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Harmonisation of discordant notes of cardiac markers and its implications for clinical decisions in cardiovascular disease

Dr Barnali Das, MD, DNB, PGDHHM, Consultant, Laboratory Medicine, Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai, India drives home the point that laboratories must take on the responsibility of being the evidence based decision makers in healthcare ecosystem managing the essential diagnostics like cardiac care and chronic conditions affecting population health or acute care. She also believes that they must drive the care-models on measurable outcome, the total cost of delivery and population risk stratification and financial risk adjustment.

On the occasion of World Heart Day, the road map for laboratory medicine in clinical decision making involves strategies for harmonising, communicating and integrating with all stakeholders; like, clinicians, diagnosticians, IVD industry and regulatory agency, in order to formulate guidelines for assisting in correct measurement, diagnosis and management of cardiovascular diseases. Laboratories must take on the responsibility of being the evidence based decision makers in healthcare ecosystem managing the essential diagnostics like cardiac care and chronic conditions affecting population health or acute care. We must drive the care-models on measurable outcome, the total cost of delivery and population risk stratification and financial risk adjustment.

Cardiovascular disease has been projected as the leading cause of death globally and it would account for more than 23 million deaths per year by 2030. In India, mortality due to cardiovascular diseases showed to have a 13 percent increase from 1990 until 2016. Cardiovascular diseases (CVD) still remains the primary cause of death worldwide as well as in India regardless of advances in diagnosis, treatment and risk assessment tools. Chest pain is one of the most common reasons for people visiting the accident and emergency department (A&E) in hospitals to rule out and rule in acute coronary syndrome (ACS). CVD has significant morbidity and mortality if not treated in a timely manner.

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The evaluation of patients with chest pain requires highly skilled resources and expensive time. Reducing patient length of stay with safe outcomes maximises care while also reducing overall costs. Early and accurate diagnosis of acute myocardial infarction is essential for successful treatment and improved outcomes.

Cardiac biomarkers can provide key insights into patients with cardiovascular disease (CVD), contributing to patient screening, admission, monitoring, treatment guide, as well as prognostication.

Cardiac Biomarkers and Lipid Profile form a very important set of tests in a pathology laboratory – a tool that clinicians and patients alike depend on, to pin down the symptoms for risk stratification treatment and relief.

However, it is these very sets of tests that have come in question. First, what is the normal and acceptable range (upper and lower limits) of different lipid and cardiac biomarkers in a particular population has been debated in different scientific fora. This is because the level of markers can vary considerably with race, gender, age, different physiological conditions and other illnesses and interfering substances. Due to the lack of proper cut off and reference intervals and sometimes due to standardised measurement procedures, standardisation and harmonisation of these assays still remains a formidable challenge.

Troponin measurement, a keystone in the diagnosis and management of ACS, detects the levels of troponin – a cardiac-specific structural protein released by damaged heart muscles. High sensitive Troponin assay help in higher analytic precision at lower concentrations, and increased clinical sensitivity for acute coronary syndrome (ACS). It can detect even small changes in troponin concentration (delta changes: increase or decrease) in particular time frame.

Sex differences are common across multiple aspects of cardiovascular care including diagnosis, treatment, and outcomes. Recognising that poorer outcomes for women vs. men post-intervention may result from delayed diagnosis of women, and with full appreciation that some men may be more aggressively treated based on use of lower upper reference limits that lack sex discrimination, the Biochemistry & Immunology team at Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute (KDAH) sought to investigate the opportunity to move from an overall URL (Upper reference limit) to sex-specific URLs consistent with guideline-based care.

However, there were concerns raised about the use of single, universal cut-off value of hs Troponin I for both men and women, as there is a potential risk of under-diagnosis in women, since they have a lower threshold value of troponin. A total of 2797 female patients and 2805 male patients were enrolled. Percentage of positive female patients with acute cardiac events if the cut-off was more than 26.2 pg/ml was 68 percent. Percentage of positive female patients with acute cardiac events if the cut-off was more than 15.6 pg/ml was 82 percent. The difference in females undetected without gender specific cut-off was 14 percent. The cut-off threshold value of hsTnI for male was decided to be 34 pg/ml. Implementation of gender-specific diagnostic threshold helped in identifying more women at increased risk of ACS or death, than a generic threshold.

