsächlich von Patienten in der NYHA III-Gruppe und sowohl in der ICM- als auch in der DCM-Gruppe verwendet.
Im zweiten Teil, der sich auf den 6-Minuten-Gehtest (6MWT) konzentriert, war die submaximale körperliche Leistungsfähigkeit eng mit den NYHA-Stadien von CHF und nicht mit der Ätiologie von CHF (ICM und DCM) verbunden. Obwohl der systolische und diastolische Blutdruck in der Kontrollgruppe signifikant höher waren als in den CHF-Gruppen, wurden keine offensichtlichen Unterschiede im systolischen Blutdruck, diastolischen Blutdruck und Herzfrequenz zwischen den Patienten mit CHF festgestellt, einschließlich zwischen den NYHA I bis III-Gruppen und den ICM- und DCM-Gruppen vor und nach dem 6MWT. Beim Vergleich der Unterschiede im systolischen Blutdruck, diastolischen Blutdruck und Herzfrequenz jeder Gruppe vor und nach dem 6MWT wurden der systolische Blutdruck, diastolische Blutdruck und Herzfrequenz nach dem 6MWT fast alle signifikant höher als vor dem 6MWT, mit Ausnahme des systolischen Blutdrucks in der NYHA III-Gruppe und des diastolischen Blutdrucks in der Kontrollgruppe.
Der dritte Teil, der sich auf Laboruntersuchungen konzentriert, zeigte, dass diese Tests den Zustand von Patienten mit CHF effektiv bewerten können und eng mit der NYHA-Klassifikation, der 6-Minuten-Gehstrecke (6MWD) und NT-proBNP zusammenhängen. Diese Laboruntersuchungen werden oft übersehen und können eine wertvolle Ergänzung zu anderen Parametern sein, die die Herzfunktion widerspiegeln, wenn Patienten mit CHF umfassend vorhergesagt und bewertet werden.
Der vierte Teil, der sich auf das Elektrokardiogramm (EKG) konzentriert, zeigte, dass EKG-Indizes einen diagnostischen Wert für CHF haben und dass das EKG ein

nichtinvasiver und unersetzlicher Ansatz zur Bewertung von Patienten mit CHF ist. Besonders die QTc-Dauer stand in engem Zusammenhang mit der NYHA-Klassifikation, der 6-Minuten-Gehstrecke (6MWD) und NT-proBNP. Die Verwendung oder Kombination von EKG-Indizes ist vorteilhaft für die Diagnose von CHF.

Schlussfolgerungen

In unserer Studie haben wir einige interessante und zuvor übersehene Trends in diesen vier Teilen bei gesunden Kontrollpersonen und Patienten mit CHF festgestellt. Wir können diese nichtinvasiven, sicheren, kostengünstigen und wiederholbaren Tests in der Routine klinischer Praxis besser und umfassender nutzen.

Abstract

Introduction

Chronic heart failure (CHF) is not an independent disease but rather a range of clinical syndromes resulting from cardiac structural and functional abnormalities and represents the terminal stage of various cardiovascular diseases [1]. Managing patients with CHF remains one of the most fundamental and challenging issues in the field of cardiovascular diseases. Due to the aging of the world's population, advances in the treatment of cardiovascular diseases, and effective secondary prevention, CHF has become increasingly prevalent. Therefore, it is crucial to accurately assess and effectively manage CHF to achieve remission. A large number of examination methods have been proposed and adopted in clinical practice to assess patients with CHF. However, some approaches are difficult and risky to perform for patients with CHF or require specialized technicians, which are also costly and complicated, limiting their clinical application to some extent [2, 3]. Therefore, it is always useful and necessary to search for comprehensive approaches to assess CHF and stratify the risk, especially non-invasive, safe, economical, and repeatable methods. Baseline characteristics and medications, the 6-minute walking test (6MWT), laboratory tests, and electrocardiogram (ECG) are among the most commonly used methods for clinically assessing and monitoring patients with CHF. However, they are often undervalued and underutilized in routine clinical work and deserve further investigation.

Aim

The aim of my dissertation was to identify previously overlooked trends in these four areas among healthy controls and patients with CHF. The underlying goal is to make better and more thorough use of these non-invasive, safe, economical, and repeatable tests in routine clinical work. In order to make better and more comprehensive use of these aspects, they are chosen to study further and identify valuable areas that may have been overlooked before.

Methods and results

A total of 108 participants were included in our study (healthy controls: n=15, patients with CHF: n=93). The mean age was 59.24 ± 11.78 years and 77.8% of the participants were male. Patients with CHF were classified into two different categories based on NYHA classification, including NYHA I to III (NYHA I: n=16, NYHA II: n=43, NYHA III: n=34), and the two myocardiopathies, including ICM and DCM (ICM: n=37, DCM: n=56). Regarding the first part, baseline characteristics and medications, significant differences were observed among the control groups and CHF groups. The age of the control group was significantly younger than that of NYHA I to III groups ($p=0.030$, $p<0.001$, $P<0.001$, respectively), and that of ICM and DCM groups ($p<0.001$ and $p=0.002$, respectively).

The age of the NYHA I group was significantly younger than that of NYHA II and III groups (p=0.013 and p=0.017, respectively), and the age of the DCM group was younger that of ICM group (p<0.001). The prevalence of atrial fibrillation in the control group was significantly lower than that in NYHA I to III groups (p=0.007, 0.003, and p=0.002, respectively) and ICM and DCM groups (p=0.001 and p=0.002, respectively). The proportion of participants with hypertension in the control group was significantly lower than that in NYHA II and III groups (p=0.011 and P=0.001, respectively) and ICM and DCM groups (p<0.001 and p=0.024, respectively), and it in DCM group was significantly lower than it in ICM group (p=0.027). CHF symptoms correlated closely with NYHA classification, and no significant differences were observed between ICM and DCM groups. ACE inhibitors and/or AT1 antagonists were frequently used in patients with CHF, particularly in mild to moderate groups. Beta-blockers and aldosterone antagonists were commonly prescribed for patients with CHF, and no distinct differences were noted among different NYHA class groups and between ICM and DCM groups. Loop diuretics, sacubitril/valsartan, and amiodarone were more frequently administered to patients with advanced CHF, and few differences observed between ICM and DCM groups. Statins, aspirin, and P2Y12 inhibitors were more commonly prescribed in the ICM group. SGLT2 inhibitors were primarily used by patients in the NYHA III group and both ICM and DCM groups.

In the second part, focusing on the 6MWT, submaximal exercise capacity was closely associated with NYHA stages of CHF rather than the etiology of CHF (ICM and DCM). Although the SBP and DBP in the control group were significantly higher than those in CHF groups, no obvious differences were observed in SBP, DBP, and HR among patients with CHF, including among NYHA I to III groups, and between ICM and DCM groups before and after 6MWT. When comparing the differences in SBP, DBP, and HR of each group before and after 6MWT separately, SBP, DBP, and HR after 6MWT were almost all significantly higher than those before 6MWT, except for SBP in the NYHA III group and DBP in the control group.

The third part, focusing on laboratory tests, demonstrated that these tests can effectively evaluate the condition of patients with CHF and are closely related to NYHA classification, 6MWD, and NT-proBNP. These laboratory tests have often been frequently overlooked and can serve as a valuable supplement to other parameters reflecting cardiac function when comprehensively predicting and assessing patients with CHF.

The fourth part, focusing on ECG, indicated that ECG indices possess diagnostic value for CHF, and ECG is a non-invasive and irreplaceable approach to assessing patients with CHF. Notably, QTc duration was most closely associated with NYHA classification, 6MWD, and NT-proBNP. Utilizing or combining ECG indices is beneficial for the diagnosis of CHF.

Conclusions

In our study, we observed some intriguing and previously overlooked trends across these four parts for healthy controls and patients with CHF. We can make better and more thorough use of these non-invasive, safe, economical, and repeatable tests in

routine clinical practice.

1. Introduction

CHF is a range of clinical syndromes resulting from cardiac structural and functional cardiac abnormalities [1, 4]. The syndrome encompasses a range of cardiac insufficiency symptoms arising from the inability to effectively pump blood out as a result of cardiac systolic and/or diastolic dysfunction, leading to blood stasis in the venous system and inadequate blood flow in the arterial system. CHF is broadly classified into three subtypes based on ejection fraction: heart failure with preserved ejection fraction (HFpEF) (EF ≥ 50%), heart failure with mid-range ejection fraction (HFmrEF) (EF 40–49%), and heart failure with reduced ejection fraction (HFrEF) (EF < 40%) [4]. HFpEF is a clinical syndrome associated with poor quality of life, substantial health-care resource use, and premature mortality and approximately 50% of HF patients have HFpEF, with a sharp increase in risk with age and common risk factors including hypertension, obesity, and coronary artery disease. Non-cardiovascular deaths are higher in HFpEF compared to HFrEF [5]. HFmrEF occupies an intermediate position between HFrEF and HFpEF, and patients with HFmrEF may benefit from therapies that have improved outcomes in HFrEF [6]. However, HFmrEF and HFpEF patients have significantly lower risk of all-cause mortality compared to HFrEF patients [7, 8]. HFrEF signifies the advanced stage of various cardiovascular diseases.

Based on current guidelines, HFrEF constitutes a burgeoning global public health concern, with prevalence escalating significantly with advancing age, affecting approximately 10% of individuals over 70 years old and forecasts indicate a continued rise in these numbers [3, 9]. Common predisposing factors encompass hypertension, coronary artery disease, diabetes, and obesity. HFrEF is associated with substantial morbidity and mortality. Prognostication varies, yet, in general, portends a high mortality rate. Indicators of prognosis include symptom severity, left ventricular ejection fraction, and comorbidities. Notably, there is an elevated risk of sudden cardiac death in individuals with HFrEF [10, 11]. Accurate diagnosis of HFrEF necessitates a comprehensive clinical evaluation, incorporating medical history, physical examination, and diagnostic tests. Key diagnostic criteria encompass symptomatic presentations such as dyspnea and fatigue, coupled with objective evidence of cardiac dysfunction. Imaging modalities, notably echocardiography, assume a pivotal role in evaluating left ventricular function and confirming the diagnosis. Biomarkers, including B-type natriuretic peptide (BNP) and NT-proBNP, frequently manifest elevated levels in heart failure, aiding in the diagnostic process [12, 13]. Contemporary guidelines advocate a multidisciplinary approach to managing HFrEF, encompassing lifestyle modifications, pharmacological interventions, and, selectively, device therapy. Pharmacological strategies commonly involve angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor type 1 (AT1), beta-blockers, and mineralocorticoid receptor antagonists. Noteworthy is the emergence of Sodium-glucose cotransporter-2 (SGLT2) inhibitors as a novel therapeutic class, demonstrating proven benefits in mitigating cardiovascular events in HFrEF patients. Device therapies, including implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT), are recommended in specific clinical scenarios [3, 14].

While HFrEF has been extensively studied, managing patients with CHF, particularly this specific subtype, remains one of the most fundamental and challenging issues in the field of cardiovascular diseases. A large number of examination methods have been proposed and adopted in clinical practice to assess patients with CHF. However, some approaches are difficult and risky to perform for patients with CHF or require specialized technicians, which are also costly and complicated, limiting their clinical application to some extent [2, 3]. Therefore, it is always useful and necessary to search for comprehensive approaches to assess CHF and stratify the risk, especially non-invasive, safe, economical, and repeatable methods. Baseline characteristics and medications, the 6-minute walking test (6MWT), laboratory tests, and electrocardiogram (ECG) are among the most commonly used methods for clinically assessing and monitoring patients with CHF. However, they are often undervalued and underutilized in routine clinical work and deserve further investigation.

1.1 Baseline characteristics and medications

Managing patients with HFrEF requires a comprehensive assessment of baseline characteristics and medications. While demographic information, vital signs, comorbidities, and symptoms vary widely among individuals, understanding these factors is crucial for tailoring effective treatments and personalized approaches in optimizing patient care. Besides, medications are the cornerstone of managing CHF. The aim of this part was to provide an overall and practical summary of the available information from included healthy controls and patients with CHF categorized based on two different categories: the NYHA classification and different cardiomyopathies, including ICM and DCM simultaneously.

1.2 Six-min walk distance

In patients with CHF, insufficient oxygen is transported to exercising muscles, and anaerobic metabolism occurs at low levels of exercise due to reduced cardiac output. It has been reported in the literature that anaerobic metabolism occurred in patients with CHF when oxygen consumption per minute reached twice the resting state, whereas it occurred in healthy controls when it reached ten times the resting state, which is an important reason for the significant decrease in exercise tolerance, limited exercise capacity, and ultimately decreased quality of life in patients with CHF [15]. The signs and symptoms of CHF are not explained by cardiopulmonary and neurohormonal patterns alone. Rogers[16] concluded that the CHF could lead to activation of skeletal muscle mechanoreceptor, resulting in increased ventilation and a sensation of chest tightness, along with fatigue and sympathetic activation. At least a quarter of patients with CHF had symptoms caused by skeletal muscle abnormalities. The most objective index to evaluate patients with CHF is peak exercise oxygen consumption (peak VO2), which is the product of the arterio-venous oxygen content difference and cardiac output after

achieving maximum exercise, reflecting the ability of cardiac output to increase in line with the body's metabolic needs. It is the best predictor of long-term event-free survival of patients with CHF. However, the instrument for detecting peak VO2 is expensive and requires specialized technicians, which is costly and complicated, limiting its clinical application to some extent. Furthermore, determining peak VO2 requires participants to exercise to the maximum. Most patients with CHF have low exercise capacity and cannot reach the maximum exercise, and it is also unsafe for patients with severe organic heart disease. Therefore, a simple, repeatable, and sensitive evaluation indicator is required. The 6MWT has all the above characteristics. The 6MWT is similar to daily living activities and can objectively reflect the actual daily activity capacity of patients. It is easily accepted by patients with CHF, especially suitable for evaluating cardiac function in patients with moderate or severe CHF, frail elderly patients, and obese patients [17, 18]. The correlation between the 6MWT and peak VO2 in the gold standard cardiopulmonary exercise testing has been confirmed by numerous studies, which have demonstrated that the 6MWT is most closely related to peak VO2, superior to exercise time and exercise power, and can replace peak VO2 as a simple and safe exercise tolerance test [17, 19-23]. Besides, it is strongly related to survival and is an independent predictor of one-year survival in patients with CHF [24] and can predict event-free survival in patients with stable coronary artery disease and the incidence and mortality of CHF [25, 26].

The clinical significance of the 6MWT in patients with CHF can include the following: pretreatment and posttreatment comparisons of both drug treatment and other treatments such as ventricular resynchronization, cardiac functional status evaluation, morbidity, and mortality assessment, and more. However, there have been few studies comparing 6MWD among a control group and different NYHA class groups, and among a control group and different cardiomyopathy groups simultaneously. Additionally, there have been few studies detecting the correlations of SBP, DBP, and HR of healthy populations and patients with CHF in the different categories before and after 6MWT. Therefore, the aim of this part was to comprehensively explore the clinical significance and evaluate the relationships of 6MWD between healthy controls and patients with CHF. We analyzed the data of the patients with CHF in two different categories: those categorized into NYHA class I to III groups and those categorized into ICM and DCM groups. Moreover, in order to learn more details and changes about healthy controls and patients with CHF before and after 6MWT, we compared the Borg scale 6-20 score after 6MWT, SBP, DBP, and HR before and after 6MWT between healthy controls and patients with CHF in the two different categories.

1.3 Laboratory tests

Laboratory tests, including blood tests and urine tests, are common, economical, and objective ways of helping doctors and other healthcare professionals assess and monitor the condition of patients with CHF. With these merits, the use of laboratory tests has increasingly become a popular means for risk stratification in patients with

cardiovascular diseases [27, 28]. Among the common clinical laboratory parameters, blood glucose has been considered an important risk indicator for atherosclerotic cardiovascular disease and CHF [29]. Urine protein is an effective risk indicator for endothelial dysfunction [30] and atherosclerotic cardiovascular disease [31]. Compared with the healthy population, patients with CHF had higher NT-proBNP, creatine, total bilirubin, blood urea nitrogen, liver enzymes, and uric acid levels and lower sodium, albumin, hemoglobin, eGFR, and total proteins [32, 33]. Leukocyte count and its subtypes are classic indicators of inflammation in CHF and have been shown to be an independent predictor of increased incidence of hospitalization and mortality in patients with CHF [34-36]. A relatively decreased lymphocyte count has been confirmed to be closely related to mortality in CHF [37, 38]. Recently, the neutrophil-to-lymphocyte ratio (NLR) and relative lymphocyte counts (RLC) have emerged as promising composite parameters of systemic inflammation and risk stratification markers in patients with cardiovascular diseases [39, 40].

Laboratory tests are objective and not subjectively influenced by physicians and patients, and these parameters can be quickly and quantitatively tested. Despite these advantages, there are few articles that thoroughly evaluate the correlations between these parameters and CHF, and comparing these parameters with the indicators that are universally considered specific and sensitive for CHF, including NYHA classification, 6MWT, and NT-proBNP simultaneously [17, 41-44]. In our study, to analyze these laboratory parameters systematically and thoroughly, we assessed the most common clinical blood and urine parameters and categorized the patients with CHF into NYHA class I to III groups and ICM and DCM groups simultaneously. In addition to assessing whether these parameters are associated with different NYHA classes and different types of cardiomyopathy, we compared the discriminative prognostic efficacy of the common laboratory parameters in distinguishing whether participants with a limitation of exercise capacity or not, and also compared these laboratory parameters with the three classic indicators.

1.4 Electrocardiogram

ECG is a non-invasive, inexpensive, and repeatable approach that plays an important role in assessing patients with CHF and is critical in detecting abnormalities that may either result in or exacerbate CHF [45]. Its common indexes include HR, PQ interval, QRS duration, QT interval, and corrected QT interval (QTc). Many studies have shown that these indexes are strongly associated with CHF as follows. Resting HR has been found to be an independent risk factor for predicting the prognosis of patients with CHF, and increased HR was closely related to increased all-cause mortality and/or cardiovascular mortality resulting from worsening CHF [46-50]. The PQ interval is defined as the time distance between the onset of the P wave and the onset of the QRS complex. In the majority of cases, its prolongation is a sign of degradation of the conduction system or increased vagal tone, and it is common in patients with CHF and related to worse survival [51, 52]. Prolonged QRS duration has been shown to be an independent risk factor for sudden cardiac death [53]. The QRS complex reflects the

depolarization of the right and left ventricles of the heart and contraction of the large ventricular muscles. It has been found that as CHF progresses, myocardial contractile function declines, and overall systolic activity becomes uncoordinated, which is manifested as abnormal electrical activity on the ECG, often with prolonged QRS duration, predisposing the patients to malignant arrhythmias and even sudden cardiac death [54].

The QT interval, the period from the beginning of the QRS complex to the end of the T wave, represents the total activity of the right and left ventricles of the heart from the beginning of depolarization to the end of repolarization [55]. Prolonged QT interval has been shown to be linked with impairment of left ventricular systolic function [56]. Prolonged QTc has been also demonstrated to be associated with cardiovascular mortality and all-cause mortality in the general population and can be considered an index for clinical stratification in CHF [57-60].

In this part, patients with CHF were also categorized into NYHA class I to III groups and ICM and DCM groups simultaneously. The purpose of this part was to investigate the common ECG indexes in healthy controls and CHF patients in the different categories. Besides, we also compared the prognostic efficacy of these parameters in distinguishing whether participants have limitations in exercise capacity or not and explored the correlation of these parameters with the three classic indicators, including NYHA classification, 6MWT, and NT-proBNP [17, 41-44].

In conclusion, CHF, especially HFrEF, stands as a focal point in heart failure research, demanding ongoing efforts to refine diagnostic practices and optimize therapeutic interventions. Multiscale phenotyping holds promise in uncovering the intricacies of HFrEF. Comprehensive assessments of baseline characteristics, exercise capacity, laboratory parameters, and ECG findings contribute to a holistic understanding of HFrEF, ultimately aiming to enhance patient outcomes in this specific subtype of CHF.

1.5 Research objectives and central hypotheses

1.5.1 Research objectives:

Objective 1: To compare and analyze baseline characteristics and medication profiles among the control group and CHF groups.

Objective 2: To assess the differences and relationships in 6MWT performance among the control group and CHF groups.

Objective 3: To investigate and compare laboratory test results among the control group and CHF groups.

Objective 4: To examine and analyze ECG parameters among the control group and CHF groups.

1.5.2 Central hypotheses:

The null hypothesis in this dissertation posits that there are no significant differences and statistical relationships among the control group and CHF groups categorized by NYHA classification and cardiomyopathy type in terms of baseline characteristics and medication usage, 6MWT performance, laboratory parameters, and ECG findings.

2. Materials and Methods

2.1 Participants

Fifteen healthy controls and 93 patients with symptomatic, stable CHF were involved. Healthy controls between the ages of 40 and 90 years old with normal ECG, outpatient blood pressure (BP), and cardiovascular findings were included. For patients with CHF, subjects between the ages of 40 and 90 years old, left ventricular EF less than 40% (HFrEF) as determined by echocardiography, and symptoms stable with New York Heart Association (NYHA) class I or III, were eligible for our study. The exclusion criteria for both healthy controls and patients with CHF were as follows:

1) Myocardial infarction or stroke or transient ischemic attack within the last month.
2) Cardiac surgery or intervention within the last month.
3) Acute decompensated heart failure (HF) or life-threatening or uncontrolled arrhythmia.
4) Hemodynamically relevant valve (more than moderate) or pericardial diseases
5) Organ transplantation or ventricular assist device therapy.
6) Other diseases (including malignant diseases) with a life expectancy of < 1 year.
7) Acute infection within the last month.
8) Severe anemia (hemoglobin < 7 g/dl).
9) Pregnancy or lactation.

Considering part of the participants with CHF, the process was conducted with considerate contingency plans to prevent and deal with possible emergency circumstances. An appropriate crash cart was readily available.

2.2 Baseline characteristics and medications

2.2.1 Methods

All participants provided their informed written consent for the use of their records for research purposes, and our study was performed in accordance with the ethical guidelines of the Declaration of Helsinki for clinical research involving human participants. The protocol was approved by the Ethics Committee of Charité – Universitätsmedizin Berlin. Participants were assessed in a quiet state and temperature-controlled room (22℃),

2.2.2 Required equipment

1) Case report forms including the baseline characteristics and medications related to our study.
2) A measuring tape.
3) Sphygmomanometer, for measuring BP and HR.
4) A crash cart including common first-aid medications.
5) Readily available oxygen.
6) Telephone.

7) Defibrillator.

2.3 Six-min walk distance

2.3.1 Execution methods

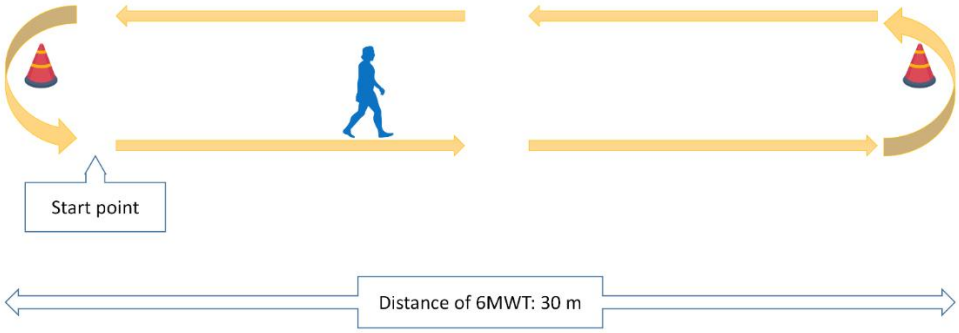

Figure 2.1. Outline of walking course.

Perceived Exertion Rating	Description of Exertion
6	No exertion
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Figure 2.2. The Borg's Rating of Perceived Exertion Scale (6-20).

The examination of 6MWT was performed according to the official guideline of the American Thoracic Society and conducted in a 30-meter long, spacious corridor with flat and hard ground, as Figure 2.1 shows [61]. Participants walked as fast as they could in a straight line until the researcher asked them to stop after 6 minutes, and the walking

distances were then measured. During the test, the following points should be noted:
1) Before starting the test, the researcher should check the distance measuring wheel and reset the meter, which should begin at zero.
2) When walking with the distance measuring wheel, the participant should walk as fast as possible in a straight line, avoiding turning around quickly and taking circular routes.
3) In the study, the researcher stood nearby without interfering with the participant. Fixed and smooth encouraging language could be used regularly, and the methods should be adopted consistently for all the participants. When the timer showed 3 minutes left, the researcher could tell the participant: “You are doing well. You have 3 minutes to go.” No other encouraging words or body language was used to urge the participants.
4) When the timer was 15 seconds left, the researcher needed to tell the participant: “In a little while, time is up. When I tell you to stop, please stop where you are, and I will come to you.” When the time was up, the researcher asked the participant to stop, sit down, and take a rest.
5) The researcher should record the participant’s blood pressure and heart rate before and after the test, and also evaluate the Borg scale 6-20 score (Figure 2.2) after the test.
6) The researcher should record the distance shown on the digital display of the distance measuring wheel and reset the meter for zeroing the counter. The researcher also needed to record the number of laps and the additional distance covered in the final partial lap using the markers on the wall and calculated the distance. If there was a wide discrepancy between these two results, then the researcher analyzed the causes and then chose and recorded the more accurate result.
7) The test environment should be quiet, well-ventilated, and comfortable.
8) If the participant stopped walking within 6 minutes and needed a break, the researcher said: “ You can rest against the wall and continue waking if possible.” Meanwhile, the timer kept timing. If the participant stopped testing before the set time and refused to continue, or the researcher stopped the testing according to the participant’s condition, let the participant sit in a chair and rest, discontinued the test, and recorded the distance, the time that the participant had walked, and the reason for canceling prematurely on the case report form (CRF).

2.3.2 Required equipment

1) Distance measuring wheel.
2) Timer.
3) A crash cart including common first-aid medications.
4) Case report form and Borg scale 6-20 form on a clipboard.
5) Readily available oxygen.
6) Sphygmomanometer, for measuring BP and HR.
7) Telephone.
8) Defibrillator.

2.3.3 Patient preparation

1) Comfortable and loose clothing.

2) Appropriate shoes.
3) Walking aids (cane, walker, etc.) if needed.
4) Usual medical regimen.
5) A light meal if needed.
6) Appropriate rest.

2.3.4 Contraindications

Absolute contraindications for the 6MWT include the following:
1) Unstable angina pectoris or acute myocardial infarction in the previous month.
2) Uncontrolled arrhythmias causing symptoms or hemodynamic compromise.
3) Acute myocarditis or pericarditis.
4) Uncontrolled acutely decompensated HF (acute pulmonary edema).
5) Acute pulmonary embolism.
6) Suspected dissecting aneurysm.
7) Severe hypoxemia at rest or acute respiratory failure.
8) Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (such as infection, renal failure, thyrotoxicosis) or mental impairment leading to inability to cooperate.

Relative contraindications for the 6MWT include the following:
1) Resting HR above 120 beats per minute.
2) Systolic blood pressure above 180 mmHg.
3) Diastolic blood pressure above 100 mmHg.
4) Activity limitation.
5) Extremely obese participant.
6) Severe valvular disease.
7) Concomitant joint, mental, or neurological diseases.

2.4 Laboratory tests

2.4.1 Methods

Participants were rested for 30 min in a quiet, and temperature-controlled room (22℃). Fasting median cubital venous blood was drawn in the morning, and urine sample were collected using a sterile container and analyzed immediately in the laboratory. All results were transferred directly from the laboratory reports, except for NLR and RLC. NLR was calculated as the ratio of neutrophil count to lymphocyte count. RLC was defined as (lymphocyte count/leukocyte count)×100.

2.4.2 Gather equipment

1) Clean tray.
2) Non-sterile gloves.
3) Tourniquet.
4) Blood sampling device (e.g., butterfly needle).

5) Blood and urine collection tubes and urine sterile container.
6) Sharps container.
7) Alcohol swab.
8) Gauze or cotton wool.
9) Sterile plaster.
10) Laboratory labels and transportation bag.
11) Case report form.

2.4.3 Other required equipment

1) A crash cart including common first-aid medications.
2) Readily available oxygen.
3) Sphygmomanometer, including measuring BP and HR.
4) Telephone.
5) Defibrillator.

2.4.4 Patient preparation

1) Wear comfortable and loose clothing.
2) Maintain the usual medical regimen.
3) Fast for at least 12 hours before the test.
4) Avoid overeating the day before the test, and refrain from consuming fatty, fried foods and alcohol 1-2 days before the test.
5) Refrain from smoking.
6) Avoiding strenuous exercise or activity.
7) Discuss any medications or supplements currently being taken with the researcher,
8) including over-the-counter medications, vitamins, and supplements.
9) Ensure appropriate rest.

2.5 Electrocardiogram

2.5.1 Methods

Participants rested for 30 minutes in a quiet, temperature-controlled room (22℃). After fasting, median cubital venous blood was drawn, both heart rate and blood pressure were measured. The participants' ECGs were then taken, interpreted, and printed out. In our study, the formula we used to calculate the QTc intervals is the most commonly used: $QTc = QT/\sqrt{RR}$, which evaluates the QT interval at a standard heart rate of 60 bpm [62, 63]. As QTc showed the best diagnostic value among ECG indexes in distinguishing between participants with a limitation of exercise capacity and those most related to NYHA classification, 6MWT, and NT-proBNP in our study, we further analyzed the QTc interval by comparing the characteristics of participants with different QTc intervals. All participants were divided into two groups based on the median of QTc interval.

2.5.2 Gather equipment

1) Sphygmomanometer, for measuring BP and HR.
2) Non-sterile gloves.
3) Electrode.
4) ECG machine.
5) Alcohol swab.
6) Case report form.

2.5.3 Other required equipment

1) A crash cart including common first-aid medications.
2) Readily available oxygen.
3) Telephone.
4) Defibrillator.

2.5.4 Patient preparation

Generally, fasting is not required but patients should avoid drinking cold water and coffee, smoking, and exercising before taking an EKG. Have the patient remove clothing above the waist or open the front. Remove any jewelry or other objects that may interfere with the test. Make the patient comfortable lying down on the exam bed. Expose the arms and legs. If necessary, shave the electrode areas or clean the exposed skin with alcohol if needed for proper electrode adhesion.

2.5.5 Limb Sensor Application

Place the sensors on a smooth, fleshy area of the upper inner arms and lower inner legs. Attach the limb leads.

2.5.6 Chest Sensor Application

Place the 6 Chest sensors on the patient's chest as follows:
V1: Fourth intercostal space at the right border of the sternum.
V2: Fourth intercostal space at the left border of the sternum.
V3: Midway between position V2 and position V4.
V4: At the mid-clavicular line in the fifth intercostal space.
V5: At the anterior axillary line on the same horizontal level as V4.
V6: At the mid-axillary line on the same horizontal level as V4 and V5.
Attach the chest leads.

2.6 Statistical analysis

All continuous data were tested for violations of normality using Shapiro-Wilks tests and are expressed as mean ± standard deviation when the variables were normally distributed, and as median (25th and 75th percentiles [minimum and maximum]) when the variables were not normally distributed. Given the relatively small size of the included participants for each group, non-parametric tests were predominantly performed. The Kruskal-Wallis Test was used to compare continuous variables, and the Mann-Whitney

U Test was used for post-hoc multiple comparisons [64]. When comparing parameters for the same subject, the Paired t-test was used when both sample sizes were 30 or more than 30 and normally distributed, while the Wilcoxon-signed rank test was chosen when one of the sample sizes was less than 30 or not normally distributed. When comparing two different groups, an independent t-test was used to compare groups with a normal distribution and both sample sizes were 30 or more than 30, and the Mann-Whitney U test was used to compare groups with non-normal distribution or when one of the sample sizes was less than 30. To quantify the level of uncertainty due to the relatively small sizes of included participants, the Monte Carlo method was jointly used to specify the 99% confidence interval (CI) for the obtained P values when comparing the continuous variables and one of the sample sizes of the variables was less than 30.

