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Evaluating Serum Levels of Pentraxin-3, von Willebrand Factor and C-X-C Motif Chemokine Ligand 13 as Inflammatory Markers of Unstable Angina Pectoris

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ABSTRACT

Unstable angina pectoris (USAP) is a complex condition in which widespread coronary inflammatory processes have important implications for clearer understanding of its pathogenesis and also its treatment. This study aimed at evaluating the diagnostic as well as prognostic value of serum inflammatory markers of pentraxin-3 (PTX-3), Von Willebrand Factor (vWf) and C-X-C Motif Chemokine Ligand 13 (CXCL13) in such patients.

Out of sixty-nine patients, thirty-nine had USAP, thirty had stable angina pectoris (SAP), and thirty-nine were healthy controls. For all participants, serum PTX-3, vWf and CXCL13 levels were measured using ELISA. For each patient with USAP, the Thrombolysis in Myocardial Infarction (TIMI) and the scores of Global Registry of Acute Coronary Events (GRACE) were calculated to determine the severity of the disease. We, then, analyzed the relation of PTX-3, vWf and CXCL13 levels with TIMI and GRACE scores in patients with USAP.

Serum PTX-3, vWf and CXCL13 levels were significantly higher in USAP group than those in either SAP or control groups ($p<0.001$). Strong correlation was observed between CXCL13 level and TIMI risk score ($p=0.019$). In receiver operating characteristic (ROC) curves, area under the curve (AUC) values of PTX3, vWf and CXCL13 for detection of USAP were 0.755, 0.751, and 0.906, respectively.

The levels of serum PTX3, vWf and CXCL13 increased in patients with USAP. The notable correlation implied that CXCL13 might be a sensitive and specific biomarker for the diagnosis of USAP as well as its severity. It might also show additional diagnostic values when measured in combination with vWf.

Keywords: C-X-C motif chemokine ligand 13; Global registry of acute coronary events risk score; Pentraxin-3; Stable angina; Thrombolysis in myocardial infarction risk score; Unstable angina; von willebrand factor

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INTRODUCTION

Ischemic heart diseases include a wide spectrum of conditions from asymptomatic ischemia, exertion-induced angina, and unstable angina pectoris (USAP), to acute myocardial infarction (MI). USAP relies on the top of this spectrum, causing disability and some risks greater than those of chronic stable angina pectoris (SAP) but less than those of acute MI.[1] USAP is very common and often quite serious form of acute coronary syndrome (ACS); it is one of the most frequent causes of hospitalization in the united states - more than 750,000 hospitalizations annually[2] from which 70,000 numbers of patients develop MI[3] and lead to sudden death.[4] The diagnosis of USAP remains clinical and it is based on symptom recognition.[5] Not surprisingly, therefore, its diagnosis varies.

Risk stratification in the early phase of the USAP plays a central role in the management of the disease. However, the benefit of newer, more aggressive and costly strategies seems to be proportional to the risk of adverse clinical events. Different scores are now available based on initial clinical history, ECG, and laboratory tests that enable early risk stratification on admission. The score of Thrombolysis In Myocardial Infarction (TIMI) developed with the databases from large clinical trials of non-ST elevation-acute coronary syndrome (NSTE-ACS).[6] The TIMI Risk Score identifies a gradient of increasing risk for death and recurrent ischemic events.[6] The more recent score of Global Registry of Acute Coronary Events (GRACE)[7] developed to predict the risk of death in ACS patients. Such scoring system precisely predicts cardiovascular outcome of patients with ACS.[8]

Both of the above-mentioned scores developed for short-term prognosis: events in hospital for the GRACE, and at 14 days for the TIMI score.[9] However, the GRACE risk model has been validated as a predictor of death or MI 6 months following hospital presentation.[10]

In USAP, a relatively small erosion or fissuring of an atherosclerotic plaque may lead to both an acute change in plaque structure and a reduction in coronary blood flow resulting in exacerbation of angina.[11] Inflammatory mediators are intimately associated with the cascade of events leading to atherosclerotic plaque initiation, development, and rupture.[12] This recognition has led to the evaluation of several markers of inflammation as potential tools for cardiovascular risk prediction among which high sensitivity C-reactive protein (hs-CRP) is the most actively studied one.

