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Effect of Bacterial Sepsis on some Biochemical and Immunological Markers in Patients with Heart Failure in Karbala Province

A dissertation submitted to Council of the College of Education for Pure Sciences – University of Kerbala, as a partial fulfillment of the requirements for the degree Doctorate of Philosophy in Biology-Zoology

by

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

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Dedication

To my dear parents, for their endless love and prayers,

To my husband, for his constant support and patience,

To my daughter, the joy and light of my life

To everyone wished me well

This work is lovingly dedicated to you.

Sara

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First of all, I would like to thank Allah for enabling Grace from the start of this work to its perfect completion. To him be Praise and Glory now and evermore.

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Finally, I would like to thank everyone who supported me in every way, and I forget to mention his name.

Sara

Summary

Cardiovascular diseases are leading causes of morbidity and mortality, with myocardial ischemia and heart failure representing two major yet distinct entities. Myocardial ischemia denotes insufficient oxygen supply to the myocardium due to coronary obstruction, whereas heart failure reflects the inability of the heart to meet systemic circulatory demands. Despite their differences, ischemia is a principal cause of heart failure, and both conditions frequently coexist, In the setting of sepsis, systemic inflammation and circulatory dysregulation exacerbate ischemia and contribute to sepsis-induced cardiomyopathy, thereby complicating diagnosis, management, and prognosis.

The present study was designed to determine the most prevalent bacterial species that cause sepsis in heart failure patients, investigate their association with heart failure risk factors, and identify their pattern of antibiotic susceptibility and identify different parameters levels that effected by bacterial infection in heart failure patients. One hundred patients were divided into four groups: Twenty-five patients with heart failure and sepsis (G1), twenty-five patients with heart failure alone (G2) ,twenty-five patients with sepsis alone (G3) and twenty-five for healthy individual (G4). They were collected directly from the coronary care unit at the Heart Center in Imam Hussein Medical City in Karbala during the period from January 2024 to August 2024. Ten ml of venous blood sample were taken from heart failure patients after admission to the Coronary Care Unit (CCU). There is an important procedure of blood culturing that should be applied, Immunological tests were performed such as, Troponin, N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP), C-type Natriuretic Peptide (CNP), Ischemia-Modified albumin (IMA), soluble CD40 Ligand (sCD40L), C-reactive protein (CRP) and Procalcitonin (PCT). General parameters such as Age (age groups included 20-39, 40-59, 60-79, 80-99 year) and Sex (male 53, female 47). Hematological Parameters (CBC) such as White blood cell (WBC) Lymphocyte

(LYM) and Neutrophil (NEU), Red blood cell (RBC), Hemoglobin (HGB), Platelet (PLT) and Hematocrit (HCT), Bacteriological tests (Identification of Bacteria and Antibiotics Susceptibility Tests).

The results of current study showed that there were no significant differences ($P \geq 0.05$) between female and male in the study groups (no heart failure with infection G3, heart failure without infection G2 and Heart failure with infection G1) compared with healthy group G4.

The results showed no significant difference ($P \geq 0.05$) between Gram-positive and Gram-negative bacteria in both the groups of infection with heart failure and without heart failure. The most common bacterial species in the heart failure group was *Staphylococcus hominis* which accounted for 10% isolates followed by *Staphylococcus haemolyticus* and *Acinetobacter baumannii* which accounted for 8% isolates for each of them. In the group of infection without heart failure (G3), *Klebsiella pneumoniae* bacteria was the most common which accounted for 16% isolates, followed by *Pseudomonas aeruginosa* and *Coagulase negative Staphylococci* which accounted for 8% isolates for each of them. All isolated species were found to be resistant to Ciprofloxacin (80%) in both groups and all isolated species were sensitive to Pefloxacin, Colistin, Ampicillin, Vancomycin, Linezolid, Streptomycin, Ceftazidime/Avibactam and Ceftolozane/Tazobactam in heart failure with infection group (G1).

The serological results demonstrated that there was increased significant ($P \leq 0.0001$) difference between the two groups with heart failure compared to the two groups without heart failure for Troponin. Also, the results showed that there was increased significant ($P \leq 0.0001$) difference for N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) , C-type natriuretic peptide (CNP) , Ischemia-modified albumin (IMA), Soluble CD40 ligand (sCD40L) , C-Reactive Protein

(CRP) and Procalcitonin (PCT) in the serum levels of study groups compare to the healthy group.

The results of Roc analysis suggested that Troponin was the most reliable biomarker for diagnosing heart failure, followed by IMA, NT-proBNP and sCD40L. Other biomarkers have varying degrees of effectiveness, with some showing fair performance.

The hematological results showed there was increased significant in the count of total white blood cell (WBC) and neutrophils in the groups of bacterial infection with and without heart failure compared to the heart failure alone group and healthy group. As current study showed a significant decrease ($P \leq 0.0001$) in the RBCs, HGB, HCT, PLT and lymphocyte count in patients compare with the healthy group.

The study concluded that the most prevalent species of bacteria were *Staphylococcus hominis* in the heart failure group and *Klebsiella pneumoniae* in the group of bacterial infection without heart failure. In addition, the isolated bacteria were highly resistant to Ciprofloxacin in both groups and highly sensitive to some antibiotics. Also, the results demonstrated that there were highly significant differences ($P \leq 0.0001$) between the groups with heart failure and bacterial infection compared to the healthy groups in Troponin , NT-pro BNP , CNP, IMA, sCD40L, CRP and PCT.

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List of Abbreviations

Abbreviated Form	Meaning
ACC	American College of Cardiology
ADP	Adenosine diphosphate
AHA	American Heart Association
AHF	Acute heart failure
ANP	Atrial natriuretic peptide
ARGs	Antimicrobial resistance genes
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ACS	Acute Coronary Syndrome
AST	Antimicrobial Susceptibility Testing
BNP	B-type natriuretic peptide
CAD	Coronary artery disease
CBC	Complete blood count
CCU	Coronary care unit
CHD	Coronary heart disease
CHF	Chronic heart failure
CMP	Cardiomyopathies
CMR	Cardiac magnetic resonance
CNP	C-type natriuretic peptide
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
cTn	Cardiac troponin
CVD	Cardio vesicular disease
DCM	Dilated cardiomyopathy
DM	Diabetes mellitus
ECG	Electrocardiogram
ECO	Echocardiography
EDTA	Ethylene Diamine Tetraacetic Acid
EF	Ejection fraction

ELISA	**Enzyme Linked Immuno Sorbent Assay**
ESAs	**Erythropoiesis stimulating agents**
ESR	**Erythrocyte sedimentation rate**
EUCAST	**European Committee on Antimicrobial Susceptibility Testing**
HACEK	**Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella**
HCM	**Hypertrophic cardiomyopathy**
HCT	**Hematocrit**
HDL	**High density lipoprotein**
HF	**Heart failure**
HFmrEF	**Heart loss with mid-range ejection fraction**
HFpEF	**Heart failure with preserved ejection fraction**
HFrEF	**Heart failure with a reduced ejection fraction**
HGB	**Hemoglobin**
HIV	**Human immune virus**
HRP	**Horse radish peroxidase**
ICUs	**Intensive Care Units**
IE	**Infective endocarditis**
IHM	**In hospital mortality**
IL-1B	**Interleukin-1 beta**
IMA	**Ischemia-modified albumin**
INLV	**Isolated noncompaction of the left ventricle**
IR	**Insulin resistance**
JVP	**Jugular venous pressure**
LVEF	**Left ventricular ejection fraction**
LVH	**Left ventricular hypertrophy**
LYM	**Lymphocyte**
MC	**Myocarditis**
MCV	**Mean Corpuscular Volume**
MDR	**Multi Drug Resistant**
MI	**Myocardial infarction**
MIC	**Minimal Inhibitory Concentration**
MMP	**Matrix metalloproteinases**

MODS	**Multiple organ dysfunction syndrome**
MPV	**Mean platelet volume**
NADH	**Nicotinamide adenine dinucleotide**
NEUT	**Neutrophil**
NT-proBNP	**N-Terminal pro-Brain Natriuretic Peptide**
NYHA	**New York Heart Association**
OTC	**Over the counter**
PAD	**Peripheral artery disease**
PCT	**Procalcitonin**
PCV	**Packed cell value**
PLT	**Platelet**
RAAS	**Renin-angiotensin-aldosterone system**
RBC	**Red Blood Cell**
RCM	**Restrictive cardiomyopathy**
RDW	**Red cell Distribution Width**
Rmp	**Rotation per minutes**
ROSs	**Reactive oxygen species**
ROC	**Receiver Operator Characteristic**
sCD40L	**Soluble CD40 ligand**
SIRS	**Systemic inflammatory response syndrome**
SOFA	**Sequential Organ Failure Assessment**
SSC	**Surviving Sepsis Campaign**
TnC	**Troponin C**
TNF	**Tumor Necrosis Factor**
TnI	**Troponin I**
TnT	**Troponin T**
UTI	**Urinary Tract Infection**
US	**United States**
WBC	**White Blood Cells**
WHO	**World Health Organization**

CHAPTER ONE
INTRODUCTION

1. Introduction

Sepsis can be defined as a potentially fatal organ infection brought on through a dysregulated host organ response to infections, In the case when underlying circulatory, metabolic, as well as cellular abnormalities raise the risk of mortality beyond what sepsis alone could cause, septic shock must be considered a subtype of sepsis, Due to their rising incidence and significant molecular, pathophysiological, genetic, and clinical complexity, septic shock and sepsis represent one of the significant and expanding global burdens as well as a challenge for emergency physicians (Singer *et al*., 2016 ; Gauer *et al*., 2020 ; Evans *et al*., 2021). The incidence of sepsis and septic shock had been rising consistently since 1991, when the first consensus definition (Sepsis1) was created Around 49 million sepsis cases as well as 11 million fatalities all over the world have been attributed to sepsis in the year 2017 (WHO, 2020 ; Chiu and Legrand , 2021). Those findings led the WHO to declare sepsis as one of the global health priorities (WHO, 2020). Such alarming increase in the incidence has been caused by a number of factors, including (a) the advance in patient's average, especially in the western nations; (b) the rise in the number of the invasive procedures; (c) widespread use of chemotherapy and immune-suppressive medications; (d) antibiotic resistance. According to WHO, (2020) ; Schlapbach, *et al* (2020) and Yealy, *et al* (2021), septic patients are at a high risk of in-hospital mortality (IHM), which is responsible for around 20% of all-cause death cases globally.

Cardiovascular biomarkers offer a promising new method of diagnosis and risk assessment in such patients, given the critical role the myocardium plays in sepsis, Since cardiovascular biomarkers target ischemia and inflammation, the two main prognostic processes in sepsis, they present a promising prospect (Ibanez *et al*., 2018).

Any structural or functional heart disorder which affects ventricular filling or the ejection regarding blood into the systemic circulation for meeting systemic demands can cause heart failure (HF), which can be defined as complex clinical syndrome, Diseases of the myocardium, endocardium, heart valves, pericardium, and vessels, as well as metabolic problems, could result in HF, The majority of HF patients experience symptoms due to compromised left ventricular myocardial functions, According to Malik *et al*.(2020), patients typically exhibit symptoms of dyspnea, fluid retention, and impaired exercise tolerance along with pulmonary as well as peripheral edema, According to Virani *et al*.(2020), there are over 6.2 million HF patients in the US and over 23 million globally; by the year 2040, that number is predicted to rise to 1.5 million yearly (Ruppar *et al*., 2016).

At the moment, left ventricular ejection fraction (LVEF) represents the most widely used term to describe HF Also, HF with the preserved ejection fraction (HFpEF) is identified by normal LVEF (≥ 50%), while HF with reduced ejection fraction (< 40%) has been identified by a reduced LVEF (HFrEF), HF patients are classified as having HF with mid-range ejection fraction (HFmrEF) if their LVEF falls between 40 and 49% (Choi *et al*.,2019). Numerous evidence lines have proposed that bacterial pathogens could play one of the major roles in regarding cardiovascular disease (CVD) pathogenesis, which includes factors of risk, like the diabetes, smoking, hypertension, and hyperlipidemia (Khademi *et al*.,2019). The primary method that bacterial infections might cause CVD is via indirectly or directly interacting with immunological and inflammatory pathways (Hogas *et al*.,2017). Infection was shown to directly damage function of endothelial through circulating endotoxins, cause local inflammation as well as smooth muscle cell proliferation, and trigger the response of innate immunity (Banach *et al*., 2004). The induction of inflammatory, pro-inflammatory, and host responses, oxidation regarding low-density lipoprotein, induction of nutrient/vitamin malabsorption, metabolic mimicry between host and antigen

cells, and host disruptions such as excessive production of ammonia are some of the indirect damaging effects of infections (Khademi *et al*., 2019).

One significant new clinical problem is infections, which can lead to HF decompensation, as well as frequently fatal acute systemic disorders including septic shock and sepsis, The development regarding multiorgan dysfunction in sepsis as well as refractory septic shock is significantly influenced by the cardiovascular system, When put to comparison with sepsis without cardiac dysfunction, mortality rates in sepsis with cardiovascular dysfunction are much higher (Kakihana *et al*., 2016). One of the main causes of HF decompensation is infections, which must be identified early and treated according to certain guidelines when sepsis and/or septic shock are present (Mesquita, 2018). One of the most significant developments in public health during the last century has been the discovery of antimicrobials. The natural products known as antibiotics are made by microorganisms or their semisynthetic counterparts, Bacteria have had to develop some types of antibiotic resistance (AR) to live because such compounds were present in the environment for a very long time (Pérez *et al*., 2020). In addition to changing their target of action or preventing the antibiotics from accumulating since they are expelled with the use of efflux pumps or through changing the membrane's permeability, bacteria could inactivate antibiotics through producing enzymes that modify them (Crofts *et al*., 2017).

1.1. Aim of The Study

The next axes are used for identifying the most prevalent bacterial species which cause sepsis in HF patients, investigate their association with HF risk factors, and ascertain their pattern of antibiotic susceptibility:

1- The next tests is performed using blood samples taken from the healthy and patient groups:

A. After the physician has identified the patients utilizing echo and Electrocardiogram, CNP, NT-proBNP, IMA, Troponin and sCD40L levels are used for confirming HF cases.

B. Measure certain parameters, such as CRP, CBC (WBC, RBC, HGB, PLT, HCT ,Lymphocyte, Neutrophil) and PCT.

C. Blood samples culturing with regard to bacterial isolation.

2- To identify the isolated bacteria and determine their pattern of antibiotic susceptibility with the use of the Vitek technique. Statistical analysis is used to compare the tested parameters between groups regarding patients and healthy.

CHAPTER TWO
LITERATURE REVIEW

2. Literature Review

2.1. Cardiovascular Diseases

A group of diseases affecting the blood vessels' capillaries, arteries, and veins is known as cardiovascular disease (CVD) (also known as heart disease) CVDs include peripheral arterial disease, kidney and brain vascular diseases, and coronary heart disease (CHD) Although there are many other causes of CVD, the most prevalent ones are hypertension and/or atherosclerosis (Tarnow *et al*., 2008).

The top causes of death worldwide are coronary artery disease (CAD), hypertension, and congestive heart failure (HF) since these diseases are responsible for more fatalities than any other, Both women and men are affected by CVDs, which account for no less than 80% of deaths in middle- and low-income nations, The most significant causes of death are likely to continue to be such diseases, About one million Americans lose their lives to CVDs yearly in the US, and the projected cost of treating these conditions was $326.6 billion in the year 2002 (Madamanchi *et al*., 2005).

Through addressing risk factors, like obesity and poor diet, tobacco use, high blood pressure, elevated lipids, diabetes, and physical inactivity, the majority of CVDs could be avoided (WHO, 2011). The heart is an aerobic organ that depends only on coronary arteries to provide it with oxygen, When at rest, the myocardium draws as much oxygen as possible from the blood it receives; therefore, if coronary blood flow is interrupted, ischemia will occur right away (PLA and Beijing, 2012). When under physical stress, the symptoms manifest as angina or chest pain, which might radiate to left arm, back, neck, jaw, or throat.

According to a research, CHD may begin when specific variables harm the coronary arteries' inner layers. Those factors are Given by Islam and Timmis (2013). They are :

1. Smoking
2. High blood pressure
3. Unhealthy levels of blood cholesterol
4. Obesity or overweight
5. No physical activities
6. Insulin resistance (IR)
7. Family history of early heart disease
8. Diabetes
9. Age (the risk for CHD increases for older people)
10. Metabolic syndrome.

Study expected 35.6 million cardiovascular deaths in 2050 (from 20.5 million in 2025) (Chong *et al*., 2024)

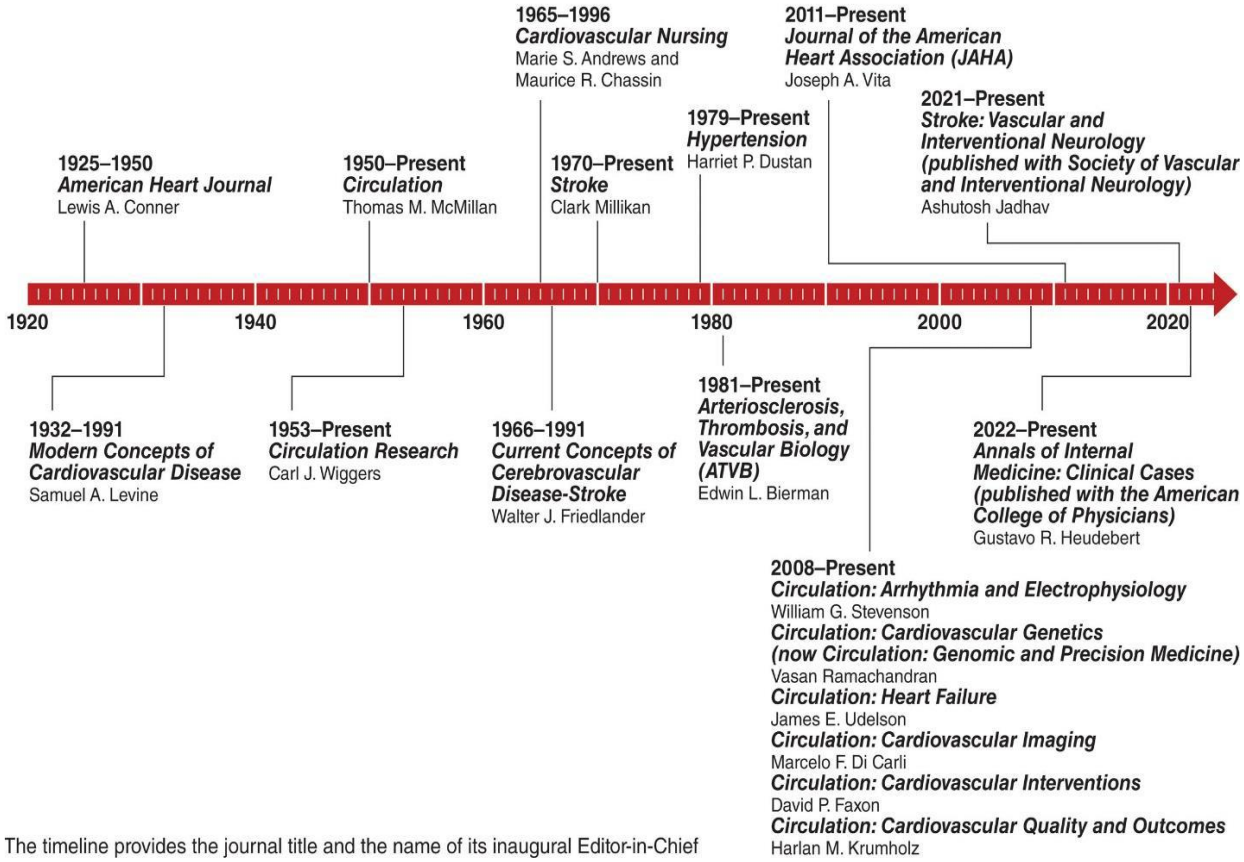


Figure (2.1): American Heart Association Scientific Journals Publication Timeline.

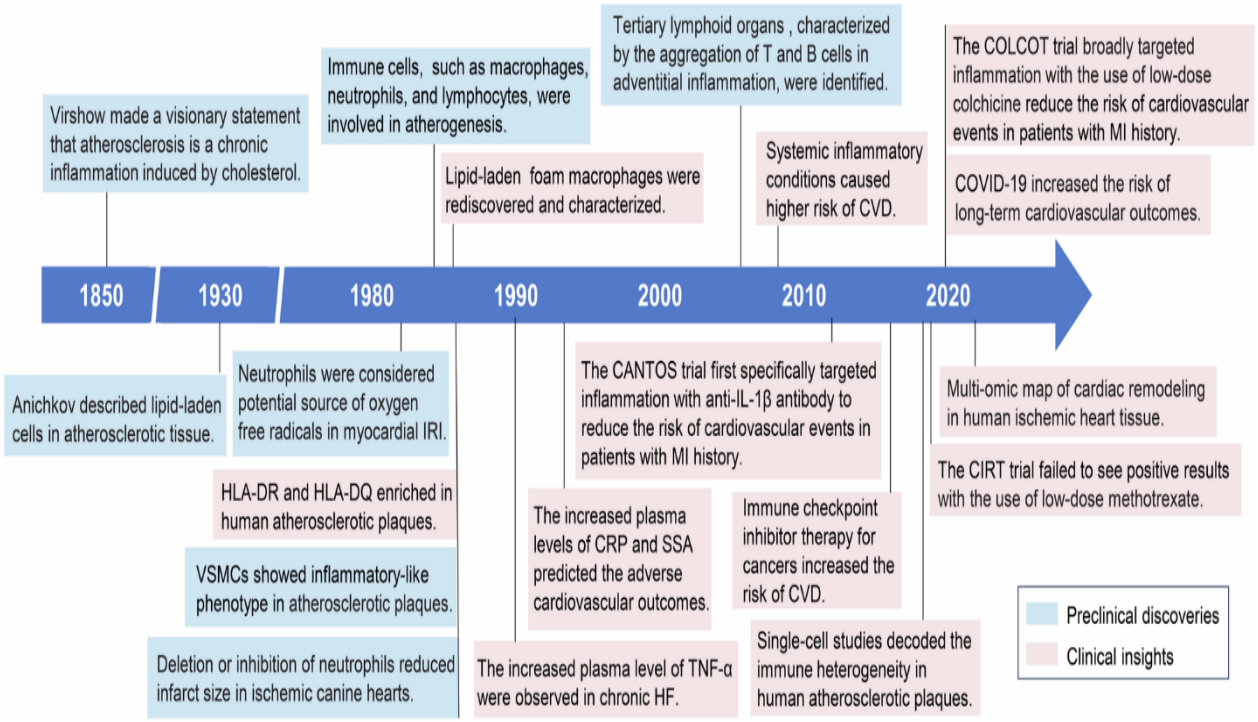


Figure (2.2): Timeline of Inflammation and Atherosclerosis Research: From Preclinical Discoveries to Clinical Insights (Elkind *et al*.,2024).

2.2. Heart Failure

A reduction in ventricular contractility and/or relaxation results in HF, a multisystem clinical syndrome (Yancy *et al*.,2013). Venous obstruction, hypertrophy and/or ventricular dilatation, and inadequate oxygen supply are the hallmarks of HF, which is brought on by dysfunctional cardiac muscle. (Lindenfeld *et al*.,2010). Depending upon left ventricular ejection fraction (LVEF), there are numerous kinds of HF (Yancy *et al*.,2013). The New York Heart Association (NYHA) defines the 4 functional classes, which are:

Class I: HF doesn't lead to the restriction of physical activity, and typical physical activity doesn't cause any signs and symptoms.

Class II: HF limits physical activities; individuals are relaxed at rest, yet regular exercise causes symptoms of Heart Failure.

Class III: Heart Failure severely restricts physical activity; individuals are relaxed at rest, yet HF symptoms arise from less than usual activity.

Class IV: HF patients experience symptoms even when they are at rest and are incapable of engaging in any physical activities without them (Inamdar and Inamdar, 2016).

NYHA Class	Definition	Limitation	Example
I	Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations.	None	Can complete any activity requiring ≤ 7 MET: • Carry 11 kg up 8 steps • Carry objects weighing 36 kg • Shovel snow • Spade soil • Ski • Play squash, handball, or basketball • Jog or walk 8 km/hour
II	Ordinary physical activity causes fatigue, dyspnea, palpitations, or angina.	Mild	Can complete any activity requiring ≤ 5 MET: • Sexual intercourse without stopping • Garden • Roller skate • Walk 7 km/hour on level ground • Climb one flight of stairs at a normal pace without symptoms
III	Comfortable at rest; less than ordinary physical activity causes fatigue, dyspnea, palpitations, or angina.	Moderate	Can complete any activity requiring ≤ 2 MET: • Shower or dress without stopping • Strip and make a bed • Clean windows • Play golf • Walk 4 km/hour
IV	Symptoms occur at rest; any physical activity increases discomfort.	Severe	Cannot do or cannot complete any activity requiring ≥ 2 MET; cannot do any of the above activities

MET = metabolic equivalent of task, a measure of how much energy is expended compared to remaining at rest.

Figure (2.3): New York Heart Association (NYHA) Classification of Heart Failure (Wang *et al*.,2025).

The American Heart Association / American College of Cardiology (AHA/ACC) staging system has four stages, which are:

Stage A: Although there is a high HF risk, neither structural heart disease nor HF symptoms are present.

Stage B: No structural heart disease, yet HF symptoms.

Stage C: Heart structural disease and HF symptoms.

Stage D: Refractory HF necessitates specialized interventions (Inamdar and Inamdar, 2016).

This approach has been used to calculate the therapeutic left ventricle ejection fraction (EF). There are three main HF phenotypes, and the distinctions between such groups are important because of variations in comorbidities, demographics and therapeutic reactions:

1. An EF of 40% or more is referred to as HF with reduced EF (HFrEF).

2. HF with preserved EF (HFpEF), where the EF is 50% or higher.

3. HFmrEF (heart loss with mid-range EF) (which is also known as HFpEF-borderline or HFpEF-improved as EF in HFrEF rises to more than 40%): according to US recommendations, EF is 40 to 49%, and according to European guidelines, it is 41 to 49%. HFmrEF is the new term for this class, which was formerly indicated the gray area between HFrEF and HFpEF (Hajouli and Ludhwani, 2020).

All individuals with HFrEF have diastolic dysfunction, but diastolic dysfunction could also happen when systolic dysfunction is not present (Hajouli and Ludhwani, 2020).

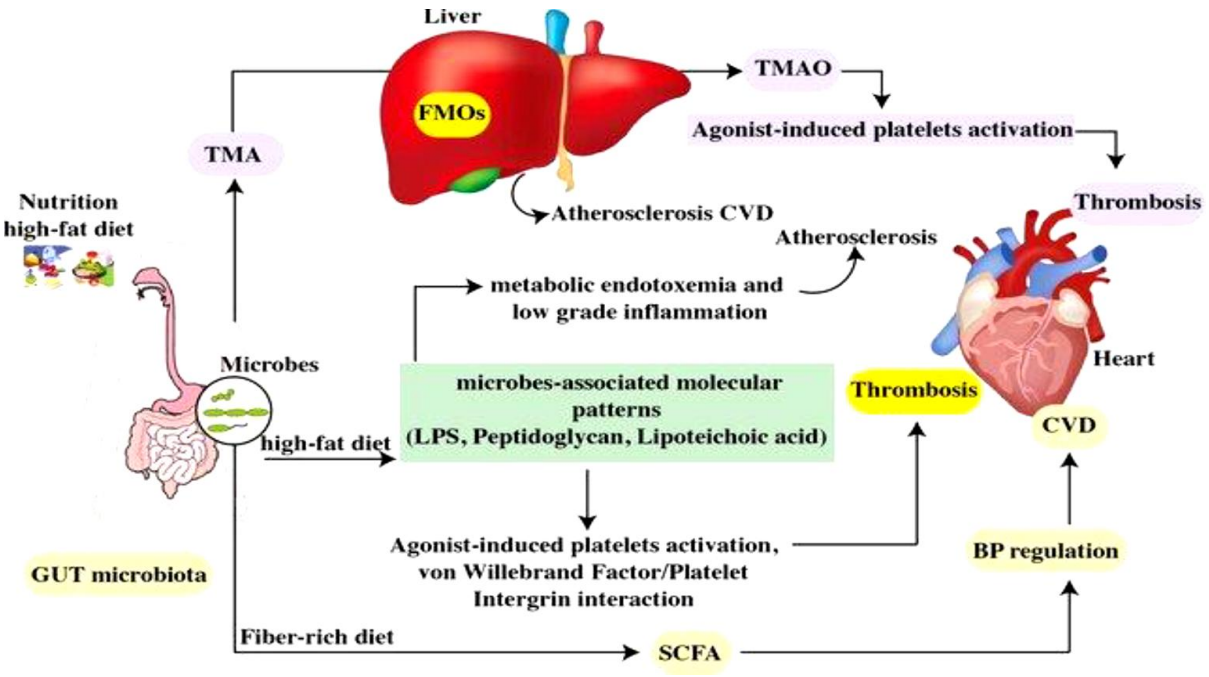


Figure (2.4): Role Microbes in Cardiovascular Disease (Luqman *et al*.,2024).

2.3. Immune System and Cardiovascular Disease

Early observations of infectious diseases lead to the understanding of the immune system's ability to defend the organism against pathogenic agents by discriminating between self and non-self. The inflammation induced by tissue damage of an organ can be sterile or due to the pathogenic infections (Van Linthout and Tschöpe 2017).