Categorical variables are expressed in frequency (percentage), and the Chi-Square Test was used for statistical analysis. When one or more expected cell counts in the cross-tabulation were five or less than five, no statistical method was used for analysis [65]. When one or more expected cell counts in the cross-tabulation were ten or between five and ten, a continuity correction test was used [66].

To visualize the differences more clearly, the variables with significant differences among these groups were presented using graphs. For continuous variables, bar graphs were used when the continuous variables were normally distributed and presented with mean and standard deviation. Box plots were used when the parameters were non-normally distributed and presented with median, the first and third quartiles, and the upper and lower whiskers. The cross symbols in the box plots indicate the mean value, and the black solid circles symbolize the outlier. For categorical variables, bar graphs were used to present the corresponding percentages.

The control group and NYHA class I to III groups were further divided into two groups: the control group and NYHA I group were categorized as the group with no limitation of exercise capacity, while NYHA II and NYHA III groups were considered the group with a limitation of exercise capacity. The receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC) and 95% CI for analyzing whether parameters had diagnostic value in distinguishing between participants with limitations of exercise capacity or not.

To establish the link strength and direction between the statistically significant variables, correlation analysis was performed by Pearson’s correlation when the variables were normally distributed and both sample sizes were 30 or more than 30, or by Spearman’s rank correlation when the variables were not normally distributed, or one of the sample sizes was less than 30. A two-sided $P \leq 0.05$ was considered a statistically significant difference.

3. Results

3.1 Baseline characteristics and medications

In total, 108 participants were included in our study (healthy controls: n=15, patients with CHF: n=93). The mean age was 59.24 ± 11.78 years and 77.8% of the participants were male. Patients with CHF were classified into two different categories based on NYHA classification, including NYHA I to III (NYHA I: n=16, NYHA II: n=43, NYHA III: n=34), and the two myocardiopathies, including ICM and DCM (ICM: n=37, DCM: n=56). Table 3.1.1 shows the baseline characteristics of all the participants, and we can find that there were some significant differences in the factors among the control group and CHF groups.

The age of the control group was significantly younger than that of NYHA I to III groups ($p=0.030$, $p<0.001$, $P<0.001$, respectively), and that of ICM and DCM groups ($p<0.001$ and $p=0.002$, respectively). The age of the NYHA I group was significantly younger than that of NYHA II and III groups ($p=0.013$ and $p=0.017$, respectively), and the age of the DCM group was younger that of ICM group ($p<0.001$). No obvious differences were observed in weight, body surface area (BSA), body mass index (BMI), BP in right and left arms, heart rate (HR), waistline, hipline, and thigh circumference.

The prevalence of atrial fibrillation in the control group was significantly lower than that in NYHA I to III groups ($p=0.007$, 0.003, and $p=0.002$, respectively) and ICM and DCM groups ($p=0.001$ and $p=0.002$, respectively), but there were no obvious differences among these CHF groups. The proportion of participants with hypertension in the control group was significantly lower than that in NYHA II and III groups ($p=0.011$ and $P=0.001$, respectively) and ICM and DCM groups ($p<0.001$ and $p=0.024$, respectively), and it in DCM group was significantly lower than it in ICM group ($p=0.027$). The proportion of dyspnea on exertion in the control group was significantly lower than that in NYHA II and III groups ($P=0.001$ and $P<0.001$, respectively) and ICM and DCM groups ($p=0.003$ and $P<0.001$, respectively), and it in the NYHA I group was significantly lower than that in NYHA II and III groups ($P=0.007$ and $P=0.001$, respectively). For orthopnea, the proportion of NYHA III group was significantly higher than that of the control group and NYHA I and II groups ($p=0.021$, $p=0.020$, and $p=0.008$, respectively), and there were no obvious differences among the control group and ICM and DCM groups. For fatigue, the presence in the control group was significantly lower than that in NYHA II and III groups (all $p<0.001$) and ICM and DCM groups ($p=0.001$ and $P<0.001$, respectively). The proportion of nocturia in the control group was significantly lower than that in NYHA II and III groups (both $p=0.001$) and ICM and DCM groups ($p=0.001$ and $P=0.002$, respectively), and the proportion in NYHA I group was significantly lower than that in NYHA III group ($p=0.031$). No obvious differences were observed in the proportion of syncope, chronic obstructive pulmonary disease (COPD), primary pulmonary hypertension (PPH), asthma, hypothyroidism, current smoker, ex-smoker, alcohol consumption, dyspnea at rest, paroxysmal nocturnal dyspnea (PND), and nighttime coughing among the control group and CHF groups.

Table 3.1.1. The baseline characteristics of healthy controls and patients with CHF being categorized into NYHA classes I to III groups and ICM and DCM groups.

	The control group n=15	**CHF group n=93**	**NYHA I n=16**	**NYHA II n=43**	**NYHA III n=34**	**ICM n=37**	**DCM n=56**	**P value[a]**
Age, year	48.20 ± 7.06	61.02 ± 11.43	54.13 ± 7.74	62.56 ± 11.68	62.32 ± 11.65	67.27 ± 11.15	56.89 ± 9.68	0.030 (0.025-0.034) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, 0.013 (0.010-0.015) between NYHA I group and NYHA II group, 0.017 (0.013-0.019) between NYHA I group and NYHA III group, <0.001 (<0.001) between the control group and ICM group, 0.002 (0.001-0.003) between the control group and DCM group, <0.001 (<0.001) between ICM group and DCM group[1]
Men, n (%)	12 (80.0)	72 (77.4)	15 (93.8)	35 (81.4)	22 (64.7)	33 (89.2)	39 (69.6)	ns[2]
Height, m	1.78 ± 0.07	1.75 ± 0.09	1.76 ± 0.07	1.77 ± 0.11	1.71 ± 0.08	1.74 ± 0.07	1.76 ± 0.11	0.007 (0.004-0.008) between the control group and NYHA III group[1]
BMI, kg/m2	27.25 ± 3.56	29.07 ±4.97	29.36 ± 3.62	28.50 ± 4.19	29.59 ± 6.50	29.64 ± 4.57	28.75 ± 5.21	ns[1]
Heart rate, bpm	63 (55-69 [50-81])	65 (57.50-73 [45-165])	61 (55-68.50 [45-83])	66 (59-79 [52-165])	68 (59.25-78.25 [45-150])	67 (62-71 [45-99])	64 (57-78.25 [45-165])	ns[1]
Atrial fibrillation, n (%)	0 (0)	44 (47.3)	7 (43.8)	20 (46.5)	17 (50.0)	17 (45.9)	27 (48.2)	0.007 between the control group and NYHA I group, 0.003 between the control group and NYHA II group, 0.002 between the control group and NYHA III group, 0.001 between the control group and ICM group, 0.002 between the control group and DCM group[2]
Syncope, n (%)	5 (33.3)	17 (18.3)	3 (18.8)	7 (16.3)	7 (20.6)	7 (18.9)	10 (17.9)	ns[2]

COPD, n (%)	0 (0)	11 (11.8)	0 (0)	8 (18.6)	3 (8.8)	6 (16.2)	5 (8.9)	ns[2]
PPH, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	ns2
Asthma, n (%)	0 (0)	2 (2.2)	0 (0)	1 (2.3)	1 (2.9)	2 (5.4)	0 (0)	ns[2]
Hypothyroidism, n (%)	1 (6.7)	17 (18.3)	2 (12.5)	4 (9.3)	11 (32.4)	4 (10.8)	13 (23.2)	ns[2]
Diabetes mellitus, n (%)	0 (0)	22 (23.7)	2 (12.5)	8 (18.6)	12 (35.3)	12 (32.4)	10 (17.9)	0.010 between the control group and NYHA III group, 0.011 between the control group and ICM group[2]
Hypertension, n (%)	2 (13.3)	55 (59.1)	8 (50.0)	24 (55.8)	23 (67.6)	27 (73.0)	28 (50.0)	0.011 between the control group and NYHA II group, 0.001 between the control group and NYHA III group, <0.001 between the control group and ICM group, 0.024 between the control group and DCM group, 0.027 between ICM group and DCM group[2]
Dyspnea on exertion, n (%)	0 (0)	49 (72.1)	2 (12.5)	24 (85.7)	23 (95.8)	18 (75.0)	31 (70.5)	0.001 between the control group and NYHA II group, <0.001 between the control group and NYHA III group, 0.007 between NYHA I group and NYHA II group, 0.001 between NYHA I group and NYHA III group, 0.003 between the control group and ICM group, <0.001 between the control group and DCM group[2]
Dyspnea at rest, n (%)	0 (0)	10 (14.7)	0 (0)	3 (10.7)	7 (29.2)	3 (12.5)	7 (15.9)	ns[2]
Orthopnea, n (%)	0 (0)	12 (17.6)	0 (0)	2 (7.1)	10 (41.7)	3 (12.5)	9 (20.5)	0.021 between the control group and NYHA III group, 0.020 between NYHA I group and NYHA III group, 0.008 between NYHA II group and NYHA III group[2]

PND, n (%)	0 (0)	13 (19.1)	1 (6.3)	5 (17.9)	7 (29.2)	5 (20.8)	8 (18.2)	ns[2]
Nighttime coughing, n (%)	0 (0)	9 (13.2)	1 (6.3)	2 (7.1)	6 (25.0)	1 (4.2)	8 (18.2)	ns[2]
Fatigue, n (%)	0 (0)	58 (85.3)	11 (68.8)	26 (92.9)	21 (87.5)	20 (83.3)	38 (86.4)	<0.001 between the control group and NYHA I group, <0.001 between the control group and NYHA II group, <0.001 between the control group and NYHA III group, 0.001 between the control group and ICM group, <0.001 between the control group and DCM group[2]
Nocturia, n (%)	0 (0)	44 (64.7)	3 (18.8)	22 (78.6)	19 (79.2)	17 (70.8)	27 (61.4)	between the control group and NYHA II group, 0.001 between the control group and NYHA III group, 0.031 between NYHA I group and NYHA III group, <0.001 between the control group and ICM group, <0.001 between the control group and DCM group[2]

Continuous variables with normal distribution are expressed as mean ± standard deviation and non-normally distributed variables as median (IQR [range]). Categorical variables are expressed as frequency (percentage).

NYHA, New York Heart Association functional classification; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PPH, primary pulmonary hypertension; PND, paroxysmal nocturnal dyspnea; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; ns, not significant.

[a] Monte Carlo was jointly used to specify the 99% CI for the obtained P values when comparing the continuous variables and one of the sample sizes of the variables was less than 30.

[1] Kruskal-Wallis Test was used to compare continuous variables, and a Mann-Whitney U Test was used for post-hoc multiple comparisons.

[2] Chi-Square Test or Continuity Correction Test was used to compare categorical variables as appropriate.

Table 3.1.2. shows the detailed comparisons of the medications by all the participants. In order to view the differences more visually, as Figure 3.1.1 to Figure 3.1.9 show, the medications which have significant differences among the control group and CHF groups

were presented using bar graphs.

Table 3.1.2. The current medication of healthy controls and patients with CHF being categorized into NYHA classes I to III groups and ICM and DCM groups.

	The control group n=15	**CHF group n=91**	**NYHA I n=16**	**NYHA II n=42**	**NYHA III n=33**	**ICM n=37**	**DCM n=54**	**P value**
ACE inhibitors	0 (0)	19 (20.9)	5 (31.3)	9 (21.4)	5 (15.2)	9 (24.3)	10 (18.5)	ns[1]
AT1 antagonists	1 (6.7)	13 (14.3)	2 (12.5)	9 (21.4)	2 (6.1)	6 (16.2)	7 (13.0)	ns[1]
ACE inhibitors / AT1 antagonists	1 (6.7)	32 (25.2)	7 (43.8)	18 (42.9)	7 (21.2)	15 (40.5)	17 (31.5)	0.037 between the control group and NYHA I group, 0.026 between the control group and NYHA II group, 0.048 between NYHA II group and NYHA III group, 0.021 between the control group and ICM group[1]
Beta-blockers	0 (0)	85 (93.4)	15 (93.8)	38 (90.5)	32 (97.0)	36 (97.3)	49 (90.7)	<0.001 between the control group and NYHA I group, <0.001 between the control group and NYHA II group, <0.001 between the control group and NYHA III group, <0.001 between the control group and ICM group, <0.001 between the control group and DCM group[1]
Thiazide diuretics	1 (6.7)	6 (6.6)	2 (12.5)	2 (4.8)	2 (6.1)	0 (0)	6 (11.1)	ns[1]
Loop diuretics	0 (0)	52 (57.1)	6 (37.5)	21 (50.0)	25 (75.8)	24 (64.9)	28 (51.9)	0.018 between the control group and NYHA I group, 0.002 between the control group and NYHA II group, <0.001 between the control group and NYHA III group, 0.022 between NYHA I group and NYHA III group, 0.023 between NYHA II group and NYHA III group, <0.001 between the control group and ICM group, 0.001 between the control

								group and DCM group[1]
Aldosterone antagonists, n (%)	0 (0)	60 (65.9)	11 (68.8)	25 (59.5)	24 (72.7)	22 (59.5)	38 (70.4)	<0.001 between the control group and NYHA I group, <0.001 between the control group and NYHA II group, <0.001 between the control group and NYHA III group, <0.001 between the control group and ICM group, <0.001 between the control group and DCM group[1]
Sacubitril / Valsartan, n (%)	0 (0)	57 (62.6)	9 (56.3)	23 (54.8)	25 (75.8)	21 (56.8)	36 (66.7)	0.001 between the control group and NYHA I group, <0.001 between the control group and NYHA II group, <0.001 between the control group and NYHA III group, <0.001 between NYHA II group and NYHA III group, 0.001 between the control group and ICM group, <0.001 between the control group and DCM group[1]
Ivabradine, n (%)	0 (0)	3 (3.3)	0 (0)	0 (0)	3 (9.1)	1 (2.7)	2 (3.7)	ns[1]
Digoxin, n (%)	0 (0)	7 (7.7)	1 (6.3)	1 (2.4)	5 (15.2)	3 (8.1)	4 (7.4)	ns[1]
Calcium antagonists, n (%)	0 (0)	9 (9.9)	1 (6.3)	4 (9.5)	4 (12.1)	5 (13.5)	4 (7.4)	ns[1]
Amiodarone, n (%)	0 (0)	15 (16.5)	1 (6.3)	5 (11.9)	9 (27.3)	5 (13.5)	10 (18.5)	0.041 between the control group and NYHA III group[1]
Statins, n (%)	0 (0)	45 (49.5)	7 (43.8)	22 (52.4)	16 (48.5)	32 (86.5)	13 (24.1)	0.007 between the control group and NYHA I group, 0.001 between the control group and NYHA II group, 0.003 between the control group and NYHA III group, <0.001 between the control group and ICM group, <0.001 between ICM group and DCM group[1]
Other lipid-lowering agents, n (%)	0 (0)	10 (11.0)	1 (6.3)	8 (19.0)	1 (3.0)	7 (18.9)	3 (5.6)	ns[1]

Aspirin, n (%)	0 (0)	41 (45.1)	7 (43.8)	19 (45.2)	15 (45.5)	27 (73.0)	14 (25.9)	0.007 between the control group and NYHA I group, 0.004 between the control group and NYHA II group, 0.002 between the control group and NYHA III group, <0.001 between the control group and ICM group, 0.030 between the control group and DCM group, <0.001 between ICM group and DCM group[1]
P2Y12 inhibitors, n (%)	0 (0)	20 (22.0)	3 (18.8)	11 (26.2)	6 (18.2)	17 (45.9)	3 (5.6)	0.001 between the control group and ICM group, <0.001 between ICM group and DCM group [1]
Vitamin K antagonists, n (%)	0 (0)	11 (12.1)	2 (12.5)	3 (7.1)	6 (18.2)	4 (10.8)	7 (13.0)	ns[1]
Other anticoagulants, n (%)	0 (0)	29 (31.9)	4 (25.0)	13 (31.0)	12 (36.4)	11 (29.7)	18 (33.3)	ns[1]
Insulin, n (%)	0 (0)	10 (11.0)	1 (6.3)	3 (7.1)	6 (18.2)	6 (16.2)	4 (7.4)	ns[1]
Metformin, n (%)	0 (0)	10 (11.0)	0 (0)	5 (11.9)	5 (15.2)	6 (16.2)	4 (7.4)	ns[1]
DPP-4 inhibitors, n (%)	0 (0)	5 (5.5)	0 (0)	3 (7.1)	2 (6.1)	2 (5.4)	3 (5.6)	ns[1]
GLP-1 agonists, n (%)	0 (0)	4 (4.4)	1 (6.3)	2 (4.8)	1 (3.0)	3 (8.1)	1 (1.9)	ns[1]
SGLT2 inhibitors, n (%)	0 (0)	26 (28.6)	4 (25.0)	9 (21.4)	13 (39.4)	9 (24.3)	17 (31.5)	0.004 between healthy group and NYHA III group, 0.046 between healthy group and ICM group, 0.015 between healthy group and DCM group[1]

Categorical variables are expressed as frequency (percentage).

NYHA, New York Heart Association functional classification; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; ACE, angiotensin-converting-enzyme; AT1, angiotensin II receptor type 1; DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; ns, not significant.

[1] Chi-Square Test or Continuity Correction Test was used to compare categorical variables as appropriate.

Figure 3.1.1 shows the comparisons of participants taking ACE inhibitors and/or angiotensin II (Ang II) receptor type 1 (AT1) antagonists among these groups, participants taking them in the control group were significantly fewer than those in NYHA I and II groups ($p=0.037$ and $p=0.026$, respectively), NYHA II group were significantly more than NYHA III group ($p=0.048$), and the ICM group were significantly higher than the control group ($p=0.021$). For beta-blockers, as Figure 3.1.2 shows, the proportion of participants who took beta-blockers in the control group was significantly lower than that in NYHA I to III groups (all $p<0.001$) and ICM and DCM groups (both $p<0.001$); however, there were few differences among CHF groups.

Concerning loop diuretics, as Figure 3.1.3 shows, the proportion in the control group was significantly lower than in NYHA I to III groups ($p=0.018$, $p=0.002$, and $p<0.001$, respectively) and ICM and DCM groups ($p<0.001$ and $p=0.001$, respectively). The proportions in NYHA I and II groups were both significantly lower than in NYHA III groups ($p=0.022$ and $p=0.023$, respectively).

For aldosterone antagonists, as Figure 3.1.4 shows, the proportion in the control group was significantly lower than it in NYHA I to III groups (all $p<0.001$) and ICM and DCM groups (both $p<0.001$), and there were no obvious significant differences among CHF groups.

For sacubitril/valsartan, as shown in Figure 3.1.5, the presence of participants taking it in the control groups was significantly lower than in NYHA I to III groups ($p=0.001$, $p<0.001$ and $p<0.001$, respectively) and ICM and DCM groups ($p=0.001$ and $p<0.001$, respectively). The NYHA II group was significantly lower than the NYHA III groups ($p<0.001$).

Concerning statins, as Figure 3.1.6 shows, the proportion of participants taking them in the control group was significantly lower than in NYHA I to III groups ($p=0.007$, $p=0.001$, and $p=0.003$, respectively), and the proportion in ICM group was significantly higher than in the control group and DCM group (both $p<0.001$).

Figure 3.1.7 shows the comparisons of aspirin. The proportion in the control group was significantly lower than in NYHA I to III groups ($p=0.007$, $p=0.004$, and $p=0.002$, respectively), and ICM and DCM groups ($p<0.001$ and $p=0.030$, respectively), and the proportion in ICM group was significantly higher than in DCM group ($p<0.001$).

For P2Y12 inhibitors, as shown in Figure 3.1.8, the proportion in the ICM group was significantly higher than in the control group and DCM group ($p=0.001$ and $p<0.001$, respectively); however, there were no obvious differences among the control group and NYHA I to III groups.

For SGLT2 inhibitors, as shown in Figure 3.1.9, SGLT2 inhibitors were more commonly used in patients in the NYHA III group ($p=0.004$) and ICM and DCM groups ($p=0.046$ and $p=0.015$, respectively) compared with the control group.

No obvious differences were found in ACE inhibitors, AT1 antagonists, thiazide diuretics, ivabradine, digoxin, calcium antagonists, amiodarone, other lipid-lowering agents, vitamin K antagonists, insulin, metformin, dipeptidyl peptidase (DPP) 4 inhibitors, and glucagon-like peptide (GLP) 1 agonists.

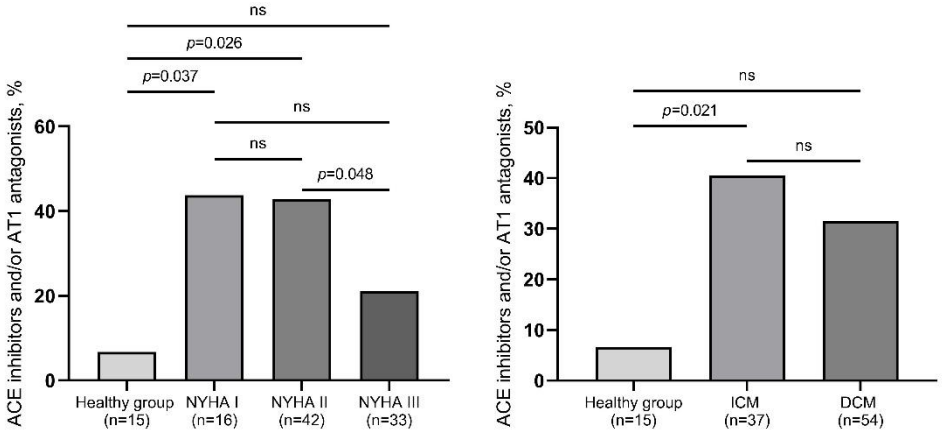

Figure 3.1.1. Comparisons of angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor type 1 antagonists in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

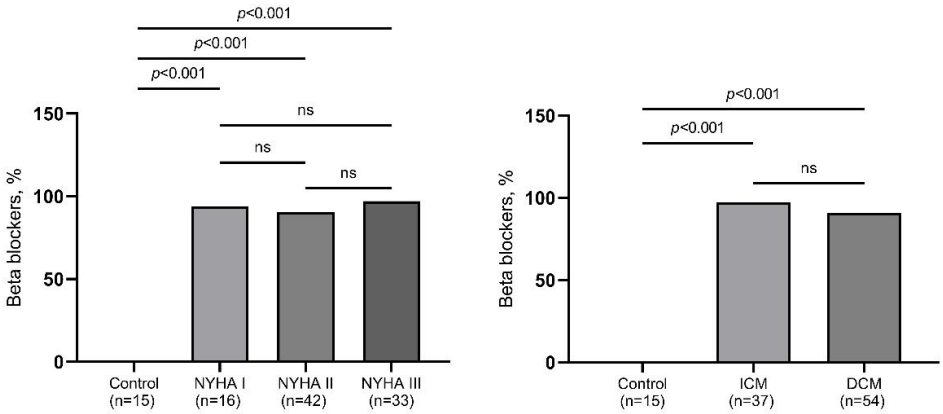

Figure 3.1.2. Comparisons of beta blockers in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

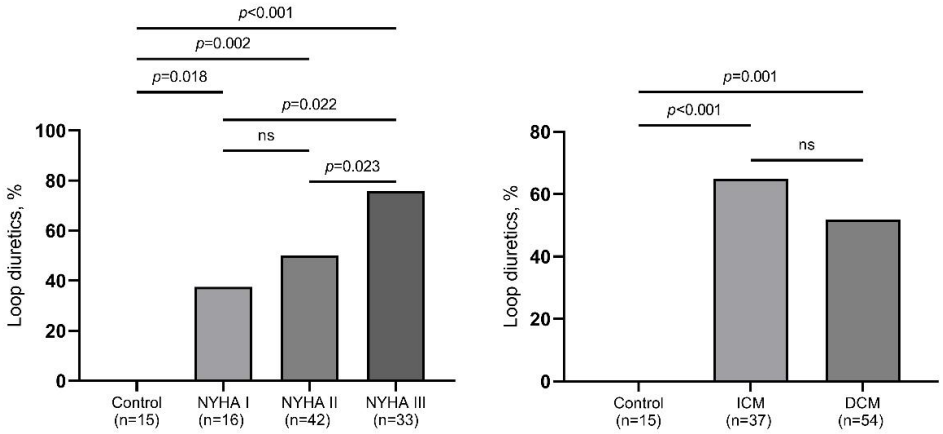

Figure 3.1.3. Comparisons of loop diuretics in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

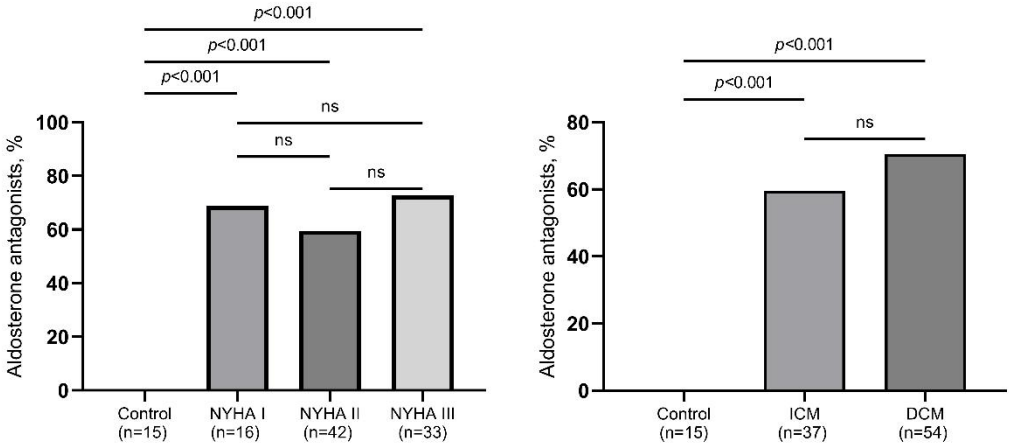

Figure 3.1.4. Comparisons of aldosterone antagonists in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

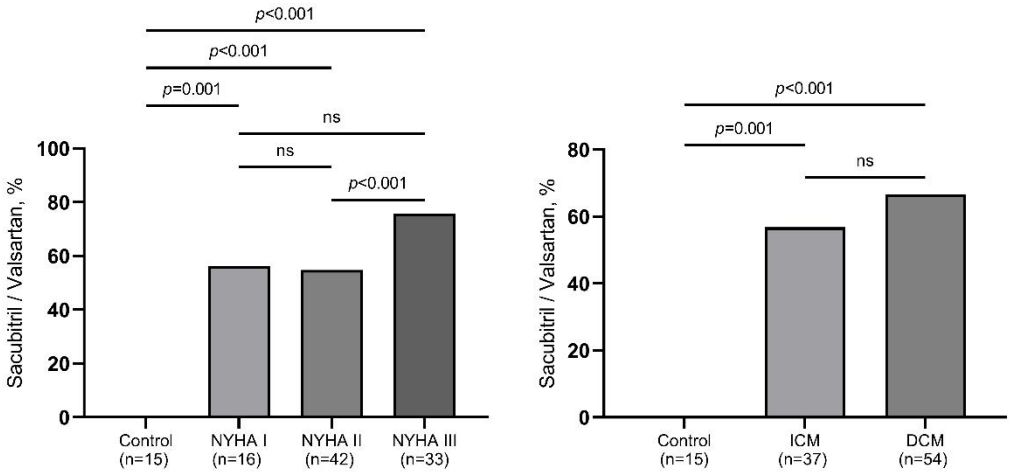

Figure 3.1.5. Comparisons of sacubitril/valsartan in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

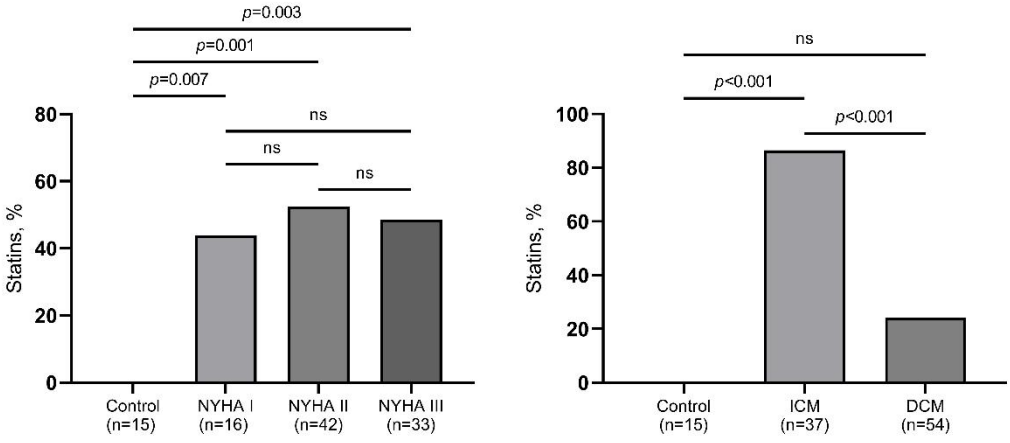

Figure 3.1.6. Comparisons of statins in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

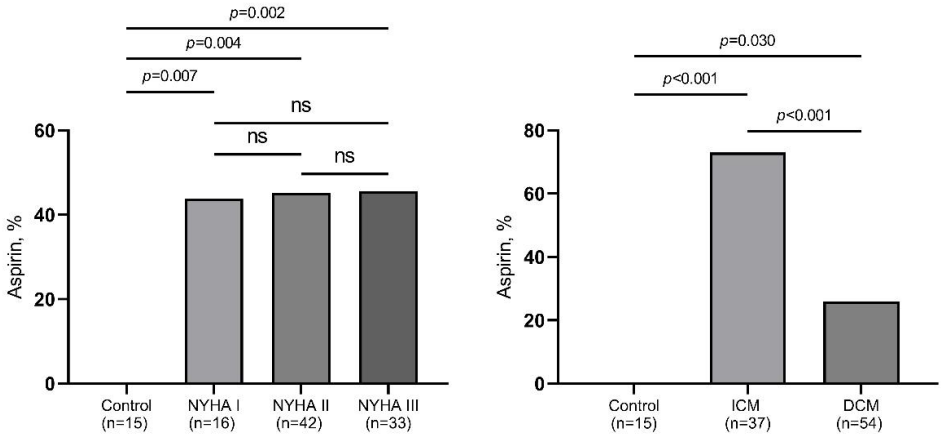

Figure 3.1.7. Comparisons of aspirin in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

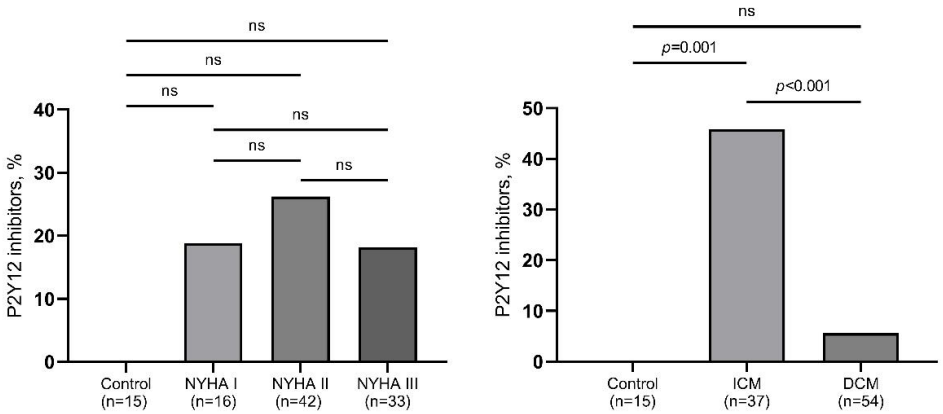

Figure 3.1.8. Comparisons of P2Y12 inhibitors in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

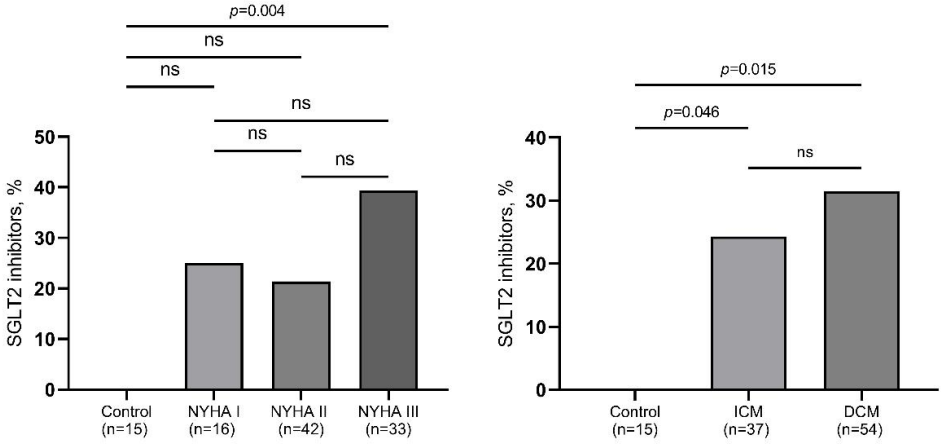

Figure 3.1.9. Comparisons of Sodium-glucose cotransporter-2 inhibitors in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

3.2 Six-min walk distance

A total of 64 participants were involved in this part (healthy controls: n=12, patients with CHF: n=52). Patients with CHF were classified into the two categories based on NYHA classification, including NYHA I to III (NYHA I: n=15, NYHA II: n=21, NYHA III: n=16), and myocardiopathies, including ICM and DCM (ICM: n=18, DCM: n=34).

