Evaluation of Cardiac Markers using Radar Chart

TAY YII CHENG, MOCHROSIN, MUHAMMAD HAIKAL SATRIA, EKO SUPRIYANTO, JASMY YUNUS
Advanced Diagnostics and Progressive Human Care Research Group
IJN-UTM Cardiovascular Engineering Center
Faculty of Biosciences and Medical Engineering
Universiti Teknologi Malaysia, MALAYSIA
eko@biomedical. utm.my

Abstract: - Cardiac markers are important parameters to diagnose and prognose cardiac injury of patients with chest pain or similar symptoms, especially when electrocardiograms do not show any abnormality. With more types of cardiac markers and their characteristics being studied, it is essential that comparison should be done in integrated and comprehensive way. In this work we proposed a comparison method of cardiac marker by visualizing radar graph for eight (8) selected characteristics of each marker. It was found that this method has the potential to assist the selection of cardiac markers based on the preferred characteristic.

Key-Words: - cardiac markers; comparison method; markers characteristics; radar graph

1 Introduction

1.1 Background

Chest pain is one of the most common syndromes for myocardiac infarction. About 5 – 10% of the visits in the emergency department are due to this particular syndrome [1]. However, most of these patients have relatively unremarkable electrocardiograms (ECG). Therefore, by relying on ECG alone, this contributes to about 2 – 5% missed rates [2,3].

In response to this, the importance of cardiac marker testing has been widely accepted and is suggested as part of the initial evaluation of patients presenting with chest [4]. Cardiac markers are useful in ruling out cardiac ischemia in chest pain patients or capturing patients with acute cardiac syndrome who otherwise have non diagnostic tests. These testing often require 6–12 h or longer observation while depending on the symptom onset time [5].

One of the most common cardiac markers is troponin. However, markers of myocardial ischemia and inflammation have the potential to differentiate chest pain patients in shorter time intervals than cardiac-specific troponin, which may lead to earlier treatment or discharge. Therefore, more studies have been done in order to discover more about the characteristics of currently used as well as novel cardiac markers.

1.2 Problem Statement

With the emerging of new cardiac markers, there is a need to judge their ability because they could have the potential to be a better cardiac marker in identifying myocardiac infarction. In order to judge the performance of the new cardiac markers, comparison of their characteristics with the currently widely used cardiac markers is essential. However, there are many characteristics that could describe the performance of each cardiac marker in identifying myocardial infarction. Among the existing literatures, it was found that the comparison was not done extensively. Most of the literatures only compare among a few cardiac markers by involving only few characteristics. Besides that, the characteristics were also compared separately, which hinders general interpretation.

1.3 Objectives

This research proposed a method to compare the characteristics of some most common and new cardiac markers in an integrated and graphical way. The comparison in a figure could facilitate general interpretation of the ability of cardiac markers in identifying myocardiac infarction without influenced by bias judgement due to common practice. Besides that, a graphical interpretation could also make the information more comprehensible.

2 Literature Review

This section will provide a general background on the cardiac markers investigated in this research and also some criteria of good cardiac markers.

2.1 Cardiac Markers

Cardiac markers are biomarkers which are produced after myocardial injury. Figure 1 shows the stages of

heart failure and the cardiac markers produced in each stage. The release of each cardiac marker is determined by the physiological response and condition in each stage. Therefore, the type of cardiac marker released at each distinct time point is specific and thus can be used for diagnosis and prognosis purpose in defining the cardiac condition of a patient.

Cardiac troponin regulates the interaction of actin and myosin. Cardiac troponin complex has 3 subunits, which are Troponin T (cTnT), Troponin I (cTnI) and Troponin C (cTnC). It is the most widely established and useful biomarker for myocardial injury. cTnI and cTnT usually used for the diagnosis of myocardiac injury because they are only expressed in cardiac muscle, which contributes to its high specificity in defining myocardial damage.

