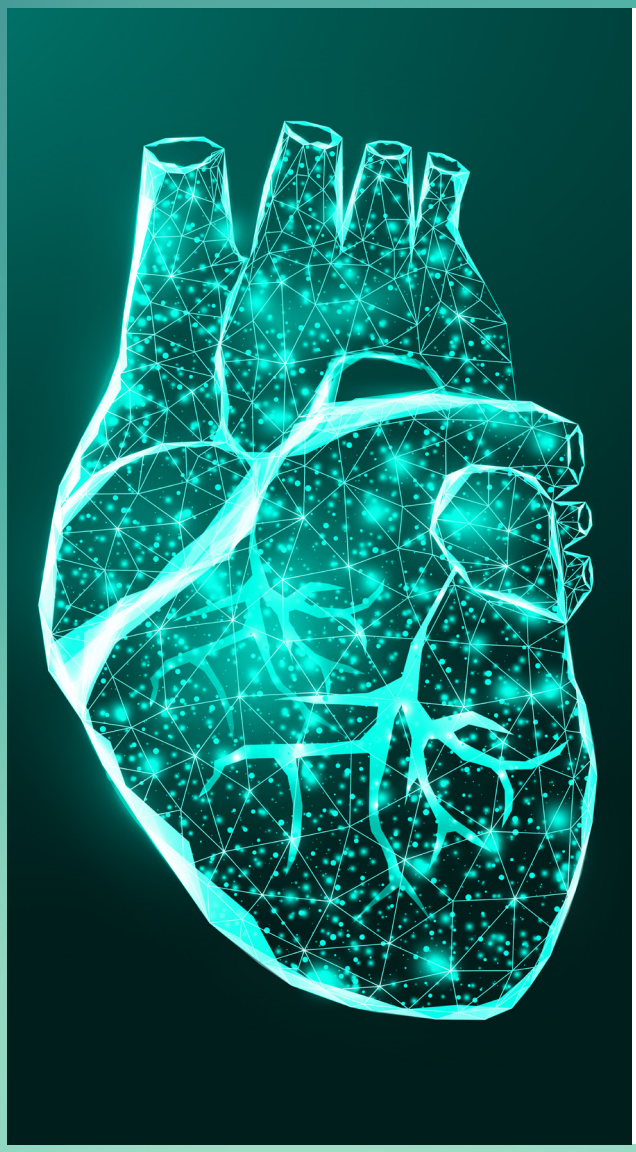
E-ISSN: 2405-819X

CARDIOVASCULAR ACADEMY SOCIETY

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

VOLUME: 11 ISSUE: 3 SEPTEMBER 2025



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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: September 2025
ISSN: 2405-8181 **E-ISSN:** 2405-819X
International scientific journal published quarterly.

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

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The **International Journal of the Cardiovascular Academy** (**IJCVA**) is indexed in **Scopus, DOAJ, Embase, CNKI** (**China National Knowledge Infrastructure**), **EBSCO Central & Eastern European Academic Source, Hinari, GOALI, ARDI, AGORA, OARE** and **ProQuest**.

The journal is published online.

Owner: Ömer Kozan on behalf of the Cardiovascular Academy Society

Responsible Manager: Mehdi Zoghi

VOLUME: **11**
ISSUE: **3**
SEPTEMBER **2025**

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY
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REVIEW

DOI: 10.4274/ijca.2025.97269
Int J Cardiovasc Acad 2025;11(3):86-96

Pre-participation Cardiovascular Evaluation for the Arbaeen Walking Ceremony, A Practical Guidance

Maryam Hajian[1], Shahram Mohaghegh[2]

[1]Department of Community Medicine, TeMS.C., Islamic Azad University Tehran Medical Sciences, Tehran, Iran
[2]Research Center for Health Management in Mass Gathering, Red Crescent Society of Islamic Republic of Iran, Tehran, Iran

Abstract

As an important mass gathering event, the Arbaeen walking ceremony has a high risk of cardiovascular events. Walkers with backpacks walk many kilometers in hot and air-polluted weather. Many of them have sedentary lifestyles and lack cardiovascular adaptation to this type of physical activity. They can be susceptible to acute cardiac events such as sudden cardiac death and myocardial infarction during their walking route. Authors of this study, who are experienced in this field, aimed to introduce practical pre-participation cardiovascular guidance based on expert opinions, sports medicine textbooks, and other related high-quality findings from the literature that would be applicable to the Arbaeen walking ceremony. An appropriate cardiovascular pre-participation evaluation can help to find those people with a high risk of cardiovascular impairments to maximize safe participation on the field in the Arbaeen walking ceremony. The last physical activity readiness questionnaire for everyone and electronic physical activity readiness medical examination and American College of Sports Medicine pre-participation screening algorithm for the general public can be used for pre-participation cardiovascular assessment for this march. For proper cardiovascular adaptation and training of high-risk pilgrims, this assessment must be done annually, 2 months at least before the walking ceremonies.

Keywords: Pre-participation evaluation, prevention, cardiovascular risk factor, cardiovascular disease

INTRODUCTION

There has been a significant increase in the number of pilgrims coming to Iraq for Arbaeen ceremonies held on the 40th day after Imam Hossein's martyrdom at Karbala since the last decade. In yearly Arbaeen ceremonies, millions of travelers of various ages go on foot from Iraq and adjoining countries to Karbala, a city 100 km southwest of Baghdad. The capital of Iraq.

They may walk hundreds of kilometers in a few days, with backpacks, alongside pilgrims who travel by vehicle on the same route.[1] As an important mass gathering event, the Arbaeen walking ceremony has a high risk of infectious and non-infectious diseases.[2,3] On the other hand, the climate in Karbala is characterized as desert and has extremely high temperatures and low rainfall. The summer temperatures are extremely high and can reach over 50 degrees Celsius.[4] Pilgrims walking to Karbala are therefore susceptible to cardiovascular strain due to environmental hazards such as heat exposure and air pollution.[5,6] For example, heart rate (HR), an important physiologic indicator of cardiovascular stress, increases with heat exposure. It has been shown that for an increase of one degree Celsius in core body temperature, HR increases by approximately 33 beats per minute.[7,8] On the other hand, the metabolic demand of walking with a backpack is considerably higher than walking without a backpack. Level walking on a firm surface with a usual speed of 2.5 mph has

To cite this article: Hajian M, Mohaghegh S. Pre-participation cardiovascular evaluation for the Arbaeen walking ceremony, a practical guidance. Int J Cardiovasc Acad. 2025;11(3):86-96

Address for Correspondence: Asst. Prof. Shahram Mohaghegh
E-mail: shahrammohaghegh5@gmail.com
ORCID ID: orcid.org/0000-0001-8744-2116

Received: 24.03.2025
Accepted: 11.07.2025
Publication Date: 15.09.2025

an energy consumption of 3 metabolic equivalents (MET). While under the same conditions, a moderate pack load has a metabolic cost of 7 MET, and the MET value increases as the pack weight, speed of walking, and uphill gradient increase. For example, walking with a speed of 5 mph (twice the usual speed of 2.5 mph) has an energy cost of 8 MET.[9] Classically, intensity of physical activity can be categorized based on its energy expenditure levels. These categories are sedentary (‹1.6 MET), light (1.6‹3 MET), moderate (3‹6 MET), vigorous (6‹9 MET), and high (≥9 MET). 1 MET equals resting energy expenditure or 3.5 mL O2 consumption/kg/min. When a physical activity intensity is rated as 2 METs, it requires twice the O2 and energy consumption as at rest.[10]

The main walking pathway of pilgrims in the Arbaeen ceremony is the 76-kilometer road between the cities of Najaf and Karbala, which takes about three days on foot. It is asphalted and level.[11] The main influential factors that can overstress their cardiovascular system are backpack weight, the pace of walking, and environmental conditions such as heat exposure. Cardiovascular emergencies were the major finding in some studies focusing on Arbaeen ceremonies. These include ischemic heart diseases, hypertension, and myocardial infarction.[4] Cardiovascular diseases (43.5%) were the primary cause of death in the 2014 Arbaeen ceremony in the Hantoosh et al.[12] report which include 54 deaths from total 124 ones 12 and were the main cause of death (90% of cases) in total 177 Iranian patients hospitalized in Iraqi hospitals in the 2012 Arbaeen event in Sadeghi et al.[13] study. A total of 84 (47%) patients were female. Mean age of cardiovascular patients was 63.29±16.87 years.[13] Also in Lami et al.[14] study in the 2014 Arbaeen ceremony in 4425 non-communicable diseases emergencies including 54.31% male and 45.69% female patients, percentage of severe hypertension as an emergency complaint was higher (29.04%) than other non-communicable disease emergencies including asthma (19.23%), ischemic heart diseases (21.1%), diabetes (16.43%), cerebrovascular accident (2.45%) and pulmonary edema (3.86%) emergencies. The age groups of patients were as follows: <20 years (5.11%), 20-39 years (18.46%), 40-49 years (39.55%) and >60 years (36.88%).[14]

The main aim of pre-participation cardiovascular evaluation before physical activities such as the Arbaeen walking ceremony is to find those people with a high risk of cardiovascular impairments. According to the American College of Cardiology (ACC), the American Heart Association (AHA), and the American College of Sports Medicine (ACSM), as the risk of sudden cardiac death (SCD) and acute coronary syndrome in susceptible persons regardless of their age increases during vigorous physical activities, screening to detect such high-risk individuals is both justified and beneficial.[15-17] Such medical screening could include a history and physical examination and if necessary exercise stress testing, or more extensive diagnostic testing. So, the authors of this article aimed to define a cardiovascular pre-participation evaluation (PPE) and related management and prevention strategies which can be done by trained primary health providers for Arbaeen walking ceremony. Nevertheless, it should be emphasized that even a comprehensive cardiac screening program will not identify all high-risk persons for SCD, and adequate preparation for cardiac emergencies is always necessary.[18,19]

METHODS

The authors who are experienced in this field relied heavily on sports medicine textbooks (Brukner Clinical Sports Medicine, ACSM guidelines for exercise testing and prescription) and expert opinions from professional societies including AHA, ACC, Canadian cardiovascular society, European Resuscitation Council, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, European Association of Preventive Cardiology, American Medical Society for Sports Medicine, Society for Cardiovascular Pathology, Canadian Medical Association, physical activity readiness questionnaire for everyone (PAR-Q+) electronic physical activity readiness medical examination (ePARmed-X+) resources and ACSM and their related journals. Also a literature review using Google Scholar, PubMed, up-to-date, and Cochrane databases was performed to identify relevant systematic reviews / meta-analysis and randomized clinical trial studies (as high quality studies) from beginning until time of study (March 2025) for review. The used key words were Iraq, Arbaeen, cardiovascular disease, myocardial infarction, ischemic heart disease, SCD, heatstroke, walking, preparticipation evaluation, acute coronary syndrome, hypertrophic cardiomyopathy (HCM), screening and prevention. The findings were summarized and appropriate information was given based on mentioned references.

RESULTS

The database search revealed only 2 systematic review / meta-analysis studies and no randomized clinical studies (Figure 1). Two systematic reviews (and / or meta-analysis) have been done by authors[4] and Harmon et al.[20]

Cardiovascular Events

A review of the literature shows that sudden cardiac arrest (SCA) or death during exercise is not a rare occurrence even in young athletes. A thorough review of 28 studies about the incidence of SCD in exercisers showed that this can vary from 1:3,000 to 1:917,000. However, studies with better methodological quality reported a higher incidence, ranging from 1:40,000 to 1:80,000.[21,22] Increasing age, and male sex are risk factors for SCD. The ratios of male to female in SCD range from 5:1 to 9:1. A 5-year prospective study, in the French general population aged 10-70 years, reported that 94% of SCD during exercise occurred in

recreational athletes, usually in the fifth decade. Also, cardiac death is not specific to competitive athletes. Based on data from the center for disease control, cardiovascular disease was the second cause of death (after malignancy), in individuals younger than 24 years old in the USA. So PPE can be recommended for both athletic and non-athletic populations[18,23] such as pilgrims participating in the Arbaeen march.

The cause and mechanism of SCD are important. Primary ventricular tachyarrhythmia (in hereditary and congenital conditions), myocardial ischemia and infarction (in master athletes), and aortic rupture or dissection (in Marfan syndrome) are 3 primary mechanisms of SCD during exercise.[24] In those over the age of 50 years, coronary artery disease (CAD) is the main cause of SCD during physical activity (more than 80% of cases), while SCD in younger athletes (<35 years old) is primarily due to hereditary or congenital structural and electrical cardiac or vascular problems[25,26] which include myocardial diseases (HCM, arrhythmogenic ventricular cardiomyopathy, and dilated cardiomyopathy), CAD / anomalies (congenital coronary artery anomalies and premature atheromatous CAD), cardiac conduction tissue abnormalities (Wolff-Parkinson-White syndrome and right ventricular outflow tachycardia), valvular heart diseases (mitral valve prolapse and congenital aortic stenosis), disorders of the aorta (Marfan syndrome), and ion channelopathies (congenital long QT syndrome, Brugada syndrome, congenital accessory electrical pathways, and catecholaminergic polymorphic ventricular tachycardia). A variety of acquired conditions are also reported in this group (younger athletes) such as infections (myocarditis), drugs (cocaine, amphetamine), electrolyte disturbances (hypokalaemia or hyperkalemia), hypothermia, hyperthermia and trauma (commotio cordis).[18] A meta-analysis of 34 studies that examined post-mortem findings of 4,605 young individuals (under the age of 35 years) who succumbed to SCD, showed that structurally normal hearts were more common than HCM both in athletic (26.7% versus 10.3% of cases) and non-athletic (30.7% versus 7.8% of cases) groups.[27] These findings have led to the

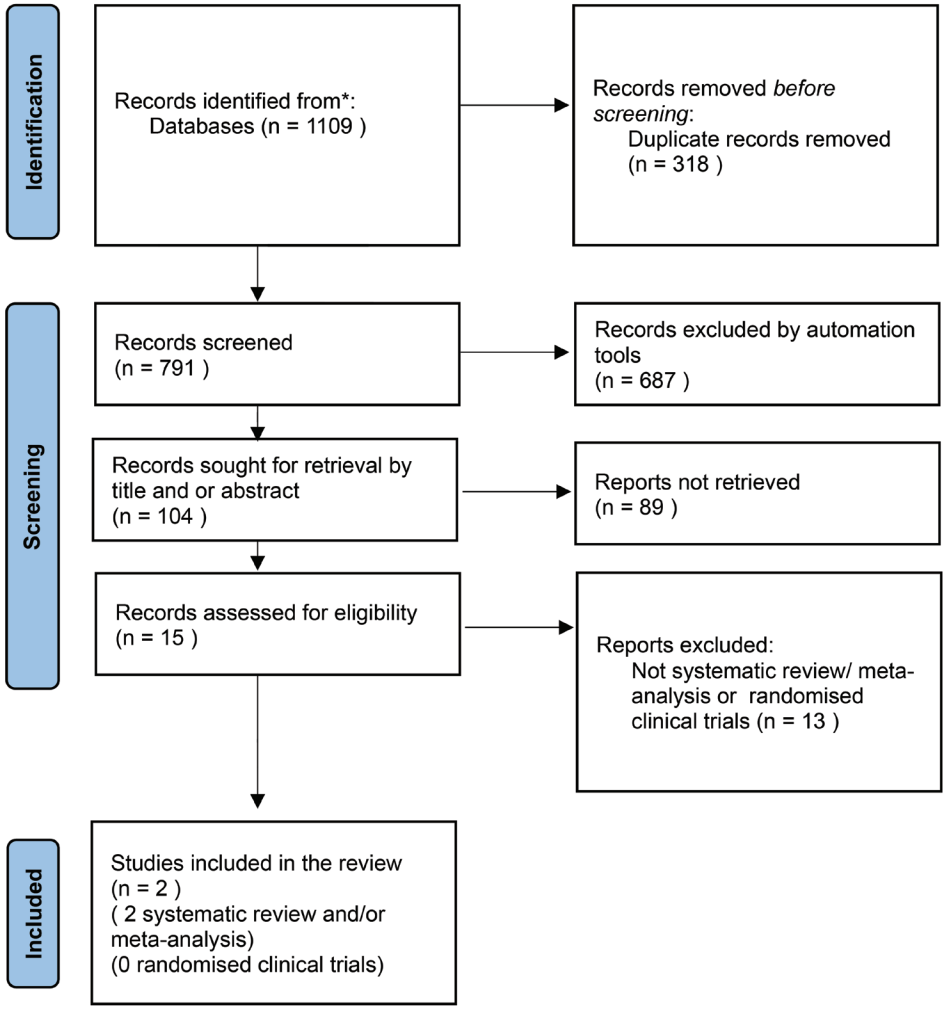

Figure 1. Flow chart of the review of databases.

use of the term sudden arrhythmic death syndrome when there is a postmortem structurally normal heart, and negative toxicology profile.[28,29] HCM, a primary myocardial pathology has a prevalence of 0.2% in the general population. This is an autosomal dominant disorder with varying clinical and morphologic characteristics. SCD can be the first manifestation in an individual. Death usually occurs in males during or immediately after exercise.[30,31]

Medical History

Although up to 80% of athletes with SCD had reported no history of cardiovascular symptoms,[32] medical history is an important component of cardiovascular PPE and can be a clue of underlying serious silent cardiac disease. In addition to sex and age, the race of pilgrims can be important factors in determining health outcomes. SCD has occurred more in black / African-American athletes than their white counterparts (3.2 times greater risk).[18,33] A sedentary lifestyle can be a major risk factor for cardiovascular events during vigorous physical activity. According to ACSM, persons with history of performing regular, organized physical activity of at least moderate intensity (target HR of 40 to 60% of HR reserve or 3‹6 MET) for minimum 30 min on 3 or more days per week during the previous 3 months are categorized as current exercisers).[34] This classification is the basis of the last ACSM pre-participation screening algorithm for the general public (Figures 2 and 3).

History of heart attack or surgery, cardiac catheterization, coronary angioplasty (percutaneous transluminal coronary angioplasty), pacemaker/implantable cardioverter defibrillator usage, ablation procedures for dysrhythmias, heart valve disease, murmur or other abnormal heart sounds, peripheral vascular disease, pulmonary disease, cerebrovascular disease (for example transient ischemic attacks and stroke), blood dyscrasias and anemia (such as systemic lupus erythematosus); deep vein thrombosis / emboli, phlebitis; pregnancy; cancer; emotional / mood diseases (depression is a cardiovascular risk factor),[35] heart failure or transplantation and congenital heart diseases must be questioned. Also, medication history (including dietary/nutritional supplements) and use of caffeine, tobacco, or recreational (illicit) drug use must be asked.[18,34]

Family history is very important as many etiological conditions of SCD are hereditary. A history of premature cardiac disease or death or a known hereditary disease, such as Brugada syndrome or cardiomyopathy, in a first-degree relative necessitates referral for a more precise cardiac examination.[36] Ventricular arrhythmias as a common pathologic mechanism in these hereditary conditions may present as syncope, epilepsy, or unexplained drowning, and so, asking about these symptoms and signs in close family members may reveal genetically transmitted cardiac diseases. Seeking post-mortem reports on first-degree relatives who suffered premature SCD is important as this can differentiate a hereditary disorder (such as HCM) from a congenital disorder such as congenital coronary artery anomalies.[18,37]

History of SCA, syncope (loss of consciousness) especially during physical activity, palpitations (an annoying perception of the heart contractions), dizziness of unknown cause, chest pain (especially with exercise, exertion, stress, cold weather and after meal), intermittent claudication (the pain, often described as a cramp in the lower extremities that is brought on by walking especially when walking uphill and disappears within 1-2 min after stopping walking, reproducible from day to day and does not occur with standing or sitting), unusual exertional dyspnea / fatigue and orthopnea or paroxysmal nocturnal dyspnea (dyspnea with onset usually 2-5 h after the sleep which may be disappeared by sitting or walking out) should also be assessed by more diagnostic workup.[18,20,34] Chest pain characteristics favoring cardiac origin include sensation of heaviness, burning, squeezing or constricting feeling, with a location in mid thorax, the substernal area, interscapular region, in arms (one or both), neck, shoulders, forearms, cheeks, teeth and fingers. Vague aches, sharp, “knifelike”, stabbing pains, respiration induced pains, pains of the left hemithorax or submammary areas, and pains after end of exercise or induced by a particular body movement are features that indicate against the ischemic origin of chest pain.[34,38]

Although in the last ACSM pre-participation screening algorithm of the general public, cardiovascular disease risk factors are not mentioned, knowledge of these risks, is necessary for a more precise assessment of the cardiovascular health of the pilgrims and, if necessary, referral for medical clearance and decisions about exercise testing and prescription. These include age (men ≥45 yrs.; women ≥55 yrs.); a family history (myocardial infarction, coronary revascularization, or sudden death before 55 yrs. in father or other male first-degree relative or before 65 yrs. in mother or other female first-degree relative); a blood glucose (fasting plasma glucose ≥100 mg/dL; or 2 h plasma glucose values in oral glucose tolerance test ≥140 mg/dL; or HbA1C ≥5.7%); blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic ≥80 mmHg, based on an average of ≥2 readings obtained on ≥2 occasions, or on antihypertensive medication); and body mass index (BMI) / waist circumference (BMI ≥30 kg/ m-2 or waist girth).

>102 cm for men and >88 cm for women), cigarette smoking (current cigarette smokers or those who quit within the previous 6 months o or exposure to environmental tobacco smoke), Chronic obstructive pulmonary disease, lipids (total serum cholesterol ≥200 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL or high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women or on lipid-lowering

medication) and sedentary lifestyle (not meeting the minimum threshold of 75-150 min/week of moderate-to-vigorous intensity physical activity). High-density lipoprotein cholesterol ≥60 mg/dL is considered a negative risk factor which means can eliminate one positive risk factor from the sum of positive risk factors.[34,39]

Physical Examination

The main components of preparticipation cardiac physical examination include measurement of body weight / height, BMI, waist circumference, pulse rate and rhythm, resting blood pressure in seated, supine, and standing states, palpation of the cardiac apical impulse and point of maximal impulse, cardiac and pulmonary auscultation, inspection and palpation of lower extremity for arterial pulses, edema, and cutaneous signs of hypercholesterolemia (tendon xanthoma and skin xanthelasma). Bilateral lower extremity edema, which is most evident at night, is a characteristic sign of heart failure or bilateral chronic venous insufficiency.[34,40] HCM and aortic stenosis the two most common causes of physical activity-

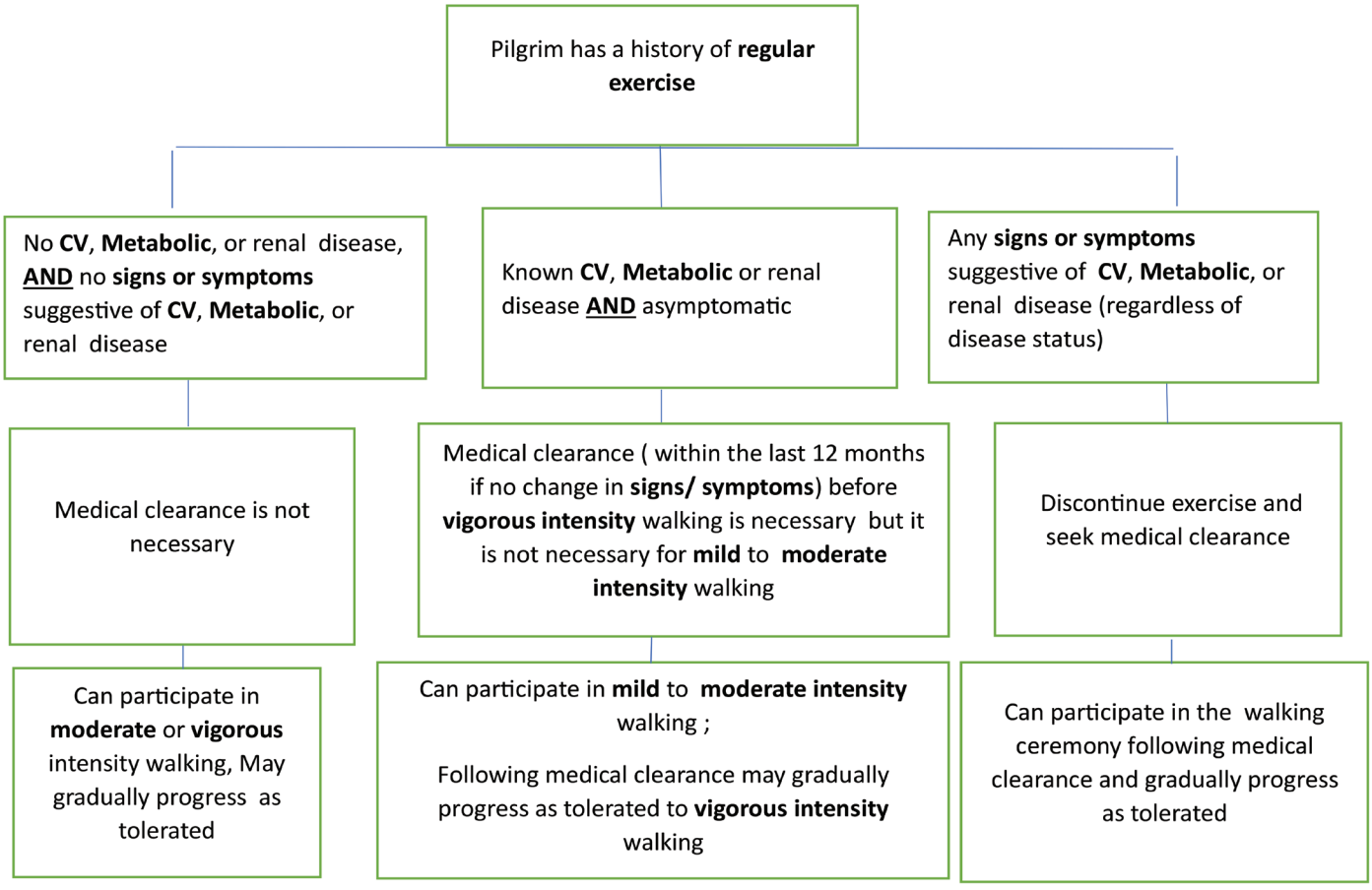

Figure 2. Pre-participation cardiovascular screening algorithm for the general public based on the American college of sports medicine (ACSM) guidelines for current exerciser pilgrims[34]

MET: Metabolic equivalent

Regular exercise is the history of participation in regular exercise of at least moderate intensity for at least 30 minutes on 3 or more days per week during the past 3 months. **Mild-intensity** walking (1.6-2.9 MET) is an intensity that causes a slight increase in heart rate and breathing (30%-39% heart rate reserve or rate of perceived exertion 9-11). **Moderate-intensity** walking and backpacking (3-5.9 MET), is an intensity that causes a considerable increase in heart rate and breathing (40%-59% heart rate reserve or rate of perceived exertion 12-13). **Vigorous intensity** walking and backpacking (6<=MET) is an intensity that causes a high increase in heart rate and breathing (60% or more heart rate reserve or rate of perceived exertion 14 or more). **Cardiovascular (CV)** disease is a cardiac, cerebrovascular, or peripheral vascular disease (hypertension is considered a CV risk factor and not a disease). **Metabolic disease** is type 1 or 2 diabetes mellitus. **CV** signs and symptoms are the following at rest or during activity: chest pain or other areas with potential ischemic origin such as neck, jaw, and arms; dyspnea; dizziness or syncope; orthopnea or paroxysmal nocturnal dyspnea; ankle edema; palpitation or tachycardia; intermittent claudication; known heart murmur; unusual fatigue with usual activities.

