ijpbs 2023;doi10.22376/ijpbs.2023.14.4.p13-17

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

Evaluation of The Utility of Serum Carcinoembryonic Antigen (Cea) Level as A Novel Biomarker in Acute Coronary Syndrome and Stable Angina

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Abstract: Carcinoembryonic antigen (CEA) is a tumour marker associated with various malignancies such as carcinoma colon, lung, and breast cancer. Nonneoplastic conditions such as obesity, ACS, inflammatory bowel disease, and chronic liver and kidney diseases are also associated with higher CEA levels. Hence, we focused on establishing the utility of Serum CEA level as a novel biomarker in ACS and Stable Angina. This was a single centre, Hospital-based Cross-Sectional Observational Study, over 1 year from November 2021 – November 2022, in the Department of Medicine at tertiary care hospital. The Institutional Ethics Committee (IEC) approved the present study protocol. The mean age of patients included in the study was 54.38 (SD± 11.53 years). Most patients (55%) belonged to the 51-70 years' group, followed by 37% of patients in the age group 31-50 years. The highest mean values of CEA were noted in patients diagnosed with STEMI; the mean was 5.09 ng/mL (SD±0.59). Patients with stable angina had the lowest CEA mean values at 2.52 ng/mL, although the standard deviation was ±0.83. The descriptive statistics between the ACS and CPK-MB values subtypes were statistically significant. The CPK-MB mean values were the highest in patients diagnosed with STEMI & NSTEMI mean CPK-MB 7.376 ng/mL (SD 1.154). CEA is a robust, novel, and sensitive biomarker for early diagnosis of ACS. Its levels correlate with the severity of ACS.

Keywords: ACS, DAILY, CEA level, CPK-MB, Type 2 Diabetes Mellitus.

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Date of Receiving 26 April, 2023

Date of Revision 4 July, 2023

Date of Acceptance 18 July, 2023

Date of Publishing 2 October, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors

Citation Dr. D.P. Lakra, Dr. M. Khande and Dr. Nidhi Jacob , Evaluation of The Utility of Serum Carcinoembryonic Antigen (Cea) Level as A Novel Biomarker in Acute Coronary Syndrome and Stable Angina.(2023).Int J Pharm Sci.14(4), p13-17 http://dx.doi.org/10.22376/ijpbs.2023.14.4.p13-17

1. INTRODUCTION

Globally, 10.6 million cases of ACS occurred in 2017, with 8.9 million ACS-related deaths. The age-standardized incidence and death rates declined from 1990 to 2017, with average annual percent change values of 1.2% and 1.3%, respectively. In 2017, the global number of ACS-related DALYs was 170.3 million.[1] In India, the prevalence in adults has increased considerably. The prevalence of ACS in rural India was estimated to be 3%–4% and 8%–10% in urban areas.[2]Coronary artery disease (CAD) remains the leading cause of death worldwide.[3] Clinical manifestations of CAD include stable angina, ACS, heart failure, and sudden death. The term ACS encompasses elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTEACS), which includes non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). [4]Approximately two-thirds of ACS presentations are with NSTE-ACS, and the remainder are STEMI.[5]Rising incidence of ACS was related to Westernized food practices in India.[6] Literature reported sedentary lifestyles as important determinants of cardiovascular diseases in India. It is also possible that the risk factors differed with lifestyle changes among migrants. ACS is a manifestation of CAD (coronary artery disease) resulting from plaque disruption in coronary arteries.[7] The common risk factors for the disease are smoking, hypertension, diabetes, hyperlipidemia, male sex, physical inactivity, family obesity, and poor nutritional practices. A family history of early myocardial infarction is also a high-risk factor. [8-10] rupture of unstable atherosclerotic plaque is a major mechanism of developing acute coronary syndrome (ACS) from stable CAD. Currently, creatinine phosphokinase MB (CPK-MB) and cardiac troponins T and I are used to diagnose myocardial necrosis. Brain natriuretic peptide (BNP), myeloperoxidase, pregnancy-associated plasma protein-A (PAPP-A), and metalloproteinase-9 are other reported useful markers for diagnosing ACS. Carcinoembryonic antigen (CEA) was first isolated from human colorectal cancer (CRC) tissue in 1965 by Gold and Freedman. It is a foetal glycoprotein. It is not usually produced in significant quantities after birth. CEA can become elevated in several pathologies. Carcinoembryonic antigen (CEA) is a tumour marker associated with various malignancies such as carcinoma colon, lung, and breast cancer. The most common clinical use is surveillance for recurrence of Colorectal Carcinoma. Serum CEA levels alsoincrease in smokers; the exact cause is unknown. Within three months after cessation, elevated CEA levels declined to within the range of non-smokers and did not appear to be influenced by previous smoking habits. Also, it is seen to be increased in cases of acute stroke. Nonneoplastic conditions such as obesity, ACS, inflammatory bowel disease, and chronic liver and kidney diseases are also associated with higher CEA levels.[11] CEA has been reported to be associated with abdominal visceral fat in Korean non-smoker females. Visceral fat is a powerful risk factor for atherosclerosis. A rise in concentrations of CEA might reflect the transformation from stable to unstable plaque in ACS. This molecule has also been reported as a useful biomarker for early diagnosis of ACS, as its level rises with the rupture of atherosclerotic plaque in coronary arteries. Hence, this molecule may also be a useful marker for early diagnosis of ACS.[12] established the role of CEA in the causation of plaque disruption/rupture, which might precipitate ACS.[13]A biomarker such as CEA can give physicians a window period to act and prevent myocardial necrosis from occurring in the first place. This can be helpful in the future to bring down ACS-related mortality and morbidity significantly. A bedside biomarker such as CEA may thus be of value in early diagnosis. Hence, we focused on establishing the utility of Serum CEA level as a novel biomarker in ACS and Stable Angina. This study aims to establish the utility of Serum CEA level as a novel biomarker in Acute Coronary Syndrome and Stable Angina.