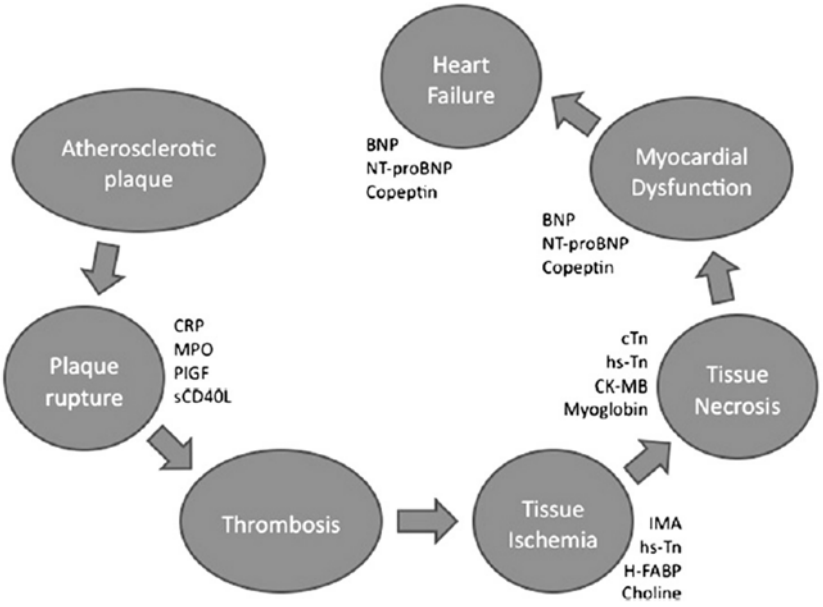

Fig. 1: Schematic representation of the pathogenesis of myocardiac infarction and its consequences. The biomarkers implicated in each process are listed next to the appropriate bubble [6]

However, the concentration of troponin inside the plasma can be affected by other pathological conditions which are not cardiac origin. Besides that, troponin levels can also be increased by the presence of pulmonary embolus, cardiac contusion, cardioversion or radiofrequency ablation, septic shock, chemotherapy (adriamycin, 5-fluorouracil), hypothyroidism and renal failure [7].

High-sensitive troponin (hs-Tn) permits the detection of very low levels of cTnT. This highly improves the overall diagnostic accuracy and also high negative predictive value in ruling out the possibility of myocardial injury in patients with suspected acute myocardial infarction. The increased sensitivity is important for patients with a short duration from symptom onset to admission [8]. However, this causes specificity to decrease.

Creatine kinase is an enzyme responsible for transferring a phosphate group from ATP to creatine. It is composed of M and B subunits that form CK-MM, CK-MB and CK-BB isoenzymes [7].

CK-MB can be found in skeletal muscle and the brain, but its presence in high concentration is unique to myocardium. Some of the false positive of CK-MB are significant skeletal injury, myocarditis, blunt chest trauma, cardiac catherization, shock, cardiac surgery and post-cardio-pulmonary resuscitation and chronic renal failure.

Myoglobin is a small cytoplasmic heme and oxygen storing protein found in skeletal and cardiac muscle. Among all the conventional biomarkers currently in use, myoglobin has the advantage of being the earliest marker to rise after acute myocardiac infarction because of its relatively small size and high cytoplasmic content [9]. However, it has lower specificity since myoglobin is present in all muscles.

C-reactive protein (CRP) is a protein produced by the liver that is upregulated in conjunction with the inflammatory response. It binds to damaged cells including those in infarcted myocardium. However, its specificity in inflammation is not high, and CRP is involved in coronary plaque atherogenesis [7].

Natriuretic peptides are vasoactive hormones secreted by the heart and work as protective hormones that counteract the physiologic abnormalities of heart injury and myocardial dysfunction. Precursor proBNP is cleaved into the active BNP hormone and inactive NTproBNP

fragment. It has a shorter half-life than NT-proBNP because they are cleared by different mechanisms [10]. Same as the other cardiac markers, BNP and NTproBNP levels are also affected by the renal condition of the patient.

Myeloperoxidase is released by macrophages and neutrophils during acute inflammation and is involved with the oxidation of lipids and destruction of the vasodilator nitric oxide. As a result of its connection to inflammation and atherosclerosis, MPO has the potential to indicate stable ischemic heart disease and acute myocardial injury, in which it serves as a marker of plaque instability.

Ischemic modified albumin is produced when circulating serum albumin contacts ischemic heart disease. The disadvantage of using Ischemic modified albumin cardiac marker is the test is not widely available [7]. Its false positive is contributed by liver cirrhosis, certain infections and also advanced cancer.

Copeptin is a glycosylated peptide that shares the same precursor as vasopressin. In severe diseases such as shock, sepsis, stroke, or cardiovascular diseases, the nonosmotic release of arginine vasopressin is portrayed by a sharp increase in plasma copeptin, which carries diagnostic and prognostic value for myocardial injury.

