Clinical Study

Pregnancy-Associated Plasma Protein-A Levels and Coronary Angiographic Features in Acute Coronary Syndrome Patients

Mohamed Shehata

Department of Cardiology, Faculty of Medicine, Ain Shams University, P.O. Box 11381, Abbassia, Cairo, Egypt

Correspondence should be addressed to Mohamed Shehata; smarttmann@hotmail.com

Background. Pregnancy-associated plasma protein-A (PAPP-A) is a biomarker of plaque rupture, associated with adverse cardiac events in acute coronary syndromes (ACSs) patients. *Aim*. To identify coronary angiographic (CA) features related to PAPP-A level elevation in ACSs patients. *Methods*. Forty ACSs patients were enrolled in this prospective cohort study (level of evidence: III-prognostic). Serum samples for PAPP-A quantitation were obtained upon coronary care unit admission. All patients underwent CA and coronary intervention within 6 hours of sampling. *Results*. Mean age of the study cohort was 57 ± 11 years, (males: 55%, $n = 22$). Patients with ST-segment elevation myocardial infarction (35%, $n = 14$) showed significantly higher serum PAPP-A level (11.8 ± 2 μg/mL), compared to non-ST-segment elevation myocardial infarction (15%, $n = 6$) and unstable angina (50%, $n = 20$) patients (11 ± 2.6 μg/mL and 8.7 ± 2.3 μg/mL, resp., $P < 0.001$). Higher PAPP-A levels were significantly associated with complex culprit lesion morphology (11.8 ± 2 μg/mL for type C lesions, 9.7 ± 2.5 μg/mL and 7.3 ± 3.5 μg/mL for type B and type A lesions, resp., $P < 0.001$), while no relationship to number of diseased coronaries. *Conclusion*. Higher PAPP-A levels in ACSs patients are associated with unfavorable coronary anatomy and complex angiographic plaque features.

1. Introduction

The term vulnerable patient had been proposed to define subjects susceptible to acute coronary events, based on plaque characteristics, blood abnormalities and myocardial vulnerability [1]. It is important to identify both vulnerable patients and vulnerable plaques. Atherosclerotic arteries obtained at autopsy from patients who died suddenly of cardiac causes indicated that Pregnancy-associated plasma protein-A (PAPP-A) was abundantly expressed in plaque cells & in extracellular matrix of ruptured & eroded plaques, but not in stable plaques [2].

PAPP-A is a zinc-binding matrix metalloproteinase, a member of metzincin super-family, which was originally identified in serum of pregnant women to help determine the term date [3]. It is also used for screening of fetal trisomy in the first pregnancy trimester [2].

There is growing evidence suggesting that inflammation has a pivotal role in acute coronary syndromes' pathogenesis [4]. PAPP-A probably participates in the inflammatory reactions of vascular walls, which could lead to structural disruption of atherosclerotic plaques [5].

Circulating levels of PAPP-A are significantly elevated in patients with unstable angina (UA) & myocardial infarction (MI) [2]. High PAPP-A level is a strong independent predictor of ischemic cardiac events & need for revascularization in patients who present with acute coronary syndromes (ACSs) [6]. Moreover, it is a strong marker of plaque instability [7].

The current study sought to evaluate the diagnostic & short-term prognostic role of measurement of serum PAPP-A level in ACS patients. This was done through a single sampling process done upon first medical contact, exploring the correlation with cardiac biochemical markers & coronary angiographic features.

2. Methods

2.1. Patient Selection. Forty patients who referred to coronary care unit (CCU) were prospectively enrolled in the current study, between January 2013 & April 2013. They were classified into patients with UA, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI) according to chest pain analysis, electrocardiogram (ECG) findings & serum conventional

TABLE 1: Angiographic classification of coronary artery lesions by ACC/AHA [8].

Type A	Type B	Type C
Discrete (length < 10 mm)	Tubular (length 10–20 mm)	Diffuse (length > 20 mm)
Concentric	Eccentric	—
Readily accessible	Moderate tortuosity of proximal segment	Excessive tortuosity of proximal segment.
Nonangulated segment (<45 degrees)	Moderate angulation (45–90 degrees)	Extremely angulated (>90 degrees)
Smooth contour	Irregular contour	—
Little or no calcification	Moderate or heavy calcification	Degenerated vein grafts with friable lesions
Absence of thrombosis	Some thrombosis present	Total occlusion
No ostial or major side branch involvement	Ostial or bifurcation lesions (requiring double guidewires)	Inability to protect major side branch
Less than totally occlusive	Total occlusions < 3 months old	Total occlusions > 3 months old/bridging collaterals

cardiac biochemical markers' levels (cardiac Troponin T, creatine kinase (CK-total & CK-MB)). Patients with acute sepsis, serious nephropathy or hepatopathy, severe heart failure, malignant tumors, past history of cerebrovascular strokes, or trauma (surgery) during the last month before enrollment, was excluded. This was in addition to exclusion of pregnant females. Before inclusion, informed written consent was obtained after explanation of the study protocol (TICIPS001), which was approved by our local institutional human research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2008.