2. MATERIALS AND METHODS

This was a single-centre, Hospital-based Prospective Cross-Sectional Observational Study. The study was performed over 1 year from November 2021 – November 2022. The study was performed in the Department of Medicine Pt. JNM Medical College and associated Dr BRAM Hospital, Raipur, Chhattisgarh. Institutional Ethics Committee approved the protocol with ref number MC/Ethics/2022/55 dated 14 March 2022. All patients presenting with ACS and Stable Angina in the Department of Medicine Pt. JNM Medical College and associated Dr. BRAM Hospital, Raipur, and willing to participate in the study. Patients presenting with ACS and Stable Angina in the Department of Medicine, Pt. JNM Medical College and associated Dr. BRAM Hospital, Raipur, and willing participants in the study were screened. Those meeting the inclusion criteria were briefed about the trial. Patient information sheets were given to all prospective participants. Written informed consent was obtained from the patients willing to participate in the study. Screening investigations were carried out, and the eligible candidates were included in the study. After the initial screening, the data regarding age, gender, and diagnosis was recorded in the case record form. After baseline investigations, anthropometric parameters like height, weight, and waist circumference were recorded. Routine Laboratory investigations were performed, including Complete Blood Count, Liver Function Tests, Renal Function Tests, Blood Sugars, Serum Lipid Parameters, and 12 lead ECG. Special Investigations like Serum CEA concentrations estimation were done as early as possible after the presentation but not beyond 24 hours after the onset of chest pain in all groups. Qualitative Trop T-Test was done using commercially available kits. Serum CPK MB concentrations were measured by an immune enzymatic method. The total 100 sample size was taken and calculated with the mean difference of serum CEA was 0.47 with a standard deviation was 0.56, 95 % confidence interval, and 80% power of the study considered.

2.1 Inclusion Criteria

1. Patients of Acute Coronary Syndrome and Stable Angina aged more than 18 years.
2. Patients are willing to participate in the study.

2.2 Exclusion Criteria

1. Patients with Known chronic inflammatory conditions
2. Past or present malignancy
3. Acute or chronic Liver Disease
4. Chronic Kidney Disease
5. Multi-Organ Dysfunction Syndrome
6. Inflammatory Bowel Disease

2.3 *Ethical Consideration*

The study was conducted after approval by the institutional

ethical committee, and written informed consent was obtained from the patients who participated in the study.