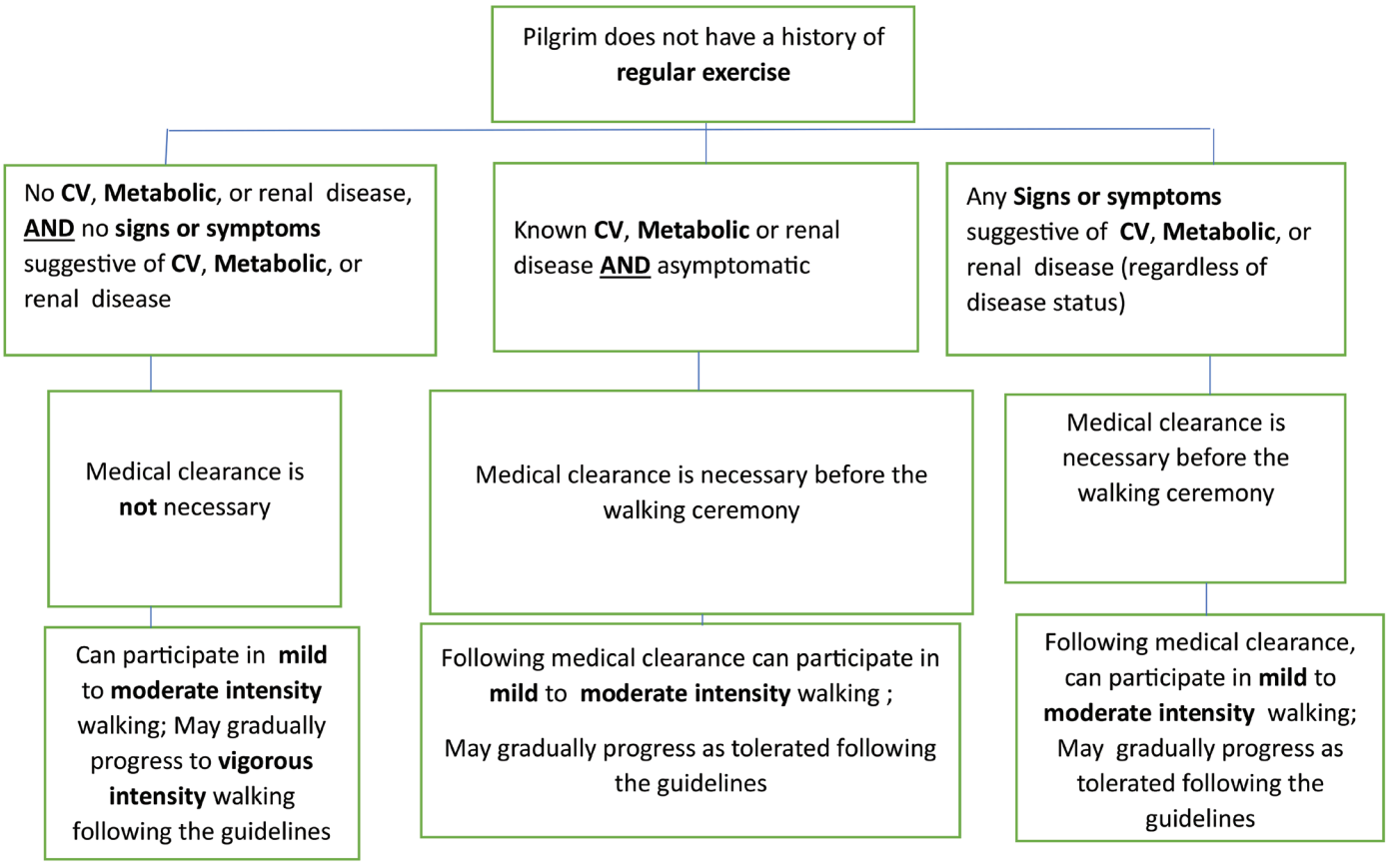

Figure 3. Pre-participation cardiovascular screening algorithm for the general public based on the American college of sports medicine (ACSM) guidelines for non-current exerciser pilgrims[34]

MET: Metabolic equivalent

Regular exercise is the history of participation in regular exercise of at least moderate intensity for at least 30 minutes on 3 or more days per week during the past 3 months. **Mild-intensity** walking (1.6-2.9 MET), is an intensity that causes a slight increase in heart rate and breathing (30%-39% heart rate reserve or rate of perceived exertion 9-11).

Moderate-intensity walking and backpacking (3-5.9 MET), is an intensity that causes a considerable increase in heart rate and breathing (40%-59% heart rate reserve or rate of perceived exertion 12-13). **Vigorous intensity** walking and backpacking (6<=MET) is an intensity that causes a high increase in heart rate and breathing (60% or more heart rate reserve or rate of perceived exertion 14 or more). **Cardiovascular (CV)** disease is a cardiac, cerebrovascular, or peripheral vascular disease (hypertension is considered a CV risk factor and not a disease). **Metabolic disease** is type 1 or 2 diabetes mellitus. **CV signs and symptoms** are the following at rest or during activity: chest pain or other areas with potential ischemic origin such as neck, jaw, and arms; dyspnea; dizziness or syncope; orthopnea or paroxysmal nocturnal dyspnea; ankle edema; palpitation or tachycardia; intermittent claudication; known heart murmur; unusual fatigue with usual activities.

related SCD, can manifest themselves as systolic ejection heart murmurs.[41] HCM patients can have resting left ventricular outflow obstruction in 25% of cases but this can rise to 50% during exertion.[18,42] Murmurs of dynamic left ventricular outflow tract obstruction become louder when the venous return is decreased, so it is recommended to examine the patient in both the supine and standing positions (and with Valsalva maneuver), specifically to identify the diagnostic murmur of HCM (if present). Such murmurs are typically early systolic, are harsh, and are heard best at the right upper sternal border.[43] On the other hand, murmurs of aortic stenosis typically attenuate when the venous return is decreased and increase with maneuvers that increase venous return (i.e., squatting).[44] In general, harsh systolic murmurs and any diastolic murmur should be considered pathologic.[18]

Other than HCM, some important causes of SCD such as arrhythmogenic ventricular cardiomyopathy, dilated cardiomyopathy, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, ventricular preexcitation,

and Brugada syndrome generally have normal physical examinations; so these cannot be excluded by physical examination findings alone.[18,45] Screening for hypertension and coarctation of the aorta is also an important aspect of the cardiovascular physical examination. Right and left arm blood pressure measurements and femoral artery palpation must be done.[18,34]

Marfan syndrome, an autosomal dominant collagen disorder (with 25% of cases from de novo mutations), with a prevalence of 1 in 5,000 to 10,000, with no gender predilection, and variable gene expression, can result in aortic dilatation, rupture/dissection, and valvular dysfunction. Despite medical improvements, aortic dissection still occurs in about one-tenth of the patients and the disorder has been responsible for approximately 3% of all exercise-related SCDs in young people. Heart failure can also occur due to aortic valve insufficiency.[18] More than half of the dissections have occurred in patients undiagnosed with this syndrome, therefore early diagnosis is important and can be lifesaving.[46] The physical stigmata of Marfan syndrome are a high-arched palate, arachnodactyly (long, slender fingers), hyperlaxity, tall height, lens dislocation (ectopia lentis), and a long arm / wing span. Cardiovascular (especially aortic root aneurysm) and ocular manifestations are primary clinical features in making an unambiguous diagnosis of suspected cases in the absence of any family history.[18,47]

DISCUSSION

Screening and Referring the Pilgrims

As mentioned before, according to the ACSM pre-participation screening algorithm for the general public (Figures 2 and 3), the current physical activity level of pilgrims is the basis of their pre-participation cardiovascular assessment. Accordingly, the pilgrims can be divided into 2 categories: those who have a history of participation in regular physical activity moderate intensity for at least 30 minutes on 3 or more days per week during the past 3 months and those who do not have such a history.[34]

Identifying individuals with known CV, metabolic, or renal diseases or those with signs or symptoms suggestive of cardiac, peripheral vascular, renal, or cerebrovascular diseases,

Types 1 and 2 diabetes mellitus are the next level of screening. In this algorithm, hypertension is considered a CV risk factor and not a disease. Finally, the desired walking intensity is an important factor in this algorithm.[34] Electrocardiographic records and other sophisticated diagnostic methods, such as echocardiography, are not included in this Algorithm, and trained health care providers can obtain necessary information based on appropriate history taking, laboratory data, and concise physical examination. This can be advantageous for the screening of a large number of pilgrims, such as those participating in the Arbaeen walking ceremony.

This algorithm is based on the direct relationship between the relative risk of SCD and acute myocardial events during vigorous-to-near maximal intensity physical activity and the presence of CVD and / or exertional symptoms,[17] and an inverse relationship with the current physical activity level of individuals.[48,49] Also, there is insufficient evidence to indicate that the presence of CVD risk factors without underlying disease poses a substantial risk of adverse exercise-related CV events. This is especially true among otherwise healthy adults. Note that this algorithm is not a substitute for appropriate cardiovascular pre-participation assessment, and decisions about a referral to a qualified specialist for medical clearance, should be made individually based on sound clinical judgment regarding all previously mentioned risk factors of cardiovascular diseases and the desired physical activity intensity of pilgrims during walking.[34] The 2021 PAR-Q+ and ePARmed-X+ 50 can be a useful adjunct for this algorithm. The tools developed have no age limits, allow for self-management, and include a three-step risk assessment process. In step one, clients answer seven general health questions using the PAR-Q+. The questions are not specific to cardiovascular problems and point to reveal heart, circulatory, balance, chronic medical, and joint problems that could make exercise difficult, or even dangerous for clients (Table 1). If all responses are “no”, they are permitted to engage in unrestricted activities following general exercise guidelines. A “yes” on any question prompts further follow-up. In step two, those who responded “yes” on the previous stage must answer additional follow-up questions related to chronic conditions (Table 2); if they respond with all “no”, they can self-clear and receive customized exercise advice, while any “yes” leads them to the ePARmed-X+. It consists of a series of medical condition specific questions designed electronically and must be completed in tandem. It has been translated into several languages and is available publicly. After finishing the ePARmed-X+, a client could be given one of three suggestions. Low risk means the client is approved for unrestricted participation in physical activities. Intermediate risk indicates that the client is authorized for low to moderate intensity exercise, but the client needs to consult or be supervised by a qualified exercise professional. High risk indicates that the client should engage in low-intensity physical activity until a physician or healthcare professional provides clearance. It is advised that they exercise under the direct supervision of a qualified exercise professional.[50,51] These tools are self-screening and can be beneficial for pre-participation screening of a large number of pilgrims. Indeed, they lower the referral rate of pilgrims. Pilgrims can be advised to follow the instructions of these tools and consult their trained primary

Table 1. The 2021 physical activity readiness questionnaire for everyone plus (PAR-Q+) general health questions[50]		
General health questions		
Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition or high blood pressure?	o	o
2) Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	o	o
3) Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	o	o
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? Please list condition(s) here:	o	o
5) Are you currently taking prescribed medications for a chronic medical condition? Please list condition(s) and medications here:	o	o
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer NO if you had a problem in the past, but it does not limit your current ability to be physically active. Please list condition(s) here:	o	o
7) Has your doctor ever said that you should only do medically supervised physical activity?	o	o

Table 2. The 2021 physical activity readiness questionnaire for everyone plus (PAR-Q+) follow- up main questions[50]
1-Do you have arthritis, osteoporosis, or back problems?
2-Do you currently have cancer of any kind?
3-Do you have a heart or cardiovascular condition? This includes coronary artery disease, heart failure, diagnosed abnormality of heart rhythm.
4-Do you currently have high blood pressure (resting blood pressure with or without medication equals or greater than 160/90 mmHg).
5-Do you have any metabolic conditions? This includes type 1 diabetes, type 2 diabetes, pre-diabetes.
6- Do you have any mental health problems or learning difficulties? This includes Alzheimer's, dementia, depression, anxiety disorder, eating disorder, psychotic disorder, intellectual disability, down syndrome.
7- Do you have any respiratory disease? This includes chronic obstructive pulmonary disease, asthma, pulmonary high blood pressure.
8- Do you have a spinal cord injury? This includes tetraplegia and paraplegia.
9- Have you had a stroke? This includes transient ischemic attack or cerebrovascular event
10-Do you have any other medical condition not listed above or do you have two or more medial conditions?

health providers accordingly when it is necessary to refer to a qualified exercise or healthcare professional. Trained primary health care providers as community health workers or who work in mobile health units can then use the ACSM algorithm in the case of pilgrims' references.

Another important consideration in using this algorithm is monitoring and training pilgrims for changes that may alter their categorization and subsequent health recommendations. For example, the development of new signs or symptoms after beginning walking can change their categorization and make it necessary to adopt new health recommendations accordingly.

Medical clearance in this algorithm is an approval from a health care professional (for example sports medicine specialist or cardiologist) to engage in exercise (walking and backpacking). The type of medical evaluations and procedures necessary for the cardiovascular clearance can vary widely, as there is not a single recommended screening test and the health care professional can choose them based on their discretion and clinical judgment. This may include more detailed taking of medical history and physical examination, resting or stress electrocardiogram / echocardiogram, computer tomography angiography (for the assessment of coronary artery calcium), or even nuclear medicine imaging studies, or coronary angiography. Accordingly, the health care professional can recommend instructions and restrictions (e.g., exercise duration and intensity) to the pilgrim in question, and continued communication between health care professionals and primary care providers is strongly recommended.[34] Also medical clearance for other non-cardiovascular problems based on PARQ+ and ePARMed-X+ can be obtained by referring the pilgrims to related health care professionals.

Management and Prevention Strategies

Effective management and prevention of acute cardiovascular events during Arbaeen walking ceremonies focus on several key strategies. These include:

1- Implementation of simplified screening and management algorithms for those with or at risk of cardiovascular disease.[52]

2- Adequate preparation for cardiac emergencies in the mobile health units. Creating efficient resuscitation protocols and enhancing the accessibility of automated external defibrillators in public spaces are the most effective methods for lowering the occurrence of SCD.[53]

3- As there is a low risk of cardiovascular events associated with participation in light-to-moderate intensity physical activity, much of the risk of these events during vigorous physical activity can be reduced by following a "progressive transitional phase" for 2-3 months before ceremony during which the duration and intensity of exercise are gradually increased (if the individual remains asymptomatic).[34] This is especially important for previously sedentary and high-risk pilgrims who want to participate in the Arbaeen walking ceremony.

4- In warm conditions, like Arbaeen walking ceremonies, it is essential to regulate core temperature while walking. Elements that impede this regulation, including lack of hydration, unsuitable clothing, and inadequate salt, and electrolyte consumption, will raise the risk of heat-related illnesses and increase cardiovascular strain. In warm conditions, pre-cooling methods are essential for postponing the rise of dangerous body temperatures, thus safeguarding walking performance and avoiding heat-related cardiovascular stress. Successful pre-cooling methods encompass ice packs, the wearing of ice vests, remaining in air-conditioned spaces, taking cold baths, and drinking chilled water. Additionally, maintaining good physical fitness greatly decreases the risk of heat-related problems.[54] Drinking and eating regularly, wearing lightweight and loose clothing, using diluted fruit juice or sports drink for walking more than 1 hour, providing 12.5 mg potassium, 45 mg sodium, and 6-8 grams of carbohydrate per 100 cc water are recommended.[55] Limiting walking during peak temperatures and instead walking at night if possible, offer other options that can help pilgrims avoid heatstroke.[4]

5- Exercise heat acclimatization causes physiological adaptations including improved fluid balance, sweating and thermoregulation, lowered body temperatures, reduced physiological and cardiovascular strains, improved skin blood flow, altered metabolism, enhanced cellular protection and a reduced risk of serious heat illness. As heat acclimatization is specific to the climatic heat conditions and physical exercise intensities, it is recommended that low-risk pilgrims be exposed gradually to climatic temperatures and walking intensities similar to those in Arbaeen walking ceremonies for about 7-10 consecutive days before the real march. Optimal heat acclimatization requires a minimum daily heat exposure of about 90-120 min (can be broken into two 45-minute / 1-hour exposures) combined with walking with equal intensities during a real march. Pilgrims should gradually increase each day of heat exposure and/ or the walking duration and intensity as tolerated.[56]

CONCLUSION

For pre-participation cardiovascular assessment of the Arbaeen march, PAR-Q+, ePARmed-X+, and the ACSM pre-participation screening algorithm for the general public can be useful tools. Adequate preparation for cardiac emergencies in the field, regulating core body temperature during walking, exercise heat acclimatization before the real march, and following a "progressive transitional phase" for 2-3 months before the ceremony especially for high-risk pilgrims are other important considerations for Arbaeen walking pilgrims. This provides enough time for both cardiovascular adaptation and the monitoring of these pilgrims.

Footnotes

Authorship Contributions

Concept: M.H., S.M., Design: M.H., S.M., Data Collection or Processing: M.H., S.M., Analysis or Interpretation: M.H., S.M., Literature Search: M.H., S.M., Writing: M.H., S.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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REVIEW

DOI: 10.4274/ijca.2025.39358
Int J Cardiovasc Acad 2025;11(3):97-106

Cardiac Toxicity of Cancer Therapies: Mechanisms, Surveillance, and Clinical Implications

Sudeep Edpuganti[1], Divina Mariya Puthooran[1], Tanmay Jape[2], Yogyaa Anand[2], Staisy Mariyam Soju[1]

[1]Tbilisi State Medical University, Faculty of Medicine, Tbilisi, Georgia
[2]Georgian National University, SEU Faculty of Medicine, Tbilisi, Georgia

Abstract

Cardiotoxicity caused by cancer treatments is a growing concern as the survival rate of cancer increases. This review synthesizes the current research on cancer therapy-related cardiac toxicity. A comprehensive literature search was performed in PubMed, Scopus, and Google Scholar (2015-2025). Chemotherapy drugs like anthracyclines cause irreversible myocardial injury via oxidative stress and mitochondrial dysfunction, while trastuzumab causes reversible dysfunction through human epidermal growth factor receptor 2 (HER2) signaling disruption. Radiation can lead to heart disease years later, and immunotherapy sometimes triggers heart inflammation. Surveillance relies on advanced imaging (e.g., global longitudinal strain echocardiography, cardiac magnetic resonance imaging) and biomarkers (troponin, B-type natriuretic peptide), though guidelines from American Society for Clinical Oncology and European Society of Cardiology differ in monitoring frequency and biomarker use. Risk stratification is essential, with high-dose anthracyclines, prior cardiovascular disease, and HER2-targeted therapies posing elevated risks. Primary prevention strategies include dexrazoxane and sodium-glucose cotransporter 2 inhibitors. Secondary prevention uses heart failure therapies. New tools; like artificial intelligence and genetic testing, may soon predict who is at risk and guide personalized care. By balancing cancer treatment success with heart safety, we can improve long-term health for survivors.

Keywords: Cardiotoxicity, cancer therapy, chemotherapy, radiation therapy, heart failure, anthracyclines

INTRODUCTION

Cardiotoxicity refers to a substance's harmful effects on the heart, which can result in cardiomyopathy, heart failure (HF), or a significant reduction in the left ventricular ejection fraction (LVEF).[1] HF, coronary artery disease (CAD), arrhythmias, QT prolongation, arterial hypertension, and peripheral vascular disease are among the cardiovascular (CV) problems that may arise from cancer treatment. Even if the morbidity and mortality of cancer have significantly decreased as a result of early detection and treatment, some of the more recent anti-cancer signaling inhibitors and traditional chemotherapeutics may have CV side effects that affect a patient's quality of life and survival.[2,3] Cardiotoxicity was categorized as mild, moderate, or severe based on the degree of myocardial damage or dysfunction seen in patients during follow-up.[4]

According to 2022 estimates, approximately 20 million individuals were newly diagnosed with cancer globally, and 9.7 million people died from the disease. Around 53.5 million people were living within five years of a cancer diagnosis, reflecting a growing global survivor population. It is estimated that 1 in 5 people will be diagnosed with cancer during their lifetime, with 1 in 9 men and 1 in 12 women dying from it.[5] In the United States, as of January 1, 2025, approximately 1 in every 18 Americans (18.6 million people)

To cite this article: Edpuganti S, Puthooran DM, Jape T, Anand Y, Soju SM. Cardiac Toxicity of Cancer Therapies: Mechanisms, Surveillance, and Clinical Implications. Int J Cardiovasc Acad. 2025;11(3):97-106

Address for Correspondence: Sudeep Edpuganti, Tbilisi State Medical University, Faculty of Medicine, Tbilisi, Georgia
E-mail: edpugantisudeep@gmail.com
ORCID ID: orcid.org/0000-0003-4857-4399

Received: 21.05.2025
Accepted: 07.08.2025
Publication Date: 15.09.2025

was a cancer survivor, a number projected to exceed 22 million by 2035.[6] The discovery of cancer drugs is advancing at a rapid pace, and survival rates are rising. We should focus on preventive strategies and on addressing the CV risks of cancer therapy.[7]

Based on a cohort study of 36,232 adult cancer survivors, ischemic heart disease, stroke, and cardiomyopathy and HF were prevalent in those with significant CV risk factors. Overall, cancer survivors with CVD had a 60% survival rate, while those without CVD had an 81% survival rate ($P < 0.01$).[8] Similarly, a 2019 systematic review (21 studies through 2018) reported that cancer therapy-related cardiac dysfunction (CTRCD) occurred in 9.3-43.8% of patients (pooled incidence ≈21%).[9]

Cardiotoxicity risk and outcomes vary substantially by race and ethnicity. For instance, Black cancer patients have been shown to have approximately 71% higher odds of developing chemotherapy-associated cardiotoxicity than White patients.[10] In a multiracial cohort of patients receiving anthracycline-based chemotherapy, non-Hispanic (NH) Black, Hispanic, and Asian individuals had a significantly higher incidence of cardiotoxicity (16.3%, 14.7%, and 18.2%, respectively), compared to NH White patients (7.2%). Even after adjusting for comorbidities, socioeconomic status, anthracycline dose, and baseline LVEF, NH Black and Hispanic individuals had independently increased risks, with hazard ratios of 2.62 and 2.37, respectively.[11]

Cardio-oncology (CO) is a field that has emerged to assist cancer patients in preventing, managing, and reducing CV disorders, as well as to help weigh the benefits and drawbacks of cancer therapies. Helping patients comprehend the trade-offs between oncologic efficacy and CV risks is crucial.[12]

Aim

This review aims to highlight the growing significance of CO in reducing CV risks among cancer survivors and guiding the creation of holistic, multidisciplinary treatment approaches that maximize CV safety and oncologic efficacy by analyzing the available data. Also, it is important to examine the mechanisms, classification, clinical implications, outcomes, and prevention of cancer-related thrombosis-central venous thrombosis, given its importance in medical practice and research.

Section 1: Literature Search Strategy

A comprehensive search of PubMed, Scopus, and Google Scholar (January 2015-May 2025) was performed. We also added some essential publications that are not within this time frame. Relevant publications were identified using key terms "cardiotoxicity", "cancer therapy", "chemotherapy", "CO", "CTRCD", "CV complications", "HF", "cardiotoxicity outcomes", and "human epidermal growth factor receptor 2 (HER2) inhibition HF". All original research and review articles written in English that involved human or relevant animal models were included.

Section 2: Classification

As is well established, chemotherapy or other concomitant cancer treatments affect the CV system. Delayed cardiotoxic effects, such as those associated with anthracyclines, can manifest many years after therapy, suggesting that patients require long-term vigilance.[13] For example, anthracycline-induced cardiomyopathy may not appear until decades posttherapy,[14] and current guidelines, therefore, recommend extended cardiac monitoring for survivors of anthracycline treatment.[15] The clinical management of these effects follows a specific approach that coordinates time, reversibility, and damage presentation, enabling reasonable anticipation. Cardiac damage is usually classified according to its clinical course as acute or chronic, and either reversible or irreversible, subclinical or symptomatic.

Acute Cardiotoxicity

Acute cardiotoxicity describes heart injury sustained during cancer treatment or within several weeks after treatment. It typically arises rapidly (often within days of therapy) and is usually transient, often reversing after the drug is stopped or with prompt cardiac support.[14] Distinctive features include arrhythmias, pericarditis, or severe left ventricle (LV) systolic dysfunction.[16,17]

Chronic Cardiotoxicity

Chronic cardiotoxicity is described as occurring months to years after the treatment has been completed. It is the consequence of cumulative myocardial injury, which is frequently caused by anthracyclines and trastuzumab.[18,19] As an example, the clinically unnoticeable stages of doxorubicin (DOX)-induced damage can last for years until it manifests as chronic HF, which, depending on dosage and several risk factors, occurs in around 5%-45% of patients.[13,19] Generally, trastuzumab toxicity is less severe, but it can be observed after anthracycline treatment.[19]

Reversible vs. Irreversible Cardiotoxicity

Reversibility is a key factor in assessing cardiac harm. Trastuzumab's effects, such as dysfunction, are generally reversible, and they will resolve after cessation of the drug. Conversely, damage caused by anthracyclines is usually irreversible due to oxidative damage and myocyte death, potentially leading to chronic HF.[20] Knowing these types, helps in deciding whether to suspend therapy or to employ protective measures with angiotensin converting enzyme (ACE) inhibitors and beta-blockers.[20]

Subclinical vs. Symptomatic Cardiotoxicity

Subclinical cardiotoxicity is characterized by the absence of symptoms and the presence of myocardial dysfunction, and it is possible to identify it through speckle-tracking echocardiography. A greater than 15% reduction in global longitudinal strain (GLS) is an indication of early dysfunction, indicated by preserved echocardiographic measures.[21,22] Symptomatic cardiotoxicity manifests as fatigue, dyspnea, and signs of HF. Early detection of subclinical changes helps prevent long-term damage.[23]

Section 3: Mechanisms of Cardiotoxicity

Cancer therapies cause cardiotoxicity via distinct mechanisms: type I (irreversible) from cytokines and type II (reversible).[24] This section discusses several mechanisms associated with cancer therapies:

Chemotherapy

Anthracyclines such as epirubicin, DOX, and daunorubicin are commonly used to treat solid and hematologic cancers. Nevertheless, disruption of sarcomeres, the production of cardiotoxic anthracycline metabolites, the production of reactive oxygen species (ROS) through inhibition of topoisomerase 2β (which triggers cell death pathways and mitochondrial dysfunction), and their transport across the cardiomyocyte membrane may all be contributors to cardiomyocyte damage.[2] Reduced ferritin and increased labile iron result from DOX's disruption of ferritin's IRE. This results in damage to the heart muscle and an increase in ROS. Receptor-interacting serine/threonine-protein kinase 3 is upregulated by DOX. DOX binds and phosphorylates calmodulin kinase II and controls the opening of the mitochondrial permeability transition pore, which causes necroptosis and apoptosis. Deactivating the Top2β gene in mice's hearts reduces DOX-induced cardiac failure, as DOX inhibition of the gene causes ROS buildup, RCD pathway activation, and mitochondrial malfunction.[25-27]

Targeted Therapy

Tumor-targeted agents such as immune checkpoint inhibitors (ICIs), protein kinase inhibitors, and vascular endothelial growth factor inhibitors each carry distinct cardiotoxic risks. Trastuzumab, an anti-HER2 antibody that has markedly improved survival in HER2-positive breast cancer, can disrupt cardiac Erb-B2 receptor tyrosine kinase 2 (ERBB2)/ERBB3 signaling by binding domain IV of the ERBB2 receptor on cardiomyocytes. This interference impairs the heart's stress response, leading to apoptosis, inflammation, microvascular injury, oxidative stress, and interstitial fibrosis.[28-30] Inhibiting neuregulin-1 / HER2 and angiotensin II/AT1 pathways further increases ROS, sensitizing myocytes to additional insults. When given with anthracyclines like DOX, trastuzumab exacerbates Top2B inhibition, accelerating apoptosis and oxidative/nitrative damage; thus, avoiding simultaneous administration reduces heartfailure risk.[28-30]

Proteasome inhibitors (e.g., carfilzomib, bortezomib) induce cardiotoxicity primarily via mitochondrial dysfunction and proteasome overload, triggering apoptosis in cardiomyocytes.[30,31] Notably, the degree of LVEF decline predicts trastuzumab-induced cardiotoxicity (hazard ratio: 2.4; 95% confidence interval: 1.2-6.03; $P = 0.049$), and in 86% of affected patients, dysfunction is eventually reversible.[32]

Radiation Therapy

Radiation induces oxidative stress and chronic inflammation, leading to endothelial dysfunction, leukocyte extravasation, vasodilation, increased permeability, and excessive eicosanoid synthesis. Overproduction of ROS, altered calcium homeostasis, and upregulated nicotinamide adenine dinucleotide phosphate oxidases damage the myocardial capillary network, causing ischemia, cardiomyocyte apoptosis, and fibrosis.[33-37] Ionizing radiation also injures coronary arteries and accelerates atherosclerosis; irreversible DNA damage occurs when intracellular antioxidants are overwhelmed, and suppression of antioxidant enzymes further increases ROS accumulation.[38,39] Ultimately, these processes promote premature CAD in irradiated patients.

