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Epicardial Adipose Tissue Thickness and Body Mass Index as Early Predictors of Thrombolysis Success in Patients with Elevated ST-Segment Myocardial Infarct

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ABSTRACT

Introduction: Early intravenous thrombolysis in elevated ST-segment myocardial infarcted patients reduces morbidity/mortality, however in non-responsive patients, it can delay the endovascular revascularization process. Increased epicardial adipose tissue thickness (EATT) is associated with adverse cardiovascular events and artery patency. Our aim was to evaluate if EATT influences the response to thrombolytic therapy in patients with acute myocardial infarction.

Material and Method: This prospective cohort study included fifty patients (40 males and 10 females) with a mean age of 60 ± 9 years old and a presumptive acute myocardial infarct diagnosis. All the patients were hospitalized in the intensive care coronary unit. According to ESC and ACC guidelines, the diagnosis of acute myocardial infarct was corroborated. Patients were treated with 0.5 mg/kg IV bolus of the specific recombinant plasminogen activator Tenecteplase. The transthoracic 2-dimensional echocardiography was performed to recognize EAT from the parasternal long-axis view.

Results: The time lapse between initial symptoms and thrombolysis was 227±43 mm. Sixteen patients showed positive reperfusion less than 90 minutes after thrombolysis, and the remaining 34 required a percutaneous coronary intervention. The mean EATT value of thrombolysis-responding patients was 2.4 ± 0.4 mm vs 6.5 ± 0.6 mm of the non-responders (p= 0.001). In responders, the percentage of body mass index (BMI) was 26.1 ± 0.02% vs 29.1± 0.02% (kg/m2) in non-responders (p= 0.001). Interestingly, an EATT value > 2.5 mm and a BMI > 26 showed a highly significant inverse correlation response to thrombolysis and positive myocardial reperfusion (r = -0.71 y 0.55, p = 0.001 respectively). These values had a prognostic sensitivity of 93% and specificity of 84%.

Conclusion: EATT and BMI could be usefull serve as early decision indicators to determine the possible response to thrombolysis and positive myocardial reperfusion in acute myocardial infarcted patients, although there is a need for studies with larger sample sizes.

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Introduction

Epicardial adipose tissue (EAT) is located between the myocardium and the visceral pericardium. It is made up mainly of adipocytes, inflammatory and immune cells, thus they have local and systemic effects (1, 2). Its main function is to serve as a source of energy and release anti-inflammatory adipokines to the myocardium (3). When it is enlarged it contributes to atherosclerotic cardiovascular disease mediated by the secretion of pro-inflammatory adipokines (IL-1, IL-6, TNFa) that go directly into the coronary lumen (2-4) and have angiocrine and vasomotor effects that regulate blood flow to the coronary arteries (5). EAT is measured using the coronary artery calcium score (6), or through transthoracic echocardiography (7).

Acute myocardial infarction results from an atheroma plaque fracture within a coronary vessel that triggers a coagulation cascade that ends in platelet aggregation and thrombus formation, thus obstructing coronary blood flow (8). Early intravenous thrombolysis reduces morbidity/mortality, but some patients do not respond thus delaying the endovascular intervention (9). Well recognized risk factors such as type 2 diabetes mellitus (10), high blood pressure, (11) white cell count (12), body mass index (13), or malnutrition (14) are implicated in a deficient response to thrombolysis. It has recently emerged that EAT thickness is related to adverse cardiovascular events (15) or enhanced cardiovascular risk (16). Interestingly, EAT has also been associated with infarct artery patency (17), defines the flow through the infarcted artery, and may affect cardiac electrical stability (18) thus reinforcing the relevance of a successful early thrombolysis event. The aim of this project was to evaluate if the response to thrombolytic therapy in patients with acute myocardial infarction is associated to epicardial adipose tissue thickness.

Material and Methods

The study was approved by the Local Committees of Research, Ethics and Biosafety of the Centro Médico Nacional '20 de Noviembre' ISSSTE, Mexico City (Protocol ID No. 611.2019) and All participants gave their written informed consent.