3. STATISTICAL ANALYSIS

Software SPSS 20.0 was used to analyze the data. One-way Analysis of variance (ANOVA) was used to compare means across the groups. The Post hoc Tukey test was used for multiple comparisons. Spearman's rank order correlation was used for the correlation between CEA and CPK MB concentrations. The unpaired T-test was used to compare mean CEA concentrations in Troponin T positive and Troponin T negative patients separately in groups A and B. If the p-value < 0.05, it was considered statistically significant.

4. RESULTS

Table no 1 shows that the mean age of patients included in the study was 54.38 (SD± 11.53 years). Most patients (55%) belonged to the 51-70 years' group, followed by 37% of patients in the age group 31-50 years. The least number of patients (1%) belonged to the 18-30 age group. Most patients in our study population were male (73%), and the remaining 27% were female. In this study, 43% of patients had type 2 diabetes mellitus. 36% of the study population were known to be hypertensive. In this study, 43% of patients had type 2 diabetes mellitus. 36% of the study population were known to be hypertensive.

Table 1: Baseline Characteristics of the study subjects.

Parameters	Subjects
Age (Mean ± S.D) in years	54.38 ± 11.53
Gender (Male) in %	73.00%
DM2 (in %)	43.00%
HTN (in %)	36.00%

Table 2: Association between Subtypes of ACS and CEA values with statistical p-value and standard deviation

CEA			
Diagnosis	Mean (ng/mL)	Std. Deviation	P value
NSTEMI	4.478	0.5723	0.033
Stable Angina	2.517	0.8298	
STEMI	5.094	0.5942	
Unstable Angina	3.480	0.2426	

Table no. 2 shows the descriptive statistics between the subtypes of ACS and CEA values, which are statistically significant. The highest mean values of CEA were noted in patients diagnosed with STEMI; the mean was 5.09 ng/mL (SD±0.59). NSTEMI patients follow the latter with a mean CEA of 4.48 ng/mL (SD±0.57) and unstable angina of 3.48 ng/mL (SD±0.24). Patients with stable angina had the lowest CEA mean values at 2.52 ng/mL, although the standard deviation is noted to be ± 0.83 (rounded to two decimal places).

Table 3: Association between the Subtypes of ACS and CPK-MB values with statistical p values and standard deviations

CPK-MB			
Diagnosis	Mean (ng/mL)	Std. Deviation	P value
NSTEMI	7.376	1.1537	0.016
Stable Angina	4.064	0.8902	
STEMI	7.376	1.1537	
Unstable Angina	4.404	0.7185	

Table No. 3 shows the descriptive statistics between the subtypes of ACS and CPK-MB values, which were statistically significant. The CPK-MB mean values were the highest in patients diagnosed with STEMI & NSTEMI mean CPK-MB 7.376 ng/mL (SD± 1.154; rounded to nearest two decimal places). Likewise, minimum mean values for patients diagnosed with stable and unstable angina were 4.404 ng/mL (SD±0.89 and 0.72, respectively, rounded to the nearest two decimal places.

5. DISCUSSION

The study showed that most cases were from 51 to 70 years of age (55%). This was followed by cases about the age group of 31 to 50 years (37%) and age group more than 70 years of age (7%). The least cases were contained in the agegroup interval of 18 to 30 years (1%). The mean age of the patients recruited in our study population was 54.38 ± 11.53. In another study by Vassalle et al.[13], 65 ± 2 was the mean age found in the diagnosis of ACS, including acute myocardial infarction and UA. Furthermore, the mean age of 66 ± 3 was evident in cases with stable angina and angiographically confirmed CAD. (Vassalle, 2010) [13] These findings were slightly different from our study data about mean age. Similarly, Ranga et al.,[12] determined that mean age of 51.33 ± 6.03 was prevalent in cases of STEMI in the age interval of 41-60 years, mean age of 51.02 ± 5.93 in NSTEMI and UA in the age interval of 40-59 years, while mean age of 52.38 ± 6.48 was observed instable angina cases in the age interval of 41-60 years. This study data was closely supporting our study data. TheSPACE registry that collected data on 5055 patients from 17 participating hospitals between December 2005 and December 2007 revealed that in their study, patients' ages ranged from 18 to 111 years with a mean of 58 years. 75% of cases were about 41–70 years, 9% belonged to less than 40 years, and 16% were more than 70 years of age. (Al-Saif, 2012) [15] SPACE registry patients, with a mean age of 58 years, were 8 years younger than the mean age of 66 years in (GRACE) registry and 6 years younger than the median of 64 years for the ACC National Cardiovascular Data Registry