Heart-type fatty-acid-binding protein (H-FABP) is a cytosolic, low-molecular-weight protein involved in fatty acid transport and metabolism. Several studies have indicated that it is a marker of myocardial ischemia even in the absence of frank necrosis.

Choline is a water-soluble essential nutrient found in the head groups of phospholipids that make up cell membranes. Choline is released into the blood after cleavage of phospholipids.

2.2 Concentration of Cardiac Markers in Plasma

The concentration of cardiac markers in plasma is affected by various factors, such as body size, size of myocardiac infarction, treatment received, presence of other pathological disorder and time passed presentation. The concentration will affect the characteristics of cardiac markers, such as sensitivity, specificity, PPV and NPV.

Figure 2 shows the concentration of some of the most commonly used cardiac marker against time. Generally, the phase can be categorized into elevation time, peak time, clearance time and also duration remain elevated.

Elevation time is the time when the cardiac marker is first detected in the plasma or sample. It determines how early a cardiac marker can provide information about the cardiac injury. Peak time is the time when the cardiac marker is at its highest concentration while clearance time is the time when the level of cardiac marker in plasma or blood is below the threshold of detection. Lastly, duration remain elevated describes how long is the cardiac marker maintain its detectability in the plasma or blood. The longer is the duration; it is less likely for physicians to miss out the clue for diagnosis and prognosis of cardiac injury.

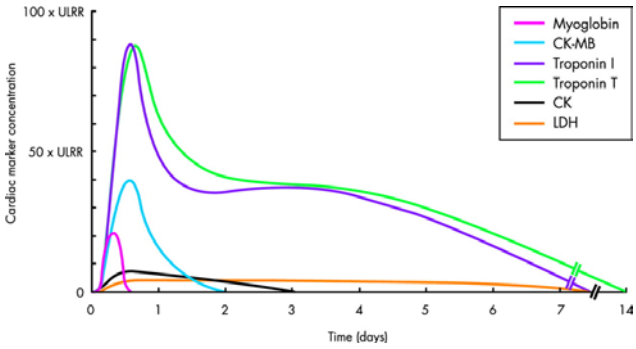

Fig.2 Concentration of cardiac markers against time.

2.3 Characteristics of Good Cardiac Markers

The performance of a cardiac marker is influence by several characteristics. First, the cardiac marker should have high sensitivity. This is contributed by having high concentration after myocardial injury. This is supported by having earlier elevation time and longer duration remain elevated.

The ideal cardiac marker is absent in and not detectable in blood of non-diseased patients. Furthermore, a good cardiac marker should also have good analytical characteristics. It should be measurable by cost-effective assay which is simple to perform, has rapid turnaround time, sufficient precision and trueness. The analytical method should be accurate and reproducible. Lastly, a good cardiac marker should also have good clinical characteristics. Clinical characteristics can be explained by the ability to influence therapy and also the ability to improve patient outcome [10].

3 Methodology

Two review journals [5, 11] are taken as the main reference to obtain a list of cardiac markers and characteristics to be compared. This is extended to include more cardiac markers and fill in the characteristics which were not covered in the main reference. This was followed by integrating the normalized data in radar charts.

3.1 Selected Characteristics

This subsection shall define the meaning for each characteristic chosen for comparison in this research. The characteristics investigated are sensitivity, specificity, PPV, NPV, diagnostic capability, prognostic capability, elevation time and duration remain elevated.

The positive predictive value (PPV) is defined as

$$\mathrm{PPV} = \frac{\text{no of true positives}}{\text{number of true positives} + \text{number of false positives}} \quad (1)$$

True positive is the event in which the test makes a positive prediction, and the subject has a positive result under proper standard, while a false positive is the event that the test makes a positive prediction but the subject has a negative result under proper standard.

The negative predictive value is defined as:

$$\mathrm{NPV} = \frac{\text{no of true negatives}}{\text{no of true negatives} + \text{no of false negatives}} \quad (2)$$

True negative is the event in which the test makes a negative prediction, and the subject has a negative result under proper standard, while a false negative is the event that the test makes a negative prediction but the subject has a positive result under proper standard.

