DETERMINATION OF REFERENCE RANGE FOR HIGH SENSITIVE TROPONIN T AMONG END STAGE RENAL DISEASE PATIENTS IN HOSPITAL RAJA PEREMPUAN ZAINAB II, KELANTAN

DR WAN NUR AIMI BINTI WAN MOHD ZAMRI

Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Pathology (Chemical Pathology)

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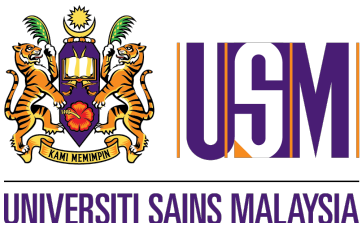

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SUPERVISOR:
DR NOOR AZLIN AZRAINI BINTI CHE SOH@YUSOF

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LIST OF ABBREVIATIONS AND SYMBOLS

ABBREVIATIONS

ACS	: Acute coronary syndrome
AMI	: Acute myocardial infarction
CAD	: Coronary artery disease
CAPD	: Continuous ambulatory peritoneal dialysis
CI	: Confidence interval
CKD	: Chronic kidney disease
cTn	: Cardiac Troponin
cTnT	: Cardiac Troponin T
cTnI	: Cardiac Troponin I
cTnC	: Cardiac Troponin C
CV	: Coefficient variation
CVD	: Cardiovascular disease
ECG	: Electrocardiogram
ESRD	: End stage renal disease
eGFR	: Estimated glomerular filtration rate
GFR	: Glomerular filtration rate
HD	: Hemodialysis
hs-TnT	: High sensitive Troponin T
hs-cTn	: High sensitive cardiac troponin
HRPZ II	: Hospital Raja Perempuan Zainab II
IQR	: Interquartile range

kD	: kiloDalton
KDIGO	: Kidney Disease Improving Global Outcome
LVH	: Left ventricular hypertrophy
MDRD	: Modification of Diet in Renal Disease
MI	: Myocardial infarction
MREC	: Medical Research and Ethics Committee
NRR	: National Renal Registry
ng/L	: nanogram per liter
NSTEMI	: Non-ST-elevation myocardial infarction
PD	: Peritoneal dialysis
SD	: Standard deviation
SPSS	: Statistical Package for the Social Science
STEMI	: ST-elevation myocardial infarction
TnC	: Troponin C
TnI	: Troponin I
TnT	: Troponin T
UA	: Unstable angina
URL	: Upper reference limit

SYMBOLS

∘C	: Degree Celcius
<	: Less than
≥	: More and equal than

ABSTRAK

Tahap troponin T boleh meningkat di kalangan pesakit yang menghidapi kegagalan buah pinggang peringkat akhir (ESRD) walaupun tanpa iskemia jantung dan ini menyukarkan diagnosis sindrom koronari secara akut (ACS). Objektif kajian ini adalah untuk menentukan tahap dan julat rujukan high sensitive troponin T (hs-TnT) dalam kalangan pesakit ESRD yang menerima rawatan dialisis tetapi tidak mempunyai tanda- tanda ACS. Kajian keratan rentas ini dijalankan di Unit Hemodialisis Hospital Raja Perempuan Zainab II, Kelantan dari Januari 2018 hingga Februari 2019. Rekod perubatan pesakit ESRD yang menjalani rawatan dialisis seperti data demografi, etiologi ESRD, jenis dan tempoh dialisis dicatatkan. Subjek yang tidak mengalami ACS layak untuk menyertai kajian ini. Tahap hs-TnT sebelum dialisis dianalisa menggunakan Cobas e411. Sejumlah 150 pesakit ESRD yang layak menyertai kajian ini dimana 62% subjek adalah perempuan dan majoriti (94%) adalah Melayu. Purata (SD) umur subjek adalah 45.19 (16.36) tahun. Median (IQR) bagi hs-TnT adalah 59.20 ng/L (83.41 ng/L). 149 (99%) subjek mempunyai tahap hs-TnT melebihi nilai cut-off di mana 98.2% adalah di kalangan pesakit hemodialisis (HD) dan 100% di kalangan pesakit dialisis peritoneal ambulatif (CAPD). 95% julat rujukan untuk hs-TnT di kalangan pesakit ESRD adalah 11.86-379.52 ng/L (2.5^{th} persentil 90% had keyakinan (CI)=9.67-14.51 ng/L and 97.5^{th} persentil 90% CI=310.06-465.31 ng/L) dengan 99th had rujukan atas ialah 526.40 ng/L (90% CI=430.13-645.48 ng/L). Kajian ini menunjukkan bahawa hampir semua subjek mempunyai tahap troponin T melebihi nilai cut-off. Pengetahuan tentang julat rujukan dan had rujukan atas boleh menjadi panduan kepada doktor apabila merawat pesakit ESRD yang mengalami tanda-tanda serangan jantung dan boleh digunakan sebagai had rujukan untuk diagnosis ACS.