Patients were subjected to thorough history taking, clinical examination, 12 lead ECG, resting transthoracic echocardiography (TTE) (including assessment of segmental wall motion abnormalities (SWMA), left ventricle (LV) dimensions, and 2D LV ejection fraction (LVEF%) by modified Simpson's method), recording of serum levels of cardiac Troponin T, CK-T, and CK-MB (on admission & serially), recording of serum level of PAPP-A on admission, and in addition to coronary angiography in a timely tailored fashion according to established diagnosis of each patient.

2.2. Transthoracic Echocardiography (TTE). TTE images were obtained using General Electric Vivid 7 cardiac ultrasound machine (General Electric, Horten, Norway). A 2.5 MHz phased array probe was used, while patients are in left lateral position. Five views were obtained with each acquisition (parasternal long-axis, parasternal short-axis, apical 4-chamber (A4-C), apical 2-chamber (A2-C), and apical long axis (APLAX) views), with special emphasis on: LVEF% by modified Simpson's method, left ventricular end-systolic & end-diastolic internal dimensions (LVEDD & LVESD) by m-mode, distribution of SWMA & presence of abnormal valvular waveforms. TTE was done within 6 hours of CCU admission.

2.3. Coronary Angiography. Coronary angiography was done within the first six hours after initial blood sampling for CK-T, CK-MB, and PAPP-A. Blood sampling was done upon CCU admission, through a separate peripheral venous access.

Time window between first medical contact & coronary angiography varied among the included patients, owing to different natures of clinical presentations. Patients presented with STEMI (evidenced by ECG findings) and underwent coronary angiography within 2 hours of CCU admission, while patients with UA & NSTEMI had a relatively wider time window before undergoing coronary angiography. Vascular access was obtained through femoral artery puncture using Seldinger's technique. Standard angiographic views were obtained, which included an average six left coronary artery and two right coronary artery injections, yielding sufficient data for quantitative angiography. Culprit coronary artery lesions are classified angiographically according to American College of Cardiology/American Heart Association (ACC/AHA) classification as shown in Table 1 [8].

2.4. Serum PAPP-A Level Measurement. It was conducted using enzyme linked immunosorbent assay (ELISA), based on sandwich principle. Collected blood sample by venipuncture was allowed to clot & serum was separated by centrifugation at room temperature. The microtiter wells were coated with polyclonal anti-PAPP-A antibodies. An aliquot of patient's blood sample was incubated in the coated well with assay buffer. After incubation, the unbound material was washed off. In the second incubation step, a sandwich complex was formed with a polyclonal anti-PAPP-A antibody peroxidase conjugate. After adding the substrate solution, the intensity of color change that developed was proportional to concentration of patient's serum PAPP-A level. The range of assay results used was 0–30 μg/mL. The antibody used was specific for human PAPP-A with no cross-reactivity to other species. Also, no drug was known to influence the accuracy of measuring serum PAPP-A level using this assay. However, some studies mentioned that intravenous (IV) heparin administration was associated with high serum PAPP-A levels [9, 10]. All patients in the present study received IV heparin. However, blood samples for serum PAPP-A levels quantitation were withdrawn upon CCU admission, that is, before administration of IV heparin.

2.5. Statistics. Data were analyzed using Statistical Package for Special Science (SPSS) software computer program version 15 & described as mean ± standard deviation (SD) for quantitative (numerical) variables and as percentage for qualitative (categorical) variables. Significance level (*P* value) & Pearson's correlation coefficient were used for assessment of the recorded values. Receiver operating characteristic (ROC) curve analysis was constructed resulting in the sensitivity-specificity plot. The optimal cut-off value of serum PAPP-A level, predicting the diagnosis of ACS, was defined by providing the maximal sum of sensitivity and specificity.