Sensitivity measures the ability of the cardiac marker to be detected at specified cutoff value. Meanwhile, specificity measures the uniqueness of the cardiac marker to myocardiac injury as such that a cardiac marker with highest specificity is only contributed by the occurrence of myocardiac injury instead of other pathology.

Diagnosis capability can be described as the capability of the cardiac marker to assist physicians in identifying the condition of past cardiac injury while prognostic capability can be described as the capability of the cardiac marker to assist physicians in predicting the condition of cardiac injury in the future.

Elevation time is the time in which the cardiac marker is first detected after the onset of symptoms. Detection is triggered when the concentration of the cardiac marker in sample is higher than the cutoff value. Besides that, the duration in which the cardiac markers remain detectable in the blood stream is also a characteristic under investigation in this research.

3.2 Data Selection

The data selection in this research does not consider the effect of cutoff value, type of assay used and other conditions which could influence the parameters of cardiac markers. Selection criteria are set beforehand in order to facilitate the selection of data with minimum bias and also ensure that all the data is selected in similar method. The first priority of the criteria is to select the set of data which is consisted of the highest percentage. Therefore, the data represented in this research will be of the possible maximum value of each characteristic.

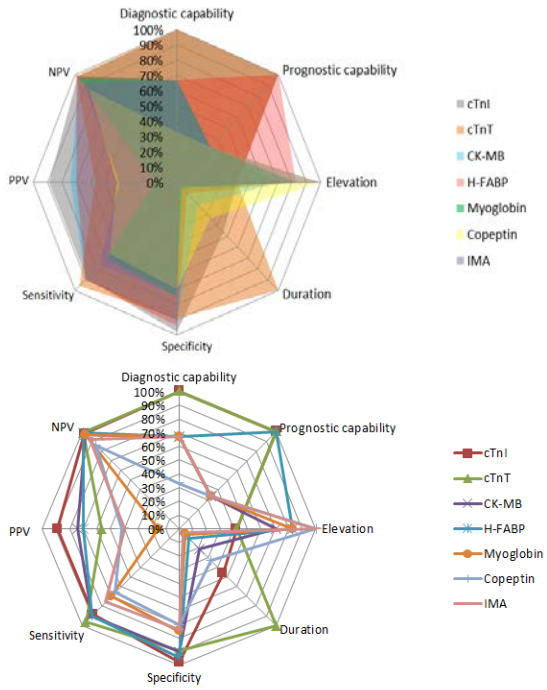

Fig. 3 Radar plot of cTnI, cTnT, CK-MB, H-FABP, myoglobin, copeptin and IMA. Area plot (top) and line plot (bottom)

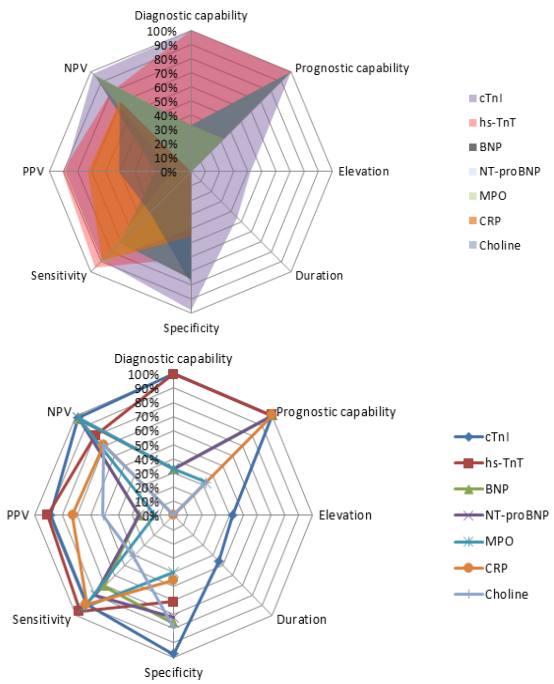

Fig. 4 Radar plot of cTnI, cTnT, hs-TnT, BNP, NTproBNP, MPO, CRP and choline. Area plot (top) and line plot (bottom)

4 Ease of Use

Figure 3 and Figure 4 show the comparison of the characteristics of cardiac marker using radar chart. The comparison is split into two parts since a large number of parameters are involved in this research. This is because combining all together will only clouds the presentation and defeats its original purpose.

