Prediction of Troponin Elevation in Non- ST Acute Coronary Syndrome Patients presenting to The Emergency Department Using Neutrophil-Lymphocyte Ratio

Thesis

Submitted for Partial Fulfillment of Master Degree in Cardiology

By

Sarah Mohamed Mahmoud Ahmed
MBBCH

Under Supervision of

Prof. Dr. Ramy Raymond
Assistant Professor of Cardiology
Faculty of Medicine – Ain Shams University

Dr. Bassam Sobhy
Lecturer of Cardiology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2019

Acknowledgment

First and foremost, I feel always indebted to **Allah**, *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Ramy Raymond,** *Assistant Professor of Cardiology, Faculty of Medicine – Ain Shams University, for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Dr. Bassam Sobhy,** *Lecturer of Cardiology, Faculty of Medicine – Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I would like to express my hearty thanks to all **my family** *for their support till this work was completed.*

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Sarah Mohamed

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
ACS	*Acute coronary syndrome*
AMI	*Acute myocardial infarction*
AST	*Aspartate transaminase*
CCU	*Coronary Care Unity*
C.I	*Confidence interval*
CABG	*Coronary artery-bypass graft*
CK	*Creatinine kinase*
cTnI	*Cardiac troponin I*
cTnT	*Cardiac troponin T*
CVD	*Cardiovascular disease*
ECG	*Electrocardiogram*
ER	*Emergency room*
Hs-cTn	*High sensitive cardiac troponin*
HSPC	*Hematopoietic stem progenitor cells*
IHD	*Ischemic heart disease*
IL	*Interleukin*
LDH	*Lactate dehydrogenase*
MI	*Myocardial infarction*
NLR	*Neutrophil lymphocyte ratio*
NSTE-ACS	*Non-ST elevation acute coronary syndrome*
NSTEMI	*Non-ST elevation myocardial infarction*
OR	*Odds ratio*
PCI	*Percutaneous coronary intervention*
STEMI	*ST elevation myocardial infarction*
TGF	*Tissue growth factor*
UA	*Unstable angina*
VEGF	*Vascular endothelial growth factor*
WBC	*White blood cells*

ABSTRACT

No significance difference in the level of hemoglobin, WBCs and platelets between the 2 groups. The neutrophil count was significantly higher in the troponin-positive group ($p < 0.001$). The median admission. NLR was significantly higher in the troponin-positive group (2 vs. 3.9, $P < 0.001$).

A cutoff point of 3.4 for NLR measured on admission had 84% sensitivity and 84% specificity in predicting follow-up troponin positivity. A highly significant correlation was found between NLR and level of troponin change (p value <0.01)

As a conclusion; NLR can be used as a diagnostic tool in the differentiation of patients with acute coronary syndrome. NLR is a non-expensive, simple and available parameter that can be used in diagnosis of NSTEMI.

Keywords: Acute Coronary Syndrome - Confidence Interval - Coronary Artery-Bypass Graft

INTRODUCTION

Total white blood cell (WBC), neutrophil, and lymphocyte counts, as well as the neutrophil–lymphocyte ratio (NLR), are considered markers of systemic inflammation. [1]

Also an elevated WBC count has been associated with cardiovascular risk.[2]

In previous reports, the NLR was especially shown to be a predictor of cardiac events and mortality in patients with stable coronary artery disease (CAD) and severity of coronary atherosclerosis. [3 4 5]

In addition, several studies showed that total WBC count, its differential, and the NLR have prognostic value in patients with acute coronary syndromes (ACSs). [6 7 8]

Increased neutrophil count has been related to myocardial infract extension [9], development of post infarction heart failure [10], impaired epicardial and microvascular perfusion [11 11] and post infarction mortality [12]

Limited studies are done on the diagnostic power of NLR in patients presenting to the emergency department with chest pain.

In countries with a lack of resources, this relatively inexpensive and very available parameter can be of great

importance and contribute to establishing the correct diagnosis in patients with chest pain, since the diagnosis of acute coronary syndrome can pose a difficult challenge.

AIM OF THE STUDY

The aim of our study is to determine the ability of neutrophil-lymphocyte ratio to predict troponin elevation in patients presenting to emergency department with non- ST segment elevation acute coronary syndrome.

Chapter 1
WHITE BLOOD CELL COUNT AND CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is one of the main causes of death in both Eastern and Western countries[13]. Despite having multiple risk factors that contribute to the development of CVD, atherosclerosis plays a pivotal role in its pathogenesis[14]

The intimal retention of apolipoprotein (apo) B-containing lipoproteins, in regions of disturbed blood flow and low shear stress, is the key initiating process of atherosclerosis [15].