Although myocardial infarction (MI)-induced trauma or ischemia/reperfusion injury results in sterile tissue damage, viral or bacterial carditis leads to damage activated by infections, both of which induce inflammatory responses. Necrotic cells in damaged tissue release endogenous damage-associated molecular patterns (DAMPs) that constitute of nucleic acids, heat-shock proteins, interleukins, cytoskeletal proteins, and mostly extracellular matrix (ECM) degradation products. Pathogens are recognized by the immune system through pathogen-associated molecular patterns (PAMPs), that include lipopolysaccharide (LPS), flagellin, dsRNA, unmethylated CpG motifs in DNA, and bacterial genomic DNA (Van Linthout and Tschöpe 2017 ; Cao *et al*., 2018). Both DAMPs and PAMPs can be recognized by pathogen recognition receptors (PRRs) found in immune and non-immune cells and induce innate immune response by recruiting neutrophils, macrophages, and dendritic cells (DCs) (Epelman *et al*., 2015).

The antigen presenting cells of innate immune system then stimulate T and B cells to mediate adaptive immune responses (Fairweather *et al*., 2004; Van Linthout and Tschöpe 2017). In recent years, immune cells in various tissues have been categorized based on their residency or recruitment to the tissue in response to inflammation. Cardiac resident and recruited immune system elements vary based on specific functions and expression profiles (Epelman *et al*., 2015 ; Cao *et al*., 2018). In steady-state, different immune cell populations were identified to be localized in various heart regions, such as B cells in the pericardium, macrophages, mast cells and DCs in coronary endothelium, and a specific population of macrophages in valves and AV node (Epelman *et al*., 2015 ; Dick and Epelman 2016; Hulsmans *et al*., 2017).

Physiological changes and pathological processes were demonstrated to change the distribution, polarization, and subtypes of immune cells in the heart. As an example, increased hematopoiesis in spleen and bone marrow supplies innate immune cells to the infarct region following MI (Epelman *et al*., 2015 ;

Dick and Epelman 2016 ; Swirski and Nahrendorf 2018). Both proliferating resident macrophages and recruited neutrophils or monocytes work in a coordinated way in clearance and repair of the injured heart tissue. coronary arteries contain innate cells, such as macrophages and DCs, arteries also contain mast cells, while AV node has greater amount of cardiac resident macrophages connected to the myocardium. Moreover, pericardial fluid contains macrophages and mast cells as innate immunity, and B cells as adaptive immunity (Swirski and Nahrendorf 2018).

Interestingly, the heart of a healthy adult mouse contains 12-fold more CD45+ leukocytes per milligram of tissue than the skeletal muscle (Ramos et al. 2017). This abundance of leukocytes in the heart may be recruited from several local lymph nodes and the lymphatic vessels. Vascular growth factors stimulate lymph angiogenesis following MI by reducing fibrosis, thus this could be a potential regulator for cardiac regeneration (Huang *et al*., 2017). In this section, the literature investigating resident immune cells of the heart in the steadystate or recruitment following inflammation will be detailed.

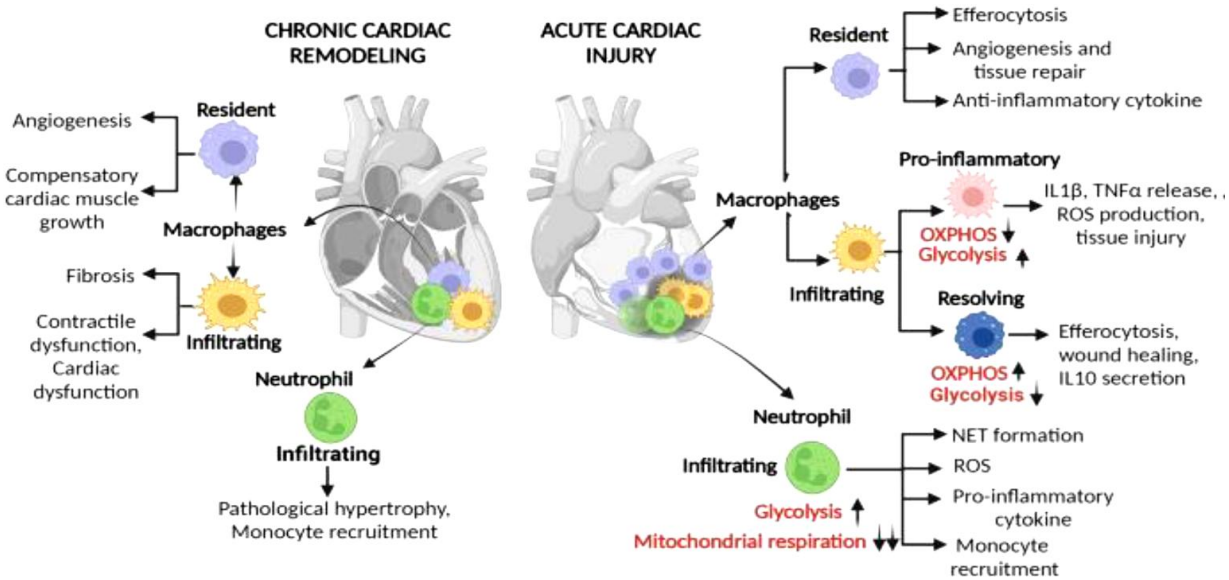


Figure (2.5): The role of innate immune cells in cardiac injury and repair (Banerjee *et al*., 2023)

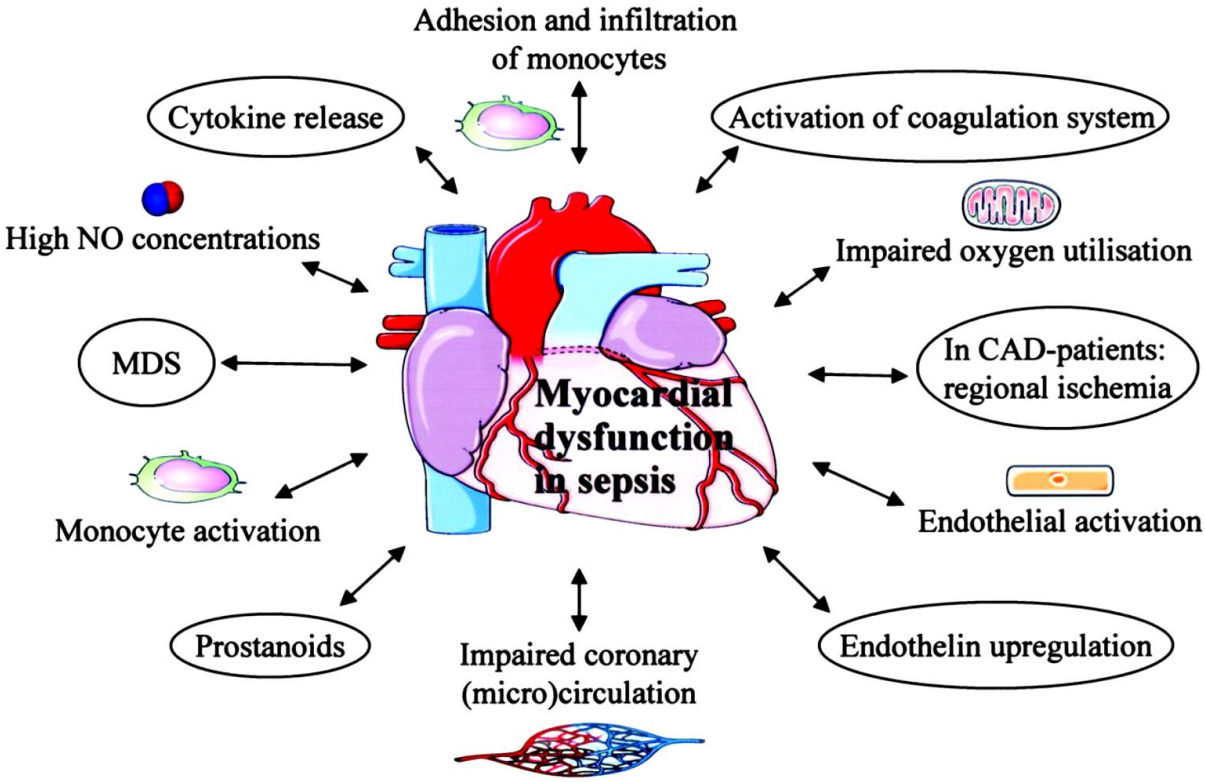


Figure (2.6): Myocardial dysfunction in sepsis (Merx and Weber, 2007).

2.4. Epidemiology

Approximately 40.0 million people worldwide suffer from HF (Vos *et al*.,2016). According to Mozaffarian *et al*.(2016), there have been over 5.7 million HF patients in the US in the year 2011, and about 870,000 of those individuals received a new diagnosis, About 1% to 2% of people are said to be affected by HF, and incidence rises with age (Ponnikowski *et al*., 2014). According to Mozaffarian *et al*.(2016), the prevalence rate is 1% for those under 40 and >10% for those over 80, with the rate doubling every ten years of life, Therefore, it is anticipated that the number of patients with HF will increase as the population ages. Additionally, the number of the patients who are at risk of developing heart failure might paradoxically rise due to the recent therapeutic improvements for CVD that have reduced mortality. Additionally, HF patients are at a significant mortality risk (20% following 1 year and 50% following 5 years) and re-hospitalization (44% within 1 year after being discharged) (Maggionni *et al*.,2013) (Ziaeian and Fonarow,2016). Compared to most cancers, HF has a

greater death rate (Mamas *et al*.,2017). Therefore, lowering social, financial, and health-related burdens requires effective management of individuals with HF (Kim and Kim,2018).

2.5. HF Risk Factors

HF risk factor are given below :

- Baseline demographics (race/ethnicity, age, height, and weight) were considered covariates of interest.
- Clinical risk factors (systolic blood pressure, diabetes mellitus, hyperlipidemia, using antihypertensive drugs, using lipid-lowering drugs, and hormone replacement treatment) and their time-updated evaluation.
- A few cancer-treatment medications.
- Additionally, HF is more likely to occur in those who have a genetic susceptibility to less common heart diseases, such as certain forms of heart muscle disease.
- Lifestyle choices (number of drinks consumed daily, physical activity [metabolic equivalents per week], and smoking status [never, former, current]) (Chaterjee *et al*., 2017).

2.6. HF Symptoms

Since HF diagnosis is based solely on the clinical symptoms and indicators, every patient with a suspected case must undergo a comprehensive history and physical examinations. It is necessary to incorporate a risk assessment and potential etiologies of HF. Heart Failure symptoms are same regardless of EF. Fluid deposition (edema, orthopnea, dyspnea, and abdominal pain from hepatic congestion and ascites in context of right HF) or decreased cardiac activity makes symptoms of HF worse with effort (anorexia, fatigue, and weakness). Among the odd symptoms include nocturnal cough, palpitations, weight loss, syncope, bendopnea (difficulty breathing while seating forward),

wheezing, depression, and dizziness. Advanced HF (cold and pallid extremities because of diminished perfusion) is indicated by peripheral vasoconstriction, narrow heart pressure (<25 mmHg because of decreased cardiac output), diaphoresis, and resting sinus tachycardia. Fluid overload is indicated by peripheral edema (edema of the limbs, scrotal edema, ascites, and hepatosplenomegaly), respiratory obstruction, and increased jugular venous pressure (JVP) (rales on exam and pleural effusions). S3 gallop, parasternal lift (a sign of right ventricular enlargement), and a displaced apical impulse (laterally past mid-clavicular line) are all present. Every clinic appointment should include an evaluation of HF symptoms and indicators for monitoring therapy response as well as stability over time. Assessing volume status and taking vital signs with each clinic visit is also beneficial (Hajouli and Ludhwani, 2020).

2.7. HF Causes

HF may be caused by several factors, such as systemic disorders, a variety of cardiac conditions, and some of genetic defects. HF etiologies differ between low - and high countries, and patients can have a combination of etiologies (Yusuf *et al*., 2014). In high-income countries, ischemic heart disease and chronic obstructive pulmonary disease (COPD) are the most common underlying causes of HF. The primary causes of heart failure (HF) in low-income nations include myocarditis, cardiomyopathy, rheumatic heart disease, and hypertensive heart disease, per a systematic analysis for the global burden of illness report (Savarese and Lund, 2017). Over two-thirds of HF cases are caused by ischemic heart disease, COPD, hypertensive heart disease, and rheumatic heart disease.

- **Coronary artery disease (CAD**): Ischemia, acute as well as chronic, directly affects myocardium and encourages re-modeling as well as formation of scars, which lowers cardiac output and contractility. The development of aneurysms was connected to such scar tissue, which further reduces contractile and relaxation function. Myocardial infarction

(MI) frequently results in ventricular dilatation, following ventricle dilatation, ventricular dilatation with annular dilation, all of which raise the risk of HF and decrease CO. Numerous tachyarrhythmias, including non-sustained ventricular tachycardia as well as atrial fibrillation/flutter, are common in CAD patients and could worsen cardiac function. In about 70% of instances, HF is linked to CAD (Purek *et al*., 2006). CAD represents one of the strong predictors of death in patients who have acute Heart Failure. Testing of viability could be helpful in identifying the patients that will benefit from the coronary re-vascularization, as the effectiveness of this procedure in lowering HF-related morbidity and death is still up for debate (Phillips *et al*., 2007).

- **High blood pressure (HBP):** HBP is one of the independent risk factors for CAD. HBP represents a probable HF cause in 1/4 to 1/3 of patients due to its high prevalence. Through activating the renin-angiotensin-aldosterone system (RAAS), HBP raises vascular resistance. The heart should pump blood against a larger afterload that is brought on by HBP for maintaining a normal CO. This results in left ventricular hypertrophy (LVH), which increases myocardial mass. Apoptosis and fibrosis may develop if blood pressure (BP) is not managed. Controlling blood pressure is essential for enhancing the prognosis of HF since LVH promotes myocardial rigidity and could cause ischemia that results in HFrEF or HFpEF. Lowering the systolic blood pressure to no more than 120 mmHg was associated with a 38% lower relative risk of HF in patients with hypertension, according to the Systolic Blood Pressure Intervention Trial (SPRINT) (Group, 2015).
- **Chronic obstructive pulmonary disease (COPD):** According to Hajouli and Ludhwani (2020), COPD raises risks of CAD and other smoking-related diseases, right HF, and heart dysrhythmia. It could also lead to pneumonic HBP.

- **Valvular heart disease**: While rheumatic valve disease could induce HF in low-income nations, valve disease degradation could lead to HF in developed nations. Aortic as well as pulmonary stenosis raise the ventricular afterload, which could lead to HF. HF may result from ventricular enlargement and functional impairment brought on by prolonged volume overload in valve's regurgitation.
- **Cardiomyopathies (CMP):** CMP can be defined as a situation when there are structural and functional defects in the heart muscle, yet no congenital heart disease, HBP, CAD, or valve problems. The five types of cardiomyopathies which could be acquired or genetically modified are hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and other unclassified cardiomyopathies (including isolated noncompaction of left ventricle [INLV] and Takotsubo syndrome). CMP may result in HFpEF, HFrEF, or HFmrEF (Hajouli and Ludhwani , 2020).

Myocarditis, infiltrative disease, congenital heart disease, peripartum cardiomyopathy, connective tissue disease, HIV, amyloidosis, obesity, long-term alcohol use, substance abuse, hyperthyroidism (could affect high-output HF), diabetes mellitus (DM), constrictive pericarditis (could lead to HFpEF) pulmonary embolism (lead to right HF), pulmonary hypertension (could lead to right HF), and chemotherapies (such as doxorubicin) (Hajouli and Ludhwani, 2020).

2.8. HF Diagnosis

The preliminary analysis is important. The initial studies ought to incorporate the next (Ponikowski *et al*., 2016):

1) Chest X-ray

2) 2-D echocardiography

3) Basic blood estimations

4) 12-lead electrocardiography (ECG),

According to Ponikowski *et al*. (2016), the following tests were crucial for basic blood estimations:

1) Renal function test

2) Serum electrolytes (potassium, sodium, and calcium)

3) Complete blood count

4) Lipid profile

5) Blood glucose (postprandial plasma glucose and fasting plasma glucose) Glycosylated hemoglobin (HbA1c)

6) Liver function test

7) Thyroid function test Iron profile serum iron, folate and ferritin, and total iron-binding capacity.

2.9. Ejection Fraction (EF %)

Volumetric fraction regarding blood that is ejected from a chamber with every one of the contractions is known as the ejection fraction (EF) As such, it might refer to the leg veins, the cardiac atrium, or the ventricle; but, if left unexplained, it typically refers to the heart's left ventricle. EF is frequently used to categorize different forms of HF and as a gauge of the heart's pumping efficiency, Despite its acknowledged shortcomings, it is utilized as a gauge of the degree of HF (Cikes and Solomon, 2016). Through dividing volume of blood that has been pumped from the left ventricle per beat (i.e., volume of the stroke) by volume of the blood that has been collected in the left ventricle at the end of the diastolic filling (i.e., end-diastolic volume), the left ventricular ejection fraction (LVEF), or EF of the left heart, is determined (Ponikowski *et al*., 2016). Ejection fractions in healthy people normally range from 50% to 65% (Marcu *et al*., 2006).

2.10. Biomarkers

2.10.1. Cardiac-Specific Troponin

Three subunits make up the troponin complex, which controls calcium-mediated contractile action of striated muscle. Those include troponin T (TnT), which attaches to tropomyosin and attaches the troponin complex to thin filament, troponin C (TnC), which binds Ca^{2+}, and troponin I (TnI), binding to the actin and inhibiting the actin-myosin interactions (Figure 2.7).

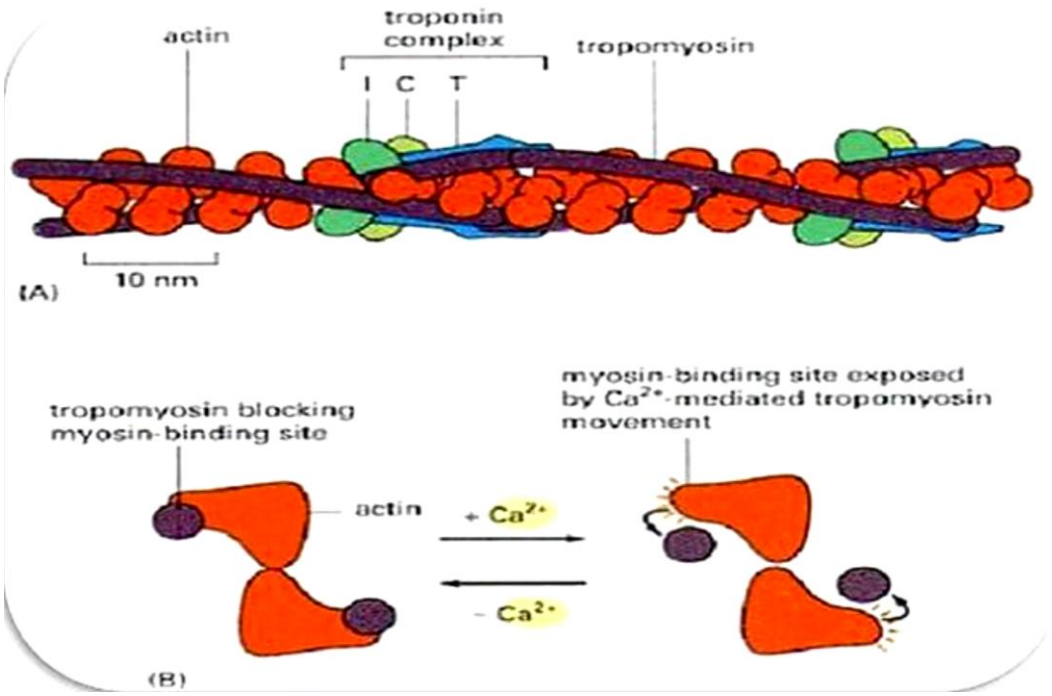


Figure (2.7): (A) The structure of TroponinI complex (B) Binding sites of cTnI with calcium (Matsumoto *et al*., 2004).

cTnI and cTnT are first released from the cytosolic pool after myocyte injury, and then they are released from the structural (myofilament-bound) pool. In cardiac and skeletal muscle, distinct genes encodeTnI and TnT, allowing for producing particular antibodies for cardiac form (cTnI and cTnT) which facilitate their quantitative measurement (Brouilette *et al*., 2007).

The revised diagnostic criteria for MI are based on the measurement of cTnI or cTnT. Clinicians need to be aware of a number of analytical concerns in the case of interpreting assay results for cTnI or cTnT (Aviles *et al*., 2002). While multiple manufacturers create cTnI assays, only one company produces cTnT

assays, which results in rather uniform cutoffs, Results of different commercial assays, particularly for cTnI, could be impacted by release pattern of the troponin complexes and their degradation to different fragments of the troponin. This information could be helpful in the future to understand pathophysiologic events such as, reperfusion and ischemia (Jaffe and Van, 2006).

Additionally, even mild forms of myocardial necrosis can be detected since cTnI and cTnT usually rise more than 20 times above the reference range Three hours after the start of chest pain, cTnI and cTnT levels in MI patients initially start to increase above the upper reference range, Elevations of cTnI may continue for 7–10 days following MI, while elevations of cTnT may continue for up to 10–14 days due to a continuous release from a degenerating contractile apparatus in the necrotic myositis, For the late diagnosis of MI, the extended time course of increase of cTnI and cTnT is beneficial, When the infarct-related artery is successfully recanalized in NSTEMI and STEMI patients, cardiac troponins are released quickly, which may be a sign of reperfusion (Antman *et al*., 2004).

2.10.2. Brain natriuretic peptide (BNP)

BNP, a peptide hormone, is released in response to cardiac myocytes' increased wall stress as well as volume expansion, as seen in Fig. (2.8). BNP aids in the lowering of aldosterone and endothelin levels in the bloodstream, natriuresis, diuresis, and vasodilation regarding the pulmonary and systemic vasculature, Therefore, plasma BNP could rise due to both corpulmonale from noncardiac pulmonary hypertension and congestive heart failure from left ventricular (LV) failure, BNP levels may rise in severe acute decompensated LVHF, albeit this effect is not specific (Leong and Ooi, 2017).

In the heart, the atrial (ANP) as well as brain (BNP) cardiac natriuretic peptides are secreted, The secretion of BNP happens constitutively from the myocytes as a response to the overload of pressure and volume in the ventricles, as is observed in HF patients.(Rademaker and Richards, 2005 ; Tang, 2007).

A peptide consisting of 32 amino acids, BNP is biologically active and possesses natriuretic and vasodilator qualities, BNP is a 108-amino acid pro-brain natriuretic peptide that is released from cardiac ventricles as a response to chamber stretching. N-terminal pro-brain natriuretic peptide (NTproBNP), the second residue following cleavage, represents a 76-amino acid peptide that does not have any known biological activity, It circulates at higher concentration levels compared to the BNP and could indicate cardiac state over extended periods of time (Hobbs *et al*., 2002).

In response to elevated wall stress, the ventricles primarily secrete the cardiac hormone known as B-type natriuretic peptide (BNP), This peptide, which is released into circulation, inhibits the renin-angiotensin-aldosterone pathway and stimulates natriuresis and diuresis (Maeda *et al*., 1998 ; Berger *et al*., 2002 ; Lisy and Babal, 2007).

As indicators of ventricular dysfunction, BNP plasma levels have garnered more attention recently (Book *et al*., 2005; Chrysohoou *et al*., 2010). Diagnoses, risk assessment, and treatment of adult patients who have got congestive HF have all been demonstrated to benefit from the measurement regarding plasma BNP concentrations (Diller *et al*., 2005; Dimopoulos *et al*., 2008; Kallistratos *et al*., 2008; Parcharidis, 2011). Additionally, BNP might be helpful in a number of other adult conditions, including arrhythmogenic right ventricular (RV) dysplasia, hypertrophic cardiomyopathy, left ventricular (LV) remodeling following myocardial infarction, and more (Panou *et al*., 2006; Koch *et al*., 2006). Lastly, it might be one of the powerful mortality predictors in adults who have congenital heart disease (CHD) (Giannakulas *et al*., 2010). Notably, there is a steady rise in the number of adult CHD patients (Parcharidis, 2011).

In chronic ambulatory HF context (Figulla *et al*., 1996 ; Waldo *et al*., 1996 ; Kober *et al*., 2008), or acute decompensated HF Moss *et al*.,(2009) and Abraham *et al*.,(2011), the value of peptide natriuretic testing is especially important in the case when the etiology of dyspnea is unclear. The physiological effects of

natriuretic peptides are diverse and include prevention of cardiac hypertrophy and ventricular fibrosis, the relaxation regarding pulmonary and vascular smooth muscle, and inhibition of neural-hormonal over-activation. Furthermore, the peptides have the potential to decrease intravascular volumes, induce lipolysis, and increase the permeability of the endothelial vasculature (Rademaker and Richards, 2005 ; Tang, 2007).

Possible causes of the elevated levels of **brain natriuretic peptide**

(Felker *et al*., 2006):

Cardiac:

- Acute coronary syndromes
- Diastolic dysfunction
- HF
- Atrial fibrillation
- Valvular heart disease (aortic stenosis and mitral valve regurgitation)

Non- Cardiac:

- Acute pulmonary embolism
- Sepsis (possibly due to tissue hypoxia or secondary myocardial depression
- Pulmonary hypertension (primary or secondary)
- Renal failure
- Chronic obstructive pulmonary disease with corpulmonale or respiratory failure
- Hyperthyroidism

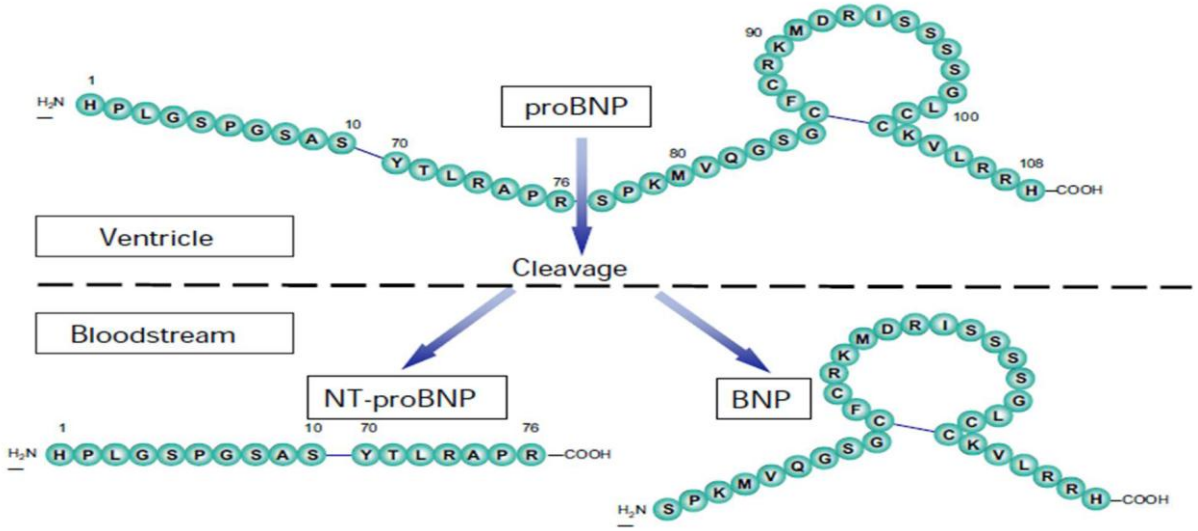


Figure (2.8): BNP and NT- proBNP Cleavage from proBNP (Hogenhuis, 2006).

2.10.2.1. N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP)

As a response to cardiac hemodynamic stress that is brought on by volume and/or pressure overload, natriuretic peptides (BNP and NT-proBNP) are secreted from the heart (Thygesen *et al*., 2012). PRIDE and ICON trials demonstrate that NT-proBNP represents a sensitive and specific indication of acute HF in patients who present to the emergency department, indicating that the amino terminal of proB-type natriuretic peptide (NT-proBNP) is a reliable biomarker for detecting people with HF, Additionally, in order to rule out other dyspnea causes in patients with suspected HF, the European Society of Cardiology and the American College of Cardiology both recommend measuring natriuretic peptides (Januzzi *et al*., 2006). In addition to giving additional assurance that patients with HF will not be overlooked, early NT-proBNP measurement could accurately rule out symptomatic patients who do not have HF Notably, a trend toward a decrease in death and rehospitalization rates is linked to the increased utilization of intermediate/intensive care among patients with the greatest NT-proBNP (Jessup *et al*., 2009).

There are various differences between NT-proBNP and BNP like in table (2.1) (Maisel *et al*., 2003 ; Wold *et al*., 2005 and Luchner *et al*., 2005).

Table (2.1): Differences between BNP and NT-proBNP

BNP	NT-proBNP
Is a hormonally active natriuretic peptide.	Hormonally inactive remnant.
The suggested normal range is 0.5 – 30 pg/mL	The suggested normal range is 68 – 112 pg/mL.
The sequence of amino acids is 77-108 from proBNP.	The sequence of amino acids is 1-76 from BNP.
Half-life time is 20 min	Half-life time is 120 min
BNP is known to be cleared from the blood by natriuretic peptide clearance receptors, by neuro endopeptidases and by the kidneys.	Little is known on the exact clearance mechanism of NT-proBNP, although it has been suggested that the kidneys play a major role in this clearance.
Have an active ring	In the form of a straight line

2.10.3. Ischemia-Modified Albumin (IMA)

In myocardium ischemia, aerobic glycolysis stops in the myocytes within seconds of vascular obstruction, leading to insufficient adenosine triphosphate synthesis and creatine phosphate depletion, which causes lactic acid, NADH accumulation, and a drop in the level of pH, As the pH decreases, cellular proteins and enzymes become increasingly dysfunctional, When ATP is depleted, plasma membrane-dependent sodium pump is less active, which causes intracellular sodium accumulation and potassium export, Calcium influx and its detrimental effects result from the calcium pump failing (Chawla *et al*., 2006; Oran and Oran, 2017).