Table 3.2.1 displays the 6MWD, SBP, DBP, HR, and Borg scale 6-20 score of healthy controls and patients with CHF in the two categories. Table 3.2.2 shows SBP, DBP, and HR before and after 6MWT in the control group and each CHF group in the two categories. As illustrated in Figure 3.2.1 to Figure 3.2.14, the variables with significant differences among the control group and CHF groups were presented using bar graphs for normally distributed variables and box plots for non-normally distributed variables.

Table 3.2.1. 6MWD, systolic blood pressure, diastolic blood pressure, heart rate and Borg scale 6-20 score of healthy controls and patients with CHF being categorized into NYHA classes I to III groups and ICM and DCM groups.

	The control group n=12	CHF group n=52	NYHA I n=15	NYHA II n=21	NYHA III n=16	ICM group n=18	DCM group n=34	P value [a]
6MWD, m	614.42 ± 38.38	513 (441.25-560 [160-715])	566.73 ± 71.13	482.19 ± 89.38	428.81 ± 137.91	440.83 ± 160.38	516.26 ± 69.88	<0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, 0.009 (0.005-0.010) between NYHA I group and NYHA II group, 0.003 (0.002-0.005) between NYHA I group and NYHA III group, 0.002 (0.001-0.003) between the control group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]
SBP before 6MWT, mmHg	140 (126.25-149.75 [112-155])	112.50 (106.25-122 [90-165])	109 (105-114 [99-155])	118 (105.50-122 [90-130])	112 (107.50-137.50 [93-165])	109.50 (100.50-121.75 [90-165])	113 (107.75-122 [92-155])	<0.001 (<0.001) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, 0.020 (0.017-0.024) between the control group and NYHA III group, 0.001 (<0.001-0.001) between the

								control group and ICM group, 0.001 (<0.001-0.001) between the control group and DCM group[1]
SBP after 6MWT, mmHg	154.50 (134-172 [106-177])	128 (117-141.25 [99-213])	128 (116-139 [111-213])	129 (119.50-145.50 [102-157])	120 (116.25-136 [99-163])	123 (115-144 [102-163])	128.50 (117-140.50 [99-213])	0.028 (0.025-0.034) between the control group and NYHA I group, 0.005 (0.003-0.007) between the control group and NYHA II group, 0.007 (0.006-0.011) between the control group and NYHA III group, 0.011 (0.006-0.012) between the control group and ICM group, 0.004 (0.002-0.006) between the control group and DCM group[1]
DBP before 6MWT, mmHg	91.17 ± 10.31	72.10 ± 13.18	72.07 ± 7.70	73.62 ± 12.93	70.13 ± 17.47	69.78 ± 15.40	73.32 ± 11.91	<0.001 (<0.001) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, <0.001 (<0.001) between the control group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]
DBP after 6MWT, mmHg	93.75 ± 10.25	80.56 ± 12.16	80.47 ± 10.64	82.43 ± 10.93	78.19 ± 15.05	80.78 ± 15.90	80.44 ± 9.90	0.004 (0.003-0.006) between the control group and NYHA I group, 0.008 (0.006-0.010) between the control group and NYHA II group, 0.001 (<0.001-0.002) between the control group and NYHA III group, 0.010 (0.009-0.014) between the control group and ICM group, 0.001 (<0.001-0.001) between the control group and DCM group[1]
HR before 6MWT, bpm	68 (61-71.75 [50- 95])	70 (60.25-79 [46-123])	70 (60-80 [51-91])	70 (61-79.5 [54-123])	70 (61-78.75 [46-102])	70 (60-79.25 [51-102])	70 (60.75-79.25 [46-123])	ns[1]
HR after 6MWT, bpm	89.50 ± 10.83	85.41 ±16.66	85.20 ± 14.55	85.10 ± 18.56	86 ± 17.06	86.39 ± 18.04	84.88 ± 16.12	ns[1]
Borg scale 6-20	9.67 ± 3.06	12.13 ±2.54	11 (8- 12 [7- 13])	13 (11.50-14.50	13 (12.25-14.75 [9-16])	12.22 ± 3.56	12.09 ± 1.85	0.011 (0.008-0.014) between the control group and NYHA II group, 0.004 (0.002-0.004) between the

				[6-18])				control group and NYHA III group, 0.006 (0.003-0.007) between NYHA I group and NYHA II group, 0.001 (<0.001-0.001) between NYHA I group and NYHA III group, 0.015 (0.013-0.016) between the control group and DCM group[1]

Continuous variables with normal distribution are expressed as mean ± standard deviation and non-normally distributed variables as median (IQR [range]).
6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association functional classification; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; ns, not significant.
[a] Monte Carlo was jointly used to specify the 99% CI for the obtained P values when comparing the continuous variables and one of the sample sizes of the variables was less than 30.
[1] Kruskal-Wallis Test was used to compare continuous variables, and a Mann-Whitney U Test was used for post-hoc multiple comparisons.

Table 3.2.2. Systolic blood pressure, diastolic blood pressure, and heart rate before and after 6MWT of healthy controls and patients with CHF being categorized into NYHA classes I to III groups and ICM and DCM groups.

	before 6MWT	**after 6MWT**	**P value [a]**
SBP-The control group, n=12	140 (126.25-149.75 [112-155])	154.50 (134-172 [106-177])	0.008 (0.003-0.009)[1]
SBP-NYHA I, n=15	109 (105-114 [99-155])	128 (116-139 [111-213])	0.001 (<0.001-0.001)[1]
SBP-NYHA II, n=21	118 (105.50-122 [90-130])	129 (119.50-145.50 [102-157])	<0.001 (<0.001-0.001)[1]
SBP-NYHA III, n=16	112 (107.50-137.50 [93-165])	120 (116.25-136 [99-163])	ns [1]
SBP-ICM, n=18	109.50 (100.50-121.75 [90-165])	123 (115-144 [102-163])	<0.001 (<0.001-0.001)[1]
SBP-DCM, n=34	113 (107.75-122 [92-155])	128.5 (117-140.50 [99-213])	<0.001[1]
DBP-The control group, n=12	91.17 ± 10.31	93.75 ± 10.25	ns [1]
DBP-NYHA I, n=15	72.07 ± 7.70	80.47 ± 10.64	0.004 (0.001-0.006)[1]
DBP-NYHA II, n=21	73.62 ± 12.93	82.43 ± 10.93	0.006 (0.003-0.007)[1]
DBP-NYHA III, n=16	70.13 ± 17.47	78.19 ± 15.05	0.030 (0.023-0.035)[1]
DBP-ICM, n=18	69.78 ± 15.40	80.78 ± 15.90	0.001 (<0.001-0.001)[1]
DBP-DCM, n=34	73.32 ± 11.91	80.44 ± 9.90	0.003[2]
HR-The control group, n=12	68 (61-71.75 [50-95])	92 (77-98 [75-106])	0.002 (0.001-0.003)[1]
HR-NYHA I, n=15	70 (60-80 [51-91])	87 (74-96 [60-108])	0.001 (<0.001-0.001)[1]
HR-NYHA II, n=21	70 (61-79.50 [54-123])	85.5 (70.75-96.25 [55-133])	0.002 (0.001-0.003)[1]
HR-NYHA III, n=16	70 (61-78.75 [46-102])	87 (68.75-99.75 [63-114])	0.007 (0.004-0.010)[1]
HR-ICM, n=18	70 (60-79.25 [51-102])	84.5 (72.75-97.75 [60-133])	<0.001 (<0.001-0.001)[1]

HR-DCM, n=34	70 (60.75-79.25 [46-123])	89 (68.50-96.50 [55-113])	<0.001[1]

Continuous variables with normal distribution are expressed as mean ± standard deviation and non-normally distributed variables as median (IQR [range]).
6MWT, 6-minute walk test; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association functional classification, ns, not significant; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy.
[a] Monte Carlo was jointly used to specify the 99% CI for the obtained P values when comparing the continuous variables and one of the sample sizes of the variables was less than 30.
[1] Wilcoxon-signed Ranks Test was used to compare groups when the sample size was less than 30 or not normally distributed.
[2] Paired t-test was used to compare groups when the sample size was 30 or more than 30 and normally distributed.

When comparing the 6MWD of the control group with different CHF groups, as shown in Figure 3.2.1, there were no significant differences in 6MWD between the control group and NYHA class I group, and between NYHA class II and III groups. However, the 6MWD of the control group was significantly longer than that of NYHA II and III groups (both p<0.001), and the 6MWD of NYHA I group was significantly longer than that of NYHA II and III groups (p=0.007 and p=0.003, respectively). The 6MWD of the control group was significantly longer than that of ICM and DCM groups (p=0.002 and p<0.001, respectively), while there was no significant difference in 6MWD between ICM and DCM groups.

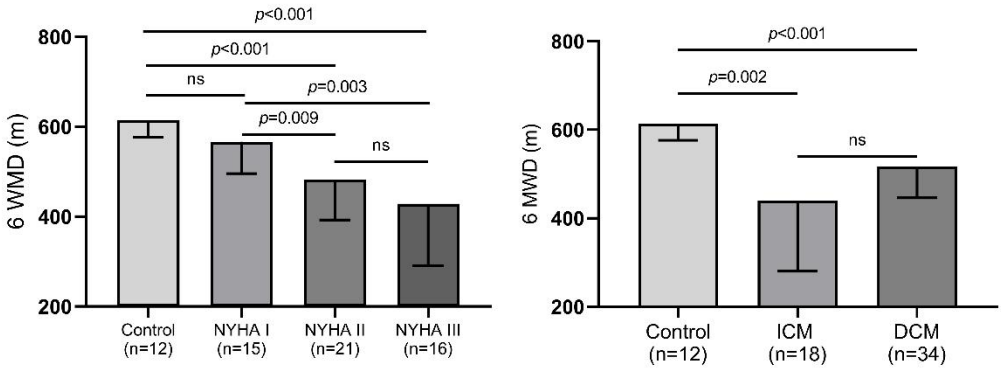

Figure 3.2.1. 6MWD of the control group and NYHA class I to III groups and of the control group and ICM and DCM groups.

For Borg scale 6-20 score after 6MWT, Figure 3.2.2 presented the opposite trends compared to the trends of 6MWD among these four groups. There were also no significant differences between the control group and NYHA class I group, and between NYHA class II and III groups. However, the Borg scale 6-20 score of the control group was significantly lower than that of NYHA II and III groups (p=0.011 and p=0.004, respectively), and the Borg scale 6-20 score of NYHA I group was significantly lower than that of NYHA II and III groups (p=0.006 and p=0.001, respectively). The Borg scale

6-20 score of the control group was significantly lower than that of DCM group (p=0.015).

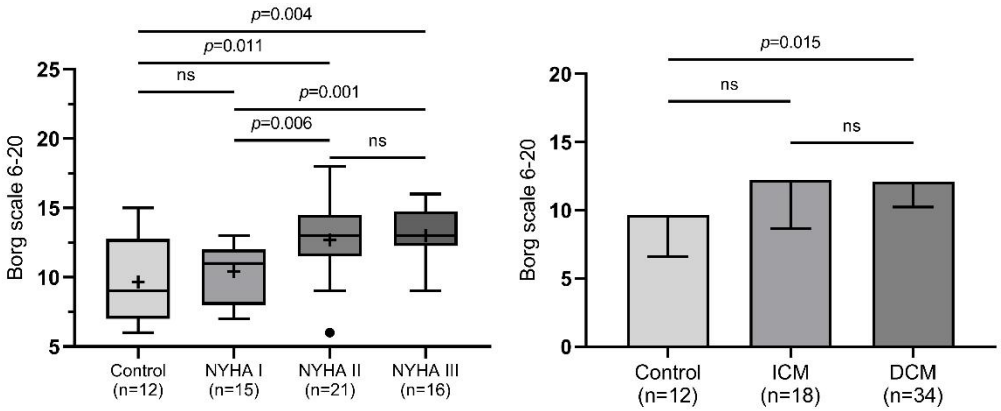

Figure 3.2.2. Borg scale 6-20 score after 6MWT of the control group and NYHA class I to III groups and of the control group and ICM and DCM groups.

When comparing SBP, DBP, and HR of the control group and NYHA class I to III groups and ICM and DCM groups before and after 6MWT, as shown in Figure 3.2.3 to Figure 3.2.8, significant differences in SBP and DBP were found among the control group and different CHF groups. The SBP of the control group before 6MWT was significantly higher than that of NYHA I to III groups ($p<0.001$, $p<0.001$, and $p=0.020$, respectively) and ICM and DCM groups (both $p=0.001$). Additionally, the SBP of the control group after 6MWT was also significantly higher than that of NYHA I to III groups ($p=0.028$, $p=0.015$, and $p=0.007$, respectively) and ICM and DCM groups ($p=0.011$ and $p=0.004$, respectively).

Regarding DBP, the trends were almost the same as those of SBP, wherein the DBP of the control group before 6MWT was significantly higher than that of NYHA I to III groups (all $p<0.001$) and ICM and DCM groups (both $p<0.001$). Moreover, the DBP of the control group after 6MWT was significantly higher than that of NYHA I to III groups ($p=0.004$, $p=0.008$ and $p=0.001$, respectively) and ICM and DCM groups ($p=0.010$ and $p=0.001$, respectively). However, no obvious differences in both SBP and DBP were observed among CHF groups, and no apparent differences in HR were found among the control group and CHF groups.

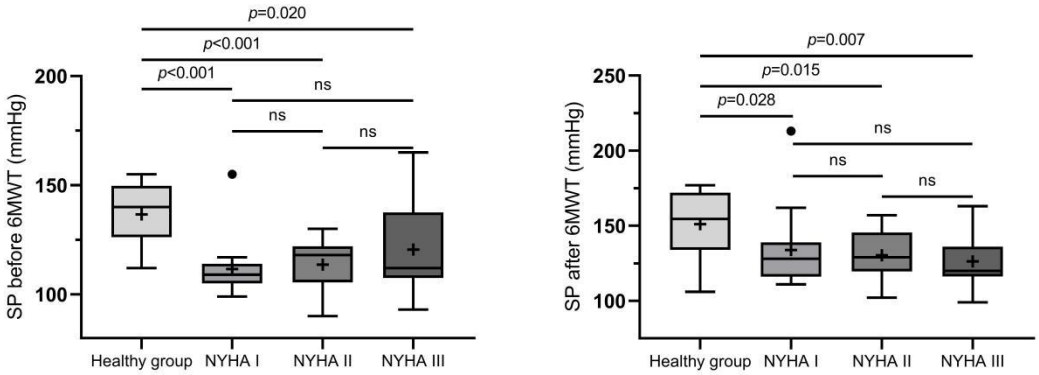

Figure 3.2.3. Systolic blood pressure of the control group and NYHA class I to III groups before and after 6MWT.

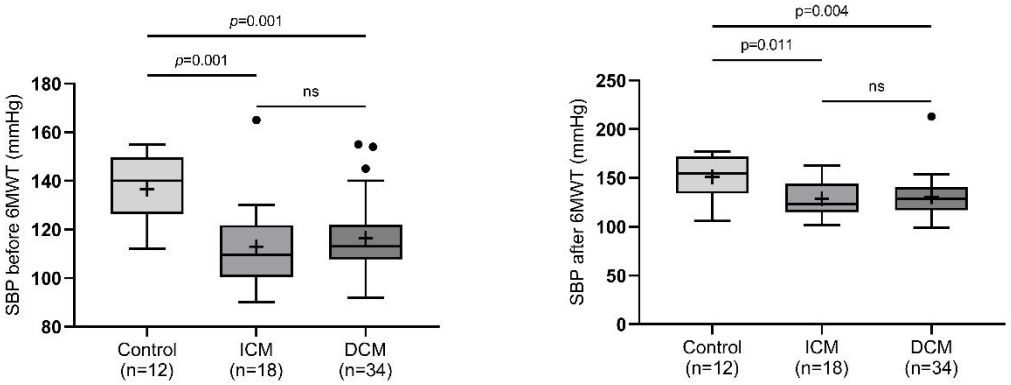

Figure 3.2.4. Systolic blood pressure of the control group and ICM and DCM groups before and after 6MWT.

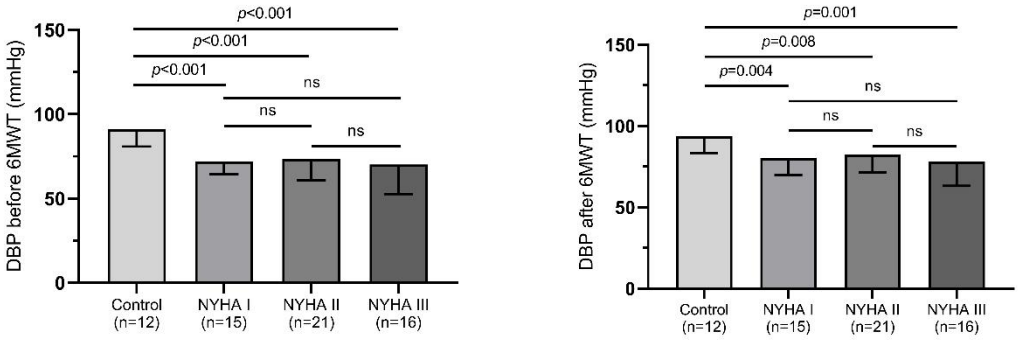

Figure 3.2.5. Diastolic blood pressure of the control group and NYHA class I to III groups before and after 6MWT.

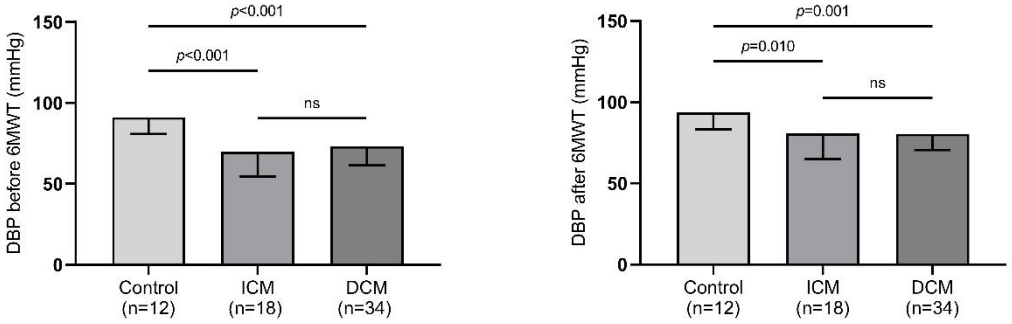

Figure 3.2.6. Diastolic blood pressure of the control group and ICM and DCM groups before and after 6MWT.

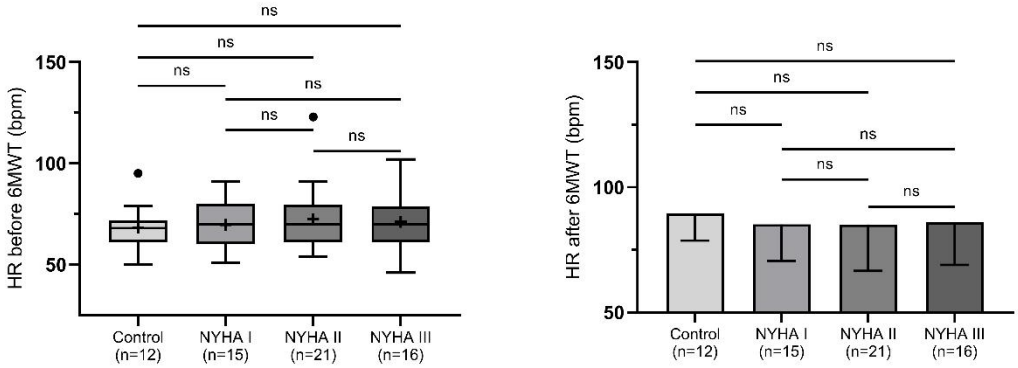

Figure 3.2.7. Heart rate of the control group and NYHA class I to III groups before and after 6MWT.

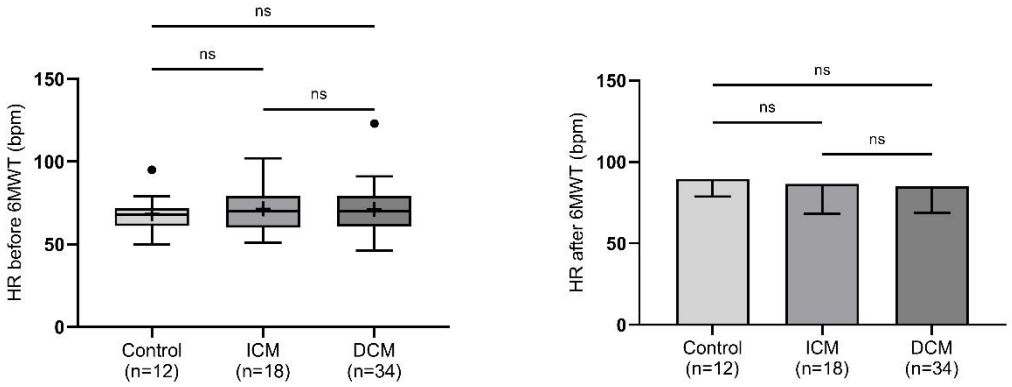

Figure 3.2.8. Heart rate of the control group and ICM and DCM groups before and after 6MWT.

From Figures 3.2.9 to 3.2.14, we can observe the differences in SBP, DBP, and HR for each group before and after the 6MWT. The SBP after 6MWT in the control group, NYHA I and II groups, and ICM and DCM groups were significantly higher than the SBP before 6MWT in each corresponding group (p=0.008, p=0.001, p<0.001, p<0.001, and

p<0.001, respectively). However, no obvious difference of SBP in NYHA III group was observed before and after 6MWT. The DBP after 6MWT in NYHA I to III groups and ICM and DCM groups were significantly higher than the DBP before 6MWT in each corresponding group (p=0.004, p=0.006, p=0.030, p=0.001, and p=0.003, respectively) and no apparent difference was observed in the control group. Regarding HR, it was significantly higher after the 6MWT in the control group, NYHA I to III groups, and ICM and DCM groups compared to the HR before 6MWT in each corresponding group (p=0.002, p=0.001, p=0.002, p=0.007, P<0.001, and P<0.001, respectively).

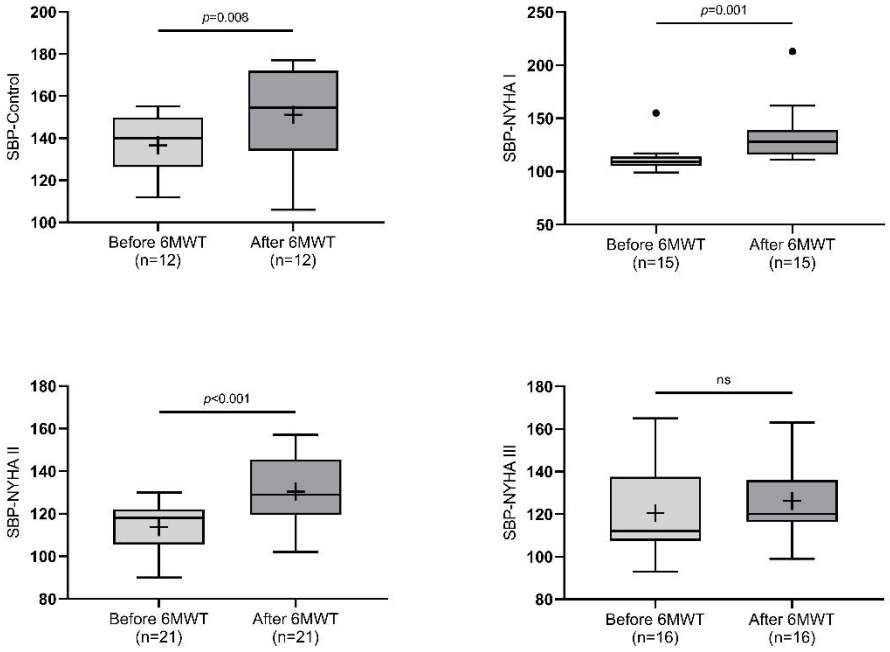

Figure 3.2.9. Systolic blood pressure before and after 6MWT in the control group and NYHA class I to III groups.

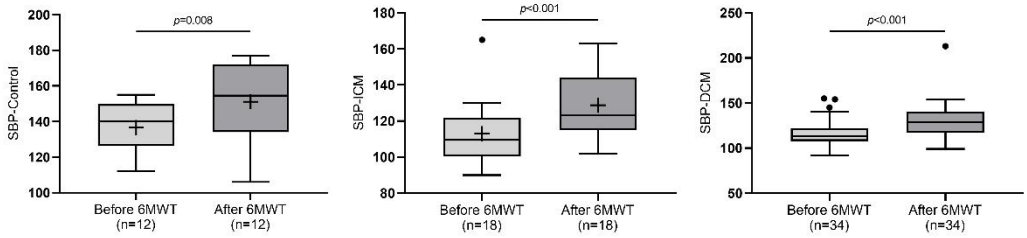

Figure 3.2.10. Systolic blood pressure before and after 6MWT in the control group and ICM and DCM groups.

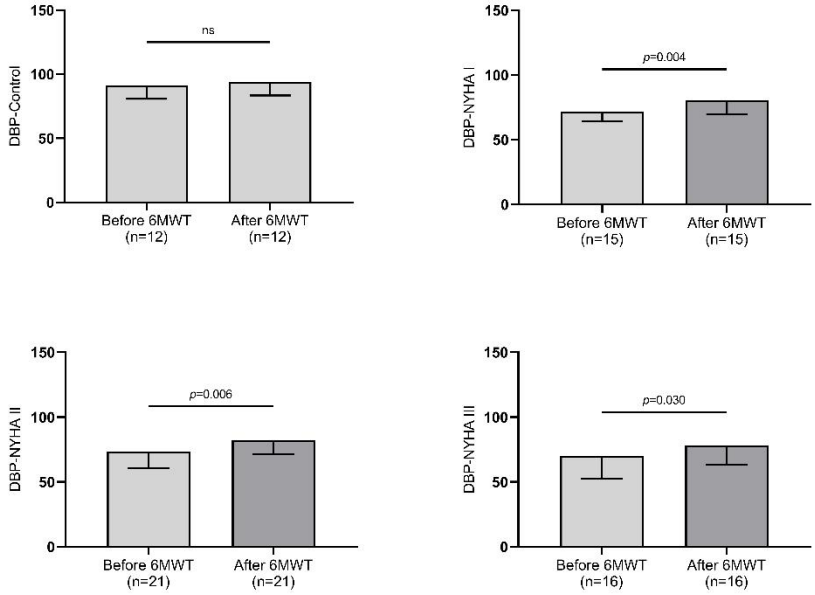

Figure 3.2.11. Diastolic blood pressure before and after 6MWT in the control group and NYHA class I to III groups.

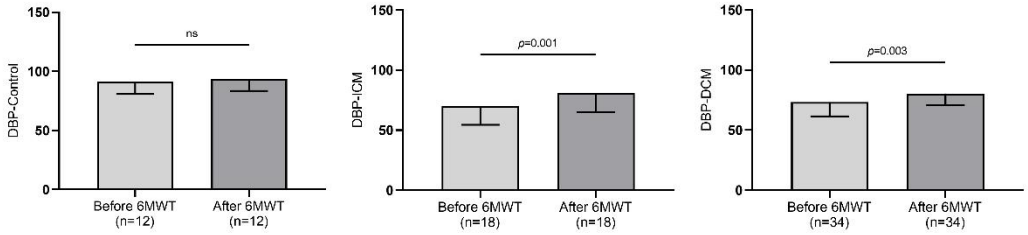

Figure 3.2.12. Diastolic blood pressure before and after 6MWT in the control group and ICM group and DCM group.

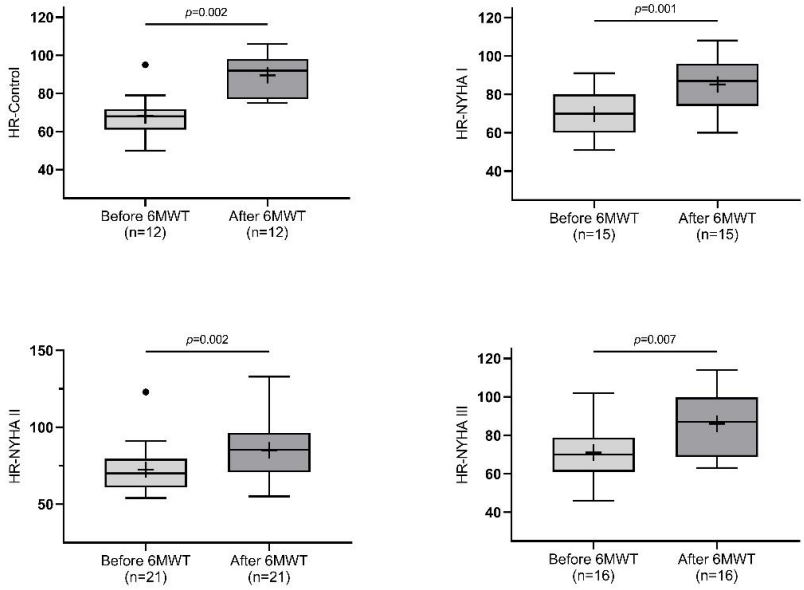

Figure 3.2.13. Heart rate before and after 6MWT in the control group and NYHA class I to III groups.

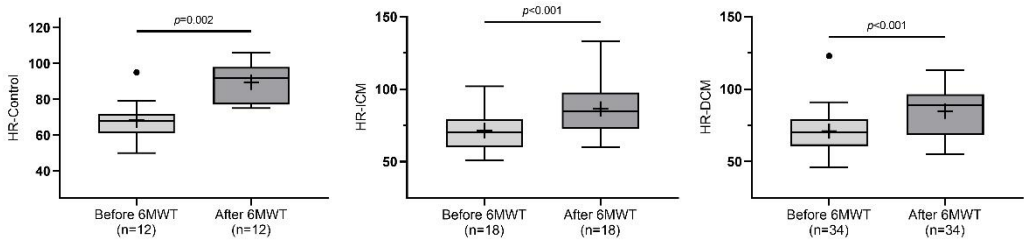

Figure 3.2.14. Heart rate before and after 6MWT in the control group and ICM group and DCM group.

As shown in Figure 3.2.15, the ROC analysis of 6MWD revealed that the AUC of 6MWD for predicting participants with limited exercise capacity was 0.850 (p<0.001, 95%CI: 0.758-0.942). The sensitivity and specificity were 0.811 and 0.741, respectively, using the optimal threshold of 6MWD for predicting participants with limited exercise capacity of 544.50 m.