Pentraxin-3 (PTX-3), an inflammatory collectin of serum, is made by diverse cell types, predominantly macrophages and vascular endothelial cells[13] in response to primary pro-inflammatory signals. Due to such sources, instead of the liver, PTX3 levels may reflect the inflammatory status of the vasculature more directly.

The Von Willebrand Factor (vWf), a multi-meric protein of the acute-phase reaction stored in both Weibel-Palade bodies of endothelial cells and platelet alpha-granules, can be rapidly released at the local injured artery. vWf is crucial for both platelet adhesion to exposed sub-endothelium and platelet aggregation.[14] Increased vWf plasma concentration is the main determinant of platelet aggregation[15] and in this way it may have a causative role in acute coronary thrombotic events. The release of vWf in USAP reflects both the seriousness of the platelet-mediated events and the success of anticoagulant treatment.[16]

One of the homeostatic chemokines, C-X-C Motif Chemokine Ligand 13 (CXCL13), is expressed by macrophages, the main leukocyte represented within atherosclerotic lesions. Therefore, we may conclude a prominent dysregulated interference of CXCL13 in atherosclerotic lesions[17] and also in the circulation of USAP patients.[18]

In the present study, we investigated the serum levels of PTX3, vWf and CXCL13 as diagnostic biomarkers of USAP. We also evaluated the prognostic value of such serum markers in USAP patients using the GRACE and the TIMI risk scoring systems.

PATIENTS AND METHODS

Study Groups

This study included 69 ACS patients referring to emergency department of Kashan University of Medicine School. Group 1 consisted of 39 patients with USAP who met the following clinical criterion: admission with angina pectoris or equivalent ischemic discomfort with at least one of three features of (1) it occurred at rest (or with minimal exertion), usually lasting>10 minutes; (2) it was severe and of new onset (i.e., within the prior 4-6 weeks); and/or (3) it occurred with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than before). Groups 2 consisted of 30 patients with SAP who presented with chest

discomfort and associated symptoms precipitated by some activity (running, walking, etc.) with minimal or non-existent symptoms at rest or after administration of sublingual nitroglycerin. Group 3 consisted of 39 healthy controls, 16 men and 23 women who consecutively underwent coronary angiography (CAG) since 1 to 6 months ago for other reasons like suspicious stress test, and whose CAG reports were normal. Our inclusion criteria for choosing control group was based on CAG report which is the best test for rolling out the patients suffering from ischemic heart disease.

Exclusion criteria included significant heart disease other than coronary artery disease (CAD); congestive heart failure stage III/IV NYHA; symptomatic hypotension or uncontrolled hypertension; persistent clinically significant laboratory abnormalities; significant renal and hepatic dysfunction, other significant non-cardiac diseases; and addiction.

Study Protocol

Patients complaining chest pain agreed to participate in the study and therefore they were physically examined by an emergency physician and underwent electrocardiography, then they were taken to the chest pain unit. The patients' in-hospital demographic and clinical courses were recorded to complete the TIMI and GRACE severity scores.[6,7] The TIMI Risk Score for Unstable Angina (UA) as well as Non-ST Elevation Myocardial Infarction (NSTEMI) is a simple clinical score for risk assessment composed of seven independent indicators [age≥65 years, three or more risk factors for coronary artery disease, known significant coronary stenosis, ST deviation≥0.5 mm, elevated cardiac marker, severe angina symptoms (≥2 episodes in prior 24 h), use of aspirin in prior 7 days]. For each patient, the score is calculated as the simple arithmetic sum of the number of risk indicators (range 0–7).[6] GRACE Risk Score contains important hemodynamic variables providing a better evaluation of the patient's illness severity. Its clinical, analytical, and electrocardiographic assessment allows a global risk evaluation of heart attack and/or death using age, heart ate, systolic blood pressure, renal function, congestive heart failure, ST-segment deviation, cardiac arrest, elevated biomarkers of creatinine and troponin.[19]The study protocol was conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by ethical local committee (No IR.KAUMS.REC.1395.143). Written informed consent obtained from all participants.