Bound copper and iron are released from intracellular stores and proteins when the pH drops, Additionally, ischemia lowers the electron carriers, which causes reactive oxygen species (ROSs), such as super oxide anions, to develop

(Worster *et al*., 2005). The histidine found in the amino terminal region of albumin is oxidatively damaged by these free radicals. Ischemia Modified Albumin is the name given to this albumin that contains a damaged amino terminal (Talwalker *et al*., 2008).

2.10.3.1. Ischemia Reduces the Electron

The amino terminal of normal albumin has binding affinity for the transitional metals such as cobalt, However, the albumin-cobalt binding assay, which measures ischemia-modified albumin in myocardial ischemia, is based on the fact that IMA is unable to bind to cobalt, In brief ischemic situations, such as following percutaneous transluminal angioplasty, ischemia-modified albumin begins to rise 6–10 minutes following ischemia, peaks at 4 hours, and then recovers to baseline after 6 hours. N-terminal oxidative damage to albumin, on the other hand, is cumulative, repairs slowly, and does not increase after six hours in cardiac ischemia (Fagan, 2002 ; Morrow and Lemos, 2003 ; Oran and Oran, 2017).

2.10.4. C-type natriuretic peptide (CNP)

Three bioactive peptides make up natriuretic peptide family: BNP, atrial natriuretic peptide (ANP), and CNP, Rat and human cardiac atria were used to extract and identify ANP for the first time in 1983–1984 (Flynn *et al*., 1983; Kangawa and Matsuo, 1984). Following this, CNP and BNP were separated from porcine brain in 1988 and 1990, respectively (Sudoh *et al*., 1988; Sudoh *et al*., 1990). The three peptides share structural similarities and bind to particular receptors on the target organs to produce their biological effects, which include vasodilatation and natriuresis, The heart is the primary site of BNP and ANP synthesis, BNP is utilized as a biomarker of HF globally (Ponikowski *et al*., 2016; Yancy *et al*., 2017; Tsutsui *et al*., 2021), ANP is now utilized extensively in Japan for treating acute heart failure (Hata *et al*., 2008; Kawase *et al*., 2018; Nogi *et al*., 2022). On the contrary, CNP is extensively expressed in the

osteochondral, vascular, and central neurological systems, and its primary target receptor is different from that of BNP and ANP. As a result, CNP behaves differently than BNP and ANP. Studies on the function of CNPs in the osteochondral system have come before research on CNPs since global CNP knockout mice (CNP KO) were reported to exhibit severe dwarfism due to the disruption regarding endochondral ossification (Chusho *et al*., 2001). Actually, a medication for achondroplasia has been created using CNP analog for clinical use (Savarirayan *et al*., 2019).

After being translated as 126-amino acid pre-propeptide, CNP is converted into the 103-residue peptide ProCNP by a signal peptidase. According to Hayek and Nemer (2011) and Wu *et al*. (2003), ProCNP is believed to be subsequently cleaved into NT-proCNP and CNP-53 by the processing enzyme furin. After that, an unidentified protease cleaved CNP-53 to create CNP-22 (Zakeri *et al*., 2013; Matsuo *et al*., 2019). According to Moyes and Hobbs (2019), CNP-22 as well as CNP-53 are found in plasma and different organs, where they both show biological action. The conserved disulfide-linked 17-amino acid ring part of CNP-22, which is made up of 22 amino acids and is substantially similar to BNP and ANP, is necessary for biological action, In contrast to ANP and BNP, CNP has a cysteine residue at C-terminus and no C-terminal tail. According to Komatsu *et al*. (2002), CNP-53's 31 amino acid N-terminal extension cleaves to produce CNP22. Across species, CNP is substantially conserved, Human CNP53 differs from rat, pig, and mouse peptides by just 2 amino acids, although amino acid sequence of CNP22 is the same in all of these peptides, The chondrocytes, brain, and vascular endothelium are among the central and peripheral tissues that express CNP. The myocardium and cardiac fibroblasts in the heart were shown to express it (Hayek and Nemer, 2011).

2.10.5. Soluble CD40 ligand (sCD40L)

The release regarding inflammatory mediators, like CD40L is one of the phases of healing following a MI (Frantz *et al*., 2009). A type II transmembrane glycoprotein, CD40 ligand (also known as CD40L or CD154) has a molecular weight of 32–39 kDa (van Kooten and Banchereau, 2000). CD40L belongs to tumor necrosis factor (TNF) superfamily and is expressed mainly by the activated B cells, activated T cells, and platelets. It can be induced on basophils, mast cells, monocyte cells, and natural killer cells in inflammatory conditions (Carbone *et al*., 1997).

As its name implies, CD40L attaches itself to CD40 to form a system that appears to be crucial for the pathogenesis of atherosclerosis as well as cellular immunity and inflammation (Laman *et al*., 1997). Nonhematopoietic cells such as fibroblasts, endothelial cells, platelets, and smooth muscle cells have also been found to exhibit this system (Henn *et al*., 2001). When CD40 binds to various cell types, inflammatory cytokines are released, adhesion molecules are expressed, matrix metalloproteinases (MMPs) are activated, and procoagulant tissue factor is produced, all of which indicate a proinflammatory and prothrombotic response (Urbich *et al*., 2002). It has been reported that a soluble form of CD40L (sCD40L), with the TNF homology region completely maintained, exhibits functions comparable to those of its transmembrane form, such as binding to CD40 and substituting CD40L+-T cells in B cell activation, among other things (Graf *et al*., 1995; Mazzei *et al*., 1995).

Increased sCD40L levels in HF may be a reflection of other pathogenic mechanisms, such as MMP activation as well as the generation of inflammatory cytokines and chemokines, according to the correlation between sCD40L and lower myocardial vasculature dysfunction. The failing myocardium might experience prolonged tissue inflammation and remodeling due to direct interactions between CD40-expressing cardiomyocytes and CD40L, regardless of the mechanisms involved. These results further corroborate greater

CD40/CD40L interaction within the myocardium by indicating increased release of sCD40L inside the coronary circulation (Santilli *et al*., 2007).

2.11. Bacterial Infections

2.11.1. Overview of Bacterial Infections

Live bacteria in the blood is referred to as bacteremia. Routine daily activities like brushing one's teeth and recovering from minor medical procedures might result in asymptomatic bacteremia. In healthy individuals, these clinically benign infections are temporary and do not cause long-term problems. Bacteremia, also known as septicemia, is a bloodstream infection which could present with various clinical symptoms in the case when the immune system's defense mechanisms fail or are overloaded. Symptoms of untreated and clinically severe bacteremia include sepsis, multiple organ dysfunction syndrome (MODS), systemic inflammatory response syndrome (SIRS), and septic shock (Dagasso *et al*., 2018)

As one of the major causes of morbidity, mortality, and medical expenses in the US, sepsis is a major issue for healthcare practitioners, whose compensation is currently partially based on sepsis performance standards Although sepsis and bacteremia are frequently used interchangeably, sepsis has lately been reclassified as a potentially fatal dysregulated host immunological response to infection (Singer *et al*., 2016). Many lines of evidence have demonstrated that bacterial infections could be a significant contributor to heart disease pathophysiology, among the many established clinical and laboratory risk factors for CVD (e.g. diabetes, hyperlipidemia, hypertension, smoking, and dyslipidemia). Through disrupting immunological as well as inflammatory processes, bacterial infections can either indirectly or directly induce CVD (Hogas *et al*., 2017). It was demonstrated that infection causes smooth muscle cell proliferation and local inflammation, stimulates innate immune response, and directly inhibits endothelial function through circulating endotoxins (Banach *et*

al., 2004). Indirectly harmful bacterial infection effects include the induction of proinflammatory, hypercoagulable, and atherogenic responses; low-density lipoprotein degradation; induction of nutrient/vitamin malabsorption; bacterial and host cell antigen mimicry; and metabolic disruptions, including excessive ammonia formation. In conclusion, recurrent bacterial infections cause an overabundance of inflammation, which triggers immune responses which negatively affect cardiovascular risk factors like cytokines, white blood cell count, heat shock proteins, fibrinogen, high density lipoprotein (HDL), triglycerides, and C-reactive protein (CRP). Among the bacteria associated with CVD risks include *Chlamydia pneumonia*, *Helicobacter pylori*, *Porphyromonas gingivalis*, and *Mycoplasma pneumonia* (Matusiak *et al*., 2016).

A rising clinical concern, infections could result in HF decompensation and, frequently, in life-threatening acute systemic disease (i.e., sepsis) and septic shock. The circulatory system is essential to development of multi-organ dysfunction in sepsis as well as refractory septic shock. A third of patients pass away within a year following a septic incident, despite the fact that the percentage of intra-hospital mortality linked to sepsis dropped from 35% in 2000 to 18% in 2002. Sepsis with cardiovascular dysfunction has significantly higher risk of mortality than sepsis without heart dysfunction (Kakihana *et al*., 2016). One of the main death causes for patients with HF is cardiac decompensation, which is brought on by infection (Alon *et al*., 2013). Although infections are a rare CVD cause, viruses and bacteria can impact devices and implants (Nielsen *et al*., 2015), pericardium (Adler *et al*., 2015), the myocardium (Hemkens and Bucher, 2014), or even thrombi (Egeblad *et al*., 2005). Yet, in the case where the bacteria infect cardiac tissue and/or valves, it causes severe conditions that often require surgery (Revilla *et al*., 2007) and are still linked to a significant risk of mortality and morbidity even with contemporary antibiotics (Olmos *et al*., 2013).

2.11.2. Bacterial Infections Related to HF

Infectious disorders of the heart are a varied and heterogeneous group of diseases that affect the myocardium, endocardium, and pericardium, and incorporate a wide range of clinical manifestations. Microorganisms which could infiltrate the heart and impact various cardiac components include fungi, bacteria, parasites, and viruses (Habib *et al*., 2015).

2.11.2.1. Infective endocarditis (IE)

The potentially fatal condition known as infective endocarditis (IE) is brought on by heart valve infection and inflammation, which are frequently malfunctioning due to underlying medical conditions. If treatment is not received, patients will develop congestive heart failure (CHF) and their health will deteriorate, IE is more common in older people, with 25% to 50% of those over 60 developing it. It is also more common when a valve replacement is done for IE. Even though it may be greater in developing nations (6–10 cases per 100000 life years), the prevalence of IE is 6–7 cases per 100,000 in wealthy nations. There is no discernible difference in death rates between IE patients who have a mechanical valve of heart or a bio-prosthetic valve of heart implanted; yet, a mechanical heart valve is typically advised for patients under 60 and a bioprosthetic heart valve is frequently prescribed for patients over 60. Bacteria and occasionally fungi are the main causes of infection. The infection may be acute or subacute, depending on the microorganism that caused it, and it typically begins slowly with vague and unspecific symptoms. A low-grade fever, pains, aches, and exhaustion can complicate the diagnosis (McIntyre *et al*., 2017). More aggressive bacteria, severe symptoms, and a quick infected valve loss or valve tissue are characteristics of acute onset. According to Singhal *et al*. (2013), IE will cause embolic infarctions, new intracardiac shunts, paravalvular, myocardial, or annular abscesses, and other potentially fatal consequences.

2.11.2.1.1. Pathophysiology

According to Lockhart *et al*. (2008), stable cardiac endothelium is resistant to the bacteremia that is caused by routine activities like brushing and chewing. But after endothelial damage, a platelet-fibrin thrombus forms due to the release regarding inflammatory cytokines as well as tissue factors, along with associated fibronectin production, which encourages bacterial adhesion (Widmer *et al*., 2006). Endothelium damage can result from direct bacterial activity, valve sclerosis, and rheumatic valvulitis, especially from *Staphylococcus aureus* (Werdan *et al*., 2014). Staphylococcal clumping factors A and B and fibronectin binding protein are two examples of bacterial adhesin proteins that are crucial pathogenicity determinants and bacterial mediators of adherence (Veloso *et al*., 2013). Bacterial invasion leads to further cycles of endothelial damage and thrombus deposition, which ultimately lead to contaminated vegetation.

2.11.2.2. Myocarditis (MC)

Myocarditis, or inflammation of the myocardium, could be a result of various substances, which include toxins, drugs, systemic disorders, and infectious agents. In poor nations, viral infections are the most common myocarditis cause (Cooper *et al*., 2014). Numerous symptoms, such as HF, palpitations, chest discomfort, cardiogenic shock, and mortality, can be brought on by myocarditis (Bozkurt *et al*., 2016). According to Caforio *et al*. (2013), myocarditis causes DCM in about 30% of instances, accounting for 9–16% of all the non-ischemic DCM in adult patients.

2.11.2.2.1. Pathophysiology

The majority of myocarditis (and associated consequences) are thought to be immune-mediated. For instance, microbial agent in infectious etiologies through respiratory enters the body or gastrointestinal system and attaches itself to some specific receptor in the heart. This leads to intra-cellular replication,

which damages and lyses cells. Immune dysfunction might result from this process, and molecular mimicry may play a significant part in exacerbating cardiac damage. If the damage is severe and persistent, dilated cardiomyopathy might ensue (Baessler *et al*., 2018).

2.11.2.3. Pericarditis

Inflammation of the pericardial layers is the hallmark of pericarditis, the most common kind of pericardial disease (Adler *et al*., 2015). It has been connected to Pericardial effusion that could lead to tamponade, or issues with cardiac filling, Both a distinct condition and a cardiac manifestation of a systemic sickness (such as an autoimmune or autoinflammatory disease) are possible ways for the disease to present itself. Although pericarditis can have both infectious and noninfectious origins, it is typically idiopathic (Chang, 2017). The prognosis and the onset of pericarditis symptoms will differ greatly (Chiabrando *et al*., 2020).

2.11.2.3.1. Pathophysiology

The same infectious agents infecting myocardium and endocardium can also harm the pericardium. Infection is the most frequent cause of pericarditis, accounting for 2/3 of the cases; the remaining one-third are caused by non-infectious diseases (Troughton *et al*., 2004). An accumulation big enough to be categorized as a pericardial effusion usually results from an increase in pericardial fluid that coincides with inflammation of the pericardium. Cardiovascular collapse may result from the pericardial fluid compressing the heart, which prevents the ventricles from filling sufficiently. The heart as well as the proximal sections of the major veins are encircled by a flask-shaped sac called the pericardium. In the case when examined cross-sectionally, it appears smooth, is composed of layers of serosal and fibrous components that have a combined thickness of 1mm-2mm, and typically contains a small fluid amount (which is

about 50 mL) (Rajiah, 2011). Even in the absence of a substantial pericardial effusion, pericarditis could occur. ECG changes associated with pericarditis can be caused by the inflammatory pericardium as well as subjacent inflammation of the superficial myocardium (Tunuguntla *et al*., 2019).

2.11.3. Bacterial Infection Symptoms

2.11.3.1. Sepsis Symptoms

Sepsis is defined as combination of systemic inflammatory response syndrome and an infection. Consequently, patients will exhibit a range of vital sign alterations in the early stages of sepsis: A temperature over 38 °C is considered a fever, whereas a temperature less than 36 °C is considered hypothermia. A heart rhythm that is over 90bpm in adults and no more than 2 standard deviations for the age in children is referred to as tachycardia. According to Mahapatra and Heffner (2017), tachypnea is defined as breathing rate of no less than 20 breaths per min. in the adults and no less than two standard deviations for age the in the children. Symptoms and signs of severe sepsis. Severe sepsis is the term used to describe sepsis with end-organ dysfunction. At this stage, oliguria or anuria, cyanosis, hypoxia, ileus, and altered mental status are some possible signs and symptoms ,Hypotension is one of the signs and symptoms of severe sepsis that patients who experience septic shock display. In addition to other distributive shock signs including warm extremities, rapid capillary refill (less than 1 sec), and bounding bursts, which is also known as the warm shock, blood pressure could be maintained throughout an early "compensated" shock stage. Vasoactive support and quick fluid resuscitation can reverse this shock stage. As septic shock advances to uncompensated stage, hypotension occurs, and patients may have thready pulses, chilled extremities, and delayed capillary refill (more than 3 sec), a symptom that is known as the cold shock (Mahapatra and Heffner, 2017).

2.11.3.2. Endocarditis Symptoms

Heart murmur and fever, the two main signs of infective endocarditis, occur in roughly 90% and 75% of patients, respectively (Cahill and Prendergast, 2016).Malaise, low-grade fever, sweating, chills, back pain, dyspnea, arthralgias, and loss of weight are examples of acute symptoms of infectious endocarditis. Alternatively, symptoms like malaise, low grade fever, sweating, back pain, chills, arthralgias, dyspnea, and weight loss that persist for weeks or months could be subacute. Among other micro-embolic or immunologic phenomena, Splinter hemorrhage, conjunctival hemorrhage, Osler nodes, Janeway lesions (i.e., vasculitic lesions of soles and palms), and Roth spots (i.e., hemorrhagic retinal lesions) are found in 5–10% of patients (Chambers and Bayer, 2020).

2.11.3.3. Myocarditis Symptoms (MC)

When a patient has suspected myocarditis, the most common clinical presentation is an upper respiratory tract infection, either new or old (Halle *et al*., 2020). The symptoms might vary greatly and include chills, fever, diarrhea, and appetite loss from a prior flu-like illness. Common heart symptoms, such as dyspnea, palpitations, and chest discomfort, could take days to manifest (Group, 2011). Patients frequently report unusual chest pressure that gets worse as they tilt their upper body forward, which suggests the presence of pericardial effusion, Myocarditis produces usually mild symptoms. Signs and symptoms include dizziness, nausea, loss of physical ability, and new-onset atrial or ventricular arrhythmias. Muscle soreness that is excessive for the amount of recent exercise might be experienced by any active patients. A 5 to 10 beat per minute increase in a patient's resting heart rate during testing could be a sub-clinical sign of inflammatory phase an active (Halle *et al*., 2020).

2.11.3.4. Pericarditis Symptoms

The most frequent initial symptoms were cough (including dysphagia) and chest pain. The most common physical test finding was tachypnea, which was followed by tachycardia. Pericardial friction rub has been observed in patients with this syndrome (Awan *et al*., 2017).

2.11.4. Causes of Bacterial Infections

Determining the primary cause of infection is crucial for both treating bacteremia patients and identifying the community of infected patients. Respiratory system and indwelling catheters, particularly central venous catheters, are frequent sources in hospitalized patients. The most frequent cause of community-acquired bacteremia is untreated UTIs. While they're more common in postoperative surgical settings, soft tissue as well as intra-abdominal infections are less common in pre-operative surgical settings. According to Antonio *et al*. (2019), *S. aureus* represents the most common gram-positive bacterium while *E. coli* is the most common cause of gram-negative related bacteremia.

2.11.5. Types of Bacterial Infections with HF

2.11.5.1. Infectious Endocarditis Bacterial :

The majority of the cases result from viridans streptococci, *Staphylococcus aureus*, *Streptococcus gallolyticus*, (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*) HACEK organisms, coagulase-negative staphylococci, and enterococci. Some of the rarer organisms include pneumococci, gram-negative bacilli, *Candida*, and polymicrobial organisms (Galar *et al*., 2019).

2.11.5.2. Infectious Myocarditis Bacterial :

Corynebacterium diphtheria, Chlamydia, Klebsiella, Mycobacterium tuberculosis, Legionella, Staphylococcus, Mycoplasma, Salmonella, Streptococcus pneumonia, Streptococcus A, Haemophilus influenza and Tryponema Pallidum (Bejiqi *et al*., 2019).

2.11.5.3. Infectious Pericarditis Bacterial :

Staphylococcus, Haemophilus, Streptococcus, Chlamydia, Neisseria, Salmonella, Legionella, Mycoplasma, Mycobacterium tuberculosis, Borrelia burgdorferi, Nocardia, Tropheryma whippelii, Treponema, Actinomyces and Rickettsia (Hoit and Oh, 2016).

2.11.6. Bacterial infection Diagnoses

2.11.6.1. Sepsis Diagnosis Biomarkers

Sepsis's laboratory and clinical signs, such as fever or leukocytosis, are neither specific or predictable. The onset of organ malfunction and mortality is often indicated by more common indications or lab criteria (such as the arterial hypotension). Better sepsis indicators are therefore required for clinical application (Meisner, 2005). "A biological characteristic measured objectively (i.e., with reproducibility and acceptable accuracy) and utilized as a marker for a pathological or physiological process, or action of a medicine" is the definition of a biomarker. There are two types of biomarkers: predictive and prognostic. Prognostic markers could be used to determine a patient's likelihood of achieving a particular outcome, regardless of treatment. Predictive markers will forecast the possible advantages (i.e., efficacy) and/or hazards (i.e., toxicity) of a treatment based on biomarker status (Dupuy *et al*., 2013). Two of such biomarkers, CRP and procalcitonin (PCT), are often employed in various labs and meet most of the criteria for a good biomarker. The liver generates CRP when there is inflammation and tissue damage. (Simon *et al*., 2004). The findings of a blood culture, CRP, or complete blood count (CBC) were considered in the study. CBC

was used for extracting the mean platelet volume (MPV), neutrophils, platelets, monocytes, and white blood cells (WBC) (Tamelytė *et al*., 2019). To look into potential infection sources, either might be ordered. Blood cultures, either alone or in combination with other possible source cultures. Prior to giving antibiotics, at least two blood cultures are advised (Joseph, 2020).

2.11.6.1.1. Procalcitonin (PCT)

Under normal conditions, thyroid C-cells create procalcitonin (PCT), a 116 amino acid precursor of calcitonin. Serum levels of PCT are typically less than 0.05 ng/mL, although various bodily tissues create high amounts of PCT when there is systemic inflammation, especially from bacterial infections. In contrast to CRP, which starts to rise following 12 hrs. to 24 hrs. and peaks at 48 hrs., it is detectable within 2-4 hrs. and peaks within 6-24 hrs. Immunosuppressive conditions such as neutropenia do not affect PCT production. Higher PCT levels are found in patients with more severe disease because they correlate with the intensity of the inflammatory insult or infection. Additionally, higher blood levels of procalcitonin are associated with a higher risk of death, suggesting that it may be useful as a prognostic indicator. PCT has certain benefits over other clinically used biomarkers like WBC count and CRP. The specificity for bacterial infection (as opposed to inflammation in general), the quick rise that follows an insult (6 hrs.), the quick decline with the immune control on the infection (24-hour half-life), the good correlation with the severity of the illness (higher levels in more severely ill), and lack of the effect of immunosuppressive and anti-inflammatory states on the production are some of the benefits of PCT over older markers (Christ-Crain and Muller, 2007; Kibe *et al*., 2011; Schuetz *et al*., 2011).

Clinical situations in which the PCT could be beneficial are the following :

- Differentiating bacterial verses viral respiratory tract infections
- Sepsis and septic shock diagnosis, risk stratification, and monitoring
- Determining the length of the antibiotic treatment in the respiratory infections

• Diagnosing systemic secondary infection post-organ transplant, post-surgery, and in multiorgan failure, severe burns, and severe trauma.

• Monitoring response to the anti-bacterial therapy

• Diagnosing sepsis and bacteremia in the adults and children (including neonates)

• Diagnosing the renal involvement in the pediatric urinary tract infections

• Differentiating the bacterial verses viral meningitis

• Diagnosing bacterial infections in the neutropenic patients

• Diagnosing septic arthritis

2.11.6.1.2. C-Reactive protein (CRP)

More complex measurements of cytokine activity, immunologic function, and cellular adhesion had all been demonstrated to be elevated among individuals at increased vascular risk, proving that CRP isn't the only inflammatory bio-marker which can predict myocardial infarction and stroke (Blake and Ridker, 2001). Yet, measurements for fibrinogen, a bio-marker that is involved in thrombosis as well as inflammation, are still poorly standardized, and methodological issues result in limiting the use of such parameter despite the consistent population-based data. Other broad systemic inflammation measures, like white blood cell count or rate of erythrocyte sedimentation, have proven unreliable in the clinical settings. There is a quite low possibility that those methods might have clinical utility since the assays needed for their assessments are either not appropriate for routine clinical uses or the protein of interest has a half-life that is too short for the clinical evaluations. On the contrary, numerous commercial platforms have standardized high-sensitivity tests for CRP. Furthermore, because CRP is so stable, it is possible to take precise measurements in the fresh as well as the frozen plasma with no need for specialized collection techniques. This is partly because CRP has long plasma half-life of 18 hrs. to 20 hrs. and a stable pentraxin structure (Blake *et al*., 2002).

2.11.6.2. Endocarditis Diagnosis

Main criteria include:

1- Positive Blood cultures for the typical microorganisms that are consistent with IE from 2 different blood cultures, and micro-organisms that are consistent with the IE from blood cultures that are consistently positive.

2- A transthoracic echocardiogram had shown positive IE imaging.

3- Cardiac CT had revealed definitive paravalvular lesions.

Some of the minor criteria include:

1- A predisposing cardiac disease or using injectable drugs.

2- A fever of no less than 38 ^{o}C.

3-Vascular lesions include septic pulmonary infarcts, conjunctival hemorrhages, intracranial hemorrhages, and large arterial emboli.

4- Serological evidence of active infection with species that are consistent with IE, microbiological confirmation, or a positive blood culture—all of which are not among the primary criteria listed above (Ren *et al*., 2019).

2.11.6.3. Findings of Laboratory

Generally, the positive predictive values of the many laboratory experiments are low, and none of them are diagnostic. The tests are just supportive in the diagnosis of IE. It is possible to find a high white cell count or other sepsis indicators, such as a high procalcitonin, CRP, or rate of erythrocyte sedimentation. Anemia from a chronic disease might develop. Creatinine levels could increase as a result of renal emboli, immune-complex-mediated nephritis, or acute tubular necrosis (Hitzeroth *et al*., 2016).

2.11.6.4. Myocarditis Diagnosis

After a light workup, patients with clinical signs as well as symptoms of acute myocarditis must be suspected, especially if they are young (25–50 years old) and do not have any prior cardiac disease history (Leong *et al*., 2018). The

first evaluation for acute myocarditis may include an ECG, echocardiography, serum troponin, and BNP. No less than 50% of the patients had elevated troponin, which is typically rather severe. If the clinical picture is right, BNP could be utilized to test for HF symptoms and ventricular strain, which could indicate myocarditis. To assess the degree of cardiac dysfunction and rule out some of the potential causes, like the valvular disease, an echocardiography could be utilized, A chest radiograph may show a pleural effusion, pulmonary vascular obstruction, or an enlarged heart, but it is neither sensitive nor specific for myocarditis. A CT angiography test may be necessary to rule out other causes of chest discomfort. Eosinophilia in a total blood count with differential could indicate eosinophilic myocarditis. Although nonspecific, CRP and erythrocyte sedimentation rate (ESR) are typically high (Al-Akchar and Kiel, 2021).

2.11.6.5. Pericarditis Diagnosis

A diagnosis is established in accordance with the most recent criteria from European Society of Cardiology. Current guidelines of the European Society of Cardiology (Adler *et al*., 2015) state that acute pericarditis must be diagnosed based on at least two of four criteria:

- ECG changes
- Pericardial rub
- Chest pain
- Pericardial effusion, new or worsening
- Increased inflammatory markers (ESR, CRP, and WBC count elevation) and imaging evidence of pericardial inflammation (CT scan, or cardiac magnetic resonance [CMR]) could be helpful with diagnoses and monitoring of the disease (Adler *et al*., 2015).

2.12. Antibiotics Susceptibility

2.12.1. Antibiotic uses

Antibiotics are medications that are utilized for curing or preventing infections caused by protozoa and bacteria. Most possibly, a narrow-spectrum antibiotic would be applied. The antibiotic's price might affect the decision. Identification of the bacteria could lower the toxicity and expense of antibiotic therapy, and the risk of developing antimicrobial resistance (Bojanić *et al*., 2018). For simple acute appendicitis, antibiotics could be utilized instead of surgery. At-risk groups, such as those with compromised immune systems (particularly in HIV cases for preventing pneumonia), those using immune-suppressive medications, cancer patients, and surgical patients, could be administered antibiotics as a preventive treatment (prophylactic). (Page-Shipp *et al*., 2018) When it comes to dental antibiotic prophylaxis, they are crucial in preventing bacteremia and infective endocarditis. In neutropenia cases, especially when it is brought on by cancer, antibiotics are frequently administered to prevent infection (Schellack *et al*., 2017). There are several ways to provide antibiotic therapy. Typically, antibiotics are administered orally. In more severe cases, antibiotics might be injected or given intravenously (Boyles *et al*., 2017). In addition to lowering systemic absorption and toxicity risks, topical application offers several benefits, such as obtaining a continuous and large antibiotic concentration at the infection site, lowering maximum amount of antibiotic available, and lowering antibiotic misuse risk (Dunn *et al*., 2017). It was demonstrated that using topical antibiotics to particular surgical wound types reduces surgical site infections. Nonetheless, there are a few broad grounds for caution with topical antibiotic use (Teklay *et al*., 2016).

2.12.2. Antibiotics Sensitivity

A laboratory is typically where antibiotic susceptibility testing (AST) is carried out (Giuliano *et al*., 2019). Once a bacterium has been identified through

the micro-biological culture, antibiotics are selected for the testing of susceptibility (Reller *et al*., 2009). One way to test for susceptibility is to expose bacteria to antibiotics and observe their reaction (i.e., phenotypic testing). Techniques could be quantitative, determining the lowest inhibitory concentration (MIC) of an antibiotic to which a bacterium is susceptible, or qualitative, indicating the presence or absence of resistance (van Belkum *et al*., 2019).