ABSTRACT

In End-stage renal disease (ESRD), troponin T can be elevated even without cardiac ischemia thus diagnosing an acute coronary syndrome (ACS) in these patients is often difficult. The objectives of our study were to evaluate the high-sensitive troponin T (hs-TnT) level and to determine its reference range in dialysis-dependent ESRD patients without ACS. This cross-sectional study was conducted at Hemodialysis Unit of the Hospital Raja Perempuan Zainab II, Kelantan from January 2018 and February 2019. Medical records of ESRD patients on dialysis were reviewed. Demographic data, etiology of ESRD, type, and duration of dialysis were recorded. Subjects with no recent (<30 days) ACS were included in this study. Pre-dialysed hs-TnT was measured using Cobas e411. A total of 150 ESRD patients were recruited with 62% were females and majority (94%) were Malays. The mean (SD) age was 45.19 (16.36) years. The hs-TnT median (IQR) was 59.20 ng/L (83.41 ng/L). 149 (99%) of our subjects had hs-TnT level above cut-off in which 98.2% and 100% were among hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients respectively. The 95% reference ranges for hs-TnT level in ESRD patients were 11.86–379.52 ng/L (2.5^{th} percentile 90% CI=9.67-14.51 ng/L and 97.5^{th} percentile 90% CI=310.06-465.31 ng/L) with the 99th percentile upper reference limit (URL) value of 526.40 ng/L (90% CI=430.13-645.48 ng/L). This study demonstrated that almost all of our subjects had elevated troponin T above the cut-off value. Knowledge of the reference range and URL may serve as guidance to the clinicians when managing ESRD patients presented with possible ACS and considered as a cut-off value for the diagnosis of ACS in ESRD patients.

CHAPTER 1

1. INTRODUCTION

1.1 Acute Myocardial Infarction (AMI)

Cardiovascular disease (CVD) is the leading cause of death globally. According to the World Health Organization, 17.9 million people died of CVD in 2016, corresponding to 31% of all deaths worldwide. In Malaysia, CVD is a major health problem, with relatively high morbidity and mortality. CVD accounted for approximately 24.5% of death in government hospitals in the year 2010 and is the leading cause of death in Malaysia (MOH, 2010).

One of the disease components of CVD is acute coronary syndrome (ACS). ACS is further subcategorized into ST-elevation acute myocardial infarction (STEMI), non-ST elevation MI (NSTEMI) and unstable angina (UA), in which all share similar presenting symptoms but differ in underlying pathology.

1.1.1 Diagnosis of AMI

Recently consensus among experts from the European Society of Cardiology, American College of Cardiology, American Heart Association, World Heart Federation Task Force had come out with a universal definition of myocardial infarction (MI) in 2018. Based on the Fourth Definition of Myocardial Infarction (2018) document, AMI and myocardial injury are based on the following criteria:

Criteria for AMI
• When there is an acute myocardial injury with clinical evidence of acute myocardial ischemia and with the detection of a rise/fall of cardiac troponin (cTn) values with at least one value above the 99th percentile upper reference limit (URL) and at least one of the following: - Symptoms of myocardial ischemia - New ischemic electrocardiogram (ECG) changes - Development of pathological Q waves - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology • Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium • Evidence of an imbalance between myocardial oxygen demand and supply unrelated to acute athero-thrombosis • Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal

Table 1: Criteria for AMI (Thygesen *et al.*, 2018)

1.1.2 Pathophysiology of AMI

More than 80% of AMI are as a result of coronary artery atherosclerosis with superimposed intraluminal thrombus (Burke and Virmani, 2007). Disruption of atherosclerotic plaque either eruption, erosion, fissuring or dissection leads to diminished blood flow to cardiomyocytes (Thygesen *et al.*, 2018). This occurs in patients with coronary artery disease (CAD). However, plaque rupture or erosion may occur in non-obstructive or no CAD patients. Other uncommon causes can be seen in patients with other conditions other than CAD such as coronary spasm, coronary embolism or respiratory failure (Thygesen *et al.*, 2018).