Immunotherapy

Cancer immunotherapies, active and passive, include cytokines, monoclonal antibodies, checkpoint inhibitors (e.g., nivolumab, pembrolizumab, ipilimumab), and bispecific T cell engagers. ICIs block cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 or its ligand, unleashing T cell activity against tumors but risking autoimmunity. When checkpoints are inhibited, T cells may attack endothelial cells (causing atherosclerosis or vasculitis) or cardiac / myocardial cells (leading to myocarditis or pericarditis).[40-42] Murine models show that CTLA-4 blockade alone can precipitate myocarditis, and in humans, shared antigens between tumor cells and cardiomyocytes can drive T cell-mediated myocardial infiltration, arrhythmias, and HF.[43-45] The mechanisms of cardiotoxicity from various cancer therapies are summarized in Table 1.

Section 4: Surveillance and Diagnostic Criteria

For accurate diagnosis of the cardiotoxicity of cancer therapies, several imaging techniques and certain biomarkers are used. Risk stratification guides tailored surveillance and management.

Table 1. Definitions and mechanisms of major cancer therapy-induced cardiotoxicities

Agent	Mechanism	Onset	Reversibility	Detection modality	Reference
Anthracyclines	Dose-related myocardial injury via ROS	Acute-chronic (weeks-years)	Often irreversible	LVEF decline on echocardiogram	[2,13,20,25-27,46,47]
HER2-targeted therapy	Inhibition of ERBB2 signalling ↓ in myocyte repair	Early (<6 mo)	Generally reversible	GLS by speckle-tracking echo	[19-22,28-30]
Tyrosine kinase inhibitors	Vascular/endothelial toxicity	Variable (weeks-months)	Variable	Blood pressure, biomarkers	[30,31,52]

↓: Indicates inhibition or downregulation, HER2: Human epidermal growth factor receptor 2, ROS: Reactive oxygen species, LVEF: Left ventricular ejection fraction, GLS: Global longitudinal strain, ERBB2: Erb-B2 receptor tyrosine kinase 2

Imaging

Echocardiography has emerged as an important tool in the diagnosis of cardiotoxicity due to cancer therapies.[46] LVEF is used to detect cardiac dysfunction and remains the mainstay to determine further management of a patient with cardiac dysfunction.[47] LVEF is not very sensitive when it comes to the detection of minute changes in LV function. Cardiotoxicity, characterized by a decrease in LVEF or HF, seems to be best predicted by a 10% to 15% reduction in GLS measured by speckle tracking echocardiography early during therapy. Global radial and circumferential strain measurements are routinely abnormal in late cancer survivors, even when LVEF is normal. However, their therapeutic utility in predicting eventual HF or ventricular dysfunction has not been investigated.[48] The routine imaging modality by which LVEF is determined is 2-dimensional (2D) echocardiography.[47] Small changes in LV contractility are also often overlooked and not detected in calculated 2D LVEF.[46] This loophole can be overcome by implementing stricter regulatory measures.

Over the last decade or so, the evaluation of GLS from speckle-tracking analysis of 2D echocardiography has become a practical and better replacement for LVEF for assessing myocardial function.[47] While 3D echocardiography provides increased precision and robustness, its accessibility is not widespread.[49] The American Society for Clinical Oncology (ASCO) endorses the determination of GLS to be conducted in cancer patients undergoing cardiotoxic therapies.[47] Guidelines direct us to compare the GLS values measured while on chemotherapy with baseline GLS values. A reduction of >15% compared to baseline is considered to be worrisome. A decrease in GLS compared to baseline or a low total GLS value during initial chemotherapy is a sign of an individual who is at high risk of developing chemotherapy-related cardiac dysfunction (CTCRD).[9,46]

Cardiac magnetic resonance (CMR) is the gold standard for detecting edema and fibrosis via T2-weighted short tau inversion recovery and late gadolinium enhancement, and also measuring ventricular volumes and function.[50,51] Additionally, Myocardial T1 mapping employs T1 relaxation times to determine the volume of distribution of gadolinium-based contrast agents, which are used to determine diffuse myocardial fibrosis, in the myocardium. Numerous CMR-based clinical studies have utilized T1 measurements and mapping to examine myocardial remodeling in cancer patients and survivors.[49] Several biomarkers have also been explored, studied, and tested as an alternative to or addition of imaging techniques for the assessment and management of cardiotoxicity.[40]

Biomarkers

High-sensitivity troponin and natriuretic peptide [B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP)] are recommended for early detection and risk stratification in CTCRD (class 1A). Although the specificity of BNP is still debated as it can also be increased without clinical HF, during severe sepsis and septic shock, and has a positive correlation with high sensitivity C-reactive protein (CRP), therefore, its specificity is still questioned.[52] Cardiotoxicity is the main cause of mortality in cancer survivors, after the cancer itself resolves.[53] Table 2 summarizes the modalities and biomarkers.

ASCO/ESC Guidelines for Risk Stratification and Monitoring

CV risk should be stratified based on the level of risk associated with the specific anti-cancer therapy being used, and each patient's CV disease history and risk factors. These suggestions are included in both sets of guidelines. Additionally, the European Society of Cardiology (ESC) guidelines suggest monitoring with 2D transthoracic echocardiography at baseline and every 3 months during anti-HER2 therapy in every single patient, regardless of risk. On the other hand, the prior ASCO guidelines suggest screening only in high-risk patients, and that the physician determines, the frequency based on clinical judgement and patient circumstances.[48] Regarding biomarkers, the ESC guidelines have a recommendation distinct from that of ASCO. According to the ESC, patients who have had prior anthracycline therapy should have their blood cardiac troponins and natriuretic peptides monitored.[54] ASCO states

Table 2: Surveillance modalities and biomarkers

Modality / Biomarker	Utility	Notes	Reference
2D Echocardiography (LVEF)	LV dysfunction detection	Insensitive to small changes	[46,47]
Speckle-Tracking Echocardiography (GLS)	Early dysfunction (≥15% reduction)	Recommended by ASCO; high sensitivity	[21,22,47,48]
3D Echocardiography	Improved precision	Limited accessibility	[49]
Cardiac MRI (T2-STIR, LGE, T1 mapping)	Edema, fibrosis, volumes	Gold standard for tissue characterization	[50,51]
High-sensitivity Troponin	Early myocardial injury	High sensitivity; specificity caveats	[52]
BNP / NT-proBNP	Heart failure risk stratification	Elevated in HF, sepsis; correlates with CRP	[52]

≥: Indicates greater than or equal to, 2D: 2-dimensional, LVEF: Left ventricular ejection fraction, GLS: Global longitudinal strain, T2-STIR: T2-weighted short tau inversion recovery, LGE: Late gadolinium enhancemen, MRI: Magnetic resonance imaging, BNP: ASCO: American Society for Clinical Oncology, HF: Heart failure, CRP: C-reactive protein

that there is still a need for further studies to clarify the role of biomarker assessment during cancer therapy.[8] (See Table 3 for a summary of ASCO vs. ESC guideline recommendations) Additionally, regarding risk stratification, patients who have been treated with high-dose anthracyclines (eg, DOX ≥250 mg/m^2), or low-dose anthracyclines (eg, DOX <250 mg/m^2), in the presence of several CV risk factors like smoking, hypertension, diabetes, dyslipidemia, obesity and compromised cardiac function (low LVEF) are considered to be at an increased risk for developing cardiac toxicity.[8,55,56]

Section 5: Clinical Manifestations and Outcomes

Acute / Early Effects

Cardiac toxicity can manifest during or shortly after treatment. For example, ICIs (e.g., nivolumab, pembrolizumab) can trigger fulminant autoimmune myocarditis, typically presenting early in therapy (median ~34 days).[57-59] Though rare (≈1% incidence), ICI myocarditis carries high mortality (~40-50%). Symptoms often include acute HF and life-threatening arrhythmias. Fluoropyrimidines [5-fluorouracil (5-FU)/capecitabine] classically cause coronary vasospasm and ischemia, leading to anginal chest pain and electrocardiography (ECG) changes mimicking acute coronary syndrome,[57] Acute toxicities may present as:

- Chest pain (angina): Often due to 5-FU-induced coronary vasospasm.[57]
- Palpitations/arrhythmias: Atrial fibrillation (~30%) and ventricular tachyarrhythmias (~27%) have been reported in ICI myocarditis.[58]
- Dyspnea: From acute HF or pulmonary edema (noted in ~5% of 5-FU cases.[57]
- Other signs: Rarely, 5-FU can cause pericarditis (≈1-2% of cases[57]) or mimic acute coronary syndrome on ECG; ICI myocarditis can also present with complete heart block or cardiogenic shock.[58]

Immediate recognition is critical. ICI myocarditis often requires prompt high-dose corticosteroids (per expert guidance), and 5-FU cardiotoxicity may require anti-anginal therapy (nitrates, calcium channel blockers) and discontinuation of the agent.[57,59]

Chronic / Late Effects

Dilated cardiomyopathy and chronic HF typically emerge months to years after treatment.[60] Anthracyclines (e.g., DOX) cause dose-related myocardial injury that usually presents late. Trastuzumab (HER2 therapy) cardiomyopathy often appears

Table 3: Guidelines recommend tailored surveillance based on risk stratification

Parameter	ASCO guidelines (2017)	ESC guidelines (2022)	Reference
Baseline assessment	LVEF, GLS, Troponin	LVEF, GLS, troponin, BNP/NT- proBNP	[8,54]
High-risk patients	Anthracycline ≥ 250 mg/m^2 + CV risk factors	Prior CVD, radiation ≥30 Gy, HER2- targeted therapy	[8,54]
Imaging frequency	Every 3-6 months during therapy	Every three months during anti-HER2 therapy	[8,54]
Biomarkers	Insufficient evidence for routine use	Troponin / BNP monitoring post - anthracycline	[8,54]
Intervention	Start HF therapy if LVEF drops ≥10% or GLS >15%	ACE inhibitors/beta-blockers for LVEF ≤ 50%	[8,54]

ASCO: American Society for Clinical Oncology, ESC: European Society of Cardiology, LVEF: Left ventricular ejection fraction, GLS: Global longitudinal strain, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, CV: Cardiovascular, ACE: Angiotensin converting enzyme, HER2: Human epidermal growth factor receptor 2

during therapy or within the first year and can improve with treatment interruption.[60] Patients may have no early symptoms; later, they develop classic HF. Symptoms of chronic cardiotoxicity include:

• Fatigue and exercise intolerance (reduced activity tolerance), the most common early complaints of HF.

• Conditions such as dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea (shortness of breath on exertion or lying flat) are important considerations in patient assessment.

• Peripheral edema and weight gain (ankle/leg swelling, bloating).

• Persistent cough or wheezing (due to pulmonary congestion).

Patients developing late cardiotoxicity often have a severely impaired prognosis.[60] Some improve substantially with standard HF therapy (ACE inhibitors, beta-blockers, etc.) For example, one series showed recovery of function in many patients if treated early.[61] However, others progress to chronic HF requiring lifelong management. The data on outcomes data suggest a worse prognosis for those with cancer therapy-related cardiomyopathy: "patients experiencing cardiotoxicity develop HF months to years after therapy, and have a severely impaired CV prognosis."[60]

Disparities: Notably, some populations show higher late cardiotoxicity rates. For example, Black women on HER2-targeted breast cancer therapy had significantly higher 1-year cardiotoxicity incidence (24%) than White women (7%).[62] This suggests enhanced surveillance may be warranted in higher-risk groups.

Outcomes: Many patients respond to guideline-directed HF therapies.[61] However, persistent dysfunction can still lead to morbidity and mortality. Even "recovered" patients remain at risk for recurrence of dysfunction. ICI myocarditis mortality has been reported around 40-50%.[59] Long-term follow-up with routine echocardiography, ECGs, and biomarkers (troponin, BNP) in collaboration with CO is recommended for all survivors.[60]

Section 6: Management and Prevention

Standard chemotherapeutic treatments as well as targeted treatments are associated with a greater risk of heart damage, such as HF and LV dysfunction. High doses of DOX and other anthracyclines are said to increase the risk of HF. However, studies have shown that therapies such as dexrazoxane, ACE inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and early detection of LV dysfunction can effectively reduce anthracycline-induced toxicity while preserving chemotherapy efficacy.[63]

Primary Prevention

Numerous medications have been investigated for their possible cardioprotective benefits during cancer treatment. Primary prevention includes dexrazoxane (10 mg/m^2 per 1 mg/m^2 DOX), and emerging agents such as SGLT2 inhibitors. Dexrazoxane is food and drug administration approved for anthracycline cardioprotection, though its use is debated (concerns include potential interference with chemotherapy efficacy and reported secondary malignancy risk in pediatric studies). SGLT2 inhibitors, which reduce oxidative stress and inflammation,[64-68] now have a class I recommendation in HF guidelines.[69] Adding to this, early detection of cardiac injury through biomarkers like troponins and natriuretic peptides, and imaging techniques such as echocardiography with strain imaging, is crucial during and after treatment.[63]

Secondary Prevention

For established cardiotoxicity, standard HF therapies are indicated. ACE inhibitors and β-blockers (classical HF therapy) are proven treatments for CTRCD.[70] Whereas statins and aldosterone antagonists remain under investigation (awaiting more trial evidence).[71] In practice, HF therapies (ACEi, β-blockers, statins, aldosterone antagonists) should be initiated when LVEF falls by ≥10% or GLS declines by >15% from baseline.[70] Notably, this recommendation applies even in the absence of elevated biomarkers. However, biomarkers should be interpreted with caution: troponin rises are very sensitive but not highly specific and over-reliance on biomarker elevations may lead to unnecessary interventions.[70]

Multidisciplinary Care

CO is an emerging subspecialty that addresses the CV toxicities in cancer patients. There is a need for equitable CO care across community and academic settings, and there is a suggestion to establish protocols and integrate telehealth to alleviate disparities.[72] Researchers have highlighted the gaps in awareness of instructions and training among healthcare professionals, and they suggest the implementation of national educational initiatives.[73] An integrated model combining CO rehabilitation with traditional cancer rehabilitation was proposed in 2023. The model highlights the importance of early intervention to address CV, physical, and psychological impairments simultaneously.[74] This combined approach could increase long-term survival. Drawing a parallel, researchers also recommend establishing an interdisciplinary CO team that combines artificial intelligence (AI) to generate precision-based risk analysis, early cardiotoxicity detection, and targeted interventions, promoting health equity.[75] Table 4 summarizes the prevention and management strategies.

Table 4: Prevention and management strategies

Strategy	Agents / Actions	Level of evidence / notes	Reference
Primary prevention	Dexrazoxane; SGLT2 inhibitors; imaging/biomarker surveillance	Dexrazoxane FDA-approved; SGLT2 class I in HF; early detection via troponin / BNP / GLS	[63-69]
Secondary prevention	ACE inhibitors; β-blockers; statins; aldosterone antagonists	Initiate if LVEF ↓≥10% or GLS ↓>15% from baseline	[70]
Multidisciplinary care	Integrated cardio-oncology teams; telehealth; rehabilitation programs	Improves equity; early intervention	[72-74]

↓: Indicates decrease, SGLT2: FDA: Food and drug administration, HF: Heart failure, BNP: B-type natriuretic peptide, GLS: Global longitudinal strain, LVEF: Left ventricular ejection fraction

Section 7: Future Directions

However, it is critical that AI models be trained on diverse, representative datasets to prevent algorithmic bias and ensure equitable benefit.[76] Blending AI and genomics into CO can greatly improve the management and avoidance of cardiac toxicity in patients undergoing treatments for cancer. AI has shown great potential in improving risk assessment and clinical decision-making, although there are certain drawbacks when it comes to clinical use and data consistency.[77] In addition, newer studies have highlighted the use of machine learning (ML) algorithms to analyze complex patient data, providing insight into cardiotoxicity mechanisms and treatment strategies.[78] For example, an AI model called AI-CTRCD was developed to predict chemotherapy-related cardiac dysfunction risk from baseline ECGs.[79] ML algorithms trained on standard echocardiographic strain measurements have been used to anticipate early cardiac injury in pediatric cancer survivors.[80] Emerging ML approaches have also identified genetic variants associated with anthracycline cardiotoxicity in childhood cancer survivors, informing integrated risk models.[81] Emerging research encourages a more comprehensive approach to risk assessment, incorporating new biomarkers and genomics into CV evaluation may personalize patient care.[82] In this spirit, emerging approaches (e.g., genomics-driven risk scores) could further refine risk stratification, but these require prospective validation in large studies.[81,83] Protein corona testing, which analyzes the layer of blood proteins that adsorb onto nanoparticles, is an AI-driven, non-invasive biomarker method to detect patterns of proteins linked to cardiotoxicity.[84] This novel approach may enable even earlier detection of cardiac injury and better outcomes. Likewise, studies of multiple blood biomarkers highlight that tracking changes in a panel of markers (not just troponin or BNP), including ultrasensitive troponin I, high-sensitivity CRP, NT-proBNP, growth differentiation factor 15 (GDF-15), myeloperoxidase, placental growth factor, soluble fms-like tyrosine kinase-1, and galectin-3 can improve risk prediction.[76,85] Some recent work emphasizes the genetic underpinnings of anthracycline cardiomyopathy and calls for large-scale genomic cohorts to refine risk classification.[82] Future research should focus on assembling large multiethnic genomic cohorts, conducting prospective AI/ML validation trials, identifying novel biomarkers beyond troponin/BNP, and explicitly designing inclusive datasets to mitigate bias.[76,83]

CONCLUSION

Cancer therapies save lives but impose significant CV risks that compromise long-term survivorship. To mitigate these threats, collaborative efforts must prioritize early detection, personalized prevention, and equitable care.

For clinicians:

- Adopt advanced surveillance: replace routine LVEF with speckle-tracking echocardiography (GLS); a >15% GLS decline signals subclinical dysfunction.
- Stratify risks proactively: consider racial disparities (e.g., 2-3× higher cardiotoxicity in Black/Hispanic patients) and prior CVD history.
- Intervene early: initiate dexrazoxane for high-dose anthracyclines; start ACEi/β-blockers at GLS/LVEF deterioration (not wait for symptoms).

For researchers:

- Resolve biomarker limitations: validate multi-marker panels (troponin + GDF-15/galectin-3) to improve specificity.

Address disparities: investigate socioeconomic/genetic drivers of racial inequities in cardiotoxicity.

- Translate AI tools: Prospectively test ECG- or imaging-based algorithms for real-world risk prediction.

For Policy-Makers:

- Fund integrated CO programs: bridge institutional silos between cardiology, oncology, and rehabilitation services.
- Ensure equitable access: mandate insurance coverage for GLS echocardiography and cardiac MRI across care settings.
- Support survivor longevity: implement lifelong cardiac monitoring for high-risk groups (e.g., pediatric cancer survivors, radiation recipients).

Surviving cancer should not entail enduring preventable heart disease. By embedding CV protection into oncology practice through vigilant monitoring, targeted therapies, and inclusive research we can secure both quantity and quality of life for cancer survivors.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.83702
Int J Cardiovasc Acad 2025;11(3):107-114

Coenzyme Q10 in Prevention of Contrast-induced Nephropathy in Patients with Acute Coronary Syndrome Undergoing Coronary Angiography

Ramy El-Sheikh, Shehab El Etriby, Islam Bastawy, Nireen Okasha

Department of Cardiology, Ain Shams University Faculty of Medicine, Cairo, Egypt

Abstract

Background and Aim: Contrast-induced nephropathy (CIN) is a serious complication of coronary angiography (CA), associated with increased morbidity and mortality. Coenzyme Q10 (CoQ10), an endogenous antioxidant, has shown promise in mitigating oxidative renal injury. This study investigated CoQ10's protective effect against CIN in acute coronary syndrome (ACS) cases undergoing CA.

Materials and Methods: In a prospective randomized clinical trial (registration number: NCT06429345, date: 19.03.2024), 300 ACS cases were enrolled between March and September 2024. Cases were randomized into a CoQ10 group (n=200) receiving oral CoQ10 and a control group (n=100) receiving standard care. Serum creatinine, estimated glomerular filtration rate (eGFR), and urine output were monitored for three days post-procedure. CIN was defined as a ≥0.5 mg/dL or ≥25% increase in serum creatinine or a ≥25% decline in eGFR within 48 hours.

Results: CIN incidence was significantly lower in the CoQ10 group (9%) compared to controls (21%) ($P = 0.004$). Postoperative serum creatinine levels were markedly lower, and eGFR notably higher, in the CoQ10 group on days two and three ($P < 0.01$). Multivariate logistic regression identified high body mass index [odds ratio (OR) =6.976, $P < 0.001$], chronic kidney disease (OR =6.288, $P = 0.001$), and balloon dilatation (OR =3.116, $P = 0.012$) as independent predictors of CIN.

Conclusion: CoQ10 supplementation significantly reduced CIN incidence in ACS cases undergoing CA. CoQ10's antioxidative and anti-inflammatory properties support its potential as a safe adjunctive therapy for CIN prevention.

Keywords: Contrast induced nephropathy, acute coronary syndrome, coenzyme Q10

INTRODUCTION

Acute kidney injury (AKI) is a major complication following cardiac catheterization, associated with prolonged hospitalization and increased mortality. Beyond its immediate impact, AKI acts as an independent prognostic risk factor, contributing to the development of atrial fibrillation, progression of chronic kidney disease (CKD), and a higher risk of myocardial infarction or the need for dialysis after discharge. A specific subset, contrast-induced (CI)-AKI, is defined by at least a 25% increase in serum creatinine or a rise of 0.5 mg/dL within 48-72 hours of contrast exposure.[1]

The development of CI-AKI is multifactorial, with predisposing factors such as CKD, older age, inadequate hydration, and comorbidities like diabetes, heart failure, and peripheral vascular disease playing key roles. Procedural risks-including nephrotoxic contrast exposure, intraoperative hypotension,

To cite this article: El-Sheikh R, El Etriby S, Bastawy I, Okasha N. Coenzyme Q10 in prevention of contrast-induced nephropathy in patients with acute coronary syndrome undergoing coronary angiography. Int J Cardiovasc Acad. 2025;11(3):107-114

Address for Correspondence: Ramy El-Sheikh MD, Department of Cardiology, Ain Shams University Faculty of Medicine, Cairo, Egypt
E-mail: 96ramymohamed22@gmail.com
ORCID ID: orcid.org/0009-0005-3714-3480

Received: 30.04.2025
Accepted: 30.06.2025
Epub: 14.07.2025
Publication Date: 15.09.2025

and blood loss-as well as postprocedural factors like anemia and prolonged intensive care unit stay, further contribute to the incidence of AKI.[2] Prevention strategies during percutaneous coronary intervention (PCI) include minimizing contrast volume, optimizing hydration, and using adjunctive pharmacotherapies such as N-acetylcysteine, statins, and renin-angiotensin-aldosterone inhibitors though with variable success.[3]

The pathophysiology of CI-AKI involves medullary ischemia, reduced nitric oxide availability, increased oxidative stress, and direct cytotoxicity to renal cells. Coenzyme Q10 (CoQ10), an endogenous antioxidant and anti-inflammatory molecule, has shown promise in mitigating oxidative and inflammatory renal injury. Emerging evidence suggests that CoQ10 supplementation offers organ-protective effects, potentially reducing the risk of CI-AKI, particularly when used alongside saline hydration in high-risk cardiac cases.[4]

This study aims to investigate the potential protective effect of CoQ10 against contrast-induced nephropathy (CIN) in acute coronary syndrome (ACS) cases undergoing coronary angiography (CA).

METHODS

This prospective randomized clinical trial (registration number: NCT06429345, date: 19.03.2024) was conducted at Ain Shams University Hospitals from March 1st to September 1st, 2024, and included 300 patients who presented with ACS, sample size calculation was performed based on a previous study involving 150 patients, which showed an approximate CIN incidence of 22% in the control group and 7% in the CoQ10 group.[5] Using these proportions, power analysis and sample size 15 program for sample size calculation was used setting power at 80% and an alpha level of 0.05 required a minimum of 168 patients to detect a statistically significant difference. To accommodate potential dropouts and missing data, we increased the total number to 300, using a 2:1 randomization ratio to obtain more experience and safety data for the CoQ10 group. Ethical approval was obtained from the Ethical Committee at Ain Shams University prior to initiating the research (approval no.: MS70/2024, date: 05.02.2025). Informed written consent was obtained from all participants, ensuring adequate privacy and confidentiality.

Randomization and Blinding of Patients

Methods of randomization: Patients were randomly assigned to either the CoQ10-treated group or the control group in a 2:1 ratio using the Research Randomizer software (https://www.randomizer.org/). To ensure allocation concealment and minimize selection bias, sequentially numbered, opaque, sealed envelopes were used. The envelopes were prepared in advance by an independent researcher not involved in patient recruitment, intervention, or outcome assessment. Study group (n=200): CoQ10 was administered orally at a dose of 400 mg before catheterization, followed by 200 mg twice daily for three consecutive days post-procedure, This dosing regimen follows the protocol used in a recent randomized clinical trial by Ahmadimoghaddam et al.[6] which reported a significant reduction in the incidence of CIN in ST elevation myocardial infarction (STEMI) patients undergoing primary PCI.

Additionally, intravenous normal saline hydration was provided prior to angiography for patients who did not require immediate intervention. Control group (n=100): cases received standard care, including intravenous saline hydration, and were administered an oral placebo capsule identical in appearance to the CoQ10 capsule to maintain blinding. A 2:1 allocation ratio was intentionally chosen to allow for more extensive evaluation of the safety and potential efficacy of CoQ10. Also, it allowed us to gain greater clinical experience with the active intervention and to improve the estimation of potential adverse events and variability within the treatment group.

1.Pre-catheterization phase:

Inclusion criteria specified patients aged ≥18 years with characteristics of ACS. Exclusion criteria included cases of renal transplants, end-stage renal disease requiring dialysis, peri-procedural bleeding, cardiogenic shock, or patients taking nephrotoxic medications such as aminoglycosides, amphotericin B, vancomycin, non-steroidal anti-inflammatory drugs (NSAIDs), cyclosporine, and tacrolimus. Patients with baseline renal impairment, including CKD stages 1-4, were included. This approach was intended to reflect the real-world clinical population at risk of CIN.

Detailed patient histories were recorded, including demographics, relevant risk factors, current pharmacologic therapies, and results of systemic and localized clinical assessments, with particular emphasis on chest pain characteristics. Electrocardiogram records, cardiac enzyme levels, random blood sugar, complete blood count, serum creatinine, urine output, estimated glomerular filtration rate (eGFR), and transthoracic echocardiography were evaluated. Left ventricular ejection fraction was assessed using the 2D Simpson method. Serum creatinine was measured using a standardized enzymatic method in the hospital's central laboratory, which undergoes regular internal quality control and external calibration procedures. eGFR was calculated using the CKD epidemiology collaboration equation. All laboratory personnel conducting the biochemical analyses were blinded to patient group assignments to minimize measurement bias.