2.12.2.1. Phenotypic methods

Dilution in broth or agar plates are employed in the assays that rely on exposing bacteria to antibiotics (Pulido *et al*., 2013). The organism being cultured and the antibiotics available locally would determine which antibiotics are employed (Reller *et al*., 2009). To guarantee precise findings, the inoculum the concentration of bacteria injected to the broth or agar have to be standardized. In order to do this, the bacterial turbidity dissolved in broth or saline is measured against solutions of McFarland standards that have the same turbidity as a suspension containing some particular bacterial concentration. Until the appropriate concentration is established, either visually or using photometry, the inoculum is added to the growth medium (Hombach *et al*., 2015). The disc diffusion approach involves picking a strain of bacteria, putting it on an agar plate, and watching grow of bacteria close to discs that have been impregnated with antibiotics (Syal *et al*., 2017). This technique is referred to as the Kirby-Bauer approach, whereas modified approaches are employed. On a plate where growing of bacteria, little paper discs carrying antibiotics are placed. A distinct inhibition zone or ring surrounding the disk indicates that the antibiotic is preventing bacteria growth. Through comparing the inhibition zone's diameter to predetermined thresholds that correspond with the MICs, bacteria are classified as intermediate, resistant or sensitive to an antibiotic. Mueller-Hinton agar is commonly employed in this test for antibiotic susceptibility (Jorgensen and

Turnidge, 2015). There are guidelines for conducting tests and interpreting the findings (Reller *et al*., 2009). Standards for agar type and depth, temperature of incubation, and analytical technique are established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Hombach *et al*., 2015). The most straightforward and affordable technique for assessing susceptibility is disc diffusion, which is also simply modified to evaluate recently developed antibiotics or formulations (Reller *et al*., 2009).

2.12.3. Antibiotics Resistance Causes

2.12.3.1. Natural resistant

The capability of a microorganism to withstand exposure to antibiotics that might typically kill it or prevent it from growing is known as antibiotic resistance (ABR) (Li and Webster, 2018). Numerous factors, like microorganism's level of resistance expression and tolerance to mechanisms of resistance, as well as chromosomal mutations (cross-resistance) or gene transfer between microorganisms via transposons, plasmids, bacteriophages, and integrons, can contribute to the emergence of an antimicrobial-resistant phenotype. Because plasmids contain resistance determinants, resistant microorganisms proliferate quickly (Giedraitienė *et al*., 2011). The most significant biochemical resistance strategies that bacteria can employ to defend themselves against various substances include enzymatic degradation, target change, reduced uptake, and over-expression of the efflux pump proteins (Gajdács, 2019). Even so, this is a common occurrence in clinical practice that dates back to the first generation of antibiotics (Monsserrat-Martinez *et al*., 2019). ABR is currently seen as a worldwide public health concern due to exponential growth and dissemination of the resistance and dearth of novel drugs to combat it (O'Neill, 2016).

2.12.3.2. Self-Medication

Using plants or medications to treat health problems without first seeking medical advice regarding indication, dosage, course, or frequency is known as self-medication. Additionally, it entails long-term treatment of a recurrent disease with a previously prescribed medication (Bennadi, 2013). For over-the-counter (OTC) drugs that are easily obtained at pharmacies with no prescription, self-medication is typical. Those drugs include cold and cough remedies, and pressure relievers (acetaminophen) (Ehigiator *et al*., 2013). Between 2.9% and 3.7% of fatalities worldwide are caused by self-medication, a global health concern with serious implications to the public health, such as drug resistance and organ destruction (Osemene and Lamikanra,2012). Numerous factors, such as education, attitudes towards healthcare, insurance plans, convenience, cost savings, and age, all have an impact on self-medication (Helal and Abou-ElWafa, 2017). It must be mentioned that if the patient is sufficiently informed about the prescription and the disease, self-medication with over-the-counter pharmaceuticals could be safe and acceptable (Gutema *et al*., 2011). In the case when self-medication is done properly and by people who know what they are doing, it can cut down on waiting times for doctors and other insurance expenses like consultation fees (Helal and Abou-ElWafa, 2017). At the same time, over-the-counter drugs are frequently seen to be harmful when used irrationally, leading to delayed or incorrect diagnoses, a variety of adverse drug reactions, and, eventually, an increase in the prevalence of disease in a community as a result of the resistance (Sharma *et al*., 2015).

2.12.3.3. Clinical Misuse

The overuse of antibiotics is one of the primary causes of ABR development. Overuse, self-medication, inappropriate prescribing, careless use, and incorrect dosage or duration of treatment are all examples of antibiotic misuse (Haddadin *et al*., 2019). The widespread antibiotics' use with no prescriptions or

the patients' total disobedience of doctor's orders are examples of how patient attitudes might contribute to antibiotic misuse (Davey *et al*., 2002). The overview of product attributes does not include information on the length of time or dosage of treatments (Wogayehu *et al*., 2020). According to Gajdács *et al*. (2020), community pharmacists continue to have a role in making sure that the antibiotics are administered responsibly. However, from a medical standpoint, efforts must be made to optimize prescribing methods to avoid overuse of antibiotics, particularly in primary care (Bianco *et al*., 2018).

2.12.3.4. Pollution Environmental

AMR represents a worldwide health issue that is brought on by misuse of antibiotics in the medicine and animal farming, and the slow rate of new antibiotic development. There has been a lot of focus lately on the characterization of the AMR in the environment, which is essential to recognizing and preventing threats to public health. This characterization had become both easier and more complex due to the availability of high-throughput technologies for identifying antimicrobial resistance genes (ARGs), Because of the present depth of sequencing technology, many ARGs are still uncharacterized and unknown, despite the fact that researchers could currently swiftly identify and assess known ARGs in the environment. The development of new mechanisms of resistance, AMR spread in the environment through horizontal gene transfer, and dissemination of mobile genetic elements make the process difficult, even though new gene discoveries are essential for stopping global AMR. Additionally, different environments like the aquatic climate have varying resistance profiles based on their location and could act as AMR reservoirs, especially as they are typically the endpoints of wastewater treatment plant discharge and agricultural runoff. Due to the fact that the majority of people get their drink of water from the sea water, which is where the waste-water is released, the aquatic environment is a good place to incorporate and propagate

AMR into the environment. Human-animal transmission of AMR may occur if runoff from animal farms finds its way into surface waters (Williams *et al*., 2016).

2.12.3.5. Food Production

Assuring the safety and quality of foods meant for human consumption, and preventing and controlling food-borne diseases throughout the process of food manufacturing, such as packaging, handling, preparation, and transportation, are the main objectives of the scientific course on food safety, One of the most significant public health issues associated with the possibility of antibiotic resistance emerging in food supply chain is resistant food-borne diseases. Yet, some basic and simple food safety practices, like convenient vegetable washing, handwashing, proper temperatures of cooking, and conditions of food storage, could efficiently reduce and monitor antibacterial resistance foodborne pathogen spread. Recently, several types of resistant bacteria were found in food products and humans (Founou *et al*., 2016). Hepatotoxicity, carcinogenicity, mutagenicity, nephropathy, toxic symptoms, allergic reactions, and antibacterial resistance are all possible outcomes of antibiotic residues in food products. Based on Mensah *et al*. (2014), anti-biotic residues in food products might result in hepatotoxicity, nephropathy, carcinogenicity, mutagenicity, allergic responses, antibacterial resistance, and toxic symptoms. Numerous food-borne diseases have been found to be resistant to a range of medications and antibiotics (Hashempour-Baltork *et al*., 2019). In the industrialized as well as developing worlds, antibiotics are frequently utilized as growth enhancers for animals. Approximately 80% of antibiotics supplied in US are primarily utilized for promoting growth and preventing infections in animals (Bartlett *et al*., 2013). It is claimed that treating livestock with antibiotics improves their overall health, which raises yields and produces higher-quality products (Michael *et al*., 2014). Humans consume antibiotics that are utilized in animals (Golkar *et al*., 2014). No less than 35 years ago, substantial antibiotic

resistance rates have been found in the farm animals as well as farmers' gut flora, marking the first documented instance of resistant bacteria moving from farm animals to humans (Bartlett *et al*., 2013). More lately, research has demonstrated that meat products from farm animals can carry antibiotic-resistant bacteria that infect humans. The following circumstances lead to this: 1) Antibiotic-resistant bacteria proliferate because susceptible bacteria in food-producing organisms are killed or suppressed by antibiotics; 2) resistant bacteria are spread to humans through food supply; and 3) these bacteria could infect people and cause illnesses that can be detrimental to their health. The environmental microbiota is impacted by the use of antibiotics in agriculture (Control and Prevention, 2013).

2.12.4. Antibiotic resistance mechanism

A- Modifications

The position of the target sections of the antibiotic and changes in the drug-related receptor might include ribosomes and enzymes (Prashanth *et al*., 2012). The most prevalent type of resistance linked to alterations in the ribosomal target is resistance to macrolide antibiotics (Shaikh *et al*., 2007). *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Neisseria meningitides* strains have developed penicillin resistance due to mutations in beta-lactamase enzymes, which are proteins that bind penicillin (Southon *et al*., 2020).

B- Enzymatic Inactivation of Antibiotics

Enzymatic inactivation is one of the best ways to combat antibiotic resistance, because most bacteria produce the enzymes needed for antibiotics degradation (Pérez-Llarena and Bou, 2016). The most prevalent examples include erythromycin-modifying enzymes, beta-lactamases, aminoglycosidase, and chloramphenicol (Suleiman *et al*., 2020).

C- Inner and Outer Membrane Permeability Reduction

Changes in permeability of external and internal membranes lead to either rapid ejection from the pump systems or decreased drug uptake into the cell (Santa and Indrawattana, 2016). A decrease in permeability of outer membrane can also result in porin alterations in resistant strain proteins, such as quinolone and aminoglycoside resistance (Li *et al*., 2012).

D-Active Pumps System

The most significant source of resistance in tetracycline group of antibiotics is the active pump mechanism. Tetracyclines are thrown out and unable to concentrate within the cell via an energy-dependent active pumping process (Li *et al*., 2020a). This mechanism of resistance is controlled by chromosomes and plasmids. According to Guo *et al*. (2020), beta-lactams, quinolones, chloramphenicol, and 14-membered macrolides are all resistant to active pumping systems.

E- Alternative Metabolic Pathway

Unlike several of the target modifications in bacteria, the most recent drug-susceptible route does not require objective development (Fatahi-Bafghi, 2019). Bacteria may prepare folic acid from the environment rather than synthesizing it, which would make it resistant to trimethoprim and sulfonamide (Tan *et al*., 2020).

CHAPTER THREE
MATERIALS AND METHODS

Materials and Methods

3.1. Materials

3.1.1. Laboratory equipments :

The primary equipment that is utilized in the presented study are listed in table (3.1).

Table (3.1): Details of the equipment's and the manufacture companies

No.	Equipment name	Manufacture company	Origin
1	Autoclave	Labtech	Korea
2	BACT/ALERT 3D	BIONMERIEUX	France
3	Blood pressure device	Rossmax	Switzerland
4	Centrifuge	Hitachi	Japan
5	Cool box	VB	China
6	Deep freezer	Shark	China
7	ECHO	Philips	Germany
8	ECG	MAC-1600	Germany
9	ELISA printer	Epson	USA
10	ELISA reader	Biotech	USA
11	Hood	Biotech	USA
12	Hot plate magnetic stirrer	Labtech	Korea
13	Ichroma	Boditech	Korea
14	Incubator	Gallenkamp	England
15	Light Microscope	Olympus	Japan

16	Oven	Memmert	Germany
17	Refrigerator	Concord	France
18	Sensitive Balance	Kern	Germany
19	VITEK 2-compact System	BIONMERIEUX	France
20	Vortex	Scientific Industries	Korea
21	Water distiller	GEL	Germany

3.1.2. Laboratory supplies :

The primary Laboratory supplies used in the presented study are listed in table (3.2).

Table (3.2): Details of the laboratory supplies

No.	Laboratory supplies	Manufacture company	Origin
1	Bunsen burner	Locally	Iraq
2	Cotton swab	Afco	Jordan
3	Cylinder	Bomex	Germany
4	Disposable syringes	Medjecte	Emirate
5	Disposable Loop	Locally	Iraq
6	EDTA Tubes	Alrawan	China
7	Filter Paper	Gallenkamp	England
8	Gel Tube	Alrawan	China
9	Micropipette	Biobasic	Canada
10	Pipette tip	Alrawan	China

11	Plastic dropper	Locally	Iraq
12	Petri dishes (Plastic)	Afco	Jordan
13	Rack	Locally	Iraq
14	Stick	Labtech	China
15	Sterile cotton	Locally	Iraq
16	Sterile cup	Afco	Jordan
17	Volumetric Flask	Jiassco	India

3.1.3 Culture Media :

The primary culture media that had been utilized in the presented study are listed in table (3.3).

Table (3.3): Details of the used culture media

No.	Media	Manufacture company	Origin
1	Blood culture bottles	BioMerieux	France
2	Blood agar	Himedia	India
3	Brain heart infusion broth	Himedia	India
4	MacConkey agar	Himedia	India
5	Mannitol Salt agar	Himedia	India

3.1.4. The Chemicals and Diagnostic kits:

The primary diagnostic kits and chemicals that have been utilized in the presented study are listed in table (3.4).

Table (3.4): Details of Diagnostic kits and Chemicals

No.	Kits	Company manufacture	Origin
1	CRP kit	Boditech	Korea
2	Ethanol	Teeba	Iraq
3	GN card	BIONMERIEUX	France
4	GP card	BIONMERIEUX	France
5	Gram Stain	Crescent	Saudi
6	Human Procalcitonin (PCT) ELISA KIT	MORNMED	China
7	Human NT-pro BNP ELISA KIT	MORNMED	China
8	Human CNP ELISA KIT	MORNMED	China
9	Human Troponin ELISA KIT	MORNMED	China
10	Human ischemia-modified albumin (IMA) ELISA KIT	MORNMED	China
11	Human sCD40L ELISA KIT	MORNMED	China

3.2. Methods

3.2.1. The Media

3.2.1.1. Preparation of Culture Media:

Based on manufacturer's instructions, a set of general culture media was prepared as well as sterilized for a period of 15 minutes through autoclaving at 121 °C. Prior to usage, the media have been cooled to a temperature of 45 °C

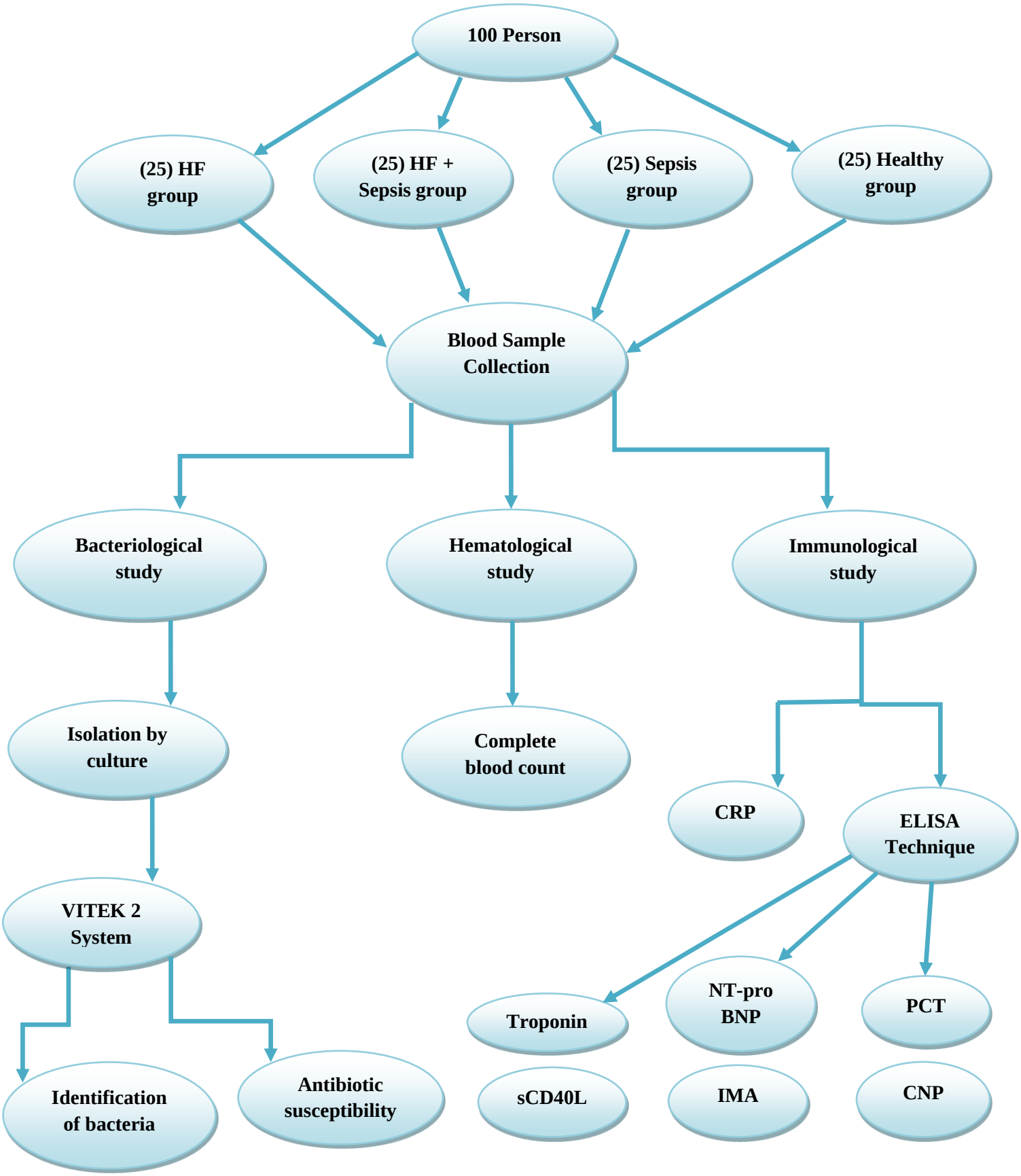
following sterilization. Table (3.5) provides the specifics of how culture media are used.

Table (3.5): Details of the use of culture media

No.	Culture Media	Utilization	References
1	Blood culture bottles	Used to detect bloodstream infections, especially bacteremia and septicemia	(Riedel and Carroll, 2010)
2	Blood agar	Used to cultivate microorganisms and determine hemolytic reaction.	(Choi *et al*.,2024)
3	Brain heart infusion broth	Use for preserving bacteria isolates at a temperature of -20 °C for long time	(Choi *et al*.,2024)
4	MacConkey agar	Used for the purpose of preliminary diagnosis, and to detect its ability to lactose fermentation	(Luis *et al.*, 2004)
5	Mannitol Salt agar	was utilized as a selective medium to identify staphylococci, along with their species	(Becker *et al.*, 2014)

3.2.2. Design of the Study

Between January and August of 2024, a comparative analysis of samples has been carried out at coronary care unit (CCU) at the Heart Center of Al-Hussein Teaching Hospital, Al-Hussein Medical City/Karbala Health Directorate. The current study included 145 samples. Forty-five patients who had sepsis with other cardiac conditions that were not considered heart failure were excluded. Patients receiving medications that directly affect cardiac biomarkers and those with other chronic diseases that affect cardiac indicators, such as chronic renal failure and tumor patients, were also excluded. The patients were diagnosed by physician and the study samples had been split into four groups: 25 samples of patients with HF alone made up the first group; 25 samples of patients with HF and sepsis or bacterial infection made up the second group; 25 samples of patients with bacterial infection in the blood made up the third group; and 25 samples of healthy individuals made up the fourth group, All of the patients, who were of both sexes (male 53, female 47) and the age groups included 20-39, 40-59, 60-79, 80-99 year, were admitted with bacterial infections and HF. After that, the research followed some steps which shown in the Scheme (3.1).



Scheme (3.1): Study design

3.2.2.1. Collection Data

Many crucial details have been collected from the patients, including age, name, weight, sex, diabetes, blood pressure, and symptoms.

3.2.2.2. Ethical Approval

All participants have been informed and each study patient had provided an informed written consent prior to the collection of samples. The Ethics Committee of the College of Education for Pure Sciences, University of Kerbala, granted approval for this study, No. 3431, on December 25, 2023.

3.2.2.3. Collection of Samples

Following admission to the CCU, approximately 10 milliliters of venous blood samples were extracted from HF patients. Important blood culture procedures were carried out according to Ntusi *et al*., 2010 , such as:

1- The process of verifying identity of patients had started, and the identity of patients were required by asking questions.

2- The patient was informed of the plans and given a description of the operation, was frequently granted verbal consent.

3- Blood culture bottles, sterile gloves, a 10-ml syringe, povidone iodine (or another appropriate skin disinfectant), a tourniquet, and a sharps disposal bin were all gathered.

4- A suitable vein was selected, and a tourniquet was applied. Alcohol or soap and water should be used for disinfecting the hands. After that, hands were then washed or rubbed until completely dry. They put on sterile gloves.

5- The puncture site has been cleaned with alcohol or povidone; aseptic procedure has been used. Two to three minutes were given for the disinfectant to dry. A green sterile cover has been positioned over the site of the blood culture with opening.

6- At least 10 ml of blood has been drawn from the patient's vein using a needle that was gently inserted (adults).

7- Tourniquet has been removed. Syringe and needle have been removed from the wound of the puncture. Pressure has been applied as a dry swab was placed on the site of the puncture, then inoculated blood in the bottle after disinfecting its top with alcohol swab.

8- The blood culture container has been gently spun (avoid severe shaking) to mix the blood and culture medium.

9- Blood culture bottle has been delivered to the lab as fast as feasible. Simultaneously, a 3.5 ml blood sample was placed in a 2 ml gel tube at the temperature of the room, allowed to clot for at least 15 mins, and after that centrifuged at 2500 rpm. Following separation, serum has been split to Eppendorf tubes. The remaining 1.5 ml of the blood has then been placed in EDTA tube and shaken for a minimum of 15 mins.

3.2.3. Bacteria Diagnosis

3.2.3.1. Samples of the Blood Culture

Blood has been extracted from a peripheral vein and put to bottles of the blood culture. BacT/ALERT® 3-D system has been utilized for initial blood culture testing. Following collection and inoculation on MacConkey agar, Blood agar, and Mannitol salt agar plates, the bacteria were incubated at 37°C in an environment with 5% CO_2 (Ha *et al.*, 2018).

3.2.3.2. Gram Stain

Gram stain This investigation was used to segregate gram positive organisms from gram negative organisms. After bacterial culture smears on a clean slide. They were then placed on a staining rack; heat fixed then flooded with crystal violet and allowed to stand for 30 seconds. The slide was then rinsed with water for 5 seconds and then covered with iodine. They were allowed to

stand for 1 minute and then rinsed with water. De-colorization was done using 95% ethanol for 15 seconds, followed by rinsing with water. Neutral red was then used as a counter stain. It was flooded for about 60 seconds and the slides rinsed with water and blot dried using a filter paper. Examination was done under a microscope at x100 under oil immersion (Ondari,2020). The organisms that when stained by gram stain become purple brown under a microscope are named gram-positive organisms, the cell 52 Chapter Three Materials and Methods membrane of those organisms consists of higher peptidoglycan content, while the cell membrane of the gram-negative organisms consists of a higher lipid content and appear red or pink when examined under the microscope after staining by gram stain.

3.2.3.3. Positive Blood Culture Conventional Workflow

After receiving a positive signal from BacT/ALERT® 3-D device, subculture on an adequate amount of solid agar media, colonies that were incubated on the agar plates have been subjected to identification as well as antibiotic susceptibility testing (AST) with the use of commercial automated Vitek-2 system (bio-Meriéux) after overnight period of incubation. AST and ID data from this conventional workflow served as the standard for comparison as the institution's protocol (Ha *et al*., 2018).

1. A standardized simple inoculum requires little handling following primary organism isolation.
2. Insert the inoculum into the Smart Carrier Station™ VITEK® 2 Cassette .
3. Barcode connects the sample and VITEK® 2 Card.
4. The instrument manages all following incubation and result readout procedures after the Cassette has been loaded.

Clinical laboratories frequently employ the automated biochemical-based VITEK® 2 Compact, which has 48 biochemical characteristics, for microbial detection (Książczyk *et al*., 2016). The VITEK2 Compact could identify micro-

organisms for as long as 4 hrs. In addition to evaluating bacterial growth with the existence of inhibitors, every one of the wells evaluates the metabolic performance of a strain, which included its capacity for acidifying, alkalizing, and hydrolyzing the substrates enzymatically. The device uses fluorescence-based instruments to identify bacterial growth as well as metabolic alterations in the microwells. The results regarded the bio-typing and bio-chemical-based approaches were affected by bacterial incubation conditions, included pH and media composition (Książczyk *et al*., 2016). A few pure culture colonies that had been grown on the Mannitol salt agar, MacConkey, or Blood agar for 18hrs to 24hrs were collected using a sterile microloop. A VITEK2 DensiChek (bio-Mérieux, France) has been used in order to calibrate bacterial suspension to the Mc-Farland Standard of Turbidity of 0.50–0.63 in 3 mL of a 0.45 sodium chloride solution. In the case when the gram stain has been negative, GN card has been put on the cassette and put in the instrument; if it were positive, GP card has been put on cassette then put in instrument. For avoiding changes in turbidity, the interval between the preparation of the suspension and the filling of the card has been smaller than 30mins. At a temperature of 35.5 °C, the cards have been incubated. Every fifteen minutes, when every one of the cards has been removed from incubator, colorimetric readings have been taken automatically. Following 10hrs to 18hrs of incubation, findings have been read (Morka *et al*., 2018).

3.2.4. Antibiotic Susceptibility Determination

A bacterial isolate's susceptibility to a set of antibiotics is ascertained via antibiotic susceptibility testing. Following being inoculated, the cards have been placed into Vitek2. In accordance with manufacturer's recommendations, which are listed below, identification and susceptibility cards have been inoculated then interpreted. In order to ensure that density and number of micro-

organisms that have been inoculated into Vitek cards have been suitable, colony counts were employed (Bazzi *et al*., 2017).

- The examination establishes if the microorganism could develop with the existence of antibiotics after it has been exposed to them.
- The clinician is informed of the MIC (i.e., Minimum Inhibitory Concentration), a measure of an organism's resistance or sensitivity to some antibiotic.
- Antibiotic resistance pathways in bacteria were identified through using antibiotic susceptibility testing. Clinicians use the results of antibiotic resistance examinations to help choose the appropriate course of care for each patient's infection.

3.2.5. Heart Failure Identification

3.2.5.1. Heart Failure Identification by ECHO and ECG

The CCU's specialty physician used ECHO and ECG to identify patients with HF.

3.2.5.2. Diagnosis of Heart Function Tests

Principle of Immunological test

A human interleukin-specific antibody was pre-coated on micro-ELISA plate used in ELISA kits, which operate on Sandwich-ELISA principle. Following the addition of standards or samples to the micro-ELISA plate wells and their combination with particular antibody, the Horseradish Peroxidase (HRP) conjugate has been progressively added to every one of the micro plate wells and allowed to incubate. Following the removal of any remaining free components, the substrate solution has been added to every well. The only wells that might seem blue are those containing HRP conjugate as well

as human antibody. Adding stop solution, which is shown by a change in the blue, finally stopped the enzyme-substrate process.