Acute mismatch of oxygen supply with increased oxygen demand, leads to myocardial injury. Established modifiable risk factors for AMI are diabetes, hypertension, dyslipidemia, obesity, smoking, stress, unhealthy diet and physical inactivity (Mahmood *et al.*, 2014). On the other hand, the non-modifiable risk factors are increasing age, sex whereby the male is at

higher risk than female, the race where the black population are at higher risk than white and family history with CAD (Mahmood *et al.*, 2014).

1.2 End Stage Renal Disease (ESRD)

ESRD is a state of permanent loss of kidney function. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 categorized end-stage renal failure based on glomerular filtration rate (GFR) category G5 (chronic kidney disease (CKD) stage 5) where the GFR is <15 ml/min.1.73 $m^{3.}$ (Levin *et al.*, 2013).

According to the 24th Report of the Malaysian Dialysis and Transplant Registry 2016 in The National Renal Registry, a total of 39711 patients received dialysis treatment in 2016 with 35781 received hemodialysis (HD) and 3930 received peritoneal dialysis (PD). In the same year in Kelantan state, a total number of 2562 received HD and PD (Goh *et al.*, 2016).

1.2.1 CKD and ESRD with AMI

CKD is an independent risk factor for CVD. For ESRD patients, CVD remained the main cause of death (Collins *et al.*, 2013; Goh *et al.*, 2016). In Malaysia, it has been reported that in 2016, CVD accounted for 33% of all death while another 16% of home death was probably due to cardiovascular events (Goh *et al.*, 2016).

CKD accelerates coronary artery atherosclerosis by several mechanisms, particularly hypertension and dyslipidemia, both of which are known risk factors for CAD (Collins *et al.*, 2013; Weiner *et al.*, 2006). Traditional risk factors for AMI in CKD and ESRD patients are similar to those with the general population. Various non-traditional risk factors facilitate the acceleration of CVD in CKD and ESRD populations. Both traditional and non-traditional risk factors imposed CKD and ESRD patients significantly at higher risk of developing CVD.

Abnormal vascular morphologies in ESRD patients is attributed to atherosclerosis and arteriosclerosis. Atherosclerosis is characterized by fibro-atheromatous plaques formation with calcification and intimal and medial thickness causing occlusive disease (Schwarz *et al.*, 2000). The plaque calcification is also at risk of rupture. Arteriosclerosis is the thickening and calcification of the medial arterial layer due to combination of few pathologies such as increased collagen contents in the vessel wall, hyperplasia and hypertrophy of the vascular smooth muscle cells resulting in wall hypertrophy and stiffening of large conduit arteries which in turn cause increase in the systolic and pulse pressures (London *et al.*, 2002).

Oxidative stress and inflammation are associated with the formation of atheromatous plaque (Weiner *et al.*, 2008). Recently mineralocorticoid excess and aldosterone have been implicated in cardiac and renal vascular injury via the mechanism of inflammation and tissue remodeling and fibrosis (Briet and Schiffrin, 2010). In addition, CKD alters calcium and phosphorus homeostasis, resulting in hypercalcemia and vascular calcification. (Giovannucci *et al.*, 2008). Anemia of kidney failure also appears to be an independent risk factor for cardiovascular mortality (Foley *et al.*, 1998).

1.3 Cardiac Biomarker: Troponins

Troponin was first described by Professor Ebashi in 1963 as ”natural tropomyosin or native tropomyosin” as it confers similar properties with tropomyosin (Ebashi and Kodama, 1965). Later this was shown to be a complex of tropomyosin and a new complex of proteins called troponins. Troponins are regulatory protein complexes located on myofibrillar thin actin filament of striated cardiac muscle as well as skeletal muscles (Garg *et al.*, 2017; Korff *et al.*, 2006). Troponins regulate the interaction between actin and myosin filaments for muscle contraction alongside with calcium ions (Garg *et al.*, 2017). Troponin complex consists of

three subunits which each subunit plays an integral role in cardiac and skeletal muscles contraction:

- Troponin T (TnT) is the tropomyosin-binding component that attaches the complex to actin
- Troponin C (TnC) is the calcium-binding component
- Troponin I (TnI) is the inhibitory component that inhibits the interaction with myosin in the absence of calcium ion.

