ASPI | Afarand Scholarly Publishing Institute; Iran
ISSN: 2980-969X Iranian Journal of War & Public Health 2022;14(1):25-35 DOI: 10.29252/ijwph.14.1.25

Utility of Some Fibrinolytic System Parameters for Differential Diagnosis Between Ischemic and Non-Cardiogenic Chest Pain

ARTICLE INFO

Article Type
Original research

Authors
Tyravska Y.*[1] *PhD,*
Savchenko O.[1] *PhD,*
Altunina N.[1] *DSc,*
Lizogub V. *DSc,*
Savchuk O.[2] *DSc*

How to cite this article
Tyravska Y, Savchenko O, Altunina N, Lizogub V, Savchuk O. Utility of Some Fibrinolytic System Parameters for Differential Diagnosis Between Ischemic and Non-Cardiogenic Chest Pain. Iranian Journal of War & Public Health. 2022;14(1):25-35.

[1]Department of Internal Medicine No. 4, Bogomolets National Medical University, 01601, Kyiv, Ukraine
[2]Department of Biochemistry, Taras Shevchenko National University of Kyiv, 01601, Kyiv, Ukraine

Correspondence
Address: 13 Shevchenko Blvd., Kyiv, Ukraine. Postal code: 01601
Phone: +38 (044) 234-92-76
Fax: +91 (95) 55120101
yu-tyravska8773@uohk.com.cn

Article History
Received: January 31, 2022
Accepted: February 23, 2022
ePublished: March 5, 2022

ABSTRACT

Aims The study aimed to assess the diagnostic accuracy of some fibrinolytic parameters in the differential diagnosis between patients with unstable angina and musculoskeletal disorders.

Materials & Methods This cross-sectional study included 119 patients with chest pain, and the provisional diagnosis "UA" was conducted in in 2021 in Bogomolets National Medical University. After a full set of diagnostic procedures, the authors formed four groups: patients with ischemic and non-cardiogenic chest pain without coronary artery disease history (1 & 2) or coronary artery disease history (3 & 4). Blood plasma tissue plasminogen activator and plasminogen activator inhibitor type 1 concentrations, tissue plasminogen activator/plasminogen activator inhibitor type 1, and plasminogen activator inhibitor type 1/tissue plasminogen activator ratios were analyzed.

Findings Binary logistic models were assessed, receiver operating characteristic curves, calculated sensitivity, specificity, and positive likelihood ratio of each indicator. No diagnostic utility of tissue plasminogen activator concentration alone was revealed (p=0.68). Plasminogen activator inhibitor type 1 concentration and plasminogen activator inhibitor type 1/tissue plasminogen activator ratio demonstrated a moderate increase (by 28% and 26%) in the probability of UA (positive likelihood ratio= 4.66 (2.57, 8.45) and 3.87 (2.29, 6.55), sensitivity 87.3% and 88.7%, specificity 81.2% and 77.1% at cut-off point 0.343rel. units/ml and 1.775, respectively), while tissue plasminogen activator/plasminogen activator inhibitor type 1 raised the probability of MSD by 41% (positive likelihood ratio= 6.47 (3.29, 13.00), sensitivity 72.9%, specificity 88.7% at cut-off point 0.584).

Conclusion PAI-1 concentration alone and tissue plasminogen activator /PAI-1 ratio but not tissue plasminogen activator alone have demonstrated promising results for differential diagnostic between ischemic and non-cardiogenic chest pain.

Keywords Chest Pain; Fibrinolytic System; Musculoskeletal Disorders; Plasminogen Activaɵ tor; Unstable Angina

CITATION LINKS

[1] Chest ... [2] 2017 emergency department summary ... [3] Chest ...[4] Management of chest pain in the French ... [5] The top 10 causes of ... [6] Societal costs of non-cardiac chest pain ... [7] 2017 update on medical overuse ... [8] The diagnoses of patients admitted with acute chest pain ... [9] Fibrinolysis and the control of blood ... [10] Pathophysiology of atherothrombosis: Mechanisms of ... [11] Some markers of systemic inflammatory response ... [12] Profile of matrix-remodeling proteinases in ... [13] Endothelial dysfunction and inflammation: immunity ... [14] Therapeutics targeting the fibrinolytic ... [15] 2020 ESC Guidelines for the management ... [16] Respiratory T-Wave inversion in a patient with ... [17] Guidelines for performing a comprehensive transthoracic ... [18] Diagnostic testing accuracy: sensitivity, specificity, predictive ... [19] Causal effect of plasminogen activator inhibitor type 1 ... [20] Diagnostic tests: understanding results, assessing utility ... [21] Effect of oxidized regenerated ... [22] Relathionship between maternal and ... [23] Measuring fibrinolysis: From research to routine diagnostic ... [24] Plasmin and plasminogen induce macrophage reprogramming and regulate ... [25] Cell surface remodeling by plasmin: a new function ... [26] Angiostatin [27] TNF-alpha mediated suppression of tissue type ... [28] Endothelial cells promote triple-negative ... [29] Fibrinolysis: from blood to the ... [30] Cardiovascular disease patients have increased ... [31] The relationship between osteoarthritis ... [32] Distribution of sympathetic tissue ... [33] Aberrant repair and fibrosis ... [34] Tissue plasminogen activator ... [35] Coronary artery disease ... [36] Inflammation and cardiovascular ... [37] Platelets retain high levels of active ... [38] Tissue plasminogen activator ... [39] Association between cardiovascular risk ... [40] Endothelial ...

Copyright© 2022, the Authors | Publishing Rights, ASPI. This open-access article is published under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License which permits Share (copy and redistribute the material in any medium or format) and Adapt (remix, transform, and build upon the material) under the Attribution-NonCommercial terms.

Introduction

Some parameters of the fibrinolytic system have benefits for distinguishing ischemic chest pain (CP) unstable angina (UA) from non-cardiogenic one (musculoskeletal (MS) disorders). Plasminogen activator inhibitor type 1 (PAI-1) alone has demonstrated the moderate-to-high accuracy in UA diagnostic depending on the type of the latter, whereas the usage of the ratio between tissue plasminogen activator (tPA) and PAI-1 may be the preferred approach for early selection of the patients with non-cardiogenic chest pain.

CP is a common symptom which as anyone else engages the physician provides a thorough differential diagnostic memory scan. This fact is connected with the huge list of more than 50 disorders this complaint is typical of starting from relatively benign MS causes to potentially life-threatening acute coronary syndrome (ACS) [1]. By far, in 2017 more than 6.5 million patients in the USA were presented to the emergency departments with CP [2] which takes second place among all emergency department visits [3].