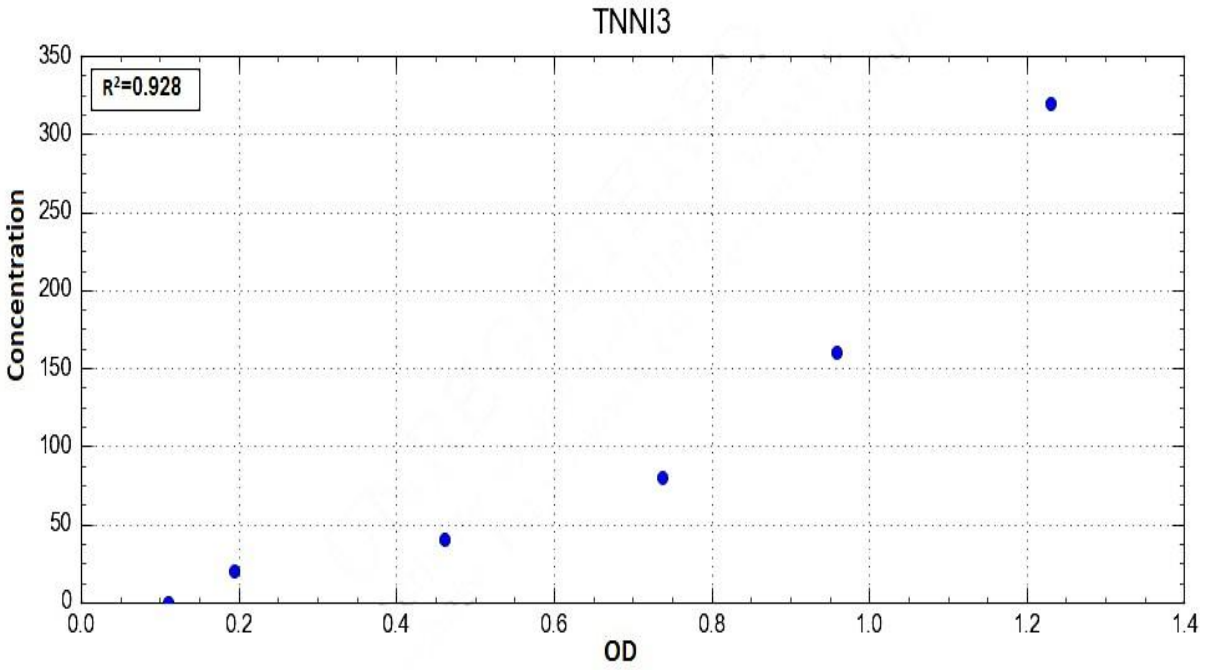


Figure (3.2) : The standard curve of Human TNNI3

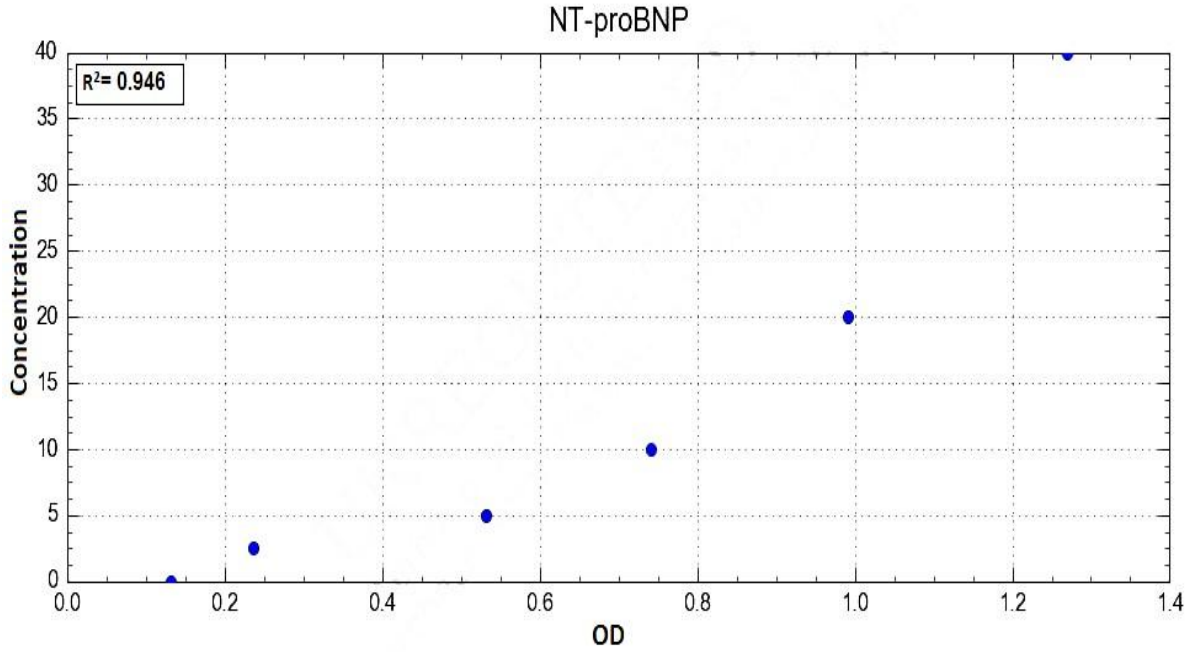


Figure (3.3) : The standard curve of NT-proBNP

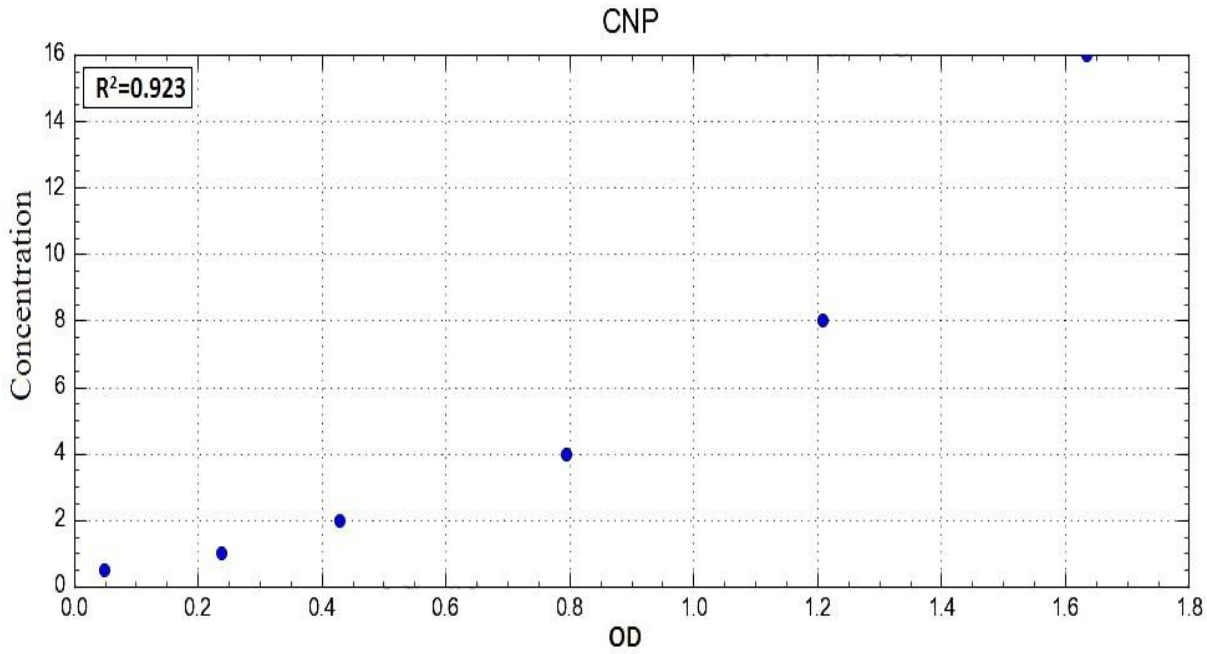


Figure (3.4) : The standard curve of CNP

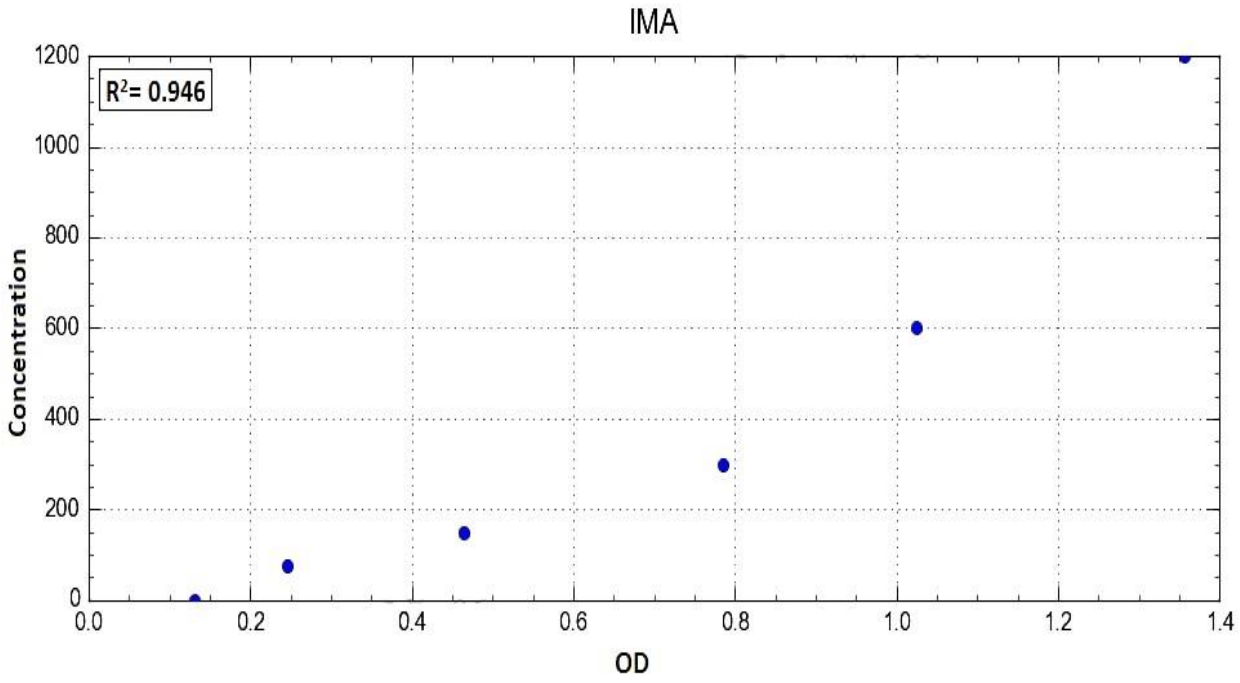


Figure (3.5) : The standard curve of Human IMA

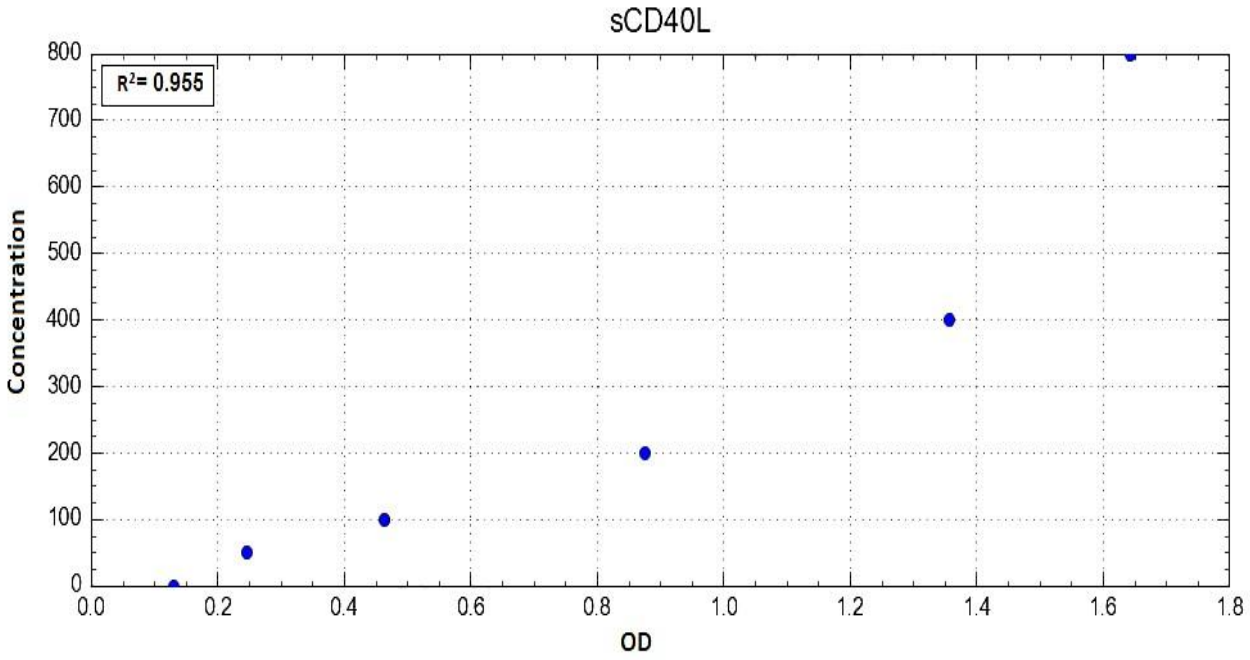


Figure (3.6) : The standard curve of Human sCD40L

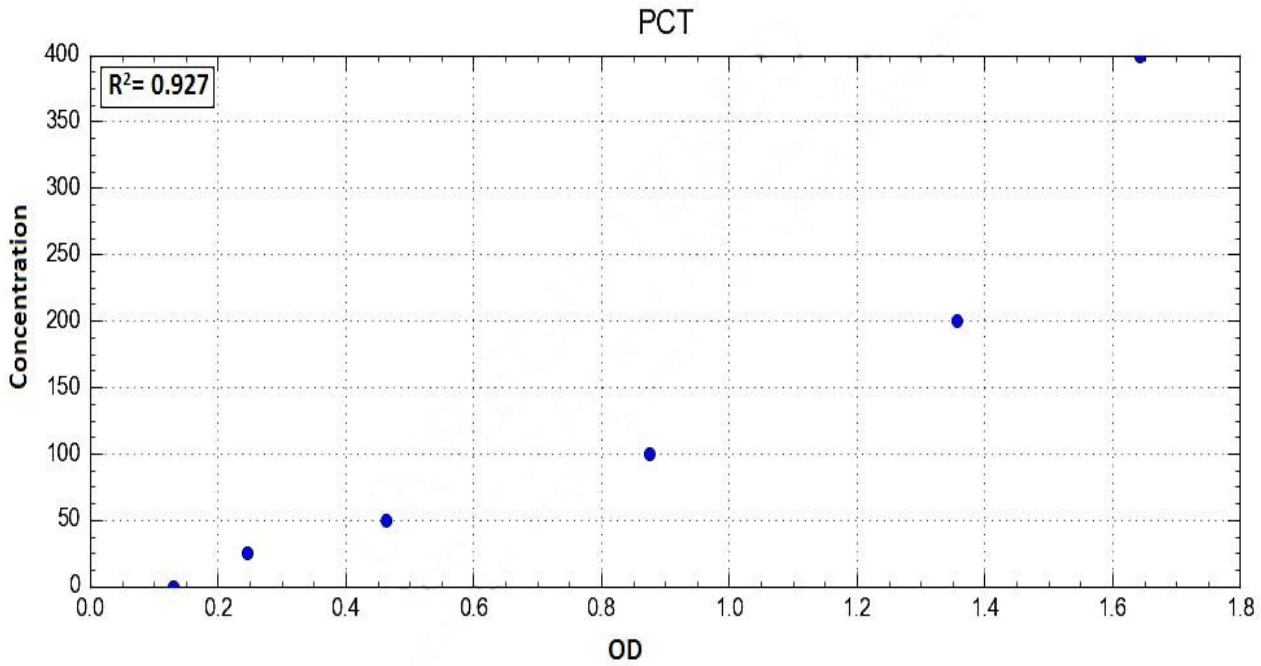


Figure (3.7) : The standard curve of Human PCT

3.2.5.2.1. C- Reactive Protein Determination (CRP)

As directed by the manufacturer:

1. An empty collector of samples has been inserted to create a puncture on top of detecting buffer tube.
2. A 10-micro-liter sample of human whole blood, serum, plasma, and control was taken using a sample collector.
3. The tubing and sample collector have been combined into a single tube.
4. The sample is shaken no less than 10 times until it is inverted and comes out of sample collector. Within 30 seconds, the sample and buffer combination have been consumed.
5. The assembled tube's top cap has been taken off, 2 drops were thrown onto paper towel prior to the reagents being added to the cartridge.
6. The cartridge's sample well only contained two drops of the mixture.
7. The device has been inserted in the holder of the instrument's for the measurements of the ichroma. The cartridge has been checked for correct alignment prior to being inserted fully in cartridge holder. Which is why, some certain arrow was put on cartridge.
8. 'Select' or 'START' button of the instrument has been hit for ichroma tests.
9. Following inserting cartridges for ichroma checks, the device can start scanning the sample-loaded cartridge three minutes later.
10. Test results have been displayed on display screen of the instrument for ichroma inspections.

3.2.6. Estimation of Complete Blood Counts

The indices of Red Blood Cell (RBC), Hemoglobin (HGB), Platelet (PLT), Hematocrit (HCT) were computed using the automated hematology analyzer (CBC). Leukocyte counts of various types, such as Lymphocytes (LYM), White blood cells (WBC) and Neutrophils (NEUT), were ascertained

with the use of the same technique. For testing, the device extracted 50 µl of blood from each sample.

3.2.7. Statistical analysis

To determine Chi-square, ANOVA (one away) at significance level (α) in ($P \leq 0.01$) and ($P \leq 0.050$), and Correlation (r), the findings were statistically evaluated in SPSS version 24 (Rosner,2022).

CHAPTER FOUR
RESULTS AND DISCUSSION

4.1. Samples

This study included 100 patients. Forty-five patients who had sepsis with other cardiac conditions that were not considered heart failure (such as angina or mild cardiomyopathy) were excluded. Patients receiving medications that directly affect cardiac biomarkers, such as beta-blockers or vasodilators that alter BNP or Troponin values, as well as steroids that may reduce the inflammatory response associated with sepsis, were also excluded. Patients with other chronic diseases that affect cardiac indicators, such as chronic renal failure and tumor patients, were also excluded. Three groups of 75 patients have been created: those with bacterial infection alone, those with bacterial infection and heart failure (HF), and those with HF alone and healthy group.

4.2. General parameters

4.2.1. Age

Table (4.1) exhibits the distribution of study groups by age, with a focus on individuals with and without heart failure and infections. The means of age of no heart failure groups were: healthy group (59.68±16.09), infection group (57.72±18.42), while the means of age of the heart failure groups were: no infection group (66.45±10.17), infection group (66.31±10.58). Additionally, there has been no significant age-based difference between groups ($P \geq 0.05$).

Table (4.1): Distribution of study groups according to age

Groups	Criteria	N	Mean (age)	SD
No heart failure	**No infection (Healthy)**	25	59.68	16.09
	Infection	25	57.72	18.42
Heart failure	**No infection**	25	66.45	10.17
	Infection	25	66.31	10.58
P value		0.0644		
LSD		NS		

The findings were consistent with a prior study that indicated no significant differences between HF patients and healthy across all age groups, with the exception of 50–59 age group, where there have been significant difference values ($P<0.05$) between healthy and patients (Arif *et al*.,2021). On the other hand, a prior study revealed that age was the primary factor of risk for HF and cardiovascular disease (CVD) in general. HF is the leading cause of death among the elderly, affecting about 1% of people over 50. This is a growing concern in the US, in which the population over the age of 65 rose from 40 million in 2007 to 51 million in the year 2017 and is expected to reach 95 million in the year 2060 (Benjamin *et al*., 2019).

According to a different study, age-related HF was one of the biggest issues facing world healthcare now because of the sharp increase in the elderly population, Age-related changes in heart function and structure are possibly influenced by both systemic as well as cardiac-specific changes in the physiology of the cells. Age-related increases in left ventricular wall thickness are due to an increase in the size regarding cardiomyocytes rather than an increase in their number. Actually, aging is linked to a decline in regenerative ability, which could be made worse by a rise in cell death. This could therefore be linked to the accumulation regarding senescent cells as well as a loss in mitochondrial function that occurs with age. Myocardial fibrosis is anticipated to grow with age due to increased inflammatory activity (Li *et al*., 2020b).

In line with another study that had showed that there had been functional alterations in the hearts of elderly persons, systolic and diastolic dysfunction as well as electrical dysfunction, such as the emergence of arrhythmias, were documented, In aging patients, atrial fibrillation, HF and other CVDs are more prevalent due to a combination of electrical and functional defects (Steenman and Lande, 2017). Significant structural and cellular changes brought on by age-related oxidative stress ultimately decrease cardiac functional ability

and contribute to the onset of CVD (Rodgers *et al*., 2019). Another study that indicated a total of 1058 patients enrolled in study with a mean of age 37.4 years± 13.7 and 86% (912/1058) were male and a higher percentage of patients were in the 20-29 years age group (Habeeb, 2024). Structural, cellular, and functional changes associated with cardiac ageing and heart failure with preserved ejection fraction (HFpEF). Key molecular mediators are considered within the framework of the established hallmarks of ageing, with particular attention to promising therapeutic candidates. We further delineate the differential impacts of ageing on cardiac structure and function in men and women, addressing hormonal and chromosomal influences (Hastings *et al*.,2024). Left ventricular diastolic dysfunction (DD) with and without heart failure with preserved ejection faction HFpEF showed significant associations with different major cardiovascular risk factors and comorbidities warranting further research for their possible role in the formation of both Asymptomatic left ventricular diastolic dysfunction ALVDD and DDwHFpEF (Wenzel *et al*.,2022).

Atrial fibrillation (AF) represents the most common arrhythmia worldwide and its prevalence exponentially increases with age. It is related to increased risk of ischemic stroke or systemic embolism, which determines a significant burden of morbidity and mortality, as widely documented in the literature. AF also constitutes a risk factor for other less investigated conditions, such as heart failure, pulmonary embolism, impairment in physical performance, reduced quality of life, development of disability, mood disorders and cognitive impairment up to dementia (Bencivenga *et al*.,2020). Aging is in fact a primary risk factor for many diseases and in particular for cardiovascular diseases and its derived morbidity and mortality (Izzo *et al*.,2021). The magnitude of the infection-CVD association showed specificity in sex, pathogen type, infection burden, and infection site. High genetic risk and infection synergistically increased the CVD risk (Zheng *et al*.,2024).

4.2.2. Sex

There have been no significant differences ($P \geq 0.05$) among the female study groups (HF with infection, HF without infection, no HF with infection, and Healthy group), according to the statistical analysis of table (4.2). Additionally, the statistical analysis's findings demonstrated that there have been no significant differences ($P \geq 0.05$) among the males in the aforementioned study groups.

Table (4.2): Demographic Characterizations

Characterization		No. (%)				Total	P value
		G4	G3	G2	G1		
Sex	Female	12	10	16	9	47	0.566 NS
	Male	13	15	9	16	53	0.512 NS
	P value	0.841 NS	0.317 NS	0.161NS	0.161NS	0.548NS	
Age (year)	20 – 39	3	5	1	1	10	0.221 NS
	40 – 59	8	9	9	6	32	0.861 NS
	60 – 79	10	8	12	14	44	0.610 NS
	80 – 99	4	3	3	4	14	0.962 NS
	P value	0.155 NS	0.303 NS	0.005 S	0.001 S	0.000 S	

G4: Healthy group G3: No heart failure with infection G2: Heart failure without infection
G1: Heart Failure with infection
NS means no significance S means significance

This is disagreement with a prior study that documented significant difference ($P \leq 0.05$) values between the number of female HF patients with infection and those without infection. There have been significant ($P \leq 0.05$) differences between the number of male HF patients who do not have the infection and those with infection, as well as between all HF patients without infection and those with infection ($P < 0.001$) (Arif *et al*.,2021). According to a prior study, women were less likely compared to men to experience an HF episode in middle-aged to older adults, yet in the oldest age groups, women were more likely to experience an HF incident compared to males. HF with preserved ejection fraction (HFpEF) was more widespread amongst women, whereas HF with reduced ejection fraction (HFrEF) was more widespread amongst men (Magnussen *et al*., 2019). Men's predisposition to coronary artery disease (CAD) and myocardial infarction and women's propensity for developing endothelial

inflammation and CAD could be the causes of such difference (Lam *et al*., 2019). Different HF symptoms indicate underlying pathophysiology as well as sex-related changes in HF symptoms (Cediel *et al*., 2021).

Studies contradicting sepsis management in HF patients indicated that this was a challenging and complicated clinical dilemma. Contrary to earlier studies, women who have HF and develop sepsis had mortality rates that are similar to males while having less signs and less comorbidities of bad outcomes. Moreover, the Surviving Sepsis Campaign is carried out more forcefully for women with HF who get sepsis compared to men. This causes more pulmonary edema events for women who have HFpEF as well as cardiogenic shock for women who have HFrEF and a higher number of problems resulting from volume overload. Regarding patients with HF who get sepsis, a carefully customized treatment is absolutely necessary (Al Abbasi *et al*., 2020). Study showed that women die from sepsis less often compared to men (Garcia *et al*., 2016). On the other hand, in the prior cohort, there has not been any variation in the rates of mortality between males and females who have HF and are experiencing sepsis. Men have more interleukin-6; women have a relative higher pro-inflammatory to anti-inflammatory cytokines' ratio (Babušíková *et al*., 2012). This results in lower mortality compared to men and more organized, a better, and better immunological response to infection in women. Additionally, one study revealed that men were more likely to have chronic comorbid conditions like HFrEF, diabetes mellitus, and CAD. These conditions have been known as independent predictors of the poor outcomes as well as mortality for sepsis patients, whether or not HF is present. Thus, women who have HF and acquire sepsis have comparable rates of mortality to males, even though they have a superior immune response to infection, a lower HFrEF frequency, and less comorbidities. This implies that women are more vulnerable compared to men to the existence of Heart Failure, its chronic neuroendocrine disarrangement and a chronic debilitating condition (Al Abbasi *et al*., 2020).

HFpEF, most studies have found higher hospitalization rates for women than for men. Mortality rates are usually not different (Tadic *et al*.,2019). Coronary vasomotor disorders and coronary microvascular dysfunction (CMD) have been increasingly recognized as important contributors to angina and adverse outcomes in patients with no obstructive CAD. CMD from functional and structural abnormalities in the microvasculature is associated with adverse cardiac events and mortality in both sexes. Women may be particularly susceptible to vasomotor disorders and CMD due to unique factors such as inflammation, mental stress, autonomic, and neuroendocrine dysfunction, which predispose to endothelial dysfunction and CMD (Waheed *et al*.,2020). Wong *et al*,(2025) suggested that sex-related pathophysiological mechanisms are present before symptoms of HF develop.

Women with HF who developed sepsis receive a more aggressive implementation of the Surviving Sepsis Campaign than men, leading to more pulmonary edema events in women with HFpEF and more cardiogenic shock in women with HFrEF. A cautiously tailored approach is desperately needed for patients with HF who develop sepsis (Al Abbasi *et al*.,2020). The mortality rates attributed to sepsis in either men or women may still be overly high due to easily correctible factors that remain unaddressed (Lakbar *et al*.,2023). In older adults, compared to women, men are at an increased risk of sepsis hospitalization, sepsis-related ICU admission, death and readmission to hospital within one year after a sepsis hospitalisation. Understanding these sex differences and their mechanisms may offer opportunities for better prevention and management and improved patient outcomes (Thompson *et al*.,2022). Revealed greater *in vivo* pro-inflammatory responses in women compared with men, with significantly higher increases in plasma TNF-α and IL-6 concentrations (Wegner *et al*.,2017). Women with HF survive longer than men and have a lower risk of sudden death. Ischemia is the most prominent cause in men, whereas hypertension and diabetes contribute to a greater extent in women (Regitz, 2020). Heart failure is a life-threatening

condition that affects women and men differently. Due to increases in mean patient age, heart failure prevalence and mortality rates are expected to increase rapidly (Wijesinghe *et al*.,2025).

4.3. Microbiological Tests

4.3.1. Isolation of Bacteria

The statistical analysis results of Figure (4.1) showed that there is not any significant differences (P value= 0.5637) between the study groups, as the number of Gram-negative bacteria =14 and Gram-positive bacteria =11 in the group of healthy with bacterial infection, while the number of Gram-negative bacteria =16 and Gram-positive bacteria =9 in heart failure group with bacterial infection.

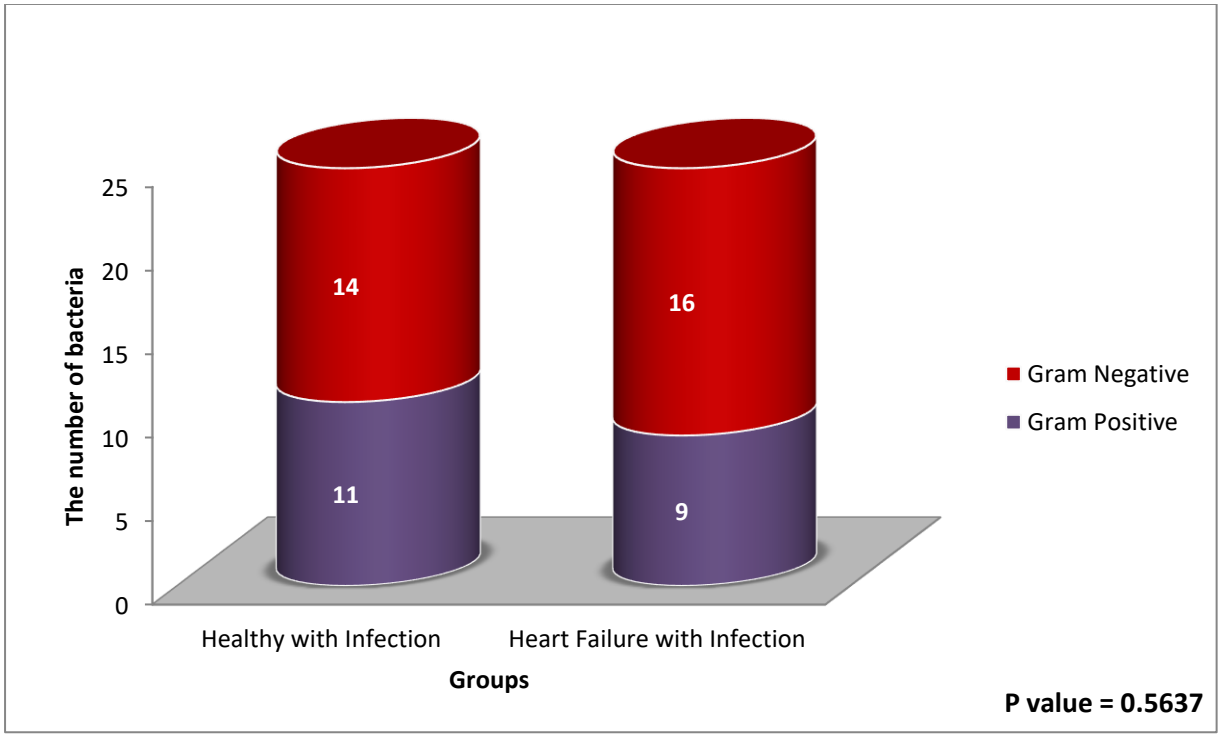


Figure (4.1): The number of bacteria in groups with infection according to response of Gram stain

From observation of Table (4.3) the results showed that the most common genius in healthy with infection group was *Klebsiella pneumoniae* which accounted for 8 (16%) isolates, followed by *Pseudomonas aeruginosa* and *Coagulase negative Staphylococci* isolates 4 (8%) , 3 (6%) isolates of *Staphylococcus hominis*, 2 (4%) isolates of *Staphylococcus aureus*, 1 (2%)

isolates for each of *Acinetobacter baumannii*, *Escherichia coli*, *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* respectively. The most widespread genius in heart failure with infection group was *Staphylococcus hominis* which accounted for 5 (10%) isolates, followed by *Acinetobacter baumannii* and *Staphylococcus haemolyticus* isolates 4 (8%), 2 (4%) isolates for each of *Coagulase negative Staphylococci*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, 1 (2%) isolates for each of *Escherichia coli* and *Staphylococcus psudintermedius*.