(Burtis *et al.*, 2012; Garg *et al.*, 2017; Korff *et al.*, 2006)

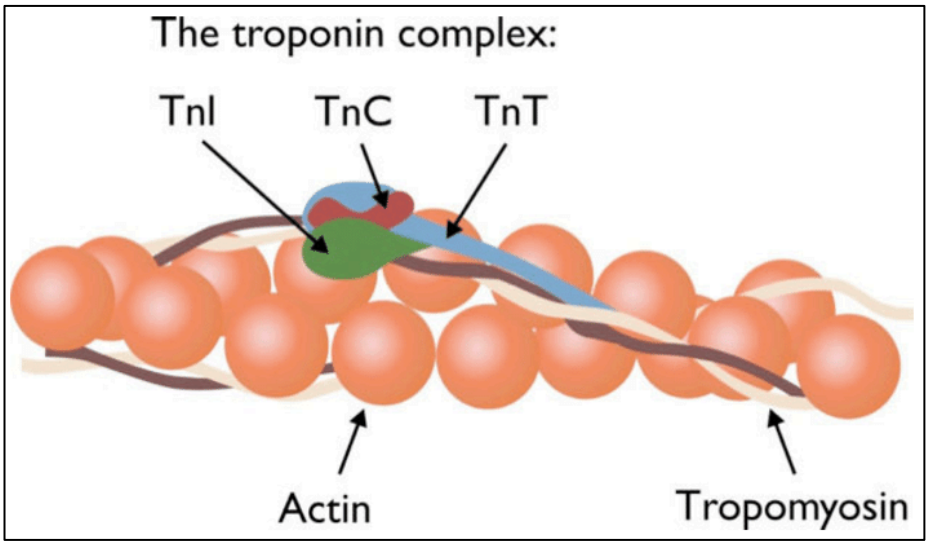

Figure 1 adopted from (Hegyi *et al.*, 2013): Troponin subunits

In circulation troponin subunits present in isoforms that varies between cardiac muscle and skeletal muscle both slow- and fast-twitch skeletal muscles. The cardiac isoform of troponin C is identical to the slow-twitch skeletal muscle isoform thus preclude the usage of cardiac troponin C (cTnC) as a cardiac-specific biomarker for AMI diagnosis (Burtis *et al.*, 2012). Troponin T and I isoforms of cardiac are specific and sensitive to cardiomyocytes. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are encoded by different unique genes than

the one that encodes for skeletal muscle isoforms (Katrukha, 2013) thus making both isoforms as preferable biomarkers for cardiac pathologies associated with necrosis especially myocardial infarction.

cTnT is a low molecular weight protein weighing 37 kD (Gaze and Collinson, 2008) and is the greatest number of the subunit that attaches the troponin complex to tropomyosin and actin filaments (Katus *et al.*, 1991). cTnT is encoded by different gene than the one that encodes for skeletal muscle isoform in which the uniqueness and the cardiac specificity lies on the 11 amino-terminal residues. But on the other hand, it had been identified that small amount of cTnT are expressed as one of the four identified isoforms in skeletal muscle in certain conditions such as in diseased human skeletal muscle such as Duchenne muscular dystrophy and polymyositis (Bodor *et al.*, 1997), in ESRD (Ricchiuti *et al.*, 1998) and during fetal development transiently until mid fetal stage (Burtis *et al.*, 2012). During this stage of fetal development, a gene is upregulated in cardiac myocytes and suppressed in skeletal myocytes (Cooper and Ordahl, 1984). Mc Laurin *et al.* demonstrated on Western blot analysis, the expression of cTnT in skeletal muscle biopsy of renal failure patients (McLaurin *et al.*, 1997) and the possible mechanism is likely linked to peripheral myopathy related to renal disease (Diesel *et al.*, 1993).