The cardiac markers are divided as such that the Figure 3 represents the more commonly used cardiac markers while Figure 4 represents the less used cardiac markers due to their novelity. One of the cardiac marker, cTnI is plotted on both figures so that it serves as a link for all cardiac markers. Although the values for elevation and duration are absent in the data set, these two axes remain on the graph so that the comparison can be done in similar way.

Besides that, the radar chart is plotted in two types of view simultaneously: Figure 3(a) and Figure 4(a) plot the radar graph by overlapping partly transparent layers, while Figure 3(b) and Figure 4(b) use line plot. The reason of having two types of visualizations is because there is a need to portray the distribution of the quality of cardiac marker for each characteristic (area plot) and a more precise representation of relative values (line plot)

From the above two radar graphs, it can be seen that the currently used cardiac markers still remain more superior to the novel cardiac markers, seeing that the color of the earlier graph is denser than the other. However, there are also some new cardiac markers which show promising ability. One such example is high-sensitivity TnT, which has considerably increase in all areas except selectivity. Besides that, there are also some cardiac markers which are specialized in certain parameters. They show significant peak in certain characteristics. All of these characteristics can be compared quite easily from the radar graph.

The data are taken from [6, 9, 11 – 20]. Data for elevation and duration remain elevated are absent for hc-TnT, BNP, NTproBNP, MPO, CRP and choline because they are relatively novel cardiac markers and the data found was not complete from the literatures found.

5 Discussion

The advantage of using radar chart for characteristics of cardiac markers comparison is to improve visualization in comprehensive way. It also contributes the comparison of cardiac marker, especially in large data set.

However, this research is restricted by a few limitations. One of the major limitations is data differences among each cardiac marker researches. As an example is in the cutoff variable, the use of different cutoff values and assay types could influence the ease of detection, which in turns affecting the sensitivity, PPV and NPV of the cardiac marker. Moreover, characteristics of cardiac markers are relying on time period of sampling taken. Therefore, data used in this research are mostly the value near maximum from the characteristic of each cardiac marker. Lastly, characteristics of combined cardiac markers are also not reviewed in this research although most of them are proven to be more superior to their single counterpart.

6 Conclusion

A new method to visualize the comparison among cardiac markers in integrated variable has been proposed. This method proposed 8 parameter characterization parameters to be compared in radar chart. This method could be further investigated with major improvement.

The potential of using radar chart for the visualized comparison of the characteristics of cardiac marker still remain considerable in future studies. It was noted that the only weaknesses of this research is at the data collection instead of the method itself, although others can argue that a weak data set may hinder unbiased interpretation. Therefore, it is strongly suggested that any future researchers who had taken interested in the possibility of this method should use the same method while being stricter in data collection.

Acknowledgements

This research is based on work supported by the flagship grant of VOT.Q.J130000.2409.03G12 with the title of Online cardiovascular diseases early detection and management system. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors.

References:

[1] Owens, P. L., Barrett, M. L., Gibson, T. B., Andrews, R. M., Weinick, R. M., & Mutter, R. L, Emergency department care in the United States: a profile of national data sources, *Annals of emergency medicine*, Vol. *56, No.* 2, 2010, pp. 150-165.

[2] Pope, J. H., Aufderheide, T. P., Ruthazer, R., Woolard, R. H., Feldman, J. A., Beshansky, J. R., ... & Selker, H. P, Missed diagnoses of acute cardiac ischemia in the emergency department, *New England Journal of Medicine*, Vol. *342, No.* 16, 2010, 1163-1170.

[3] Christenson, J., Innes, G., McKnight, D., Boychuk, B., Grafstein, E., Thompson, C. R., ... & Singer, J., Safety and efficiency of emergency department assessment of chest discomfort. *Canadian Medical Association Journal*, Vol. *170, No.* 12, 2010, pp. 1803-1807.

[4] Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 2007;50:e1–157.

[5] Lin, S., Yokoyama, H., Rac, V. E., & Brooks, S. C., Novel biomarkers in diagnosing cardiac ischemia in the emergency department: a systematic review, *Resuscitation*, Vol. *83, No.* 6, 2007, pp. 684-691.

[6] Kehl, D. W., Iqbal, N., Fard, A., Kipper, B. A., Landa, A. D. L. P., & Maisel, A. S., Biomarkers in acute myocardial injury. *Translational Research*, *159*(4), 201, 252-264.