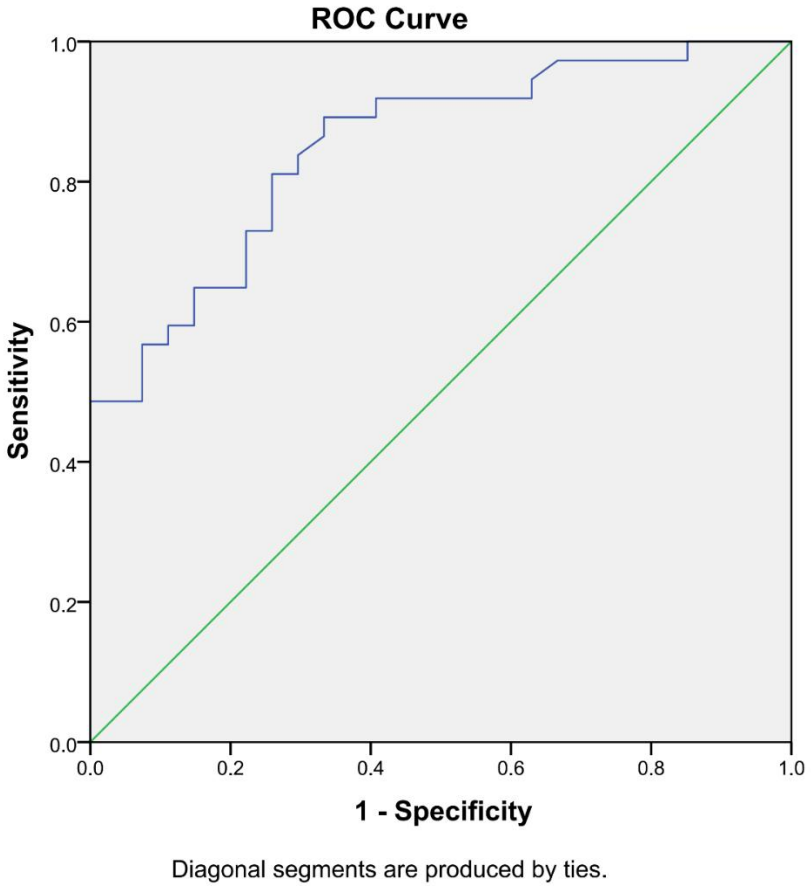

Figure 3.2.15. ROC curve of 6MWD. The area under the ROC Curve of 6MWD for predicting participants with a limitation of exercise capacity was 0.850 (p<0.001, 95%CI:

0.758-0.942), and the sensitivity and specificity were 0.811 and 0.741, respectively. The optimal threshold of 6MWD for predicting participants with a limitation of exercise capacity was 544.50 m.

3.3 Laboratory tests

This part included 88 participants (healthy controls: n=14, patients with CHF: n=74). Patients with CHF were classified into the two categories based on the NYHA classification, including NYHA I to III (NYHA I: n=16, NYHA II: n=33, NYHA III: n=25), and the myocardiopathies, including ICM and DCM (ICM: n=24, DCM: n=50).

Table 3.3.1 displays the blood and urine parameters of healthy controls and patients with CHF. As illustrated in Figure 3.3.1 to Figure 3.3.36, in order to visualize the differences in these parameters more clearly, the parameters with significant differences when comparing the control group with different NYHA class groups or comparing the control group with ICM and DCM groups were presented using bar graphs for the variables with normal distribution and box plots for the variables were non-normally distributed.

Table 3.3.1 The blood and urine parameters of healthy controls and patients with CHF being categorized into NYHA classes I to III groups and ICM and DCM groups.

	The control group n=14	**CHF group n=74**	**NYHA I n=16**	**NYHA II n=33**	**NYHA III n=25**	**ICM n=24**	**DCM n=50**	**P value[a]**
Hemoglobin, g/dl	14.90 (14.05 - 15.93 [13.30 - 16.90])	14.60 (13 - 15.35 [3.90 - 17.70])	14.60 (13.6- 15.85 [12.80- 16.60])	14.90 (14.50 - 16 [6.90 - 17.70])	13 (11.75 - 14.50 [3.90- 17.50])	14.65 (12.58 - 15.15 [9.70 - 17.60])	14.55 (13.23 - 15.43 [3.90 - 17.70])	0.002 (<0.001-0.002) between the control group and NYHA III group, 0.004 (0.001-0.004) between NYHA I group and NYHA III group, <0.001 (<0.001) between NYHA II group and NYHA III group[1]
Hematocrit, l/l	0.44 (0.41 - 0.46 [0.40 - 0.49])	0.43 (0.39 - 0.45 [0.13 - 0.52])	0.43 (0.41 - 0.45 [0.37 - 0.50])	0.45 (0.42 - 0.47 [0.20 - 0.52])	0.39 (0.37 - 0.41 [0.19 - 0.50])	0.43 (0.37- 0.46 [0.32 - 0.52])	0.42 (0.39 - 0.45 [0.13 - 0.52])	0.001 (<0.001-0.001) between the control group and NYHA III group, 0.004 (0.002-0.005) between NYHA I

								group and NYHA III group, <0.001 (<0.001) between NYHA II group and NYHA III group[1]
Erythrocytes, pl	5.10 (4.80 - 5.38 [4.70 - 5.60])	4.70 (4.40 - 5 [1.40 - 6.40])	4.70 (4.53 - 5.15 [4.10 - 6])	4.90 (4.70 - 5.20 [2.30 - 6.40])	4.50 (4.20 - 4.75 [1.40 - 5.70])	4.80 (4.28-5.05 [3.30 - 5.70])	4.70 (4.40 - 5 [1.40 - 6.40])	0.050 (0.043-0.054) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA III group, 0.005 (0.003-0.007) between the control group and DCM group[1]
Leukocytes, nl	5.93 (5.34 - 6.77 [4.50 - 7.42])	7.12 (5.89 - 7.83 [4.17 - 14.90])	6.47 (5.74 - 7.25 [4.17 -10.49])	6.93 (5.49 - 8.12 [4.40-12.43])	7.43 (6.53 - 7.97 [5.02 -14.90])	7.18 (6.13-8.27 [4.40-11.08])	7.07 (5.82 - 7.74 [4.17 - 14.90])	0.001 (<0.001-0.001) between the control group and NYHA III group, 0.017 (0.012-0.018) between NYHA I group and NYHA III group, 0.003 (0.002-0.004) between NYHA II group and NYHA III group, 0.015 (0.011-0.016) between the control group and ICM group, 0.024 (0.019-0.027) between the control group and DCM group[1]
Thrombocytes, nl	251.50 (236.75 - 271.25 [173- 320])	227 (200.25 - 266.25 [56 - 469])	213 (178.25-239.50 [162-286])	235 (201 - 267 [119 - 469])	228 (205.50 - 296 [56 - 429])	209.50 (190 - 259.25 [117 - 429])	233.50 (203.75 - 280.75 [56 - 469])	0.133 (0.127-0.140)[1]
MCV, fl	85.75 ± 2.16	89.46 ± 5.31	89.94 ± 5.61	90.08 ± 4.19	88.42 ± 6.33	88.15 (86-92.85	89.10 (86 - 92.55	0.031 (0.027-0.036) between the control

						[69.80-97])	[80.50-100. 80])	group and NYHA I group, <0.001 (<0.001-0.001) between the control group and NYHA II group, 0.033 (0.027-0.036) between the control group and NYHA III group, 0.023 (0.019-0.027) between the control group and ICM group, 0.001 (<0.001-0.002) between the control group and DCM group[1]
MCH, pg	28.90 (28.28 - 30.43 [27.70 - 30.80])	30.50 (29.23 - 31.55 [21.40 - 34])	30.30 (29.35 - 32.30 [27.60 - 33.50])	30.80 (30- 31.70 [27.10 - 34])	30.40 (28.35 - 31.15 [21.40 - 32.50])	30.25 (28.58 - 31.83 [21.40 - 32.60])	30.50 (29.73 - 31.45 [25.10 - 34])	0.029 (0.024-0.032) between the control group and NYHA I group, 0.003 (0.001-0.003) between the control group and NYHA II group, 0.005 (0.003-0.006) between the control group and DCM group [1]
MCHC, g/dl	34.09 ± 0.98	33.82 ± 1.29	34.12 ± 1.28	34.01 ± 0.96	33.40 ± 1.56	33.72 ± 1.38	33.87 ± 1.26	ns[1]
MPV, fl	10.50 (9.78- 11.23 [8.60- 12.30])	10.80 (10.10- 11.68 [8.50- 15.60])	10.95 (10.20 - 11.80 [9.60- 14])	10.60 (10- 11.60 [8.90 - 12.60])	11 (10.65 - 11.70 [8.50- 15.60])	10.90 (10.25 - 11.83 [9.60 - 14])	10.80 (10 - 11.60 [8.50- 15.60])	ns[1]
RDW-CV, %	12.50 (12.13 - 12.83 [11.60 - 13.60])	13.30 (12.73- 14.35 [11.60- 18.10])	13.05 (12.70- 13.38 [12.20- 14.20])	13.30 (12.70 - 14.60 [11.70 - 16.90])	13.80 (12.95 - 15.50 [11.60 - 18.10])	13.80 (12.78 - 15.03 [12.20 - 17.60])	13.30 (12.70 - 14.10 [11.60 - 18.10])	0.010 (0.006-0.011) between the control group and NYHA I group, 0.001 (<0.001-0.001) between the control group and NYHA II group,

								<0.001 (<0.001-0.001) between the control group and NYHA III group, 0.027 (0.023-0.032) between NYHA I group and NYHA III group, 0.001 (<0.001-0.001) between the control group and ICM group, <0.001 (<0.001-0.001) between the control group and DCM group[1]
Neutrophils, nl	3.11 ± 0.63	4.52 ± 1.47	4.13 ± 1.08	4.49 ± 1.79	4.84 ± 1.28	4.52 (3.37-5.42 [2.39-8.40])	4.23 (3.34-5.17 [2.35-8.27])	0.003 (0.002-0.007) between the control group and NYHA I group, 0.010 (0.006-0.011) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, 0.001 (<0.001) between the control group and ICM group, 0.001 (<0.001-0.002) between the control group and DCM group[1]
Immature granulocytes, nl	0.02 (0.01-0.02 [0.01-0.03])	0.03 (0.01 - 0.03 [0.01 - 0.19])	0.02 (0.01-0.03 [0.01-0.06])	0.03 (0.01 - 0.04 [0.01 - 0.19])	0.03 (0.02 - 0.03 [0.01-0.13])	0.03 (0.02-0.04 [0.01 - 0.19])	0.02 (0.01-0.03 [0.01-0.13])	0.007 (0.004-0.008) between the control group and ICM group, 0.045 (0.040-0.050) between The control group and DCM group[1]
Immature granulocytes, %	0.30 (0.20-0.30 [0.20-0.60])	0.40 (0.20 - 0.50	0.30 (0.20-0.48 [0.20-0.70])	0.40 (0.20 - 0.53	0.35 (0.30 - 0.48 [0.10-1.70])	0.40 (0.30-0.50 [0.20-2.70])	0.40 (0.20-0.55 [0.10-1.70])	ns[1]

		[0.10 - 2.70]		[0.10 - 2.70])				
Lymphocytes, nl	2.08 ± 0.49	1.71 ± 0.64	1.61 ± 0.51	1.86 ± 0.72	1.60 ± 0.62	1.64 ± 0.66	1.74 ± 0.64	ns[1]
Monocytes, nl	0.46 (0.38-0.56 [0.33-0.70])	0.59 (0.49 - 0.68 [0.25-1.28])	0.60 (0.44-0.68 [0.25-0.83])	0.57 (0.47-0.65 [0.34-0.89])	0.62 (0.54-0.68 [0.37-1.28])	0.63 (0.48-0.71 [0.32-1.28])	0.59 (0.49-0.68 [0.25-0.90])	0.034 (0.033-0.043) between the control group and NYHA II group, 0.005 (0.003-0.006) between the control group and NYHA III group, 0.018 (0.015-0.020) between the control group and ICM group, 0.017 (0.014-0.021) between The control group and DCM group[1]
Eosinophils, nl	0.17 (0.09-0.34 [0.05-0.71])	0.11 (0.07-0.22 [0.02-0.72])	0.11 (0.06-0.19 [0.04-0.39])	0.09 (0.07-0.19 [0.02-0.72])	0.20 (0.09-0.32 [0.02-0.68])	0.13 (0.09-0.26 [0.04-0.45])	0.10 (0.07-0.21 [0.02-0.72])	ns[1]
Basophils, nl	0.05 (0.03-0.07 [0.03-0.1])	0.04 (0.03-0.06 [0.01-0.14])	0.03 (0.02-0.07 [0.01-0.08])	0.04 (0.03-0.05 [0.01-0.09])	0.04 (0.03-0.07 [0.02-0.14])	0.05 (0.03-0.07 [0.02-0.14])	0.03 (0.03-0.05 [0.01-0.09])	ns[1]
Neutrophils, %	52.39 ± 6.06	63.28 ± 8.73	63.20 (56.95- 68 [51.90-76.20])	62.60 (53.50-68.33 [43.40-78.60])	65.50 (58.85-70.80 [51.80-87.10])	64.35 ± 9.16	62.74 ± 8.57	<0.001 (<0.001) between the control group and NYHA I group, 0.004 (0.003-0.006) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, <0.001 (<0.001-0.001) between the control

								group and ICM group, <0.001 (<0.001-0.001) between The control group and DCM group[1]
Lymphocytes, %	33.70 ± 6.26	24.49 ± 7.76	24.81 ± 5.72	26.62 ± 8.55	21.64 ± 7.44	23.19 ± 8.59	25.11 ± 7.36	(<0.001-0.002) between the control group and NYHA I group, 0.002 (0.001-0.004) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, <0.001 (<0.001-0.001) between the control group and ICM group, <0.001 (<0.001-0.001) between the control group and DCM group[1]
Monocytes,%	8.07 ± 1.54	8.61 ± 2.39	8.95 (6.78-10.05 [5.10-13.80])	8.90 (6.40-9.80 [4.20-15.20])	8.40 (6.93-9.88 [3.60-13.30])	8.85 ± 2.70	8.50 ± 2.25	ns[1]
Eosinophils, %	2.80 (1.40-4.20 [0.80-7.10])	1.70 (1-2.90 [0.30-13.50])	1.70 (1.03-2.95 [0.60-5.70])	1.60 (1-2.70 [0.30-8.80])	2.15 (1.20-4.08 [0.30-13.50])	1.80 (1.15-2.95 [0.60-6.90])	1.70 (0.93-2.95 [0.30-13.50])	ns[1]
Basophils, %	0.90 (0.55-1.20 [0.40-1.60])	0.50 (0.40-0.80 [0-1.30])	0.50 (0.40-0.95 [0.20-1.30])	0.60 (0.40-0.70 [0-1.20])	0.55 (0.40-1 [0.30-1.30])	0.60 (0.45-1.05 [0.30-1.30])	0.50 (0.40-0.78 [0-1.20])	0.018 (0.013-0.020) between the control group and NYHA I group, 0.009 (0.005-0.010) between the control group and NYHA II group, 0.050 (0.047-0.059) between the control

								group and NYHA III group, 0.002 (<0.001-0.002) between the control group and DCM group[1]
I/T quotient	0.005 (0.004-0.006 [0.003-0.01])	0.006 (0.004-0.008 0.002-0.039))[	0.005 (0.003-0.007 [0.003-0.013])	0.007 (0.004-0.008 [0.002-0.039])	0.0055 (0.004-0.007 [0.002-0.024])	0.006 (0.005-0.007 [0.003-0.039])	0.006 (0.004-0.008 [0.002-0.024])	ns[1]
NLR	1.41 (1.25-1.78 [0.96-3.41])	2.50 (2-3.54 [0.96-20.39])	2.50 (2.02-3.39 [1.59-5.01])	2.46 (1.63-3.38 [0.96-8.04])	2.71 (2.17-3.99 [1.45-20.39])	3.38 (1.95-4.09 [0.99-8.04])	2.46 (2.01-3.30 [0.96-20.39])	<0.001 (<0.001-0.001) between the control group and NYHA I group, 0.003 (0.001-0.004) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, <0.001 (<0.001-0.001) between the control group and ICM group, <0.001 (<0.001) between The control group and DCM group[1]
RLC	35.23 ± 6.70	24.64 ± 7.91	24.822 ± 5.73	26.89 ± 8.78	21.73 ± 7.59	23.19 ± 8.59	25.37 ± 7.55	<0.001 (<0.001-0.001) between the control group and NYHA I group, 0.001 (<0.001-0.002) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, <0.001 (<0.001) between the control

								group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]
Glucose, mg/dl	85 (83- 89.25 [74- 100])	97 (88- 114.75 [74- 256])	95 (83.75- 106.25 [78- 162])	99.5 (92- 118.50 [76- 193])	95.50 (88- 117 [74- 256])	103 (92- 117 [82- 193])	97 (87- 114 [74- 256])	<0.001 (<0.001-0.001) between the control group and NYHA II group, 0.003 (0.001-0.004) between the control group and NYHA III group, <0.001 (<0.001-0.001) between the control group and ICM group, 0.002 (0.001-0.002) between the control group and DCM group[1]
Creatinine, mg/dl	0.97 (0.86- 1.05 [0.73- 1.11])	0.97 (0.88- 1.14 [0.58- 4.97])	0.96 (0.86- 0.99 [0.64- 1.08])	1.02 (0.89- 1.21 [0.58- 1.87])	0.95 (0.86- 1.38 [0.62- 4.97])	0.91 (0.86- 1.17 [0.62- 1.65])	0.99 (0.88- 1.12 [0.58- 4.97])	ns)[1]
eGFR, ml/min/1.73 m^2	89 (82.25- 91 [69- 91])	83 (61.50- 91 [14- 91])	89.50 (83.50- 91 [70- 91])	75.50 (58.75- 91 [41- 91])	71 (53- 91 [14- 91])	84 (58-91 [41-91])	78.50 (62.75- 91 [14- 91])	0.039 (0.035-0.045) between the control group and NYHA II group, 0.043 (0.037-0.048) between the control group and NYHA III group, 0.020 (0.015-0.022) between NYHA I group and NYHA II group, 0.023 (0.021-0.029) between NYHA I group and NYHA III group[1]
Urea, mg/dl	28 (24- 31.75 [17- 40])	34 (27- 41.10 [15- 147])	31 (26.25- 36.50 [18- 38])	35.50 (28.25- 44.50	33 (25.50- 46 [16- 147])	35 (24- 48 [17- 70])	33 (27-40 [15-147])	ns[1]

				[15-70])				
Uric acid, mg/dl	4.95 (4.58-5.70 [4-7.50])	6 (4.80-7.48 [3.10-10.90])	5.40 (5.20-6.68 [4.80-9.30])	6.30 (4.80-7.93 [3.10-9.10])	5.30 (4.13-7.25 [3.90-10.90])	6.60 (5.40-8.10 [4.10-10.60])	5.30 (4.60-7.20 [3.10-10.90])	0.016 (0.011-0.017) between the control group and ICM group[1]
Total bilirubin, mg/dl	0.63 (0.39-0.99 [0.38-1.83])	0.50 (0.37-0.69 [0.17-2.09])	0.58 (0.49-0.90 [0.27-2.09])	0.51 (0.36-0.70 [0.19-1.24])	0.4 (0.33-0.66 [0.17-1.41])	0.48 (0.36-0.70 [0.19-1.41])	0.53 (0.37-0.69 [0.17-2.09])	0.022 (0.018-0.025) between the control group and NYHA III group, 0.022 (0.017-0.024) between NYHA I group and NYHA III group[1]
Albumin, g/l	45.75 ± 2.17	43.92 ± 5.65	46.21 ± 2.79	44.54 ± 2.61	41.24 ± 8.93	44.19 ± 2.76	43.80 ± 6.61	0.005 (0.004-0.008) between the control group and NYHA III group, 0.040 (0.037-0.047) between NYHA I group and NYHA II group, 0.002 (0.001-0.002) between NYHA I group and NYHA III group, 0.047 (0.039-0.050) between NYHA II group and NYHA III group[1]
Troponin, ng/l	5 (3- 6.25 [2-13])	12 (8-22.50 [2-154])	9.50 (6.75-14.50 [2-46])	12 (7.25-20.75 [2-83])	13 (9.25-30.75 [3-154])	14 (9- 26 [5- 51])	11 (7-21.50 [2-154])	(<0.001-0.002) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001-0.001) between the control group and NYHA III group, <0.001 (<0.001)

								between the control group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]
Ferritin, ug/l	147.20 (81-198.55 [26.70-338.60])	195 (79.30-268.80 [29.80-1530.90])	232.05 (149.33-285.28 [30.60-430.30])	206.20 (90.70-279 [49.50-1530.90])	119.40 (43.35-250.03 [29.80-815.70])	172.40 (67.20-268.20 [30.10-329.40])	200.65 (80.38-271.28 [29.80-1530.90])	ns[1]
Total cholesterol, mg/dl	197.50 ± 40.93	180.55 ± 46.22	175.56 ± 50.57	188.09 ± 43.44	173.83 ± 47.32	150.39 ± 34.65	194.71 ± 44.38	0.001 (0.001-0.003) between the control group and ICM group, <0.001 (<0.001) between ICM group and DCM group[1]
HDL-cholesterol, mg/dl	58 (47.75-67.25 [40-71])	48 (42-57 [29-119])	47 (35.50-56 [32- 73])	50 (43.75-57 [29-104])	47.20 (42-58 [32-119])	46 (42- 56 [33-104])	51.50 (43-58 [29-119])	ns[1]
Non-HDL, mg/dl	148 (115.25-158.75 [70-218])	128 (93-163 [46-240])	133.50 (87.75-169.75 [46-189])	128.50 (103.25-163 [59-240])	113 (77-154 [69-215])	99 (86-105 [46-182])	137 (123-171.50 [59-240])	0.001 (<0.001-0.001) between the control group and ICM group, <0.001 (<0.001) between ICM group and DCM group[1]
LDL, mg/dl	128.29 ± 32.34	106.90 ± 39.41	109.81 ± 43.64	107.31 ± 36.62	104.40 ± 41.63	79.09 ± 28.57	119.95 ± 37.14	<0.001 (<0.001) between the control group and ICM group, <0.001 (<0.001) between ICM group and DCM group[1]
Triglycerides, mg/dl	93 (68-134.50 [57-193])	117 (78.25-179.25 [54- 556])	107.50 (73.25-175.50 [54-213])	161.50 (94-201.50 [56-556])	90.50 (65.75- 150 [54- 301])	103 (71-168 [54-556])	119 (81-181 [58-308])	0.007 (0.004-0.008) between the control group and NYHA II group, 0.005 (0.002-0.006) between NYHA II group and NYHA III group[1]
ALT, U/l	26 (20-38.50 [14-69])	24 (17-38 [6-124])	25.50 (17-46.25 [13-124])	27.50 (20-40.75	20 (15-31 [6-44])	20 (17-44 [7-124])	26 (17.25-37.50 [6-109])	ns[1]

				[12-109])				
AST, U/l	24.50 (20.50-28.50 [16-32])	25 (19-31.75 [14- 55])	26 (18.25-33 [14-55])	25.50 (21.25-32.75 [14-52])	22 (19-27.75 [14-54])	25 (19-34 [14-50])	25 (19-31 [14-55])	ns[1]
Creatine kinase, U/l	102 (75.75-146 [59-303])	95 (67.25-132.75 [17-1465])	110.50 (82-206 [43-640])	91 (58.50-128.75 [28-318])	79.50 (59-129.25 [17-1465])	86 (53-138 [25-453])	98 (71-126 [17-1465])	ns[1]
CK-MB, U/l	12.40 (10.90-15.95 [8-37])	13.95 (10.93-19.58 [2-55])	17.05 (12.38-21.30 [10-33])	13.90 (9.63-19.28 [2-55])	13.25 (10.33-19.72 [4-36])	15.90 (12.90-20.50 [7-55])	13.20 (9.95-19.20 [2-36])	ns[1]
CK-MB, %	13 (9-17.50 [6-24])	15 (10-23.75 [2-74])	12 (8-25.25 [3-47])	15.50 (10-27.25 [3-64])	16 (13-21.75 [2-74])	19 (11- 28 [4- 59])	14 (9.50-22 [2-74])	ns[1]
NT-proBNP, ng/l	33 (22.25-65 [10-278])	394.50 (186-955.50 [4-35218])	260 (123-591.50 [50-1259])	393.50 (226.50-842.25 [4-5388])	767 (252.50-1553 [50-35218])	402 (364-1131 [195-5388])	325 (120.50-953 [4-35218])	<0.001 (<0.001) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, 0.024 (0.017-0.025) between NYHA I group and NYHA III group, <0.001 (<0.001) between the control group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]

MR-proANP, pmol/l	56 (42-67 [21-123])	115 (76-206 [28-742])	76 (68-101.25 [41-224])	124 (95.50-207 [43-433])	157.50 (67.25- 252 [28- 742])	136 (86-213 [52-433])	109 (70.25-189.25 [28-742])	0.010 (0.007-0.012) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, 0.002 (0.001-0.002) between the control group and NYHA III group, 0.002 (<0.001-0.002) between NYHA I group and NYHA II group, <0.001 (<0.001) between the control group and ICM group, 0.001 (<0.001) between the control group and DCM group[1]
Gamma-GT, U/l	22 (16-36.50 [15-129])	32 (23.25-65.75 [10- 353])	30 (24.25-57.50 [19-135])	36 (25-65 [10-293])	26.10 (19.75- 67 [11-353])	30 (25-56 [10-246])	36 (22.50-70.50 [11-353])	ns[1]
LDH, U/l	177 ± 29.63	224.39 ± 55.53	204.06 ± 39.64	226.13 ± 52.01	235.63 ± 66.52	222 (189-266 [147-347])	213 (191-239.50 [140-440])	(<0.001-0.002) between the control group and NYHA II group, 0.001 (0.001-0.003) between the control group and NYHA III group, 0.004 (0.002-0.004) between the control group and ICM group, 0.003 (0.001-0.003) between The control

								group and DCM group[1]
HbA1c,%	5.40 (5-5.50 [4.70-5.80])	5.80 (5.50-6.18 [4.90-11])	5.80 (5.33-6.40 [5.10-7.50])	5.70 (5.50-6 [5-7.30])	5.85 (5.53-6.65 [4.90-11])	5.90 (5.60-6.70 [5-8.40])	5.70 (5.50-5.95 [4.90-11])	0.010 (0.005-0.012) between the control group and NYHA I group, <0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, <0.001 (<0.001) between the control group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]
HbA1c, mmol/mol	35 (31-37 [28-39.90])	39.35 (36.45-43.33 [30.20-96.20])	39.80 (34.25-46.75 [31.90- 58])	38 (36.70-41.50 [31- 53])	40.50 (37.40- 50 [30.20-96.20])	41.15 (37.85-47.95 [31-68])	38.50 (36-41.50 [30.20-96.20])	0.012 (0.009-0.015) between the control group and NYHA I group, 0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001-0.001) between the control group and NYHA III group, <0.001 (<0.001-0.001) between the control group and ICM group, 0.001 (<0.001-0.002) between the control group and DCM group[1]

CRP, mg/l	0.95 (0.60-1.33 [0.20-4.60])	1.60 (0.65-3.90 [0.22-139.20])	1.10 (0.70-1.80 [0.50-5.70])	1.60 (0.60-3.60 [0.50-139.20])	3.10 (0.70-11.50 [0.22-44.80])	1.30 (0.60-4.08 [0.50-20.80])	1.60 (0.70-3.90 [0.22-139.20])	ns[1]
Transferrin, g/l	2.55 ± 0.35	2.49 ± 0.48	2.46 ± 0.46	2.48 ± 0.34	2.52 ± 0.65	2.42 (2.24-2.79 [1.54-4.16])	2.43 (2.26-2.80 [1.10-3.51])	ns[1]
Prothrombin activity, %	95.50 (90.75-100 [81-103])	87 (68.25-97.75 [24- 111])	86.50 (66.25-96.50 [25-100])	91 (82.25-99.75 [25-108])	82 (50.50-96 [24-111])	87 (49-97.25 [25-100])	87 (68.75-98 [24-111])	0.013 (0.009-0.015) between the control group and NYHA I group, 0.007 (0.004-0.008) between the control group and NYHA III group, 0.018 (0.014-0.020) between The control group and ICM group, 0.028 (0.026-0.034) between The control group and DCM group[1]
INR	1.03 (1-1.07 [1-1.15])	1.07 (1.02-1.25 [0.97-2.91])	1.08 (1.02-1.33 [1-2.91])	1.05 (1.01-1.11 [0.98-2.49])	1.12 (1.03-1.39 [0.97-2.90])	1.07 (1.02-1.63 [1-2.49])	1.07 (1.02-1.25 [0.97-2.91])	0.014 (0.009-0.016) between the control group and NYHA I group, 0.009 (0.006-0.010) between the control group and NYHA III group[1]
Fibrinogen, g/l	2.84 ± 0.53	3.51 ± 1.14	3.04 ± 0.50	3.52 ± 1.21	3.83 ± 1.29	3.17 (2.78-3.99 [1.53-4.72])	3.39 (2.89-4.01 [1.68-7.90])	0.026 (0.020-0.028) between the control group and NYHA II group, 0.002 (<0.001-0.002) between the control group and NYHA III group, 0.011 (0.008-0.013)

								between NYHA I group and NYHA III group, 0.009 (0.005-0.010) between The control group and DCM group[1]
FT3, ng/l	3.25 (2.31-3.80 [0.91-4.17])	3.06 (2.54-3.35 [0.92-4.26])	3.29 (3.09-3.74 [1.16-4.26])	3.15 (2.86-3.35 [0.92-3.99])	2.62 (2.19-3.04 [1.03-3.75])	3.16 (2.24-3.60 [0.94-4.26])	3.05 (2.69-3.33 [0.92-3.96])	0.001 (<0.001-0.002) between NYHA I group and NYHA III group, 0.005 (0.003-0.006) between NYHA II group and NYHA III group[1]
FT4, ng/l	12.19 ± 1.58	13.42 ± 2.41	13.24 ± 2.35	13.16 ± 2.44	13.88 ± 2.45	13.84 ± 2.90	13.24 ± 2.17	ns[1]
TSH, mU/l	1.73 (1.41-2.36 [0.91-3.79])	1.39 (0.88-2.33 [0.32-38.30])	1.16 (0.69-2.06 [0.47-3.67])	1.4 (0.97-1.85 [0.45-38.30])	1.77 (0.89-2.74 [0.32-17])	1.47 (0.70-3.08 [0.51-17])	1.38 (0.90-2.29 [0.32-38.30])	ns[1]
Sodium, mmol/l	140 (139-141.25 [138- 144])	140 (138-141 [132-144])	139.50 (138- 140 [137- 142])	139 (136-140.75 [132-144])	140 (139-141 [133-144])	140 (139-141 [132-143])	139 (137.75-140 [133-144])	ns[1]
Potassium, mmol/l	3.95 (3.78-4.30 [3.50-4.40])	4.20 (4-4.40 [3.40-5.70])	4.10 (3.90-4.30 [3.50-4.40])	4.15 (3.90-4.50 [3.40-5.70])	4.20 (4-4.40 [3.40-5.20])	4.30 (4.10-4.40 [3.50-5])	4.10 (3.90-4.40 [3.40-5.70])	ns[1]
Iron, umol/l	17.65 (14.63-20.98 [10.40-41.20])	15.40 (11.83-19.50 [5.30-34.40])	17.80 (14.13-24.05 [8.40-31.10])	17.20 (13.80-19.70 [10-34.40])	11.60 (10.30-15.50 [5.30-21.20])	14.50 (11.50- 18 [5.30-32.70])	17 (11.90-19.70 [6.80-34.40])	0.001 (<0.001-0.002) between the control group and NYHA III group, 0.002 (0.001-0.004) between NYHA I group and NYHA III group, 0.001(<0.001-0.001)

								between NYHA II group and NYHA III group[1]
Transferrin saturation, %	29.60 (22.50-33.95 [18-66.10])	25.60 (19.18-32.03 [4.10-63.80])	27 (25.10-34 [14-57.80])	29.50 (21.60-36.30 [13.40-63.80])	21.10 (15.25-27.33 [4.10-39.60])	23.80 (19.20- 32 [5.10-46.60])	25.70 (19.10-32.10 [4.10-63.80])	0.019 (0.014-0.021) between the control group and NYHA III group, 0.008 (0.005-0.009) between NYHA I group and NYHA III group, 0.005 (0.002-0.006) between NYHA II group and NYHA III group[1]
Urine pH	5.50 (5-6.13 [5- 8])	5.50 (5-6.50 [5-9])	5.50 (5-6.50 [5-7.50])	5.50 (5-6.38 [5-9])	5.5 (5- 7 [5-7.50])	5.50 (5-6.50 [5-7.50])	5.50 (5-6.50 [5- 9])	ns[1]
Urine specific gravity	1.016 ± 0.006	1.016 ± 0.007	1.016 (1.011-1.020 [1.008-1.031])	1.016 (1.014-1.020 [1.002-1.032])	1.014 (1.010-1.021 [1.007-1.042])	1.018 ± 0.008	1.015 ± 0.007	ns[1]
Urine glucose, n(%)	0 (0)	15 (22.4)	4 (25)	6 (21.4)	5 (21.7)	5 (21.7)	10 (22.7)	ns[2]
Urine protein, n(%)	0 (0)	12 (17.9)	0 (0)	6 (21.4)	6 (26.1)	4 (17.4)	8 (18.2)	ns[2]

Continuous variables with normal distribution are expressed as mean ± standard deviation and non-normally distributed variables as median (IQR [range]). Categorical variables are expressed as frequency (percentage).