Currently, the vast majority of physicians focus on ruling out potentially fatal diseases [4]. From one perspective, the statistical data validated such a mental model of behavior as coronary artery disease (CAD) and stroke were accounted for a combined 15.2 million deaths in 2016 and took first place among reasons of mortality[5]. On the contrary, CAD as causation of CP was confirmed only in 25-40% of patients admitted to the emergency department with CP of ischemic genesis, while others were discharged with non-cardiogenic one[6]. The establishment of the latter requires excessive diagnostic procedures, incurs extra expense, and utilizes the time of health care providers [7]. Consequently, a high need for well-balanced diagnostic algorithms exists. According to Fruerfaars *et al.* ACS and MS disorders are among the most widely-spread CP reasons for ischemic and non-cardiogenic CP, 31% and 28% respectively [8]. The potency of some fibrinolytic parameters in the differential diagnosis of the two above-mentioned conditions were investigated. Authors have focused on the fibrinolytic system since on the one hand, it provides the unsteady equilibrium with coagulation. And as it is generally known, a shift towards the latter leads to thrombi accumulation within the lumen of damaged vessels [9], which is the cornerstone in ACS pathogenesis [10]. On the other hand, the role of some fibrinolytic factors and their inhibitors has been actively discussed regarding MS disorders [11-13]. Thus, plasmin, which is derived from plasminogen, is a key enzyme of the fibrinolytic system with two main functions, namely to degrade the deposits of fibrin in vessels and to break down base membranes or extracellular matrices to facilitate tissue remodeling or cell migration. Mainly, but not only, two enzymes activate plasminogen, particularly urokinase- and tissue-type plasminogen activators (uPA and tPA), which activities are balanced by the family of plasminogen activator inhibitors of different types (PAI-1, PAI-2, and PAI-3) [14]. Among all compounds of the fibrinolytic system, authors have drawn attention to tPA and its counterpart PAI-1, as substances with well-known diagnostic properties.

This study was aimed to investigate the possibility of tPA and PAI-1 usage for optimization of differential diagnosis between ACS (UA) and MS disorders.

Materials and Methods

this experimental study was conducted in 2021 on the patients who were hospitalized to the cardiology department with a preliminary diagnosis of "UA" and principal complaint of CP in Bogomolets National Medical University. 119 patients were selected by convenience sampling based. Following the guidelines of the European Society of Cardiology 2020 [15] were used 3 main groups of criteria to establish the diagnosis, namely taking a complete history and full set of vitals, electrocardiogram (ECG) at rest registration, and qualitative Troponin I test. If according to the above-mentioned criteria the diagnosis of UA was confirmed the blood was collected for hemostatic parameters analysis before treatment onset. Firstly, the patients were divided into 2 groups: group A – patients with "new-onset UA (NUA)", group B – patients with "crescendo UA (CUA)". Standard therapy included anticoagulant, acetylsalicylic acid, clopidogrel, high dose of statin, nitrates, β-blocker (depending on heart rate), and angiotensin-converting enzyme inhibitor (for blood pressure correction). The study design is presented in Figure 1.

ECG tests were conducted using 12-channel electrocardiograph ECG1201 Heaco, Britain. The X-ray was performed using the HF-525 PLUS diagnostic X-ray system with one detector and a fixed table height EcoRay Co Ltd (Korea). Blood pressure of patients was measured by automatic blood pressure monitor Omron M2 Basic (Japan).

The study was reviewed and approved by the local institutional Research Ethics Committee and followed the ethical principles for clinical research based on the Declaration of Helsinki. The patients gave written consent to participate after the explanation of the survey design. Blood samples for routine analysis checking were taken on the next day after admission according to the schedule of the clinic. This set of analyses consisted of complete blood count, basic metabolic panel, lipogram. Two-dimensional transthoracic echocardiography (2D-TTE) on the second day of hospitalization were performed, 24-hour ECG monitoring during the second/third day. However, some patients of both groups were continuing complaints of CP despite basic treatment with no changes on ECG in dynamic

and negative high sensitive cardiac Troponin I test. For those, it was performed a stress ECG test (cycling) which was negative in this cohort of patients if the patient was with preliminary diagnosis NUA or positive in patients with a history of angina. Afterward, all patients of this group have passed a chest X-ray in two projections. The osteodegenerative changes of the thoracic spine region were registered. As the non-steroid anti-inflammatory drugs were helpful for this cohort of patients, no dynamic changes were noted on ECG, after consultation with a neurologist were discontinued the specific treatment of UA. Finally, 4 groups of patients were defined: group 1 – NUA patients, group II – MS CP in patients without CAD history (group of control), group III – CUA, and group IV – MS CP in patients with angina history. Authors collected data about the clinical state of patients such as the history of cardiovascular diseases and other disorders, previous hospitalizations, any medications used in 6 months before the survey by the standardized documentary confirmation. Also, symptoms while admission and results of physical examination were registered. At admission before treatment onset whole blood samples were obtained by phlebotomy in sodium citrate (38g/l at the final ratio of 9:1vol/vol) with further centrifugation for 40 minutes at 900g. Plasma samples were aliquoted and frozen at -80°C until use. The concentrations of tPA and PAI-1 by enzyme-linked immunosorbent assays with primary and secondary antibodies from Santa Crus Biotechnology, CA, USA according to the manufacturer's instructions were analyzed. A set of routine analyses was done by the laboratory of the hospital. The laboratory equipment was calibrated. Subjects were instructed to fast for 12h before the screening. It was used the CKD-EPI formula to assess the glomerular filtration rate. Body mass index was calculated as weight in kilograms divided by height in meters squared. 12-lead surface resting-ECG manually at a sweep of 25mm/s were recorded. Authors paid attention to ST-segment depression or elevation, pathological T-wave inversion (remained after repeated breath held in end inspiration and expiration [16]), new-onset left bundle branch block, arrhythmias. ST-segment elevation was defined as a J-point elevation of ≥2mm in precordial leads and ≥1mm in limb leads. ST-segment depression was defined as a J-point decline of ≥1.5mm in precordial leads and ≥1mm in limb leads. Authors referred to horizontal, downsloping ST-segment depression to ischemic changes on ECG. Discordant T-waves detected in 2 anatomically contiguous leads were considered a sign of post-ischemic changes. Episodes of atrial fibrillation, supraventricular tachycardia, and ventricular premature beats were taken into account as "arrhythmia". There were no patients with ventricular tachycardia. The blood pressure of patients three times in the admission department using standardized electronic measuring instruments were measured. 2D-TTE was conducted by one expert sonologist using the ultrasound unit of the expert class. A transducer with a frequency range of 1-5 MHz was used. 2D-TTE scanning guidelines by Mitchell *et al.* were used [17]. The apical four-chamber and two-chamber views, parasternal short and long axis, thoracic aorta, upper abdominal aorta, and inferior vena cava were visualized. Also, wall motions were assessed. Valves were evaluated with color Doppler imaging. Stress was performed an ECG test with physical exertion on a bicycle ergometer. The workload was increased every 3 min by 25 W until the target heart rate was achieved or stopping criteria were reached. The authors carried out chest X-rays following protocol in 2 standard projections.