Lipid-rich macrophages –foam cells – appear early in the intima and can be found in around 40% of newborns; with regression before the age of 2.

Preatheroma is recognized when small pools of extracellular lipids are found in the intima, however atheroma is formed of an easily discernible core of extracellular lipid

By the age of 40, 95% of people start to have complicated lesions in the form of; the appearance of fissures, hematoma, and thrombi; and calcification. When any of the previously mentioned lesions interferes with tissue oxygenation either because of the lesion size or the lesion ruptures and occludes the vessel, that's when the problem occurs.

Of the two, rupture of the lesion is far more dangerous as it could results in sudden events as myocardial infarction and stroke. [16]

Although leukocytes are known to be keepers of the immune system. Yet they can also contribute to disease. Virtually every leukocyte class has a role in the atherosclerosis process and its complications. Some leukocytes are atherogenic while others are atheroprotective; some maintain the inflammation process after myocardial infarction while others resolve it. This heterogeneity in their functions provides a chance for therapeutic intervention through targeting specific disease-promoting functions and sparing those required for normal homeostasis.

In 1974, studies found that the WBC count was a strong predictor of infarction[17].similar to that of serum total cholesterol or a single determination of blood pressure.

In addition, it was found that smokers with WBC count greater than 9000 per l had four times increased risk to develop AMI, than smokers with WBC count below 6000 per l [18]. Another study showed that people with a total WBC count greater than 10 000 per had twice the risk than those with WBC count at or below 4000 per l. This was independent of gender, smoking history, blood pressure, and cholesterol level. [19]

Therefore, An elevated WBC was found to be a marker for the disease process that leads to vascular injury and ischemia[20]. Also, a high WBC count might be demonstrated as a manifestation of a "hematological stress syndrome". [21]

Leucocytes in Acute Myocardial infarction

Acute MI is a traumatic event that affects multiple organ systems. Hours after injury, increased angiotensin-2 signaling triggers the recruitment of monocytes derived from a reservoir in the splenic red pulp[22].

In the very first few days after infarction, the recruitment of leukocytes remains at high levels [23]. In order to meet the demand, the bone marrow and the spleen increases their production. So the question is how do the myelopoietic sites know the need for cells in the heart?

The answer is; Pain and anxiety. They stimulate the sympathetic nervous system and activate neuro-immune synapses to produce noradrenaline that binds to β3 adrenergic receptors present on mesenchymal stem cells (MSC)[24]. As a result the MSC inactivate the hematopoietic stem/progenitor cells (HSPC) retention factor CXCL12, which in turn liberate HSPC into circulation. These cells go to the spleen and stimulate extramedullary myelopoiesis to produce monocytes beyond its baseline reservoir function.

In addition to increased level of monocyte production, other local changes happens in the spleen as increased levels of IL-1β and stem cell factor (SCF/kit ligand)[11, 12].

Leucocytes and microvascular Injury

Three mechanisms are identified that may contribute to microvascular injury.

1. *Pressure-dependent plugging of microvessels by leukocytes:*

The internal diameters of most nutritive capillaries are smaller than the leukocyte diameter. Thus, the WBCs passage in the capillaries is frequently associated with slowing, or stoppage of blood flow for moments[25].

2. *Rheological abnormalities of leukocytes:*

Increased leukocyte adhesiveness alter the rheological property of the leucocytes. Craddock et al. found that granulocytes are able to make aggregates as platelets that embolize to microvascular sites[26]. This process has been demonstrated in vitro as a response to complement activation (with the activation of C5a), bacterial oligopeptide chemotaxins[27], immune complexes[28], and leukotriene B4 [29]

3. ***Endothelial cell injury caused by leukocytes***

This was explained in vivo by the help of fluorescent intravital microscopy[30] that showed enhanced neutrophil adhesion to endothelial cells and aggregation.

Aside from neutrophils, At the first days the distressed tissue expresses CCL2 [31] that attracts Ly-6Chigh monocytes, then switches to the expression of CX3CL1 that attractsLy-6Clow monocytes[32]. This change in the behavior of the infarct tissue is of unknown cause but it could be explained as different monocyte subsets do function differently.

On one hand, Ly-6Chigh monocytes are rich in rich inpro-inflammatory mediators including proteases that are strictly regulated to balance wound debridement with tissue destabilization.

Although both are phagocytic, the early inflammatory subset is particularly rich in pro-inflammatory mediators. These include proteases, which are strictly regulated to balance wound debridement with tissue destabilization in order to avoid infarct expansion or even rupture.

On the other hand, Ly-6C low monocytes provide vascular endothelial growth factor (VEGF) and TGFβ thus support angiogenesis and extracellular matrix synthesis[32]