Table (4.3): The type of bacteria in the study groups with infection

Bacteria	Number of bacteria in group		Total(%)
	Healthy with infection	Heart failure with infection	
Acinetobacter baumannii	1 (2%)	4 (8%)	5 (10%)
Coagulase negative Staphylococci	4 (8%)	2 (4%)	6 (12%)
Enterococcus faecalis	0 (0 %)	2 (4%)	2 (4%)
Escherichia coli	1 (2%)	1 (2%)	2 (4%)
Klebsiella pneumoniae	8 (16%)	2 (4%)	10(20%)
Pseudomonas aeruginosa	4 (8%)	2 (4%)	6 (12%)
Staphylococcus psudintermedius	0 (0 %)	1 (2%)	1 (2%)
Staphylococcus epidermidis	1 (2%)	0 (0%)	1 (2%)
Staphylococcus aureus	2 (4%)	2 (4%)	4 (8%)
Staphylococcus haemolyticus	1 (2%)	4 (8%)	5 (10%)
Staphylococcus hominis	3 (6%)	5 (10%)	8 (16%)
Total (%)	**25 (50%)**	**25 (50%)**	**50 (100%)**

These results were agreed with a previous study which indicated that were the most species of bacteria in patients with heart failure is *S. hominis* in significant differences from other kinds of species (Arif *et al*.,2021). An earlier study indicated that hospitalized heart failure patients had significantly higher incidence of bacterial infections, particularly with pathogens like *Klebsiella*, *Staphylococcus* and *Pseudomonas* species (Ng *et al*.,2022). Another study was carried out on patients who have infective endocarditis that micro-biological findings included: *Streptococcus pyogenes*, n (%) 1 (2.90%), *Streptococcus* sp., n (%) 12 (34.30%), Non-haemolytic *Streptococci*, n (%) 10 (28.60%), *S. agalactiae*, n (%) 1 (2.90%), *S. aureus*, n (%) 2 (5.90%), *Staphylococcus* sp., n

(%) 9 (25.70%), *Enterococcus* sp., n (%) 5 (14.30%), negative coagulase *staphylococci,* n (%) 7 (20.00%), *E. faecium,* n (%) 1 (2.90%), *Enterococcus faecalis*, n (%) 3 (8.60%)(Kreitmann *et al*., 2020). Non-haemolytic *Streptococci* were a part of the next species: S*treptococcus* oralis, *S. mutans*, *S. gallolyticus*, *S. homans*, *S. parasanguinis*, *S. agalactiae,* and *S. bovis.* Negative coagulase *Staphylococci* were a part the next species: *S. epidermidis*, *S. hominis,* and *S. warneri* (Kreitman *et al*., 2020). Microorganism leading to IE is *Staphylococcus aureus*, females were more likely to have culture-negative IE, and men were more likely to be infected with *Streptococcus viridans* (Slouha *et al*.,2023)Pneumonia (43.9%) was the most common type of infection, followed by UTI (38.2%), skin and soft tissue infections (9.8%), and others (8.2%) in patients with HF (Chen *et al*., 2023). Methicillin-resistant *Staphylococcus aureus* (MRSA)-specific patterns within a hospital-onset sepsis cohort using electronic health record (EHR) data available at time of illness onset (Cohen *et al*.,2025).

4.3.2. Tests of Antibiotics susceptibility

4.3.2.1. Antibiotics Susceptibility for Heart Failure Group with Infection

From inspecting results of Table (4.4) of Antibiotics susceptibility profile for heart failure group with infection it was found that all species had been isolated were resistance to Ciprofloxacin 80% , Benzylpencillin and Oxacillin 56%, where's all species had be isolated were sensitive to the Pefloxacin, Colistin, Ampicillin, Ceftazidime, Ceftolozane, Vancomycin, Linezolid and Streptomycin.

Table (4.4): Antibiotic Susceptibility profile for 25 isolates of bacteria by Vitek 2 system in heart failure group with infection (R-resistance, I-intermediate, S-sensitive).

Antibiotic	R	I	S	Resistance percentage%
Ticarcillin	4	0	21	16
Ticarcillin/ Clavlanic Acid	4	0	21	16
Piperacillin	4	0	21	16
Piperacillin/Tazobactam	6	0	19	24
Ceftazidime	8	0	17	32
Cefepime	8	0	17	32

Aztreonam	2	0	23	8
Imipenem	8	0	17	32
Meropenem	6	0	19	24
Amikacin	4	0	21	16
Gentamicin	10	0	15	40
Gentamicin High Level (synergy)	2	0	23	8
Tobramycin	4	0	21	16
Ciprofloxacin	20	0	5	80
Pefloxacin	0	0	25	0
Minocycline	2	0	23	8
Colistin	0	0	25	0
Rifampicin	6	0	19	24
Trimethoprim/Sulfamethoxazole	6	0	19	24
Ampicillin	0	0	25	0
Ampicillin /Sulbactam	2	0	23	8
Cefotaxime	2	0	23	8
Ceftazidime/Avibactam	0	0	25	0
Ceftolozane/Tazobactam	0	0	25	0
Tigecycline	2	0	23	8
Cefazolin	2	0	23	8
Levofloxacin	2	0	23	8
Tetracycline	10	0	15	40
Vancomycin	0	2	23	0
Teicoplanin	2	0	23	8
Linezolid	0	0	25	0
Erythromycin	12	0	13	48
Streptomycin	0	0	25	0
Streptomycin High Level (synergy)	2	0	23	8
Benzylpencillin	14	0	11	56
Oxacillin	14	0	11	56
Moxifloxacin	4	6	21	16
Clindamycin	6	0	19	32
Fusidic acid	12	0	13	48

4.3.2.2. Antibiotics Susceptibility for Healthy Group with Infection

From the examination of results of Table (4.5) of Antibiotics susceptibility profile for healthy group with infection it was found that all species had be isolated were resistance to Ciprofloxacin 80%, Gentamicin 76% and Ceftazidime 56%, where's all species had be isolated were sensitive to the Gentamicin High Level, Pefloxacin, Minocycline, Colistin, Ampicillin, Cefazolin, Levofloxacin, Vancomycin, Teicoplanin, Linezolid, Streptomycin and Streptomycin High Level.

Table (4.5): Antibiotic Susceptibility profile for 25 isolates of bacteria by Vitek 2 system in healthy group with infection (R-resistance, I-intermediate, S-sensitive).

Antibiotic	R	I	S	Resistance percentage%
Ticarcillin	4	0	21	16
Ticarcillin/ Clavlanic Acid	4	0	21	16
Piperacillin	4	0	21	16
Piperacillin/Tazobactam	10	0	15	40
Ceftazidime	14	0	11	56
Cefepime	12	0	13	48
Aztreonam	4	0	21	16
Imipenem	12	0	13	48
Meropenem	12	0	13	48
Amikacin	6	2	17	24
Gentamicin	19	0	6	76
Gentamicin High Level (synergy)	0	0	25	0
Tobramycin	2	0	23	8
Ciprofloxacin	20	4	1	80
Pefloxacin	0	0	25	0
Minocycline	0	4	21	0
Colistin	0	0	25	0
Rifampicin	2	0	23	8
Trimethoprim/Sulfamethoxazole	12	0	13	48
Ampicillin	0	0	25	0
Ampicillin /Sulbactam	8	0	17	24
Cefotaxime	12	0	13	48
Ceftazidime/Avibactam	6	0	19	24
Ceftolozane/Tazobactam	6	0	19	24
Tigecycline	2	0	23	8
Cefazolin	0	0	25	0
Levofloxacin	0	0	25	0
Tetracycline	8	0	17	32
Vancomycin	0	0	25	0
Teicoplanin	0	0	25	0
Linezolid	0	0	25	0
Erythromycin	6	0	19	24
Streptomycin	0	0	25	0
Streptomycin High Level (synergy)	0	0	25	0
Benzylpencillin	10	0	15	40
Oxacillin	10	0	15	40
Moxifloxacin	2	4	19	8
Clindamycin	4	0	21	16
Fusidic acid	10	0	15	40

According to a prior study, multidrug-resistant pulmonary pathogens, specifically *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, were substantially more common in older patients with cardiovascular disease, such as HF. These patients also had greater resistance to imipenem, ciprofloxacin, and ceftazidime (Liu *et al*.,2023). According to another study, *S. hominis* was shown to be resistant to the following antibiotics: 92.2% Oxacillin, 96.9% Penicillin, 84.4% Cefoxitin, 98.4% Erythromycin, 79.7% Levofloxacin, 85.9% Clindamycin, 62.5% Trimethoprim/Sulfamethoxazole, 79.7% Moxifloxacin, 9.4% Gentamicin, and 9.4% Rifampicin. However, there was 0% resistance to Linezolid and Vancomycin, (100%) Oxacillin, (100%) Penicillin, (91.7%) Cefoxitin, (91.7%) Erythromycin, (100%) Levofloxacin, (50%) Clindamycin, (66.7%) Trimethoprim/Sulfamethoxazole, (100%) Moxifloxacin, (75%) Gentamicin, and (16.7%) Rifampicin were all found to be resistant to *S. haemolyticus*. *S. haemolyticus* revealed: Ten species had benzyl penicillin resistance, one species had ciprofloxacin resistance, three species had oxacillin resistance, two species had cefoxitin resistance, six species had ampicillin resistance, one species had norfloxacin resistance, two species had gentamicin resistance, one species had erythromycin resistance, four species had tetracycline resistance, and one species had tri-methoprim/sulfa-methoxazole resistance (Cui *et al*., 2019). However, there is no resistance to Chloramphenicol or Doxycycline (Boamah *et al*., 2017).

It has been demonstrated that *Acinetobacter baumanii* cannot be treated by Piperacillin-tazobactam, Piperacillin, Imipenem, Cefotaxime, Ticarcillin-clavulanate, Ticarcillin, Levofloxacin, Ceftazidime, Tobramycin, Ciprofloxacin, Ceftriaxone, and Gentamicin. However, it demonstrated sensitivity to Trimethoprim/Sulfamethoxazole, Amikacin, and Doxycycline. According to Lahmidi *et al*. (2020), it is merely an intermediate to Tetracycline. According to Ioannou *et al*. (2021), *Acinetobacter baumanii* exhibited resistance

to the following antibiotics: 5 of 6 (i.e., 83.30%), Sulbactam, 5 of 7 (i.e., 71.40%), Carbapenems, 6 of 9 (i.e., 66.70%), Quinolones, n 4 of 8 (i.e., 50.0%), Aminoglycosides, 4 of 11 (i.e., 36.40%), and Colistin, 0 of 7 (i.e., 0.0). According to a different Nepalese study by Thapa and Sapkota (2019). *S. aureus* and CoNS are the most susceptible to Vancomycin and Amikacin. Additionally, *S. epidermidis* and *S. aureus* were shown to be highly resistant to Ciprofloxacin, Vancomycin, and Tetracycline amongst pathogens that have high rates of clinical detection in the Wang *et al*.(2022) study. Gram-positive as well as Gram-negative bacterial types were included in multidrug resistant (MDR) bacteria category Because antibiotic overuse causes bacteria to develop resistance, the pattern of antibiotic sensitivity differs among studies and within the same institutions over time, Many antibiotic prescriptions have been made in clinical settings without first identifying the infectious germ or performing a test of antibiotic sensitivity, which is one of the many causes contributing to this major crisis.

Furthermore, even after they start feeling better, patients usually do not take their medications exactly as directed, which increases the likelihood that the bacteria may become resistant to the drugs (Lebea and Davies, 2017). Bacterial myocarditis may present in the context of severe sepsis (Ferrero *et al*.,2020). The *S. cohnii*, *S. hominis*, and *S. sciuri* isolates showed a high resistance (66%) to ampicillin, levofl oxacin, erythromycin, and ceftriaxone, and the majority of the isolates were methicillin-resistant(Garza-González *et al*.,2011). *A. baumannii* patient isolates were resistance for eravacycline, omadacycline, and plazomicin but were highly effective combinations, cefepime and amikacin and cefepime and ampicillin–sulbactam (Halim *et al*.,2024).

4.4. Heart Function Tests

4.4.1. Troponin

The statistical analysis of table (4.6) revealed that, when compared to the healthy and patients with infection alone, patients with HF without bacterial infection had a highly significant increase (P < 0.0000**) in troponin concentrations. Troponin concentrations were (145.98, 22.39, and 17.44) ng/ml for heart patients without bacterial infection, patients with infection only, and the healthy group, respectively. The same statistical table showed that HF patients with bacterial infections had significantly greater troponin concentrations (P < 0.0000**) compared to patients with infection alone and the healthy group. Troponin levels in HF patients with bacterial infections, patients with infections alone, and the healthy group were (144.85, 22.39, and 17.44) ng/ml, respectively.

Table (4.6): Mean of Troponin (ng/ml) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	17.44	12.83
	Infection	25	22.39	12.98
Heart failure	**No infection**	25	145.98	37.95
	Infection	25	144.85	30.62
P value		0.0000 **		
LSD		101.954		

** indicates high significances differences ($P \leq 0.001$)

Heart failure patients have markedly higher Troponin levels compared to those without heart failure, regardless of infection status. This suggested heart failure itself is strongly associated with elevated troponin. Infection in non-heart failure patients leads to a small increase in troponin, but the difference is minor compared to the gap between heart failure and non-heart failure groups. This suggests that heart failure significantly raises troponin levels, while infection has a limited effect. Troponin concentrations in HF patients without bacterial infection and the healthy group were 924.526ng/ml and 0.100ng/ml, respectively, the results of this study were consistent with a prior study that demonstrated a highly significant increase (p < 0.0010) in troponin concentration level in HF

patients with no bacterial infection compared with the control group. Additionally, troponin concentration in HF patients with bacterial infection has been significantly higher ($p < 0.001$) than in the healthy group (Arif *et al*.,2021). Another study that indicated that troponin levels were significantly higher in heart patients compared to healthy controls, reflecting inflammation and myocardial damage in Iraqi patients (Nasser *et al*.,2024). Suggest that elevated cardiac biomarker troponin I are associated with significantly higher risk of a major adverse cardiac event MACE and are powerful predictors in clinical setting (Mbeta *et al*.,2025).

This fitted with previous studies that demonstrated that myocardial tissue with strong clinical sensitivity as well as specificity could display cardiac troponin (cTn). Moreover, other studies were able to identify cTn early on, in the case when necrosis was moderate or even nonexistent, by applying different methods (like improved myocyte turnover or increased cell wall permeability). These properties have become cTn the chosen biomarker for both acute myocardial infarction as well as the standard biomarker with regard to myocardial infraction (Cediel *et al*., 2020). Moreover, the HF population showed often high levels of cTn. In up to 74% of patients who have stable chronic heart failure and up to 93% of patients who have acute heart failure, cTn levels are higher than the 99th percentile of reference value, according to Eggers and Lindahl (2017). A positive troponin level revealed an association between the length regarding mechanical ventilation in patients hospitalized to ICU and the myocardial damage in sepsis patients who have been intubated. Another study linked greater risk of cardiovascular issues following sepsis to raised troponin levels throughout the condition. Tracking troponin levels might help in identifying patients who are more vulnerable, so guiding more comprehensive surveillance and early treatments and so lowering long-term cardiovascular risks (Garcia *et al*., 2021).

A total of 61% of patients treated with sepsis exhibited positive troponin, 36% of patients in another study had raised troponin (Bessiere *et al*., 2013). This has been on par with the Sheyin *et al*. study (60.5%), from 2015. Studies on the subject of sepsis and septic shock produced contradictory results on links between increased clinical outcomes and troponin. Numerous researches that included this study that have been carried out by Sheyin *et al*. (2015), Yang *et al*. (2016), and Vallabhajosyula *et al*. (2017)—have related unfavorable results and increased mortality in patients admitted with sepsis to troponin elevation (Abdulla *et al*., 2019). Another study that indicated that inpatient high-sensitivity cardiac troponin T hs-cTnT levels predict Cardiovascular death CV death/ hospitalization heart failure HFH in patients. In particular, in the subgroup of chronic HF patients, hs-cTnT is predictive of CV death/HFH (D'Amato *et al*.,2024). Revealed that elevated cardiac troponin for sepsis patients was a predictor of hospital and long-term mortality. Clinicians may treat septic patients with elevated cardiac troponin more cautious to avoid extra death (Zheng *et al*.,2023).

4.4.2. N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP)

The statistical analysis of the results in Table (4.7) showed that there was a high significant increase ($P \leq 0.0000^{**}$) in the mean of NT-proBNP in patients of HF with and without bacterial infection comparison to the healthy individuals, as the mean of NT-proBNP for HF patients with and without bacterial infection and the healthy (21.40 , 18.11 and 4.50) ng/ dl, respectively. Additionally, from the same Table (4.6) showed that there was a significant increase ($P \leq 0.0000^{**}$) in the mean of NT-proBNP in patients with bacterial infection without heart failure comparison to the healthy, as the mean of NT-proBNP (14.53 and 4.50) ng/ dl, respectively.

Table (4.7) : Mean of NT-proBNP (ng/dl) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	4.50	2.01
	Infection	25	14.53	4.13
Heart failure	**No infection**	25	18.11	4.58
	Infection	25	21.40	4.25
P value		0.0000 **		
LSD		2.069		

** indicates high significances differences ($P \leq 0.001$)

The outcomes imply that NT-proBNP is a useful biomarketer for assessing HF and could be raised in situations of infection since suggesting that both HF and infection considerably affect NT-proBNP levels. This emphasizes its part in evaluating cardiac stress and possible HF exacerbations in individuals concurrently infected. Previous research demonstrated that NT-proBNP is a major biomarker for HF diagnosis; hence, the results showed that patients with HF have noticeably higher NT-proBNP levels, which guides doctors in assessing the degree of the condition. Apart from identifying HF, NT-proBNP is utilized for evaluating patient responses to the treatments (Yancy *et al*., 2017). Jiang *et al*. (2019) conducted research concluding that NT-proBNP is significantly correlated with patient clinical outcomes. Patients with HF who simultaneously had infections exhibited higher levels of NT-proBNP, suggesting a higher death or complication risk. Particularly throughout infections, the research advised routine monitoring of NT-proBNP in HF sufferers. NT-proBNP levels were elevated in patients with HF, which were negatively correlated with LVEF, and their levels increased with the improvement of cardiac function, independent of the cause of HF. The combination of these three indices is of great significance in the diagnosis and prognosis of HF (Wang *et al*.,2021).

Another study underlined the need of NT-proBNP as an HF diagnostic tool. Whether the cause is inflammation or another, it has been found that a change in NT-proBNP can indicate a worsening of the disease. It underlined the need of adding NT-proBNP into a comprehensive patient assessment since it improves

the outcomes of treatment (McCullough *et al*., 2020). According to another study Okamoto *et al*., (2019), natriuretic peptides are peptide hormones that are mainly released by cardiac muscles as a response to increased blood volumes as well as wall stress, two crucial elements of the cardio-vascular physiology. Brain natriuretic peptide (BNP) can be defined as a natriuretic peptide often found and released in situations leading to rising myocardial wall pressure and expansion of volume. Decreasing sympathetic activity, lowering cardiac preload, relaxing vasomotor tone, boosting renal blood flow, and so encouraging sodium excretion and diuresis are among BNP's physiological effects (Potter *et al*., 2009). Plasma natriuretic peptide became increasingly relevant in clinical decision-making on the diagnosis, management, and risk assessment of HF (Maisel *et al*., 2018 ; Ibrahim and Januzzi, 2015). The valuable prognostic role of NT-proBNP in predicting overall adverse outcome, cardiovascular events, and mortality in HFpEF patients. Our findings underscore the importance of further study to establish standardized thresholds and investigate NT-proBNP’s potential in predicting morbidity and mortality (Ammar *et al*.,2025).

NT-proBNP levels can be a useful adjunct in the diagnosis of hypertensive heart disease, particularly in the assessment of diastolic dysfunction and left ventricular hypertrophy (Mouzarou *et al*.,2025). NT-proBNP were identified as significant predictors of rehospitalization in HF patients (Osser *et al*.,2024). HF with mildly reduced/preserved ejection fraction had a low NT-proBNP level. Although these patients have a favorable prognosis, compared to those with a high NT-proBNP level, theyhave similarly impaired health status which should be a target for treatment (Kondo *et al*.,2024). Elevated levels of BNP and NT-proBNP were significantly related to the mortality of patients with sepsis and had a moderate prognostic value in predicting the mortality of patients with sepsis (Song *et al*.,2024).

4.4.3. C-type natriuretic peptide (CNP)

According to statistical analyses of the results in Table (4.8), the mean CNP in HF patients with and without bacterial infections was significantly higher (P ≤ 0.0000**) than in the healthy group, the CNP mean for HF patients with and without bacterial infection was (7.50, 6.06, and 0.76) ng/dl at the healthy group. Additionally, table (4.7) demonstrated that there was a significant increase ($P \leq 0.0000^{**}$) in the mean of CNP in patients with bacterial infection without HF comparison to the healthy, as the mean of CNP (7.48 and 0.76) ng/dl, respectively.

Table (4.8): Mean of CNP (ng/dl) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	0.76	0.63
	Infection	25	7.48	1.72
Heart failure	**No infection**	25	6.06	2.67
	Infection	25	7.50	2.33
P value		0.0000 **		
LSD		3.737		

** indicates high significances differences ($P \leq 0.001$)

Findings showed that raised CNP levels are caused in part by both HF and infection. This might point to higher cardiac stress or damage connected to these disorders. These important variations draw attention to CNP's potential as a biomarketer for evaluating cardiac performance in several clinical settings. According to a past study, BNP/NT-proBNP is a major biomarketer of HF; levels of other natriuretic peptides, like CNP, are much raised in HF, especially in relation with cardiac fibrosis, endothelial dysfunction, and inflammation (Gaggin and Januzzi, 2023). Another study found that a possible early sepsis diagnosis is CNP, this study focused especially on CNP levels in sepsis severe infection, the finding that sepsis patients had noticeably higher CNP levels than both critically sick patients without sepsis and healthy (Chen *et al*., 2021) underlined the function of CNP as an indication of inflammation. Previous studies by Hobbs and Moyes (2019) indicate that CNP is a complex paracrine regulator in the human

heart. In response to many stimuli, including proinflammatory cytokines (IL-1β, TNF-α), endothelial cells as well as cardiac fibroblasts induce CNP production. They also demonstrated how CNP regulates blood pressure and blood vessels tone as well as a range of cardio-vascular effects that include angiogenesis, inflammation, smooth muscle and endothelial cell proliferation, hypertrophy, cardiomyocyte contraction, atherosclerosis, fibrosis, and cardiac electrophysiology (Moyes and Hobbs, 2019).

Inflammation associated with higher circulating NP levels, suggested that inflammation may be a trigger for NP release and inflammatory conditions should be considered when interpreting NP levels (Fish-Trotter *et al*.,2020). Accumulating evidence indicated that CNP not only modulates vascular tone and blood pressure, but also governs a wide range of cardiovascular effects including the control of inflammation, angiogenesis, smooth muscle and endothelial cell proliferation, atherosclerosis, cardiomyocyte contractility, hypertrophy, fibrosis, and cardiac electrophysiology. The novel physiological functions ascribed to CNP, the receptors/signalling mechanisms involved in mediating its cardioprotective effects (Moyes and Hobbs,2019). C-type NP (CNP), mainly expressed by endothelial cells, they also exert several paracrine and autocrine activities on the heart itself, contributing to cardiovascular (CV) health. In addition to their natriuretic, vasorelaxant, metabolic and antiproliferative systemic properties, NPs prevent cardiac hypertrophy, fibrosis, arrhythmias and cardiomyopathies, counteracting the development and progression of heart failure (HF) (Sarzani *et al*.,2022). Recombinant human brain natriuretic peptide (rhBNP) can regulate expression of IL-6, TNF-α, and IL-10 in LPS-activated RAW 264.7 cell line (Li *et al*.,2018).

4.4.4. Ischemia-modified albumin (IMA）

As the mean regarding IMA for heart patients without bacterial infection as well as patients with infection only and the healthy (485.25, 245.14, and 101.49) ng/ml, respectively, the statistical analysis of Table (4.9) revealed high significant increase ($P \leq 0.0000$**) in the mean of IMA in patients with HF with no bacterial infections compared to patients with infection only and the healthy. Additionally, the results of the same statistical table have shown a high significant increase ($P \leq 0.0000$**) in the mean of IMA in HF patients who have bacterial infection compared with the healthy and patients with infection only, as the mean of IMA for heart patients who have bacterial infection and patients who have infection only and the healthy (452.86, 245.14, and 101.49) ng/ml.

Table (4.9): Mean of IMA (ng/ml) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	101.49	58.35
	Infection	25	245.14	135.38
Heart failure	**No infection**	25	485.25	101.30
	Infection	25	452.86	113.34
P value		0.0000 **		
LSD		96.673		

** indicates high significances differences ($P \leq 0.001$)

The findings of this research showed that raised IMA levels are a result of both infection and HF, suggesting increased ischemia stress in such conditions. This result lends credence to the possibility of using IMA as a biomarker to evaluate myocardial ischemia in patients with HF, particularly when infection is present. According to prior research, in MI patients who present to EU, serum IMA seems to be a sensitive indicator regarding myocardial ischemia. Its function in a definitive biochemical ruling out method and its capacity to identify ischemia prior to myocyte loss would enable earlier and more precise management decisions. Additionally, these authors reported that for the early diagnosis of MI, IMA concentrations have been much better than cTn concentrations within the same time frame. They discovered that the ROC value was 0.933 (p=0.0001). The

results show that the specificity and sensitivity are 89% and 88%, respectively. Albumin-cobalt binding test found that N-terminus of the albumin changed structurally in myocardial ischemia, therefore reducing metal binding capacity. The test can detect an IMA elevation three hours after ACS symptoms started (Gurumurthy *et al*., 2015; Aydin *et al*., 2019). Bhagwan *et al*. (2003) claim that those with myocardial ischemia exhibit reduced binding to Co^{+2} compared to those free from the condition. Another study indicated that The IMA level, especially at least 110 U/mL, may be a useful predictor of death for patients with severe sepsis (Yin *et al*.,2017). Ischemic modified albumin IMA elevated in patients with acute coronary syndrome ACS is associated with an increased incidence of major cardiovascular adverse events MACE (Mou *et al*.,2021). Study confirmed elevated IMA levels in ACS patients, supporting its diagnostic potential (Ralapanawa *et al*.,2024).

Minutes of myocardial ischemia starting are well known to cause acidosis, hypoxia, and damage from free radicals followed by a disruption regarding the sodium/calcium ion pumps in membrane. The NH_2 terminus of albumin which has a great affinity for transition metals like Ni^{+2} and Cu^{+2} changes. Cobalt ions thereby lose their capacity to attach to albumin. Bernstein *et al*. (1997) report evidence suggesting that alterations in albumin are involved in the mechanisms behind ischemia/reperfusion. These processes could include acidosis, extracellular and endothelial hypoxia, free radical damage, disruption regarding ATP-dependent sodium as well as calcium pump, therefore exposing free iron and copper ions. In another study, IMA turned shown to be a predictor of short-term death in individuals with severe sepsis. The much higher levels of IMA in non-survivors and their linkage with critical care scoring systems like APACHE II and SOFA clearly show the efficacy related to IMA as a predictive tool in septic situations, particularly in the absence of cardiac illness (Yin *et al*., 2017).

A study by Cetin *et al*. (2021) indicates that septic patients particularly those with cardiovascular issues had higher IMA. The link between raised mortality as well as IMA values more than 250 ng/mL underlined the prognostic relevance of the peptide in systemic illnesses. They showed that doctors in emergency departments shouldn't base their prognosis of patients suffering from sepsis or septic shock just on serum IMA levels (Cetin *et al*., 2021). Previous studies revealed that IMA and coronary collateral circulation were favorably associated. These results validate IMA's susceptibility to ischemia (Chen *et al*., 2020) and confirm its rise in HF, where the myocardial oxygen delivery is hampered. Various studies have linked the degree of peripheral artery disease (PAD) to adjusted IMA of the patients. This confirms the theory that IMA usually shows ischemia conditions (Özsin *et al*., 2024), especially in non-infectious vascular diseases. Another study indicated that IMA levels are a useful biomarker for diagnosing sepsis/ septic shock early, and their combination with lactate levels can enhance the predictive power for early diagnosis of sepsis/septic shock in the emergency department (Choo *et al*.,2020).

Previous studies have linked IMA favorably with oxidative markers and raised in both chronic and acute ischemic heart disease. Regarding chronic HF, this emphasizes the need of employing IMA as a marker in both stable and unstable cardiac ischemia (Nepal *et al*.,2017). Another study by Tiwari (2023) looked at the possibilities of Ischemia Modified Albumin (IMA) as a novel marker in ischemic heart disease. The findings show that IMA levels were greatly depending on the clinical situation; larger levels were observed in patients with sepsis, pancreatitis, CAD, and stroke among other disorders.

The IMA level is closely related to coronary collateral circulation CCC. Higher IMA levels can be used as an effective predictor in patients with chronic total occlusive CTO (Chen *et al*.,2020). Ischemia modified albumin is a novel marker of ischemia generated due to hypooxygenation and increased hydroxyl

free radicals in low pH (Gursoy *et al*.,2017). Ischemia-modified albumin may be utilized as a novel marker of ischemia to rule out acute coronary syndrome along with troponin and electrocardiogram in the emergency departments (Nepal *et al*.,2017). IMA levels rise with the progression of acute pancreatitis AP. Lower levels of adjusted IMA predict the severity of AP (Sahin *et al*.,2018).