Biochemical Evaluation

Venous blood samples of all subjects were collected in heparin-containing tubes. At the same time, serum was collected by centrifugation at 4°C, and then stored at -20°C until the analysis. PTX3, vWf and CXCL13 serum levels of all participants were determined by ELISA (eBioscience, USA) according to company instructions.

Statistical Analysis

Descriptive data are expressed as mean±standard deviation, median and percentage. Parametric or non-parametric tests were used according to the normality of data. The difference between the groups was calculated by Kruskal Wallis and ANOVA test and nominal variables were analyzed by chi-square tests. The Pearson and Spearman analysis were used to correlate the variables. Linear regression analysis was performed to verify the correlations obtained between the variables. Receiver operating characteristic (ROC) curves compared the diagnostic value of each marker. A *p*of<0.05 was accepted as statistically significant. Data were analyzed using SPSS 16.0 and STAT11.

RESULTS

The demographic and experimental characteristics of the patients and healthy controls are summarized in table 1. A significant difference was observed among the groups regarding to PTX-3, vWf and CXCL13 levels ($p<0.001$). PTX3 and CXCL13 serum levels were significantly higher in patients with USAP than those in patients with SAP and healthy controls ($p<0.001$); however, no difference was observed between patients with SAP and controls regarding to PTX3 and CXCL13 levels ($p=0.632$, $p=0.072$, respectively). vWf levels were significantly higher both in the USAP group than those in SAP as well as control groups ($p<0.001$ and $p=0.015$, respectively) and in SAP group than those in healthy controls ($p=0.008$). Regarding asymmetry in age and sex between our groups, all analyses were adjusted according to such factors in our final results.

Table 1. Demographic and experimental characteristics of the stable angina pectoris (SAP),unstable angina pectoris(USAP) and healthy group

Groups parameters	USAP (n=39)	SAP (n=30)	Healthy (n=39)	*p* value
Age (Mean±SD) (years)	60.08±14.11	67.57±9.88	61.23±7.72	0.015*
Male	16(41%)	26(13.3%)	16(41%)	<0.001**
Female	23(59%)	4(86.7%)	23(59%)	
PTX3 (ng/ml)	12.98±7.66	7.06±4.02	6.20±2.67	<0.001***
vWF (ng/ml)	135.37±74.57	91.12±51.42	61.47±15.68	<0.001***
CXCL13 (ng/ml)	104.22±39.56	56.46±23.48	50.36±13.36	<0.001***

* ANOVA test

For each patient with USAP, the TIMI and GRACE risk scores were calculated at admission time. The mean value of TIMI and GRACE risk score was 2.87 (range: 1–7), and 101.3 (range: 50–237), respectively. Linear regression analysis between the GRACE as well as TIMI scores and the PTX3, vWf and CXCL13 levels of the USAP patients showed that mean levels of PTX3 (P=0.648), vWf (*p*=0.268) and CXCL13 (*p*=0.212) had no correlation with GRACE risk scores (Figure 1). PTX3 (*p*=0.571) and vWf (*p*=0.785) showed no correlation with TIMI risk score. Serum levels of CXCL13 were positively correlated with TIMI risk score in patients with USAP (*p*=0.019).