Treatment was initiated immediately with appropriate medications, including antiplatelets, anticoagulants, nitrates, and beta-blockers. Emergency angiography was performed without delay in cases with ongoing ST-segment elevation (STE)

or non-STE (NSTE)-ACS accompanied by very high-risk criteria. High-risk NSTE-ACS cases were scheduled for early invasive intervention within 24 hours, while those with unstable angina received inpatient invasive assessment during hospitalization.

Additionally, intravenous normal saline hydration was provided prior to angiography in cases for whom immediate intervention was not required.

2.Intervention phase (catheterization):

CA was performed by an expert interventional cardiologist using the same type of contrast media, with the volume limited to 1-2 mL/kg to account for the iodine dose.

3.Post-catheterization:

All patients were admitted to the coronary care unit for monitoring and follow-up. Serum creatinine, eGFR, hemoglobin, and urine output (mL/kg/h) were assessed for three days post-catheterization. CIN was defined as either a ≥25% increase in serum creatinine from baseline, or a ≥25% decline in eGFR within 48 hours post-procedure. After catheterization, participants in the study group continued receiving 200 mg of CoQ10 orally twice daily for three days. Any side effects of CoQ10, such as nausea or skin rashes, were managed with appropriate antiemetic or antiallergic medications.

Statistical Analysis

The collected data were coded and entered into IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA), for statistical analysis. Shapiro-Wilk test was used to assess the distribution of the quantitative variables. Quantitative variables were expressed as mean ± standard deviation and range, when parametric, and median with interquartile range when non-parametric, whereas categorical variables were summarized as frequencies and percentages. Group comparisons for categorical variables were performed using the chi-square test or Fisher's exact test when applicable. Depending on the distribution pattern, continuous variables were analyzed using either the independent samples t-test (for normal distribution) or the Mann-Whitney U test (for non-normal distribution). Comparisons between more than two groups with non-parametric data were made using the Kruskal-Wallis test. The 2:1 randomization ratio was taken into account by using statistical tests that are robust to unequal group sizes, ensuring valid intergroup comparisons. A 95% confidence interval (CI) was calculated for key outcomes to reflect estimate precision. A *P*-value <0.05 was considered statistically significant. Also, Bonferroni correction was applied for multiple comparisons to control the family-wise error rate. Adjusted *P*-values were reported where applicable. For logistic regression analysis, variables included in the multivariate model were selected based on statistical significance in univariate analysis, using a Bonferroni-adjusted *P*-value threshold of less than 0.01 to account for multiple testing. This conservative approach was adopted to minimize false-positive findings. Multicollinearity was assessed using variance inflation factors (VIF), with all included predictors demonstrating acceptable VIF values (<2).

RESULTS

Baseline Demographic Data Characteristics and Risk Factors

There was no statistically significant difference between the groups in terms of age, body mass index (BMI), sex, smoking status, and ACS type [non-STEMI (NSTEMI) vs. STEMI]. In addition, the prevalence of baseline comorbidities and cardiovascular risk factors was comparable between the two groups (Table 1).

Laboratory Investigations and Vital Data

No statistically significant variation was observed between the two groups with regard to baseline laboratory parameters prior to catheterization (including serum creatinine, eGFR). Additionally, intraoperative contrast volume and access route (femoral or radial, stenting, balloon dilatation, stent length and size, or procedure time) were comparable between the two groups (Table 2).

Description of Postoperative Serum Creatinine and eGFR

The serum creatinine levels on the three consecutive postoperative days were markedly lower in the CoQ10-treated group compared to controls, with a *P*-value of 0.0002 on day 1 and <0.0001 on both days 2 and 3. Alternatively, the eGFR on the first postoperative day did not differ notably between the two groups. However, on days two and three, eGFR was notably higher in the CoQ10-treated group compared to the placebo controls, with *P*-values of 0.006 and 0.002, respectively (Table 3).

Postoperative Incidence of CIN

The CoQ10-treated group had a significantly lower incidence of CIN compared to the control (placebo) group ($P = 0.004$) (Figure 1).

Incidence of (CIN) in Relation to Demographic Data, Patient Characteristics and Comorbidities

No statistically significant differences were found between the CIN and no CIN groups regarding age, gender, smoking status, or comorbidities. In contrast, the CIN group showed a significantly higher BMI, with a mean difference of 2.42 kg/m² (95% CI: 1.12-3.72; $P = 0.0002$; Bonferroni-adjusted $P = 0.008$), as well as a significantly greater prevalence of CKD ($P = 0.0057$; Bonferroni-adjusted $P = 0.008$) (Table 4).

Table 1: Comparison of baseline demographics, clinical characteristics and comorbidities between the studied groups

		Study G	Control G	Difference	Test value	*P*-value
		No =200	No =100	Mean (95% CI)		
Age	Mean ± SD	58.42±9.92	56.99±11.82	1.43 (1.12-3.98)	1.099•	0.273
	Range	30-84	31-92			
Sex	Female	52 (26%)	20 (20%)	-	1.316#	0.251
	Male	148 (74%)	80 (80%)			
BMI	Mean ± SD	28.47±2.46	29.19±4.91	0.72 (0.12-1.56)	-1.704•	0.089
	Range	23.39-36.51	19.69-47.88			
Smoking	No	83 (41.5%)	41 (41%)	-	0.007#	0.934
	Yes	117 (58.5%)	59 (59%)			
Type of ACS	NSTEMI	53 (26.5%)	31 (31.0%)	-	0.670*	0.413
	STEMI	147 (73.5%)	69 (69.0%)			
HTN	No	88 (44%)	48 (48%)	-	0.430*	0.512
	Yes	112 (56%)	52 (52%)			
Diabetes	No	106 (53%)	48 (48%)	-	0.667*	0.414
	Yes	94 (47%)	52 (52%)			
CKD	No	190 (95%)	91 (91%)	-	1.798*	0.180
	Yes	10 (5%)	9 (9%)			

*: Statically significant, #: Chi-square test, •: Independent t-test, BMI: Body mass index, ACS: Acute coronary syndrome, HTN: Hypertension, CKD: Chronic kidney disease, CI: Confidence interval, SD: Standard deviation, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction

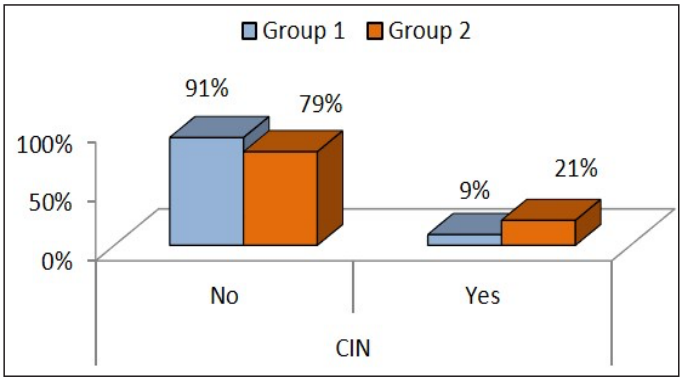

Figure 1: Comparison between study coenzyme treated group 1 and control placebo group 2 regarding postoperative CIN of the studied patients.

CIN: Contrast-induced nephropath

Univariate and Multivariate Logistic Regression Analysis of Factors Associated with the Incidence of CIN Among the Studied Cases

The univariate logistic regression analysis revealed a substantial increase in the occurrence of CIN among cases with high BMI and CKD, with *P*-values of <0.001 and 0.003, respectively. In the multivariate logistic regression analysis, BMI >31.2 kg/m² emerged as the most significant independent predictor of CIN, with an adjusted OR of 4.831 (95% CI: 2.249-10.375, $P < 0.001$). CKD was also significantly associated with CIN (adjusted OR: 2.700, 95% CI: 1.171-6.225, $P = 0.020$) (Table 5).

DISCUSSION

In this randomized clinical trial involving 300 CA procedures, CIN developed in 39 patients, representing 13% of the cohort. CIN was defined by an absolute increase in serum creatinine of ≥0.5 mg/dL, a relative increase of ≥25% from baseline, or a decrease of ≥25% in eGFR over 48 hours. The controls had a CIN incidence of 21% (21 out of 100 cases), whereas the CoQ10-treated group had a significantly lower incidence of 9% (18 out of 200 cases) ($P = 0.004$).

Among populations with minimal predisposing risk factors, the incidence of CIN is estimated to vary between 0.6% and 2.3%. Among cases requiring PCI during an acute myocardial infarction, the incidence has been reported to rise to 19% and to vary between 4.4% and 28% in other studies.[7,8] Previous clinical trials have documented a postoperative CIN incidence ranging from 13.1% to 30.3%.[9,10]

The variation in CIN incidence across studies can be attributed to differences in risk factors, contrast media type and volume, and CIN definitions. A recent study using a similar CIN definition reported an incidence of 14%,[6] while another study that defined CIN solely based on postoperative increases in serum creatinine reported a lower incidence of 10.7%.[9] High CIN rates following PCI, particularly primary PCI, are often linked to hemodynamic instability and inadequate prophylaxis.[11]

Our study found no notable variations in preoperative basal creatinine levels, demographic data, Killip classification, or contrast media between the control and CoQ10-treated

groups. The observed intergroup variation in postoperative creatinine and eGFR suggests a potential beneficial impact of CoQ10 administration. Specifically, the treated group showed a significantly lower incidence of CIN ($P = 0.004$), as evidenced by lower postoperative creatinine levels and higher eGFR. These findings are consistent with previous research,[12] which also identified changes in serum creatinine ≥0.1 mg/dL and decreases in eGFR ≤1.1 mL/min/1.73 m² as strong independent predictors of CIN. Our results align with these observations and further support the potential of CoQ10 in mitigating contrast-induced renal dysfunction.

The renal impairment in CIN cases is explained by the direct toxic effect of the contrast media, the associated pro-inflammatory effects, the greater reactive oxygen species (ROS) generation and the frequent hemodynamic instability.[13,14]

Table 2: Comparison of pre-operative laboratory investigations and operative data between the studied groups

		Study G	Control G	Difference	Test value	*P*-value
		No =200	No =100	Mean (95% CI)		
Preoperative serum creatinine	Mean ± SD	0.87±0.28	0.89±0.29	0.02 (0.05-0.09)	-0.611•	0.542
	Range	0.32-2.22	0.5-1.8			
Preoperative GFR	Mean ± SD	93.62±27.63	99.12±34.46	5.5 (-1.75-12.748)	-1.491•	0.137
	Range	29.5-163.2	39.8-194			
Contrast volume	Median (IQR)	200 (150-210)	200 (10-255)	3.65 (-14.515-21.82)	-0.094≠	0.925
	Range	50-350	50-350			
Access	Femoral	195 (97.5%)	97 (97%)	-	0.064#	0.800
	Radial	5 (2.5%)	3 (3%)			
Stenting	No	11 (5.5%)	7 (7%)	-	0.266#	0.606
	Yes	189 (94.5%)	93 (93%)			
Balloon dilatation	No	83 (41.5%)	35 (35%)	-	1.180#	0.277
	Yes	117 (58.5%)	65 (65%)			
Stent size	Mean ± SD	2.97±0.41	3.06±0.29	0.09 (0.00-0.18)	-1.955•	0.052
	Range	1.5-3.5	2.5-3.5			
Stent length	Mean ± SD	25.93±6.9	26.71±7.06	0.78 (-0.89-2.45)	-0.913•	0.362
	Range	12-48	18-48			
Procedure time	Median (IQR)	28 (22-37.5)	28 (22-30)	0.475 (-2.894-3.844)	-0.347≠	0.729
	Range	10-70	10-70			

#: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test, GFR: Glomerular filtration rate, SD: Standard deviation, IQR: Interquartile range, CI: Confidence interval

Table 3: Comparison of postoperative serum creatinine and eGFR between the studied groups

			Study G	Control G	Difference	Test value	*P*-value
			No =200	No =100	Mean (95% CI)		
Serum creatinine	**1 day**	**Mean ± SD**	0.88±0.31	1.04±0.37	0.16 (-0.08-0.24)	-3.833•	0.0002*
		Range	0.33-2.15	0.6-2.5			
	2 days	**Mean ± SD**	0.91±0.36	1.11±0.47	0.2 (-0.10-0.29)	-4.134•	<0.0001*
		Range	0.4-2.49	0.5-2.9			
	3 days	**Mean ± SD**	0.93±0.38	1.16±0.47	0.23 (-0.13-0.32)	-4.552•	<0.0001*
		Range	0.3-2.3	0.6-2.6			
eGFR	**1 day**	**Mean ± SD**	89.83±23.26	84.64±27.46	5.19 (0.77-11.15)	1.714•	0.088
		Range	32-136	29-147.6			
	2 days	**Mean ± SD**	90.35±25.53	81.38±28.35	8.97 (-2.58-15.36)	2.766•	0.006*
		Range	28-180.72	26.5-148			
	3 days	**Mean ± SD**	88.51±23.83	78.91±29.01	9.6 (-3.41-15.78)	3.055•	0.002*
		Range	27-129	25.5-160.2			

*: Statically significant. •: Independent t-test, CI: Confidence interval, eGFR: Estimated glomerular filtration rate, SD: Standard deviation

Table 4: Relation of CIN Incidence to demographic data and patient characteristics and comorbidities

		CIN		Difference (95% CI)	Test value	*P*-value	Adjusted *P*-value (Bonferroni)
		No CIN (No =261)	CIN (No =39)				
Age	**Mean ± SD**	57.54±10.34	60.64±11.92	3.1 (-0.47-6.67)	-1.713•	0.088	0.704
	Range	30-84	36-92				
Sex	**Female**	58 (22.2%)	14 (35.9%)	-	3.479#	0.062	0.496
	Male	203 (77.8%)	25 (64.1%)				
BMI	**Mean ± SD**	28.39±2.81	30.81±6.02	2.42 (1.27-3.57)	-4.152•	0.0002*	**0.008***
	Range	19.69-42.97	21.5-47.88				
Type of ACS	**NSTEMI** **STEMI**	75 (28.7%) 186 (71.3%)	9 (23.1%) 30 (76.9%)	-	0.539*	0.463	1.000
HTN	**No**	117 (44.8%)	19 (48.7%)	-	0.207*	0.649	1.000
	Yes	144 (55.2%)	20 (51.3%)				
Diabetes	**No**	136 (52.1%)	18 (46.2%)	-	0.481*	0.488	1.000
	Yes	125 (47.9%)	21 (53.8%)				
CKD	**No**	249 (95.4%)	32 (82.1%)	-	10.195*	0.0057*	**0.008***
	Yes	12 (4.6%)	7 (17.9%)				
Balloon dilatation	**No**	110 (42.1%)	8 (20.8%)	-	6.654	0.010*	0.080
	Yes	151 (57.9%)	31 (79.5%)				

*: Statically significant, #: Chi-square test, •: Independent t-test, ACS: Acute coronary syndrome, HTN: Hypertension, CKD: Chronic kidney disease, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, CIN: Contrast-induced nephropath, CI: Confidence interval

Table 5: Predictors of CIN by logistic regression

	Univariate				Multivariate				VIF
	P-value	OR	95% CI for OR		*P*-value	OR	95% CI for OR		
			Lower	Upper			Lower	Upper	
BMI >31.2	<0.001*	5.000	2.358	10.604	<0.001*	4.831	2.249	10.375	1.001
CKD	0.003	4.539	1.666	12.365	0.020	2.700	1.171	6.225	1.001

*: Statically significant, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, VIF: Variable inflation factor, CKD: Chronic kidney disease

The protective effects of CoQ10 have been well-documented in several studies. In one trial involving 150 cases with coronary heart disease undergoing elective cardiac catheterization, the combination of CoQ10 and trimetazidine markedly reduced the incidence of CIN to 6.67% compared to 21.3% in the placebo group.[5] Similarly, a 2023 study involving 153 cases with STEMI found that CoQ10, used alongside saline hydration, decreased CIN incidence to 8% compared to 20% in the controls.[6] CoQ10's nephroprotective effect is primarily ascribed to its antioxidative and anti-inflammatory effect.[4]

CoQ10 counteracts the adverse effects of contrast media by mitigating direct cytotoxicity and abnormal energy metabolism caused by impaired mitochondrial enzyme activity.[15] As a crucial component of the mitochondrial respiratory chain, CoQ10 facilitates adenosine triphosphate synthesis through oxidative phosphorylation. Furthermore, contrast media generates ROS, leading to oxidative stress and decreased antioxidant enzyme activity.[15] CoQ10 helps maintain redox balance and regulates ROS generation, thereby protecting cells from oxidative damage.[16] Additionally, CoQ10 elevates the total antioxidant capacity in kidney tissue.[17]

Contrast media also induce renal interstitial inflammation by increasing immune cell migration and cytokine accumulation, which triggers systemic inflammation.[14] CoQ10 has demonstrated anti-inflammatory effects and regulates lysosomal function.[18] Furthermore, contrast media alter renal hemodynamics by increasing vasoconstrictors (e.g., renin, angiotensin, aldosterone, endothelin) and decreasing vasodilators (e.g., nitric oxide, prostacyclin), leading to medullary hypoxia. CoQ10 improves vasoactive hormone balance.[13,19]

Our findings align with previous research suggesting CoQ10's renal protective role against various forms of AKI, including those induced by drugs (e.g., NSAIDs),[20] contrast media,[5] sepsis,[21] and ischemia-reperfusion injury.[22]

Given the association between CIN and adverse outcomes in hospitalized cases, several predictive scoring systems have been developed to identify individuals at heightened risk. In the present study, the majority of variables included in the Mehran risk score-such as age, hypotension, cardiovascular comorbidities, diabetes mellitus, anemia, contrast volume, baseline serum creatinine, and a history of renal impairment-were assessed. No substantial differences were found between the two groups with respect to any of these parameters.[23]

Elevated baseline serum creatinine levels (defined as ≥1 mg/dL in females and ≥1.3 mg/dL in males) have been described as clinically notable risk factors for CIN.[24] However, the univariate and multivariate logistic regression analysis in our study did not detect basal preoperative creatinine as a risk factor. This contradiction may be attributed to the lower basal values in the cases selected for our study where the means were 0.87±0.28 in the study group versus 0.89±0.29 in controls, $P = 0.542$. Several studies have emphasized that serum creatinine alone is an inadequate and insensitive marker of renal function, and that CIN may still develop in cases without established CKD.[25]

In our analysis, both elevated BMI and CKD demonstrated significant associations with the development of CIN. These findings align with prior research highlighting obesity and renal dysfunction as key risk factors for CIN. High BMI, often reflective of underlying atherosclerosis, dyslipidemia, and metabolic syndrome, may exacerbate renal susceptibility to contrast-induced injury.[26] Similarly, pre-existing CKD, particularly when accompanied by elevated blood urea nitrogen, has been consistently linked to increased CIN risk.[10] Notably, in the multivariate model, BMI emerged as the most powerful independent predictor of CIN, underscoring the impact of metabolic factors in renal outcomes following contrast exposure.

Interestingly, contrast media and diabetes were not significant risk factors in our study, despite 53.8% of CIN cases being in diabetic individuals. This may be attributed to pre- and post-contrast media intravenous hydration, which mitigates the impact of contrast doses and prevents dehydration in diabetic cases.[26]

In the analysis of ACS types, differentiating between STEMI and NSTEMI, there were no notable variations between the control and treatment groups or between CIN and non-CIN cases.[27] This observation suggests that the risk of CIN is comparable in both STEMI and NSTEMI cases. This finding aligns with a study involving 1,041 ACS cases, which reported no notable variations in CIN incidence between STEMI and NSTEMI groups.[28]

These results contrast with some studies that propose STEMI is associated with a higher CIN risk due to factors such as larger contrast volumes and the urgency of immediate revascularization.[9,29]

Short-term follow-up in our study, showed no poor intrahospital outcomes, with no need for dialysis or reported mortality. However, CIN outcomes vary widely in the literature, with reports ranging from renal function recovery within 10 to 14 days to higher rates of dialysis and mortality. This variability highlights the critical need for ongoing research aimed at elucidating the underlying mechanisms of CIN and developing strategies to reduce its associated risks.[30,31]

Study Limitations

This study has several limitations. First, it was conducted at a single center, which may limit the generalizability of the findings to broader or more diverse patient populations. Second, the sample size, while statistically adequate for detecting differences in CIN incidence, remains relatively small. These factors restrict the external validity of the results. Therefore, multicenter randomized trials with larger cohorts are needed to confirm the reproducibility and broader applicability of our findings.

Consequently, stratification of cases across the entire spectrum of renal dysfunction was not feasible, as conservative treatment strategies were predominantly employed in individuals with severely reduced eGFR. In addition, the type and volume of contrast media administered were not standardized but varied according to availability and clinical urgency, introducing potential variability in exposure.

Although renal function was monitored for up to 72 hours post-procedure, aligning with standard CIN definitions, we acknowledge that this short-term follow-up may not fully capture persistent or delayed renal dysfunction. Future studies with extended follow-up are warranted to assess the long-term renal outcomes associated with contrast exposure and CoQ10 administration. Lastly, although blood and urinary CoQ10 levels could serve as valuable biomarkers for monitoring treatment efficacy and renal delivery, such analyses were not performed due to feasibility constraints.

CONCLUSION

CoQ10 therapy yielded a significant reduction in the incidence of CIN in patients with ACS who underwent CA. CoQ10 can be used as an agent to reduce the incidence of CIN, owing to its antioxidant and anti-inflammatory effects. BMI, a history of CKD, and intraoperative balloon dilation may be considered significant risk factors for CIN.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethical Committee at Ain Shams University prior to initiating the research (approval no.: MS70/2024, date: 05.02.2025).

Informed Consent: Informed written consent was obtained from all participants, ensuring adequate privacy and confidentiality.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.E.S., S.E.E., I.B., N.O., Design: I.B., Data Collection or Processing: S.E.E., N.O., Analysis or Interpretation: N.O., Literature Search: R.E.S., Writing: R.E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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EDITORIAL COMMENT

DOI: 10.4274/ijca.2025.08370
Int J Cardiovasc Acad 2025;11(3):115-116

Coenzyme Q10 in Contrast-induced Nephropathy - A Step Forward in Renal Protection?

Mehdi Zoghi

Department of Cardiology, Ege University Faculty of Medicine, İzmir, Türkiye

Contrast-induced nephropathy (CIN) remains a significant clinical challenge, particularly among patients with acute coronary syndrome (ACS) undergoing coronary angiography. Despite advances in hydration strategies and the use of iso- or low-osmolar contrast agents, CIN continues to be associated with increased morbidity, mortality, and healthcare costs. Against this backdrop, the prospective randomized clinical trial conducted by El-Sheikh et al.[1] and colleagues offers important insights into the potential renoprotective role of coenzyme Q10 (CoQ10) - a naturally occurring antioxidant - in this high-risk population.

Key Findings and Clinical Significance

This single-center trial enrolled 300 ACS patients randomized to receive either oral CoQ10 supplementation (n=200) or standard care (n=100). The incidence of CIN - defined as a ≥0.5 mg/dL or ≥25% rise in serum creatinine, or a ≥25% decline in estimated glomerular filtration rate (eGFR) within 48 hours - was significantly lower in the CoQ10 group (9%) compared to the control group (21%) (P =0.004), Furthermore, postoperative serum creatinine levels were lower and eGFR were higher in the CoQ10 group on days two and three, suggesting sustained renal protection.

Multivariate logistic regression identified high body mass index, pre-existing CKD, and balloon dilatation during the procedure as independent predictors of CIN. These findings provide valuable stratification parameters for identifying patients who may benefit the most from adjunctive therapies like CoQ10.

Mechanistic Rationale for CoQ10 in CIN

CoQ10 plays a vital role in mitochondrial electron transport and cellular energy metabolism, with robust antioxidant and anti-inflammatory properties. The pathogenesis of CIN involves oxidative stress, tubular ischemia, and endothelial dysfunction - all processes that CoQ10 could theoretically mitigate. Preclinical studies have shown CoQ10's ability to preserve renal function in models of ischemia-reperfusion injury and toxin-induced nephropathy, but this study is among the first to demonstrate that its clinically significant benefits in a well-defined cardiovascular population (Figure 1).

Practical Implications and Future Directions

This study opens an important dialogue about the use of adjunctive antioxidant therapy for CIN prevention. CoQ10 is readily available, inexpensive, and generally well tolerated, making it an appealing option for at-risk patients. However, as a single-center study, its findings should be interpreted with caution. Larger, multi-center, placebo-controlled trials are warranted to confirm these results, evaluate long-term renal outcomes, and explore optimal dosing strategies.

To cite this article: Zoghi M. Coenzyme Q10 in contrast-induced nephropathy - a step forward in renal protection?. Int J Cardiovasc Acad. 2025;11(3):115-116

Address for Correspondence: Prof. Dr. Mehdi Zoghi, Department of Cardiology, Ege University Faculty of Medicine, İzmir, Türkiye
E-mail: mehdi_zoghi@hotmail.com
ORCID ID: orcid.org/0000-0002-8156-2675

Received: 14.07.2025
Accepted: 03.09.2025
Publication Date: 15.09.2025

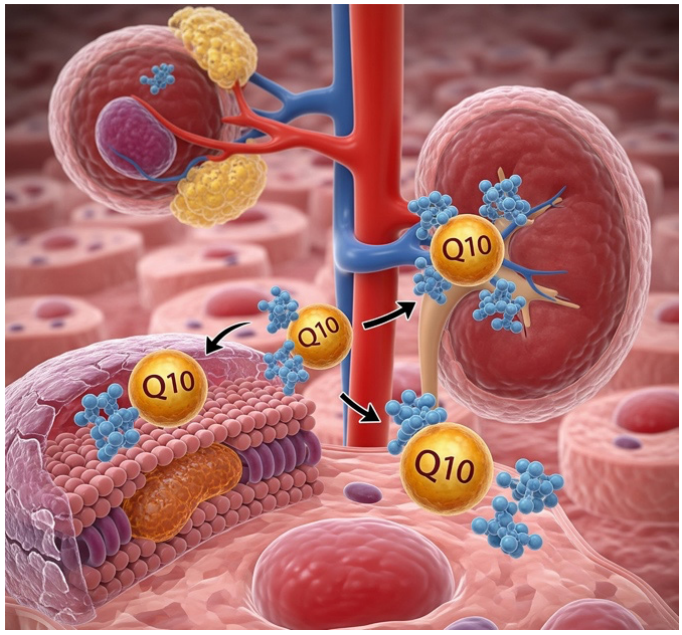

Figure 1: Protecting kidneys in contrast angiography: the role of CoQ10

Moreover, the study raises intriguing questions: How does CoQ10 compare with other antioxidants like N-acetylcysteine or ascorbic acid? Could CoQ10 be part of a broader "renal protection bundle" in high-risk interventions? Should its use be expanded beyond coronary angiography to other contrast-dependent procedures?

Conclusion

The work of El-Sheikh et al.[1] provides compelling preliminary evidence that CoQ10 may reduce the incidence of CIN in ACS patients undergoing coronary angiography. If validated in larger trials, this could represent a paradigm shift in CIN prevention - from reactive management to proactive renal protection using a physiologically grounded and low-risk intervention.

CoQ10 may well become a valuable addition to the armamentarium against CIN - signaling a new era in preventive nephrocardiology.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.78300
Int J Cardiovasc Acad 2025;11(3):117-122

The Predictive Value of H_2FPEF Score for Contrast Induced Nephropathy in NSTEMI Patients Undergoing Emergency PCI

Al-Shimaa Mohamed Sabry, El Sayed Abd El Khalek El Darky, Mohamed Abdelhameed Elsharawy, Mahmoud Said Abd Al Naby

Department of Cardiology, Benha University Faculty of Medicine, Benha, Egypt

Abstract

Background and Aim: Contrast-induced nephropathy (CIN) is acute kidney damage that occurs after recent radiographic contrast media exposure. The aim of our study was to evaluate the association of H_2FPEF score with CIN in patients with non-ST-segment elevation myocardial infarction (NSTEMI) undergoing emergency coronary angiography and percutaneous coronary intervention (PCI).