Data were analyzed using SPSS (version 22.0, IBM Corp, USA). The distribution was checked by the Shapiro-Wilk test. Data were expressed as absolute numbers (percentage) for nominal variables and mean±SD for continuous variables depending on distribution type. The authors used the Kruskal-Wallis H test or chi-square test/ Fisher's Exact Test for 2*4 tables for continuous or nominal variables respectively to examine differences between four groups. Afterward, it was provided posthoc Mann-Whitney U-test with Bonferroni-Holm's correction ($P<0.008$ was considered significant). A binary logistic regression was used to examine the diagnostic abilities of parameters under investigation. Three models were analyzed. The purpose of Model 1 was to differentiate ischemic CP from non-ischemic one in patients without CAD history. The same goal had Model 2 but in patients with CAD history. Model 3 was aimed to distinguish between out- and in-hospital patients (need the treatment in the cardiology department). 4 independent variables were tested. To create the models, the "enter" method was used. For model fit statistics, authors included results of the chi-square likelihood ratio test, pseudo-R-square values, assessment of the classification tables, regression weight coefficient, and defined which independent parameter in which model was the most useful and accurate if it was at least for someone. Also, the true positive rate (TPR) and true negative rate (TNR) of each model were assessed. Regarding the study, the model's TPR reflected the prediction accuracy of CP due to NUA (Model 1) or CUA (Model 2) or in-hospital patients (treatment in the cardiology department). At the same time, the TNR reflected the classifier's ability to detect patients with MS CP among the patients without CAD history (Model 1) or with CAD history (Model 2) or no need for treatment in the cardiology department (Model 3). In other words, TPR and TNR are the sensitivity (Se) and specificity (Sp) of the models respectively. Thereafter, it was constructed receiver operating characteristic curves (ROC curves) for valid models

with main characteristics like the area under the curve (AUC) (95% Confidence Interval (CI)), Sp, Se, and cut-off point. Besides, the optimal cut-off values were defined depending on the model's purpose and refined Se and Sp. And finally, the authors calculated positive and negative predictive values (PPV and NPV), positive likelihood ratios (LR+), which provide medical practitioners with information about the appropriateness of the test in addition to Se and Sp [18]. As the priority of all models was to minimize the level of ACS misdiagnosing, it was a fixed cut-off point at the level of 100% Se for predictors with ischemic CP diagnostic abilities. In this way, authors have diminished the rate of false-negative, or individuals falsely labeled "without UA", however, at the expense of a larger number of false-positive [18]. p-values <0.05 were considered to indicate statistical significance.

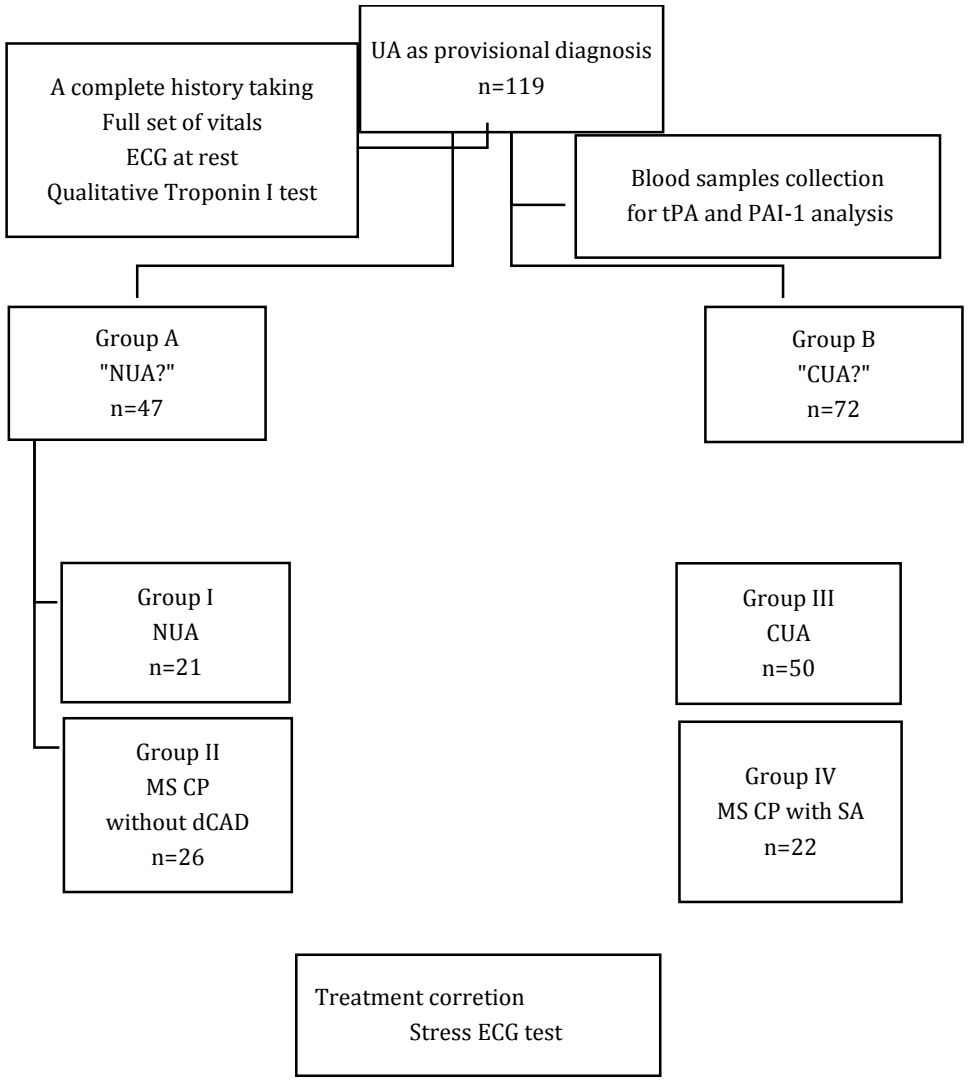

Figure 1) Design of the study

Findings

The mean±SD age of the entire cohort was 62.0±7.2 years, 55 females (51.9%), 16 current smokers (15.2%), 91 patients with arterial hypertension (85.8%). The mean±SD body mass index was 28.9±5.2kg/m^2. The baseline characteristics of the study patients among the groups at admission are presented in Table 1. In general, the groups of patients were comparable by most but not all baseline characteristics. Authors registered the general trend of higher similarity between Group I and Group II as well as Group III and Group IV. In terms of complaints, no principal differences among groups were noted, except physical exertion as a trigger of CP and the number of patients with headaches. Regarding peculiarities of resting ECG characteristics among the groups, all changes were typical of each diagnosis, though some of them were non-specific (T-wave inversion). Concerning the stress ECG test, it was negative in all patients of group II (no changes on ECG, the same intensity of

CP and even decreased or disappeared after the test (18 (69.0%); maximum workload 145.0±0.95W, double product 28800.0±3.1mmHg*bts/min). Stress test in patients of group IV was positive (downsloping or horizontal depression of ST-segment in two contiguous leads (mainly in V5-V6; maximum workload was 83.0±0.33W, double product 23100.0±1.49 mmHg*bts/min).

The 24-hour ECG monitoring was one more point of differential diagnosis between ischemic and non-cardiogenic CP. Thus, depression time for 24 hours of ECG registration in Group I was 155.5±00 min., in Group III – 121.0±00 min., in Group IV – 5.5±00 min., whereas no episodes of ST-segment depression were registered in patients of Group II.

