Prognostic Value of Prothrombin Time in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Introduction: There are some studies regarding the prognostic value of coagulation abnormalities both in heart failure and acute pulmonary embolism patients. However, it is unclear whether prothrombin time (PT) at presentation will be associated with long-term mortality in acute coronary syndrome (ACS) patients not on anticoagulant therapy. Thus, we investigated the prognostic role of initial PT in such patients.

Patients and Methods: A total of 1100 consecutive patients with ACS undergoing percutaneous coronary intervention (PCI) who were not receiving anticoagulant therapy were included in the study, retrospectively. PT was measured on admission in these patients before anticoagulation therapy. The study population was divided into three groups based on the PT values: A high-PT group (PT ≥ 14 sec, n= 50), intermediate-PT group (12.5 < PT < 14 sec, n= 169), and low-PT group (PT ≤ 12.5 sec, n= 881). The primary end point was all-cause death during the median follow-up of 30.5 months.

Results: The rate of the primary end point was 15% in the low-PT group, 27% in the intermediate-PT group, and 52% in the high-PT group (p< 0.001). For long-term mortality, a significantly higher mortality risk was observed in high-PT group (HR: 2.648, 95% CI: 1.590-4.410, p< 0.001) compared with the others group in multivariate analysis. The addition of PT to a multivariable model that included the left ventricular ejection fraction, histories of diabetes mellitus and stroke, age, hemoglobin, creatinine, white blood cell count, total bilirubin levels and Killip class led to a significant net reclassification improvement (NRI) of 26.7% (p< 0.001) and an integrated discrimination improvement of 0.022 (p= 0.001).

Conclusion: Our findings suggest that prolonged initial PT in the absence of anticoagulant therapy can be associated with all-cause mortality in ACS patients who were undergoing PCI. In addition, PT may be used to identify the high-risk patients with ACS.

Key Words: Prothrombin time; anticoagulation; acute coronary syndromes; mortality

Perkütan Koroner Girişim Yapılan Akut Koroner Sendromlu Hastalarda Protrombin Zamanın Prognostik Değeri

ÖZET

Giriş: Hem kalp yetersizliği hem de akut pulmoner embolili hastalarda koagülasyon anormalliklerinin prognostik değeri ile ilgili bazı çalışmalar vardır. Fakat, antikoagülan tedavi almayan akut koroner sendrom (AKS) hastalarında kabuldeki protrombin zaman (PZ)'ın uzun dönemde mortaliteyle ilişkili olup olmadığı belli değildir. Bu yüzden, biz bu hastalarda başlangıç PZ'nin prognostik rolünü araştırdık.

Hastalar ve Yöntem: Çalışmaya retrospektif olarak perkütan koroner girişim (PKG) uygulanan AKS'li ardışık 1.100 hasta alındı. Antikoagülan tedavi başlanmadan önce hastaların PZ'si ölçüldü. Hastalar PZ'sine göre; yüksek (≥ 14 saniye, n= 50), orta (12.5 < PZ < 14 saniye, n= 169) ve düşük (≤ 12.5 saniye, n= 881) olmak üzere üç gruba ayrıldı. Primer sonlanım noktası ortalama 30.5 aylık takipte tüm nedenlere bağlı ölüm olarak belirlendi.

Bulgular: Uzun dönem total mortalite oranı, düşük, orta ve yüksek PZ gruplarında sırasıyla: %15, %27 ve %52 idi (p< 0.001). Çok değişkenli analizde yüksek PZ mortalite ile ilişkili bulundu (HR: 2.648, %95 CI: 1.590-4.410, p< 0.001). Sol ventrikül ejeksiyon fraksiyonu, diyabet öyküsü, inme, yaş, hemoglobin, kreatinin, beyaz

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küre sayısı, total bilirubin seviyeleri ve Killip sınıfını içeren çok değişkenli bir modele PZ'nin eklenmesi %26.7'lik bir net yeniden sınıflandırma iyileşmesi (p< 0.001) ve 0.022'lik total bir ayrımcılık iyileşmesi (p= 0.001) sağladı.

Sonuç: Antikoagülan tedavinin yokluğunda başlangıç PZ'nin uzaması, AKS hastalarında artmış mortaliteyle ilişkili olabilir. Ayrıca, PZ yüksek riskli AKS hastaları belirlemek için kullanılabilir.

Anahtar Kelimeler: Protrombin zamanı; antikoagülasyon; akut koroner sendromlar; mortalite

INTRODUCTION

Acute coronary syndrome (ACS), a category that includes unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), is a significant global health problem and a leading cause of death related to cardiovascular diseases[1].