3. Results

The study population (40 patients) included 22 male patients (55%) and 18 female patients (45%) with a mean age of 57.08 ± 11.11 years. Descriptive data analysis showed that; 26 (65%) patients were diabetic, 17 (42.5%) patients were hypertensive, 24 (60%) patients were dyslipidemic, 21 (52.5%) patients were smokers, and 16 (40%) patients had family history for ischemic heart diseases. Upon CCU admission, mean serum CK-T level was 385.3 ± 332.15 IU/L, mean CK-MB level was 48 ± 32.92 IU/L, and mean serum PAPP-A level was 10.14 ± 2.67 μg/mL.

All patients underwent coronary angiography. Concerning number of coronary arteries showing significant ($\geq$70% diameter stenosis) stenosis, it was found that 17 (42.5%) patients had single vessel affection, 10 (25%) patients had two vessels affection, and 13 (32.5%) patients had more than two vessels affection. According to ACC/AHA angiographic classification, it was found that 20 (50%) patients showed atherosclerotic plaques type A, 6 (15%) patients showed atherosclerotic plaques type B, and 14 (35%) patients showed atherosclerotic plaques type C. Patients were categorized according to the characteristics of the *culprit* lesion only.

Mean serum PAPP-A level among male patients was 9.38 ± 3.42 μg/mL, while it was 8.29 ± 3.8 μg/mL among females. There was no significant ($P > 0.05$) correlation between serum PAPP-A level & patients' baseline clinical characteristics (age, gender, and risk factors for ischemic heart diseases).

3.1. Biochemical Markers. There was a statistically significant positive correlation between patients' serum CK levels (CK-T & CK-MB) & PAPP-A levels measured upon CCU admission with a Pearson's correlation coefficient of 0.604 (CK-T) & 0.597 (CK-MB).

Mean serum PAPP-A level among patients with positive Troponin T test (20, 50%) was recorded to be 11.6 ± 2.2 μg/mL, while it was 7.06 ± 3.26 μg/mL among patients with negative Troponin T test. There was a statistically significant positive correlation between Troponin T test positivity and serum PAPP-A level ($P < 0.001$), being higher in Troponin T positive patients.

3.2. Angiographic Findings. Mean serum PAPP-A level among patients with single vessel affection was recorded to be 9.38 ± 3.89 μg/mL, while it was 8.12 ± 3.1 μg/mL among patients with two vessels affection & 8.73 ± 3.68 μg/mL among patients with more than two vessels affection. Results showed no statistically significant correlation between serum PAPP-A level & number of coronary vessels showing significant stenosis.

Mean serum PAPP-A level among patients with coronary atherosclerotic plaque type A was recorded to be 7.32 ± 3.5 μg/mL while it was 9.75 ± 2.54 μg/mL among patients with plaque type B & 11.78 ± 2 μg/mL among patients with plaque type C. There was a statistically significant positive correlation between complexity of coronary artery lesions and serum PAPP-A level ($P < 0.001$), being higher in patients with plaque types B & C.

Mean serum PAPP-A level among patients with UA (20, 50%) was recorded to be 8.72 ± 2.39 μg/mL, while it was 11.78 ± 2 μg/mL among patients with STEMI (14, 35%) & 11 ± 2.63 μg/mL among patients with NSTEMI (6, 15%). There was a statistically significant correlation between the final diagnoses of the included patients and serum PAPP-A levels ($P < 0.001$), being higher among patients with acute MI (STEMI & NSTEMI).

So, it was found that there was a statistically significant correlation between serum PAPP-A level (measured upon CCU admission) and each of the following: initial CK-T level, initial CK-MB level, cardiac Troponin T positivity upon CCU admission, coronary artery lesion complexity, and final diagnosis of the ischemic event.

Receiver operating characteristic (ROC) curve analysis (Figure 1) of obtained serum PAPP-A levels (among patients with Troponin T positive & negative results) reached an optimal cut-off value of 7.75 μg/mL for prediction of final diagnosis of ACS. This cut-off value yielded a sensitivity of 80%, specificity of 90%, positive predictive value (PPV) of 97%, and negative predictive value (NPV) of 53% (Area under the curve = 0.97).

4. Discussion

Early diagnosis of ACSs is an important challenging issue that throws itself on to the top of physicians' considerations, especially in emergency rooms.

Currently, ACSs are diagnosed using the combination of patients' history, ECG, and biochemical markers of myocardial necrosis [11]. Convincing evidence suggests that both inflammatory as well as thrombotic mechanisms are involved in pathogenesis of ACSs. The availability of a sensitive & specific marker of early plaque instability, whose level becomes elevated before or even in the absence of myocardial necrosis, should improve the diagnostic and therapeutic decision making [12].