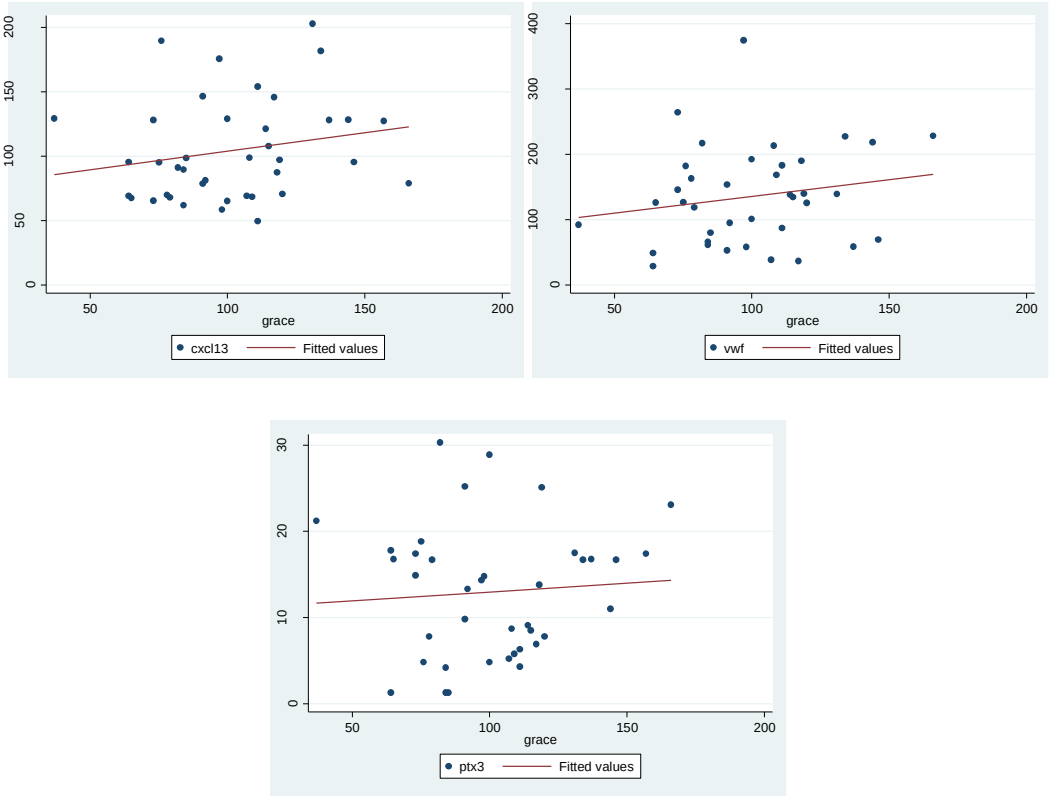
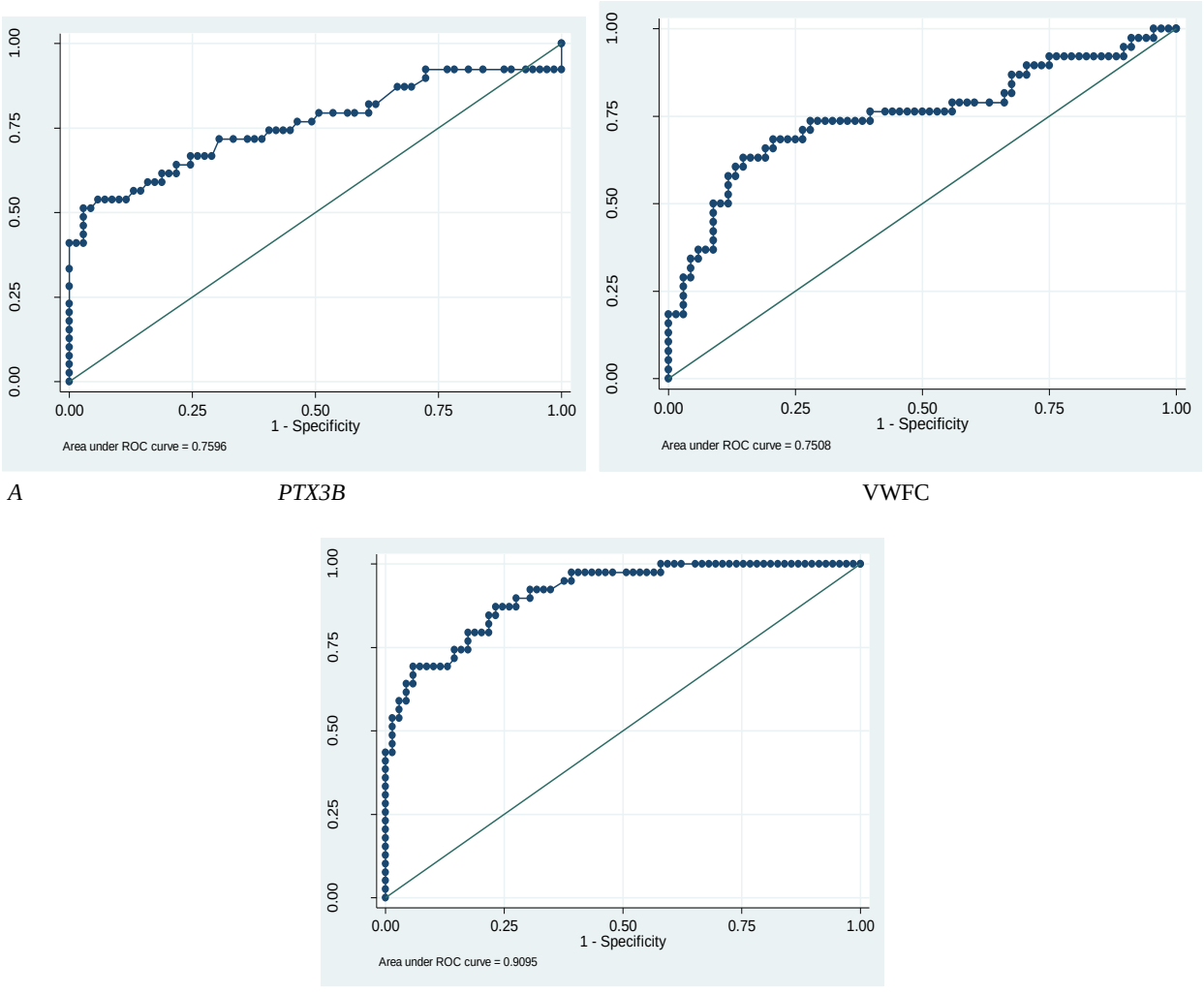