There is a strong association between ACS and the disruption of vulnerable atherosclerotic plaques and subsequent thrombus formation. The rupture or erosion of these plaques initiates the thrombotic process by exposing the prothrombotic content of necrotic cores to circulating thrombocytes[2,3]. Thereafter, the activation of both circulating platelets and the coagulation cascade results in thrombin formation[4].

Prothrombin time (PT) or international normalized ratio (INR) is accepted as a reliable marker of coagulation abnormalities. It is regulated by various coagulation factors synthesized in the liver and is used to monitor vitamin-K-dependent anticoagulation therapy. PT may also reflect hepatic dysfunction and coagulation abnormalities such as disseminated intravascular coagulation (DIC). Prolonged PT has been reported to be associated with poor clinical outcomes in critically ill patients[5,6]. Similarly, it has recently been shown that an increase in PT is associated with high mortality in patients with both heart failure and acute pulmonary embolism[7,8].

To the best of our knowledge, there are no data about whether initial PT at presentation will affect the long-term prognosis of ACS patients. Thus, this study evaluated the association of initial PT with all-cause mortality in patients with ACS treated with percutaneous coronary intervention (PCI) who had not received anticoagulant therapy.

PATIENTS and METHODS

Study Population

Conducted from January 2008 to July 2015, this retrospective study included a total of 1.193 consecutive patients with ACS treated with PCI. To be enrolled in the study, patients had to have clinical and angiography-proven ACS and baseline PT measurements. Fifty nine patients with incomplete data, two with a history of liver cirrhosis, and thirty two who had received anticoagulant therapy (vitamin-K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, or enoxaparin) were excluded from the analysis. Consequently, the final study population consisted of 1.100 patients (Figure 1). The cut-off points of PT were determined according to the reference range of the reagent RecombiPlasTin (manufacturer-datasheet ACL TOP: 9.4 – 12.5 seconds) and reference values used in previous studies (PT ≥ 14 sec)[9]. Based on the PT cut-off points, the study population was divided into a high-PT group (PT ≥ 14 sec, n= 50), intermediate-PT group (12.5 < PT < 14 sec, n= 169), and low-PT group (PT ≤ 12.5 sec n= 881). The local ethics committee approved the study (the number of the local ethics committee: 322). The study conforms to the Declaration of Helsinki.

Blood Sampling and PT Measurement

All the measurements of PT, activated partial thromboplastin time (aPTT), and INR were performed at the presentation of the patients prior to the initiation of anticoagulant therapy and coronary angiography. The blood-collection tubes contained 3.2% sodium citrate (0.5 mL citrate, 4.5 mL blood) for INR, PT, and aPTT measurements. Samples were immediately centrifuged for routine testing, and the analysis was performed within 1 h after sampling. The reagent HemosIL RecombiPlasTin 2G (Instrumentation Laboratory, Bedford, MA, USA) was used to measure INR. The reagent HemosIL SynthASil (Instrumentation Laboratory, Bedford, MA, USA) was used to perform the measurement of a PTT. Complete blood count was determined via an Abbott Cell-Dyn 3700 autoanalyzer using commercial assay kits (Abbott Diagnostic, CA, US). Siemens Healthcare Diagnostic Products kits and calibrators (Marburg, Germany) was used to perform the biochemical measurements.

Echocardiographic Analysis

Echocardiographic examinations were performed for all the patients. The left ventricular ejection fraction (LVEF) was calculated after measuring the end-diastolic and end-systolic left ventricle (LV) volumes in the apical four-chamber and two-chamber views using the modified Simpson's method.

Treatment

All the coronary angiography and PCI procedures were performed via the transfemoral route by experienced interventional cardiologists. Both the UA and NSTEMI patients underwent coronary angiography with subsequent PCI within the first 48 h. Primary PCI for STEMI was performed according to the current guidelines[10]. The diagnosis of CAD was confirmed by coronary angiography in all the patients and consisted of documentation of a significant disease (defined as coronary stenosis ≥ 50% luminal narrowing in at least one of the major coronary arteries) or an infarct-related artery. The angiographic data of the patients were evaluated from catheter laboratory records. All the patients were treated according to good clinical