In the current study, PAPP-A as a one of matrix metalloproteinases that is highly expressed in unstable coronary atherosclerotic plaques was studied to determine its value in patients with ACSs (especially those with initial negative cardiac Troponin T results), undergoing coronary angiography & possible subsequent intervention.

This study included 40 patients (22 male patients) with mean age of 57.08 ± 11.11 years who presented to CCU after emergency room triage, with chest pain of cardiac origin. They were then categorized according to clinical
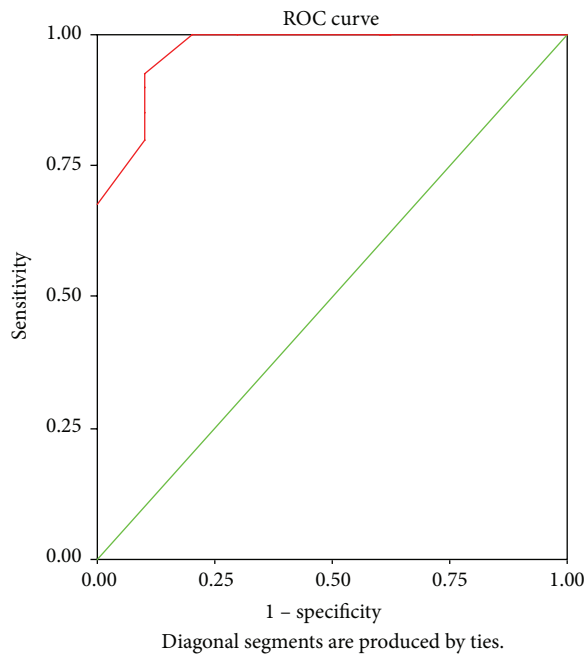
FIGURE 1: ROC curve plotted for the purpose of obtaining an optimal PAPP-A cut-off value for diagnosis of acute coronary syndromes.

presentation, careful history taking, serial ECGs, and cardiac biochemical markers (Troponin T, CK-T, and CK-MB) pattern into patients with UA, STEMI, or NSTEMI.

It was shown that major demographic data, that is, age and gender, did not show a significant correlation with serum PAPP-A level. However, a prior study showed that there was a direct correlation between serum PAPP-A levels & patients' age. Also, it was reported that male patients showed significantly higher PAPP-A levels with a mean level of $6.4 \pm 4.2\,\mu g/mL$ versus $5.2 \pm 1.8\,\mu g/mL$ among females. This was an unexplained finding as declared by the study group. However, this study was conducted on patients with chronic stable angina [13].

4.1. Correlation with Risk Factors & Biochemical Markers.

In the current study, it was found that there was no significant correlation between serum PAPP-A levels & prevalence of major risk factors for ischemic heart disease. Other studies reported the same results in patients with ACSs [14]. This is attributed to the fact that PAPP-A reflects atherosclerotic plaque vulnerability regardless of patients' risk profile. However, a prior study showed a direct correlation between serum PAPP-A level & serum total cholesterol level in patients with asymptomatic hypercholesterolemia. It was claimed that PAPP-A level may not only reflect plaque instability but also it reflects the overall atherosclerotic burden & risk profile [15]. Moreover, another study reported higher PAPP-A levels among hypertensive chronic stable angina patients when compared with normotensive patients [13].

The current study showed a direct positive correlation between serum PAPP-A level, serum CK-T and CK-MB levels, and cardiac Troponin T positivity recorded upon CCU

admission. A prior study also demonstrated the same results [16]. It is worth mentioning that a prior study reported that serum PAPP-A level measurement is less specific than cardiac Troponin T testing as regards predicting cardiac adverse events in CCU [17].

4.2. Correlation with Angiographic Findings.

High serum PAPP-A level is not only a marker of plaque instability favoring the progression to acute MI but also an indicative of poor prognosis owing to unfavorable coronary findings encountered during angiography. This might predict a high failure rate during coronary intervention.

In the current study, there was no significant correlation between serum PAPP-A level & number of coronaries showing significant (>70%) stenosis. This might support the growing evidence that relates serum PAPP-A level to coronary plaques' instability rather than coronary plaques' number, that is, one vulnerable plaque predicts a worse outcome, when compared with two or more stable plaques. On the contrary, a previous study showed a direct positive correlation between serum PAPP-A level and number of diseased coronaries [13]. However, this study was conducted on chronic stable angina patients.

The current study showed positive correlation between angiographic complexity of coronary lesions & serum PAPP-A level. Mean serum PAPP-A level in patients with culprit lesions type A was found to be significantly less than that recorded in patients with culprit lesions types B & C. The author hypothesizes that it is possible to anticipate the presence of complex coronary anatomy with a considerable thrombus burden, through determining serum PAPP-A level. Thus, a challenging percutaneous coronary intervention (PCI) procedure could be anticipated regardless of Troponin T test results. In other words, serum PAPP-A elevation indicates complicated plaque instability with/without established myocardial injury.