Patients

This prospective cohort study included fifty patients (40 males and 10 females) with a mean age of 60 ± 9 years old and a presumptive acute myocardial infarct diagnosis. Following referral by their health-care units all the patients were hospitalized in the intensive care coronary unit, National Medical Center '20 de Noviembre' ISSSTE, Mexico City, Mexico. An echocardiography was performed and the diagnosis of acute myocardial infarct according to the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) guidelines (> 3 mm elevation of the ST-segment, elevated cardiac troponin above the 99th percentile URL, and 2-fold increase of creatine phosphokinase MB) (19-21) was corroborated. Patients with pericardial effusion, peripheral artery disease, mitral valve insufficiency, or left ventricle wall rupture were excluded, as were patients who had undergone coronary artery bypass grafting or aortic and mitral valve repair or replacement. The Body Mass Index (BMI) was calculated, after the height and body weights were measured using the BMI= kg/m2 formula; 5 ml blood samples were obtained for a 28 parameters blood chemistry analysis at arrival at the Intensive Care Unit.

Echocardiographic evaluation

Patients were treated with 0.5 mg/kg IV bolus of the specific recombinant plasminogen activator Tenecteplase and the transthoracic echocardiography was simultaneously performed using the Phillips EPIQ 7 ultrasound machine with a PureWave transducer (Philips N.V., USA). One well-trained cardiologist who was blind to the original patient characteristics according to a standardized protocol, performed the echocardiographic examination.

Measurement of EAT thickness

EATT was recognized as an echo-free space located between the visceral pericardium and the outer wall of the myocardium on 2-

dimensional echocardiography. To standardize the measuring point, the aortic annulus was used as an anatomical reference. From the parasternal long axis view, EAT thickness was measured perpendicularly on the free wall of right ventricle at end-systole for 3 consecutive cardiac beats (22).

Statistical analysis

Results are presented as the mean ± standard deviation of the mean. Pearson & Rho Spearman to correlation analysis. Logistic and linear regression to independence effect. Chi square and Students T test were used to determine the difference between responders and non-responders to thrombolysis treatment and ROC curve test was used for prognostic value of EATT and BMI percentage to positive response of thrombolysis, for a p value < 0.05 was considered as statistically significant. SPSS v 28 software was used to analyze the information.

Results

The table 1 shows the risk factors, left ventricular area affected of patients possessing myocardial infarction and the heart failure severity proposed by Killip and Kimball classification. An elevated percentage had type 2 diabetes mellitus (66%) and high blood pressure (60%); almost half had dyslipidemia or were smokers; fifty-eight percent were overweight (BMI >25 but <30) and thirty-two were obese (BMI >30); the inferior wall of the left ventricle was the most frequent affected area followed by the anterior and lateral walls and 33 of the patients belonged to class I which conveys no clinical signs of heart failure, 7 were classified as class II which conveys mild heart failure, 2 were classified as class III which conveys severe heart failure with pulmonary edema and 8 were classified as class IV that include cardiogenic shock and severe heart.

The time lapse between initial symptoms and thrombolysis was 227 ± 43 min. Sixteen patients showed positive reperfusion in less than 90 minutes after thrombolysis, whereas 34 didn´t, thus requiring a percutaneous coronary intervention (PCI). No significant differences between risk factors on the efficacy of thrombolysis were observed (Table 2). The 30-day follow-up showed NYHA functional class I in 40 patients (80%) and NYHA II in 7 patients (14%). Three male patients classified as class IV Killip Kimball index requiring ICP (6%) died, although none was due to the consequence of the procedure.

Table 1. Cardiovascular disease risk factors and Killip Kimball stratification of patients*.

Risk Factors		N
Diabetes Mellitus		33
Hypertension		30
Dyslipidemia		24
Smoking		24
Body Mass Index	Normal	5
	Overweight	29
	Obese	16
Left Ventricular area affected	Anterior	22
	Lower	24
	Lateral	4
Killip and Kimball classification	I	33
	II	7
	III	2
	IV	8

* Parameters determined before the thrombolysis procedure was performed.