4.4.5. Soluble CD40 ligand (sCD40L)

As the mean CD40L for heart patients without bacterial infection, patients with infection only, and the healthy was (444.15, 254.63, and 123.94) ng/ml, respectively, the statistical analysis of Table (4.10) showed that the mean CD40L for patients with HF without bacterial infection was significantly higher ($P \leq 0.0000$**) than for the healthy and patients with infection only. The same statistical table also revealed that the mean of CD40L for patients with bacterial infection-related HF was significantly higher ($P \leq 0.0000$**) than that of patients with infection alone and the healthy group. The mean CD40L values for patients with bacterial infection and infection-only patients and the healthy group were (384.86, 254.63, and 123.94) ng/ml, respectively.

Table (4.10): Mean of CD40L (ng/ml) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	123.94	49.47
	Infection	25	254.63	115.47
Heart failure	**No infection**	25	444.15	128.36
	Infection	25	384.86	113.34
P value		0.0000 **		
LSD		122.629		

** indicates high significances differences ($P \leq 0.001$)

According to the findings of the present study, raised CD40L levels are a result of both infection and HF, indicating increased immune activation in such conditions. This lends credence to CD40L's potential application as a biomarker for evaluating immunological response in HF patients, particularly when infections are present. In spite of infection status, HF patients had

considerably greater CD40L levels than non-HF patients. CD40L levels were increased by infection, however the increase was more noticeable in HF patients. The majority of published research discussed the function of sCD40L as a biomarker of outcome in patients suffering from septic shock or severe sepsis. For example, Chew *et al*. (2010) discovered that non-surviving sepsis patients had greater levels of circulating sCD40L compared to surviving sepsis patients. A group of 186 patients with severe sepsis at the time of diagnosis had higher circulating sCD40L levels, which have been independently linked to mortality at 30 days, according to a Spanish multicenter prospective observational study by Lorente *et al*. (2011). They found that non-survivor patients had higher serum sCD40L levels for the first week than did survivors. For such reasons, the authors proposed that serum sCD40L levels in the first week may be utilized as a biomarker for sepsis mortality and that there was a correlation between such levels as well as sepsis mortality. Because of its inflammatory effects on myocardial and vascular tissue, Ueland *et al*. (2005) showed that soluble CD40L is higher in both chronic and acute HF and is linked to worse outcomes.

Another studies indicated that sCD40L levels increased in the first 3 days after ICU admission, and serum sCD40L levels are associated with the mortality of patients with sepsis. Thus, serum sCD40L may be used as a reliable biomarker and therapeutic target in sepsis (Liang *et al*.,2021). CD40L exerts multiple functions depending on the cell-cell interactions involved, sought to investigate the function of the most relevant CD40L-expressing cell types in atherosclerosis: T cells and platelets (Lacy *et al*.,2021). Costimulatory molecules CD40 and its ligand CD40L are found on a variety of immune cells, where they are responsible to regulate pro- and anti-inflammatory processes, as well as differentiation, proliferation and survival of immune cells (Witkowski *et al*.,2024). CD40L was highly expressed in the plasma of CLP mice. Knock out of CD40L inhibited the

activation of DC cell and Th17 differentiation while promoting the Th2 differentiation (Yu *et al*.,2025).

Platelets also have a major inflammatory and immune function in antibacterial defence, essentially through their Toll-like Receptors (TLRs) and Sialic acid-binding immunoglobulin-type lectin (SIGLEC). Platelet activation also contributes to the extensive release of anti- or pro-inflammatory mediators such as IL-1b, RANTES (Regulated on Activation, Normal T Expressed and Secreted) or CD154, also known as the CD40-ligand. Platelets are involved in the direct activation of immune cells, polynuclear neutrophils (PNNs) and dendritic cells via the CD40L/CD40 complex. As a general rule, all of the studies presented in this review show that platelets are capable of covering most of the stages of inflammation, primarily through the CD40L/CD40 interaction, thus confirming their own role in this pathophysiological condition (Cognasse *et al*.,2022). Platelet CD40L proves to be an interesting target for various inflammatory diseases (Bendas *et al*.,2024). Another study indicated that the concentrations of sCD40L is closely related to the formation and type of carotid Atherosclerosis plaque in patients with acute cerebral infarction (Xu *et al*.,2024).

According to a different study, CD40L serves as a link between adaptive and innate immunity and is highly enhanced in systemic infections, like sepsis (Zhu *et al*.,2022). With regard to healthy population, CD40L is mostly expressed on platelets, B lymphocytes, and T lymphocytes. The fact that normal arteries do not express CD40L and that the vascular endothelium cells just express a minimal quantity of CD40L has long been known. Prior research indicated that vascular smooth muscle cells, endothelial cells, T lymphocytes, monocytes/macrophages, and platelets of patients with coronary atherosclerosis (AS) expressed CD40 and CD40L. Additionally, AS patients as well as experimental atherosclerotic plaques have elevated levels of CD40L and CD40 (Chen *et al*., 2017). Static platelets do not express CD40L on their surface.

CD40L could be expressed on the surface of platelets when they are activated by thrombin, collagen, or adenosine diphosphate (ADP) (Wang *et al*., 2012). CD40L may enter the bloodstream as soluble CD40L (sCD40L) when it is expressed on platelet membrane surface. Activated platelets provide almost 95% of circulating blood's sCD40L, the active version of CD40L (Fan *et al*., 2004). Increased CD40L might be one of the causes of platelet activation, since it has been shown to up-regulate P-selectin expression in platelets (Inwald *et al*., 2003). CD40L plays a key role in the pathogenesis regarding atherosclerosis as a ligand of the inflammatory signaling pathway. Prior research demonstrated that during infection, myocardial infarction, and atherosclerosis, CD40L might bind to its receptors on the surface of macrophages and encourage the release of inflammatory factors (Napoleão *et al*.,2017 ; Bustamante *et al*.,2016).

4.4.6. C-Reactive Protein (CRP)

The statistical analysis results that have been listed in Table 4.11 showed that there has been a high significant increase ($P \leq 0.0000$**) in the average of the CRP in patients with infection only comparison with the healthy, and patients of HF without bacterial infection, as the mean of CRP for patients with infection only and the healthy and patients of heart failure without bacterial infection (64.77, 4.454 and 1.518) mg/l, respectively. High significant increase ($P \leq 0.0000$**) in results of the same statistical table in mean of CRP in HF patients with bacterial infection comparison with the healthy, and patients of heart failure without bacterial infections, as mean of CRP for HF patients with bacterial infection and the healthy and patients of heart failure with no bacterial infection (14.73, 4.454 and 1.518) mg /l, respectively.

Table (4.11): Mean of CRP (mg /l) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	4.454	1.84
	Infection	25	64.77	5.05
Heart failure	**No infection**	25	1.518	1.97
	Infection	25	14.73	9.20
P value		0.0000 **		
LSD		9.931		

** indicates high significances differences ($P \leq 0.001$)

The findings showed that infection causes CRP levels, a measure of systemic inflammation, to rise noticeably. Although CRP levels in HF patients were higher than those in non-infection patients with HF, there were differences in the inflammatory responses between the two groups. This research supports the use of CRP as a biomarker to assess inflammation in different clinical settings. This is consistent with studies showing that increased CRP levels at hospital admission as well as vegetation lengths at diagnosis have been independent predictors of the in-hospital deaths in IE patients (Nunes *et al*., 2018). This also holds true in the case when considering patient complications and characteristics including the beginning of HF as well as embolic events. This is similar to a different study that revealed the CRP is a generally utilized clinical biomarker of inflammation used for the differential diagnoses as well as bacterial infectious illness monitoring. Regarding sepsis, CRP is linked to many factors in the diagnosis and is rather related with infection. Arellano-Navarro *et al*. (2018) claim that CRP could thus be used as a vital additional index for the sepsis identification.

Usually fairly low, serum CRP levels are released by WBCs and other inflammatory cells in response to a bacterial infection, therefore activating liver cells. The inflammatory process begins 6–12 hours following CRP is identified since it is generated in 4–6 hours and peaks at 36–50 hours (Magrini *et al.*, 2014). CRP is one of numerous proteins that are frequently referred to as acute phase reactants, They are utilized to track alterations in inflammation linked to a variety of autoimmune and infectious disorders, Since there is a correlation between a

slight increase in CRP as well as major cardiovascular events in the future, the American Heart Association and the Centers for Disease Control have recommended that patients at intermediate risk of coronary heart disease (CHD) may benefit from having their CRP measured, Whether CRP contributes to atherosclerotic disease (artery hardening) or acts as a marker of heart disease has not yet been established, It was demonstrated that vascular disorders and CRP are closely related. For atherosclerosis and illnesses associated with it, CRP is a potent independent risk factor (Lusic *et al*., 2006; Verma *et al*., 2006).

CRP as well as procalcitonin levels have been utilized as indicators to track the development of sepsis in prior research by Zhou *et al*. (2025), and they demonstrated elevated levels throughout the acute infection stages. According to another research, patients with HF, infection, and inflammation from post-endocarditis had considerably higher CRP (Aydın and Demirkıran ,2025). According to another research, HF patients with endocarditis or sepsis had significantly higher CRP levels both post- and pre-operatively (Koltonova *et al*.,2024). The hs-CRP, PCT, and sCD14-ST are independent indicators of paediatric sepsis due to their high prognostic values (Sakyi *et al*.,2020). The CRP/albumin ratio (CAR), a new inflammatory marker that can predict the development of embolic events in patients diagnosed with infective endocarditis, CRP serves as a rapid indicator of acute inflammation, providing clinicians with timely insights to diagnose and monitor various diseases, particularly infections and autoimmune disorders (Kelesoglu *et al*.,2023). Another study indicated that procalcitonin PCT-24 hours, CRP-24 hours, the change of perioperative PCT and CRP were valuable predictors of major complications occurring within 30 days after non-cardiac surgery in the elderly (Alkouri *et al*.,2022). Greater CRP is independently associated with an increased risk of recurrent CVD and mortality, irrespective of previous CVD location (Burger *et al*.,2023). CRP level is a strong

independent predictor of mortality at 1 month and 1-year in Cardiogenic shock CS (Roubille *et al*.,2024).

4.4.7. Procalcitonin (PCT)

In table (4.12) statistical analysis revealed that, when compared to healthy, the mean PCT for patients with infection alone and HF patients with bacterial infection had increased significantly ($P \leq 0.0000$**). HF patients with bacterial infection, patients with infection alone, and the healthy group had respective PCT means of (394.70, 393.91, and 65.95) ng/ml. Additionally, the results of same statistical table have shown a very significant rise ($P \leq 0.0000$**) in the mean PCT in HF patients who did not have a bacterial infection as compared to the healthy. The PCT means for HF patients without bacterial infections and the healthy group were (324.67 and 65.95) ng/ml, respectively.

Table (4.12): Mean of Procalcitonin (ng/ml) in the study groups

Groups	Criteria	N	Mean	SD
No heart failure	**No infection (Healthy)**	25	65.95	31.24
	Infection	25	393.91	84.48
Heart failure	**No infection**	25	324.67	130.97
	Infection	25	394.70	114.24
P value		0.0000 **		
LSD		187.977		

** indicates high significances differences ($P \leq 0.001$)

PCT levels in individuals with infection have been much greater than in healthy group. HF patients show higher PCT levels, which point to a strong inflammatory response akin to that of patients with infections. The results revealed that both HF and infections contribute to high procalcitonin levels, which signal major inflammatory activity. The findings give validity to the prospect of employing PCT as a biomarker to spot infections and evaluate inflammatory reactions in HF patients. The findings of this study match earlier studies demonstrating the important part procalcitonin (PCT) performs in the diagnosis and treatment regarding bacterial infections. Especially from fungal

and viral infections, many studies have shown PCT's remarkable specificity and sensitivity in separating bacterial infections from other origins. Research by Becker *et al*. (2004) and Schuetz *et al*. (2017) shows that PCT significantly influences antibiotic stewardship since it enables doctors to make the best treatment decisions, which may include, in certain cases, lowering their resistance and overuse or, more generally, avoiding the use of antibiotics altogether. These studies really show how well PCT marks bacteria for sepsis, pneumonias, and urinary tract infections. Additionally, the way that non-bacterial and bacterial infections are explained in routine clinical practice supports such results, supports the future of PCT as a reliable diagnostic biomarker regarding diseases, and advocates for its inclusion in clinical guidelines for infection diagnostics, in which there is a high need for such resources and typically no access to rapid diagnostic tools (Spiridonova *et al*.,2024 ; Parrey *et al*.,2024). Another study indicated that relationship between PCT and AKI in septic shock patients, and PCT could be used as a potential biomarker of AKI in female patients younger than 75 years with bacterial septic shock (Fu *et al*.,2021). The PCT/ALB ratio was an important indicator for predicting septic shock and 28-day mortality in sepsis patients compared to PCT or ALB alone (Wang *et al*.,2023).

According to different research through Khanna *et al*. (2025), PCT has been consistently higher than 0.5 ng/mL in patients with sepsis or septic shock, suggesting that it might be one of the helpful markers for risk stratification as well as early detection. In keeping with previous studies that have demonstrated that PCT levels are not just an indicator of infection, yet could indicate the severity regarding that infection, there is an association between high PCT as well as disease severity markers like Sequential Organ Failure Assessment (SOFA) score. Schuetz *et al*. (2017) claim that PCT can be utilized as a prediction test for septic patients, so providing doctors with important knowledge on how to rank

treatment choices. This result matches their research. Enhancing the odds of recovery for critically ill patients depends on an early identification of sepsis; thus, PCT is a quantitative and dependable biomarker that might be used to evaluate the degree of the infection and direct the suitable treatment actions (Farooq *et al*.,2024).

Previous study showed Patients with severe infection had very high PCT levels. The study emphasized PCT as a marker for bacterial load and inflammation severity, particularly in ICU settings (Zhou *et al*.,2025). Another study showed PCT was elevated in patients with infection and comorbid cardiovascular conditions. Infection-only groups showed significantly higher PCT than those with only cardiac diseases (Barušić *et al*.,2025). Another study showed in cardiac patients, PCT and CRP rose postoperatively, and were used as early indicators of post-surgical infections and inflammation (Giovannico *et al*.,2025).

4.4.8. ROC Analysis

4.4.8.1 The model predicts the working characteristic curves based on the Cardio biomarkers (Heart failure)

Regarding to the model predicts the working characteristic curves of the subjects based on the immunological markers for the Heart failure. Troponin (100%), IMA and NT-proBNP (94.5% and 90.1%, respectively), sCD40L (89.2%) are the important predictors.

95% confidence intervals provide a measure of reliability of the predictive capacity of each marker. Interestingly, high cutoff values of 1,000 for Troponin, 0.988 for IMA, 0.965 for NT-proBNP and 0.960 for sCD40L indicate extremely high diagnostic accuracy, as is illustrated in table (4.13) and figure (4.2).

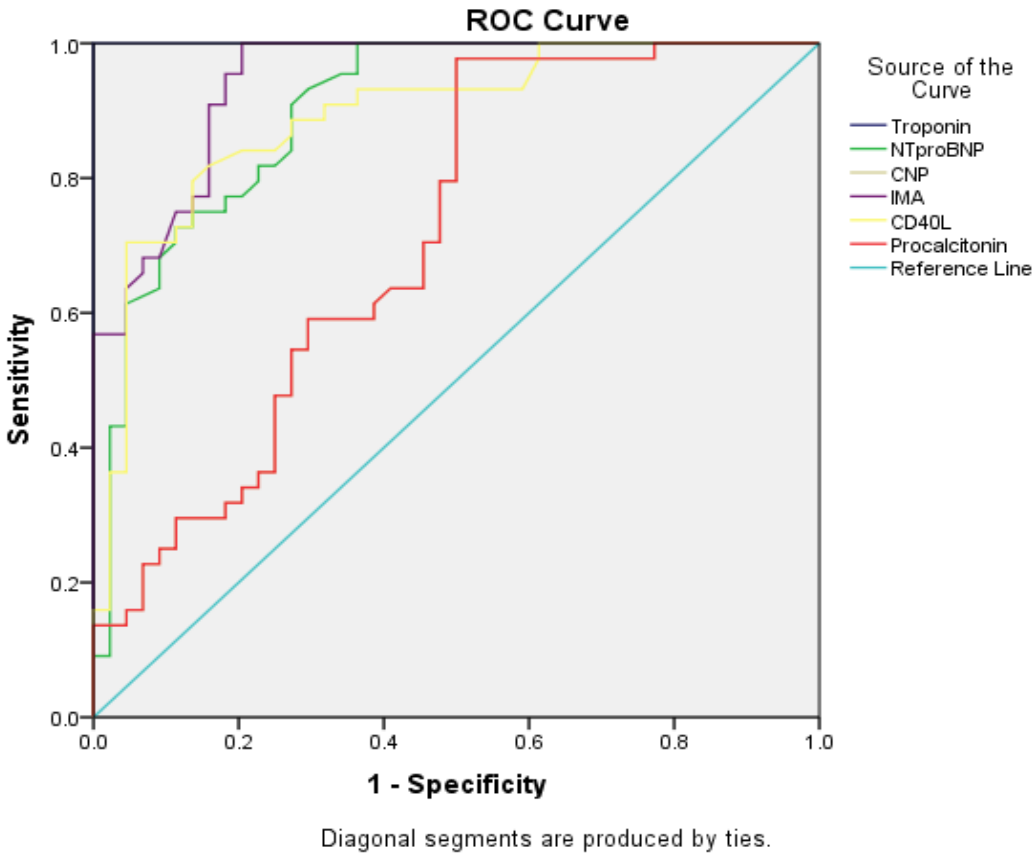
Table(4.13): Model prediction of subject working characteristic curves according to the Cardio biomarkers (Heart failure).

Metrics		Cardiac Biomarkers					
		Troponin	NT-pro BNP	CNP	IMA	sCD40L	Procalciton in
Std. Error [a]		0.000	0.032	0.055	0.022	0.035	0.055
Asymptotic Sig. [b]		0.000	0.000	0.001	0.000	0.000	0.001
Asymptotic 95% Confidence Interval	Lower Bound	1.000	0.838	0.603	0.902	0.823	0.603
	Upper Bound	1.000	0.965	0.821	0.988	0.960	0.821
Cutoff point		66.72	13.41	1.55	273.63	371.79	104.61
Area Under Curve (AUC) %		100	90.1	71.2	94.5	89.2	71.2
		Excellent	Excellent	Fair	Excellent	Good	Fair
Sensitivity %		100	90.9	97.7	100	70.5	97.7
Specificity %		100	72.7	50.0	79.5	95.5	50.0
Positive Predictive Value (PPV)%		100	64.51	66.15	83.01	94.59	66.15
Negative Predictive Value (NPV)%		100	86.48	95.65	100.00	76.36	95.65

The test result variable(s): NT-proBNP, CNP, IMA, sCD40L, Procalcitonin has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5



Figure(4.2): Receiver Operator Characteristic (ROC) curve analysis for the calculation of Troponin, NT pro BNP, CNP, IMA, CD 40L and Procalcitonin possible diagnostic cutoff value.

Troponin is the optimal forecasting markers for the prediction of HF based on their high sensitivity, specificity, and very error-free AUC, making them both optimal selections for prelimmary diagnosis as well as validation. In addition to having high accuracy, as well as positive predictive value (PPV) and negative predictive value (NPV), IMA, NT-proBNP and sCD40L also possess outstanding predictive powers.

The results suggested that Troponin was the most reliable biomarker for diagnosing heart failure, followed by sCD40L. Other biomarkers have varying degrees of effectiveness, with some showing fair performance. The significant p-values highlight that these metrics are statistically reliable for clinical use.

4.5. Hematological Tests

4.5.1. White Blood Cell (WBC)

Statistical analyses of the result in Table (4.14) revealed that the mean WBC in patients with HF with infection was significantly higher (P ≤ 0.0000**) than in patients with HF without infection and the healthy group. WBC mean for patients with HF who have an infection, those who do not, and the healthy group (16.65, 8.21, and 7.05) is 10^3/µl. Additionally, the same statistical table showed a highly significant increase (P ≤ 0.0000**) in mean WBC in patients with infection alone compared to HF patients without infection and the healthy. The WBC mean for HF patients without infection, patients with infection only, and the healthy group (15.81, 8.21, and 7.05) is 10^3/µl, respectively.

Table (4.14): Mean of WBC (10^3/ µl) in the study groups

Groups	Criteria	N	Mean	SD	Normal rang
No heart failure	**No infection (Healthy)**	25	7.05	1.59	5000-10000/ mm^3
	Infection	25	15.81	6.71	
Heart failure	**No infection**	25	8.21	1.97	
	Infection	25	16.65	5.15	
P value		0.0000**			
LSD		4.26			

** indicates high significances differences ($P \leq 0.001$)

WBC levels were elevated significantly in patients with infections compared to healthy group. Heart failure patients showed increased WBC counts even without infection, and this elevation is further enhanced during infections. The results indicated that infections lead to a substantial increase in WBC levels, reflecting an immune response. Heart failure patients also demonstrate elevated WBC counts, suggesting that they have a heightened inflammatory response. This research backs up using WBC counts as a biomarker to evaluate inflammatory and infection state in patients with and without HF. This finding is consistent with study conducted in Baghdad by Abood (2021), which found that there were differences in the mean WBC count between the patients and the healthy individual group. Additionally, different study through Yang *et al*. (2016)

revealed that the sepsis group had a higher mean WBC count compared to non-sepsis group. According to certain research, the WBC count is linked to a number of risk factors for CVD. A higher WBC count is a predictor of hospitalization for Hear Failure, all-cause death and acute myocardial infarction AMI but not for stroke in patients with concurrent Type 2 diabetes mellitus and established coronary artery disease CAD (Kawabe *et al*.,2021). CRP and WBC as equally suitable prognostic markers at the early stages of cardiogenic shock, each at its preferential point in time (Dudda *et al*.,2023).

Another study demonstrated that patients with chronic heart failure still showed moderate elevations in WBC compared to healthy individual, attributed to chronic inflammation and comorbid stress (Omar *et al*.,2025). A study done by Beltran *et al*. (2025) indicated that Patients with infection and heart disease had significantly raised WBC counts, showing acute inflammatory surge, despite immunocompromised status. Another study indicated that postoperative cardiac infection led to WBC surge of 23,000/mm³, showing strong leukocytosis in cardiac infection cases (Ayub and Tewari .,2025).

Prior research has shown a favorable correlation between a higher WBC count and a higher risk of CHD in middle-age and older adults (Chen *et al*., 2018). Additionally, WBC count is a commonly available indicator of inflammation in clinical practice, and it is consistent with another research that found chronic inflammation to be a major characteristic of atherosclerosis. Especially monocyte levels, WBC counts were independently correlated risk factors for CVDs. For those without symptoms, WBC could thus be one of the readily available and practical markers of CVDs (Kim *et al*., 2017). Another study indicated that High peripheral monocyte count was an independent and incremental predictor of HF-related events in non-HFpEF, rather than in patients with HFpEF (Nozuhara *et al*.,2025).

Furthermore, consistent with recent study demonstrating that a higher leucocyte count in HF is a poor predictive marker is HF itself. Large population

studies indicate that a leucocyte count has been associated to long-term incidence of heart failure hospitalizations in middle-aged men as well as a higher count of neutrophils is related to the development of the incident HF (Shah *et al*., 2017). Furthermore, independent of all-cause mortality in patients with ischemic left ventricular (LV) dysfunction is leucocyte counts of >7000cells/μL, according to another study. A prospective observational study of a community-based population found a greater risk of incident HFpEF associated with a higher leucocyte count (Gong *et al*., 2018).

4.5.2. Red Blood Cell (RBC)

The statistical analysis of the result in Table (4.15) showed that there was a significant decrease ($P \leq 0.0000^{**}$) in the mean of RBC in patients of heart failure with and without infection comparison to the healthy, as the mean of RBC for heart failure patients with and without infection and the healthy (4.38, 4.42 and 5.20) 10^6/μl, respectively. There is significant decrease ($P \leq 0.0000^{**}$) in the results of the same statistical table in the mean of RBC in patients with infection only comprised to heart failure patients with and without infection and the healthy, , as the mean of RBC for patients with infection only, heart failure patients with and without infection and the healthy (3.87, 4.38, 4.42 and 5.20) 10^6/μl, respectively.

Table (4.15): Mean of RBC (10^6/μl) in the study groups

Groups	Criteria	N	Mean	SD	Normal rang
No heart failure	**No infection (Healthy)**	25	5.20	0.47	Male 4.7-6.1 Female 4.2-5.4
	Infection	25	3.87	0.72	
Heart failure	**No infection**	25	4.42	0.74	
	Infection	25	4.38	0.79	
P value		0.0000**			
LSD		0.338			

** indicates high significances differences ($P \leq 0.001$)

Patients with infections had far lower RBC levels than healthy group, which reflected the effect of infection on RBC survival or production. Although their

levels do not much vary depending on infection, HF patients demonstrated lower RBC counts than healthy. The findings showed that infections cause a significant drop in RBC levels, which can be related to different causes including inhibition of bone marrow or inflammation. In patients with HF, although RBC levels are lower than in healthy people, the existence of infection does not notably diminish such levels. This result emphasizes the significance of monitoring RBC levels in people infected, particularly considering HF. RBCs mostly serve to oxygen tissues and organs (Wang *et al*., 2020). Previous studies revealed clinical evidence connecting anemia to several major CVD effects, such as thromboembolic events that is, venous thrombosis which are risk factors for HF. Anemia is common in patients with HF and often associated with iron deficiency. Both anemia and iron deficiency are associated with an increase in all-cause and cardiovascular mortality (Cleland *et al*.,2016). Decreasing quantiles of the Hb/RDW ratio were associated with reduced survival rates and reduced event-free survival from death or cardiovascular-hospitalizations (Rahamim *et al*.,2022).

Therapeutic interventions meant to raise the number of the RBCs in circulation e.g., through giving erythropoiesis-stimulating agents (ESAs) for stimulating the bone marrow's production of RBCs or by transfusion of blood did not frequently work, either, in tested cohorts (Yin *et al*., 2017). Higher MCV, RDW, and RBC count (Wang *et al*., 2020) were also significantly linked, according to another study, to more severe coronary artery stenosis. Coronary artery stenosis reduces blood flow as well as oxygen to the heart muscle, therefore leading to myocardial infarction or sudden cardiac death (Paradis *et al*., 2014). This is in line with studies revealing common changes in erythrocyte levels in HF patients and suggested several factors as the cause (Murphy, 2014). Different studies indicate that individuals with septic HF who have low RBC counts and transfusion demands also have notable anemia when both diseases coexist (Gao

et al., 2025). low levels of serum iron may be beneficial in the early phase of critically ill patients with sepsis, persistent iron deficiency may result in iron metabolism disorder, which is not conducive to the recovery of vital organ functions (Zhang *et al*.,2024).

4.5.3. Hemoglobin (HGB)

The statistical analysis of the result in Table (4.16) showed that there was a significant decrease ($P \leq 0.0000^{**}$) in the mean of HGB in patients of HF with and without infection comparison to the healthy group, as the mean of HGB for HF patients with and without infection and the healthy group (12.68, 12.05 and 14.08) g/dl, respectively. There is a significant decrease ($P \leq 0.0000^{**}$) in the results of the same statistical table in the mean of HGB in patients with infection only comparison to HF patients with and without infection and the healthy group, as the mean of HGB for patients with infection only, HF patients with and without infection and the healthy group (10.45, 12.68, 12.05 and 14.08) g/dl, respectively.

Table (4.16): Mean of HGB (g/dl) in the study groups

Groups	Criteria	N	Mean	SD	Normal range
No heart failure	**No infection (Healthy)**	25	14.08	1.25	Male 14-18 g/dl Female 12-16 g/dl
	Infection	25	10.45	1.92	
Heart failure	**No infection**	25	12.05	1.76	
	Infection	25	12.68	2.17	
P value		0.0000**			
LSD		0.733			

** indicates high significances differences ($P \leq 0.001$)

The results indicated that infections lead to a substantial decrease in hemoglobin levels, which could be attributed to inflammatory responses or anemia related to chronic disease. In heart failure patients, while hemoglobin levels were lower than in healthy individuals, the presence of infection does not lead to a significant further decline. This finding confirms the importance of monitoring hemoglobin levels in patients, particularly in the context of infections and heart failure. These results agreed with (Salisbury and Kosiborod., 2010;

Palazzuol *et al*., 2011). There is a compromised process via which tissue hypoxia as well as nitric oxide (NO) release result in reducing arteriolar resistance and peripheral vasodilatation, which explains why estimates regarding the prevalence of anemia in HF patients have varied greatly. These processes result in elevated sympathetic activation, decreased blood pressure, renal vasoconstriction, decreased renal function, and renin-angiotensin-aldosterone system activation. Fluid retention, antidiuretic hormone production, left ventricular (LV) dilatation and hypertrophy, brain natriuretic peptide (BNP) release, worsening heart failure, and myocardial stress symptoms are the outcomes. More anemia is the ultimate result, completing the vicious circle. Yet, this suggests that while red cell mass stays constant, there may be a drop in Hb concentration as well as oxygen content when volume overload is present (Silverberg *et al*.,2009) .