NYHA, New York Heart Association functional classification; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; RDW-CV, red cell distribution width - coefficient of variation; NLR, neutrophil to lymphocyte ratio; RLC, relative lymphocyte count; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-myoglobin binding; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; LDH, lactate dehydrogenase; HbA1c, glycated hemoglobin; CRP, C-reactive protein; INR, international normalized ratio; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; ns, not significant.

[a] Monte Carlo was jointly used to specify the 99% CI for the obtained P values when comparing the continuous variables and one of the sample sizes of the variables was less than 30.
[1] Kruskal-Wallis Test was used to compare continuous variables, and a Mann-Whitney U Test was used for post-hoc multiple comparisons.
[2] Chi-Square Test or Continuity Correction Test was used to compare categorical variables as appropriate.

When comparing hemoglobin and hematocrit levels of the control group with patients with CHF in the two categories, as shown in Figure 3.3.1 and Figure 3.3.2, hemoglobin levels in the NYHA III group were significantly lower than those of the control group, NYHA I and II groups (p=0.002, p=0.004, and p<0.001, respectively). Hematocrit levels in the NYHA III group were also significantly lower than those of the control group, NYHA I and II groups (p=0.001, p=0.004, and p<0.001, respectively). However, there were no significant differences in hemoglobin and hematocrit levels among the control group and ICM and DCM groups. Regarding erythrocytes, as Figure 3.3.3 shows, the control group had significantly higher levels than those of the NYHA I and III groups and the DCM group (p=0.050, p<0.001, and p=0.005, respectively). There were no significant differences in erythrocytes levels among NYHA I to III groups, and between ICM and DCM groups.

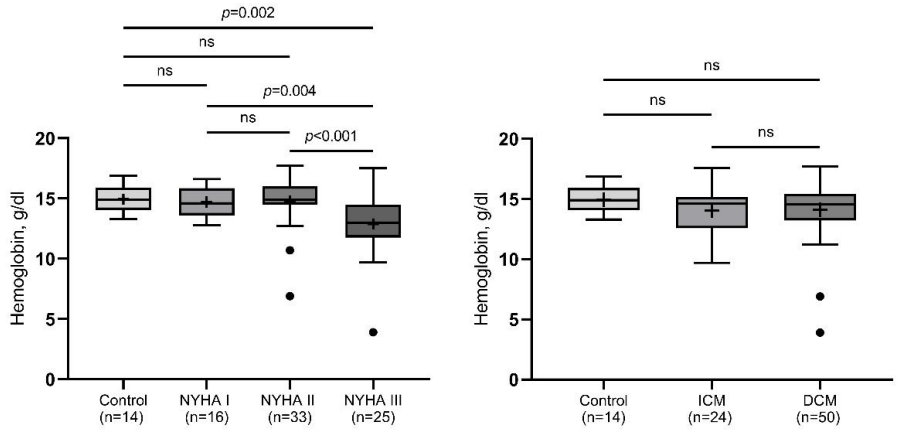

Figure 3.3.1. Comparisons of hemoglobin levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

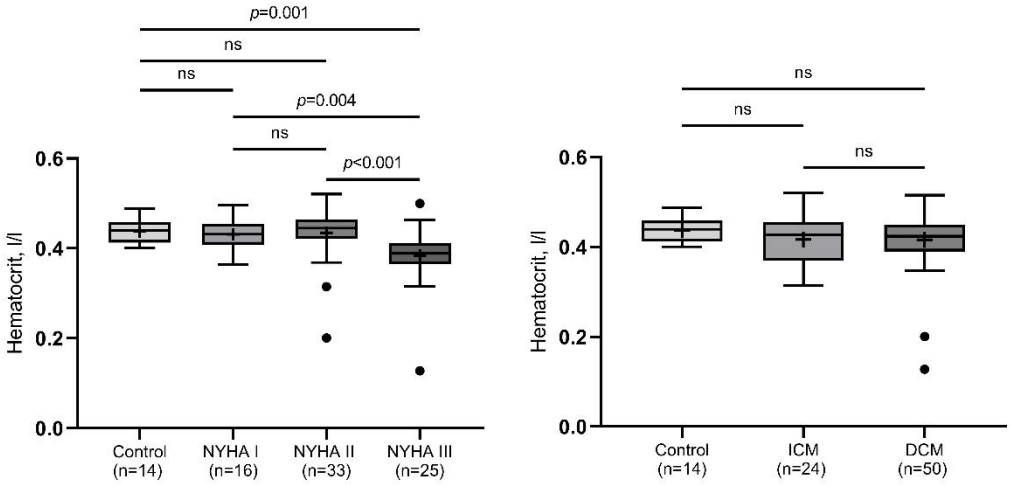

Figure 3.3.2. Comparisons of hematocrit levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

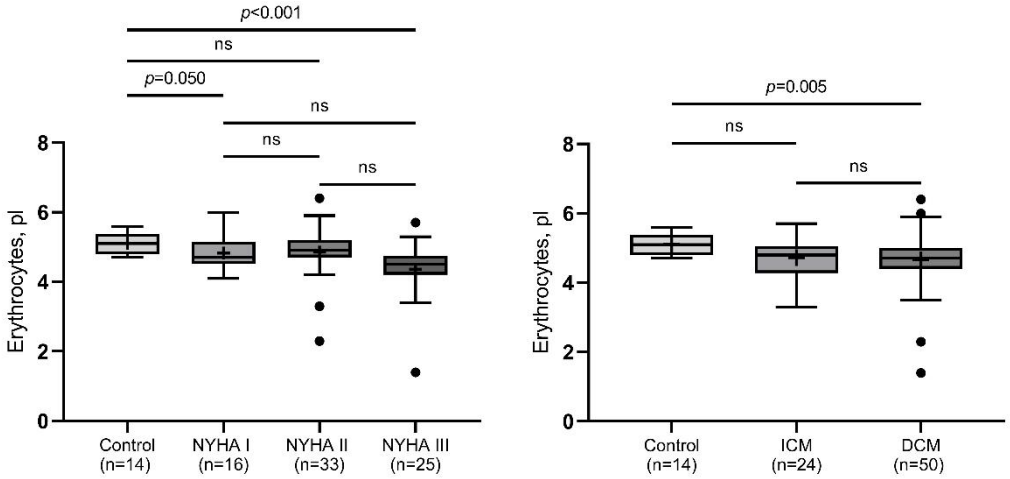

Figure 3.3.3. Comparisons of erythrocytes levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

For mean corpuscular volume (MCV), as shown in Figure 3.3.4, the control group had significantly lower levels than those of the NYHA I to III groups and ICM and DCM groups (p=0.031, p<0.001, p=0.033, p=0.023, and p=0.001, respectively). There were no significant differences in MCV among CHF groups. For mean corpuscular hemoglobin (MCH), as shown in Figure 3.3.5, the control group had significantly lower levels than those of the NYHA I and II groups and the DCM group (p=0.029, p=0.003, and p=0.005, respectively). There were also no significant differences in MCH among CHF groups. For red cell distribution width - coefficient of variation (RDW-CV), as shown in Figure 3.3.6, the control group had significantly lower levels than those of the NYHA I to III groups (p=0.010, p=0.001 and p<0.001, respectively) and the ICM and DCM groups (p=0.001 and p<0.001, respectively). In addition, EDW-CV in the NYHA I group was significantly

lower than that of NYHA III group (p=0.027), and there were no significant differences in RDW-CV between the ICM and DCM groups.

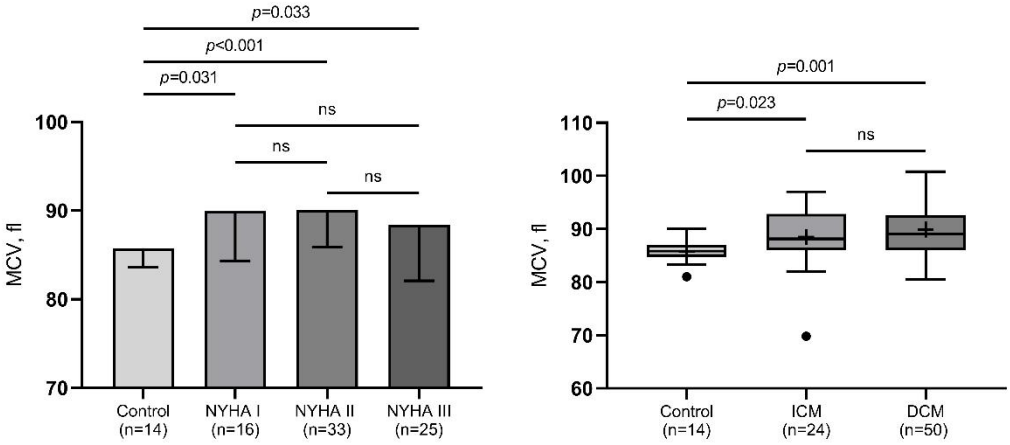

Figure 3.3.4. Comparisons of mean corpuscular volume levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups

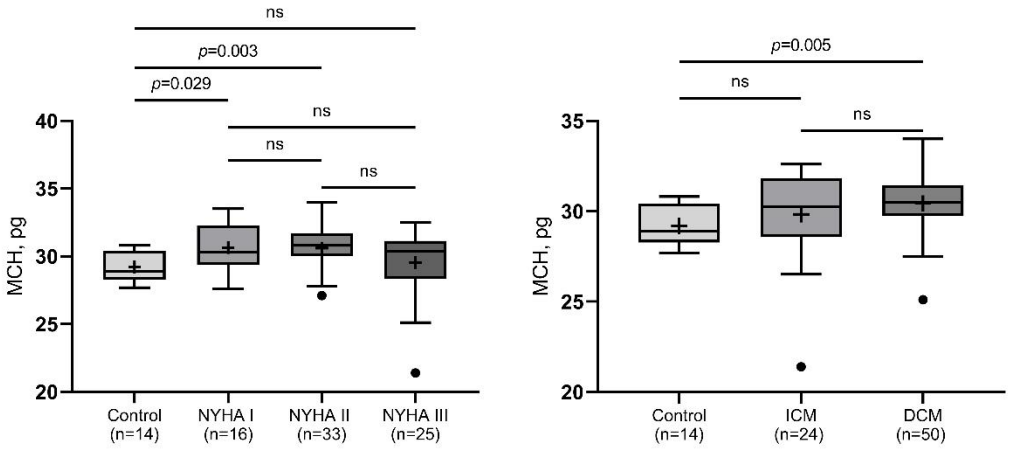

Figure 3.3.5. Comparisons of mean corpuscular hemoglobin levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

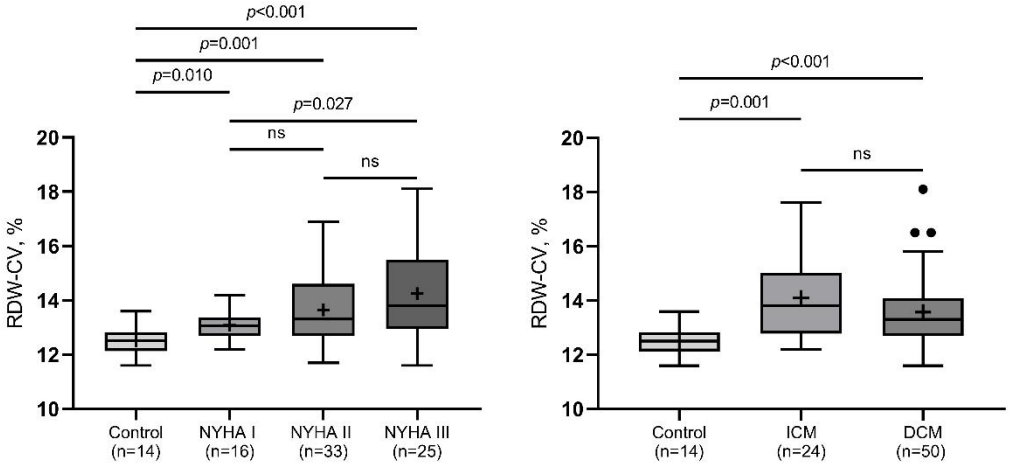

Figure 3.3.6. Comparisons of red cell distribution width - coefficient of variation in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

Regarding iron and transferrin saturation, as shown in Figure 3.3.7 and Figure 3.3.8, the trends were the same for these two parameters, with the NYHA III group showing significantly lower levels than those of the control group and the NYHA I and II groups (iron: p=0.001, p=0.002, and p=0.001, respectively; transferrin saturation: p=0.019, p=0.008, and p=0.005, respectively). There were no significant differences in iron and transferrin saturation among the control group and ICM and DCM groups.

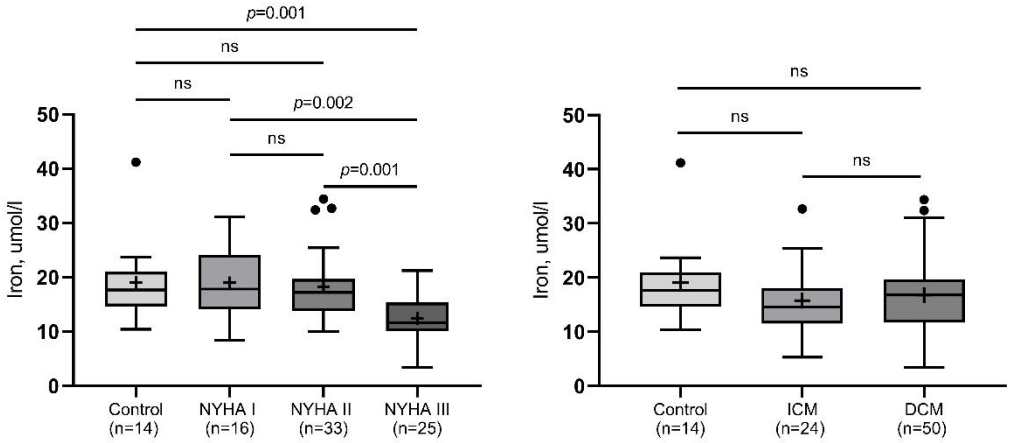

Figure 3.3.7. Comparisons of iron levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

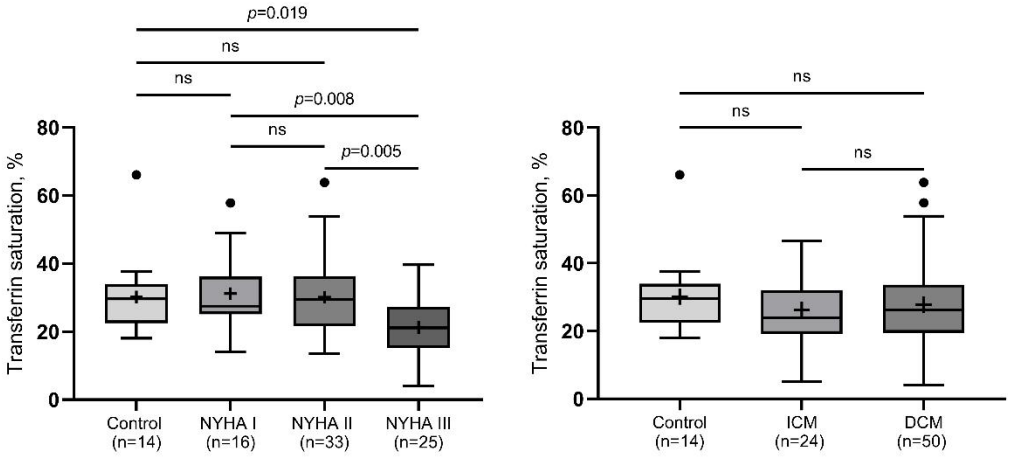

Figure 3.3.8. Comparisons of transferrin saturation levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

Regarding inflammatory parameters, Figures 3.3.9 to 3.3.17 present whether and where there were statistical differences among the control group and CHF groups. Concerning the absolute leukocyte count, as shown in Figure 3.3.9, it in NYHA III group was significantly higher than that of the control group, and NYHA I and II groups (p=0.001, p=0.017, and p=0.003, respectively), and it in ICM and DCM groups were significantly higher than that of the control group (p=0.015 and p=0.024, respectively). There were no significant differences in the absolute leukocyte count between ICM and DCM groups.

For the absolute neutrophil count, as shown in Figure 3.3.10, it in the control group was significantly lower than that of the NYHA I to III groups (p=0.003, p=0.010, and p<0.001, respectively) and the ICM and DCM groups (both P=0.001), with no significant differences among the CHF groups.

For immature granulocyte, as shown in Figure 3.3.11, there were few differences among the control group and NYHA class groups, whereas it in the control group was significantly lower than that of the ICM and DCM groups (p=0.007 and p=0.045, respectively).

For absolute monocyte count, as shown in Figure 3.3.12, it in the control group was significantly lower than that of the NYHA II and III groups (p=0.034 and p=0.005, respectively) and the ICM and DCM groups (p=0.018 and p=0.017, respectively), with no significant differences among CHF groups.

For the proportion of neutrophils in leukocytes, as shown in Figure 3.3.13, it in the control group was significantly lower than that of NYHA I to III groups (p<0.001, p=0.004 and p<0.001, respectively) and the ICM and DCM groups (both p<0.001), with no significant differences among CHF groups.

For the proportion of lymphocytes in leukocytes, as shown in Figure 3.3.14, the trends were the opposite to the proportion of neutrophils, with the proportion in the control group being significantly higher than that of the NYHA I to III groups (p=0.001, p=0.002, and p<0.001, respectively) and the ICM and DCM groups (both p<0.001), and no significant differences among the CHF groups.

For the proportion of basophils in leukocytes, as shown in Figure 3.15, it in the control group was significantly higher than that of NYHA I to III groups and the DCM group (p=0.018, p=0.009, p=0.050, and p=0.002, respectively), with no significant differences among the CHF groups as well.

Concerning NLR and RLC, as shown in Figure 3.3.16 and Figure 3.3.17, there were opposite trends of these two parameters. The NLR of the control group was significantly lower than that of the NYHA I to III groups (p<0.001, p=0.003, and p<0.001, respectively) and the ICM and DCM groups (both p<0.001). In contrast, the RLC of the control group was significantly higher than that of the NYHA I to III groups (p<0.001, p=0.001, and p<0.001, respectively) and the ICM and DCM groups (both p<0.001). There were no significant differences in NLR and RLC among the CHF groups.

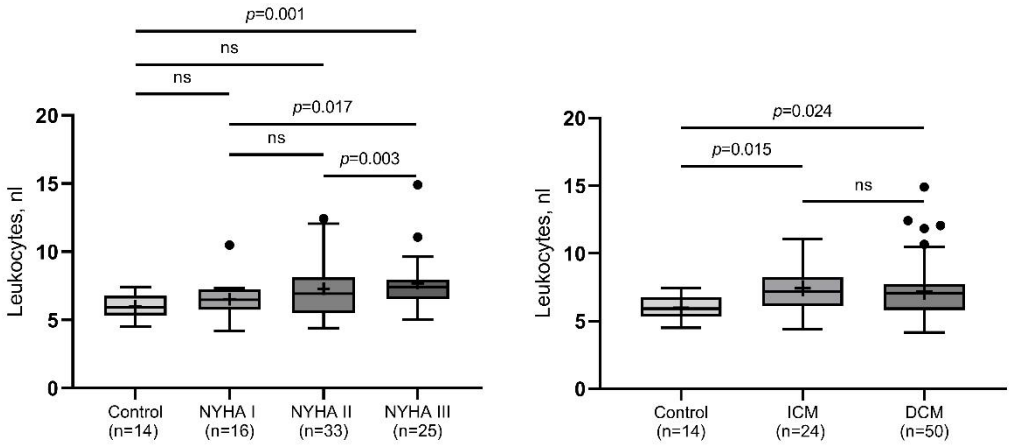

Figure 3.3.9. Comparisons of leukocytes levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

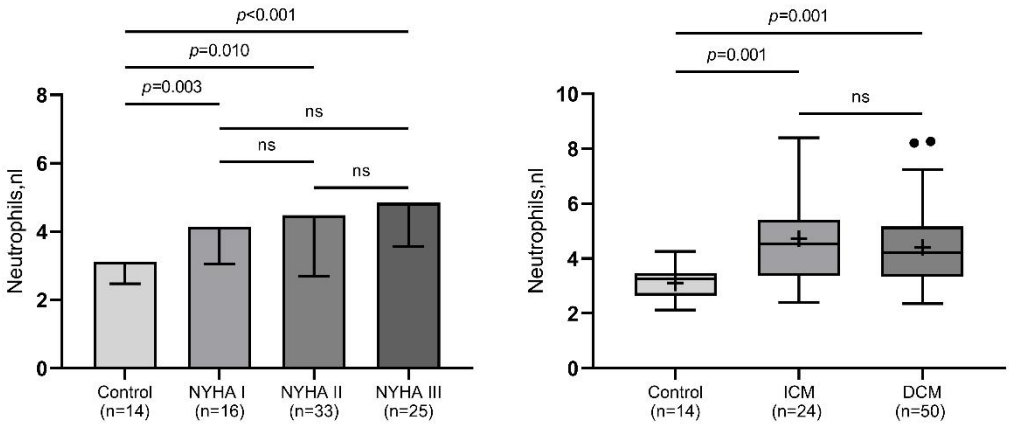

Figure 3.3.10. Comparisons of neutrophils levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

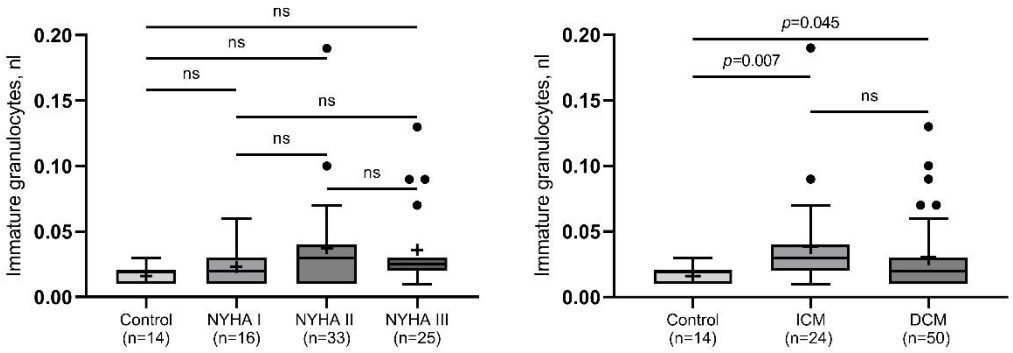

Figure 3.3.11. Comparisons of immature granulocytes levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

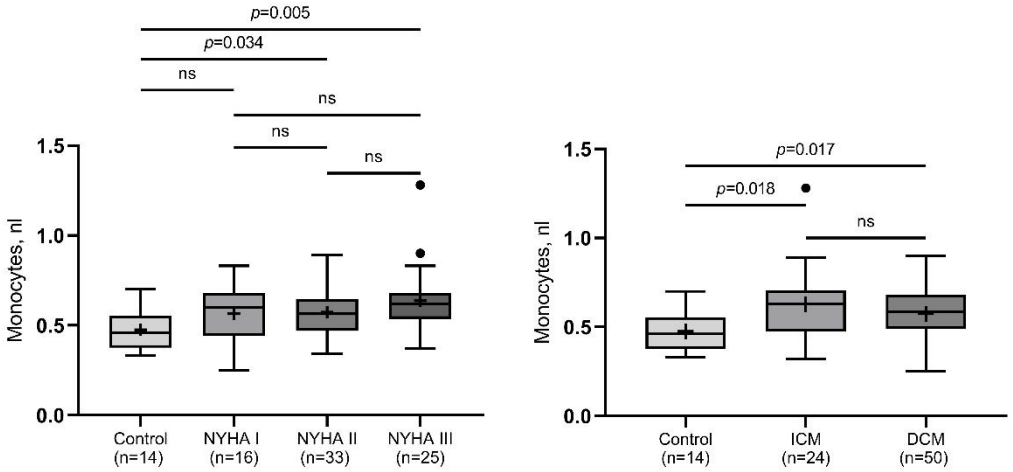

Figure 3.3.12. Comparisons of monocytes levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

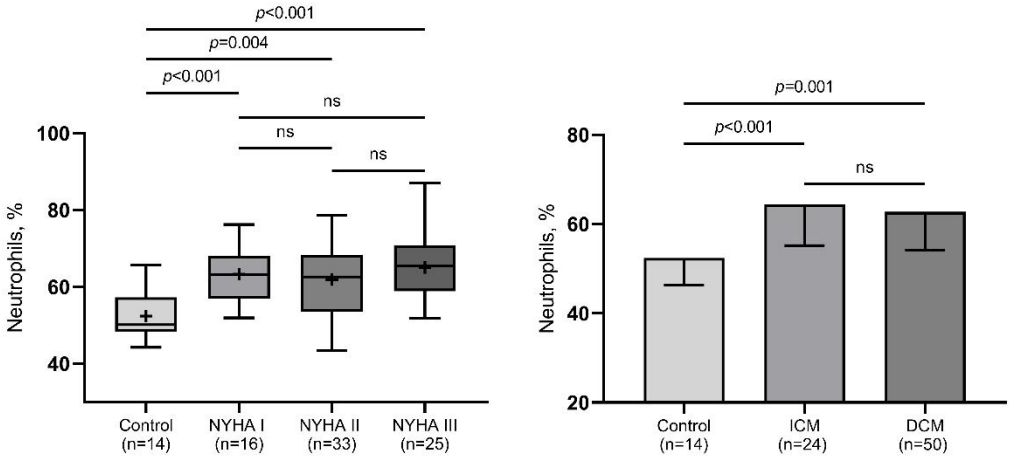

Figure 3.3.13. Comparisons of the proportion of neutrophils in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

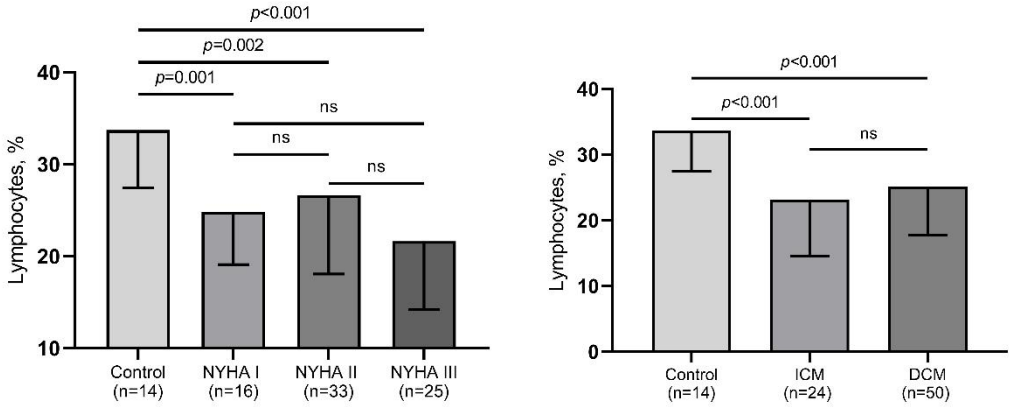

Figure 3.3.14. Comparisons of the proportion of lymphocytes in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

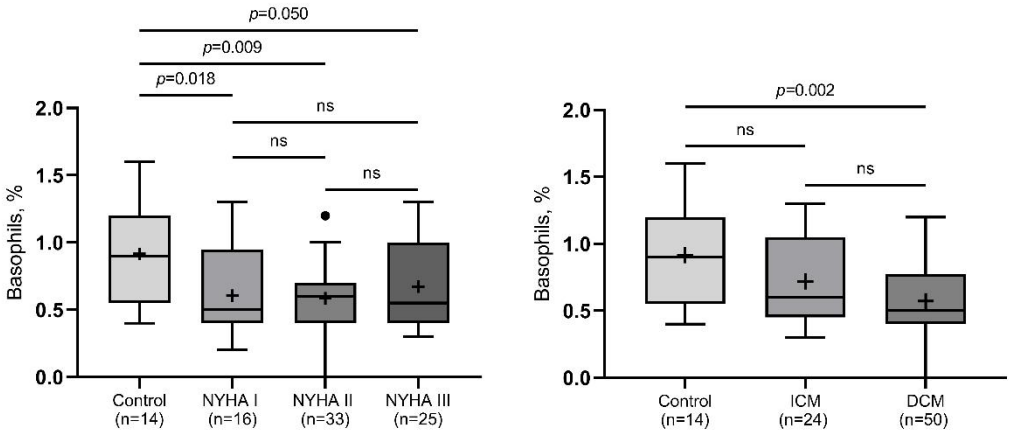

Figure 3.3.15. Comparisons of the proportion of basophils in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

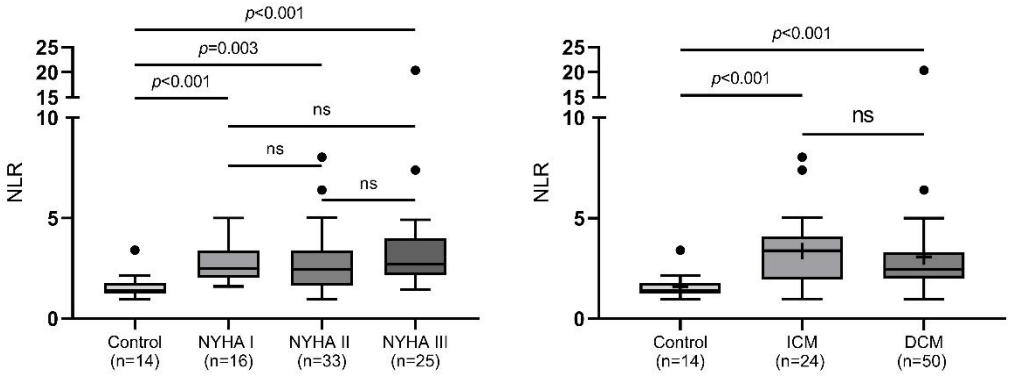

Figure 3.3.16. Comparisons of neutrophil to lymphocyte ratio in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

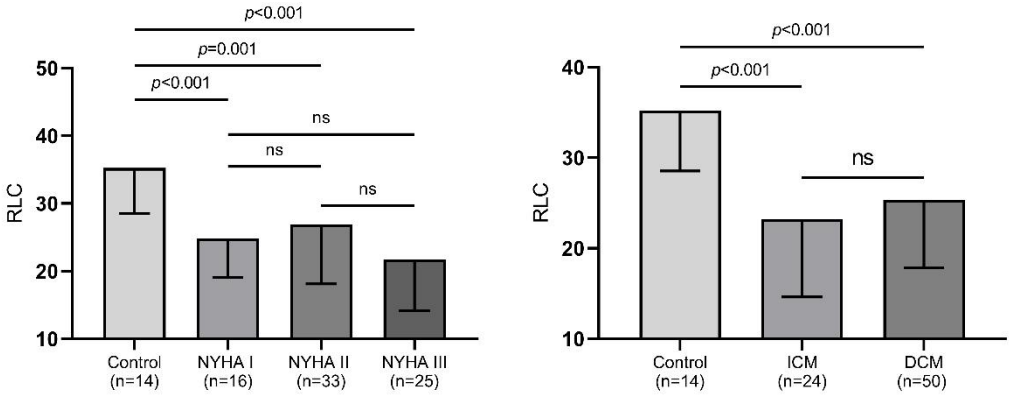

Figure 3.3.17. Comparisons of relative lymphocyte count in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

Figure 3.3.18 shows the comparisons of estimated glomerular filtration rate (eGFR), and we can observe that the eGFR of the control group was significantly higher than that of NYHA II and III groups (p=0.039 and p=0.043, respectively), and the eGFR of the NYHA I group was also significantly higher than that of NYHA II and III groups (p=0.020 and p=0.023, respectively). However, there were few differences in eGFR among the control group and ICM and DCM groups. For uric acid, as shown in Figure 3.3.19, only one significant difference was found: uric acid in the control group was significantly lower than that in the ICM group (p=0.016), and no obvious differences were observed among other groups.