Materials and Methods: This prospective single center study included 600 patients with NSTEMI scheduled for both emergency coronary angiography and PCI. They were classified into 2 groups according to the incidence of CIN: the first group included 89 patients who developed CIN, and the second group included 511 patients without CIN. All studied cases were clinically evaluated. Echocardiographic assessment, coronary angiography and PCI were done.

Results: Age, hypertension, diabetes mellitus (DM), presence of heart failure and atrial fibrillation, pulmonary artery systolic pressure and H_2FPEF were found to be significant predictors of CIN after emergency PCI. Multivariate logistic regression analysis detected age, DM, and H_2FPEF as the only significant predictors of CIN after emergency PCI. H_2FPEF score can predict CIN with AUC of 0.575 and *P*-value of 0.020, at cutoff >1, with 85.39% sensitivity, 50.49% specificity, 16.1% positive predictive value and 89.8% negative predictive value.

Conclusion: H_2FPEF score shows a statistically significant but limited discriminatory ability in predicting CIN. Its utility as a standalone predictor appears limited and requires further validation.

Keywords: H_2FPEF score, coronary angiography, contrast induced nephropathy

INTRODUCTION

Contrast-induced nephropathy (CIN) refers to impaired renal function following the administration of radiographic contrast media. CIN has several mechanisms. It may occur due to medullary ischemia, vasoconstriction, oxidative stress, or the direct toxic effects of contrast media. It is associated with prolonged hospitalization, increased morbidity, and mortality.[1]

The risk of CIN is lower when less nephrotoxic low osmolar contrast agents are used and when improved prevention strategies are implemented. However, its incidence after coronary angiography is still high and represents an important cause of morbidity and mortality,[2] especially after primary percutaneous coronary intervention (PCI).[3]

Therefore, detecting patients with coronary artery disease (CAD) at increased risk of CIN, as well as using effective prevention strategies, is clinically important. H_2FPEF score can be useful in the etiological differentiation of unexplained dyspnea [preserved- ejection-fraction heart failure (HF) or non-cardiac].[4]

To cite this article: Sabry ASM, El Darky ESAEK, Elsharawy MA, Al Naby MSA. The predictive value of H_2FPEF score for contrast induced nephropathy in NSTEMI patients undergoing emergency PCI. Int J Cardiovasc Acad. 2025;11(3):117-122

Address for Correspondence: Asst. Prof. Al-Shimaa Mohamed Sabry, Department of Cardiology, Benha University Faculty of Medicine, Benha, Egypt
E-mail: shimaa.sabry@fmed.bu.edu.eg
ORCID ID: orcid.org/0000-0003-4502-1553

Received: 19.08.2024
Accepted: 08.07.2025
Publication Date: 15.09.2025

Thus, we hypothesized that the H_2FPEF score can be used to detect the probability of a kidney function deterioration and progression of CIN in non-ST-elevation myocardial infarction (NSTEMI) patients before commencing the needed invasive treatment. The aim of this study is to evaluate the role of the H_2FPEF score in detecting CIN in NSTEMI patients undergoing emergency PCI.

METHODS

Study Design and Population

This prospective, single center study at Benha University Hospitals, Egypt included 600 patients with NSTEMI scheduled for emergency coronary angiography and PCI throughout the period from February 2023 to September 2024. The exclusion criteria included patients with a history of coronary artery bypass grafting, a history of valve replacement, reduced left ventricular ejection fraction (LVEF) (LVEF <40%), chronic kidney disease [patients with baseline estimated glomerular filtration rate 30 mL/min], and patient refusal. Patients were classified into 2 groups according to the incidence of CIN; the first group included 89 patients who developed CIN and the second group included 511 patients without CIN.

This research was approved by research Ethics Committee of Benha University, Faculty of Medicine, Egypt (approval no: MS 7-8-2023, date: 02.06.2024). All participants provided written informed consent.

Definitions

H_2FPEF score was calculated from clinical and echocardiographic data. The score ranges from 0 to 9 depending on the following data: obesity [body mass index (BMI) >30 kg/m^2] (2 points), use of ≥2 antihypertensive medications (1 point), history of atrial fibrillation (AF) (3 points), pulmonary artery systolic pressure (PASP) >35mmHg (1 point), age >60 years (1 point), E/e' >9 (1 point).[5]

CIN is considered if serum creatinine rises by 25% from baseline or the absolute serum creatinine level rises by 0.5 mg/dL within 48-72 hours following contrast media exposure.[6]

Echocardiographic Measurements

Transthoracic echocardiography measurements were performed using the Vivid 7 ultrasound machine (GE Vingmed Sound, Horten, Norway), with a 2.5-3.5 MHz transducer, in accordance with American Society of Echocardiography guidelines.[7] Modified Simpson's method was used to evaluate LV systolic function.

We measured the ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (e') using tissue Doppler imaging (E/e'). PASP was calculated as (4× tricuspid regurgitation pressure gradient) + right atrial pressure.

Coronary Angiography and PCI

We used low-osmolar, nonionic contrast media (Iohexol, omnipaque 350 mg/mL) during PCI procedures. Patients with GFR <60 mL/min./1.73 m^2 received intravenous hydration using normal saline at a rate of 1 mL/kg/hr (or 0.5 mL/kg/hr in HF patients). Aspirin (300 mg) and a P2Y12 antagonist (clopidogrel 600 mg or ticagrelor 180 mg) were given before PCI. During the procedure, unfractionated heparin (70-100 U/kg) was used. Glycoprotein IIb/IIIa inhibitors were used according to the operator's discretion.

Follow-up

The patients were followed up by monitoring plasma creatinine levels and calculating the GFR to determine the development of CIN.

Statistical Analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative variables were expressed as a mean and standard deviation. Comparison between groups was done using unpaired Student's t-test. However, qualitative variables were expressed as frequencies and percentages (%), and Chi-square tests or Fisher's exact tests were used for comparison. We used logistic regression analysis to detect CIN predictors. The receiver operating characteristic (ROC) curve was used to identify the H_2FPEF score cutoff value to predict CIN. *P*-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics are presented in Table 1. The incidence of CIN was 14.83%. Patients in the CIN group were significantly older ($P = 0.016$). Hypertension (HTN) ($P = 0.022$), smoking ($P = 0.037$), hyperlipidemia ($P = 0.006$), and AF ($P = 0.001$) were significantly more prevalent in the CIN group. The CIN group had significantly higher BMI (28.9±3.19 vs. 27.9±3.11 kg/m^2, $P = 0.005$). However, there was no statistically significant difference between the 2 groups regarding gender, prevalence of stroke, diabetes mellitus (DM), HF, and prior PCI; height, heart rate, weight, systolic, and diastolic blood pressure.

Regarding the renal function tests, no significant statistical differences were detected between the two groups in terms of baseline serum creatinine, GFR, and blood urea nitrogen.

The CIN group had significantly higher H_2FPEF scores. Regarding the individual components of the H_2FPEF score, the number of patients with BMI >30 Kg/m^2, HTN, AF, and aged patients were significantly higher in the CIN group (Table 2).

Table 1: Demographic and clinical data of the studied groups

	Non-CIN group (n=511)	CIN group (n=89)	*P*-value
Age (years)	60.4±9.1	62.9±8.67	0.016*
Male gender	286 (55.97%)	47 (52.81%)	0.580
Smoking	232 (45.4%)	51 (57.3%)	0.037*
Hypertension	237 (46.38%)	53 (59.55%)	0.022*
Diabetes mellitus	1 (34.64%)	26 (29.21%)	0.318
Hyperlipidemia	1 (45.01%)	54 (60.67%)	0.006*
Stroke	2 (3.52%)	6 (6.74%)	0.153
AF	2 (9%)	27 (30.34%)	0.001*
HF	2 (44.23%)	37 (41.57%)	0.641
Previous PCI	2 (7.44%)	5 (5.62%)	0.539
Weight (Kg)	77.5±7.69	77.1±7.18	0.646
Height (m)	1.66±0.04	1.67±0.04	0.309
BMI (kg/m^2)	27.9±3.11	28.9±3.19	0.005*
HR (beats/min)	84.8±8.87	84.8±9.07	0.96
SBP (mmHg)	125.9±9.84	124.8±9.78	0.367
DBP (mmHg)	80.4±7.46	80.1±6.99	0.725
Hb (g/dL)	11.73±0.88	11.67±0.83	0.589
Na+ (mmoL/dL)	141.1±2.59	140.7±2.75	0.300
K+ (mmoL/dL)	4.56±0.57	4.56±0.60	0.966
Total cholesterol (mg/dL)	145.65±19.42	143.87±18.74	0.574
TG (mg/dL)	176.5±25.92	175.8±25.15	0.808
HDL (mg/dL)	43.5±2.91	43.4±3.14	0.645
LDL (mg/dL)	104.98±14.97	105.75±14.4	0.652
eGFR (mL/min/1.73 m^2)			
Baseline	94.8±12.64	93.6±10.87	0.404
After	96.9±13.3	98.2±9.96	0.365
Serum creatinine (mg/dL)			
Baseline	1.21±0.12	1.24±0.12	0.062
After	1.32±0.31	1.87±0.75	**0.001***
BUN (mg/dL)			
Baseline	29.95±3.22	31.09±2.9	0.12
After	30.6±3.79	34.7±3.44	**0.001***
LVEDV (mL)	45.04±2.62	44.7±2.61	0.299
LVESV (mL)	36.1±4.1	37.2±3.7	**0.016***
WMSI	1.50±0.25	1.53±0.26	0.244
E	66.9±7.42	66.7±7.1	0.854
e’	6.6±1.13	6.4±1.08	0.087
E/e’ ratio	10.5±2.23	10.8±2.13	0.232
PASP (mmHg)	29.20±5.88	29.22±5.98	0.97
Contrast volume (cc)	216.75±39.84	218.96±41.5	0.46
H_2FPEF	2.8±1.58	3.2±1.71	**0.012***

*: Statistically significant as *P*-value <0.05.

CIN: Contrast induced nephropathy, AF: Atrial fibrillation, HF: Heart failure, PCI: Percutaneous coronary intervention, BMI: Body mass index, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: Hemoglobin, TG: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, LVEDV: Left ventricular end-diastole volume, LVESV: Left ventricular end-systolic volume, WMSI: Wall motion score index, E/e’: Early mitral inflow velocity to early diastolic mitral annulus velocity ratio, PASP: Pulmonary artery systolic pressure, H_2FPEF: Obesity “H”, hypertension “H”, atrial fibrillation “F”, pulmonary hypertension “P”, an age >60 years “E”, and E/e’ >9 “F”

Table 2: H_2FPEF score and its components of the studied groups

	Non-CIN group (n=511)	CIN group (n=89)	*P*-value
H_2FPEF (Mean ± SD)	2.8±1.58	3.2±1.71	**0.012***
BMI (>30 kg/m^2)	146 (28.57%)	36 (40.45%)	**0.024***
HTN	237 (46.38%)	53 (59.55%)	**0.022***
AF	2 (9%)	27 (30.34%)	**0.001***
Pulmonary hypertension	29 (5.7%)	6 (6.7%)	0.72
Elderly (age>60 years)	254 (49.71%)	58 (65.17%)	**0.007***
E/e' ratio (>9)	363 (71.04%)	66 (74.16%)	0.547

*: Statistically significant as *P*-value <0.05.

H_2FPEF: Obesity "H", hypertension "H", atrial fibrillation "F", pulmonary hypertension "P", an age >60 years "E", and E/e' > 9 "F", BMI: Body mass index, HTN: Hypertension, AF: Atrial fibrillation, E/e': Early mitral inflow velocity to early diastolic mitral annulus velocity ratio

Using the univariate logistic regression analysis, older age, HTN, DM, AF, HF, PASP, and H_2FPEF score were significant predictors of the incidence of CIN. However, multivariate regression analysis revealed that age, DM, and H_2FPEF score were the only significant predictors for the incidence of CIN (Table 3). An ROC curve was performed to detect the diagnostic accuracy of H_2FPEF score to predict the incidence of CIN. The H_2FPEF score can predict CIN with an AUC of 0.575 and a *P*-value of 0.020 at a cutoff of >1 demonstrating 85.39% sensitivity, 50.49% specificity, 16.1% positive predictive value (PPV), and 89.8% negative predictive value (NPV) (Figure 1).

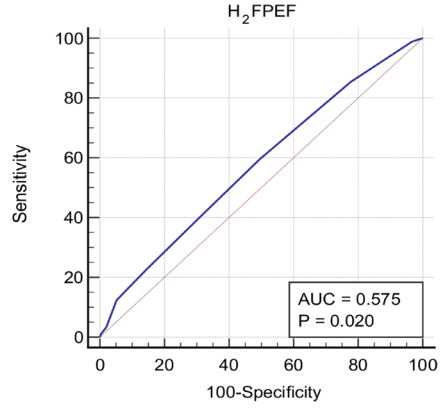

Figure 1: ROC curve analysis of H_2FPEF for prediction of the incidence of CIN

ROC: Receiver operating characteristic, CIN: Contrast-induced nephropathy

DISCUSSION

PCI remains the gold standard for management of acute coronary syndrome (ACS). Even if successful revascularization was achieved, CIN is associated with increased mortality, morbidity, and prolonged hospital stay.[8]

H_2FPEF is a simple score based on clinical and echocardiographic data. It was previously used in several studies to detect the severity and complexity of CAD.[9] Our study was done to determine whether this score can predict CIN in ACS patients undergoing PCI.

Our study revealed that the incidence of CIN was 14.83%. Similarly, Wang et al.[10] reported an incidence of CIN of 15.33% in ACS patients undergoing PCI. Also, Imadoğlu et al.[11] found that CIN occurred in 18.5% of ACS patients.

CIN development has several well-established risk factors such as renal impairment, older age (> 65 years), presence of HF, DM, non-steroidal anti-inflammatory and other nephrotoxic drugs, long-standing hypotension, dehydration, and high doses of contrast medium. Contrast-medium osmolality has, also, a major role in CIN development.[12]

Our study revealed that patients with CIN were significantly older and with a higher prevalence of HTN, dyslipidemia, smoking, and AF. A finding consistent with Imadoğlu et al.[11] who reported that ACS patients who had CIN were older, diabetics, and smokers.

The present study reported that the CIN group had a significantly higher H_2FPEF score. Regarding the individual components of the H_2FPEF score, the CIN group had a significantly higher number of patients with BMI >30 kg/m^2, HTN, AF, and elderly patients. Based on univariate logistic regression analysis, we found that age, HTN, DM, AF, HF, PASP, and H_2FPEF score are significant predictors for the incidence of CIN. Multivariate regression analysis revealed that age, DM, and H_2FPEF were the only significant independent predictors for CIN after emergency PCI. Similarly, Ozbeyaz et al.[13] found that significantly higher H_2FPEF scores were present in the CIN patients (4.10±1.92 vs. 2.28±1.56, $P < 0.001$). Also, they found that H_2FPEF score is an independent predictor of CIN development [odds ratio 1.633 95% confidence interval (1.473-1.811), $P < 0.001$] together with age, DM, PASP, and left anterior descending as an infarct-related artery. In addition, they supported our results by concluding that H_2FPEF score is a predictor of CIN in ACS patients undergoing PCI.

Table 3: Logistic regression analysis for prediction of CIN

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)	1.032 (1.0058 to 1.0589)	**0.016***	1.035 (1.0085 to 1.0623)	**0.009***
Sex	0.587 (0.3664 to 0.9431)	0.28	1.355 (0.7058 to 2.602)	0.361
BMI (kg/m^2)	1.069 (0.9972 to 1.1476)	0.060	1.067 (0.9940 to 1.1472)	0.072
Smoking	1.114 (0.7062 to 1.7588)	0.641	0.662 (0.3217 to 1.3644)	0.264
Hypertension	0.587 (0.3718 to 0.9285)	**0.023***	0.658 (0.3501 to 1.2383)	0.195
Diabetes mellitus	0.619 (0.3932 to 0.9763)	**0.039***	0.565 (0.3507 to 0.9115)	**0.019***
Hyperlipidemia	1.123 (0.7097 to 1.7779)	0.619	0.930 (0.7122 to 1.2150)	0.595
Stroke	0.505 (0.1948 to 1.3096)	0.160	0.465 (0.1731 to 1.2528)	0.130
AF	0.227 (0.1318 to 0.3914)	**<0.001***	0.931 (0.7130 to 1.2158)	0.600
HF	0.530 (0.3350 to 0.8401)	**0.007***	1.032 (0.6354 to 1.6766)	0.898
Previous PCI	1.349 (0.5163 to 3.5280)	0.541	1.364 (0.4969 to 3.7464)	0.546
HR (beats/min)	0.999 (0.9743 to 1.0250)	0.960	1.00 (0.9750 to 1.0257)	0.998
SBP (mmHg)	0.989 (0.9670 to 1.0125)	0.366	0.989 (0.9669 to 1.0124)	0.364
DBP (mmHg)	0.994 (0.9647 to 1.0253)	0.725	0.994 (0.9644 to 1.0251)	0.715
Hb (g/dL)	1.120 (1.0417 to 1.2046)	0.42	0.942 (0.7266 to 1.2202)	0.649
Na+ (mmoL/dL)	0.931 (0.7194 to 1.2054)	0.588	0.954 (0.8748 to 1.0408)	0.290
K+ (mmoL/dL)	0.996 (0.9917 to 1.0021)	0.248	1.005 (0.6760 to 1.4935)	0.981
TG (mg/dL)	0.955 (0.8759 to 1.0416)	0.299	0.999 (0.9898 to 1.0073)	0.736
HDL (mg/dL)	0.982 (0.9097 to 1.0603)	0.644	0.983 (0.9102 to 1.0612)	0.658
LDL (mg/dL)	1.003 (0.9884 to 1.0188)	0.652	1.004 (0.9886 to 1.0191)	0.632
eGFR (mL/min/1.73 m^2)	0.992 (0.9743 to 1.0105)	0.403	0.989 (0.9701 to 1.0082)	0.258
Serum creatinine (mg/dL)	6.492 (0.9783 to 43.0791)	0.053	1.077 (0.9719 to 1.1946)	0.156
BUN (mg/dL)	0.991 (0.6685 to 1.4707)	0.966	1.465 (0.5822 to 3.6896)	0.417
LVEDV (mL)	0.957 (0.8762 to 1.0414)	0.289	0.957 (0.8763 to 1.0461)	0.335
LVESV (mL)	0.954 (0.8754 to 1.0412)	0.294	0.967 (0.8851 to 1.0577)	0.468
WMSI	1.690 (0.6983 to 4.0932)	0.244	1.815 (0.7233 to 4.5559)	0.204
E/e' ratio	1.062 (0.9618 to 1.1743)	0.232	1.059 (0.9565 to 1.1721)	0.270
PASP (mmHg)	1.005 (1.0001 to 1.0115)	**0.046***	2.101 (1.1353 to 3.8881)	0.18
Contrast volume (cc)	1.001 (0.9632 to 1.0397)	0.970	1.005 (0.9996 to 1.0113)	0.069
H_2FPEF	1.188 (1.0378 to 1.3604)	**0.012***	0.218 (0.1198 to 0.3982)	**<0.001***

*: Statistically significant as *P*-value <0.05.

BMI: Body mass index, AF: Atrial fibrillation, HF: Heart failure, PCI: Percutaneous coronary intervention, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: Hemoglobin, TG: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, LVEDV: Left ventricular end-diastole volume, LVESV: Left ventricular end-systolic volume, WMSI: Wall motion score index, E/e': Early mitral inflow velocity to early diastolic mitral annulus velocity ratio, PASP: Pulmonary artery systolic pressure, OR: Odds ratio, CI: Confidence interval

We further investigated the diagnostic accuracy of H_2FPEF for predicting the incidence of CIN, and we found that H_2FPEF can significantly predict the incidence of CIN ($P = 0.020$) with AUC of 0.575, at cut-off >1, with 85.39% sensitivity, 50.49% specificity, 16.1% PPV, and 89.8% NPV. Despite being statistically significant, the low AUC implies limited diagnostic accuracy. Therefore, it can be used to identify patients at increased risk of developing CIN. The NPV (89.8%) is good, suggesting that if the score is ≤ 1, it's highly likely the patient will not develop CIN. This high NPV might be a more practical takeaway for the score than its low PPV (16.1%). Similarly, Ozbeyaz et al.[13] evaluated the relationship between the H_2FPEF score and CIN in ACS patients undergoing PCI. The ROC curve identified an H_2FPEF score of 2.5 as an optimal cut-off value to predict CIN development with a sensitivity of 79.8% and a specificity of 64.1%. The difference in optimal cut-off values could be due to differences in the patient populations, as they studied patients with ACS; however, we assessed only patients with STEMI.

Study Limitations

This study had some limitations. Firstly, the modest AUC of the ROC indicates weak predictive capacity. Additionally, there was no external validation cohort. Also, it was a single center research, evaluating only patients with NSTEMI with a small sample size. The small number of patients developing CIN might influence the generalizability of findings. Finally, intraobserver and interobserver variability could not be excluded.

CONCLUSION

H_2FPEF score shows a statistically significant, but limited discriminatory ability in predicting CIN after emergency PCI in NSTEMI patients. Its utility as a standalone predictor appears limited and requires further validation. However it can be used to identify patients at increased risk of CIN.

Ethics

Ethics Committee Approval: This research was approved by research Ethics Committee of Benha University, Faculty of Medicine, Egypt (approval no: MS 7-8-2023, date: 02.06.2024).

Informed Consent: All participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S.M.S., M.A.E., M.S.A.A.N., Concept: A.S.M.S., E.S.A.E.K.E.D., M.S.A.A.N., Design: A.S.M.S., E.S.A.E.K.E.D., M.S.A.A.N., Data Collection or Processing: A.S.M.S., M.A.E., M.S.A.A.N., Analysis or Interpretation: A.S.M.S., E.S.A.E.K.E.D., M.A.E., M.S.A.A.N., Literature Search: A.S.M.S., M.A.E., M.S.A.A.N., Writing: A.S.M.S., M.A.E., M.S.A.A.N.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/ijca.2025.99609
Int J Cardiovasc Acad 2025;11(3):123-124

Risk Stratification for Contrast-induced Nephropathy in NSTEMI: Does the H_2FPEF Score Add Value?

Sinem Çakal

University of Health Science Türkiye, Department of Cardiology, Haseki Training and Research Hospital, İstanbul, Türkiye

Contrast-induced nephropathy (CIN) remains a significant complication following percutaneous coronary intervention (PCI), with the potential to worsen patient outcomes by increasing morbidity, mortality, and healthcare costs due to prolonged hospitalizations. Identifying reliable predictors of CIN is thus of great clinical importance. This study provides valuable insights into the prediction of CIN in patients with non-ST-segment elevation myocardial infarction undergoing emergency PCI. This prospective, single-center study included 600 patients. The authors investigated the predictive value of the heart failure with preserved ejection fraction score, a score initially designed to help distinguish H_2FPEF from other causes of dyspnea. By integrating clinical and echocardiographic parameters such as age, body mass index, hypertension, atrial fibrillation (AF), pulmonary artery systolic pressure, and E/e' ratio, the H_2FPEF score offers a practical tool, easily accessible at the bedside.

The authors found that patients who developed CIN had significantly higher H_2FPEF scores. Multivariate logistic regression identified age, diabetes mellitus, and the H_2FPEF score as independent predictors of CIN, with an area under the curve (AUC) of 0.575 for the score at a cutoff >1. The score demonstrated high sensitivity (85.39%) but modest specificity (50.49%) and a low positive predictive value (16.1%), while maintaining a relatively high negative predictive value (89.8%). These findings are consistent with and extend previous observations, suggesting that the H_2FPEF score is useful beyond its initial application. Previous studies have shown that components of the H_2FPEF score, such as age, body mass index, and AF, are individually associated with increased risk of CIN. By combining these into a single score, the study suggests a potentially simplified approach to risk assessment. However, the modest AUC and the low positive predictive value underline the limited discriminatory power of the H_2FPEF score as a standalone predictive tool. Although it may help identify low-risk patients (given its high negative predictive value), relying solely on this score for preprocedural risk stratification may lead to under- or overestimation of true risk in some patients.

Several limitations should be emphasized. The single-center design and relatively small sample of patients developing CIN (only 89 out of 600) may restrict external validity. The study lacks an external validation cohort, which would be crucial to confirm the reproducibility of these findings in diverse clinical settings. Additionally, the absence of standardized hydration or contrast volume protocols might have introduced variability in CIN occurrence. Another important point is the potential for integrating the H_2FPEF score with other established risk scores for CIN, such as the Mehran risk score. Combining clinical scores with novel biomarkers (eg., cystatin C, neutrophil gelatinase-associated lipocalin) or advanced imaging parameters may further enhance predictive accuracy. From a clinical perspective, while the results suggest that a higher H_2FPEF score is associated with increased CIN risk, the practical implications remain to be fully defined. The score might be used to identify patients who require more aggressive preventive strategies (eg., optimized hydration, minimization of contrast volume,

To cite this article: Çakal S. Risk stratification for contrast-induced nephropathy in NSTEMI: does the H2FPEF score add value?. Int J Cardiovasc Acad. 2025;11(3):123-124

Address for Correspondence: Asst. Prof. Sinem Çakal, University of Health Science Türkiye, Department of Cardiology, Haseki Training and Research Hospital, İstanbul, Türkiye
E-mail: sinemdnzcakal@gmail.com
ORCID ID: orcid.org/0000-0003-2714-4584

Received: 14.07.2025
Accepted: 03.09.2025
Publication Date: 15.09.2025

or avoidance of nephrotoxic agents). However, it should not replace comprehensive clinical assessment and individual risk assessment unless it has strong predictive capacity. In conclusion, Sabry et al.[1] have contributed significantly to the ongoing efforts to improve the risk stratification for CIN in patients undergoing PCI. The study highlights the need for further large-scale, multicenter studies to confirm these preliminary findings and explore combined models incorporating the H_2FPEF score. Until then, the score should be viewed as an adjunct rather than a definitive decision-making tool.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.28247
Int J Cardiovasc Acad 2025;11(3):125-132

De Ritis Ratio as a Prognostic Marker for Mid-term Mortality in Femoropopliteal Artery Disease

Hasan Çağlayan Kandemir[1], Nart Zafer Baytuğan[2]

[1]University of Health Sciences Türkiye, Clinic of Cardiology, Kocaeli City Hospital, Kocaeli, Türkiye
[2]Clinic of Cardiology, Gebze Fatih State Hospital, Gebze, Türkiye

Abstract

Background and Aim: Peripheral arterial disease (PAD) is recognized as an increasing cause of cardiovascular (CV) morbidity and mortality with advancing age, affecting millions of people worldwide. CV mortality and all-cause mortality may be predicted by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in patients with PAD. We examined the effect of the AST/ALT ratio on mid-term prognosis in PAD.

Materials and Methods: A retrospective, single-center, observational study was conducted between January 2023 and December 2024. 156 patients with femoropopliteal artery lesions who underwent endovascular intervention were evaluated, and 150 patients with similar demographic characteristics and no history of PAD were included in the control group. De Ritis ratio (DRR) was calculated as the AST/ALT ratio on admission. A *P*-value < 0.05 was considered statistically significant in all analyses.

Results: The study participants were divided into three groups: survivors (n=135, 44.1%), non-survivors (n=21, 6.8%), and the control group (n=150, 49%). The average follow-up period was 20.50±9.56 months. During follow-up, 21 deaths occurred, 12 (57.1%), due to cardiac causes and 9 (42.9%), due to non-cardiac causes. A significant difference was observed in the DRR levels between the survivor (1.27±0.59) and non-survivor (1.66±0.98) groups ($P = 0.002$). For the DRR, the optimal cut-off value was found to be 1.78. In multivariate logistic regression analysis high DRR was an independent predictor of cardiac ($P < 0.001$), non-cardiac ($P = 0.023$), and all-cause mortality ($P = 0.004$)

Conclusion: DRR is a simple and effective inflammation-related marker that can be used to determine future adverse CV events in patients with PAD. These findings indicate that an elevated DRR may be a manifestation of systemic conditions rather than isolated liver damage.