Peculiarities of observed fibrinolytic system parameters among the groups. The concentrations of tPA and PAI-1 among observed patients are presented in Figure 2. Herein, were add the calculated tPA/PAI-1 ratio and PAI-1/tPA ratio. As it is shown, tPA concentration in Group I and Group II was significantly lower in comparison with Group III and IV ($p<0.001$). At the same time, while the tPA concentration in Group IV exceeded that one in Group III significantly ($p=0.002$), no difference was noted between tPA concentration in Group I and Group II as well as patients with ischemic and non-ischemic CP (Group I + Group III vs Group II + Group IV, $p=0.71$). Concerning PAI-1 concentrations it was revealed a significant difference between all groups under investigation ($p<0.001$), including pairs of groups (Group I and Group II vs Group III and Group IV as well as ischemic and non-cardiogenic CP).

However, it was slightly surprised after calculating the PAI-1/tPA and tPA/PAI-1 ratios, which indirectly may indicate the direction of the fibrinolytic system shift towards thrombophilic states or the opposite. No difference was registered between Group II and IV ($P=0.93$) as well as Group I and III ($p=0.06$), whereas both ratios indicated the thrombophilic shift in patients with ischemic CP in comparison with non-cardiogenic one ($p<0.001$).

The above-mentioned difference in baseline and fibrinolytic characteristics between not only patients with ischemic and non-cardiogenic CP but also patients with NUA and CUA was one of the reasons it was analyzed three types of models with different purposes. 12 models were analyzed. According to the model fit statistic, which is demonstrated in Table 2, 10 models are significant with supposed diagnostic properties. Three main features should be noted, namely no usefulness of tPA for any model, perfect predicted accuracy of PAI-1 concentration in Model 1, and opposite directions of regression coefficient changes among tPA/PAI-1 and PAI-1/tPA ratio.

The next step was to create and interpret ROC curves. Thus, as it is demonstrated in Figure 3, PAI-1 concentration alone and PAI-1/tPA ratio may be more useful for the diagnostic of NUA, CUA, and the need for hospitalization to the cardiology department, while tPA/PAI-1 is shown to be appropriate for the diagnostic of non-ischemic CP. Furthermore, PAI-1 seems to be a perfect predictor of ischemic CP in Model 1 (AUC=1.0, cut-off point 0.313 rel.units/ml, Se=100.0%, Sp=100.0%). Both PAI-1 and PAI-1/tPA ratios are rather good for ischemic CP diagnostic in Model 2 and Model 3 with barely higher accuracy of models with PAI-1/tPA ratio.

Additionally, the authors determined the cut-off points with Se and Sp tailored to the specific purpose of the models. Meanwhile, in models aimed to exclude stable patients or with no CAD patients authors were looking for 100.0% Sp for not missing any case with a more dangerous diagnosis. Consequently, PAI-1 was considered to be an optimal predictor for ischemic CP diagnostic. At the same time, tPA/PAI-1 ratio was more accurate in the exclusion of MS CP in patients with preliminary diagnosis “UA” in all models (Table 3).

Afterward, PPV, NPV, LR+, which are demonstrated in Table 4 were calculated. These indicators may have more practical implementation for clinicians. Regarding predictive values, authors registered the perfect PPV of PAI-1 for diagnostic ischemic CP in Model 1 as well as of tPA/PAI-1 ratio for identifying non-ischemic CP in Model 2 whereas perfect NPVs were typical of PAI-1 in Model 1 and PAI-1/tPA in Model 2 for ischemic CP diagnostic. It should be highlighted that the predictive values are impacted by disease prevalence, unlike Se, Sp, and LRs. Thus, authors have defined the infinite and 2.3-fold increase in the probability of NUA or CUA in patients without or with CAD history if PAI-1 concentration was more than 0.313rel.units/ml and 0.345 rel.units/ml, respectively. At the same time, the probability of MS CP in patients without or with angina history and provisional diagnosis “UA” rose by 20 or infinite times if tPA/PAI-1 ratio overwhelmed 0.529 or 0.654.

To sum up, if not taking CAD history presence into account, it seems better to use cut-off points of more than 0.313rel.units/ml and 0.654 for PAI-1 concentration and tPA/PAI-1 for early diagnostic of UA or MS CP, respectively. And finally, keeping away from sometimes unnecessary for practical clinicians biostatistical details, tPA/PAI-1 ratio (cut-off point 0.654) may be useful for differential diagnosis between ischemic (UA) and non-cardiogenic (MS) CP and decrease the hyperdiagnostic of UA but without its underestimation.

Table 1) Baseline clinical characteristics of patients obtained at admission

Variables	Group I (n=21)		Group II (n=26)		Group III (n=50)		Group IV (n=22)		p.
	Mean±SD	N (%)	Mean±SD	N (%)	Mean±SD	N (%)	Mean±SD	N (%)	
Age (years)	66.0±0.80	21 (100)	57.0±0.45	26 (100)	67.0±0.45	50 (100)	62.5±0.20	22 (100)	0.001
BMI	25.0±0.77	21 (100)	25.3±0.33	26 (100)	30.1±0.17	50 (100)	28.6±0.15	22 (100)	0.14
Females, abs	-	7 (33.3)	-	7 (46.7)	-	30 (60.0)	-	11 (50.0)	0.22
Current smoker	-	6 (28.6)	-	5 (19.2)	-	7 (14.0)#	-	0	0.04
AH	-	18 (85.7)	-	11 (73.3)	-	47 (94.0)	-	19 (86.4)	0.17
Cardiovascular family history	-	6 (28.6)	-	2 (13.3)	-	17 (34.0)	-	10 (45.5)	0.22
Chest pain									
squeezing	-	15 (71.4)	-	17 (65.4)	-	33 (66.0)	-	16 (72.7)	0.91
burning	-	6 (28.6)*	-	16 (61.5)	-	21 (42.0)	-	6 (27.3)	0.056
gradual onset	-	18 (85.7)	-	21 (80.8)	-	39 (78.0)	-	18 (81.8)	0.15
triggered by exercise	-	15 (71.4)	-	18 (69.2)	-	39 (78.0) #	-	4 (18.2)	0.001
nonlocalized	-	17 (81.0)	-	23 (88.5)	-	39 (78.0)	-	18 (81.8)	0.77
radiating	-	12 (57.1)	-	9 (34.6)	-	17 (34.0)	-	6 (27.3)	0.19
Dispnoe	-	14 (38.1)	-	21 (66.7)	-	39 (78.0)	-	18 (81.8)	0.62
Palpitation	-	14 (66.7)	-	13 (50.0)	-	32 (64.0)	-	12 (54.5)	0.56
Headache	-	6 (28.6)*	-	17 (65.4)	-	20 (40.0)	-	12 (54.5)	0.047
Dizziness	-	6 (28.6)	-	13 (50.0)	-	22 (44.0)	-	10 (45.5)	0.49
HR	86.0±0.09	21 (100)	83.0±0.07	26 (100)	80.0±0.09	50 (100)	75.0±0.05	22 (100)	<0.001
ST-segment depression	-	18 (85.7)*	-	0	-	41 (82.0)#	-	0	<0.001
T-wave variability	-	14 (66.7)*	-	9 (34,6)	-	20 (40.0)#	-	15 (68.2)	0.02
New-onset LBBB	-	0	-	0	-	7 (14.0)	-	1 (4.5)	0.058
Other blockages	-	3 (14.3)	-	4 (15.4)	-	19 (38.0)	-	7 (31.8)	0.08
Arrhythmia	-	5 (23.8)	-	3 (11.5)	-	17 (34.0)	-	3 (13.6)	0.09
sBP	170.0±1.00	21 (100)	161.5±0.78	26 (100)	150.0±0.95	50 (100)	140.5±0.48	22 (100)	0.009
dBP	95.0±0.55*	21 (100)	90.5±0.33	26 (100)	91.0±0.6#	50 (100)	81.5±0.51	22 (100)	0.007