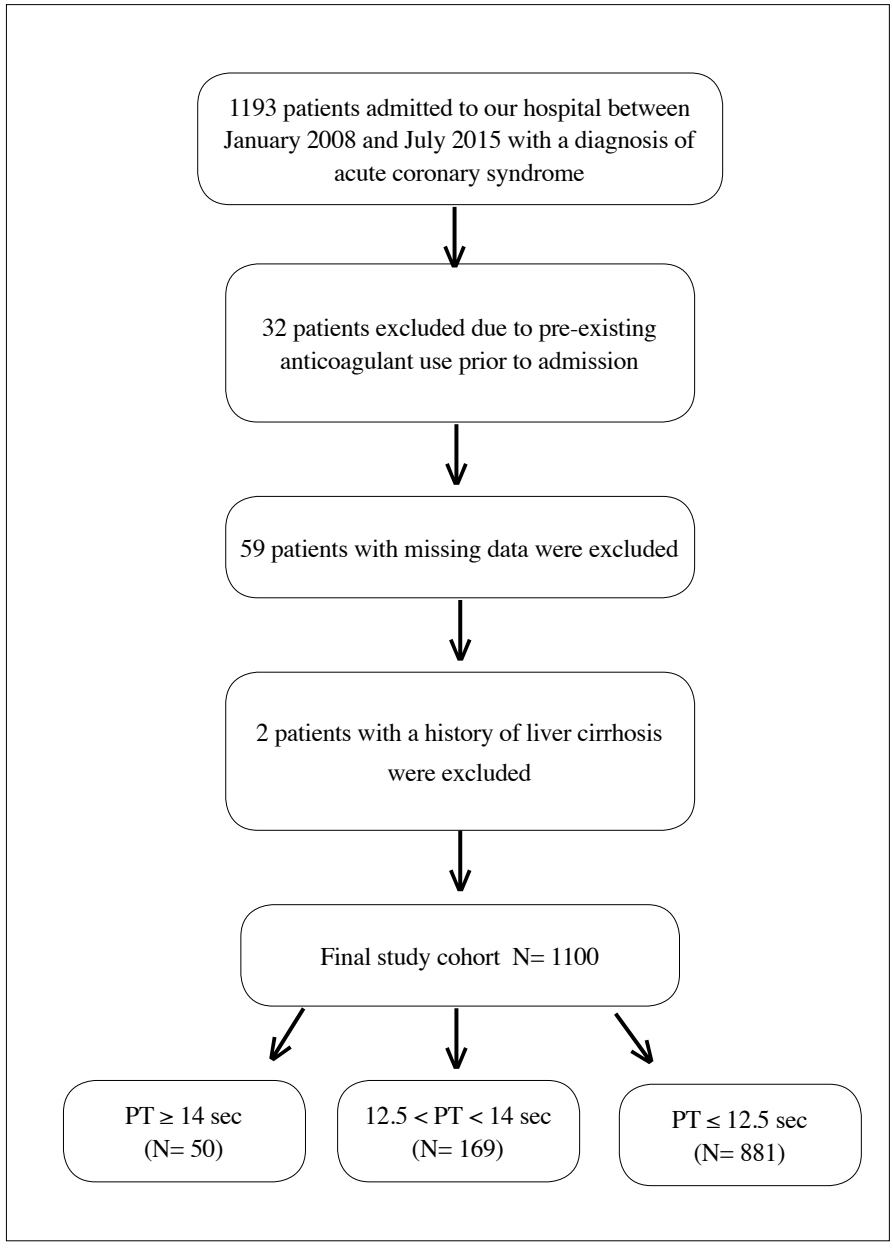

Figure 1. Derivation of study cohort. The flow chart represents the derivation of the study cohort from the original population of 1193 patients.

practice and the current guidelines[10,11]. The type of stent and the use of thrombectomy devices, predilation, poststenting adjunctive balloon inflation, intravascular ultrasound, intra-aortic balloon counterpulsation, or glycoprotein IIb/IIIa inhibitors were all left to the operators' discretion. Dual antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors, and statins were administered according to the European Society of Cardiology guidelines[10,11].

Definition

According to the criteria of the universal definition of myocardial infarction, the diagnosis was established in the presence of an increasing/decreasing pattern in cardiac troponin I values, with at least one measurement above the 99th percentile together with evidence of myocardial ischemia[12]. Additionally, myocardial infarction was classified as STEMI or NSTEMI according to current guidelines[10,11]. STEMI involves the

presence of (1) ST-segment elevation consistent with myocardial infarction of ≥ 2 mm in adjacent chest leads and/or ST-segment elevation of ≥ 1 mm in two or more standard leads or new left bundle branch block (LBBB) and (2) positive cardiac necrosis markers. NSTEMI involves the absence of (1) ST-segment elevation consistent with myocardial infarction (MI) or recent LBBB and (2) positive cardiac necrosis markers. UA involves (1) the absence of ST-segment elevation consistent with MI or new LBBB, (2) the presence of negative cardiac necrosis markers, and (3) the presence of angina pectoris (or an equivalent type of ischemic discomfort) with any one of the following three features: (a) prolonged (> 20 min) angina occurring at rest, (b) new-onset angina of at least Canadian Cardiovascular Society (CCS) class III severity, or (c) recent acceleration of angina reflected by an increase in severity of at least one CCS class to at least CCS class III[11]. Cardiovascular risk factors (arterial hypertension, diabetes, hypercholesterolemia, and smoking) were defined according to the accepted criteria.