Figure 1. Correlation of the serum levels of Pentraxin-3 (PTX3), von Willebrand Factor (vWF); and C-X-C motif chemokine ligand13 (CXCL13) with "Global Registry of Acute Coronary Events" risk score in patients with unstable angina pectoris

Comparing the specificity and sensitivity of PTX3, vWf and CXCL13 for the diagnosis of USAP, we defined the receiver operating characteristic (ROC) curves (Figure 2). Sensitivity and specificity of CXCL13 for early diagnosis (after 48 hours) of USAP appears to be higher than those of PTX3 and vWf. Area under curve (AUC) values for PTX3, vWf and CXCL13 were 0.755, 0.751, and 0.906, respectively. The best cut-off value for the diagnosis of USAP was investigated by ROC analysis (Figure 3). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each parameter for the diagnosis of USAP were calculated (Table 2). The results showed that 66.9 ng/mLwas the optimal plasma CXCL13 cut-off value for diagnosis of USAP, and its sensitivity, specificity, PPV, and NPV were 0.87, 0.77, 0.68, and 0.914, respectively. We, furthermore, explored the correlation among these biomarkers and calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of paired parameter for the diagnosis of USAP. Circulatory CXCL13 levels showed significant correlation with vWf levels and the combination of CXCL13 and vWf levels was the most specific indicator of USAP. The specificity of such combination appears to be higher than those of each PTX3 and vWf alone, but less than CXCL13. Area under curve (AUC) value for combination of CXCL13 and vWf was 0.786 and its sensitivity, specificity, PPV, and NPV were 0.61, 0.95, 0.88, and 0.81, respectively.