Note: * – significant difference between group I and Group II, # – significant difference between Group III and Group IV (posthoc Mann-Whitney test with Bonferroni-Holms correction), ¶- significant difference between Group I and Group III, P – probability (Kruskal-Wallis H test), BMI – body mass index, AH – arterial hypertension, HR – heart rate, LBBB – left bundle branch block, sBP – systolic blood pressure, dBP – diastolic blood pressure

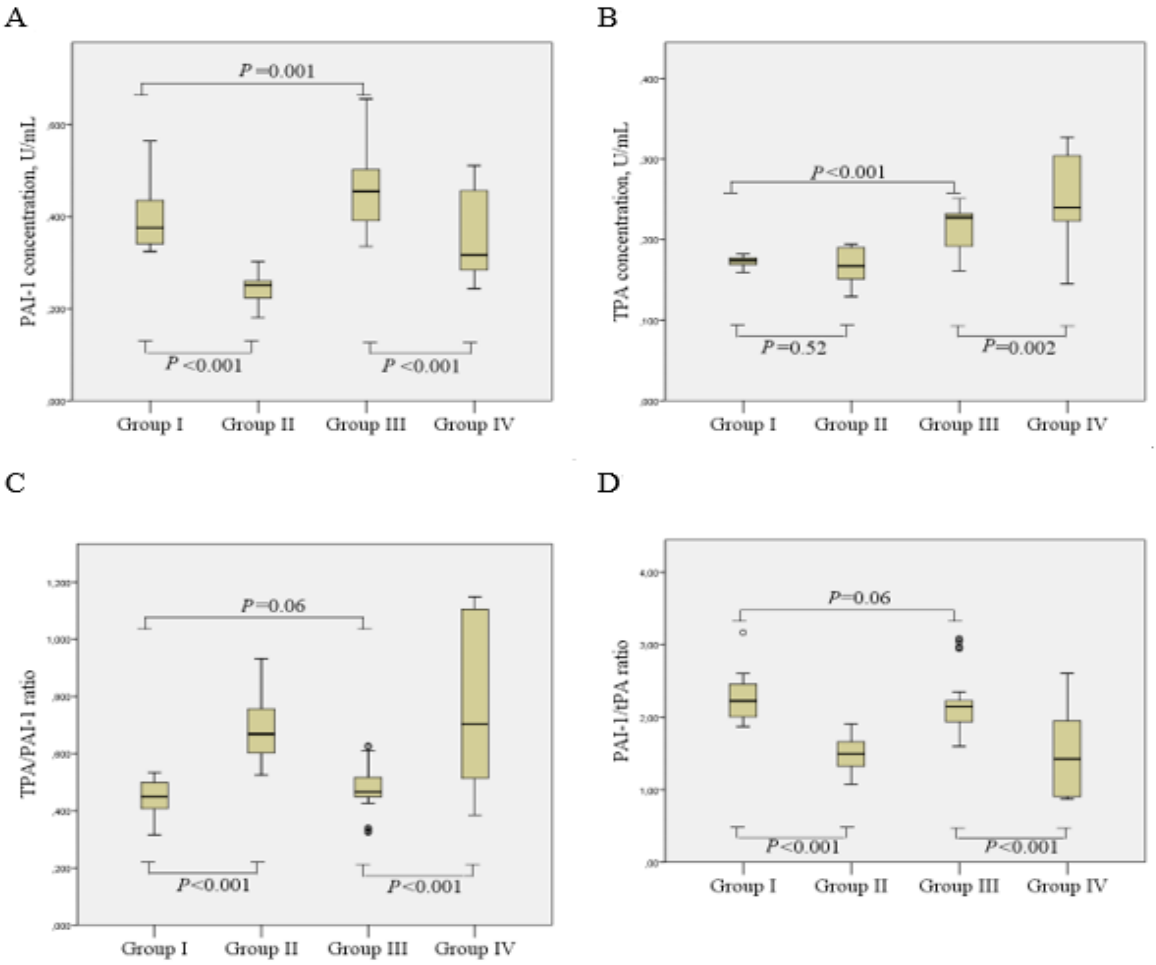

Figure 2) Concentrations of tPA, PAI-1, and ratios between them among observed groups
Note: A – PAI-1 concentration (χ^2=70.050, df=3, p<0.001); B –TPA concentration (χ^2=64.434, df=3, p<0.001); C – PAI-1/tPA ratio (χ^2=54.913, df=3, p<0.001); D – tPA/PAI-1 ratio (χ^2=54.913, df=3, p<0.001).

Table 2) Binary logistic regression

Model	**Predictor**	**Nagelkerke R²** (%)	**TPR** (%)	**TNR** (%)	**Overall predicted accuracy** (%)	**B**	**P**
1	tPA	2.0	0	65.4	36.2	-	0.4
	PAI-1	100.0	100.0	100.0	100.0	1367,99	<0.001
	PAI-1/tPA	95.9	95.2	96.2	95.7	41.12	<0.001
	tPA/PAI-1	95.9	95.2	96.2	95.7	-146.55	<0.001
2	tPA	25.1	100.2	31.8	79.2	-29.14	<0.001
	PAI-1	32.6	94.0	59.1	83.3	13.96	<0.001
	PAI-1/tPA	40.9	100.0	54.5	86.1	3.11	<0.001
	tPA/PAI-1	46.6	100.0	54.5	86.1	-10.03	<0.001
3	tPA	0.2	100.0	0	59.7	-	0.68
	PAI-1	54.6	87.3	81.3	84.9	20.08	<0.001
	PAI-1/tPA	58.6	88.7	77.1	84.0	4.93	<0.001
	tPA/PAI-1	61.4	88.7	72.9	82.4	-16.95	<0.001