The mean EATT value in all patients was 5.8 ± 2.1 mm, however significant difference between responders and non-responders was observed (2.8±0.4 mm vs 6.5±0.6, p = 0.001). Patients that responded positively to thrombolysis had a mean EATT value of 2.4 ± 0.4 mm and a BMI of 26.1 ± 0.02% as opposed to patients who did not respond to thrombolysis and required an PCI, with values of 6.5 ± 0.6 mm for EATT and 29.1± 0.02% for BMI (p = 0.001 for each). These values had a prognostic sensitivity of 93% and specificity of 84% (Figure. 1). It was very interesting to observe that an EATT value >2.5 mm and a BMI higher than 26 showed a highly significant inverse correlation (r = -0.71 y 0.55, p = 0.001 respectively), as well as, with an independent effect (p = 0.001) on positive response to thrombolysis and positive myocardial reperfusion (Table 3).

Discussion

Epicardial adipose tissue (EAT) is a fat depot localized between the myocardial surface and the visceral layer of the pericardium (23). In normal conditions epicardial adipose tissue is a unique buffering pool in the homeostasis of the myocardium (24) that protects against hypothermia and mechanical stress. In obese individuals EAT promotes the development of cardiovascular diseases (25). The median epicardial adipose tissue thickness (EATT) values varies enormously from 9 ± 2.96 mm, in cardiological outpatients with similar anthropometric parameters to our population (6) to 1.36 ± 0.7 mm in healthy Hispanic adolescent controls (26). EAT thickness is regulated by age, gender, ethnicity (27, 28) and most importantly body mass index (13). Although EATT correlates significantly with BMI, the thickness is not secondary to hypertrophy of the epicardial tissue adipocytes but to epicardial remodeling via adipocyte proliferation (29). Enhanced adipocyte proliferation decreases adiponectin secretion and boosts leptin secretion increasing local inflammation, oxidative stress and adhesion of monocytes and macrophages (30) thus destabilizing atherosclerotic plaques. It has been recently recognized that local inflammation influences coronary microvascular dysfunction and that EATT can discriminate between the presence or the absence of dysfunction (31).

Table 2. Differential analysis of cardiovascular disease risk factors upon the success of the thrombolysis procedure.

	Thrombolysis therapy		P value
	Responders*	Not responders	
Smoking (years)	24±15	21±12	0.87**
Diabetes Mellitus (years)	9±2	10±3	0.54***
Glycosylated hemoglobin %	6±3	7±3	0.22**
Dyslipidemia (years)	5±1	7±2	0.43***
Low-Density Lipoprotein (mg/dl)	174±15	182±15	0.14***
High-Density Lipoprotein (mg/dl)	58±9	48±10	0.29***
Triglycerides (mg/dl)	160±9	178±12	0.16***
Cholesterol (mg/dl)	210±12	152±11	0.09***

* Responders are those patients that showed a positive reperfusion response less than 90 minutes after thrombolysis, not responders were those patients that 6 h after thrombolysis did not show a reduction in the ECG ST segment and/or a reduction in troponin or CPK mb serum values and had to have an ICP.

** P value was calculated using Chi2 .

*** The student´s T test.

In this study, it is clearly established that an EATT value greater than 2.4 mm together with a BMI greater than 26% tags the outcome of the infarcted patient; these values are strong indicators that the early thrombolytic procedure in patient having both abnormal values will not be successful >90% of the occasions. These results emphasize that EATT is a parameter that needs to be considered along BMI as a prognostic marker for the outcome of myocardial infarcted patients with an elevated ST segment that require a reperfusion process, either thrombolysis or PCI. As the EATT/BMI association proved to be highly significant when in-hospital mortality was evaluated we had to consider the Killip-Kimball classification, which is a cornerstone in the evaluation and prognosis of patients suffering an acute myocardial infarction (32).

It has been clearly established that in-hospital mortality for patients with myocardial infarction and an ST-segment elevation increases from 9.9% in class I Killip patients to nearly 95% in class IV patients and a BMI > 30 kg/m2 is a significant contributor to the bad prognosis (33). Similar tendencies are observed in patients treated in more optimal conditions (34. 35). The results confirmed the prognostic value of the Killip classification. But most importantly our results demonstrate that the evaluation of BMI and EATT, two simple parameters easily determined in an acute coronary unit or an emergency room, should always be contemplated before ascertaining the success of a reperfusion procedure especially in individuals with a Killip class III or IV.