A number of prior clinical trials pointed that high levels of serum PAPP-A are associated with adverse cardiovascular events during mid & long term followup of patients presented with ACSs [18, 19]. One of these studies concluded that serum PAPP-A level of $>6\,\mu g/mL$ was independently associated with recurrent cardiovascular events in patients with non-ST-segment ACS (NST-ACS) [18]. These findings supported the use of PAPP-A as a prognostic marker in patients with ACS. In the current study, the author aimed at exploring the short-term prognostic value of this promising marker of plaque vulnerability. To the best of the author's knowledge, no previous clinical studies evaluated the association between high serum PAPP-A levels and the complexity of coronary artery lesions in ACS patients.

4.3. Measuring Serum PAPP-A Level.

Prior studies utilized different techniques for measuring serum PAPP-A level, for example, high sensitive fluorescent immunoassay & ultra-sensitive PAPP-A immunoassay [2]. The current study used sandwich ELISA technique that was used in a prior study [14]. Blood sampling was done prior to start of IV heparin therapy, aiming at excluding any possible misleading elevations of serum PAPP-A levels. A previous study documented higher

serum PAPP-A levels in a group of STEMI patients & in animal models treated with IV heparin [9]. This is most probably related to PAPP-A detachment from blood vessels' walls, induced by heparin.

Until recently, most commercially available assays for PAPP-A serum level measurement were designed to measure higher concentrations of PAPP-A, that is, during pregnancy. These assays do not meet the required sensitivity to detect serum PAPP-A level in patients with ACSs. Fortunately, ultrasensitive PAPP-A assay has recently become available for the purpose of diagnosing ACSs [16].

4.4. Clinical Implications. High serum PAPP-A levels measured before PCI in ACS patients call for proper readiness to tackle a complex coronary artery lesion with mostly a considerable thrombus burden. This requires having suitable pharmacological agents (e.g., glycoprotein IIb/IIIa inhibitors) & mechanical aids (e.g., thrombus aspiration devices) in hand. Thus, high serum PAPP-A level could help risk stratification of ACS patients upon CCU admission, identifying patients at high risk of in-hospital adverse events. This additionally implies the presence of an experienced interventionist capable of dealing with such interventional difficulties, expected to be found in coronary angiograms. Moreover, expected higher treatment costs should be taken into consideration. The current study reached a serum PAPP-A cut-off value (7.75 μg/mL) that predicted the final diagnosis of ACS. This could be of special importance in patients with initial negative Troponin results. Similarly, a prior study that included heparin naïve ACS patients stated that serum PAPP-A levels strongly predicted the diagnosis of ACS with a PPV & NPV close to those obtained by the current study. In Troponin-negative ACS patients, PAPP-A helped to reach the correct final diagnosis [10]. This identifies a high risk sub-population with high serum PAPP-A level & negative Troponin results. These patients are expected to have unfavorable angiographic outcomes & technical difficulties during PCI, in spite of initial negative Troponin results. Moreover, this subpopulation of patients should be regarded as a high risk category among ACS patients. This can have an impact on oral pharmacological treatment in CCU. This includes, for example, statins intake, as evidenced by a prior study that showed that high dose (80 mg) statins intake in ACS patients undergoing PCI was associated with significant decrease of serum PAPP-A levels after one month [20]. On the other hand, a previous study showed that long term regular intake of high dose (four grams) of n-3 fatty acids after acute MI was associated with higher serum levels of PAPP-A [21].

5. Conclusion

High serum PAPP-A level is associated with unfavorable coronary anatomy and high probability of lesion complexity in initial coronary angiograms of ACS patients. A cut-off value of 7.75 μg/mL for serum PAPP-A level predicted the final diagnosis of ACS, with a sensitivity of 80% & specificity of 90%.

Limitations of the Study

This is a single-centre study with a small sample size of the cohort. Large scale studies are still needed to confirm the obtained results. Serial serum PAPP-A level sampling was not included in the study protocol. Furthermore, followup of major adverse cardiovascular events was also not included. Both items were outside the scope of the present study, which aimed at evaluating the value of serum PAPP-A (single measurement) in augmenting the diagnostic & the interventional aspects in ACS patients. Further studies with wider scope are needed for evaluation of long term impact of high serum PAPP-A levels in ACS patients.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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