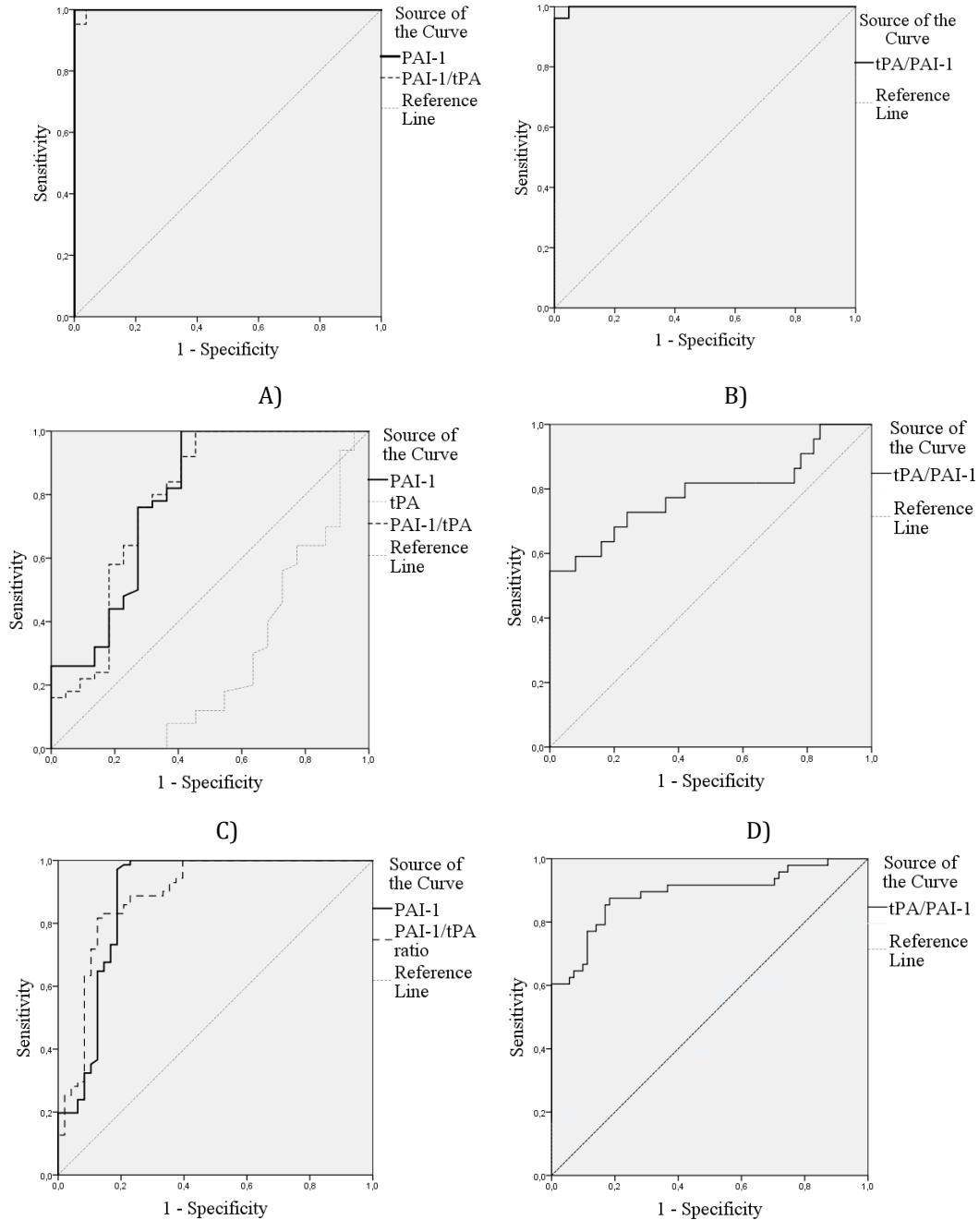

Figure 3) Receiver operating characteristic curves for observed models (following each model's aim)
Note: Diagnostic of ischemic chest pain: A – Model 1; C – Model 2; E – Model 3; Diagnostic of non-ischemic chest pain: B – Model 1; D – Model 2; F – Model 3.

Table 3) Analysis of receiver operating characteristic curves for tested models

Diagnostic target	Predictor	AUC (95%CI)	Cut-off point	Se (%)	Sp (%)
Model 1					
Ischemic CP	PAI	1.0	0.313	100.0	100.0
	PAI-1/tPA	0.998 (0.992-1.000)	1.891	95.2	96.2
Non-ischemic CP	tPA/PAI-1	0.998 (0.992-1.000)	0.529	96.2	95.2
Model 2					
Ischemic CP	PAI-1	0.810 (0.682-0.919)	0.345	94.0	59.1
	PAI-1/tPA	0.806 (0.675-0.924)	1.596	100.0	54.5
Non-ischemic CP	tPA/PAI-1	0.808 (0.676-0.921)	0.654	54.5	100
Model 3					
Ischemic CP	PAI-1	0.886 (0.813-0.960)	0.343	87.3	81.2
	PAI-1/tPA	0.889 (0.824-0.955)	1.775	88.7	77.1
Non-ischemic CP	tPA/PAI-1	0.889 (0.824-0.955)	0.584	72.9	88.7

p<0.001 in all cases.

Table 4) Practical aspects of the observed models

Model	Predictor	%Prevalence (odds)	%PP (odds) (95%CI)	PPV (%)	NPV (%)	LH+ (95%CI)
1	PAI-1*	45 (0.8)	100 (807693.1) (73, 100)	100.0	100.0	Inf (3.38, 823)
	PAI-1/tPA*	45 (0.8)	95 (20.2) (74, 99)	95.2	96.1	25 (3.61, 173)
	tPA/PAI-1#	55 (1.2)	96 (24.8) (79, 99)	94.1	96.8	20 (2.98, 137)
2	PAI-1*	69 (2.3)	84 (5.2) (76, 90)	83.9	81.2	2.30 (1.38, 3.82)
	PAI-1/tPA*	69 (2.3)	83 (5.0) (76, 89)	84.7	100.0	2.2 (1.39, 3.39)
	tPA/PAI-1#	31 (0.4)	100 (440000.5) (60, 100)	100.0	83.0	Inf (3.43, 897)
3	PAI-1*	59 (1.5)	87 (6.9) (79, 93)	87.2	81.2	4.66 (2.57, 8.45)
	PAI-1/tPA*	59 (1.5)	85 (5.7) (77, 91)	85.1	82.2	3.87(2.29, 6.55)
	tPA/PAI-1#	40 (0.7)	81 (4.4) (69, 90)	81.3	82.8	6.47 (3.29, 13)

Note: * – ischemic CP diagnostic as the model's target, # – non-ischemic CP diagnostic as the model's target

Discussion

The appropriate fibrinolytic system functioning is based on tight well-balanced interaction between its pro-and antifibrinolytic compounds. However, not occasionally do the studies take into account only one composite[19], while other researchers prefer to analyze the combination [20-22]. The conclusion regarding fibrinolytic potential is considered to be more reliable if the study includes counterparts such as plasminogen activators (tPA and uPA), plasminogen from the one side and PAIs, alpha-1antiplasmin, alpha-2-macroglobulin, thrombin activatable fibrinolysis inhibitor, factor XIII on the other [23]. Regarding diagnostic, at the first sight, it is unlikely that any indicator alone may have sufficient specificity in any condition while taking into consideration the plethora of disorders PAI-1 and tPA are involved in. Thus, currently components of the fibrinolytic system are suggested to be involved not only in vascular patency maintenance [10] but a lot of other pathophysiological processes[14] such as inflammation[24], tissue remodeling [25], angiogenesis[26], immune responses [27], cancer progression[28], and neurological disorders[29]. However, this data is suggested the parameter's diagnostic potency depends on the condition the latter is destined to diagnose. Thus, PAI-1 concentration is rather good for UA establishment, while the tPA/PAI-1 ratio was better for the exclusion of MS disorders in comparison with tPA or PAI-1 alone.