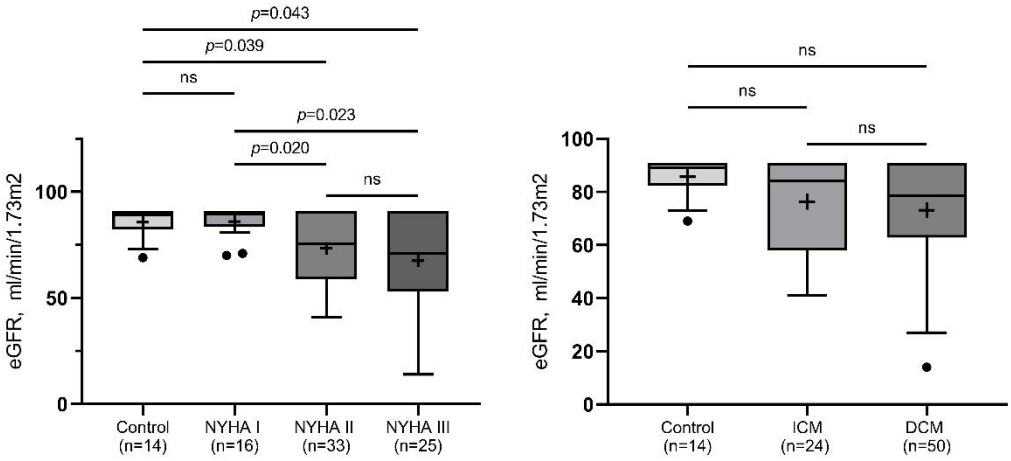

Figure 3.3.18. Comparisons of estimated glomerular filtration rate in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

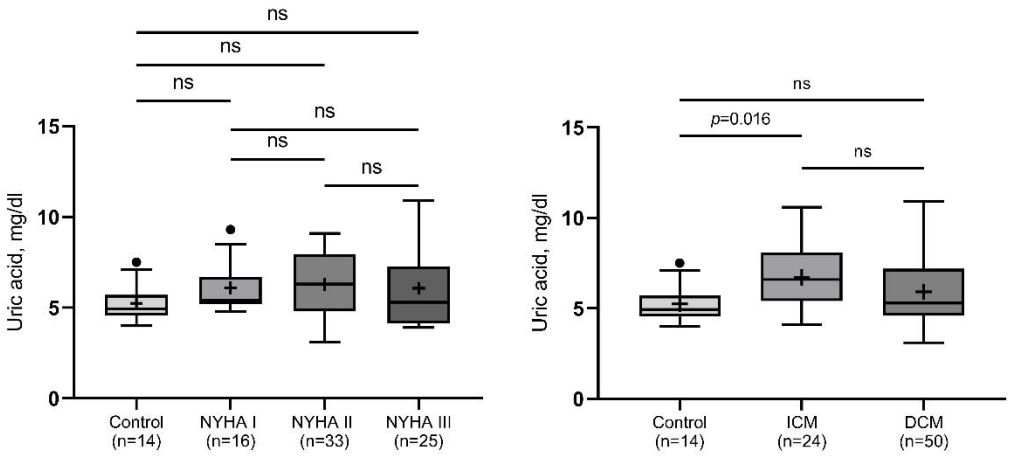

Figure 3.3.19. Comparisons of uric acid levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

For free triiodothyronine (FT3), as shown in Figure 3.3.20, it of the NYHA III group was significantly lower than that of the NYHA I and NYHA II groups (p=0.001 and p=0.005, respectively), and there were no significant differences in FT3 among the control group and ICM and DCM groups.

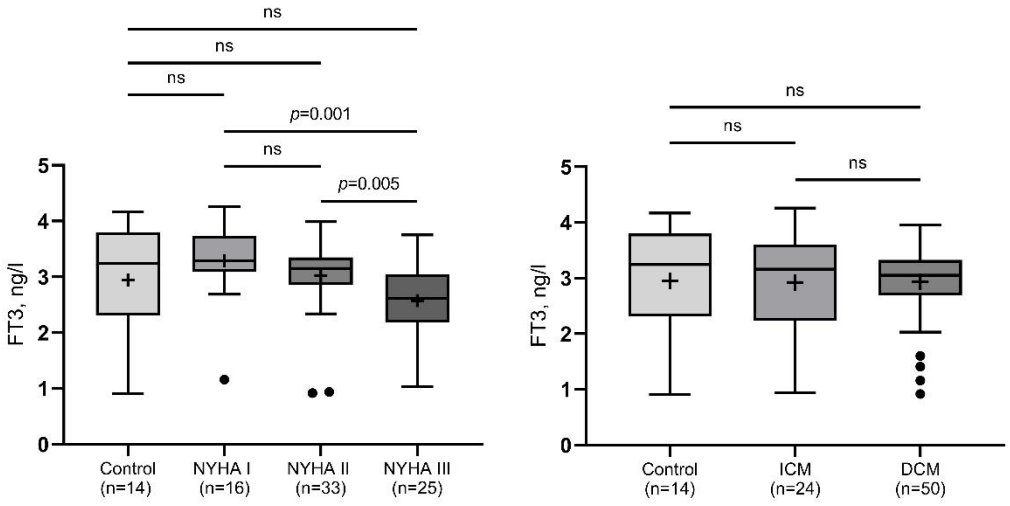

Figure 3.3.20. Comparisons of free triiodothyronine levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

Concerning total bilirubin, as shown in Figure 3.3.21, it of the NYHA III group was significantly lower than it of the control group and NYHA I group (both p=0.022). There were few differences in total bilirubin among the control group and ICM and DCM groups.

For albumin, as shown in Figure 3.3.22, it of the NYHA III group was significantly lower than it of the control group and NYHA I and II groups (p=0.005, p=0.002, and p=0.047, respectively). Besides, albumin of the NYHA II group was significantly lower than it of

NYHA I group (p=0.040).

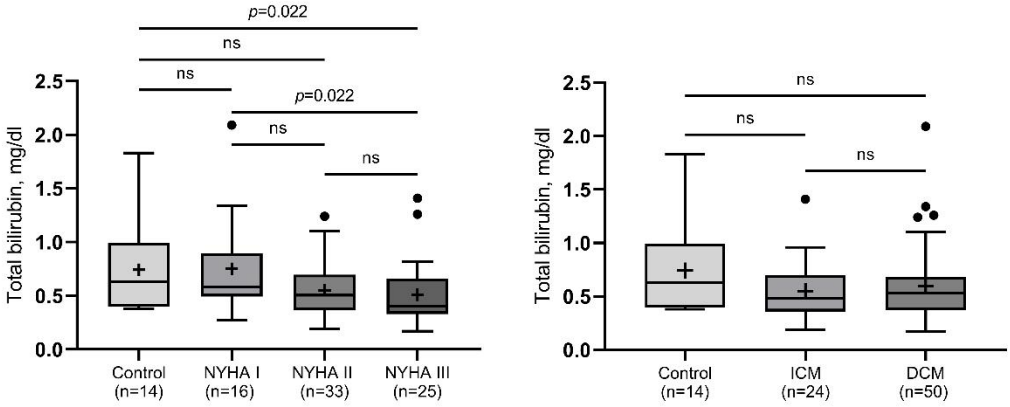

Figure 3.3.21. Comparisons of total bilirubin levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

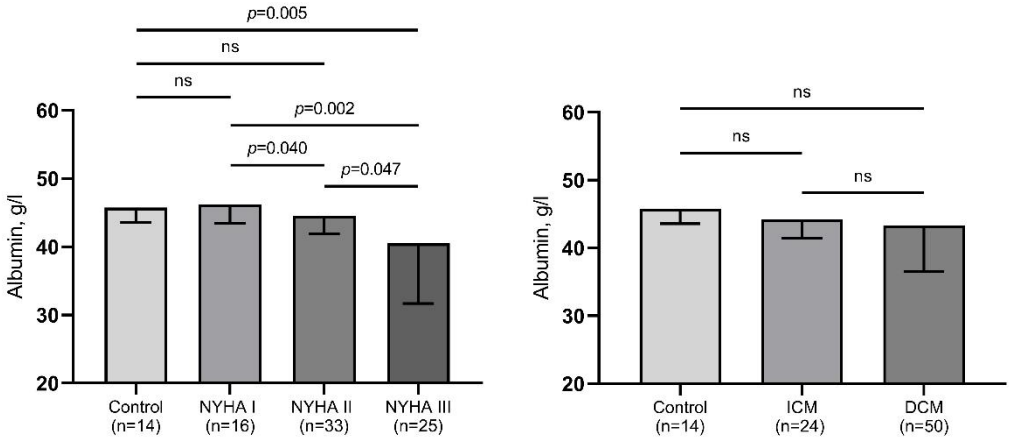

Figure 3.3.22. Comparisons of albumin levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

Regarding lipid profile tests, Figures 3.3.23 to 3.3.26 present the statistical differences in cholesterol, non-high density lipoprotein levels (non-HDL), low-density lipoprotein (LDL), and triglycerides among the control group and CHF groups.

For total cholesterol, as shown in Figure 3.3.23, there were no obvious differences among the control group and NYHA I to III groups, and only it in ICM group was significantly lower than it in control group and DCM group (p=0.004 and p<0.001, respectively).

For non-high-density lipoprotein (non-HDL) and low-density lipoprotein (LDL), as shown in Figure 3.3.24 and Figure 3.3.25, the trends of these two parameters were the same as the trend of total cholesterol; these two parameters in the ICM group were significantly lower than those in the control group and DCM group (non-HDL: p=0.001 and p<0.001, respectively; LDL: both p<0.001).

For triglycerides, as shown in Figure 3.3.26, triglycerides in the NYHA II group were significantly higher than those in the control group and NYHA III group (p=0.007 and p<0.005, respectively).

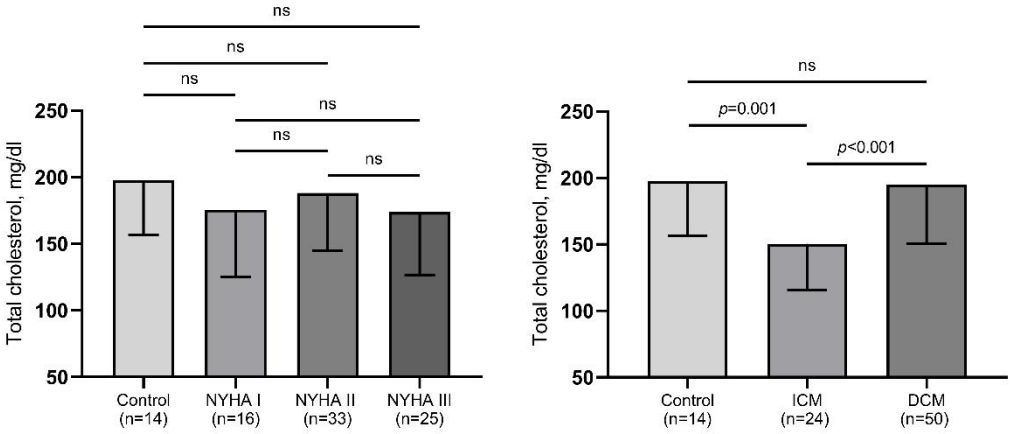

Figure 3.3.23. Comparisons of total cholesterol levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

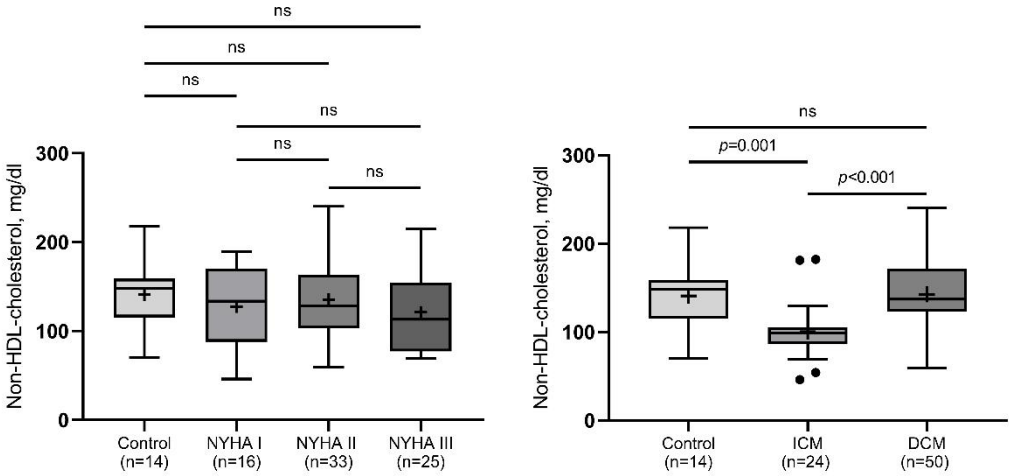

Figure 3.3.24. Comparisons of non-high density lipoprotein levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

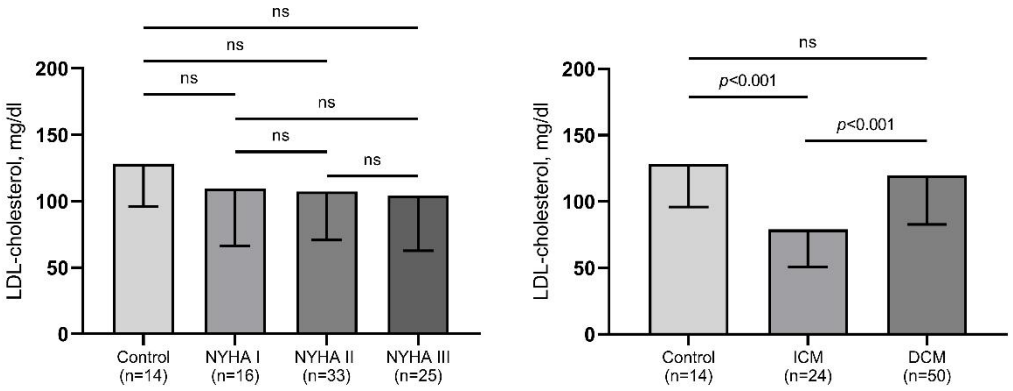

Figure 3.3.25. Comparisons of low-density lipoprotein levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

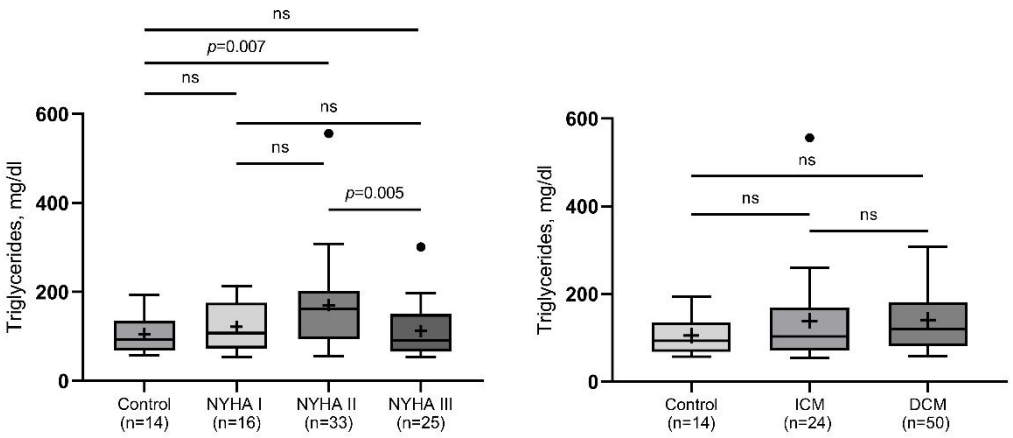

Figure 3.3.26. Comparisons of triglycerides levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

For lactate dehydrogenase (LDH), as shown in Figure 3.3.27, it in the control group was significantly lower than it in the NYHA II and III groups (both p=0.001) and ICM and DCM groups (p=0.004 and p=0.003, respectively), and there were no significant differences in LDH among CHF groups.

For troponin, as shown in Figure 3.3.28, it in the control group was significantly lower than it in NYHA I to III groups (p=0.001, p<0.001, and p<0.001, respectively) and ICM and DCM groups (both p<0.001), and there were no significant differences in troponin among CHF groups.

Concerning N-terminal pro-B-type natriuretic peptide (NT-proBNP) and mid-regional pro-atrial natriuretic peptide (MR-proANP), as shown in Figure 3.3.29 and Figure 3.3.30, the trends of these two parameters are the same; these two parameters in the control group were significantly lower than those in NYHA I to III groups (NT-proBNP: all p<0.001; MR-proANP: p=0.010, p<0.001 and p=0.002, respectively) and ICM and DCM groups (NT-proBNP: both p<0.001; MR-proANP: p<0.001 and p=0.001, respectively), and it in the NYHA I group was significantly lower than it in the NYHA III group (NT-proBNP: p=0.024; MR-proANP: p=0.002).

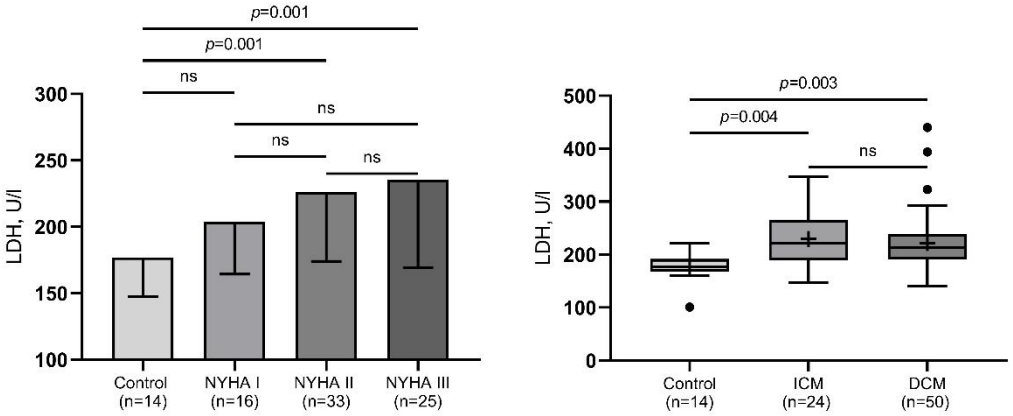

Figure 3.3.27. Comparisons of lactate dehydrogenase levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

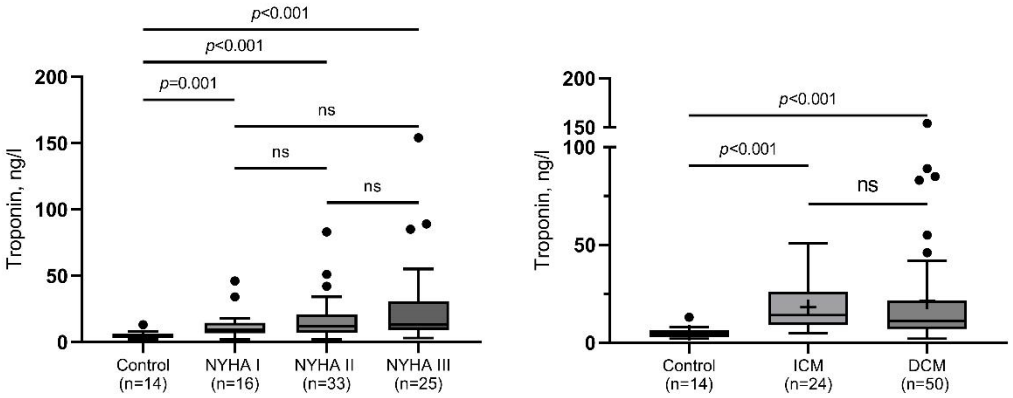

Figure 3.3.28. Comparisons of troponin levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

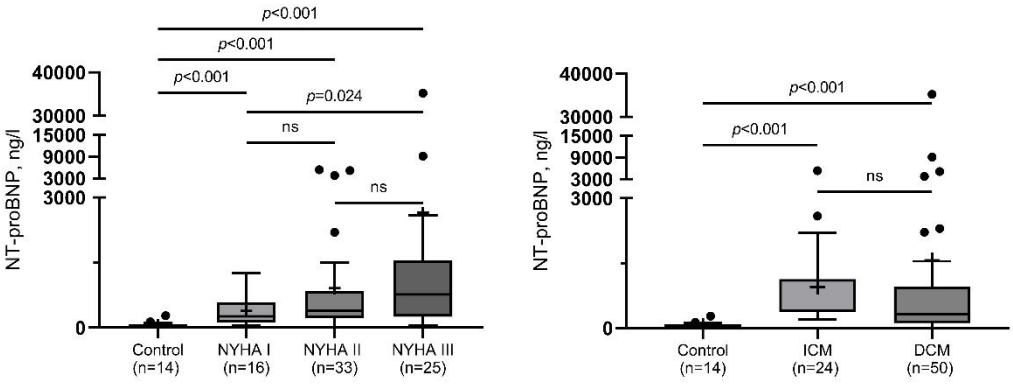

Figure 3.3.29. Comparisons of N-terminal pro-B-type natriuretic peptide levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

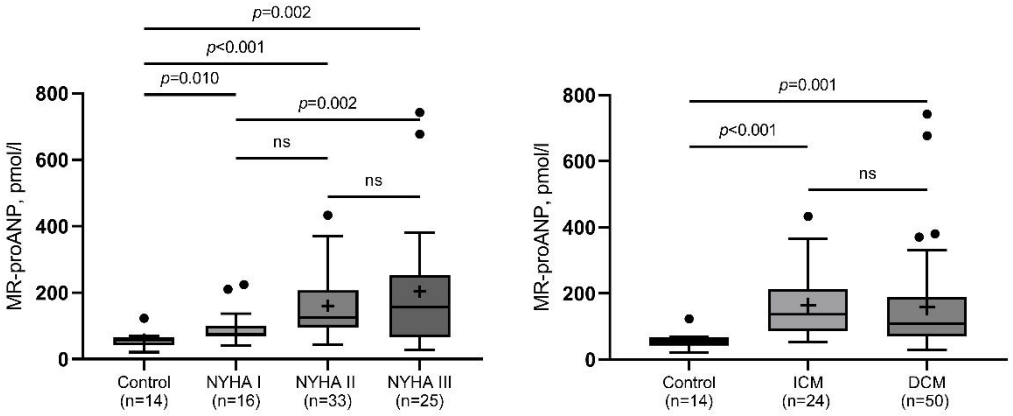

Figure 3.3.30. Comparisons of mid-regional pro-atrial natriuretic peptide levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

The following three figures, including Figures 3.3.31 to 3.3.33, indicate the differences in blood glucose-related parameters among the control group and CHF groups. For glucose, as shown in Figure 3.3.31, it in the control group was significantly lower than it in NYHA II and III groups ($p<0.001$ and $p=0.003$, respectively) and ICM and DCM groups ($p<0.001$ and $p=0.002$, respectively), and there were no significant differences in glucose among CHF groups. Concerning the proportion of glycated hemoglobin (HbA1c%) and the absolute glycated hemoglobin count (HbA1c), as shown in Figure 3.3.32 and Figure 3.3.33, the trends were the same; these two parameters of the control group were significantly lower than those in NYHA I to III groups (HbA1c%: $p=0.010$, $p<0.001$, and $p<0.001$, respectively; HbA1c: $p=0.012$, $p=0.001$, and $p<0.001$, respectively) and ICM and DCM groups (HbA1c%: both $p<0.001$; HbA1c: $p<0.001$ and $p=0.001$, respectively), and there were no significant differences in these two parameters among CHF groups as well.

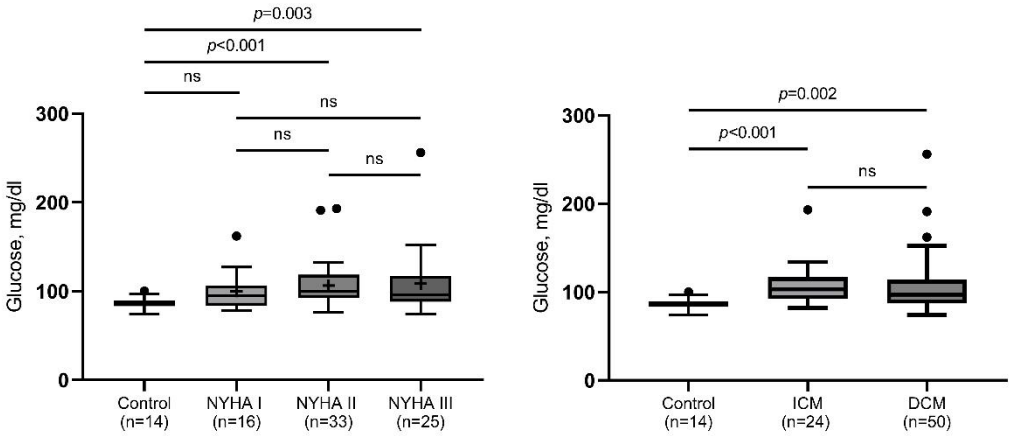

Figure 3.3.31. Comparisons of glucose levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

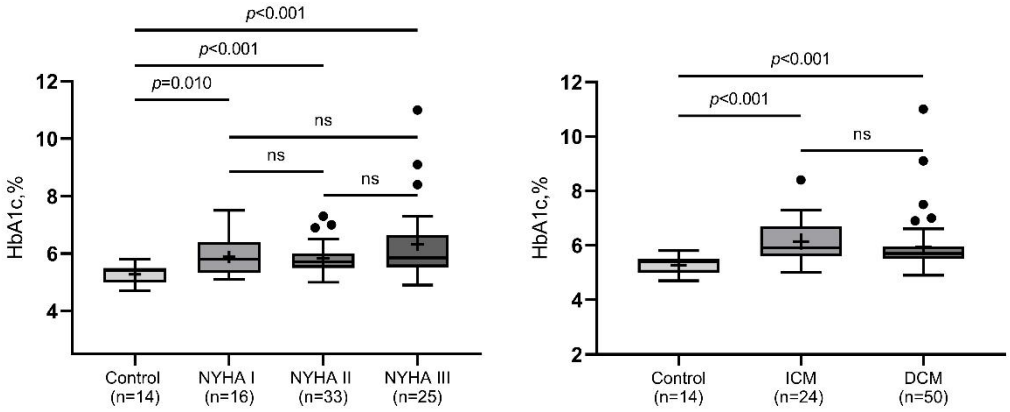

Figure 3.3.32. Comparisons of the proportion of glycated hemoglobin in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

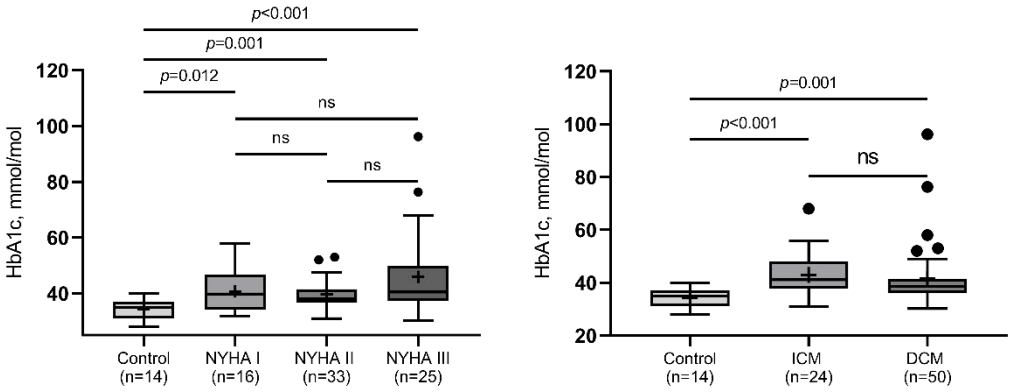

Figure 3.3.33. Comparisons of glycated hemoglobin levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

Figures 3.3.34 to 3.3.36 illustrate three coagulation-related indicators that had statistically significant differences among the control group and CHF groups. For prothrombin activity**,** as shown in Figure 3.3.34, it in the control group was significantly higher than it in NYHA I and III groups (p=0.013 and p=0.007, respectively) and ICM and DCM groups (p=0.018 and p=0.028, respectively), and there were no significant differences in prothrombin activity among CHF groups.

For international normalized ratio (INR), as shown in Figure 3.3.35, it in the control group was significantly lower than it in NYHA I and III groups (p=0.014 and p=0.009, respectively), and there were also no significant differences in INR among CHF groups.

For fibrinogen, as shown in Figure 3.3.36, it in the control group was significantly lower than it in NYHA II and III groups and DCM group (p=0.026, p=0.002, and p=0.009, respectively), and it in NYHA I group was significantly lower than it in NYHA III group (p=0.011), but there were no significant differences in fibrinogen activity among CHF groups as well.

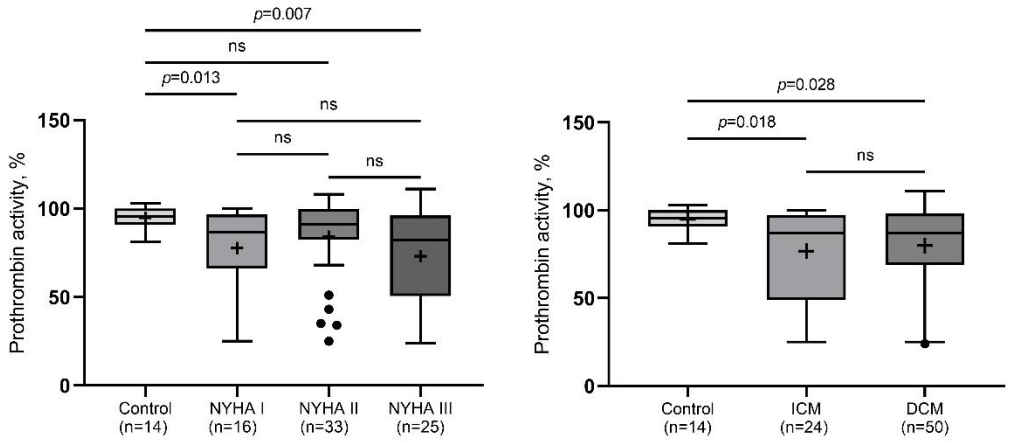

Figure 3.3.34. Comparisons of prothrombin activity levels in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

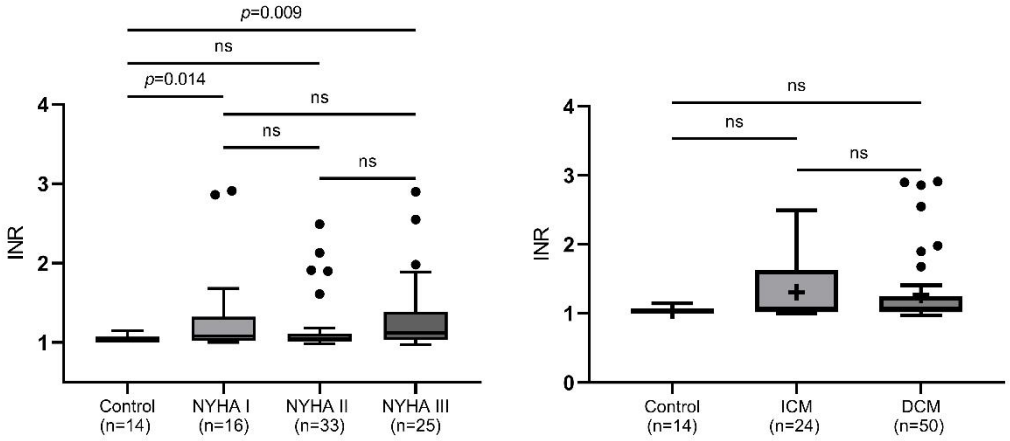

Figure 3.3.35. Comparisons of international normalized ratio in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

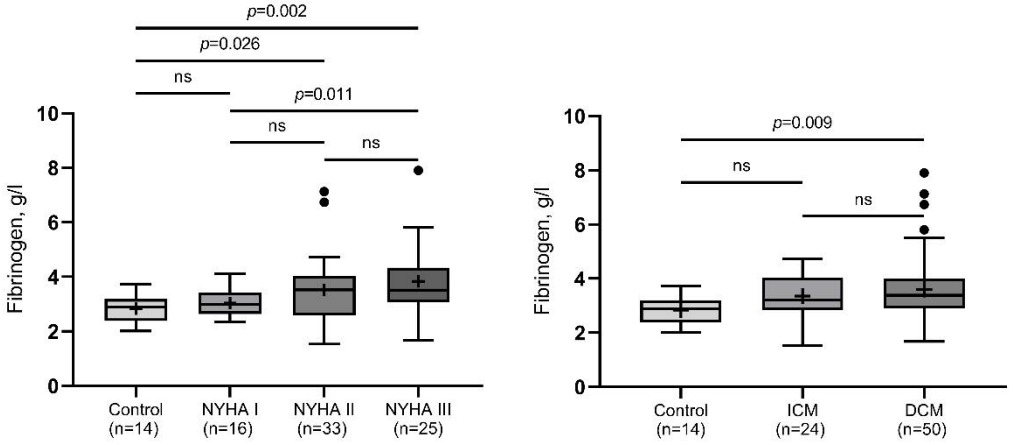

Figure 3.3.36. Comparisons of fibrinogen levels in the control group and NYHA

class I to III groups and in the control group and ICM and DCM groups.