Keywords: Peripheral arterial disease, mortality, De Ritis ratio, inflammation, angioplasty

INTRODUCTION

Peripheral arterial disease (PAD) has been identified as a major contributing factor to cardiovascular (CV) morbidity and mortality, affecting millions of people worldwide, particularly among the aging population.[1] It is well established that classical atherosclerotic risk factors, including advanced age, hyperlipidemia, diabetes mellitus (DM), hypertension, and smoking, exhibit a strong correlation with an increased risk of PAD.[1] Although PAD has received less attention than other atherosclerotic diseases, the increased interest in PAD in recent years has led to new insights into the association between thrombosis and inflammation. Inflammation has been identified as a pivotal factor in the development and progression of systemic atherosclerosis, and many studies have linked inflammatory biomarkers to PAD.[1] Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are easily obtainable, practical, and routinely measured values in

To cite this article: Çağlayan HÇ, Baytuğan NZ. De Ritis ratio as a prognostic marker for mid-term mortality in femoropopliteal artery disease. Int J Cardiovasc Acad. 2025;11(3):125-132

Address for Correspondence: Hasan Çağlayan Kandemir MD, University of Health Sciences Türkiye, Clinic of Cardiology, Kocaeli City Hospital, Kocaeli, Türkiye
E-mail: nartzafer@hotmail.com
ORCID ID: orcid.org/0000-0001-5003-6632

Received: 28.03.2025
Accepted: 10.07.2025
Publication Date: 15.09.2025

clinical practice. These enzymes play crucial roles in systemic processes. ALT is primarily located in the hepatocyte cytoplasm. In contrast, AST is abundant in many organs and systems and is expressed in the mitochondria.[2] Serum AST and ALT levels are altered by oxidative stress and hepatocyte damage.

The De Ritis ratio (DRR) (AST/ALT ratio) was initially developed by De Ritis et al.[3] in 1957 for the prognostic evaluation of several liver diseases. The DRR is a complex and valuable parameter that provides important data about the metabolic status of the patient. In healthy humans, the release of AST and ALT into plasma is typically maintained at a constant rate due to the programmed regeneration of hepatocytes, with a DRR slightly less than one.[4] Recent findings suggest that DRR is associated with many adverse CV outcomes, such as acute coronary syndromes, atherosclerotic CV disease, acute and chronic heart failure, cardiac arrest, hypertension, and acute ischemic stroke.[5-12] However, the relationship between DRR and prediction of the mid-term prognosis of patients with PAD is not well established.

We aimed to evaluate the DRR level during percutaneous transluminal angioplasty (PTA) for PAD lesions and its association with mid-term cardiac and all-cause mortality.

METHODS

We conducted a retrospective, single-center study from January 2023 to December 2024. The study population comprised 177 patients with femoropopliteal artery (FPA) lesions who underwent endovascular intervention in our catheterization laboratory. However, 21 patients for whom sufficient follow-up data were unavailable were excluded, and finally 156 patients were evaluated. In addition, 150 patients with similar demographic characteristics and no history of PAD were included in the control group.

In the management guidelines for patients with PAD, we used the resting ankle-brachial index (ABI) as the primary diagnostic tool. ABI ≤0.90 in both limbs is diagnostic for PAD.[13] All patients enrolled before the procedure were symptomatic for PAD, had an ABI <0.90, and showed evidence of severe PAD on non-invasive testing (B-mode Doppler ultrasonography and/or computed tomography angiography). Laboratory findings were obtained from an electronic database. Complete blood counts and biochemical parameters, including fasting blood glucose, AST, ALT, creatinine, high-sensitivity C-reactive protein (hs-CRP), and D-dimer levels, were evaluated on admission. DRR was calculated as the ratio of AST to ALT levels. Blood samples were collected in standard tubes containing ethylenediaminetetraacetic acid to obtain complete blood cell counts. Patients aged <18 years were excluded: unavailable follow-up data, malignancy, chronic inflammatory disease, hematologic disease, chronic liver disease, hepatitis, and fatty liver disease. This study was conducted in accordance with the principles of the Declaration of Helsinki. In addition, approval was obtained from the local Ethics Committee University of Health Sciences Türkiye, Kocaeli City Hospital (approval number: 2024-55, date: 13.06.2024). A signed informed consent form was obtained from each patient enrolled in the study.

Clinical Data Collection and Follow-up

The clinical condition of the patients, their additional disease history, smoking status, mortality, and specific cause of death were recorded. The causes of death were determined by analyzing the death certificates available for all deceased individuals. The classification of deaths as cardiac or non-cardiac was determined using death certificates based on the International Classification of Diseases, 9th revision. After the procedure, the patients were referred for follow-up visits at the 1st, 3rd, 6th, and 12th months. During these visits, physical examinations were conducted and patients were asked about any symptoms they might have experienced.

Background

Angiographic Procedure

Prior to the implementation of the procedure, Doppler ultrasound evaluations were conducted for all patients to visualize the extent and morphology of the FPA lesion. Following the insertion of a 6-8F introducer sheath and diagnostic angiography, intravenous heparin was administered at a dose of 100 µg/kg. An antegrade contralateral strategy was employed, utilizing a Judkins right catheter (5-6F) with a hydrophilic guide wire to successfully traverse the lesions. In most cases, the standard guide wire utilized was 0.018 inches in diameter.

Statistical Analysis

Statistical analyses were performed using number cruncher statistical system (NCSS) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). Chi-squared and Fisher's exact tests were used to compare categorical variables, which are presented as absolute and relative frequencies. The data were evaluated for conformity to a normal distribution using the Shapiro-Wilk test and box plots. No significant deviations from normality were detected. Data was expressed as mean ± standard deviation, and an unpaired Student's t-test was used to assess the statistical significance of differences. One-way analysis of variance was used for comparisons of three or more groups, and the Games-Howell test was used to determine the groups contributing to the differences in the outcome. The optimal cut-offs for DRR's capacity to predict cardiac and all-cause mortality were established using receiver operating characteristic (ROC) curve analyses. Kaplan-Meier survival analysis was used to

assess survival outcomes. The parameters were analyzed using univariate and multivariate logistic regression models. Univariate and multivariate Cox proportional hazards regression analyses were conducted to determine the factors influencing mortality. Multivariate logistic regression analysis was performed using a backward selection method. The results were analyzed with a 95% confidence interval, and the significance level was set at $P < 0.05$.

RESULTS

The study included 306 participants, comprising 156 patients in the study group and 150 patients in the control group. Among the participants, 235 (76.8%) were men and 71 (23.2%) were women. The median age of the patients was 64±12.5 years. The study participants were divided into three groups: survivors (n=135, 44.1%), non-survivors (n=21, 6.8%), and the control group (n=150, 49%) (Table 1). 12 (57.1%) deaths were due to cardiac causes, whereas 9 (42.9%) deaths were due to non-cardiac causes. The basic clinical, demographic, and laboratory characteristics of the patients are presented in Table 1. The average follow-up period was 20.50±9.56 months.

Drug-coated balloons were used in 90.9% of the patients. A comparison of the characteristics of survivors and non-survivors revealed that the non-survivors were older ($P < 0.001$), but the two groups did not differ significantly in terms of other chronic diseases or smoking status (Table 1). Statistically significant correlations were identified between ABI ($P = 0.026$), the severity of stenosis ($P = 0.033$), and mortality ($P = 0.026$).

Hematological tests showed that non-survivors had lower levels of hemoglobin, hematocrit, and lymphocytes, but higher WBC, neutrophil, and monocyte counts (Table 2). Platelet count and red cell distribution width values were similar. A comparative analysis of biochemical parameters revealed higher levels of AST, ALT, hs-CRP, creatinine, and D-dimer in non-survivors. However, fasting blood glucose and uric acid levels were similar (Table 2).

DRR and Survival Analysis

A statistically significant difference was observed in the DRR levels between the survivor (1.27±0.59) and non-survivor (1.66±0.98) groups ($P = 0.002$). (Table 2 and Figure 1). All non-survivor groups, stratified by cardiac and non-cardiac causes of death, had higher DRR levels than survivors. (Table 2). The study identified a cut-off value of 1.78 as the optimal metric for determining DRR. Out of the total patients, 47 exhibited DRR levels greater than 1.78, accounting for a prevalence of 30.1%. Kaplan-Meier analysis demonstrated that patients with a DRR ≥1.78 exhibited a significantly higher rate of all-cause mortality than those with a DRR <1.78 ($P = 0.002$) (Figure 2).

ROC curve analysis revealed that the area under the curve (AUC), specificity, and sensitivity of the DRR for all-cause mortality were 0.67, 89.88%, and 41.5%, respectively ($P = 0.001$) (Figure 3A). Furthermore, the DRR for cardiac mortality had an AUC, specificity, and sensitivity of 0.74, 91.1%, and 47%, respectively ($P = 0.001$). (Figure 3B). Univariate and multivariate Cox proportional hazard regression analyses were

Table 1: The demographic and clinical characteristics of the patients

	Control (n=150)	Survival (n=135, 86.5%)	Non-survival (n=21, 13.4%)	*P*-value
Gender (female), n (%)	34 (22.6)	31 (22.9)	6 (28.5)	0.335
Age	64.33±10.21	63.19±11.20	77.07±16.29	0.001
Smoking, n (%)	47 (31.3)	44 (32.6)	8 (38.1)	0.474
Follow-up time (mounts)	20.11±6.33	21.33±13.41	19.61±10.31	0.341
Residual lesion	-	30.0±15.0	25.0±10.0	0.660
Degree of stenosis	-	85.0±5.50	95.0±10.0	0.033
Total balloon	-	101	20	-
Drug eluting balloon, n (%)	-	94 (93.0)	16 (80.0)	0.013
ABI	-	0.85±0.37	0.73±0.41	0.026
Past medical history				
DM, n (%)	63 (42.0)	45 (35.5)	7 (33.3)	0.821
HT, n (%)	59 (39.3)	58 (42.9)	9 (42.8)	0.902
HL, n (%)	35 (23.3)	35 (25.9)	7 (33.3)	0.102
Previous CAD, n (%)	28 (18.6)	23 (17.0)	5 (23.8)	0.699
AF, n (%)	5 (3.3)	6 (4.4)	1 (4.7)	0.443

ABI: Ankle-brachial index, AF: Atrial fibrillation, CAD: Coronary artery disease, DM: Diabetes mellitus, HT: Hypertension

Table 2: Laboratory values of study population

	Control (n=150)	Survival (n=135)	Non-survival (n=21)	*P*-value
Hemoglobin, g/dL	12.88±2.44	12.92±2.18	10.40±1.78	0.021
Hematocrit	38.01±6.55	38.76±5.74	31.90±4.63	0.033
WBC x 103/mL	9350.7±2451.4	8977.4±2445.8	13431.5±7562.2	0.022
Platelet x103/L	255.28±42.12	249.78±68.62	257.90±101.75	0.640
Lymphocyte x103/µL	2.44±0.17	2.17±0.81	1.47±0.77	0.001
Neutrophil x103/µL	5.87±3.10	5.65±1.92	10.68±7.39	0.001
Monocyte x103/µL	0.66±0.14	0.76±0.24	0.89±0.35	0.038
RDW	13.03±3.13	13.61±1.86	13.86±2.71	0.904
Creatinine, mg/dL	1.09±0.71	1.18±0.92	1.77±1.23	0.001
Glucose mg/dL	146.6±57.15	158.68±84.13	157.72±76.1	0.677
AST mg/dL	26.10±18.30	21.50±18.49	39.05±55.22	0.001
ALT mg/dL	25.44±13.77	18.81±13.89	36.77±90.36	0.001
De Ritis ratio	1.09±0.43	1.27±0.59	1.66±0.98	0.002
De Ritis ratio$^{\alpha}$	1.34±0.69	1.27±0.59	1.69±0.96$^{\beta}$	0.003
De Ritis ratio$^{\mu}$	1.34±0.69	1.27±0.59	1.62±0.55$^{\mu}$	0.013
D-dimer ng/mL	0.89±0.41	1.07±0.91	2.63±2.86	0.003
Uric acid, mg/dL	4.20±2.71	5.22±1.65	6.02±3.28	0.088
hs-CRP, mg/L	11.50±10.33	19.63±42.66	70.83±61.53	0.001

RDW: Red cell distribution width, ALT: Alanine aminotransferase, AST: Aspartate transaminase, hs-CRP: High sensitivity C-reactive protein, WBC: White blood cell, $^{\alpha}$: Cardiac causes, $^{\mu}$: Non-cardiac causes

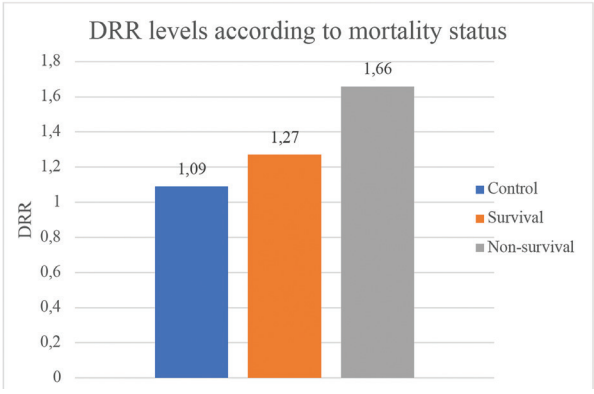

Figure 1. DRR levels according to mortality status
DRR: De Ritis ratio

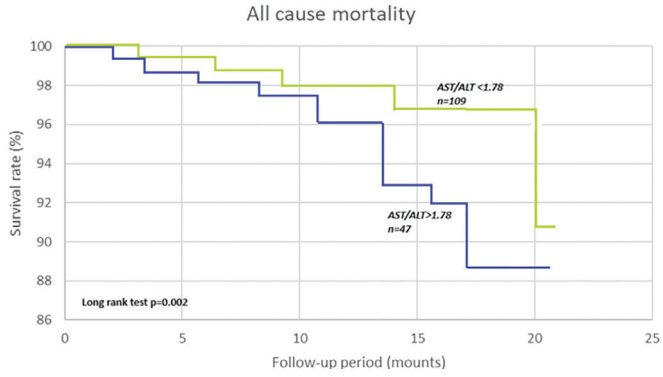

Figure 2. Kaplan-Meier analysis detecting for all-cause mortality
AST/ALT: Aspartate aminotransferase/alanine aminotransferase

performed to determine the factors influencing cardiac and all-cause mortality (Table 3). In univariate evaluations, DRR levels were significantly associated with all-cause, cardiac, and non-cardiac mortality (Table 3). After adjusting for confounding risk factors, multivariate Cox proportional hazards regression analysis showed that a high DRR was an independent predictor of cardiac ($P < 0.001$), non-cardiac ($P = 0.023$), and all-cause mortality ($P = 0.004$) (Table 3). The evaluation results were obtained using the backward-elimination method. Variables that were found to have significant or near-significant ($P < 0.200$) effects in the univariate evaluations were included in the multivariate evaluations (Table 4). We tested the independent association of DRR with the risk of all-cause, cardiac, and non-cardiac mortality using multivariate regression models that included a large number of risk factors and potential confounders (Table 4).

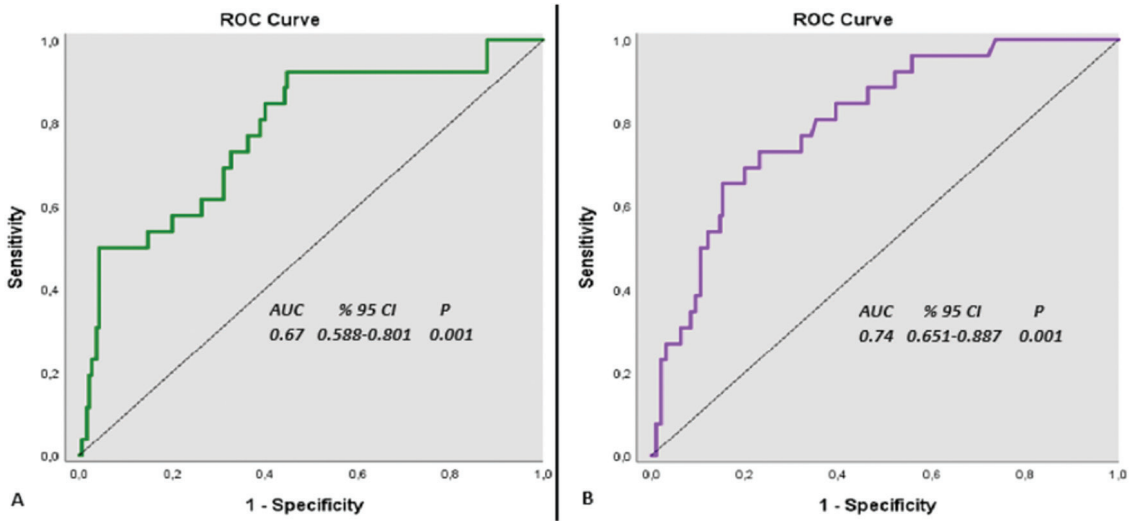

Figure 3: A) ROC curve analysis of DRR in predicting all-cause mortality B) ROC curve analysis of DRR in predicting cardiac mortality

ROC: Receiver operating characteristic, DRR: De Ritis ratio, AUC: Area under the curve, CI: Confidence interval

Table 3: Uni-variate Cox proportional hazard regression analysis of DRR for predicting cardiac, non-cardiac and all-cause mortality

Variables DRR >1.78	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95%CI)	*P*-value
All-cause mortality (n=21)	2.57 (1.51-4.70)	0.002	2.93 (1.33-5.07)	0.004
Cardiac mortality (n=12)	3.57 (0.94-7.52)	0.001	2.91[α] (1.52-3.85)	0.002
			2.56[μ] (1.75-4.31)	0.001
Non-cardiac mortality (n=9)	1.77 (0.89-3.44)	0.002	2.66[α] (1.44-4.63)	0.020
			1.58[μ] (0.96-4.05)	0.023

[α]: Adjusted for age, gender, ankle-brachial index, smoking, and diabetes mellitus, [μ]: Adjusted for age, gender, ankle-brachial index, D-dimer, and restenosis, CI: Confidence interval, DRR: De Ritis ratio, HR: Hazard ratio

Table 4: Cox multivariate analysis for predicting of all-cause, cardiac and non-cardiac mortality

	All-cause mortality			Cardiac mortality			Non-cardiac mortality		
	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
Female gander	1.78	1.24-3.62	0.039	1.55	0.51-3.62	0.669	1.44	0.76-2.77	0.418
Hypertension	2.55	1.98-4.78	0.076	2.27	1.23-4.01	0.034	2.09	1.44-3.68	0.311
Diabetes mellitus	1.79	0.87-2.88	0.224	1.03	0.48-1.71	0.020	0.97	0.55-3.67	0.032
Age	1.44	1.36-3.56	0.577	1.77	1.22-3.77	0.479	0.88	0.67-2.78	0.711
Smoking	0.21	0.15-1.06	0.709	0.78	0.56-1.79	0.088	2.35	1.66-4.75	0.041
hs-CRP	1.56	1.02-2.96	0.045	1.49	0.68-3.28	0.002	1.67	1.32-3.56	0.669
Hemoglobin	0.77	0.51-1.71	0.429	1.07	0.82-2.04	0.155	2.79	2.01-5.03	0.078

CI: Confidence interval, hs-CRP: High sensitivity C-reactive protein, HR: Hazard ratio

DISCUSSION

The present study examined the relationship between DRR levels during PTA and mid-term prognosis in patients with PAD. To the best of our knowledge, no studies have been conducted on this subject. Our results showed that higher DRR levels were significantly correlated with an increased risk of mid-term cardiac and all-cause mortality. This suggests that DRR may be a valuable tool for assessing the risk of adverse outcomes predicted by PAD.

The typical symptom of PAD is intermittent claudication in the lower limbs. It is characterized by muscle cramping, pain, and fatigue that occur during physical exertion and are typically relieved by rest. In patients with FPA, symptoms may occur in the buttock or thigh and generally correspond to the proximal level of occlusion. Medical approaches, PTA, and surgery are treatment options for FPA. Revascularization is the primary treatment option for lower extremity PAD. Endovascular intervention offers advantages over other treatment options; it is therefore increasingly recommended.[14]

Patients with symptomatic PAD have an increased risk of mortality. A meta-analysis of 16 studies involving 48,294 subjects found an association between ABI and mortality.[15] In the present study, an inverse correlation between ABI values and mortality was identified, which is consistent with the findings reported in previous literature. The higher risk of comorbidities, advanced age, and multiple organ failure in patients with low ABI may have led to an increased mortality rate.

Classic CV risk factors can affect all vascular beds and are associated with an increased risk of developing arterial disease. However, their effects vary among vascular beds.[16] PAD can be associated with other atherosclerotic diseases, such as coronary artery disease, carotid artery disease, and abdominal aortic aneurysms. Atherosclerosis is a chronic inflammatory vascular disease that affects the entire body. A significant connection exists between the immune system and inflammatory responses in the progression of atherosclerosis.[17] Recent studies have revealed that inflammation and lipid metabolism play important roles in PAD pathogenesis.[17] Masoudkabir et al.[18] showed that serum ALT and AST levels were independently associated with inflammatory conditions and subclinical atherosclerosis. This association remained independent of traditional CV risk factors and was positively correlated with the risk and severity of premature atherosclerotic disease. In addition, elevated hepatic transaminase levels indicate an increased burden of non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and atherosclerotic disease.[19] In this respect, there is strong evidence of the "co-occurrence" of NAFLD, metabolic syndrome, and vascular disease. NAFLD is closely linked to classic coronary artery risk factors.[19,20] Zou et al.[21] demonstrated that NAFLD was linked to an elevated possibility of PAD following adjustment for demographic factors.

In our study, we found that inflammatory markers such as hs-CRP, D-dimer, and WBC increased with DRR in the non-survival group. These findings suggest that the DRR is an indicator of inflammatory responses. In addition, no significant differences were observed in the conventional risk factors for atherosclerotic CV disease among the groups. These results reveal the necessity for novel risk markers that extend beyond the traditional risk factors associated with PAD.

The liver accounts for only 2-3% of the total body weight but receives 25% of the cardiac output. The complex vascular system of the liver, combined with its high metabolic activity, increases its susceptibility to perfusion disorders, leading to several molecular and hemodynamic changes. Recent studies investigating the relationship between ALT and AST levels, AST/ALT ratio, and cardiac and all-cause mortality have yielded conflicting results. An analysis of the literature suggests that the DRR may predict adverse CV outcomes, particularly in selected patient groups. In contrast, a related study that concentrated on people aged ≥55 years found that ALT and AST were linked to death from all causes.[22] Furthermore, a recent meta-analysis that included information from over 9 million participants and 200,000 deaths found regional differences in the association between ALT levels and the risk of death from all causes in the general population, as well as a relatively weak relationship between AST levels and mortality.[23] In a 10-year follow-up cohort in the United Kingdom, Weng et al.[24] found an association between a high DRR and an increased risk of developing coronary artery disease in men. This association was not observed in women. In light of these findings, the authors recommended that DRR should not be included in CV disease risk prediction models for general primary care. In a long-term follow-up study in Japan, high DRR was determined to be an independent risk factor for CV mortality in the general population.[25] Similar results were obtained in 2529 DM outpatients who were followed up for 6 years. Increased DRR was significantly associated with an augmented risk of mortality from any cause and CV mortality.[26]

Liu et al.[27] analyzed data from 10,900 patients in the Chinese hypertension registry and revealed that the prevalence of PAD was 3.2%. Furthermore, the study indicated that DRR is independently associated with PAD risk, and that a DRR of ≥1.65 may be useful in identifying patients with high vascular risk.[27] In another study in which patients with PAD were followed for approximately 5 years, CV events were significantly higher in patients with DRR levels greater than 1.67.[28]

A recent study demonstrated a significant association between increased DRR and an elevated risk of all-cause mortality. We

also found that an optimal cut-off value of DRR ≥1.78 was a significant predictor of increased risk of cardiac and overall mortality in patients with PAD.

Study Limitation

This study has the following limitations. First, the study did not have a fixed follow-up period, which introduced variability and may have affected the accuracy of mortality estimates. The derived optimal DRR cut-off of 1.78 requires external validation in larger, independent cohorts. Its clinical utility is based on its reproducibility. Patients with chronic liver disease, hepatitis, and fatty liver disease were excluded. These conditions often coexist with CV disease; therefore, their exclusion may limit the study's applicability. Furthermore, the study was conducted at a single center and utilized a retrospective research design. The patient sample size was relatively small in this study. The duration of the subsequent period was comparatively brief.

CONCLUSION

The prevalence of PAD is increasing in tandem with the rise in patients exhibiting atherosclerotic risk factors and an aging population. Although many risk factors for PAD are similar to those of other atherosclerotic diseases, it is crucial to identify risk factors for disease progression and treatment. As patients with PAD have an elevated CV risk, the optimization of their treatment and/or different/stricter follow-ups are required. Furthermore, although DRR does not change the treatment approach, it can be considered an important new marker in patients with PAD. DRR is a simple and effective inflammation-related marker that can be used to determine future adverse CV events in patients with PAD. These findings indicate that an elevated DRR may be a manifestation of systemic conditions rather than isolated liver damage.

Ethics

Ethics Committee Approval: In addition, approval was obtained from the local Ethics Committee University of Health Sciences Türkiye, Kocaeli City Hospital (approval number: 2024-55, date: 13.06.2024).

Informed Consent: A signed informed consent form was obtained from each patient enrolled in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ç.K., N.Z.B., Concept: H.Ç.K., Design: H.Ç.K., N.Z.B., Data Collection or Processing: N.Z.B., Analysis or Interpretation: H.Ç.K., Literature Search: H.Ç.K., Writing: H.Ç.K., N.Z.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.20982
Int J Cardiovasc Acad 2025;11(3):133-146

Effect of Stent Post Dilatation Versus No Post Dilatation in Patients with STEMI Treated by Primary PCI on No Reflow and in-hospital Outcome

Sarah Gamal, Hussein Shaalan, Tamer M. Abu Arab, Mina M. Iskandar

Department of Cardiology, Ain Shams University Faculty of Medicine, Cairo, Egypt

Abstract

Background and Aim: Percutaneous coronary intervention (PCI) remains the primary modality of choice for achieving reperfusion in patients with acute coronary syndrome. However, complications such as no-reflow phenomenon can occur. Stent post-dilatation (SPD) is common in non-infarct settings, however its use during acute myocardial infarction is controversial. To investigate impact of SPD versus no SPD in ST elevation myocardial infarction (STEMI) cases undergoing primary PCI on incidence of no-reflow phenomenon and in-hospital outcomes.

Materials and Methods: A prospective, single-center, randomized controlled trial was conducted on 300 STEMI cases who presented to Ain Shams University Hospitals between February 2024 and August 2024. Following successful stent implantation, confirmed thrombolysis in myocardial infarction (TIMI) III flow, and adequate stent expansion, cases were randomly stratified into two groups: group I (n=150), which underwent SPD, and group II (n=150), which did not receive SPD. Post-procedural TIMI flow and myocardial blush grade (MBG) were assessed and compared between the two groups. In-hospital clinical outcomes were likewise evaluated.

Results: Cases who underwent SPD (group I) showed significantly lower TIMI flow and MBG than cases in group II; consequently, group I showed elevated prevalence of transient no-reflow (43.3% vs. 4% in group II). There is a relation between SPD and occurrence of no-reflow. In-hospital major adverse cardiac events rates were comparable between two groups, with no substantial variation detected. Longer chest pain duration, higher non-compliant (NC) balloon inflation pressure, higher NC balloon to stent size ratio, and longer stent length were strongly and negatively correlated with TIMI flow and MBG outcomes, leading to poorer post procedural results.

Conclusion: Post-stent dilatation during primary PCI in STEMI patients was associated with a higher incidence of transient no-reflow immediately following the procedure. However, this did not translate into a significant difference in short-term-in-hospital clinical outcomes-likely due to prompt intra-procedural management of no-reflow.