(NCDR), Acute Coronary Treatment Intervention Outcomes Network (ACTION) registry and the CREATE registry from India with a mean age of 57 years.(Granger, 2003) [16] (Peterson, 2010) [17] (Xavier, 2008) [18]Gender wise, our study appraised remarkable male sex predilection with the majorityof males (73%) and few females(27%). We were supported by Vassalleet al.,[13] with the male sex predominance of 76% and 85% in diagnosing acute myocardial infarction, UA, and stable angina, respectively. Some studies have suggested sex differences in the presentation and treatment of ACS, but these studies have many uncertainties and discrepancies. (Quyyumi, 2006) [19](Alexander 2001) [20] ACS affects men more than women in the general population of Chinesediabetic patients. (Duan, 2014)[21] Claassen et al[22] also reported that coronary vascular disease in women develops 7 to 10 years later than in men, potentially because of a protective effect of estrogens. Epidemiological studies, including the Framingham study, showed that CHD presents earlier in men than women. Therefore, younger women benefit from the protective effects of endogenous estrogens, including estradiol, which may inhibit age-related vascular remodelings, such as vascular smooth muscle cell proliferation and endothelial dysfunction. (Duan, 2014) [21] Also, estradiol lowers cholesterol levels and improves vascular tone. Therefore, the male prevalence of CHD and the gap between men and women begin to narrow after menopause, which has been recognized as a risk factor for ACS due to the reduction in endogenous estrogen. (Duan, 2014) [21](Shaw, 2006) [23] Men had a higher incidence of ACS than women (24.1% vs. 17.0%, p<0.001) in a study by Duan et al.[21] All these findings agreed with our study data regarding male gender predominance in ACS. In the study, any association between CEA and the different subtypes of ACS was evaluated. It was observed that mean CEA value was maximum amongst the patients diagnosed with STEMI (5.094 ± 0.5942). This was followed by a mean CEA value of 4.478 ± 0.5723 in cases of NSTEMI and 3.480 ± 0.2426 in cases of UA. A minimum mean value of CEA was found in patients diagnosed with Stable angina (2.517 ± 0.8298). Accordingly, descriptive statistics between the ACS and CEA values subtypes were statistically significant (All P-values= 0.033). CEA is a cell surface adhesion molecule of the immunoglobulin superfamily. Somatic mutation theory has considered similar pathogenic mechanisms for atherosclerosis and tumorigeneses.[14] ACS is often accompanied by different degrees of myocardial ischemia, injury, necrosis, and inflammation. The progression of ACS has long been assessed by detecting changes in myocardial necrosis markers (e.g., myoglobin, CKMB, and cTnI) and inflammatory markers (e.g., C-reactive protein and CRP). As per Vassalle et al.,[13] mean CEA concentrations were significantly higher in acute myocardial infarction and unstable angina than in unstable angina. When CEA concentrations were categorized according to the 50th percentile (corresponding to a value of 2.05 ng/mL), CEA concentration 92 exceeded this value in 70%, 39%, and 33% of subjects belonging to acute myocardial infarction, unstable angina compared with those found unstable angina (P-value < 0.001). According to Ranga et al.,[12] STEMI had significantly higher values of CEA as compared to patients with NSTEMI (P-value < 0.05). STEMI and NSTEMI/Unstable Angina groups had significantly higher CEA values than the stable angina group (P-value < 0.001 and 0.001, respectively). Patients with Unstable Angina had significantly higher CEA concentrations than stable CAD patients (P-value < 0.001). No statistically significant difference between stable angina and the control group regarding serum CEA concentrations (P-value= 1.00). All these study findings extended their positive support to the current study data. 5. The study evaluated the association between CPK-MB and STEMI, NSTEMI, stable angina, and UA. The mean CPK-MB value was maximum and shared the same value amongst the patients diagnosed with STEMI and NSTEMI (7.376 ± 1.1537). This was followed by a mean CPK-MB value of 4.404 ± 0.7185 in cases of UA. A minimum mean value of CPK-MB was found in patients diagnosed with Stable angina (4.064 ± 0.8902). Descriptive 93 statistics between the subtypes of ACS and CPK-MB values were statistically significant (All P-values= 0.016). Serum levels of CPK-MB are directly related to the severity of ACS, morbidity, and mortality. Concentrations of CPK-MB were significantly higher in patients with STEMI as compared to NSTEMI/UA group (130.95 ± 108.32 IU/dl and 62.19 ± 67.33 IU/dl, respectively, P-value < 0.001) according to Ranga et al.[12] They also appraised that, mean concentration of CEA in patients with ACS (STEMI and NSTEMI/UA groups taken together) was 4.52 ± 2.97 ng/ml indicating highly significant and strong positive correlation between CEA and CPK-MB concentrations (R ¼ 0.809 and p < 0.001). In STEMI, a stronger correlation was found between CEA and CPK-MB compared to patients with NSTEMI (R ¼ 0.866 and 0.648, respectively, p < 0.001). A strong correlation was found when patients with STEMI and NSTEMI were analyzed (R ¼ 0.781, p < 0.001). However, when patients with NSTEMI and UA were analyzed separately about the correlation between these two markers, a highly significant and stronger correlation coefficient (R ¼ 0.950 (p < 0.001) in NSTEMI group was observed but not in the Unstable Angina patients (R ¼ 0.319 and p ¼ 0.197)[12] These findings agreed with the current study data. In the present study, the mean CEA value was highest in STEMI (5.094±0.5942) followed by 4.478±0.5723 in NSTEMI, 3.480±0.2426 in UA, and 2.517±0.8298 in Stable angina. Descriptive statistics between the ACS and CEA values subtypes showed statistical significance (p-value=0.033). Mean CPK-MB values were highest in STEMI (7.376±1.1537), followed by 4.404±0.7185 in UA and 4.064±0.8902 unstable angina. Descriptive statistics between the subtypes of ACS and CEA values were of statistical significance (p-value=0.016)