Unlike cTnT, cTnI only has one cardiac isoform in heart tissue and is not expressed in skeletal muscle or other tissues during fetal development or in degenerative/regenerative muscle diseases (Burtis *et al.*, 2012). Thus, cTnI is more cardiac-specific than cTnT. Yet, cTnT or cTnI are organ-specific but not disease-specific as both can be released as a result of ischemic, non-ischemic and extra-cardiac conditions.

1.3.1 Cardiac troponin (cTn) in AMI

The majority of cTn in circulation is bound to proteins and small portions are in free form in cytosol. 94% to 97% troponins are found primarily in myofibrils and 3% to 8% (6-8% of cTnT and 2-4% of cTnI) are found on cytoplasmic (Adams *et al.*, 1994; Gaze and Collinson, 2008; Katus *et al.*, 1991). cTn is released from myocytes following cardiac damage into the circulation in free-forms, binary complexes and non-covalent ternary complexes (Gaze and Collinson, 2008). Initially, the cytoplasmic pool is released followed by breakdown and release of the bound troponin complex (Gaze and Collinson, 2008). Following myocardial injury, cTn appear in plasma after two to four hours of onset of symptoms, peak at 12-48 hour and persist up to 21 days in the blood circulation thereafter (Katrukha, 2013), where the half-life of cTnT is five to 14 days and cTnI is four to 10 days in blood (Nigam, 2007). As such, cTn are the preferred biomarkers for the detection of cardiac injury and have long assisted physicians in improving diagnostic strategies for the effective management of patients with chest pain.

Since the elevated cTn values indicative of myocardial injury and ischemia, they do not necessarily indicate the pathophysiology mechanism of the injury and ischemia. cTn values can be elevated in many other conditions not only in MI. Table 2 shows the causes of elevated cTn.

Myocardial injury related to acute myocardial ischemia

- Atherosclerotic plaque disruption with thrombosis

Myocardial injury related to AMI because of oxygen supply/demand imbalance

Reduced myocardial perfusion

- Coronary artery spasm, microvascular dysfunction
- Coronary embolism
- Coronary artery dissection
- Sustained bradyarrhythmias
- Hypotension or shock
- Severe anemia

Increased myocardial oxygen demand

- Sustained tachyarrhythmias
- Severe hypertension with or without left ventricular hypertrophy (LVH)

Other causes of myocardial injury

Cardiac conditions

- Heart failure
- Myocarditis
- Cardiomyopathy
- Takotsubo syndrome
- Coronary revascularization procedure
- Cardiac procedure other than revascularization
- Catheter ablation
- Defibrillator shocks
- Cardiac contusion

Systemic conditions

- Sepsis, infectious disease
- Chronic kidney disease
- Stroke, subarachnoid hemorrhage
- Pulmonary embolism, pulmonary hypertension
- Infiltrative diseases eg amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critically ill patients
- Strenuous exercise

Table 2: Causes for the elevation of cTn adopted from (Agewall *et al.*, 2010; Kelley *et al.*, 2009; Thygesen *et al.*, 2018)

With the advancement of troponin assays and improvement of its sensitivity nowadays especially widely used of high sensitive cardiac troponin (hs-cTn) assay, the rate of detection of myocardial injuries in various non-ACS conditions has been increased, thus imposed risk of misinterpretation of cTn values (Garg *et al.*, 2017; Mueller *et al.*, 2013; Nigam, 2007).

1.3.2 cTn in ESRD

Patients with ESRD had been known to have a greater incidence of chronically elevated cTn compared to non-ESRD patients even without MI (Musso *et al.*, 1999; Parikh and Seliger, 2015; Seliger *et al.*, 2012). Consequently, interpreting cTn values in ESRD patients is challenging, particularly cTnT concentrations in the absence of any signs or symptoms of AMI (Parikh and Seliger, 2015; Thygesen *et al.*, 2018).