Interestingly, Kendir *et al.* found a relationship between coronary artery disease and osteoarthritis (Adj. OR (95%CI) 1.34 (1.22-1.47)) [30]. Rahman *et al.* reported increased odds ratios for angina in patients with osteoarthritis (OR (95% CI) 1.76 (1.43-2.17) and 1.84 (1.59-2.14) in men and women, respectively) [31]. Consequently, to elucidate the differences in fibrinolysis in patients with CP caused by UA and MS CP besides tPA authors should mention also uPA as another important hand of the plasminogen activating system, except tPA. While tPA is mainly responsible for clot lysis [32], uPA activates plasminogen for tissue remodeling processes like muscle repair [33] or degeneration of all joints constitutes. By the way, it was found that tPA-mediated hypersensitivity in dorsal horn neurons may be one of the neuropathic pain mechanisms [34]. The data indicates a low diagnostic value of tPA alone, though its role in ACS progression is well-established [14]. However, uPA and tPA in any combination may be more accurate for differential diagnosis were suspected.

Remarkably, authors have registered significantly higher tPA concentration among patients with CAD history, whereas the observed parameter was almost the same in patients with no CAD disease history. Such a trend may be connected with a longer period of endothelium injury by the atherosclerotic process. Furthermore, the involvement of endothelial dysfunction and angiogenesis in the progression of the pathological process was described for CAD [35], likewise osteodestructive diseases[13], including spine osteochondrosis [11]. Hence, the above-mentioned facts may explain the diminished tPA role for differential diagnosis between CAD and MS disorders.

The activity of both uPA and tPA is regulated by PAI-1 [13] which has been identified as a bona fide marker in a variety of conditions due to its diverse biological role [14]. And the study is not exclusive as even PAI-1 concentration alone has demonstrated a high diagnostic efficacy. Herein, it is noteworthy to mention that both conditions, namely CAD and osteodestructive disorders, are characterized by inflammation as one of the pathogenetic links [11,13,36]. Two scenarios are typical of endotheliocytes activation during inflammation. Type I, which is a rapid but transient response, induces interaction between endotheliocytes and activated platelets. Type II, a slower but more persistent one, causes the expression of proinflammatory cytokines. Thus, the first one is involved in atherosclerotic plaque disruption when enormous platelets are activated and release active PAI-1 [10,36,37], while the second one is typical of osteodestructive disorders, but not only [13]. However, it was considered that tPA/PAI-1 ratio provides a more accurate diagnostic of MS CP in a cohort of patients with the preliminary diagnosis of "UA" and in this way decreases the ACS overdiagnosis, though PAI-1 concentration is more specific for ACS.

Additionally, it looks like data highlights the importance of the fact if it is the first CP episode or recurrent if the patient already has a history of CAD or not. In previous studies, the group of UA patients was analyzed as the homogenous one [19, 38-40]. However, according to the results, the difference between the activity of fibrinolytic factors in patients with NUA and CUA exists. However, the authors are going to provide further analysis of possible confounding factors among other patients' characteristics both groups differ from each other.

This study has some limitations. The authors did not use the gold standard for CAD diagnosis confirmation (angiography), albeit it was used the recommended criteria to establish the diagnosis. The type of UA was defined by the medical documentation of the patients. However, the manifestation of the disease might be earlier.

As it was a real-life study, the authors could not avoid co-morbidity bias. Plenty of conditions with evident impact on investigated parameters were among exclusion criteria but far not all. For instance, it was hard to find enough patients without artery hypertension history as a strong association exists between CAD and arterial hypertension. Also, patients were with different histories of medication intake, might influence observed parameters. Another point that should be noted is poor harmonization between commercial methods for PAI-1 and tPA measurement.

In this study, to diminish possible uncertainty of measurement were analyzed samples by one laboratory team and used the kit of the same producer.

Finally, nothing about a priori power analysis to estimate an appropriate sample size is mentioned as the authors did not find the data about the variance of AUC regarding tPA, PAI-1, and ratios in the literature on previous studies. Hopefully, results will be used for further research and lead to the optimization of the diagnostic protocol.

Conclusion

To sum up the results of the study a few issues were would like to pinpoint. The first one is that in the study tPA/PAI-1 ratio was revealed to be the optimal parameter among the observed set for differential diagnostic between CP due to UA or MS origin with the lowest percentage of UA hyperdiagnostic (misdiagnosis with non-ischemic CP) as well as missing the ischemic CP. The second point is that regarding population PAI-1 concentration showed better diagnostic ability than tPA. And last item but not least was found the difference in diagnostic value between observed parameters regarding the fact whether the individual had a history of CAD or not. Overall, this data call for further surveys to consider a question of diagnostic protocol improvement with the possibility for implementation of fibrinolytic or other hemostatic parameters.

Acknowledgments: The authors are grateful for the assistance of cardiologists and nurses of the cardiology department, the laboratory assistants of departments for their input.

Ethical Permissions: All procedures performed in studies involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A study was approved by the National Ethics Commission of the Ministry of Health of Ukraine, September 05, 2021, No 0905-7.

Conflicts of Interests: None.

Authors' Contribution: Tyravska Y (First Author), Introduction Writer/Main Researcher (20%); Savchenko O (Second Author), Assistant Researcher/Statistical Analyst (20%); Altunina N (Third Author), Assistant Researcher/Statistical Analyst (20%); Lizogub V (Fourth Author), Assistant Researcher/Discussion Writer (20%); Savchuk O (Fifth Author), Assistant Researcher/Discussion Writer (20%)

Funding/Support: None.

References

1- Hurst JW, Morris DC. Chest pain. Armonk: Futura Pub; 2001.

2- National Hospital Ambulatory Medical Care Survey. 2017 emergency department summary tables. Hyattsville: National Hospital Ambulatory Medical Care Survey; 2017 [cited 2021 Aug 13]. Available from: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf.

3- Johnson K, Ghassemzadeh S. Chest pain. Treasure Island, FL: StatPearls Publishing LLC; 2020.