Study limitations

The results of this study with 50 patients clearly established a specific value of EATT (Greater than 2.4 mm) combined with a BMI greater than 26% in infarcted patient exist a strong possibilities (>90%) failure of the early thrombolytic procedure, condition that can contribute to making therapeutic decisions, especially when the patient's condition is critical. However, we also consider that a study with a larger sample size is necessary to confirm the findings of this study. On the other hand, our findings suggest that it is necessary to study the coronary inflammatory scenery conditioned by EATT, to understand the thrombolytic effect better and look for the use of other alternatives therapeutics for acute infarcted patients, because this cardiological pathology continues to represent the principal mortality.

Conclusion

EATT and BMI could serve as early decision indicators to determine the possible response to thrombolysis and positive myocardial reperfusion in acute myocardial infarcted patients, although there is a need for studies with larger sample sizes.

Table 3. Association between Epicardial Adipose Tissue Thickness and Thrombolytic Therapy response.

	r	P	Multivariate P
EATT (mm)	-0.72**	0.001****	0.001
Body Mass Index	-0.55**	0.001****	0.001
Diabetes Mellitus	0.14*	0.32***	0.40
Hypertension	0.05*	0.71***	0.21
Dyslipidemia	0.25*	0.68***	0.70
Smoking	0.23*	0.10***	0.18

- **EEAT**: Epicardial Adipose Tissue Thickness.
* Rho Spearman test .
**Pearson test were used to evaluate correlation .
***The multivariate analysis with logistic.
**** linear regression.

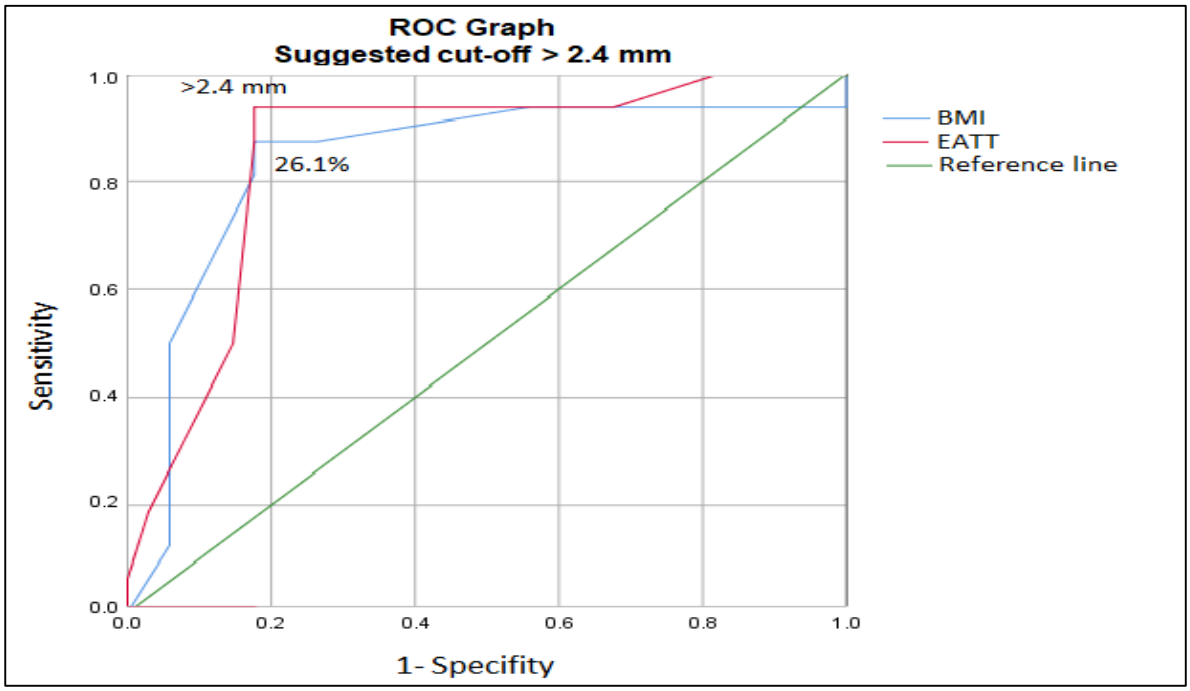

Figure 1. ROC graph suggested cut off>2.4 mm .Predictive ROC Curve of not response to thrombolysis therapy using epicardial adipose tissue thickness and body mass index.