6. CONCLUSION

All the findings consistently indicate that CEA can be a potential novel biomarker for diagnosing ACS and its risk factors. CEA is a robust, novel, and sensitive biomarker for early diagnosis of ACS. Its levels correlate with the severity of ACS. CEA concentrations were significantly higher in ACS patients who were positive for the qualitative Troponin T test (STEMI and NSTEMI patients) than those who were negative for this test (UA patients). CEA concentrations were significantly higher in UA patients as compared to stable CAD. One of the drawbacks of Troponins as cardiac biomarkers for diagnosis of ACS is that their levels get raised only when overt myocardial necrosis has already occurred. The latest efforts are directed at discovering a cardiac biomarker whose levels get raised significantly even before the start of actual myocardial necrosis. A biomarker such as CEA can give physicians a window period to act and prevent myocardial necrosis from occurring in the first place. This can be helpful in the future to bring down ACS-related mortality and morbidity significantly. ACS incidence increases with age, and the risk increases with diabetes mellitus. Male predominance reflects the sex difference in the risk of ACS. It may also be a very useful diagnostic value when imaging

gives ambiguous results. However, further studies in a larger patient population must confirm such a relationship.

7. AUTHORS CONTRIBUTION STATEMENT

Dr. Nidhi Jacob gathered the data for this study. Dr. D. P. Lakra and Dr. M. Khande conceptualized, and necessary inputs were given to the study's design. Dr. M. Khande and Dr. Nidhi Jacob analysed these data. All authors discussed the methodology and results and contributed to the final manuscript.

8. ABBREVIATIONS

ACS -Acute Coronary Syndrome
BNP -Brain Natriuretic Peptide
CAD -Coronary Artery Disease
CEA -Carcinoembryonic Antigen
CRC -Colorectal Cancer
CPK-MB -Creatinine Phosphokinase – MB
PAPP-A -Pregnancy Associated Plasma Protein-A
NSTEMI -Non-ST elevation Myocardial Infarction
STEMI -ST elevation Myocardial Infarction
UA -Unstable Angina

9. CONFLICT OF INTEREST

Conflict of interest of declared none.