In the ROC analyses, although 6MWT and laboratory tests represent two disparate domains, they suggest that some parameters in laboratory tests show prognostic information very similar to 6MWT in determining whether participants had limitations in exercise capacity. As seen in Figure 3.3.37 and Table 3.3.2, there were significant negative correlations between some parameters and exercise capacity limitation, i.e., the lower the parameters, the worse the exercise capacity limitation. The highest accuracy for limitations in exercise capacity was found for the following parameters: 6MWD (AUC: 0.885, 95% CI:0.801-0.969, p<0.001), eGFR (AUC: 0.658, 95% CI: 0.515-0.801, p=0.042), total bilirubin (AUC: 0.753, 95% CI: 0.624-0.882, p=0.001), and albumin (AUC: 0.677, 95% CI: 0.535-0.818, p=0.023). However, as seen in Figure 3.3.38 and Table 3.3.3, there were significant positive correlations between some parameters and exercise capacity limitation, i.e., the higher the parameters, the worse the exercise capacity limitation. The parameters that most accurately predicted limitations of exercise capacity were as follows: leukocytes (AUC: 0.707, 95% CI: 0.577-0.836, p=0.007), RDW-DV (AUC: 0.746, 95% CI: 0.627-0.864, p<0.001), neutrophils (AUC: 0.672, 95% CI: 0.535-0.809, p=0.024), glucose (AUC: 0.684, 95% CI: 0.542-0.826, p=0.016), troponin (AUC: 0.709, 95% CI: 0.576-0.841, p=0.006), NT-proBNP (AUC: 0.761, 95% CI: 0.637-0.886, p=0.001), MR-proANP (AUC: 0.786, 95% CI: 0.669-0.903, p<0.001), LDH (AUC: 0.709, 95% CI: 0.578-0.839, p=0.006), HbA1c% (AUC: 0.665, 95% CI: 0.517-0.814, p=0.030), HbA1c (AUC: 0.664, 95% CI: 0.515-0.812, p=0.032), and fibrinogen (AUC: 0.752, 95% CI: 0.631-0.873, p=0.001).

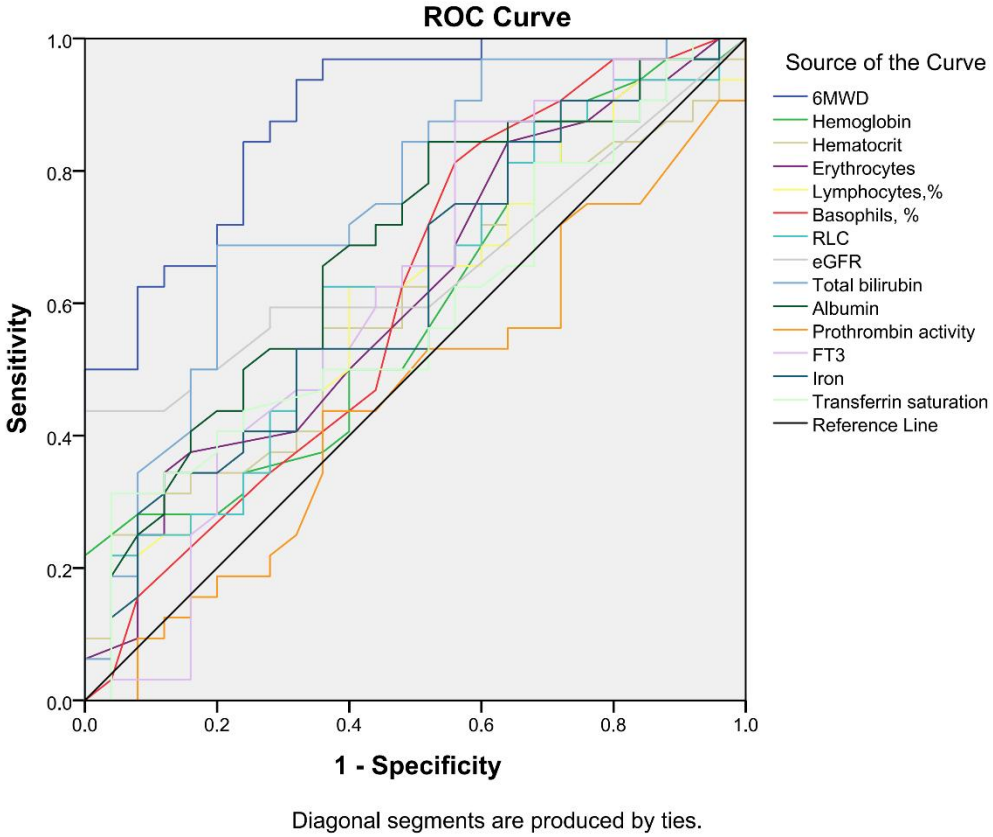

Figure 3.3.37. ROC curve of statistically significant examined blood and urine parameters where smaller test result indicates more positive test. The area under ROC Curve of the statistically significant examined variables was for predicting participants with a limitation of exercise capacity.

Table 3.3.2. ROC analysis results of statistically significant examined blood and urine parameters where smaller test result indicates more positive test.

Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Lower Bound	Upper Bound
6MWD	.885	.043	.000	.801	.969
Hemoglobin	.593	.076	.231	.444	.742
Hematocrit	.592	.075	.237	.444	.740
Erythrocytes	.614	.075	.143	.466	.761
Lymphocytes, %	.597	.076	.210	.449	.746
Basophils, %	.608	.078	.164	.456	.761
RLC	.617	.075	.131	.470	.765
eGFR	.658	.073	.042	.515	.801
Total bilirubin	.753	.066	.001	.624	.882

Albumin	.677	.072	.023	.535	.818
Prothrombin activity	.459	.077	.596	.307	.610
FT3	.616	.078	.137	.462	.769
Iron	.618	.075	.131	.470	.765
Transferrin saturation	.591	.076	.244	.442	.740

6MWD, 6-minute walk distance; RLC, relative lymphocyte count; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine.
All numerical values in the table should be intended as follow: .885 means 0.885.

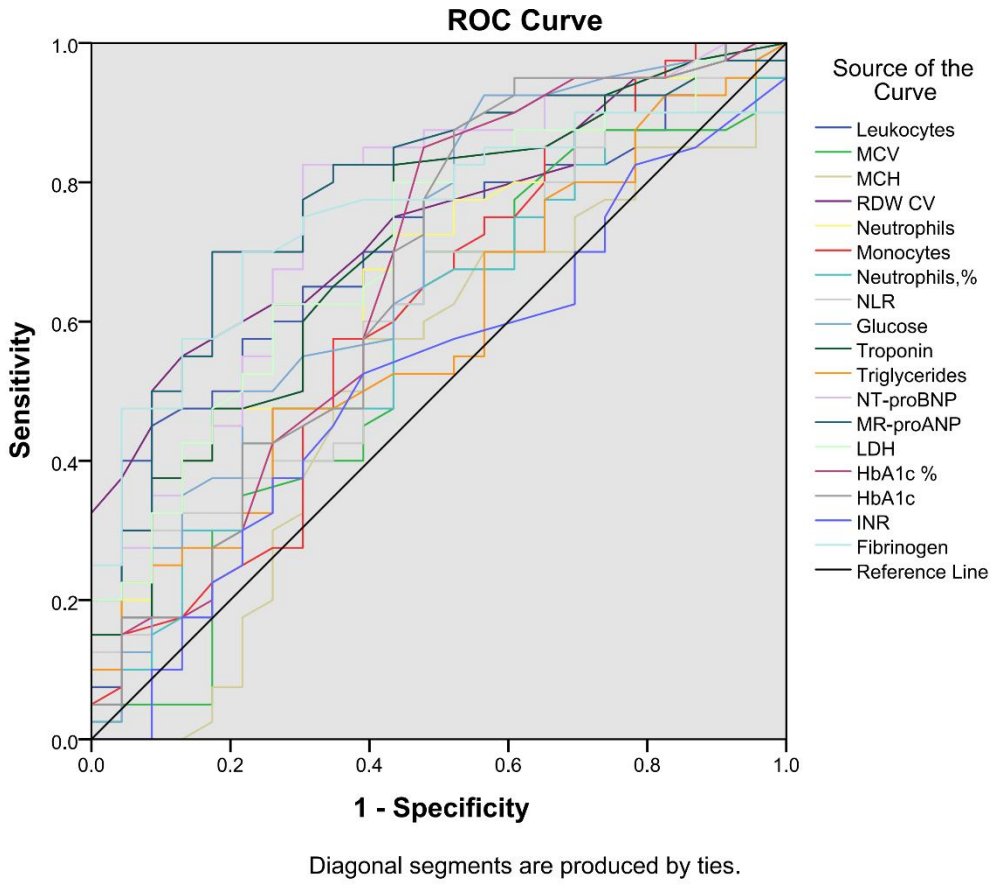

Figure 3.3.38. ROC curve of statistically significant examined blood and urine parameters where larger test result indicates more positive test. The area under ROC Curve of the statistically significant examined variables was for predicting participants with a limitation of exercise capacity.

Table 3.3.3. ROC analysis results of statistically significant examined blood and urine parameters where a larger test result indicates a more positive test.

Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Lower Bound	Upper Bound
Leukocytes	.707	.066	.007	.577	.836

MCV	.566	.078	.384	.413	.719
MCH	.516	.079	.836	.361	.671
RDW-CV, %	.746	.061	.001	.627	.864
Neutrophils	.672	.070	.024	.535	.809
Monocytes	.612	.076	.140	.463	.762
Neutrophils,%	.595	.074	.214	.449	.740
NLR	.613	.073	.138	.470	.756
Glucose	.684	.072	.016	.542	.826
Troponin	.709	.068	.006	.576	.841
Triglycerides	.586	.073	.259	.442	.730
NT-proBNP	.761	.064	.001	.637	.886
MR-proANP	.786	.060	.000	.669	.903
LDH	.709	.067	.006	.578	.839
HbA1c, %	.665	.076	.030	.517	.814
HbA1c	.664	.076	.032	.515	.812
INR	.523	.076	.764	.374	.671
Fibrinogen	.752	.062	.001	.631	.873

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW-CV, red cell distribution width - coefficient of variation; NLR, neutrophil to lymphocyte ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; LDH, lactate dehydrogenase; HbA1c, glycated hemoglobin; INR, international normalized ratio.
All numerical values in the table should be intended as follow: .707 means 0.707.

Correlation analyses indicated that some parameters were positively or negatively correlated with NYHA class, 6MWD, NT-proBNP which are universally considered the specific and sensitive indicators of CHF. The correlation coefficients between hemoglobin and NYHA class, 6MWD, and NT-proBNP were -0.340 ($p=0.001$), 0.303 ($p=0.013$), and -0.385 ($p<0.001$), respectively. The correlation coefficients between erythrocytes and NYHA class, 6MWD, and NT-proBNP were -0.373 ($p<0.001$), 0.407 ($p=0.001$), and -0.423 ($p<0.001$), respectively. RDW-CV was correlated with NYHA class ($r=0.435$, $p<0.001$), 6MWD ($r=-0.541$, $p<0.001$), and NT-proBNP ($r=0.535$, $p<0.001$). Neutrophils was correlated with NYHA class ($r=0.413$, $p<0.001$), 6MWD ($r=-0.331$, $p<0.010$), and NT-proBNP ($r=0.478$, $p<0.001$). NLR was correlated with NYHA class ($r=0.408$, $p<0.001$), 6MWD ($r=-0.311$, $p=0.016$), and NT-proBNP ($r=0.489$, $p<0.001$). RLC was correlated with NYHA class ($r=-0.427$, $p<0.001$), 6MWD ($r=0.316$, $p=0.014$), and NT-proBNP ($r=-0.510$, $p<0.001$). eGFR was correlated with NYHA class ($r=-0.306$, $p=0.004$), 6MWD ($r=0.310$, $p=0.011$), and NT-proBNP ($r=-0.498$, $p<0.001$). Troponin was correlated with NYHA class ($r=0.422$, $p<0.001$), 6MWD ($r=-0.443$, $p<0.001$), and NT-proBNP ($r=0.676$, $p<0.001$). MR-ANP was correlated with NYHA class ($r=0.433$, $p<0.001$), 6MWD ($r=-0.477$, $p<0.001$), and NT-proBNP ($r=0.816$, $p<0.001$). Fibrinogen was correlated with NYHA class ($r=0.372$, $p<0.001$), 6MWD ($r=-0.444$, $p<0.001$), and NT-proBNP ($r=0.303$, $p=0.005$).

Table 3.3.4. Correlations of NYHA class, 6MWD, and NT-proBNP with statistically significant examined blood and urine parameters.

	NYHA class		6MWD		NT-proBNP	
	r	P value	r	P value	r	P value
NYHA class	1.000	.	-0.590	<0.001	0.531	<0.001
6MWD	-0.590	<0.001	1.000	.	-0.510	<0.001
Hemoglobin	-0.340	0.001	0.303	0.013	-0.385	<0.001
Hematocrit	-0.360	0.001	0.277	0.023	-0.358	0.001
Erythrocytes	-0.373	<0.001	0.407	0.001	-0.423	<0.001
Leukocytes	0.363	0.001	-0.293	0.016	0.359	0.001
MCV	0.163	0.135	-0.302	0.013	0.273	0.012
MCH	0.074	0.498	-0.222	0.072	0.098	0.371
RDW-CV, %	0.435	<0.001	-0.541	<0.001	0.535	<0.001
Neutrophils	0.413	<0.001	-0.331	0.010	0.478	<0.001
Monocytes	0.281	0.014	-0.260	0.045	0.174	0.132
Neutrophils, %	0.354	0.002	-0.273	0.035	0.462	<0.001
Lymphocytes	-0.405	<0.001	0.284	0.027	-0.455	<0.001
Basophils	-0.144	0.208	0.217	0.093	-0.241	0.034
NLR	0.408	<0.001	-0.311	0.016	0.489	<0.001
RLC	-0.427	<0.001	0.316	0.014	-0.510	<0.001
Glucose	0.301	0.005	-0.365	0.003	0.233	0.033
eGFR	-0.306	0.004	0.310	0.011	-0.498	<0.001
Total bilirubin	-0.311	0.004	0.246	0.045	-0.103	0.344
Albumin	-0.393	<0.001	0.251	0.044	-0.388	<0.001
Troponin	0.422	<0.001	-0.443	<0.001	0.676	<0.001
Triglycerides	0.016	0.886	-0.244	0.047	0.020	0.858
NT-proBNP	0.531	<0.001	-0.510	<0.001	1.000	.
MR-proANP	0.433	<0.001	-0.477	<0.001	0.816	<0.001
LDH	0.341	0.001	-0.234	0.061	0.364	0.001
HbA1c %	0.357	0.001	-0.463	<0.001	0.260	0.017
HbA1c	0.361	0.001	-0.454	<0.001	0.274	0.012
Prothrombin activity	-0.232	0.031	0.148	0.236	-0.343	0.001
INR	0.206	0.057	-0.136	0.276	0.333	0.002
Fibrinogen	0.372	<0.001	-0.444	<0.001	0.303	0.005
FT3	-0.353	0.001	0.267	0.029	-0.323	0.003
Iron	-0.390	<0.001	0.172	0.164	-0.328	0.002
Transferrin saturation	-0.297	0.006	0.175	0.161	-0.248	0.023

6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional classification; eGFR, estimated glomerular filtration rate; RDW-CV, red cell distribution width - coefficient of variation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional

pro-atrial natriuretic peptide; LDH, lactate dehydrogenase; HbA1c, glycated hemoglobin.
Pearson's correlation or Spearman's rank correlation was applied to compare the correlation between continuous variables as appropriate.

3.4 Electrocardiogram

This part included 81 participants (healthy controls: n=15, patients with CHF: n=66). Patients with CHF were classified into the two categories based on NYHA classification including NYHA I to III (NYHA I: n=16, NYHA II: n=28, NYHA III: n=22), and the myocardiopathies including ICM and DCM (ICM: n=24, DCM: n=42).

Table 3.4.1 shows the ECG indexes of healthy controls and patients with CHF and indicates that there were significant differences in QRS and QTc comparing the control group with different NYHA class groups and comparing the control group with ICM and DCM groups. In Figure 3.4.1 and Figure 3.4.2, the significant differences were presented using bar graphs when the variables were with normal distribution and box plots when the variables were non-normally distributed.

Table 3.4.1. ECG indexes of healthy controls and patients with CHF being categorized into NYHA classes I to III groups and ICM and DCM groups.

	The control group n=15	**CHF group n=66**	**NYHA I n=16**	**NYHA II n=28**	**NYHA III n=22**	**ICM n=24**	**DCM n=42**	**P value[a]**
HR, bpm	58.93 ± 7.46	66.56 ± 14.78	54.50 (49.50-67.75 [43- 84])	65.50 (59- 79 [53-122])	65 (59-72.25 [47-93])	65.33 ± 13.39	67.26 ± 15.64	ns[1]
PQ interval, ms	158.40 ± 20.91	168 (152-182 [110-276])	171.07 ± 32.51	172.92 ± 34.66	167.11 ± 27.06	172 (156-190 [110-276])	166 (147.75-177 [122-238])	ns[1]
QRS duration, ms	98 (82-100 [74-106])	118 (99-152 [[78-198])	109 (97.50-130 [86-198])	119.50 (93- 151 [78-194])	138 (103-156 [78-186])	108 (97-153.50 [78-194])	124 (99-150.50 [78-198])	0.002 (0.001-0.002) between the control group and NYHA I group, 0.003 (0.001-0.004) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, 0.003 (0.001-0.003) between the control group and ICM group,

								<0.001 (<0.001-0.001) between the control group and DCM group[1]
QT interval, ms	414.27 ± 32.04	441.27 ± 65.63	449 (428-472 [146-478])	438 (391.50-483 [292-574])	473 (393.50-517 [376-544])	437.36 ± 50.33	443.43 ± 73.22	ns[1]
QTc interval, ms	410.40 ± 24.28	462.30 ± 57.86	427.88 ± 75.64	470.61 ± 47.11	476.77 ± 46.98	455.63 ± 53.94	466.12 ± 60.28	<0.001 (<0.001) between the control group and NYHA II group, <0.001 (<0.001) between the control group and NYHA III group, 0.023 (0.018-0.025) between NYHA I group and NYHA III group, 0.007 (0.005-0.009) between the control group and ICM group, <0.001 (<0.001) between the control group and DCM group[1]

Continuous variables with normal distribution are expressed as mean ± standard deviation and non-normally distributed variables as median (IQR [range]).
NYHA, New York Heart Association functional classification; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; HR, heart rate; QTc, corrected QT interval.
[a] Monte Carlo was jointly used to specify the 99% CI for the obtained P values when comparing the continuous variables and one of the sample sizes of the variables was less than 30.
[1] Kruskal-Wallis Test was used to compare continuous variables, and a Mann-Whitney U Test was used for post-hoc multiple comparisons.

When comparing QRS duration of the control group with patients with CHF, as shown in Figure 3.4.1, the QRS duration of the control group was significantly shorter than that of NYHA I to III groups (p=0.002, p=0.003, and p<0.001, respectively) and ICM and DCM groups (p=0.003 and p<0.001, respectively). Nevertheless, there were no obvious differences among CHF groups. For QTc interval, as shown in Figure 3.4.2, that of the control group was significantly shorter than that of NYHA II and III groups (both p<0.001) and that of ICM and DCM groups (p=0.007 and p<0.001, respectively), and that of NYHA I group was significantly shorter than that of NYHA III group (p=0.023). There were no obvious differences in QTc interval between ICM and DCM groups.

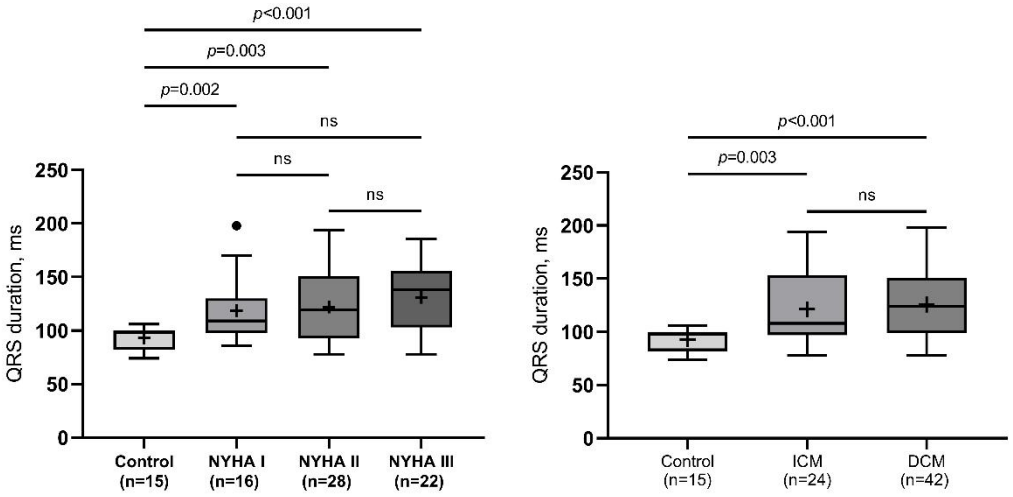

Figure 3.4.1. Comparisons of QRS duration in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

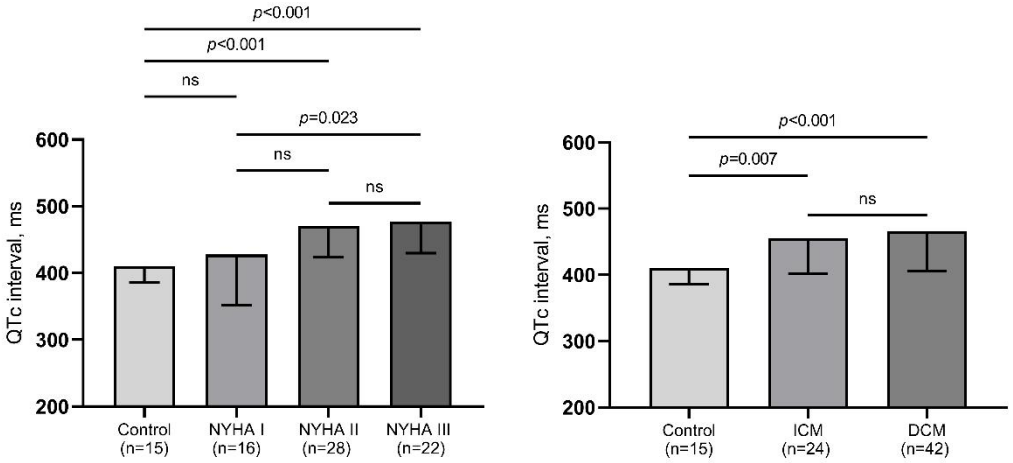

Figure 3.4.2. Comparisons of QTc interval in the control group and NYHA class I to III groups and in the control group and ICM and DCM groups.

The ROC analyses, presented in Figure 3.4.3 and Table 3.4.2, revealed significant correlations between some parameters and exercise capacity limitation. The parameters with the highest accuracy for predicting limitation of exercise capacity were as follows: 6MWD (AUC: 0.839, 95% CI: 0.738-0.940, p<0.001), NT-proBNP (AUC: 0.799, 95% CI: 0.684-0.914, p<0.001), HR (AUC: 0.690, 95% CI: 0.551-0.829, p=0.013), and QTc interval (AUC: 0.799, 95% CI: 0.660-0.899, p<0.001).

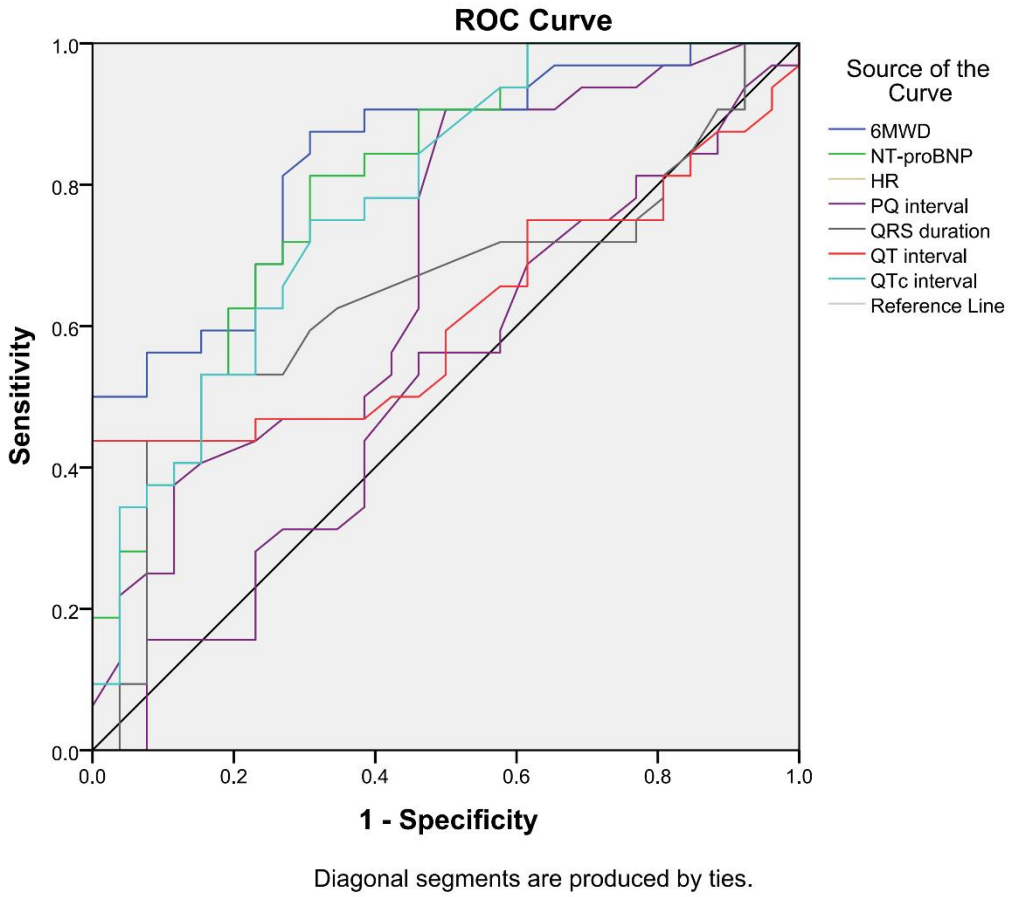

Figure 3.4.3. ROC curve of 6 MWD, NT-proBNP, and ECG indexes. The area under the ROC Curve of the variables was for predicting participants with limitations of exercise capacity.

Table 3.4.2. ROC analysis results of 6 MWD, NT-proBNP, and ECG indexes.

Area Under the Curve					
				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Lower Bound	Upper Bound
6MWD	.839	.051	.000	.738	.940
NT-proBNP	.799	.059	.000	.684	.914
HR	.690	.071	.013	.551	.829
PQ interval	.516	.077	.833	.365	.668
QRS duration	.644	.074	.062	.498	.790
QT interval	.617	.075	.127	.470	.764
QTc interval	.779	.061	.000	.660	.899

All numerical values in the table should be intended as follow: .839 means 0.839.
HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; 6MWD, 6-minute

walk distance.

The correlation analysis, as shown in Table 3.4.3, indicated that certain parameters were positively or negatively correlated with NYHA class, 6MWD, and NT-proBNP, which are universally recognized as specific and sensitive indicators of CHF [7, 31-34]. The correlation coefficients between QRS duration and NYHA class, 6MWD, and NT-proBNP were 0.385 (p<0.001), -0.365 (p=0.003), and 0.249 (p=0.029), respectively. QT interval was found to be correlated with NYHA class (r=0.247, p=0.030), 6MWD (r=-0.267, p=0.036), and NT-proBNP (r=0.274, p=0.018), while QTc interval was correlated with NYHA class (r=0.490, p<0.001), 6MWD (r=-0.474, p<0.001), and NT-proBNP (r=0.469, p<0.001).

Table 3.4.3. Correlations of NYHA class, 6MWD, and NT-proBNP with blood pressure and ECG indexes.

	NYHA class		**6MWD**		**NT-proBNP**	
	r	p	r	p	r	p
NYHA class	1.000	.	-0.620	<0.001	0.563	<0.001
NT-proBNP	0.563	<0.001	-0.504	<0.001	1.000	.
6MWD	-0.620	<0.001	1.000	.	-0.504	<0.001
SBP	-0.164	0.143	0.148	0.242	-0.305	0.007
DBP	-0.136	0.226	0.091	0.476	-0.306	0.007
PP	-0.135	0.230	0.138	0.275	-0.171	0.138
HR	0.268	0.015	-0.201	0.112	0.167	0.146
PQ interval	0.096	0.414	0.064	0.628	0.051	0.672
QRS duration	0.385	<0.001	-0.365	0.003	0.249	0.029
QT interval	0.247	0.030	-0.267	0.036	0.274	0.018
QTc interval	0.490	<0.001	-0.474	<0.001	0.469	<0.001

NYHA, New York Heart Association functional classification; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

QTc interval showed the best diagnostic value among the ECG indexes for distinguishing patients with CHF who had limitations of exercise capacity and was most closely related to NYHA classification, 6MWT, and NT-proBNP in our study. To further investigate the characteristics of participants with different QTc intervals, all participants were divided into two groups based on the median of QTc interval. As Table 3.4.4. shows, in the QTc ≥ 450 ms group, NT-proBNP was significantly higher than that in the QTc < 450 ms group (p=0.001). Furthermore, the 6MWD of the QTc ≥ 450 ms group was significantly shorter than that of the QTc < 450 ms group (P<0.001). Moreover, the QRS duration and QT interval of the QTc ≥ 450 ms group were significantly shorter than these of the QTc < 450 ms group (both p<0.001). Additionally, patients with DCM and those with a limitation of exercise capacity in the QTc ≥ 450 ms group were significantly more prevalent than those in the QTc < 450 ms group (p=0.003 and P<0.001,

Table 3.4.4. Comparisons between participants with different QTc interval.