References:

1. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends in Endocrinology & Metabolism. 2011 Nov 1;22(11):450-7..
2. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003 Nov 18;108(20):2460-6..
3. Iacobellis G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nature Reviews Endocrinology. 2015 Jun;11(6):363-71..
4. Villasante Fricke AC, Iacobellis G. Epicardial adipose tissue: clinical biomarker of cardio-metabolic risk. International journal of molecular sciences. 2019 Nov 28;20(23):5989.
5. Sacks HS, Fain JN, Cheema P, Bahouth SW, Garrett E, Wolf RY, et al. Depot-specific overexpression of proinflammatory, redox, endothelial cell, and angiogenic genes in epicardial fat adjacent to severe stable coronary atherosclerosis. Metabolic syndrome and related disorders. 2011 Dec 1;9(6):433-9.
6. Gać P, Macek P, Poręba M, Kornafel-Flak O, Mazur G, Poręba R. Thickness of epicardial and pericoronary adipose tissue measured using 128-slice MSCT as predictors for risk of significant coronary artery diseases. Irish Journal of Medical Science (1971-). 2021 May;190:555-66..
7. Eroğlu S. How do we measure epicardial adipose tissue thickness by transthoracic echocardiography?. Anatolian journal of cardiology. 2015 May;15(5):416.
8. Shao C, Wang J, Tian J, Tang YD. Coronary artery disease: from mechanism to clinical practice. Coronary Artery Disease: Therapeutics and Drug Discovery. 2020:1-36.
9. Bhaskar S, Stanwell P, Cordato D, Attia J, Levi C. Reperfusion therapy in acute ischemic stroke: dawn of a new era?. BMC neurology. 2018 Dec;18:1-26.
10. Akbas EM, Hamur H, Demirtas L, Bakirci EM, Ozcicek A, Ozcicek F, et al. Predictors of epicardial adipose tissue in patients with type 2 diabetes mellitus. Diabetology & metabolic syndrome. 2014 Dec;6(1):1-8.
11. Yılmaz S, Sen F, Temizhan A. Epicardial Adipose Tissue Thickness, Is It a Reason or a Consequence?. Angiology. 2016 Mar;67(3):293-..
12. Lee YY, Tee MH, Zurkurnai Y, Than W, Sapawi M, Suhairi I. Thrombolytic failure with streptokinase in acute myocardial infarction using electrocardiogram criteria. Singapore medical journal. 2008 Apr 1;49(4):304.
13. Gorter PM, van Lindert AS, de Vos AM, Meijs MF, van der Graaf Y, Doevendans PA, et al. Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. Atherosclerosis. 2008 Apr 1;197(2):896-903.
14. Sarı M, Çakmak EÖ, Karagöz A, Yılmaz F, Aytürk M, Fidan S, et al. Subacute lower extremity arterial thrombosis; early outcomes of catheter