Therefore, implementation of sex-specific upper reference limits identified an additional 14 percent of at risk women with potential acute myocardial infarction. This in turn also decreased the number of men being diagnosed by 3 percent.

Furthermore, high sensitive Troponin I assay can function as predictive biomarkers for cardiovascular risk stratification (high/ moderate/ low risk) in the general population. The evaluation of high sensitive Troponin assay in comparison to existing risk stratification algorithms and biomarkers also show promising results wherein there is improvement in the prognostic accuracy. The addition of a high sensitive Troponin I (hsTnI) assay to current risk-stratification tools like hsCRP, lipid-profile can enhance risk prediction in case of CVD and over-all cardiovascular deaths in asymptomatic individual thereby alerting clinicians in order to prevent future CVDs. We have evaluated high sensitive Troponin I as a risk stratification tool in a small study. In our study, 3.3 percent showed were elevated risk based on cut-off values used in cardiovascular risk stratification in general population.

Lipid Association of India (LAI) published their first expert consensus statement for management (LAIECS-1) of dyslipidemia in Indians in 2016, aiming to address this growing concern of cardiovascular morbidity and mortality. Smoking, sedentary lifestyle, obesity, hypertension, and diabetes are all contributing factors to atherosclerotic cardiovascular disease (ASCVD); however, dyslipidemia is the major condition responsible for atherosclerosis. The prevalence of dyslipidemia defined according to National Cholesterol Education Programme (NCEP) guidelines, is very high in Indians, with 79 percent having at least one lipid abnormality, 72.3 percent with decreased high density lipoprotein cholesterol (HDL-C) levels, 29.5 percent having hypertriglyceridemia in 29.5 percent and 11.8 percent showing elevated low density lipoprotein cholesterol

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(LDL-C) levels. Therefore, optimal management of dyslipidemia paves the way of the epidemic of ASCVD along with control of other risk factors.

As a primary target, LAI in 2016 recommended a LDL-Cholesterol level of <50 mg/dl and a Non HDL-Cholesterol (co primary target) level of <80 mg/dl for patients of Very High Risk group (VHRG) which includes patients of atherosclerotic Cardiovascular Disease (ASCVD). LDL-C and Non HDL-C Target for High Risk group are <70 mg/dl and <100 mg/dl respectively. LDL-C and Non HDL-C Target for Moderate and Low Risk groups are <100 mg/dl and <130 mg/dl respectively (reference LAIECS-1 in 2016). New extreme risk groups (ERG) with category A and B have been introduced in the LAIECS-3 in 2020. Furthermore, National Lipid Association of US in their recent scientific statement published in March 2021 also recommended strict LDL-C goal for extreme risk group for prevention of atherosclerotic cardiovascular disease in South Asians in the US.

Coronavirus disease-2019, caused by the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) entry into the cells via human angiotensin converting enzyme 2 (ACE 2) receptor, which is expressed mainly in the lungs and also in the cardiovascular system. A significant rise in cardiac biomarkers like natriuetic peptides and troponins is observed in COVID-19. This significant increase is seen to associate with COVID-19 complications and increases mortality. The possible mechanisms of cardiac injury in COVID-19 patients stated in several publications include inflammation, cytokine storm, micro/macro thrombosis, direct viral invasion and supply or demand imbalance. The cardiac biomarkers are believed to aid triaging, clinical decision making, risk-stratification and prognostication of patients with COVID-19.

Based on the association of cardiovascular disease with COVID-19 infection and the importance of understanding the influence of COVID-19 on cardiovascular system, we have studied the cardiac makers, NT pro BNP and hs Troponin I in COVID-19 patients. On analysing the data it was seen that both NT pro BNP and hs Troponin I levels are significantly higher in case group (COVID-19 patients with chest pain complaints) compared to the control group (healthy individuals). NT pro BNP and hs Troponin I have an excellent accuracy with Area under Curve (AUC) of 1.0 and 0.91 respectively. Both NT pro BNP as well as hs Troponins are excellent biomarker for cardiac injury.