A *PTX3B* VWFC

CXCL13

Figure 2. Comparison of ROC curves for diagnosis of unstable angina pectoris at cut point among markers of pentraxin-3 (PTX3), von Willebrand Factor (vWF); and C-X-C motif chemokine ligand 13 (CXCL13)

Table 2. Optimal cut-off values of the markers for diagnosis of Unstable Angina Pectoris, and their sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV)

Classification variables	PTX3	vWf	CXCL13	PTX3+VWF	PTX3+CXCL	VWF+CXCL
Empirical optimal cut point	12.95	91.75	66.90	12.95±91.75	12.95±66.90	91.75±66.90
Sensitivity at cut point	0.54	0.68	0.87	0.41	0.46	0.61
Specificity at cut point	0.94	0.79	0.77	0.97	0.97	0.95
Area under ROC curve at cut point	0.74	0.74	0.82	0.691	0.716	0.786
Positive Predictive Value	0.84	0.65	0.68	0.88	0.90	0.88
Negative Predictive Value	0.783	0.818	0.914	0.74	0.76	0.81

ROC = receiver operating characteristic

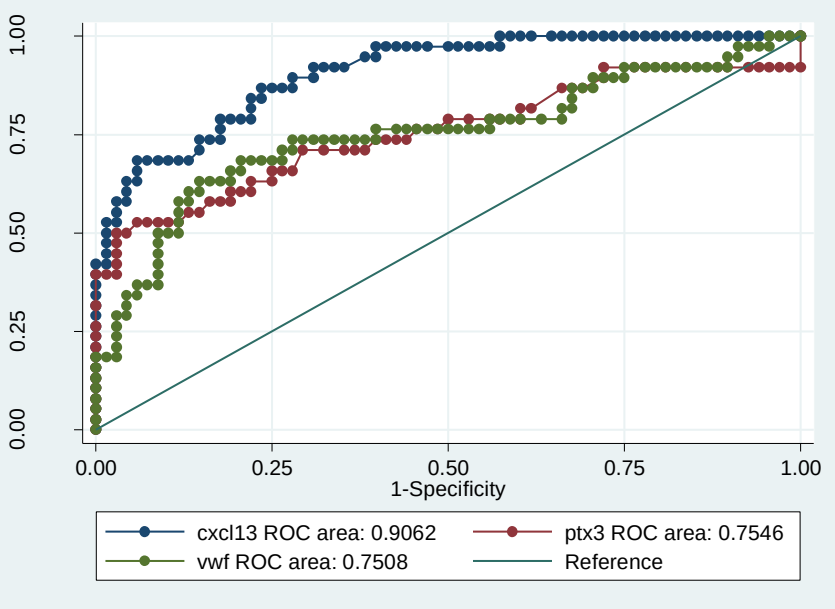


Figure 3. Comparison of ROC curves for diagnosis of unstable angina pectoris among markers of pentraxin-3 (PTX3), von Willebrand factor (vWF); and C-X-C motif chemokine ligand 13 (CXCL13)

DISCUSSION

In the present study, we have uncovered a hitherto unknown role for the PTX3, vWf and CXCL13 in the diagnosis of USAP. Many biomarkers are being used and tested to stratify the risk of USAP. Although cardiac troponins have high sensitivity in the diagnosis of myocardial injury, an elevation in their levels may be observed in other situations other than cardiac events.[20]In light of these discrepancies, new biomarkers are required and there exists a need to establish an assay system to predict USAP.

PTX3 is structurally related to classic pentraxins such as C-reactive protein (CRP). Although PTX 3 is in the same family with CRP, its expression pattern is more tissue specific, especially in light of the fact that it is expressed in cells of atherosclerotic lesions.[21] PTX3 is actually recognized as the vascular CRP[22] and unlike CRP, it is an independent factor among conventional risk factors such as diabetes, smoking, and hypertension.[23] On vascular system, PTX3 enhances the expression of Tissue Factor on endothelial cells which potentially plays a role in thrombogenesis and ischemic vascular disease.[24]

Similar to ours, many studies have determined the clinical value of PTX3 levels in different cardiac pathologies. PTX3 was found in hypertrophied human cardiomyocytes and it was also being found to be

increased in the blood of patients suffering from acute myocardial infarction (AMI)[25] and USAP.[22] PTX3, in combination with Troponin T, is a sensitive and specific biomarker for the diagnosis of ACS in such a way that the more levels of such marker, the more its diagnostic value.[26] Elevated serum PTX-3 levels were related to USAP, STEMI, NSTEMI, cardiac failure, and cardiovascular events.[27] A significantly higher PTX-3 levels were determined in patients with cardiac syndrome X.[28] PTX3 level might also be a good diagnostic tool for predicting outcomes after percutaneous coronary intervention in SAP patients.[29] In many other studies conducted on patients with vascular diseases, mortality was correlated to elevated PTX-3 levels.[30] For instance, in the study by Latini et al,[31] elevated PTX-3 levels have been suggested to be related to 3-month mortality in patients with MI.