directed thrombolysis with alteplase and importance of malnutrition assessed by CONUT score. Turk Kardiyol Dern Ars. 2021 Oct 1;49(7):568-78.
15. Chen YC, Lee WH, Lee MK, Hsu PC, Tsai WC, Chu CY, et al. Epicardial adipose tissue thickness is not associated with adverse cardiovascular events in patients undergoing haemodialysis. Scientific Reports. 2020 Apr 14;10(1):6281.
16. Nerlekar N, Thakur U, Lin A, Koh JQ, Potter E, Liu D, et al. The Natural history of Epicardial Adipose Tissue Volume and Attenuation: A long-term prospective cohort follow-up study. Scientific reports. 2020 Apr 28;10(1):7109.
17. Sen F, Yilmaz S, Balci KG, Gül M, Balci MM, Akboga MK, et al. The relationship between epicardial adipose tissue thickness and infarct-related artery patency in patients with ST-segment elevation myocardial infarction. Angiology. 2016 Mar;67(3):281-6.
18. Mortara A, Specchia G, La Rovere MT, Bigger Jr JT, Marcus FI, Camm JA, et al. Patency of infarct-related artery: effect of restoration of anterograde flow on vagal reflexes. Circulation. 1996 Mar 15;93(6):1114-22.
19. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018 Nov 13;138(20):e618-51.
20. Domanski MJ. Prognostic implications of troponin T and creatine kinase-MB elevation after coronary artery bypass grafting. American Heart Journal. 2012 Nov 1;164(5):636-7.
21. Writing Committee Members, Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2022 Jan 18;79(2):197-215.
22. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. Journal of the American Society of Echocardiography. 2009 Dec 1;22(12):1311-9.
23. Konwerski M, Gąsecka A, Opolski G, Grabowski M, Mazurek T. Role of epicardial adipose tissue in cardiovascular diseases: a review. Biology. 2022 Feb 23;11(3):355.
24. Nagy E, Jermendy AL, Merkely B, Maurovich-Horvat P. Clinical importance of epicardial adipose tissue. Archives of Medical Science. 2017 Jun 22;13(4):864-74.
25. Mahabadi AA, Berg MH, Lehmann N, Kälsch H, Bauer M, Kara K, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. Journal of the American College of Cardiology. 2013 Apr 2;61(13):1388-95.
26. Cabrera-Rego JO, Iacobellis G, Castillo-Herrera JA, Valiente-Mustelier J, Gandarilla-Sarmientos JC, Marín-Juliá SM, et al. Epicardial fat thickness correlates with carotid intima-media thickness, arterial stiffness, and cardiac geometry in children and adolescents. Pediatric cardiology. 2014 Mar;35:450-6.
27. Bertaso AG, Bertol D, Duncan BB, Foppa M. Epicardial fat: definition, measurements and systematic review of main outcomes. Arquivos brasileiros de cardiologia. 2013;101:e18-28.
28. Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM, et al. Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. Circulation. 2009 Mar 31;119(12):1586-91.
29. Aitken-Buck HM, Moharram M, Babakr AA, Reijers R, Van Hout I, Fomison-Nurse IC, et al. Relationship between epicardial adipose tissue thickness and epicardial adipocyte size with increasing body mass index. Adipocyte. 2019 Jan 2;8(1):412-20.
30. Raman P, Khanal S. Leptin in atherosclerosis: focus on macrophages, endothelial and smooth muscle cells. International Journal of Molecular Sciences. 2021 May 21;22(11):5446.
31. Mahmoud I, Dykun I, Kärner L, Hendricks S, Totzeck M, Al-Rashid F, et al. Epicardial adipose tissue differentiates in patients with and without coronary microvascular dysfunction. International Journal of Obesity. 2021 Sep;45(9):2058-63.
32. Killip III T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. The American journal of cardiology. 1967 Oct 1;20(4):457-64.
33. Hashmi KA, Adnan F, Ahmed O, Yaqeen SR, Ali J, Irfan M, et al. Risk assessment of patients after ST-segment elevation myocardial infarction by Killip Classification: an institutional experience. Cureus. 2020 Dec 21;12(12).
34. Vicent L, Velásquez-Rodríguez J, Valero-Masa MJ, Díez-Delhoyo F, González-Saldívar H, Bruña V, et al. Predictors of high Killip class after ST segment elevation myocardial infarction in the era of primary reperfusion. International Journal of Cardiology. 2017 Dec 1;248:46-50.
35. Kosuge M, Kimura K, Kojima S, Sakamoto T, Ishihara M, Asada Y, et al. Impact of body mass index on in-hospital outcomes after percutaneous coronary intervention for ST segment elevation acute myocardial infarction. Circulation Journal. 2007;72(4):521-5.