With hs-cTn assay, the majority of ESRD patients will have an elevation of cTn above the 99th URL (Twerenbold *et al.*, 2015). Chronic increases of cTn are seen in cTnT and to a lesser extent cTnI in ESRD without an AMI (Herzog, 2017; Seliger *et al.*, 2012). Primarily the elevation of cTn is attributed to lack of assay specificity whereby cross-reactivity of the assay with skeletal isoform (Herzog, 2017). With the development of hs-cTn assays, improvement of assay specificity and lack of cross-reactivity (for example with cTnT mRNA in skeletal muscle), chronic increase in cTn in asymptomatic ESRD patients is in fact direct cardiac damage (Ricchiuti *et al.*, 1998).

The mechanism of chronically elevated cTn in dialysis patients is not known for certain. CKD patients have associated co-morbidities that are known to cause a high level of cTn such as LVH and heart failure that could lead to sub-endothelial ischemia and subclinical cardiac damage (Bloch *et al.*, 2014; Ferrer-Hita *et al.*, 2007; Fu *et al.*, 2018; Iliou *et al.*, 2001). This is possibly exacerbated by reduced renal clearance (Bloch *et al.*, 2014; Iliou *et al.*, 2001). Chronic myocardial strain due to hypertension, anemia, chronic fluids overload,

and cardiac remodeling and shunt flow may also cause elevated cTn in ESRD patients (London, 2002; Wang and Lai, 2008). Another theory hypothesized is that high urea levels in blood cause injury and subsequent regeneration of cardiac muscles (Freda *et al.*, 2002). This theory is termed as uremia induced skeletal myopathy and is supported by the morphology changes of skeletal muscle observed under electron and light microscopy in patients on maintenance dialysis (Diesel *et al.*, 1993).

In ESRD patients with chest pain, elevated hs-cTn is highly sensitive for AMI, although the specificity is maybe limited. But in asymptomatic patients, few approaches have been evaluated to assist in AMI diagnosis. To increase specificity, serial changes particularly absolute changes are necessitated to distinguish between acute from chronic elevation (Reichlin *et al.*, 2011; Stacy *et al.*, 2014) but not helpful to distinguish between types of AMI (Sandoval *et al.*, 2014).

The majority of ESRD patients have concomitant diabetes and they can present with asymptomatic or atypical symptoms of MI such as fatigue or dyspnea. These symptoms may be dialysis-related, not necessarily angina-related. The ECG also can be inconclusive. ECG is the mainstay in the initial diagnosis of patients with suspected ACS which will dictate the management. However, ECG in dialysis patients showed diverse wave patterns of abnormalities (Abe *et al.*, 1996) and ST-elevation can be seen in other medical conditions such as acute pericarditis, LVH, left bundle branch block, Brugada syndrome and stress cardiomyopathy (Thygesen *et al.*, 2007).

Higher hs-cTn cut-off values or estimated GFR (eGFR)-range-specific optimal cut-off values may be applied when diagnosing AMI in ESRD patients (Twerenbold *et al.*, 2015; Yang *et al.*, 2017).

1.4 Rationale of Study

cTn level in ESRD patients is elevated above the 99th percentile URL even in the absence of AMI. KDIGO recommended clinicians to interpret cTn levels in CKD and ESRD patients in context with appropriate clinical setting and appropriate blood sampling timing (Levin *et al.*, 2013). This study was carried out to provide knowledge on the proportion of the adult ESRD patients with elevated cTnT above the 99th percentile of URL using hs-TnT assay among our population and to recommend a reference range of hs-TnT.

Given the association of ESRD with cardiovascular mortality and morbidity with the chronically elevated cTn in ESRD patients and complexity of presenting symptoms and non-conclusive ECG findings, it is important for clinicians to accurately diagnose and manage elevated cTn, as in this study we are focusing on hs-TnT, especially in dialysis patients who have no symptoms of ACS. This knowledge will be valuable in providing a reliable interpretation that can be applied in our population in relation to the diagnosis of ACS. The aim of our study is to determine the proportion of the adult ESRD patients with cTnT level beyond the URL of the hs-TnT test (14 ng/L) and to determine the hs-TnT reference range among this population.

CHAPTER 2

2. OBJECTIVE

2.1 General Objective:

To assess the hs-TnT level in dialysis-dependent ESRD patients in HRPZ II who have no recent (< 30 days) ACS.

2.2 Specific Objectives:

1. To determine the proportion of adult ESRD patients with a hs-TnT level beyond the normal range of the test
2. To determine the reference range of hs-TnT level among adults ESRD patients in HRPZ II.