Keywords: STEMI, percutaneous coronary intervention, no-reflow phenomenon, TIMI flow, myocardial blush grade, post-dilatation, in-hospital outcomes

INTRODUCTION

Since the advent of coronary stents, percutaneous coronary intervention (PCI) has become a reliable and effective therapeutic strategy, widely adopted as a primary treatment modality for ST elevation myocardial infarction (STEMI).[1]

Nonetheless, a subset of cases undergoing primary PCI fails to achieve effective reperfusion. The no-reflow phenomenon, first identified in humans by Ito et al.[2] in 1992, refers to the absence of adequate myocardial perfusion despite successful reopening of the epicardial coronary artery.

To cite this article: Gamal S, Shaalan H, Abu Arab TM, Iskandar MM. Effect of stent post dilatation versus no post dilatation in patients with STEMI treated by primary PCI on no reflow and in-hospital outcome. Int J Cardiovasc Acad. 2025;11(3):133-146

Address for Correspondence: Sarah Gamal, MD, Department of Cardiology, Ain Shams University Faculty of Medicine, Cairo, Egypt
E-mail: sarah-gamal@med.asu.edu.eg
ORCID ID: orcid.org/0009-0003-1692-3766

Received: 26.05.2025
Accepted: 07.08.2025
Publication Date: 15.09.2025

Angiographic no-reflow is characterized by thrombolysis in myocardial infarction (TIMI) flow less than 3, or TIMI 3 flow with myocardial blush grade (MBG) 0 or 1 without mechanical obstruction. The development of the no-reflow phenomenon following primary PCI in STEMI patients represents a critical indicator of unfavorable prognosis.[3]

Stent mal-apposition and under-expansion are thought to be major factors contributing to adverse clinical outcomes caused by stent thrombosis and in-stent restenosis in the drug-eluting stent (DES) era.[4]

The role of stent post-dilatation (SPD) during primary PCI in STEMI remains controversial. While SPD is traditionally performed to ensure optimal stent expansion and apposition, concerns have emerged regarding its potential to provoke distal embolization, microvascular obstruction, or mechanical injury, potentially leading to the no-reflow phenomenon and adverse outcomes.[5]

Given this ongoing debate, our study aimed to address the following research question:

"Does SPD during primary PCI in STEMI patients increase the incidence of the no-reflow phenomenon and influence the in-hospital clinical outcomes compared to no post-dilatation?"

We hypothesized that SPD, although intended to optimize stent deployment, may paradoxically increase the risk of no-reflow due to microvascular compromise or embolization in the highly thrombotic setting of STEMI. This study sought to prospectively evaluate the impact of SPD versus no-SPD on no-reflow and in-hospital clinical outcomes.

METHODS

This study is a prospective, single-center, randomized controlled trial, which included 300 STEMI cases presented to emergency departments of Ain Shams University Hospitals, for the period from February 2024 to August 2024 where all cases were randomly divided after successful primary PCI with stent implantation, confirmed TIMI III flow, and adequate stent expansion, into 2 groups in a 1:1 ratio. Group I included 150 cases who underwent SPD; group II included 150 cases who did not undergo SPD. Patients with stent under-expansion of 20% or more or TIMI flow less than III were excluded from the study, prior to randomization (Figure 1).

The sample size was calculated, based on prior data suggesting that there is a potential difference of approximately 20% in no-reflow incidence between groups. With an alpha error of 0.05 and power of 80%, a minimum of 135 patients per group was required. To account for potential dropouts, 150 patients were enrolled in each arm.

The study protocol was approved by Ain Shams University Faculty of Medicine Scientific and Ethical Committee (protocol no: FMASU MS82/2024, date: 06.02.2024). Written informed consent was secured from all participants, with strict adherence to ethical standards ensuring protection of privacy and confidentiality of personal data.

Cases were eligible for inclusion if they presented with STEMI within 12 hours of symptom onset, meeting established criteria for primary PCI [symptoms indicative of myocardial ischemia, such as persistent chest pain, accompanied by electrocardiography (ECG) changes consistent with STEMI or its equivalents]. Additional inclusion criteria required that cases have undergone primary PCI with a successfully placed angiographic stent, defined by achieving less than 20% residual stenosis and restoration of TIMI grade III flow. Cases were excluded if they presented more than 12 hours after symptom onset, received fibrinolytic therapy, did not undergo stent implantation, required bifurcation stenting, or presented with cardiogenic shock. Additional exclusion criteria included severe stent under-expansion necessitating urgent post-dilatation, a heavy thrombus burden (mainly grade 4 with thrombus size double vessel diameter), requirement for aggressive pre-dilatation with large non-compliant balloons (>2.5 mm), or enrollment in other study protocols targeting no-reflow. These criteria were designed to ensure a homogeneous study population for evaluating the specific effect of SPD. However, it is important to note that these exclusions inherently limit the generalizability of our findings to more complex STEMI patients. Relevant clinical data on cases were collected and tabulated.

All enrolled cases were managed according to a standardized protocol. The protocol was initiated by obtaining written informed consent. This was followed by thorough history taking, physical examination, and acquisition of a 12-lead ECG within 10 minutes of presentation, and within 10 minutes after intervention. Laboratory assessments included blood glucose, complete blood count, lipid profile, renal function tests, and cardiac biomarkers. Antiplatelet therapy comprised an oral loading dose of 300 mg acetylsalicylic acid, along with 180 mg ticagrelor; alternatively, 600 mg clopidogrel was administered in cases where ticagrelor was contraindicated or unavailable.

Diagnostic coronary angiography was done using radial or femoral access, and the culprit vessel was identified. TIMI thrombus score and TIMI flow grade were recorded, and lesion was classified according to American College of Cardiology / American Heart Association classification.[6] Primary PCIs were done according to the recommendations of current European Society of Cardiology guidelines. DESs were utilized in all primary PCI procedures, with stent dimensions and placement sites selected according to the operator's clinical decision.

Unfractionated heparin was administered intra-procedurally at a dose ranging from 70 to 100 IU/kg. In cases exhibiting a substantial thrombus burden, the use of manual thrombus aspiration and bailout glycoprotein (GP) IIb/IIIa inhibitors was determined based on the operator's clinical decision. Pre-dilatation might be done if needed using a small balloon under low atmospheric pressure.

Following stent placement, clear stent imaging (Philips Stent Boost, GE Stent Viz) was used in all cases to evaluate stent expansion. Cases that needed urgent post-stent dilatation (stent under-expansion 20% or more), were excluded. TIMI flow was assessed and cases with TIMI flow less than III were excluded from the study.

Subsequently, patients who achieved TIMI III flow and demonstrated adequate stent expansion, defined as stent under-expansion of less than 20% confirmed by clear stent imaging, were randomized into two groups. Group I consists of cases who underwent SPD. Group II includes cases who didn't undergo SPD, using a random sequence generated via the Rand function in Excel 2023, created prior to study initiation. Allocation was concealed using sealed opaque envelopes, which were sequentially numbered and opened only after TIMI III flow was confirmed. This ensured that treatment assignment was not influenced by procedural characteristics or operator preference prior to randomization.

Randomization was intentionally performed after achieving TIMI III flow and confirming adequate stent expansion to ensure that the impact of SPD would be evaluated specifically on microvascular perfusion and myocardial tissue-level outcomes. This approach was chosen to eliminate confounding factors related to epicardial flow restoration and mechanical stent optimization, thereby isolating the effects of SPD on TIMI flow and MBG.

Post-dilatation was performed at 14-18 atmospheric pressure, with an NC balloon of a size 0.25-0.5 mm larger in diameter than stent size, based on the operator's assessment of the proximal and distal reference vessel diameters and visual evaluation of stent apposition. The balloon length typically matched the stented segment to ensure uniform expansion. Immediately after SPD, in the first group TIMI flow and MBG were reassessed. In cases where no reflow was detected post-SPD, operators employed adjunctive pharmacologic or mechanical maneuvers to restore flow. These included intracoronary vasodilators (adenosine, verapamil), aspiration thrombectomy when embolization was suspected, low-pressure ballooning, and the administration of GP IIb/IIIa inhibitors. The choice and combination of these therapies was applied according to operator discretion.

All procedures were performed by a pool of four experienced interventional cardiologists, each with extensive expertise in primary PCI. Operators followed a standardized procedural protocol for both PCI and SPD, including guidance on balloon sizing and inflation pressures. Despite this standardization, inter-operator variability in procedural technique cannot be entirely excluded.

Due to the procedural nature of SPD, operator blinding was not possible. However, post-procedural TIMI flow and MBG were independently assessed by two experienced interventional cardiologists who were blinded to the treatment allocation. In cases of discrepancy between the two assessors, a third senior cardiologist, also blinded to group assignment, provided adjudication to reach consensus.

No-reflow was defined as either a TIMI flow grade of less than III, or a TIMI III flow accompanied by a MBG of 0 or 1, in the absence of angiographic evidence of vessel dissection, distal embolic cutoff, or mechanical obstruction.[1]

The primary angiographic endpoint was occurrence of no-reflow, assessed immediately after SPD in the intervention group or at the end of the procedure in the no-SPD group.

All cases were admitted to coronary care unit and were kept on dual antiplatelet therapy and anti-ischemic medications. The cases' vital data, ECG, and cardiac enzymes were followed up. An echocardiogram was performed on all cases.

The duration of hospital stay was calculated. Adverse events such as heart failure (HF), occurrence of ventricular aneurysms, ST re-elevation, cardiac death, and non-cardiac death were counted.

The primary clinical endpoint was in-hospital major adverse cardiovascular events (MACE), defined as a composite of cardiac death, re-infarction, target vessel revascularization (TVR), stroke, cardiogenic shock requiring inotropic support, and life-threatening ventricular arrhythmias.

The secondary endpoints included the incidence of post-PCI chest pain, defined as recurrent chest discomfort >15 minutes within 24 hours post-PCI, impaired left ventricular (LV) systolic function, mechanical complications, LV thrombus, major bleeding, prolonged hospital stay.

The data analysis followed an intention-to-treat principle, where all randomized patients were analyzed according to their assigned group, regardless of any procedural deviations or post-randomization events.

Statistical Analysis

Data were collected, revised, coded, and entered into the Statistical Package for the Social Sciences (IBM SPSS) version 27 IBM Corp. was released in 2020. IBM SPSS Statistics for Windows,

Version 27.0. Armonk, NY: IBM Corp. The quantitative data were presented as means, standard deviations, and ranges. Also, qualitative variables were presented as numbers and percentages. The one-sample Kolmogorov-Smirnov test can be used to test whether a variable is normally distributed. The comparison between groups regarding qualitative data was done using the chi-square test. The comparison between two independent groups with quantitative data was done using an independent t-test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. Univariate and multivariate logistic regression analysis were used to assess predictors of no reflow. A *P*-value of <0.05 was considered statistically significant. Where applicable, 95% confidence intervals (CI) were calculated to assess the precision of the estimated effects.

RESULTS

This study encompassed 300 patients with STEMI, all of whom were treated with primary PCI involving stenting of the culprit vessel. Patients who achieved TIMI grade III flow were subsequently randomized into two groups: group I (n=150), who underwent SPD, and group II (n=150), who did not undergo post-dilatation.

No substantial variations were detected between two groups in terms of demographic characteristics, cardiovascular risk factors, clinical presentation, angiographic findings, or interventional data as shown in Tables 1 and 2.

As shown in Table 3, comparison of TIMI flow and MBG between two groups revealed that patients in group I, who underwent SPD, had significantly lower TIMI flow and MBG, with a higher incidence of no-reflow immediately following SPD (22% vs. 0% for TIMI flow less than III and 43.3% vs. 4% for MBG less than II, as shown in Figure 2a and 2b). This indicates a significant relation between SPD and no-reflow occurrence, as shown in Figure 3. However, the majority of these instances were transient, with successful restoration of TIMI III flow following vasodilators, GP IIb/IIIa, or additional ballooning maneuvers. Final angiographic flow was comparable between groups, despite the higher transient no-reflow rate in the SPD group. Group I experienced a higher incidence of post-PCI chest pain, lasting over 15 minutes, within the first 24 hours (14.6% compared to 5.3% in group II). Among those in group I, eight patients (36.3%) showed transient ECG changes such as ST-segment shifts or T wave inversions, while this was observed in only two patients (25%) in group II. An elevation in cardiac troponin levels indicating myocardial injury was

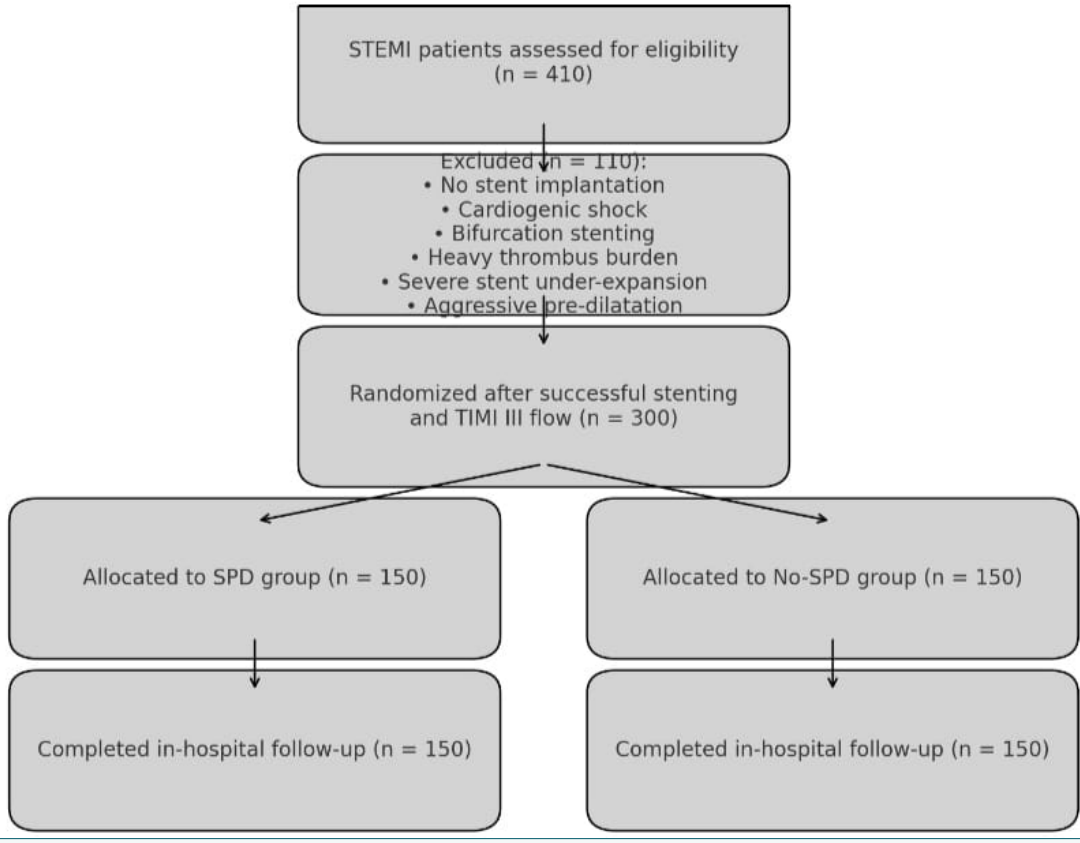


Figure 1: CONSORT flow diagram illustrating patient enrollment, exclusion, randomization, allocation, and follow-up
STEMI: ST elevation myocardial infarction, TIMI: Thrombolysis in myocardial infarction SPD: Stent post-dilatation

Table 1: Comparison between group I and group II regarding demographic data, risk factors and presentation of the studied patients

No. =150		Group I No. =150	Group II	Test value	*P*-value	Sig.
Demographic data						
Gender	Female	35 (23.3%)	33 (22.0%)	0.076*	0.783	NS
	Male	115 (76.7%)	117 (78.0%)			
Age	Mean ± SD	54.61±10.43	55.95±10.43	-1.118•	0.265	NS
	Range	23-77	28-76			
Risk factors						
Diabetes mellitus		69 (46.0%)	60 (40.0%)	1.102*	0.294	NS
Hypertension		70 (46.7%)	62 (41.3%)	0.866*	0.352	NS
Smoking		95 (63.3%)	98 (65.3%)	0.131*	0.718	NS
Dyslipidemia		110 (73.3%)	103 (68.7%)	0.793*	0.373	NS
Family history		65 (43.3%)	53 (35.3%)	2.012*	0.156	NS
CKD		13 (8.7%)	15 (10.0%)	0.158*	0.691	NS
Presentation						
ECG	Anterior STEMI	71 (47.3%)	75 (50.0%)	10.176*	0.179	NS
	Infroposterior STEMI	23 (15.3%)	27 (18.0%)			
	Infroposterolateral STEMI	3 (2.0%)	2 (1.3%)			
	Inferior STEMI	43 (28.7%)	38 (25.3%)			
	Lateral STEMI	0 (0.0%)	4 (2.7%)			
	Anterolateral STEMI	6 (4.0%)	1 (0.7%)			
	Posterior STEMI	0 (0.0%)	1 (0.7%)			
	Inferolateral STEMI	4 (2.7%)	2 (1.3%)			
Killip class	I	135 (90.0%)	145 (96.7%)	5.595*	0.061	NS
	II	11 (7.3%)	3 (2.0%)			
	III	4 (2.7%)	2 (1.3%)			
	IV	0	0			
Preloading	Ticagrelor	135 (90.0%)	130 (86.7%)	0.809*	0.369	NS
	Clopidogrel	15 (10.0%)	20 (13.3%)			
Chest pian duation (hours)	Mean ± SD	6.6±2.68	6.49±2.68	0.345•	0.731	NS
	Range	1-12	1-12			
Time to wire crossing (minutes)	Mean ± SD	34.67±10.03	35.57±10.34	-0.765•	0.445	NS
	Range	20-60	20-60			

P-value >0.05: Non significant, *P*-value <0.05: Significant, *P*-value <0.01: Highly significant

*: Chi-square test, •: Independent t-test, SD: Standard deviation, NS: Non-significant, CKD: Chronic kidney disease, STEMI: ST elevation myocardial infarction, ECG: Electrocardiography

found in 5 patients with chest pain (22.7%) in group I and in 1 patient (12.5%) in group II. However, none of these cases fulfilled the criteria for reinfarction. The in-hospital clinical outcomes were largely comparable between the SPD and no-SPD groups. Mortality occurred in 2 patients (1.3%) in the SPD group versus 1 patient (0.6%) in the no-SPD group, a difference that was not statistically significant ($P = 0.330$). Reinfarction, urgent revascularization, and cerebrovascular stroke (CVS) did not occur in either group (0%). The incidence of cardiogenic shock requiring inotropic support was slightly higher in the SPD group (2.7%) compared to the no-SPD group (1.3%), though this difference was not statistically significant ($P = 0.410$). Similarly, ventricular tachycardia was noted in 2.0% of SPD cases and 1.3% of no-SPD cases ($P = 0.652$), and major bleeding was rare and not significantly different (0.7% vs. 0%, $P = 0.317$). Group I had a longer hospital stay (median 2 (2-4) days) compared to Group II (median 2 (1.5-3) days).

The analysis reveals that higher pressure during NC balloon inflation and a larger difference between NC balloon and stent

Table 2: Comparison between group I and group II regarding angiographic and interventional data of the studied patients

Angiographic data						
Approach	Femoral	147 (98.0%)	150 (100.0%)	3.030*	0.082	NS
	Radial	3 (2.0%)	0 (0.0%)			
Culprit lesion	LAD	77 (51.3%)	75 (50.0%)	8.378*	0.079	NS
	LCX	8 (5.3%)	15 (10.0%)			
	RCA	59 (39.3%)	54 (36%)			
	Diagonal	0 (0.0%)	4 (2.7%)			
	OM	6 (4.0%)	2 (1.3%)			
Culprit lesion site	Proximal	76 (51.4%)	89 (59.8%)	7.232*	0.204	NS
	Distal	7 (4.7%)	11 (7.4%)			
	Mid	62 (41.9%)	49 (32.9%)			
	Ostial	3 (2.0%)	0 (0.0%)			
Type of lesion	A	26 (17.3%)	27 (18.0%)	0.789*	0.674	NS
	B	34 (22.7%)	40 (26.7%)			
	C	90 (60.0%)	83 (55.3%)			
Vessel diameter (QCA)	Mean ± SD	3.19±0.34	3.2±0.42	-0.218•	0.828	NS
	Range	2.25-4.5	2-5			
Lesion length	Short (<20 mm)	60 (40.0%)	67 (44.7%)	0.669*	0.413	NS
	Long (>20 mm)	90 (60.0%)	83 (55.3%)			
TIMI flow (pre)	0	70 (46.7%)	76 (50.7%)	3.078*	0.380	NS
	I	24 (16.0%)	14 (9.3%)			
	II	38 (25.3%)	42 (28.0%)			
	III	18 (12.0%)	18 (12.0%)			
Thrombus grade	0	4 (2.7%)	0 (0.0%)	6.025*	0.110	NS
	I	62 (41.3%)	53 (35.3%)			
	II	42 (28.0%)	44 (29.3%)			
	III	42 (28.0%)	53 (35.3%)			
Interventional data						
Thrombus aspiration	Yes	0 (0.0%)	2 (1.3%)	2.013*	0.156	NS
GP IIb/IIIa	Yes	44 (29.3%)	49 (32.7%)	0.390*	0.533	NS
Pre-dilatation	Yes	84 (56.0%)	77 (51.3%)	0.657*	0.418	NS
Pre-dilatation balloon size	Mean ± SD	2.131±0.281	2.173±0.308	0.913•	0.362	NS
	Range	1.5-2.5	1.5-2.5			
Pressure of pre-dilatation	Mean ± SD	17.62±1.8	17.41±2.31	0.658•	0.511	NS
	Range	12-20	10-20			
Stent	Promus	42 (28.0%)	38 (25.3%)	2.352*	0.309	NS
	Xience	71 (47.3%)	63 (42.0%)			
	Onyx	37 (24.7%)	49 (32.7%)			
Stent diameter	Mean ± SD	3.157±0.357	3.197±0.410	0.901•	0.368	NS
	Range	2.25-4	2.25 -5			
Stent length	Mean ± SD	30.373±5.654	29.127±6.222	1.816•	0.070	NS
	Range	18-38	12-38			
Stent pressure	Mean ± SD	13.59±1.68	13.55±1.48	0.183•	0.855	NS
	Range	11-18	11-16			
NC balloon length	Mean ± SD	14.627±2.646	-	-	-	-
	Range	8-20	-			
NC balloon pressure	Mean ± SD	16.43±1.27	-	-	-	-
	Range	14-18	-			
Difference between NC & stent size	Mean ± SD	0.39±0.12	-	-	-	-
	Range	0.25-0.5	-			

P-value >0.05: Non significant, *P*-value < 0.05: Significant, *P*-value < 0.01: Highly significant

*: Chi-square test; •: Independent t-test

TIMI: Thrombolysis in myocardial infarction, LAD: left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, OM: Obtuse marginal artery, QCA: Quantitative coronary angiography, GP: Glycoprotein, NC: Non-compliant, SD: Standard deviation, NS: Non-significant, GP: Glycoprotein

Table 3: Comparison between group I and group II regarding post-procedural results and in-hospital outcome of the studied patients

No. =150		Group I No. =150	Group II	Test value	*P*-value	Sig.
Results						
TIMI flow post	0	0 (0.0%)	0 (0.0%)	37.079*	0.000	HS
	I	4 (2.7%)	0 (0.0%)			
	II	29 (19.3%)	0 (0.0%)			
	III	117 (78.0%)	150 (100.0%)			
MBG	0	42 (28.0%)	0 (0.0%)	76.058*	0.000	HS
	I	23 (15.3%)	6 (4.0%)			
	II	27 (18.0%)	21 (14.0%)			
	III	58 (38.7%)	123 (82.0%)			
No reflow (TIMI flow < III or TIMI III flow with MBG grade of 0, 1).		65 (43.3%)	6 (4%)	64.201*	0.000	HS
Systolic BP	Mean ± SD	117.8±15.1	115.4±14.87	1.387•	0.166	NS
	Range	90-160	90-150			
Diastolic BP	Mean ± SD	73.93±8.74	73.87±10.54	0.060•	0.952	NS
	Range	60-100	60-100			
Heart rate	Mean ± SD	76.21±12.3	80.61±12.27	-3.101•	0.002	HS
	Range	45-110	50-110			
Post PCI chest pain		22 (14.6%)	8 (5.3%)	2.73	0.0064	HS
Echocardiography						
EF %	Mean ± SD	42.34±7.77	42.42±8.33	-0.086•	0.932	NS
	Range	30-66	29-65			
LVEDD (mm)	Mean ± SD	52.28±3.35	51.83±4.89	0.923•	0.357	NS
	Range	42-59	38-62			
LVESD (mm)	Mean ± SD	34.47±3.23	34.57±4.63	-0.203•	0.840	NS
	Range	27-45	24-55			
Mechanical complications	No	150 (100%)	150 (100.0%)	-	-	-
	Yes	0 (100%)	0 (0.0%)			
LV thrombus	No	147 (98.0%)	148 (98.7%)	0.203*	0.652	NS
	Yes	3 (2.0%)	2 (1.3%)			
In hospital MACE						
Mortality	No	148 (98.7%)	149 (99.4%)	0.330*	0.566	NS
	Yes	2 (1.3%)	1 (0.6%)			
Reinfarction	No	150 (100.0%)	150 (100.0%)	-	-	-
	Yes	0 (0.0%)	0 (0.0%)			
Urgent revascularization	No	150 (100.0%)	150 (100.0%)	-	-	-
	Yes	0 (0.0%)	0 (0.0%)			
CVS	No	150 (100.0%)	150 (100.0%)	-	-	-
	Yes	0 (0.0%)	0 (0.0%)			
Cardiogenic shock requiring IV supports	No	146 (97.3%)	148 (98.7%)	0.680*	0.410	NS
	Yes	4 (2.7%)	2 (1.3%)			
Malignant ventricular arrythmia	No	147 (98.0%)	148 (98.7%)	0.203*	0.652	NS
	Yes	3 (2.0%)	2 (1.3%)			
Major bleeding	No	149 (99.3%)	150 (100.0%)	1.003*	0.317	NS
	Yes	1 (0.7%)	0 (0.0%)			
Hospital stay (days)	Median (IQR)	2 (2-4)	2 (1.5-3)	3.204	0.001	HS

P-value >0.05: Non significant, *P*-value <0.05: Significant, *P*-value <0.01: Highly significant

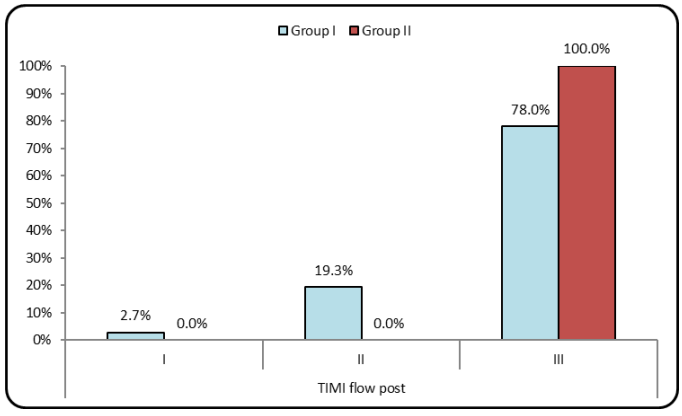
*: Chi-square test, •: Independent t-test, TIMI: Thrombolysis in myocardial infarction, BP: Blood pressure, CVS: Cerebrovascular stroke, EF: Ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, MACE: Major adverse cardiovascular events, NS: Non-significant, LV: Left ventricular, IQR: Interquartile range, SD: Standard deviation

sizes are both strongly associated with poorer TIMI flow post-procedure and MBG outcomes, indicating poorer results with increased pressure and size discrepancies. Additionally, longer stents correlate negatively with both TIMI flow and MBG, suggesting that longer stents may lead to worse outcomes with SPD. The duration of chest pain is also negatively correlated with both TIMI flow and MBG, indicating that prolonged chest pain is linked to poorer post-procedural results as shown in Table 4 and Figures 4-7.