10. REFERENCES

1. Wang F, Yu Y, Mubarik S, Zhang Y, Liu X, Cheng Y, Yu C, Cao J. Global burden of ischemic heart disease and attributable risk factors, 1990–2017: A secondary analysis based on the global burden of disease study 2017. Clinical Epidemiology. 2021; 13:859.
2. Singh SS, Paul SK, Pal R, Thatkar PV. Acute coronary syndrome-related mortality audit in a teaching hospital at Port Blair, India. J Family Med Prim Care. 2017 Jul-Sep;6(3):502-508.
3. Kotecha T, Rakhit RD. Acute coronary syndromes. Clin Med (Lond). 2016 Dec;16(Suppl 6):s43-s48. doi: 10.7861/clinmedicine.16-6-s43.
4. Yeh RW. Sidney S. Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010; 362:2155–65.
5. Weston C, Gavalova L, Whittaker T, Van Leeven R. Annual Public Report April 2013 - March 2014. London: MINAP NICOR; 2014. Myocardial Ischaemia National Audit Project: how the NHS cares for patients with heart attack. www.ucl.ac.uk/nicor/audits/minap/documents/annual_reports/min ap-public-report-2014. [Accessed 9 November 2016].
6. Singh SS, Paul SK, Pal R, Thatkar PV. Acute coronary syndrome-related mortality audit in a teaching hospital at Port Blair, India. J Family Med Prim Care. 2017 Jul-Sep;6(3):502-508.
7. Bracey A, Meyers HP. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Aug 6, 2021. Posterior Myocardial Ischemia.
8. Voudris KV, Kavinsky CJ. Advances in Management of Stable Coronary Artery Disease: the Role of Revascularization? Curr Treat Options Cardiovasc Med. 2019 Mar 11;21(3):15.
9. Pop C, Matei C, Petris A. Anticoagulation in Acute Coronary Syndrome: Review of Major Therapeutic Advances. Am J Ther. 2019 Mar/Apr;26(2):e184-e197.
10. Singh A, Museedi AS, Grossman SA. Acute Coronary Syndrome. [Updated 2022 Jul 11]. In: StatPearls [Internet]. Treasure Island (FL): 101 StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459157.
11. Stevens DP, Mackay IR, Busselton Population Studies Group. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet 1973; 2:1238-9.
12. Ranga GS, Muktesh G, Sharma SB, Madhu SV. A study of carcinoembryonic antigen concentrations in patients with coronary artery disease. Journal of Acute Medicine. 2016 Mar 1;6(1):11-8.
13. Vassalle C, Pratalli L, Ndreu, R Battaglia D and Andreassi MG. Carcinoembryogenic antigen concentrations in patients with acute coronary syndrome. Clin Chem Lab Med 2010; 48:1339-43.
14. Stevens DP, Mackay IR, Busselton Population Studies Group. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet 1973; 2:1238-9.
15. .Al-Saif SM, Alhabib KF, Ullah A, Hersi A, Alfaleh H, Alnemer K, Tarabin A, Abuosa A, Kashour T, Al-Murayeh M. Age and its relationship to acute coronary syndromes in the Saudi Project for Assessment of Coronary Events (SPACE) registry: The SPACE age study. J Saudi Heart Assoc. 2012 Jan;24(1):9-16.
16. Granger C.B. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163:2345–2353.
17. Peterson E.D. The NCDR ACTION Registry-GWTG: transforming contemporary acute myocardial infarction clinical care. Heart. 2010;96:1798–1802.
18. Xavier D, P. Pais, P.J. Devereaux, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet, 371 (2008), pp. 1435-1442
19. Quyyumi AA. Women and ischemic heart disease: Pathophysiologic implications from the women's ischemia syndrome evaluation (WISE) study and future research steps. J Am Coll Cardiol. 2006;47: S66–S71.
20. Alexander KP, Peterson ED. Medical and surgical management of coronary artery disease in women. Am J Manag Care. 2001;7: 951–956.
21. Duan JG, Chen XY, Wang L, Lau A, Wong A, Thomas GN, Tomlinson B, Liu R, Chan JC, Leung TW, Mok V, Wong KS. Sex differences in epidemiology and risk factors of acute coronary syndrome in Chinese patients with type 2 diabetes: a long-term prospective cohort study. PLoS One. 2015 Apr 1;10(4):e0122031.
22. Claassen M, Sybrandy KC, Appelman YE, Asselbergs FW. Gender gap in acute coronary heart disease: Myth or reality? World journal of cardiology. 2012;4: 36–47.
23. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, et al. Insights from the nhlbi-sponsored women's ischemia syndrome evaluation (WISE) study: Part I: Gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006;47: S4–S20.