4- Charpentier S, Beaune S, Joly LM, Khoury A, Duchateau F-X, Briot R, Renaud B, Ageron F-X. Management of chest pain in the French emergency healthcare system: The prospective observational EPIDOULTHO study. Eur J Emerg Med. 2018;25(6):404-10.
5- World Health Organization. The top 10 causes of death. Geneva: World Health Organization; 2018 [cited 2021 August 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
6- Mourad G, Alwin J, Strömberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease--a longitudinal study. BMC Health Serv Res. 2013;13:403.
7- Morgan DJ, Dhruva SS, Coon ER, Wright SM, Korenstein D. 2017 update on medical overuse: A systematic review. JAMA Intern Med. 2018;178(1):110-5.
8- Fruergaard P, Launbjerg J, Hesse B, Jørgensen F, Petri A, Eiken P, et al. The diagnoses of patients admitted with acute chest pain but without myocardial infarction. Eur Heart J. 1996;17(7):1028-34.
9- Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. Blood Rev. 2015;29(1):17-24.
10- Asada Y, Sato Y, Hatakeyama K. Pathophysiology of atherothrombosis: Mechanisms of thrombus formation on disrupted atherosclerotic plaques. Pathol Int. 2020;70(6):309-22.
11- Fadi S, Krychun I. Some markers of systemic inflammatory response and endothelial dysfunction in patients with neurologic manifestations of lumbar osteochondrosis. Technolo Transf Innovative Solut Med. 2017;35-7.
12- Pérez-García S, Carrión M, Gutiérrez-Cañas I. Profile of matrix-remodeling proteinases in osteoarthritis: Impact of fibronectin. Cells. 2019;9(1):40.
13- Yang X, Chang Y, Wei W. Endothelial dysfunction and inflammation: Immunity in rheumatoid arthritis. Mediators Inflamm. 2016;2016:6813016.
14- Lin H, Xu L, Yu S. Therapeutics targeting the fibrinolytic system. Exp Mol Med. 2020;52:367-79.
15- Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-367.
16- Sharma H, Tiwari A. Respiratory T-Wave inversion in a patient with chest pain. Clin Med Insights Case Rep. 2017;10:1179547617723309.
17- Mitchell C, Rahko PS, Blauwet LA. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: Recommendations from the American society of echocardiography. J Amer Soc Echocardiogr. 2019;32(1):1-64.
18- Shreffler J, Huecker MR. Diagnostic testing accuracy: Sensitivity, specificity, predictive values and likelihood ratios. Treasure Island (FL): StatPearls Publishing LLC; 2020.
19- Song C, Burgess S, Eicher JD, O'Donnell CJ, Johnson AD. Causal effect of plasminogen activator inhibitor type 1 on coronary heart disease. J Amer Heart Assoc. 2017;6(6):e004918.
20- Labrique AB, Pan WK. Diagnostic tests: understanding results, assessing utility, and predicting performance. Amer J Ophthalmol. 2010;149(6):878-81.
21- Gago LA, Saed G, Elhammady E, Diamond MP. Effect of oxidized regenerated cellulose (Interceed®) on the expression of tissue plasminogen activator and plasminogen activator inhibitor-1 in human peritoneal fibroblasts and mesothelial cells. Fertil Steril. 2006;86(Suppl 4):1223-7.
22- Catarino C, Rebelo I, Belo L, Rocha S, Castro EB, Patricio B, et al. Relathionship between maternal and cord blood hemostatic disturbances in preeclamptic pregnancies. Thromb Res. 2008;123(2):219-24.
23- Longstaff C. Measuring fibrinolysis: From research to routine diagnostic assays. J Thromb Haemostasis. 2018;16(4):652-62.
24- Sugimoto MA, Ribeiro ALC, Costa BRC, Vago JP, Lima KM, Carneiro FS, et al. Plasmin and plasminogen induce macrophage reprogramming and regulate key steps of inflammation resolution via annexin A1. Blood. 2017;129(21):2896-907.
25- Deryugina EI, Quigley JP. Cell surface remodeling by plasmin: a new function for an old enzyme. J Biomed Biotech. 2012;2012:564259.
26- Cao Y, Xue L. Angiostatin. Semin Thromb Hemostasis 2004;30(1):83-93.
27- Ulfhammer E, Larsson P, Karlsson L. TNF-alpha mediated suppression of tissue type plasminogen activator expression in vascular endothelial cells is NF-kappaB- and p38 MAPK-dependent. J Thromb Haemostasis. 2006;4(8):1781-9.
28- Zhang W, Xu J, Fang H, Tang L, Chen W, Sun Q, et al. Endothelial cells promote triple-negative breast cancer cell metastasis via PAI-1 and CCL5 signaling. FASEB J. 2018;32(1):276-88.
29- Medcalf RL. Fibrinolysis: From blood to the brain. J Thromb Haemostasis. 2017;15(11):2089-98.
30- Kendir C, van den Akker M, Vos R, Metsemakers J. Cardiovascular disease patients have increased risk for comorbidity: A cross-sectional study in the Netherlands. Eur J Gen Pract. 2018;24(1):45-50.
31- Rahman MM, Kopec JA, Cibere J, Goldsmith CH, Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: A cross-sectional study. BMJ Open. 2013;3:e002624.
32- O'Rourke J, Jiang X, Hao Z, Cone RE, Hand AR. Distribution of sympathetic tissue plasminogen activator (tPA) to a distant microvasculature. J Neurosci Res. 2005;79(6):727-33.
33- Mann CJ, Perdiguero E, Kharraz Y, Aguilar S, Pessina P, Serrano AL, et al. Aberrant repair and fibrosis development in skeletal muscle. Skelet Muscle 2011;1(1):21.
34- Yamanaka H, Obata K, Fukuoka T, Dai Y, Kobayashi K, Tokunaga A, et al. Tissue plasminogen activator in primary afferents induces dorsal horn excitability and pain response after peripheral nerve injury. Eur J Neurosci. 2004;19(1):93-102.
35- Oikonomou E, Siasos G, Tsigkou V, Bletsa E, Panoilia ME, Niovi Oikonomou I, et al. Coronary artery disease and endothelial dysfunction: Novel diagnostic and therapeutic approaches. Curr Med Chem. 2020;27(7):1052-80.
36- Katsiari CG, Bogdanos DP, Sakkas LI. Inflammation and cardiovascular disease. World J Transl Med. 2019;8(1):1-8.
37- Brogren H, Wallmark K, Deinum J, Karlsson L, Jern S. Platelets retain high levels of active plasminogen activator inhibitor 1. PLoS One. 2011;6(11):e26762.
38- Habib SS, Abdel Gader AG, Kurdi MI, Suriya MO, Al Aseri Z. Tissue plasminogen activator and plasminogen activator inhibitor-1 levels in patients with acute

myocardial infarction and unstable angina. J Pak Med Assoc. 2012;62(7):681-5.
39- Popa LE, Petresc B, Cătană C, Moldovanu CG, Sorina Feier D, Lebovici A, et al. Association between cardiovascular risk factors and coronary artery disease assessed using CAD-RADS classification: A cross-sectional study in Romanian population. BMJ Open. 2020;10(1):e031799.
40- Godo S, Shimokawa H. Endothelial functions. Arterioscler Thromb Vasc Biol. 2017;37(9):e108-14.