[7] Singh, T. P., Nigam, A. K., Gupta, A. K., & Singh, B., Cardiac biomarkers: when to test?–physician perspective. *Journal, Indian Academy of Clinical Medicine*, *12*(2), 2011.

[8] Xu, R. Y., Zhu, X. F., Yang, Y., & Ye, P., High-sensitive cardiac troponin T, *Journal of geriatric cardiology: JGC*, *10*(1), 2013, 102.

[9] Melanson, S. F., Lewandrowski, E. L., Januzzi, J. L., & Lewandrowski, K. B, Reevaluation of Myoglobin for Acute Chest Pain Evaluation Would False-Positive Results on "First-Draw" Specimens Lead to Increased Hospital Admissions?, *American journal of clinical pathology*, Vol. 121, No.6, 2004, pp. 804-808.

[10] Ramasamy, I., Biochemical markers in acute coronary syndrome. *Clinica chimica acta*, Vol. 412, No. 15, 2011, 1279-1296.

[11] Slot, M. H. B., van der Heijden, G. J., Stelpstra, S. D., Hoes, A. W., & Rutten, F. H., Point-of-care tests in suspected acute myocardial infarction: a systematic review. *International journal of cardiology*, Vol 168, No. 6, 2013, pp. 5355-5362.

[12] Schreiber,, D. (2014, December 18). Cardiac Markers . Retrieved May 10, 2015, from http://emedicine.medscape.com/article/811905-overview#a9

[13] Tucker, J. F., Collins, R. A., Anderson, A. J., Hauser, J., Kalas, J., & Apple, F. S, Early diagnostic efficiency of cardiac troponin I and troponin T for acute myocardial infarction. *Academic Emergency Medicine*, Vol. 4, No. 1, 1997, pp. 13-21.

[14] Lee, Y. W., Kim, H. J., Cho, Y. H., Shin, H. B., Choi, T. Y., & Lee, Y. K., Application of albumin-adjusted ischemia modified albumin index as an early screening marker for acute coronary syndrome. *Clinica Chimica Acta*, Vol. 384, No. 1, 2007, pp. 24-27.

[15] McMahon, C. G., Lamont, J. V., Curtin, E., McConnell, R. I., Crockard, M., Kurth, M. J., ... & Fitzgerald, S. P., . Diagnostic accuracy of heart-type fatty acid–binding protein for the early diagnosis of acute myocardial infarction, *The American journal of emergency medicine*, Vol. 30, No. 2, 2012, pp. 267-274.

[16] Keller, T., Tzikas, S., Zeller, T., Czyz, E., Lillpopp, L., Ojeda, F. M., ... & Blankenberg, S., Copeptin improves early diagnosis of acute myocardial infarction, *Journal of the American College of Cardiology*, Vol 55, No. 19, 2010, pp. 2096-2106.

[17] Weber, M., Bazzino, O., Estrada, J. L. N., de Miguel, R., Salzberg, S., Fuselli, J. J., ... & Hamm, C, Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome, *American heart journal*, Vol. 162, No. 1, 2011, pp. 81-88.

[18] Esporcatte, R., Rey, H. C. V., Rangel, F. O. D., Rocha, R. M., Mendonça Filho, H. T. F. D., Dohmann, H. F. R., & Albanesi Filho, F. M., Predictive value of myeloperoxidase to identify high risk patients admitted to the hospital with acute chest pain, *Arquivos brasileiros de cardiologia*, Vol. 89, No. 6, 2007, pp. 377-384.

[19] Ferroni, P., Rosa, A., Di Franco, M., Palmirotta, R., Guadagni, F., Davì, G., ... & Basili, S., . Prognostic significance of interleukin-6 measurement in the diagnosis of acute myocardial infarction in emergency department. *Clinica chimica acta*, Vol. 381, No. 2, 2007, pp. 151-156.

[20] Danne, O., Möckel, M., Lueders, C., Mügge, C., Zschunke, G. A., Lufft, H., ... & Frei, U, Prognostic implications of elevated whole blood choline levels in acute coronary syndromes, *The American journal of cardiology*, Vol. 91, No. 9, 2003, pp. 1060-1067.

[21] L.K. Wee, T. Y. Min, A. Arooj, E. Supriyanto, Nuchal Translucency Marker Detection Based On Artificial, *WSEAS Transactions on Information Secience and Applications*, 2010, p. 1025-1036.