The box plot of NT pro BNP in COVID-19 patients with chest pain (case group) showed the first quartile (Q1/25th percentile) of 625.23 pg/ml, third quartile (Q3/75th percentile) of 11441.5 pg/ml, with a median of 3638.5 pg/ml and whiskers to 126.4 pg/ml and 23924 pg/ml.

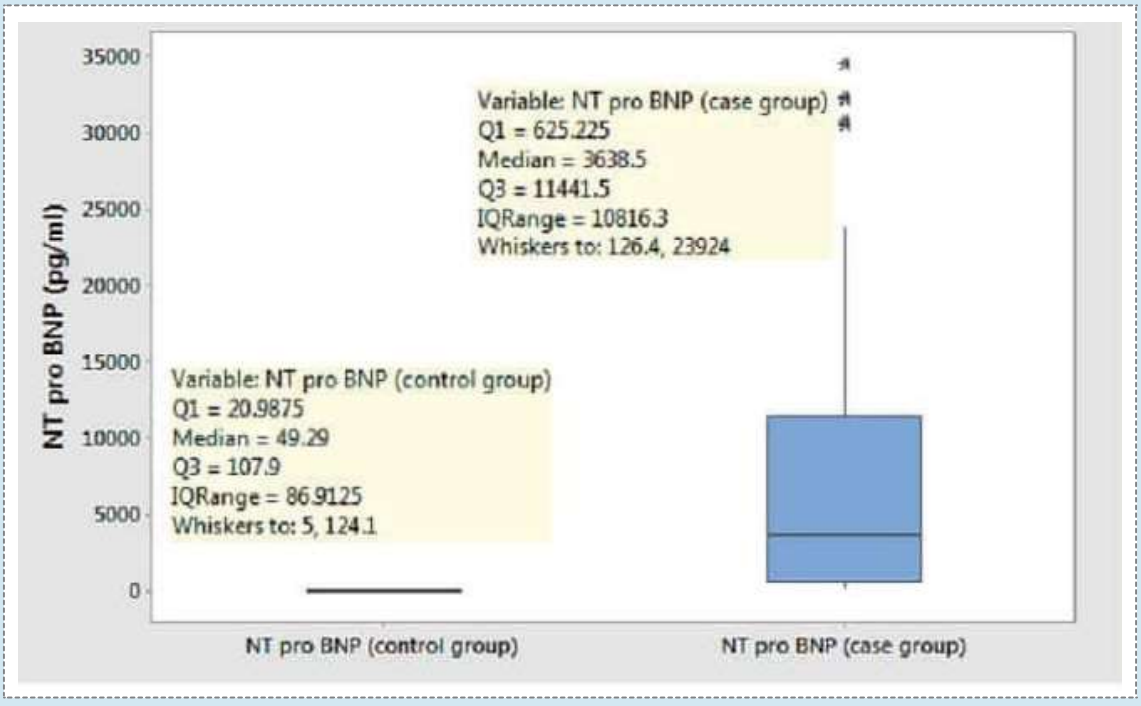

Figure: Box plot – Data representation of NT pro BNP in COVID-19 cases presenting with chest pain (control and case group)

The box plot of hs Troponin I (COVID-19 case group) showed Q1 of 37.18 pg/ml, Q3 of 1410.78 pg/ml, with a median of 101.2 pg/ml and whiskers to 1.6 pg/ml and 2984.1 pg/ml.

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The role of laboratory physicians has been challenged many times in the past. Therefore, in the constant quest to develop a harmonised healthcare ecosystem, it is essential to provide evidence of how the laboratory medicine is playing crucial roles in improved clinical outcomes, contributing to patient screening, admission, staging, monitoring, treatment guide, as well as prognostication.

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