HFpEF had the greatest mean corpuscular volume and recorded Hb concentration among the two other phenotypes, according to prior research (Akintunde *et al*., 2021). Another study indicated that patients with heart disease and any type of proatherosclerotic condition are at a higher risk when anemia is present. In patients with CVD, anemia emerged as a novel treatment target that improved oxygen delivery. According to Mozos (2015), complete blood count anomalies and hemorheological parameters are practical, affordable, and generally accessible methods for the prognosis and management of patients with HF, CHD, arrhythmias, hypertension, and stroke. Additionally, anemic patients had lower cardiac echo measures indicating diastolic function, like left atrial dimension, than non-anemic patients. This contradicts research suggesting that anemic patients may have a more advanced stage of HF than the no-anemic patients (Okuono *et al*., 2019) to compensate for the HF patients' deficiencies or as a result of the drugs. Anemia in heart failure remains an enigma. Perhaps, anemia is a marker of severe disease, rather than the cause of poor outcome in these patients (Sharma *et al*.,2021). Mild anemia, is an independent risk factor for

cardiovascular and renal events in hypertensive outpatients whose blood pressure is well-controlled (Kim-Mitsuyama *et al*.,2019).

4.5.4. Hematocrit (HCT)

The statistical analysis of the results in Table (4.17) had revealed that, when compared to the healthy, the mean of HCT in HF patients with and without infection decreased significantly ($P \leq 0.0000$**). As the mean HCT for patients with and without HF, as well as the healthy group (38.79, 35.57, and 42.9) %, respectively. Additionally, the same statistical table had shown a significant drop ($P \leq 0.0000$**) in mean HCT in patients who have the infection alone when compared to HF patients with and without infection as well as the healthy. HF patients with and without infection, as well as the healthy group, had corresponding means of HCT of (31.76, 38.79, 35.57, and 42.9) % respectively.

Table (4.17): Mean of HCT % in the study groups

Groups	Criteria	N	Mean	SD	Normal range
No heart failure	**No infection (Healthy)**	25	42.9	3.64	Male 0.40-0.54
	Infection	25	31.76	5.30	
Heart failure	**No infection**	25	35.57	6.46	
	Infection	25	38.79	6.76	Female 0.36-0.46
P value		0.0000**			
LSD		4.82			

** indicates high significances differences ($P \leq 0.001$)

HCT levels were significantly lower in patients with infections compared to healthy group, reflecting the impact of infection on red blood cell volume and overall blood composition. Heart failure patients exhibited lower hematocrit levels than healthy, and while there is a slight increase with infection, it remains below the normal range. The results indicated that infections lead to a significant decrease in hematocrit levels, potentially due to fluid shifts or anemia. In heart failure patients, although hematocrit levels are lower than in healthy individuals, the presence of infection does not lead to a substantial further decline. This finding highlights the importance of monitoring hematocrit levels in patients,

particularly those with infections and heart failure, to assess their overall hematological status. The results agreed with a previous study indicated that Hematocrit levels were significantly lower in critically ill patients, especially those with infections or cardiovascular comorbidities (Mousa *et al*., 2025). Another study used hematocrit as a marker for inflammation and cardiovascular risk in patients with infections (Nakhleh *et al*., 2025). Another study indicated that Low and high levels of Hct, Hb and RBCs were associated with vascular smooth muscle dysfunction, and low Hct levels were associated with abnormal vascular structure (Kishimoto *et al*.,2020). Hematocrit should be used as a reference in sepsis care. Early management of hematocrit is critical in patients with sepsis (Chen and Chen,2025). HCT is one of the risk factors for Coronary Heart Disease . Combining HCT with traditional risk factors may be helpful for non-invasive diagnosis of CHD. In addition, the level of HCT may also help to judge the future prognosis of patients with coronary artery stenosis greater than 50% without revascularization (Xie *et al*.,2025). In patients hospitalized with AHF, an increased HCT during hospitalization is associated with a lower risk of all-cause mortality than a decreased or unchanged HCT. Furthermore, all-cause mortality does not differ significantly between patients with unchanged and decreased HCT values (Zhou *et al*.,2017).

It has been difficult to find prior research that showed a correlation between HCT and the short-term consequences regarding acute decompensated HF. A higher HCT has been suggested to be connected with a lower risk of cardiac-related events in AHF patients, according to another research that looked at the relationship between HCT and the outcomes related to AHF patients, such as re-hospitalization. According to one study, HCT might be a separate prognostic indicator for patients with AHF, much as BNP as well as serum creatinine (Yan and Chen, 2020). The blood volume is often increased because of weakened left ventricular systolic function, increased reabsorption of sodium and

water through renal tubules, and a decreased glomerular filtration rate. This leads to dilute anemia and sodium retention, along with decreased hemoglobin as well as HCT (Waldum *et al*., 2012). According to Alexandrakis and Tsirakis (2012), HCT is a measure of the degree of anemia and sodium retention, which are associated with renal dysfunction and have an impact on the prognosis of HF patients. Many factors are probably involved, even if the precise mechanisms that underly the relationship between HCT and prognosis regarding patients with AHF are still unknown. For example, there may be a connection between renal function as well as HCT (Ter Maaten *et al*., 2016). Another data suggests that in patients hospitalized with AHF, a brief variation in HCT concentration represents a separate risk factor for mortality. A decreased risk of mortality is linked to the top tertile of the HCT changes (ΔHCT > 1.50%) throughout the hospitalization (Zhou *et al*., 2017).

4.5.5. Platelet (PLT)

The statistical analysis of the result in Table (4.18) showed that there was a significant decrease ($P \leq 0.0128^{*}$) in the mean of PLT in patients of HF with and without infection comparison to the healthy, as the mean of PLT for HF patients with and without infection and the healthy (211.27, 217.36 and 288.63) cells/µl, respectively. Additionally, the mean PLT in patients with infection alone showed insignificant decrease (P ≤ 0. 0128*) when compared to the healthy in the same statistical table. The PLT mean for patients with infection alone was (229.27) cells/µl, while the healthy groups was (288.63) cells/µl.

Table (4.18): Mean of PLT (cells/µL) in the study groups

Groups	Criteria	N	Mean	SD	Normal range
No heart failure	**No infection (Healthy)**	25	288.63	74.57	150000-400000
	Infection	25	229.27	115.88	
Heart failure	**No infection**	25	217.36	67.19	
	Infection	25	211.27	98.33	
P value		0.0128*			
LSD		62.32			

* indicates significance differences ($P \leq 0.05$)

The results indicated that infections lead to a significant decrease in platelet levels, which may be attributed to increased consumption or reduced production of platelets during inflammatory states. In heart failure patients, while platelet counts are already lower than in healthy individuals, the presence of infection does not significantly exacerbate this reduction. Monitoring platelet levels in patients, particularly those with infections and heart failure, is essential for assessing their hematological status and overall health. This is consistent with other research that found low PLT to be a risk factor for both HF prehospitalization and all-cause death. In patients who had been first diagnosed with HF with reduced EF (40%) it was shown that thrombocytopenia (100,000/micro-liter) has been linked to 1-year death (Mojadidi *et al*., 2016). According to earlier research, systemic physiological alterations as well as cardiac issues can cause acute heart failure (AHF). The severity regarding AHF might be indicated by the PLT, which could also reflect such systemic alterations. AHF patients with preserved as well as decreased EF demonstrated that thrombocytopenia was linked to a poorer outcome in these patients. According to the findings of a prior research, patients with AHF who had lower PLT had a worse prognosis. PLT could be easily used as a risk marker in AHF and is frequently assessed in clinical settings (Yamaguchi *et al*., 2018).

Through hemolysis and bleeding or bone marrow dysfunction, sepsis could result in anemia (Kliegman *et al*., 2016). Biomarkers of platelet activation may become a valuable instrument for acute event prognosis in thrombotic diseases (Baidildinova *et al*.,2021). Thrombocytopenia is significantly correlated with in-hospital infection and major adverse clinical events MACE and might be used as a prognostic tool in patients with ST-elevation myocardial infarction STEMI (Wang *et al*.,2021). clinical prediction of the risk of postoperative thrombocytopenia in critically ill patients with heart disease (Song *et al*.,2024).

4.5.6. Lymphocyte (LYM)

The statistical analysis of the result in Table (4.19) showed that there was a significant decrease ($P \leq 0.0000^{**}$) in the mean of LYM in patients of HF with and without infection comparison to the healthy, as the mean of LYM for HF patients with and without infection and the healthy (13.61, 15.50 and 36.02) cells/µl, respectively. Additionally, the mean LYM in patients with infection alone decreased significantly (P ≤ 0.0000**) when compared to the healthy group in the same statistical table. Patients with infection alone had LYM values of (12.49) and (36.02) cells/l, respectively.

Table (4.19): Mean of LYM (cells/µL) in the study groups

Groups	Criteria	N	Mean	SD	Normal range
No heart failure	**No infection (Healthy)**	25	36.02	7.52	1000-4000 / mm^3
	Infection	25	12.49	11.57	
Heart failure	**No infection**	25	15.50	11.16	
	Infection	25	13.61	9.65	
P value		0.0000**			
LSD		11.58			

** indicates high significances differences ($P \leq 0.001$)

The results indicated that infections lead to a substantial decrease in lymphocyte levels, which may reflect immune system dysregulation. In heart failure patients, while lymphocyte percentages are already lower than in healthy individuals, the presence of infection does not lead to a significant further decline. This finding highlights the importance of monitoring lymphocyte levels in patients, particularly those with infections and heart failure, to assess their immune status and response to infection. This is in line with the findings of earlier research that supported the prognostic significance regarding lymphopenia in AHF patients, highlighting the significance of immune system in AHF pathophysiology and showing how a straightforward and common test could predict the patient's outcome. This theory is supported by recent data indicating that the number of lymphocytes varies depending on the pharmaceutical treatment (Carubelli *et al*., 2017). Additionally, it is consistent

with another research that supports earlier findings that a low lymphocyte count, which is a component of routine blood testing, might be helpful in identifying outpatients with HF who are at a higher risk of death, offering an extra tool for detecting patients who require close supervision (Marçula *et al*., 2015). According to another study, patients with severe sepsis had significantly lower lymphocyte counts, and the investigators linked lymphopenia to immunological dysfunction as well as mortality (Shrivastava *et al*.,2025). Absolute lymphocyte count (ALC) categories had a higher risk of mortality of heart failure patients (Majmundar *et al*.,2022). Elevated neutrophil-to-lymphocyte ratio (NLR) is consistently associated with increased mortality in patients with heart failure (HF) (Rawat and Vyas,2025).

4.5.7. Neutrophil (NEUT)

Statistical analyses of results in Table (4.20) revealed that the mean of NEUT in patients with HF with infection was significantly higher ($P \leq 0.0000$**) than in patients with HF without infection and the healthy group. Infection-free HF patients, HF patients with infection, and the healthy group had NEUT means of (13.54, 6.41, and 4.03) cells/µl, respectively. Additionally, the findings of the same statistical table showed a very significant rise ($P \leq 0.0000$**) in the mean of NEUT in patients with infection alone as compared to the healthy group and HF patients without infection. The NEUT mean for HF patients without infection, patients with infection only, and the healthy group was (12.43, 6.41, and 4.03) cells/µl, respectively.

Table (4.20): Mean of NEUT (cells/µL) in the study groups

Groups	Criteria	N	Mean	SD	Normal rang
No heart failure	**No infection (Healthy)**	25	4.03	1.20	2500-8000 / mm^3
	Infection	25	12.43	6.76	
Heart failure	**No infection**	25	6.41	2.35	
	Infection	25	13.54	5.45	
P value		0.0000**			
LSD		3.43			

** indicates high significances differences ($P \leq 0.001$)

Neutrophil counts were significantly higher in patients with infections compared to healthy group, reflecting the immune system's response to infection. Heart failure patients showed elevated neutrophil counts even without infection, and this count increases further during infections. The results indicated that infections lead to a substantial increase in neutrophil levels, which is expected as neutrophils play a critical role in fighting infections. In heart failure patients, while neutrophil counts were already elevated, the presence of infection leads to an additional significant increase. This finding underscores the importance of monitoring neutrophil levels in patients, particularly those with infections and heart failure, to assess their inflammatory response and overall immune status. This is consistent with earlier research that demonstrated neutrophils play an important part after myocardial infarction (MI), which is the most frequent HF cause. According to Soehnlein *et al*. (2017), neutrophils penetrate the infarcted myocardium and cause tissue damage. In experimental models of myocarditis, neutrophils might have a significant impact (Woudstra *et al*., 2017, Bracamonte-Baran and Čiháková, 2017). According to Bracamonte-Baran and Čiháková, (2017), an innate response that is mediated through neutrophils as well as monocytes/macrophages is significant in most myocarditis since it not only primes the auto-immune process but also initiates tissue damage and repair. A higher neutrophil count has been linked to a higher risk of serious cardiac events, such as myocardial infarction and the early onset of HF, according to another study. Through a number of processes, such as attracting other immune cells and releasing inflammatory mediators, neutrophils can cause cardiac damage (Gopalkrishna *et al*., 2020).

Previous study marked neutrophilia in sepsis, with neutrophil activation predicting multi-organ dysfunction, particularly in patients with underlying heart conditions (Shrivastava *et al*.,2025). Another research by Moriot *et al*., (2025) indicated that Neutrophil counts strongly associated with infection complications, particularly in patients with cardiovascular comorbidities. Increased NLR levels

were independently associated with unfavorable clinical prognosis in patients with sepsis (Liu *et al*.,2016). Neutrophils are closely related to the severity and prognosis of patients with Myocardial infarction MI, and neutrophil to lymphocyte ratio in post-MI patients had predictive value for major adverse cardiac events (Zhang *et al*.,2022). High neutrophil counts were associated with atherosclerotic cardiovascular disease, supporting that high blood neutrophil counts is a causal risk factor for atherosclerotic cardiovascular disease (Luo *et al*.,2023).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The study has reached to some conclusions, They are at the following :

1- The most prevalent species of bacteria found in heart failure isolates patients with infection was *Staphylococcus hominis* and from patients with infection only was *Klebsiella pneumoniae* .

2- The most bacterial isolates were resistant to Ciprofloxacin and Gentamicin in study groups, whereas, Vancomycin, Linezolid, Pefloxacin, and Colistin were effective in most isolates.

3- Troponin, NT-proBNP, CNP, IMA, and sCD40L were elevated in patients with HF, especially in combination with bacterial infection and the results of Roc analysis suggested that Troponin was the most reliable biomarker for diagnosing heart failure, followed by IMA, NT-proBNP and sCD40L.

4- CRP and PCT levels were elevated in infection only patients and HF patients with infection, indicating a systemic inflammatory response.

5- Patients with infections showed decreased levels of red blood cells (RBC), hemoglobin (HGB), and hematocrit (HCT), reflecting the impact of infection on blood composition. Heart failure patients also had lower counts in these parameters, suggesting a potential link between heart failure and anemia.

6- Decreases in platelet counts and lymphocyte percentages were observed in both heart failure and infection groups. This may indicate a compromised immune system and increased risk of adverse outcomes in these patients.

7- Neutrophil counts and white blood cell (WBC) counts were significantly elevated in patients with infections and HF patients with infection, highlighting their role in the immune response.

Recommendations

Below are some recommendations :

1- Before administering antibiotics to individuals suspected of sepsis, a blood culturing test should be performed to prevent the development of further resistance.

2- To study of the genes which are responsible for heart failure, also possible.

3- To study the effect of HF on hormonal status, also recommended.

4- There is a necessity for careful monitoring of biomarkers and hematological parameters in heart failure patients, especially during episodes of infection. Routine assessment can aid in early detection of complications and guide therapeutic interventions.

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APPENDICES

Holy Karbala governorate
Karbala Health Department
Training and Human Development Center
Research and knowledge management division

جمهورية العراق

محافظة كربلاء المقدسة
دائرة صحة كربلاء المقدسة
مركز التدريب والتنمية البشرية
شعبة ادارة البحوث والمعرفة

العدد: ٢٤٢١
التاريخ: / / ٢٠٢٣

إلى / جامعة كربلاء/ كلية التربية للعلوم الصرفة

الموضوع /تسهيل مهمة

دائرة صحة كربلاء المقدسة
قسم التدريب والتنمية البشرية

تحية طيبة....

كتابكم المرقم د.ع / ٢٣٦ في ٢٠٢٣/١٢/٧

نود إعلامكم بأنه لا مانع لدينا من تسهيل مهمة طالبة الدكتوراه/قسم علوم الحياة (ساره سعيد حسن محمد علي) لإنجاز بحثها الموسوم:

"Effect of sepsis on cardiac biomarkers and study of resistant bacteria in patients with cardiac disease in Karbala "

في مؤسستنا الصحية / مركز كربلاء لأمراض وجراحة القلب/ وبأشراف الدكتور (احمد قاسم جعفر الحيدري) على ان لا تتحمل دائرتنا اي نفقات مادية مع الاحترام ٠

الدكتور
نعيم عبيد المشهداني
طب الدكتورة

م/ تقوى خضر عبد الكريم
مدير مركز التدريب والتنمية البشرية
٢٠٢٣/

نسخة منه الى
- مركز كربلاء لأمراض وجراحة القلب / لإجراء اللازم مع الاحترام.
- مدينة الامام الحسين(ع) الطبية / لإجراء اللازم مع الاحترام .
- مستشفى الامام الحسن المجتبى(ع) / لإجراء اللازم مع الاحترام.
- مركز التدريب والتنمية البشرية / شعبة ادارة البحوث والمعرفة مع الاوليات .

وزارة الصحة
دائرة صحة كربلاء
مركز التدريب والتنمية البشرية
لجنة البحوث

استمارة رقم ٢٠٢١/٠٣

رقم القار : ٢٠٢٣٢٧٠

تاريخ القرار ٢٠٢٣/١٢/٢٥

قرار لجنة البحوث

درست لجنة البحوث في دائرة صحة كربلاء مشروع البحث ذي الرقم (٢٠٢٣٢٧٠) المعنون

لانجاز بحثها الموسوم

((Effect of sepsis on cardiac biomarkers and study of resistant bacteria in patients with cardiac disease in Karbala))

والمقدم من الباحثة:- **(ساره سعيد حسن محمد علي)**

الى شعبة ادارة المعرفة / وحدة ادارة البحوث في مركز التدريب والتنمية البشرية في دائرة صحة كربلاء بتاريخ ٢٠٢٣/١٢/٢٥ وقررت:

قبول مشروع البحث اعلاه كونه مستوفيا للمعايير المعتمدة في وزارة الصحة والخاصة بتنفيذ البحوث ولا مانع من تنفيذه في مؤسسات الدائرة.

دكتور
نعيم عبيد المشهداني
طبيب اختصاص
مقرر لجنة البحوث

25/12/2023

المرفقات:

-Choose an item.

ملاحظات:

- تم تخويل عضو لجنة البحوث (د.تقوى خضر عبد الكريم) او مقرر اللجنة (د.نعيم عبيد طلال) للتوقيع على هذا القرار استنادا الى النظام الداخلي للجنة البحوث.
- الموافقة تعني ان مشروع البحث قد استوفى المعايير الاخلاقية والعلمية لإجراء البحث والمعتمدة في وزارة الصحة، اما التنفيذ فيعتمد على التزام الباحث بتعليمات المؤسسة الصحية التي سينفذ فيها البحث.

Questionnaire

Case no.

Date :

Name :

Age :

Gender : ☐ **Male** ☐ **Female**

Address :

Profession :

Type of infection: ☐ **HF** ☐ **HF+ Infection** ☐ **Infection** ☐ **Control**

Duration of Infection :

Clinical Symptoms :

Medical history :

Ejection Fraction % :

Organism Quantity:
Selected Organism : Staphylococcus hominis ssp hominis
BP Infection Site:
Source: H-F. + Infection **Collected:**

Comments:	

Identification Information	**Analysis Time:**	5.77 hours	**Status:**	Final
Selected Organism	99% Probability	**Staphylococcus hominis ssp hominis**		
	Bionumber:	000000014220231		
ID Analysis Messages				

Susceptibility Information	**Analysis Time:**	10.88 hours	**Status:**	Final

Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
Cefoxitin Screen	POS	+	Erythromycin	>= 8	R
Benzylpenicillin	>= 0.5	R	Clindamycin	>= 8	R
Ampicillin			Linezolid	2	S
Oxacillin	>= 4	R	Teicoplanin	<= 0.5	S
Imipenem			Vancomycin	<= 0.5	S
Gentamicin High Level (synergy)			Tetracycline	<= 1	S
Streptomycin High Level (synergy)			Tigecycline	<= 0.12	S
Gentamicin	4	*R	Fosfomycin		
Ciprofloxacin	4	R	Fusidic Acid	>= 32	R
Moxifloxacin	1	I	Rifampicin	>= 32	R
Inducible Clindamycin Resistance	NEG	-	Trimethoprim/ Sulfamethoxazole	80	R

***= AES modified **= User modified**

AES Findings	
Confidence:	Consistent

Organism Quantity:
Selected Organism : Klebsiella pneumoniae ssp pneumoniae
BP Infection Site:
Source: Inf -
Collected:

Comments:	

Identification Information	**Analysis Time:**	5.83 hours	**Status:**	Final
Selected Organism	98% Probability	**Klebsiella pneumoniae ssp pneumoniae**		
	Bionumber:	6603734453164010		
ID Analysis Messages				

Susceptibility Information	**Analysis Time:**	10.97 hours	**Status:**	Final

Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
Ampicillin/Sulbactam	>= 32	R	Meropenem	>= 16	R
Piperacillin/Tazobactam	>= 128	R	Amikacin	32	R
Cefotaxime	>= 64	R	Gentamicin	>= 16	R
Ceftazidime	>= 64	R	Ciprofloxacin	>= 4	R
Ceftazidime/Avibactam	0.5	S	Tigecycline	>= 8	R
Ceftolozane/Tazobactam	>= 32	R	Colistin		
Cefepime	>= 32	R	Trimethoprim/ Sulfamethoxazole	<= 20	S
Imipenem	4	R			

AES Findings	
Confidence:	Consistent

الخلاصة

تعد أمراض القلب والأوعية الدموية من الأسباب الرئيسية للمرض والوفيات، حيث يمثل نقص تروية عضلة القلب والفشل القلبي حالتين رئيسيتين ومتميزتين. يشير نقص تروية عضلة القلب إلى عدم كفاية إمداد عضلة القلب بالأكسجين بسبب انسداد الشريان التاجي، بينما يعكس فشل القلب عدم قدرة القلب على تلبية متطلبات الدورة الدموية الجهازية. وعلى الرغم من اختلافهما، يُعد نقص التروية السبب الرئيسي لفشل القلب، وكثيرا ما تتعايش كلتا الحالتين. في حالة تعفن الدم، يفاقم الالتهاب الجهازي واضطراب الدورة الدموية نقص التروية ويساهمان في اعتلال عضلة القلب الناجم عن تعفن الدم، مما يعقد التشخيص والإدارة والتنبؤ. صُممت هذه الدراسة لتحديد أكثر أنواع البكتريا شيوعا المسؤولة عن تعفن الدم لدى مرضى الفشل القلبي، ودراسة علاقتها بعوامل الخطورة لفشل القلب، وتحديد نمط حساسيتها للمضادات الحياتية، وتحديد مستويات المعايير المختلفة التي تتأثر بالعدوى البكتيرية لدى مرضى فشل القلب. قسم مائة مريض إلى أربع مجاميع: (25) مريض مصاب بفشل القلب وتسمم الدم المجموعة الاولىG1، (25) مريض مصاب بفشل القلب فقط المجموعة الثانية G2، (25) مريض مصاب بتسمم الدم فقط المجموعة الثالثة G3 و (25) شخص من الافراد الاصحاء المجموعة الرابعة G4. جُمعت هذه العينات مباشرة من وحدة العناية المركزة في مركز القلب بمدينة الإمام الحسين الطبية في كربلاء خلال الفترة من كانون الثاني 2024 إلى آب 2024. أخذت 10 مل من عينات الدم الوريدي من مرضى فشل القلب بعد دخولهم وحدة العناية القلبية. تم اجراء الاختبارات المناعية مثل: التروبونين Troponin ، الببتيد المدر للصوديوم الدماغي الطرفي الأميني -N Terminal pro-Brain Natriuretic Peptide (NT-proBNP)، الببتيد المدر للصوديوم من النوع C-type Natriuretic Peptide C (CNP)، الألبومين المُعدل بالإقفار Ischemia-Modified albumin (IMA)، ربيطة CD40 الذائبة soluble CD40 Ligand (sCD40L)، البروتين التفاعلي-C C-reactive protein (CRP) والبروكالسيتونين Procalcitonin (PCT). بعض المعايير العامة مثل العمر (تضمنت الفئات العمرية 20-39 ، 40-59 ، 60-79 ، 80-99 سنة) و الجنس (عدد الذكور 53 و عدد الاناث 47)، المعايير الدمية CBC مثل خلايا الدم البيضاء White blood cell (WBC) و التي تشمل الخلايا اللمفاوية Lymphocyte (LYM) و الخلايا العدلة Neutrophil (NEU) ، كريات الدم الحمراء Red blood cell (RBC) ، خضاب الدم Hemoglobin (HGB) ، الصفيحات الدموية Platelet (PLT) و مكداس الدم Hematocrit (HCT). الاختبارات الميكروبية (اختبارات تشخيص البكتيريا واختبارات الحساسية للمضادات الحياتية).

أظهرت نتائج الدراسة الحالية عدم وجود فروق معنوية ($P \geq 0.05$) بين الإناث والذكور في المجاميع الثلاثة G1، G2، G3 مقارنة مع مجموعة الاصحاء G4. وأظهرت النتائج عدم وجود فروق

معنوية ($P \geq 0.05$) بين البكتريا الموجبة لصبغة غرام والبكتريا السالبة لصبغة غرام في كل من مجموعتي الإصابة بالفشل القلبي وعدم الإصابة به. كانت اكثر أنواع البكتريا شيوعا في مجموعة الفشل القلبي هي *Staphylococcus hominis* والتي شكلت 10% من العزلات تليها بكتيريا *Acinetobacter baumannii* و *Staphylococcus haemolyticus* أذ شكلت 8% لكل منهما، في مجموعة العدوى فقط بدون الفشل القلبي (G3) كانت بكتريا *Klebsiella pneumoniae* هي الأكثر شيوعًا أذ شكلت 16% من العزلات، تليها بكتريا *Pseudomonas aeruginosa* و *Coagulase negative Staphylococci* أذ شكلت 8% لكل منهما. وُجد أن جميع الأنواع المعزولة كانت مقاومة للمضاد الحياتي Ciprofloxacin (80%) في كلتا المجموعتين، وكانت جميع الأنواع المعزولة حساسة لكل من المضادات الحياتية Streptomycin ، Linezolid ، Vancomycin ، Ampicillin ، Colistin ، Pefloxacin ، Ceftazidime/Avibactam و Ceftolozane/Tazobactam في مجموعة مرضى فشل القلب المصابين بالعدوى (G1).

أظهرت نتائج الفحص المناعي وجود فروق معنوية ($P \leq 0.0001$) كبيرة بين المجموعتين المصابتين بفشل القلب مقارنة بالمجموعتين غير المصابة به فيما يتعلق بالتروبونين، كما أظهرت النتائج وجود فروق معنوية ($P \leq 0.0001$) كبيرة لكل من (NT-proBNP) ، (CNP) ، (IMA) ، (sCD40L) ، (CRP) ، والبروكالسيتونين في مستويات مصل الدم لمجاميع الدراسة مقارنة مع مجموعة الاصحاء ، اظهرت نتائج تحليل ROC الى ان التروبونين كان المؤشر الحيوي الاكثر موثوقية لتشخيص فشل القلب يليه IMA ، NT-proBNP وsCD40L . وتتفاوت فعالية المؤشرات الحيوية الاخرى حيث اظهر بعضها اداءا جيدا.

أظهرت نتائج فحص الدم وجود ارتفاع معنوي في عدد خلايا الدم البيضاء الكلي (WBC) والعدلات في مجموعات العدوى البكتيرية مع فشل القلب ومن دونه، مقارنة بمجموعة فشل القلب فقط ومجموعة الاصحاء، كما أظهرت نتائج الدراسة الحالية انخفاضا معنويا ($P \leq 0.0001$) في عدد كريات الدم الحمراء RBC ، HGB ، HCT ، عدد الصفائح الدموية و عدد الخلايا اللمفاوية لدى المرضى مقارنة مع مجموعة الاصحاء.

يمكن الاستنتاج بان أكثر أنواع البكتريا شيوعا هي *Staphylococcus hominis* في مجموعة مرضى الفشل القلبي و *Klebsiella pneumoniae* في مجموعة المرضى غير المصابين بالفشل القلبي، بالإضافة إلى ذلك، أظهرت البكتريا المعزولة مقاومة عالية ل Ciprofloxacin في كلتا المجموعتين وحساسية عالية لبعض المضادات الحيوية. كما أظهرت النتائج وجود فروق معنوية كبيرة ($P \leq 0.0001$) بين المجموعة المصابة بفشل القلب مع العدوى البكتيرية مقارنة مع مجموعة الاصحاء في مستويات Troponin و NT-pro BNP و CNP و IMA و sCD40L و CRP و PCT.

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جـــامعة كربلاء
كلية التربية للعلوم الصرفة
قسم علوم الحياة

تأثير تعفن الدم البكتيري على بعض المؤشرات الكيميائية الحيوية والمناعية في مرضى فشل القلب في محافظة كربلاء

اطروحة مقدمة

الى مجلس كلية التربية للعلوم الصرفة - جامعة كربلاء

وهي جزء من متطلبات نيل شهادة الدكتوراه فلسفة في علوم الحياة - علم الحيوان

من قبل

ساره سعيد حسن الربيعي

بكالوريوس علوم حياة / كلية التربية للعلوم الصرفة / جامعة كربلاء / 2013

ماجستير علوم حياة / كلية التربية للعلوم الصرفة / جامعة كربلاء / 2016

بإشراف

أ.د .علاء عبد الحسين الدعمي الطبيب الاختصاص د. احمد قاسم الحيدري

1447هـ 2025 م