Conversely, stent diameter and NC balloon length do not significantly affect TIMI flow or MBG.

Although multiple clinical and procedural variables were included in the regression analysis, only the factors presented in Table 5 showed statistically significant associations with no-reflow. In univariate analysis, several variables were significantly associated with no-reflow, including stent-post dilatation, hypertension, chronic kidney disease (CKD), high SPD pressure (>16 atm), and a size discrepancy >0.25 mm between the NC balloon and stent. Among these, CKD and SPD pressure >16 atm remained independent predictors in multivariate analysis.

(a)



(b)

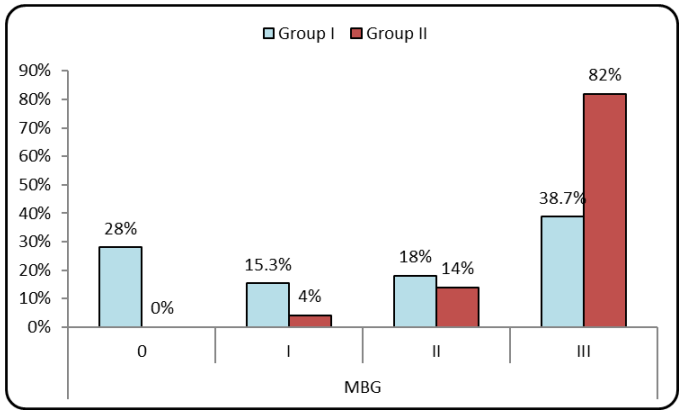


Figure 2: Comparative assessment of post-procedural TIMI flow (a) and myocardial blush grade (MBG) (b) between group I and group II among studied cases

TIMI: Thrombolysis in myocardial infarction, MBG: Myocardial blush grade

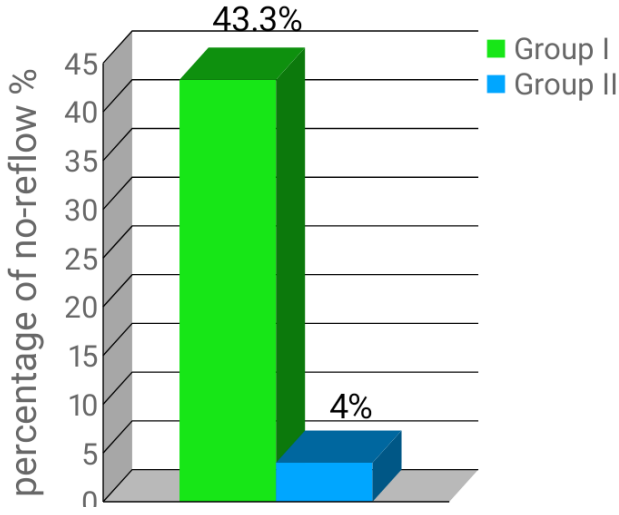


Figure 3: Comparison between group I and group II regarding post-procedural no-reflow of studied cases

Table 4: Correlations between various parameters (chest pain duration, stent diameter, length, NC balloon length, size and pressure) and TIMI Flow & MBG post operative

	TIMI flow post		MBG	
	r	*P*-value	r	*P*-value
Pressure of NC balloon inflation	-0.380**	0.000	-0.387**	0.000
Difference between NC & stent size	-0.319**	0.000	-0.299**	0.000
NC balloon length	0.137	0.093	0.020	0.809
Stent diameter	0.099	0.227	0.105	0.200
Stent length	-0.262**	0.001	-0.186*	0.023
Chest pain duration	-0.279**	0.001	-0.169*	0.039

*: Significant; **: Highly significant, Spearman correlation coefficient, TIMI: Thrombolysis in myocardial infarction, MBG: Myocardial blush grade, NC: Non-compliant

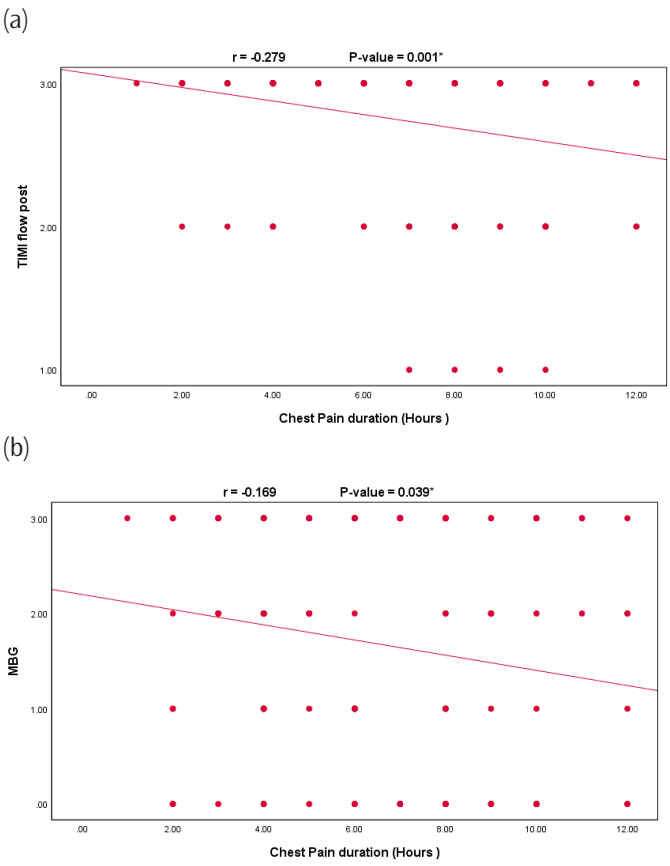


Figure 4: Correlation between TIMI flow (a) & MBG (b) and chest pain duration

**: Significant, TIMI: Thrombolysis in myocardial infarction, MBG: Myocardial blush grade*

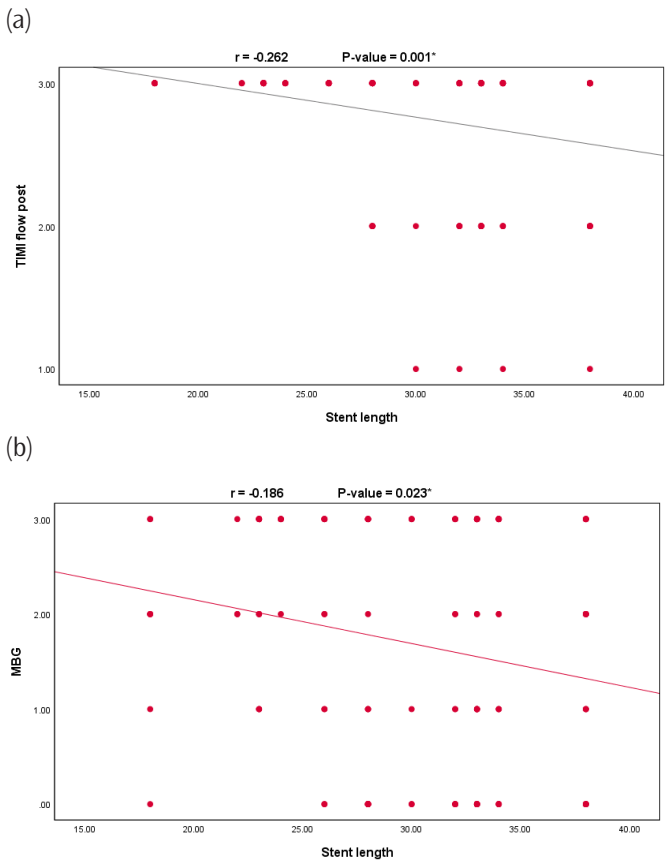


Figure 5: Correlation between TIMI flow (a) & MBG (b) and stent length

**: Significant, TIMI: Thrombolysis in myocardial infarction, MBG: Myocardial blush grade*

DISCUSSION

SPD has been acknowledged to enhance both angiographic results and clinical outcomes in patients with stable coronary artery disease. However, its application in the context of acute myocardial infarction (AMI) remains a subject of concern due to potential risks associated with its use in this acute setting.[7]

The clinical value of post-dilatation during stenting for AMI has been debated, with prior studies reporting conflicting outcomes. Zhang et al.[8] were first to demonstrate that employing post-dilatation in this setting may elevate the long-term risk of mortality or recurrent MI.

Conversely, other research has indicated that post-stent dilatation in the setting of AMI may be linked to a reduced risk of TVR and overall MACEs during a clinical follow-up period of up to five years.[9]

Our study was conducted at Ain Shams University Hospitals, which is considered a high-volume tertiary PCI center that provides primary PCI service 24/7, with an average time-to-wire crossing of 30-45 minutes; this was reflected in our study (mean time-to-wire crossing was 34.67±10.03 minutes in group I and 35.57± 0.34 minutes in group II).

In our study, patients in group I, who underwent SPD, exhibited significantly lower TIMI flow and MBG compared to patients in group II, who did not undergo SPD. As a result, group I had a higher incidence of no-reflow.

As per the study protocol, only patients who achieved TIMI III flow after stenting were included; thus, all patients in group II had TIMI III flow. However, in group I, TIMI III flow was affected after SPD, so only 117 patients (78%) persisted to have TIMI III flow. Additionally, 4 patients had TIMI I flow, and 29 patients had TIMI II flow.

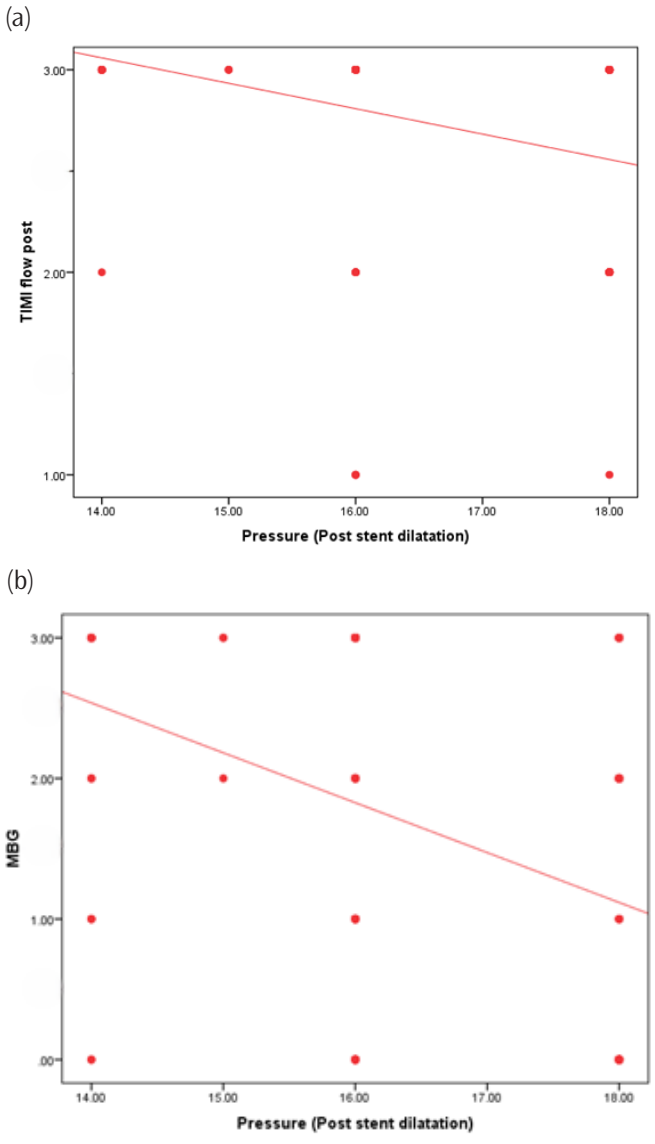


Figure 6: Correlation between TIMI flow (a) & MBG (b) and pressure of NC balloon inflation

TIMI: Thrombolysis in myocardial infarction, MBG: Myocardial blush grade, NC: Non-compliant

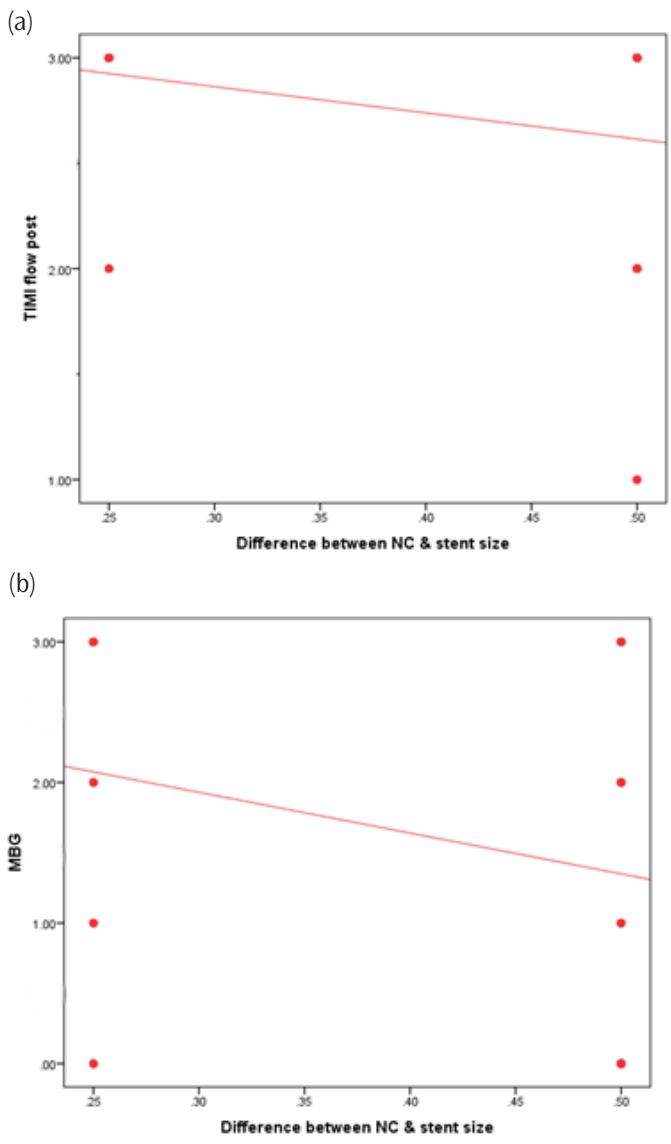


Figure 7: Correlation between TIMI flow (a) & MBG (b)and difference between NC and stent size

TIMI: Thrombolysis in myocardial infarction, MBG: Myocardial blush grade, NC: Non-compliant

Table 5: Univariate and multivariate logistic regression analysis to assess factors associated with no reflow

	Univariate				Multivariate			
	P-value	OR	95% CI for OR		*P*-value	OR	95% CI for OR	
			Lower	Upper			Lower	Upper
Stent-post dilatation	**0.000**	18.353	7.626	44.167	-	-	-	-
Hypertension	**0.039**	1.763	1.029	3.021	-	-	-	-
Dyslipidemia	0.051	1.905	0.997	3.640	-	-	-	-
CKD	**0.046**	2.286	1.016	5.143	**0.009**	8.134	1.695	39.041
SPD inflation pressure >16 atm	**0.004**	2.786	1.384	5.606	**0.007**	2.717	1.322	5.587
Difference between NC & stent size >0.25 mm	**0.021**	2.199	1.128	4.286	-	-	-	-

OR: Odds ratio, CI: Confidence interval, NC: Non-compliant, CKD: Chronic kidney disease, SPD: Stent post-dilatation

Regarding MBG, most patients (96%) in group II with no SPD achieved MBG II (21 patients) and III (123 patients); only 6 patients had MBG I. However, in group I with SPD, 42 patients had MBG 0, 23 patients had MBG I, and only 85 patients (56.7%) achieved MBG II (27 patients) and MBG III (58 patients).

As a result, no-reflow by its definition (TIMI flow less than III or TIMI III flow with MBG grade of 0, 1) occured in 65 patients in group I versus 6 patients in group II (43.3% vs. 4%).

We concluded that there's a significant relationship between SPD in the setting of primary PCI and the occurrence of no reflow. It is important to note that all patients achieved TIMI III flow immediately post-stenting prior to randomization. Therefore, the observed reduction in TIMI flow grade and MBG within the SPD group reflects the direct procedural impact of SPD itself. This methodological aspect is a critical consideration when interpreting the relationship between SPD and post-procedural microvascular outcomes in our study. Our finding that SPD was associated with lower TIMI flow, reduced MBG, and a higher incidence of no-reflow, is paradoxical and challenges conventional beliefs regarding SPD's benefits in primary PCI. Several mechanisms may explain this phenomenon. First, SPD may promote distal embolization by dislodging thrombotic material or plaque debris, even in patients with apparent TIMI III flow post-stenting. Second, the high-pressure inflation with an oversized NC balloon could induce microvascular spasm or direct microvascular injury. Third, while no angiographically visible dissections were recorded, subtle dissections or intimal tears below the detection threshold may have occurred, adversely affecting perfusion. Fourth, SPD might exacerbate microvascular compression or contribute to myocardial edema, aggravating microvascular obstruction. Collectively, these potential mechanisms suggest that SPD, in the context of STEMI, may have unintended deleterious effects on microvascular integrity, warranting further investigation with advanced imaging modalities and microcirculatory assessments. Our study's higher observed no-reflow rates in the SPD group reflect a transient deterioration in coronary flow immediately post-SPD. This indicates a temporary issue, rather than permanent microvascular damage, as evidenced by final angiographic equivalence between groups after adjunctive management. This distinction is critical, as it suggests that SPD may acutely provoke microvascular compromise, possibly via the mentioned mechanisms, but that such effects are often reversible with appropriate intra-procedural strategies. Therefore, while SPD may transiently impair myocardial perfusion, careful technique and adjunctive measures can mitigate these risks. Our regression analysis highlights that, while the application of SPD itself did not independently predict no-reflow after adjustment, the use of high inflation pressures during SPD (>16 atm) was an independent predictor. This implies that procedural technique, specifically the degree of mechanical stress on the vessel wall, may play a more critical role in microvascular injury.

The results of our study were harmonized with those reported in a retrospective study by Senoz and Yurdam[1] which evaluated 255 STEMI patients who underwent primary PCI. Of these, 115 patients received SPD, while 140 did not. The incidence of no-reflow (TIMI 0-2) at baseline and immediately after stent implantation was comparable between SPD and non-SPD groups (94.4% vs. 95.4%, $P = 0.757$; and 23.1% vs. 20.4%, $P = 0.621$, respectively). However, final no-reflow rate was markedly elevated among patients in the SPD group (22.2% vs. 9.3%, $P = 0.009$).

To note that our study is different from that of Senoz and Yurdam[1] as we did a prospective randomized trial that excluded patients with angiographic evidence of heavy thrombus burden, patients with less than TIMI III flow after stenting and those who needed aggressive pre-dilatation using large NC balloons >2.5 mm as these factors could increase risk of no-reflow and potentially affect results.

Even though the group of SPD in our study experienced no-reflow more than other group.

Our results were further aligned with a meta-analysis by Putra et al.[10] which encompassed ten studies and reported that SPD was performed in 40.7% of patients. The analysis revealed a significant association between post-dilatation and an elevated risk of no-reflow during primary PCI, with an odds ratio of 1.33 (95% CI: 1.12-1.58; $P = 0.001$).

Our study was discordant with the post-dilatation STEMI trial, [11] a prospective observational study, which found that SPD with NC balloons in STEMI patients undergoing primary PCI significantly improved stent expansion, apposition, and post-PCI FFR, though it had no overall significant effect on coronary microcirculation.

The discrepancy between our findings and those of the post-dilatation STEMI trial may, in part, be explained by our exclusion of patients with marked stent underexpansion, who required immediate post-dilatation. In contrast, the post-dilatation STEMI trial permitted operator-driven decision-making regarding post-dilatation, and patients deemed not to require it were excluded from the study population.

As mentioned, in our study, no-reflow assessment was done immediately post-dilatation and not in the final one, as operators had managed no-reflow with different measures to improve flow. This was successful in most of the patients, explaining why both groups had a similar in-hospital outcome.

As for the in-hospital outcome, there was substantial variation between the two groups in post-PCI chest pain, which was more frequent in group I.

Echocardiographic assessment performed on the day following primary PCI revealed no substantial variations between study groups in terms of ejection fraction, cardiac chamber dimensions, or mechanical complications.

In a study by Morishima et al.[12] 120 consecutive patients experiencing their first AMI and treated with percutaneous transluminal coronary angioplasty (PTCA), in the absence of flow-limiting lesions, were evaluated. Based on post-PTCA cineangiographic findings, patients were categorized into a no-reflow group (n=30) and a reflow group with TIMI grade 3 flow (n=90). Over a mean follow-up period of 5.8±1.2 years, survivors in the no-reflow group exhibited significantly higher LV end-diastolic and end-systolic volume indices, elevated plasma brain natriuretic peptide levels, and reduced LV ejection fractions compared to those in the reflow group. These findings suggest that the no-reflow phenomenon may contribute to adverse LV remodeling.

So good initial post PCI echocardiography may not indicate good late outcome and long term follow up is mandatory.

In-hospital MACE was generally similar between the SPD and no-SPD groups. Mortality rates were low and not significantly different (1.3% vs. 0.6%, $P = 0.330$). No cases of reinfarction, urgent revascularization, or CVS occurred in either group. Incidences of cardiogenic shock (2.7% vs. 1.3%, $P = 0.410$), ventricular arrhythmia (2.0% vs. 1.3%, $P = 0.652$), and major bleeding (0.7% vs. 0%, $P = 0.317$), were slightly higher in the SPD group, but none of these differences reached statistical significance.

This is consistent with findings of Gao et al.[4] who conducted a prospective study involving 336 AMI patients, of whom 199 (59.2%) underwent post-stent dilation. There were no substantial variations between the two groups in terms of HF, ventricular aneurysm, stent thrombosis, cardiac death, non-cardiac death, or severe hemorrhage ($P > 0.05$). Follow-ups at 30 days post-procedure showed no differences in stent thrombosis, TVR, or MACE.

Although our study did not find notable variations in clinical outcomes between two groups due to relatively short follow-up period, and may be due to good final flow after measures taken by operators to deal with no-reflow.

Additional research has emphasized long-term implications of the no-reflow phenomenon. In a study by Kim et al.[13] data from 4,329 patients with AMI enrolled in a Korean multicenter registry were analyzed. Among these, 4,071 patients exhibited no evidence of no-reflow, while 213 experienced transient no-reflow, and 45 had persistent no-reflow following PCI.

Over a three-year follow-up period, patients in the persistent no-reflow group demonstrated significantly higher rates of all-cause mortality (HR: 1.98; 95% CI: 1.08-3.65; $P = 0.028$) and cardiac mortality (HR: 3.28; 95% CI: 1.54-6.95; $P = 0.002$) relative to the normal reflow group. Transient no-reflow was associated with an elevated risk of all-cause mortality only relative to the normal reflow group (HR: 1.58; 95% CI: 1.11-2.24; $P = 0.010$). Additionally, when comparing transient to persistent no-reflow, the latter was linked to a markedly higher all-cause mortality rate (46.7% vs. 24.4%, log-rank $P = 0.033$).

In a study by Choo et al.[14] a total of 2,017 patients with STEMI who underwent primary PCI were consecutively enrolled in the Korean multi-center AMI registry. The primary endpoint was all-cause mortality, and the no-reflow phenomenon was identified in 262 patients, representing 13.0% of the cohort. Patients exhibiting no-reflow phenomenon, demonstrated a markedly elevated mortality rate relative to those with successful reflow (30.2% vs. 18.3%, $P < 0.001$). Multivariate analysis using the Cox proportional hazards model identified no-reflow as an independent predictor of long-term mortality (adjusted hazard ratio: 1.45; 95% CI: 1.12-1.86; $P = 0.004$).

Additionally, in our study, correlations between chest pain duration and procedural parameters, including stent diameter, stent length, NC balloon length, inflation size and pressure, and TIMI flow and MBG post-operative, revealed that longer chest pain duration, higher NC balloon inflation pressure, higher NC balloon to stent size ratio, and longer stent length were strongly and negatively correlated with TIMI flow and MBG outcomes, leading to poorer post-procedural results.

Conversely, stent diameter and NC balloon length didn't significantly affect TIMI flow or MBG.

In summary, routine SPD in the setting of primary PCI, after excluding the urgent need for this technique, is usually associated with transient no-reflow and may result in a poor outcome. However, this was not proven in our study due to several factors, such as no-reflow being managed by operators in most of the patients and the very short in-hospital follow-up period.

Future research should incorporate mechanistic studies using advanced intracoronary imaging modalities, such as optical coherence tomography or intravascular ultrasound (IVUS), to precisely evaluate stent expansion, residual plaque burden, and potential plaque disruption induced by SPD. Additionally, techniques such as microvascular resistance measurements, index of microcirculatory resistance, or coronary flow reserve could provide functional insights into microvascular integrity post-SPD.

Randomized trials integrating these imaging and physiological assessments could help delineate the direct relationship between SPD, distal embolization, microvascular dysfunction, and clinical outcomes in STEMI. Such studies would also guide the development of refined SPD protocols that balance stent optimization with microvascular protection.

Study Limitations

This study is limited by its single-center design and short in-hospital follow-up duration. Additionally, assessment of myocardial perfusion relied solely on TIMI flow and MBG, whereas more advanced modalities such as MRI or myocardial contrast echocardiography could provide more comprehensive evaluations. Furthermore, IVUS-guided PCI was not available during the study period. A key limitation of our study is that randomization occurred only after successful stent placement and restoration of TIMI III flow. This excludes patients with stent under-expansion or poor initial flow, reducing the generalizability of the results. Additionally, high-risk STEMI patients, such as with cardiogenic shock, heavy thrombus, bifurcation lesions, or needing aggressive pre-dilatation, were not included. Since these patients are at greater risk for no-reflow and may respond differently to SPD, our findings mainly apply to lower-risk STEMI patients with optimal initial outcomes and should not be extended to more complex patients without further research. In addition, the study was conducted by a team of multiple operators, which may have introduced inter-operator variability, despite following standardized protocols for PCI and SPD. Especially within the SPD group, procedural variation occurred as procedural variation balloon size was ultimately chosen based on individual operator judgment, potentially leading to minor inconsistencies in SPD across patients. Also, despite randomization, there remains potential for residual confounding from unmeasured variables that may have influenced the incidence of no-reflow. Finally, blinding was not feasible for operators due to the nature of the intervention.

CONCLUSION

Post-stent dilatation during primary PCI in STEMI patients was associated with a higher incidence of transient no-reflow immediately following the procedure. However, this did not translate into a significant difference in short-term in-hospital clinical outcomes, likely due to prompt intra-procedural management of no-reflow.

Our study does not support routine stent-post dilatation in the setting of primary PCI, especially with long chest pain duration, long stents, large difference between stent and NC balloon size, and with high NC pressure as these factors had negative correlation with TIMI flow and MBG. However, given the study's single-center nature, operator-dependent variability, lack of blinding, and short follow-up, larger studies are needed before definitive practice recommendations can be made.

Ethics

Ethics Committee Approval: The study protocol was approved by Ain Shams University Faculty of Medicine Scientific and Ethical Committee (protocol no: FMASU MS82/2024, date: 06.02.2024).

Informed Consent: Written informed consent was secured from all participants, with strict adherence to ethical standards ensuring protection of privacy and confidentiality of personal data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.S., T.M.A.A., M.M.I., Concept: H.S., T.M.A.A., Design: S.G., T.M.A.A., Data Collection or Processing: S.G., H.S., T.M.A.A., M.M.I., Analysis or Interpretation: S.G., H.S., T.M.A.A., M.M.I., Literature Search: S.G., M.M.I., Writing: S.G., M.M.I.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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