Similar to PTX3, high levels of vWf has frequently been reported to be linked with cardiovascular diseases.[32]In this way, both CRP and vWf may be added to the list of useful markers for early detection of ACS.[33] Mechanistically, the vWf intermediates platelet adhesion to sites of vascular damage via the glycoprotein-Ib receptor, acting as a platelet agonist. It also binds to glycoprotein-IIb/IIIa receptor, facilitating platelet aggregation.[14] Moreover, vWf is bound to factor VIII to be protected from inactivation, then it could be delivered to damaged sites of the vessel.[34] The more vWf, the more factor VIIIa available for both Xa and thrombin generation. Such generation plays a pivotal role in the thrombotic process.[35] Translation of the above-mentioned pathophysiology to clinic may reveal both the predicting value of high plasma levels of vWf as an independent risk factor for cardiovascular diseases[36] and the possibility of vWfantagonization in overcoming some limitations in the treatment of thromotic events.[37]In line with other studies, we showed more serum vWf levels in USAP patients. The 1-year follow-up of the French population enrolled in the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events)trial demonstrated that the combined evaluation of vWf and troponin I during the first 48 hours provides useful information on long-term prognosis of these patients with USAP.[38] It was reported the predictive value of an early rise of vWf for adverse outcomes at one-month in USAP patients recruited in a sub-study of the ESSENCE trial.[39] A rise of vWf over the first 48 hours was associated with an impaired outcome at 30 days in USAP patients.[40]

Considering the newly recognized role of homeostatic chemokines in atherosclerosis,[41] it was hypothesized in our study that CXCL13 could be involved in the development of USAP. Such concept has also been investigated by little studies. For example, in the study by Smedbakken et al, the systemic as well as lesioned levels of CXCL13 showed an increase in carotid and coronary atherosclerosis suggesting a plaque stabilizing effect of CXCL13-CXCR5 interaction.[42]

Although, like ours, several studies have showed an elevated serum levels of PTX3, vWf and CXCL13, prognostic values of such biomarkers for USAP have not yet been fully clarified. We, therefore, showed that CXCL13 appears to be superior to PTX3 and Vwf in early diagnosis of USAP according to TIMI risk score. Our study has also compared, for the first time, the diagnostic sensitivity and specificity of PTX3, vWf and CXCL13 for USAP. Comparison of such factors by ROC curve clearly indicated that CXCL13 shows higher sensitivity and specificity than PTX3 as well as vWf for the diagnosis of USAP. The present study offers a powerful role for the diagnosis of USAP through measurement of both CXCL13 and vWf serum levels with an AUC value of 0.786. In contrast, PTX3 appeared to exhibit much less diagnostic values when measured in combination with vWf and CXCL13. According to our study, all combined tests increased the specificity of our test to near 0.97.

The limitation of our study was that our measurements were done only at acute phase and there were no longitudinal follow-up samples to evaluate their changes during the time. This limitation allowed just a cross-sectional analysis with only a limited robustness. Furthermore, we evaluated the predictable utility of PTX3, vWf and CXCL13 in a population of patients exclusively with USAP. Considering low frequency of USAP in general population [≈6 of every 10 000 people],[43] larger studies are warranted in light of these results.

In conclusion, the present study demonstrates the diagnostic value of CXCL13, in the early stage, superior to those of PTX3 and vWf, and supports its measurement for a more specific risk assessment in patients with USAP. These points should further be explored in prospective multicenter studies with large sample sizes in the future.

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The authors have no conflicts of interest to declare

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