	QTc < 450 ms n=40	**QTc ≥ 450 ms n=41**	**P value**
Age, year	54.88 ± 9.54	59 ± 11.08	0.077[1]
Men, n (%)	34 (85.0)	31 (75.6)	0.434[2]
SBP, mmHg	126.78 ± 17.01	126.93 ± 16.62	0.968[1]
DBP, mmHg	78 (72.75-83.50 [58-106])	79 (71-89 [58-105])	0.505[3]
PP, mmHg	47.50 (41.25-54 [25-89])	46 (39.50-55.50 [15-73])	0.688[3]
HR, bpm	60.50 (53.25-69.75 [43-99])	66 (59-74.50 [47-122])	0.060[3]
NT-proBNP, ng/l	213 (39-387 [10-3802])	529.50 (192-1139.50 [24-9140])	0.001[3]
6MWD, m	572.50 (519.25-612.75 [237-698])	480 (423-525.25 [160-715])	<0.001[3]
PQ interval, ms	167.32 ± 22.86	168.94 ± 36.13	0.819[1]
QRS duration, ms	99.15 ± 16.71	137.15 ± 30.27	<0.001[1]
QT interval, ms	402.36 ± 55.40	470.55 ± 46.45	<0.001[1]
QTc interval, ms	409.65 ± 41.24	494.68 ± 33.93	<0.001[1]
ICM, n (%)	12 (30.0)	12 (29.3)	0.943[2]
DCM, n (%)	14 (35.0)	28 (68.3)	0.003[2]
NYHA I, n (%)	9 (22.5)	7 (17.1)	0.738[2]
NYHA II, n (%)	10 (25.0)	18 (43.9)	0.074[2]
NYHA III, n (%)	7 (17.5)	15 (36.6)	0.054[2]
Limitation of exercise capacity, n (%)	17 (42.5)	33 (80.5)	<0.001[2]

Continuous variables with normal distribution are expressed as mean ± standard deviation and non-normally distributed variables as median (IQR [range]). Categorical variables are expressed as frequency (percentage).

QTc, corrected QT interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 6MWD, 6-minute walk distance; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; NYHA, New York Heart Association functional classification.

[1] Independent t-test was used to compare groups with normal distribution.

[2] Chi-Square Test or Continuity Correction Test was used to compare categorical variables as appropriate.

[3] Mann-Whitney U test was used to compare groups with non-normal distribution.

4. Discussion

4.1 Baseline characteristics and medications

The analysis of baseline characteristics and medication usage among healthy controls and patients with CHF categorized by NYHA classification or by ICM and DCM revealed several interesting and previously overlooked trends. Specifically, healthy controls were found younger than patients with CHF, and patients in NYHA class I were younger than those in higher NYHA classes. Patients with ICM were older than those with DCM, which is consistent with previous studies [67, 68]. The rate of atrial fibrillation in healthy controls was lower than in CHF patients, but few differences were found among NYHA I to III groups or between ICM and DCM groups. The prevalence of hypertension was higher in higher NYHA class groups and in the ICM group. As expected, symptoms such as dyspnea on exertion and at rest, orthopnea, primary pulmonary hypertension, fatigue, and nocturia were more frequent in higher NYHA classes, but no significant differences were observed between ICM and DCM groups. Therefore, these symptoms were closely related to NYHA classification, but they may not be useful for distinguishing between ICM and DCM.

The patients in NYHA I and II groups and in the ICM group were more likely to be treated with ACE inhibitors and/or Ang-II receptor type 1 (AT1) antagonists. It is wildly recognized that inhibiting the renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the treatment of patients with CHF [69-73]. Numerous clinical studies have demonstrated that blockade of RAAS, including the use of ACE inhibitors and AT1 antagonists, improves morbidity and mortality in patients with CHF [74-79]. The lower usage of these medications in the NYHA III group may be related to the concerns regarding their primary side effect, hypotension, in patients with advanced CHF [80, 81].

Beta-blockers are commonly used in the treatment of patients with CHF due to their ability to block the sympathetic nervous system [82], which has been shown to reduce the incidence of arrhythmias, improve CHF symptoms, and extend lifespan [83]. Guidelines from both the ACCE/AHA and the European Society of Cardiology recommend beta-blockers for the management in CHF patients [3, 11]. In our study, we found that beta-blockers were commonly used in patients with CHF, with no significant differences in usage among different NYHA class groups and between ICM and DCM groups.

Loop diuretics are commonly used to target fluid retention and congestion, which are primary symptoms of CHF [84]. In our study, we observed that loop diuretics were widely used in CHF patients, with higher usage rates in higher NYHA class. However, there were few differences in loop diuretic between ICM and DCM groups.

Aldosterone results in sodium and fluid retention by increasing the reabsorption of sodium and water and the excretion of potassium [85]. Increased aldosterone levels are proven to be closely correlated with the pathophysiology of CHF [86]. Aldosterone antagonists are used to prevent aldosterone from binding and stimulating the cytoplasmic aldosterone receptor, and then foster excretion of sodium and conservation of potassium [87]. In our study, we found that aldosterone antagonists were frequently

used in patients with CHF, with no obvious differences in usage among NYHA I to III groups and between ICM and DCM groups.

Neprilysin metabolizes vasoactive peptides including natriuretic peptides, bradykinin, and Ang-II, while sacubitril/valsartan is a medication that consists of a neprilysin inhibitor (sacubitril) and an Ang-II receptor blocker (valsartan) [88]. It promotes diuresis, natriuresis, and vasodilation by inhibiting the degradation of natriuretic peptides, while also reducing vasoconstriction and aldosterone release by inhibiting Ang-II [88]. In our study, we observed that sacubitril/valsartan was commonly used in CHF patients, especially in those in NYHA class III, with no significant differences in usage between ICM and DCM groups.

Statins are widely used in patients with hyperlipidemia and cardiovascular diseases due to their multifaceted advantages, including cholesterol-lowering, endothelial improvement, anti-oxidative and anti-inflammatory effects, neovascularization, and immunomodulatory performance [89]. Therefore, statins play a crucial role in patients with cardiovascular diseases, including CHF [90]. In our study, statins were more commonly used in patients with CHF compared to healthy controls, but there were few differences among NYHA I to III groups. However, the prevalence of patients with ICM taking statins was significantly higher than patients with DCM. This can be explained by the fact that ICM is secondary to ischemic heart disease and an ultimate outcome of coronary artery disease and mainly caused by arteriosclerosis.

Aspirin is commonly used to reduce pain, fever, and inflammation, and to diminish mortality after a sudden cardiac attack. It is also taken long-term to prevent ischemic strokes and blood clots in high-risk populations. CHF is prone to be pro-thrombotic and may require antithrombotic treatment due to its comorbidities and decreased cardiac output [91]. In our study, aspirin was commonly used in patients with CHF, and there were also no obvious differences among NYHA I to III groups. However, a higher frequency of aspirin usage was found in patients with ICM compared with those with DCM. This can be explained by the fact that ICM is mainly caused by arteriosclerosis and platelet adhesion, activation, and aggregation are pivotal in atherothrombosis. P2Y12 inhibitors, another group of antiplatelet drugs, were also found to be more commonly used in the ICM group.

SGLT2 inhibitors block glucose transport proteins that facilitate the reabsorption of glucose in the proximal tubules of the kidney, resulting in modest reductions of glucose levels in patients with type 2 diabetes [92]. SGLT2 receptors are overexpressed in patients with diabetes, increasing glucose reabsorption and glycemia [93]. SGLT2 inhibitors also have a mild diuretic effect and promote calorie loss through glycosuria, resulting in sustained weight reduction over time [92]. In addition to pharmacodynamic effects that assist in the excretion of glucose, SGLT2 inhibitors have multidimensional cardiovascular benefits in CHF. They have a mild diuretic effect and decrease sodium, resulting in sodium homeostasis and a decrease in plasma volume and BP [93]. The reduced circulating volume decreases preload and afterload is decreased with lower BP, improving cardiac blood flow [93]. SGLT2 inhibitors also have a demonstrated ability to improve arterial stiffness through smooth muscle relaxation [93]. Other cardiovascular benefits that are not clearly understood include protective effects on cardiac myocytes

and the promotion of ketone production, which can be used by the heart for energy generation and ultimately improve cardiac function [93]. In our study, the presence of diabetes mellitus was obviously higher in NYHA III class group and ICM group compared with the control group, and SGLT2 inhibitors were more used in patients with NYHA III group and ICM and DCM groups compared to the control group. However, there was no significant difference between the ICM and DCM groups.

4.2 Six-min walk distance

The 6MWT is a submaximal and well-tolerated exercise test commonly used to assess the functional status of CHF patients. In our study, the 6MWD of the control group was significantly longer than that of NYHA II and III groups, as well as the ICM and DCM groups. Furthermore, the 6MWD of the NYHA I group was significantly longer than that of the NYHA II and III groups. Thus, the higher the NYHA class, the shorter the 6MWD; however, no significant differences were observed between the ICM and DCM groups.

Regarding the Borg scale 6-20 score, we found that the trends of it after the 6MWT when comparing the control group with CHF groups were almost the inverse of the trends observed for the 6MWD. The Borg scale 6-20 scores after the 6MWT for the control group and NYHA I were statistically lower than those of the NYHA II and III groups, and the control group had significantly lower scores than the DCM group. However, there were few differences between the control group and NYHA I group, NYHA II and III groups, and ICM and DCM groups.

Based on these two parameters of the 6MWT, we found that exercise capacity and tolerance of healthy controls and patients in the NYHA I group were significantly better than those of patients in the NYHA II and III groups. Additionally, the exercise capacity and tolerance of healthy controls were markedly better than those of patients with DCM. Nevertheless, exercise capacity and tolerance were similar between healthy controls and patients in the NYHA I group, patients in the NYHA II and III groups, and patients with ICM and DCM. Consequently, exercise capacity and tolerance appear to be closely related to the cardiac function of CHF rather than the specific type of cardiomyopathy.

In terms of SBP, DBP, and HR among healthy controls and patients with CHF, we found that both SBP and DBP of healthy controls were significantly higher than patients in NYHA I to III groups and ICM and DCM groups before and after 6MWT. However, unexpectedly, no significant differences in SBP and DBP were observed among patients in NYHA I to III groups and between ICM and DCM groups. Additionally, there were few significant differences in HR among all these groups both before and after 6MWT.

When comparing SBP, DBP, and HR of each group before and after 6MWT separately, these three indicators were almost all significantly higher after the 6MWT compared to those before 6MWT, except for SBP in the NYHA III group and DBP in the control group. No significant differences were found in SBP in the NYHA III group and DBP in the control group before and after the 6MWT. The lack of an obvious difference in SBP in NYHA III group may be due to the fact that the submaximal activity of patients with severe cardiac dysfunction is already close to their maximum [94]. Additionally, patients' emotional, psychological, and physical factors may have stabilized over time due to the

long-term progression and treatment of CHF, but the compensatory ability of cardiac function has decreased [94]. The absence of a significant difference in DBP in the control group may be attributed to the better vascular elasticity and cardiac reserve of participants in the control group [95, 96].

The ROC analysis of the 6MWD demonstrated strong prognostic value. The longer the 6MWD, the greater the exercise tolerance of the participant, and the better the cardiac function, which means 6MWD is significantly inversely related to the limitation of exercise capacity. This finding is consistent with previous studies [17, 97, 98].

4.3 Laboratory tests

In this section, we discovered some intriguing and unexpected trends by comparing commonly used clinical laboratory parameters. These results suggest that certain parameters might often be overlooked but could play a more crucial role in predicting and assessing the condition of patients with CHF.

Comparisons of hemoglobin, hematocrit, and erythrocytes among the control group and CHF groups revealed that patients in the NYHA III group had a significantly higher prevalence of anemia, with few differences observed among other groups. For MCV, all CHF groups were significantly higher than the control group, indicating that erythrocytes in patients with CHF were larger than those in healthy controls [99]. Although macrocytosis may not cause symptoms in and of itself, it can indicate some underlying health conditions [100]. Common causes of macrocytosis include deficiencies of vitamin B-12 or folate[101], alcohol consumption[102], liver disease[103], hypothyroidism[104], and more. For MCH, the DCM group, as well as the NYHA I and II groups, were significantly higher than the control group. The most common cause for this is vitamin B-12 and folate deficiency [105]. Regarding RDW-CV%, the control group was significantly lower than CHF groups, and the NYHA I group was significantly lower than NYHA III group. However, no significant differences were observed between ICM and DCM groups. High RDW-CV% may also indicate nutrient deficiencies such as iron, folate, or vitamin B-12 [99]. For iron and transferrin saturation, the trends among these groups were consistent, with the NYHA III group being significantly lower than the control group and NYHA I and II groups. No significant differences were observed among the control group and ICM and DCM groups. Iron deficiency is a common comorbidity in patients with CHF, with nearly 50% of CHF patients having low iron levels, regardless of anemia [106, 107]. Iron deficiency can result from cardiac cachexia, impaired iron absorption, chronic diseases or inflammation, and gastrointestinal blood losses related to the use of aspirin, antiplatelet agents, anticoagulants, and other medications [108-111]. Taking all the above parameters in account, our findings suggest that patients with CHF are predisposed to anemia, with higher NYHA class correlating with increased prevalence of anemia, particularly macrocytic anemias when considering both RDW-CV% and MCV. Nevertheless, no significant differences were observed between patients with ICM and DCM. Patients with severe cardiac function are more likely to experience iron deficiency, regardless of whether they have ICM or DCM. Additionally, the diets of patients with CHF

may be deficient in vitamin B-12 or folate, or these patients may not absorb these nutrients properly.

In terms of inflammatory parameters, the NYHA III group had significantly higher leukocyte levels than the control group, as well as the NYHA I and II groups. Moreover, both ICM and DCM groups had significantly higher leukocyte levels than the control group. However, there were few differences between the control group and NYHA I and II groups or between the ICM and DCM groups. For neutrophils, NYHA I to III groups and ICM and DCM groups all exhibited significantly higher levels than the control group, however, no significant differences were observed among NYHA I to III groups or between ICM and DCM groups. Regarding immature granulocytes, ICM and DCM groups had significantly higher levels than the control group, but there were no significant differences between ICM and DCM groups or among the control group and NYHA I to III groups. For monocytes, NYHA II and III groups and ICM and DCM groups showed significantly higher levels than the control group, with no significant differences among CHF groups. In the case of basophils, the control group had significantly higher levels than NYHA I to III groups and the DCM group, but no significant differences were observed among CHF groups. For NLR, CHF groups were significantly higher than the control groups, with few differences among CHF groups. For RLC, the trends were opposite to those of NLR, CHF groups were significantly lower than the control group, and no significant differences were observed among CHF groups. These inflammatory parameters indicate that almost all the inflammatory parameters in NYHA I to III groups and ICM and DCM groups are significantly higher than those in the control group. However, no significant differences were observed among NYHA I to III groups or between ICM and DCM groups, other than leukocytes, where the NYHA III group was higher than other groups. These results suggest an inflammatory reaction exists in patients with CHF regardless of NYHA classification, even in patient with NYHA I who have no limitation of exercise capacity and irrespective of whether they have ICM or DCM. Most of the inflammatory parameters, including the most representative parameters such as neutrophils, which are associated with a quicker response, and lymphocytes, which are linked with a more adaptive long-term response of the immune system[112], are similar, with no significant differences observed among NYHA I to III groups or between ICM and DCM groups.

Renal dysfunction is significantly associated with an increased risk of hospitalization and mortality in patients with cardiac failure due to CHF [113, 114]. Decreased eGFR is linked to increased mortality risk in patients with CHF, whether at baseline or during treatment [114]. High levels of uric acid are significantly related to declines in eGFR and CHF [115, 116]. In our study, eGFR levels in the NYHA II and NYHA III groups were significantly higher than those in the control group and NYHA I group; however, few differences were observed between the control group and NYHA I group, NYHA II and III groups, or among the control group and ICM and DCM groups. For Uric acid, the ICM group was significantly higher than the control group, but no obvious differences were found among other groups. These results suggest that as cardiac function worsens, renal dysfunction become more severe, but this does not appear to be related to different types of cardiomyopathy.

Advanced CHF can lead to hormonal and immunologic alterations, with FT3 levels decreasing in 24.5% of patients with CHF [117]. FT3 has been proven to be crucial for modulating heart rate, cardiac contraction, and arterial peripheral resistance [118, 119]. Furthermore, low-FT3 syndrome is an independent risk indicator of mortality in patients with CHF [120]. Our study's finding was consistent in that FT3 levels in the NYHA III group were significantly lower than those in the NYHA I and II groups, and there were no obvious differences between the ICM and DCM groups.

The relationship between total bilirubin levels and CHF is complex and varies in researching findings. While some studies showed elevated total bilirubin levels in CHF patients, our study, like some others, found lower levels in advanced CHF [121]. This discrepancy may be attributed to several interrelated factors. Firstly, increased oxidative stress in advanced CHF may lead to greater bilirubin consumption as an antioxidant. Secondly, hepatic congestion and impaired hepatic function, common in advanced CHF, can also lower the production of bilirubin.

In accordance with Starling's law, advanced hypoalbuminemia can destabilize both latent and chronic conditions of cardiac function [122]. Serum albumin is conducive to maintaining myocardial fluid balance, and hypoalbuminemia may result in myocardial edema and deteriorate myocardial function [123, 124]. Hypoalbuminemia is also related to diuretic resistance and fluid retention [125, 126]. Furthermore, serum albumin has antioxidant functions and anti-inflammatory properties [127, 128]. Therefore, serum albumin is negatively related to the outcome in patients with CHF. In our study, the albumin levels of NYHA III were significantly lower than those of other groups, and those of the NYHA II group were significantly lower than those of the NYHA I group. However, there were few differences among the control group and the ICM and DCM groups. Therefore, hypoalbuminemia is more frequently in patients with higher NYHA classification, and there may be no significant differences between the ICM and DCM groups.

Hyperlipidemia is a common metabolic disorder, and improved lipid conditions can reverse cardiac dysfunction [129]. In our lipid profile tests, total cholesterol, non-HDL, LDL of ICM group were significantly lower than those of the control group and DCM group, and there were no obvious differences among other groups. From Figure 3.1.6, we could see that patients in the NYHA I to III groups had a higher frequency of taking statins compared to patients in the control groups, and patients in the ICM group had a higher frequency compared to the control group and DCM group. This may explain why the lipid parameters of the ICM group were lower and more carefully controlled than those of the control group and DCM group. Therefore, although hyperlipidemia is common in patients with CHF, our study findings show that the lipid conditions of the patients with CHF were well improved, especially for those with ICM.

LDH is a cytoplasmic enzyme present in almost all body tissues. The enzyme converts pyruvate, the final product of glycolysis, to lactate when oxygen is in short supply and is released into the blood [130]. Elevated LDH can indicate myocardial injuries and/or damage to other cells in the body, including the lungs, liver, gall bladder, and muscles [131-133]. Therefore, it is necessary to test other parameters simultaneously when diagnosing cardiac dysfunction. In our study, the LDH levels of the NYHA II and III

groups and the ICM and DCM groups were significantly higher than the control group. However, there were no apparent differences among the NYHA I to III groups and between the ICM and DCM groups. This suggests that myocardial injury exists in patients with CHF, particularly in those with advanced CHF, but there were no evident differences between ICM and DCM.

After the cardiomyocyte membrane is disrupted, the troponin in the cytosol and the structural troponin, including troponin fragments, will pass into the extracellular space and blood. Therefore, elevated troponin is related to the extent of the myocardial injury [134, 135]. In our study, troponin of the NYHA I to III groups and ICM and DCM groups were significantly higher than those of the control group. However, there were few differences among the NYHA I to III groups and between ICM and DCM groups. This indicates that there were no significant differences in patients with CHF, regardless of their NYHA class and the type of cardiomyopathy they had.

NT-proBNP is primarily synthesized in ventricular cardiomyocytes and secreted by the left ventricle in response to ventricle distension, overload pressure, myocardial ischemia, and injury. NT-proBNP is a sensitive parameter reflecting ventricular function and fluid overload and is routinely used to assist in the diagnosis of cardiac dysfunction [136]. MR-proANP, similar to NT-proBNP, belongs to a family of cardiac- and vascular-derived hormones [137]. Both are crucial in maintaining cardiovascular homeostasis, fluid balance, and blood pressure [138-140]. MR-proANP is predominantly secreted by the right atrium following the atrial stretch in HF [138, 141]. In our study, the trends of NT-proBNP and MR-proANP were the same, and these two parameters in the control group were significantly lower than those in the NYHA I to III groups and ICM and DCM groups. Additionally, NYHA III was significantly higher than NYHA I group. However, there were no evident differences between ICM and DCM groups. Therefore, NT-proBNP and MR-proANP are much higher in patients with CHF and are closely related to NYHA classification. However, they may not distinguish between ICM and DCM.

Patients with higher blood glucose have an independently increased risk of CHF [142]. Elevated blood glucose has been recognized to be closely associated with macrovascular diseases, left ventricular hypertrophy, concentric remodeling, and increased mortality [143-147]. Our laboratory findings showed that NYHA II and III groups and ICM and DCM groups had significantly higher levels than the control group, but there were no significant differences among CHF groups. For HbA1c, CHF groups were significantly higher than the control group, and there were no significant differences among CHF groups as well. From Table 3.1.2, we found the medications to lower blood glucose among these groups were almost similar, including insulin, metformin, DPP-4 inhibitors, GLP-1 agonists. Therefore, we could learn that patients with CHF still have higher blood glucose levels compared with healthy populations under effective glucose-lowering drugs, but there were no obvious differences in different NYHA classes and different types of cardiomyopathy.

For coagulation-related tests, prothrombin activity in CHF groups was significantly lower than in the control group. INR of NYHA I and III groups was significantly higher than the control group. However, there were no apparent differences in these

parameters among CHF groups. From Table 3.1.2, there were no obvious differences in antithrombotic drugs used among NYHA I to III groups. However, the usage of antiplatelet drugs was significantly more frequently in ICM groups compared to DCM groups. In our study, we learned that coagulation dysfunction may exist in patients with CHF under antithrombotic therapies. However, there were no apparent differences in coagulation function among NYHA I to NYHA III groups and between ICM and DCM groups. Fibrinogen, produced by the liver and activated during the coagulating process, is an indication of thrombosis and inflammation [148, 149]. Moreover, fibrinogen is closely associated with mortality in patients with advanced CHF [150]. In our study, the findings were consistent: fibrinogen levels in the control group were significantly lower than in NYHA II and III groups, and levels in the NYHA I group were significantly lower than in the NYHA III group. Furthermore, fibrinogen levels were significantly lower in the control group compared to the DCM group.

From our findings, the ROC curve demonstrated that the AUC for total bilirubin, leukocytes, RDW-CV, troponin, NT-proBNP, MR-proANP, LDH, and fibrinogen in laboratory tests were similar to that of 6MWD, indicating good diagnostic value in distinguishing between participants with limited exercise capacity or not [151].

Correlation coefficients represent the linear interdependence between two variables. By comparing RDW-CV, RLC, troponin, and MR-proANP with NYHA class, 6MWD, NT-proBNP, which are generally considered specific and sensitive indicators of CHF, the findings demonstrated that RDW-CV, RLC, troponin, and MR-proANP were fairly related to the three universally accepted parameters and could be considered effective indicators of CHF [152].

4.4 Electrocardiogram

By comparing common ECG indexes, the analysis of QRS duration among the control group and CHF groups revealed that the QRS duration of healthy controls were significantly shorter than that of patients with CHF. However, there were no notable differences among NYHA I to III groups and between ICM and DCM groups. The QRS complex represents ventricle depolarization, and its normal range is 0.06 to 0.1 seconds. Prolonged QRS duration indicates impaired conduction within the ventricles [153]. In patients with CHF, the prevalence of prolonged QRS (≥120 ms) ranges from 14% to 47%, with 30% being generally accepted [154]. Left bundle branch block (LBBB) occurs more frequently than right bundle branch block (RBBB) [154]. In our study, the QRS duration of the control group was significantly shorter than that of patients with CHF. However, there were no notable differences among CHF groups, and it may not stratify the risk in different NYHA classes and different cardiomyopathies.

The comparisons of QTc duration among the control group and CHF groups demonstrated that the QTc duration of the control group was significantly shorter than that of NYHA II and III groups and ICM and DCM groups, and that of NYHA I group was significantly shorter than that of NYHA III groups. However, there were also no significant differences between ICM and DCM groups. Long QT syndrome represents an

abnormally functioning electrical system of the heart that can lead to potentially lethal arrhythmia, such as torsades de pointes, which may result in syncope or sudden cardiac arrest. The QTc is the corrected QT interval and estimates the QT interval at a standard heart rate of 60 bpm. In our study, QTc duration was closely related to NYHA classification, indicating that the longer the QTc, the more severe the cardiac function.

The ROC curve in our study showed that the AUC of the QTc interval was similar to that of 6MWD and NT-proBNP and had strong diagnostic value in distinguishing between participants with limited exercise capacity or not [151].

Correlation analyses indicated that the QTc interval was consistently related to NYHA class, 6MWD, and NT-proBNP, with the QTc duration being positively related to NYHA classification and NT-proBNP, and negatively correlated with 6MWT. Consequently, a prolonged QTc interval represented the deterioration of cardiac function and decreased exercise tolerance and could be considered an effective indicator of CHF [152].

Upon conducting ROC analyses and correlation analyses, QTc demonstrated the best power to evaluate the risk stratification of patients with CHF compared to other ECG indices, including QRS duration. In further categorization based on QTc, we found that NT-proBNP levels in the QTc ≥ 450 ms group were significantly higher than those in the QTc < 450 ms group, and 6MWD in the QTc ≥ 450 ms group was significantly shorter than that in the QTc < 450 ms group. For ECG indices, QRS duration and QT interval in the QTc ≥ 450 ms group were significantly higher than those in the QTc < 450 ms group. The frequency of participants with exercise capacity limitation in the QTc ≥ 450 ms group was significantly higher than that in the QTc < 450 ms group. These findings were consistent with previous results in our study. Interestingly, we found the frequency of patients with DCM was significantly higher in the QTc ≥ 450 ms group than in the QTc < 450 ms group. From previous studies, the correlation between the QTc interval and DCM may be related to SCN5A mutation [155-158].

ECG indices demonstrated diagnostic value for CHF, and ECG is a non-invasive and irreplaceable approach for assessing patients with CHF. In particular, the QTc duration was most closely related to NYHA classification, 6MWD, and NT-proBNP. Utilizing or combining ECG indices is beneficial for the diagnosis of CHF.

5. Conclusions

5.1 Summary

The primary objectives of this dissertation were to investigate four aspects, including baseline characteristics and medications, 6MWT, common laboratory parameters, and ECG indices of healthy controls and patients with CHF comprehensively and systematically, and to optimize the utilization of these prevalent clinical tests. In our study, patients with CHF were categorized based on two different categories: NYHA classification and cardiomyopathies, including ICM and DCM, simultaneously.

Regarding the first part, baseline characteristics and medications, significant differences were observed among the control groups and CHF groups. Healthy controls and patients in NYHA class I were younger than patients in higher NYHA classes, while patients with DCM were younger than those with ICM. Atrial fibrillation and hypertension were more common in patients with CHF. CHF symptoms correlated closely with NYHA classification, and no significant differences were observed between ICM and DCM groups. ACE inhibitors and/or AT1 antagonists were frequently used in patients with CHF, particularly in mild to moderate groups. Beta-blockers and aldosterone antagonists were commonly prescribed for patients with CHF, and no distinct differences were noted among different NYHA class groups and between ICM and DCM groups. Loop diuretics, sacubitril/valsartan, and amiodarone were more frequently administered to patients with advanced CHF, and few differences observed between ICM and DCM groups. Statins, aspirin, and P2Y12 inhibitors were more commonly prescribed in the ICM group. SGLT2 inhibitors were primarily used by patients in the NYHA III group and both ICM and DCM groups.

In the second part, focusing on the 6MWT, submaximal exercise capacity was closely associated with NYHA stages of CHF rather than the etiology of CHF (ICM and DCM). Although the SBP and DBP in the control group were significantly higher than those in CHF groups, no obvious differences were observed in SBP, DBP, and HR among patients with CHF, including among NYHA I to III groups, and between ICM and DCM groups before and after 6MWT. When comparing the differences in SBP, DBP, and HR of each group before and after 6MWT separately, SBP, DBP, and HR after 6MWT were almost all significantly higher than those before 6MWT, except for SBP in the NYHA III group and DBP in the control group.

The conclusions of the third part, focusing on laboratory tests, demonstrated that these tests can effectively evaluate the condition of patients with CHF and are closely related to NYHA classification, 6MWD, and NT-proBNP. These laboratory tests have often been frequently overlooked and can serve as a valuable supplement to other parameters reflecting cardiac function when comprehensively predicting and assessing patients with CHF.

The conclusions of the fourth part, focusing on ECG, indicated that ECG indices possess diagnostic value for CHF, and ECG is a non-invasive and irreplaceable approach to assessing patients with CHF. Notably, QTc duration was most closely associated with NYHA classification, 6MWD, and NT-proBNP. Utilizing or combining ECG indices is

beneficial for the diagnosis of CHF.

In our study, we observed some intriguing and previously overlooked trends across these four parts for healthy controls and patients with CHF. We can make better and more thorough use of these non-invasive, safe, economical, and repeatable tests in routine clinical practice.

5.2 Limitations

The limitations of our study primarily lie in two aspects: (1) the sample size of each group was relatively small. Consequently, the low statistical power and potential selection bias warrant consideration. Further large-scale studies are necessary to derive more robust conclusions. (2) patients with NYHA IV were not involved, as they are often hospitalized and face numerous restrictions and significant risks in performing any exercise capacity tests.

6. References

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Statutory Declaration

“I, Xiaodan Gong, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic Multiscale phenoTYPing in Heart Failure (Multiskalen PhenoTYPing bei Herzinsuffizienz), independently and without the support of third parties and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citation guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, and statistical processing) and results (in particular regarding figures, charts, and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other people and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

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Publication list

The following papers were published during the completion of my doctoral study period (in chronological order).

1. The first and corresponding author.
   Gong X. Malignant hyperthermia when dantrolene is not readily available.
   BMC Anesthesiol. 2021 Apr 16;21(1):119. doi: 10.1186/s12871-021-01328-3. PMID: 33863282; PMCID: PMC8051048.

2. The first and corresponding author.
   Gong X, Hu M, Li M. Relationship of arterial tonometry and exercise in patients with chronic heart failure: a systematic review with meta-analysis and trial sequential analysis.
   BMC Cardiovasc Disord. 2022 Aug 1;22(1):345. doi: 10.1186/s12872-022-02792-6. PMID: 35909113.

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Statistical Certificate

CHARITÉ

CharitéCentrum für Human- und Gesundheitswissenschaften

Charité | Campus Charité Mitte | 10117 Berlin

Institut für Biometrie und klinische Epidemiologie (iBikE)

Direktor: Prof. Dr. Frank Konietschke

Postanschrift:
Charitéplatz 1 | 10117 Berlin
Besucheranschrift:
Reinhardtstr. 58 | 10117 Berlin

Tel. +49 (0)30 450 562171
frank.konietschke@charite.de
https://biometrie.charite.de/

Name, Vorname: Gong, Xiaodan

Emailadresse: xiaodan.gong@charite.de
Matrikelnummer: 227766
PromotionsbetreuerIn: Prof. Dr. Burkert Pieske

Promotionsinstitution / Klinik: CC11 Medizinische Klinik m.S.

Kardiologie CVK

Bescheinigung

Hiermit bescheinige ich, dass Frau Xiaodan Gong innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 18.07.2022

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Aufgrund der kleinen Fallzahl sollen vorwiegend Nicht-parametrische Tests durchgeführt werden.
- Bei der Beschreibung der Daten immer angeben, dass es sich hierbei um eine kleine Stichprobe handelt und die Aussagekraft dadurch reduziert ist.
- Angabe von Konfidenzintervalle um die Unsicherheit zu quantifizieren.
- Bei kategorialen Daten mit kleiner gleich fünf Ausprägungen pro Zelle wird von jeglichen statistischen Tests abgeraten.

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

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CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN
Institut für Biometrie und
Klinische Epidemiologie
Campus Charité Mitte
Charitéplatz 1 | D-10117 Berlin
Sitz: Reinhardtstr. 58