The primary study end point was defined as the occurrence of all-cause total mortality during the median follow-up of 30.5 months. In addition, cardiac death, myocardial reinfarction, stroke/ transient ischemic attack (TIA), target-vessel revascularization (TVR), and heart failure admission were assessed. Reinfarction was defined according to the third universal definition of MI[11]. TVR was defined as any revascularization procedure, including bypass surgery, involving the initially treated artery. Stroke/ TIA was defined as an acute neurological deficit accompanied by brain imaging compatible with a recent ischemic or hemorrhagic event. Bleeding events were defined using the criteria of the Academic Research Consortium definition[13].

Follow-up

By design, although the study represents a retrospective analysis, monitoring and event data were obtained from a prospective order. The patients were followed for clinical events such as deaths, MI, stroke, and heart failure during the median follow-up of 30.5 months. The follow-up data were obtained from hospital records or by interviewing (in person or by telephone) patients, their families, or their personal physicians.

Statistical Analysis

Continuous variables were presented as means ± SD or medians with inter-quartile ranges (IQR), whereas categorical variables were described as numbers and percentages. The differences between the two groups were compared using the chi-square test (or Fisher's exact) for categorical variables and with analysis of variances (ANOVA) or Kruskal-Wallis test for continuous variables, as appropriate. The relationship between PT and the other demographic/biochemical parameters was assessed with Pearson's correlation analysis. The predictive values of a multivariable model and a combination of PT and a multivariable model were estimated by comparing the areas under the receivers operating characteristic (ROC) curve. DeLong's test was used to compare the AUC from each of models, which were analyzed by use of Analyse-it software program[14]. Moreover, the increased discriminative value after the addition of PT to a multivariable model was also estimated using the net reclassification improvement (NRI) and Integrated Discrimination Improvement[15]. The cumulative survival curves for total mortality were estimated with Kaplan-Meier plots. A log-rank test was used to analyze the significant differences in survival curves. A multivariate Cox regression analysis was performed to identify independent predictors for the primary end point. Factors entered into the multivariate model comprised those with p-values < 0.1 from the univariate analysis and variables with known prognostic value. Two-sided p-values < 0.05 were considered statistically significant. The statistical tests were performed with SPSS version 16 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics

Table 1 lists the baseline characteristics of the study patients. Overall the mean age was 62 ± 12 years and there were 26% females. The median follow-up period was 30.5 months. The patients in the high-PT group were older than the patients in the other groups. Compared with the low-PT group, the history of heart failure and higher Killip class were more frequent both in the intermediate and high-PT groups. On the other hand, the use of angiotensin-converting enzyme inhibitors and beta-blockers were lower both in the low and high-PT groups than the low-PT group (Table 1). The major bleeding rates were similar between groups.

Laboratory Findings

Table 2 shows the laboratory variables of the groups. The LVEF was significantly lower both in the high and intermediate-PT group than in the other groups (p< 0.001). Both the high-PT and intermediate-PT group had higher levels of white blood count (WBC) than the low-PT group did.

In the correlation analysis, PT was inversely and weakly correlated with LVEF (r= –0.23, p< 0.001), hemoglobin levels (r= -0.10, p< 0.001), but positively correlated with age (r= 0.14, < 0.001), WBC count (r= 0.11, p< 0.001), creatinine (r= 0.11, p= 0.001), total bilirubin (r= 0.27, p< 0.001), and alanine aminotransferase (ALT) levels (r= 0.08, p= 0.013).

PT and Clinical Outcomes

Table 1 presents the clinical outcomes. Long-term all-cause mortality rate was 15% in the low-PT group, 27% in the intermediate-PT group, and 52% in the high-PT group (p < 0.001, Table 1). Furthermore, Cardiac-cause mortality was higher in the high-PT group compared with the others (Table 1). Similarly, 30-day mortality rate was 3% in the low-PT group, 8% in the intermediate-PT group, and 20% in high-PT group.

Table 1. Baseline characteristics of the study population

Variable	Low-group (n= 881)	Intermediate-group (n= 169)	High-group (n= 50)	p
Age (year)	61 ± 12	63 ± 13	68 ± 11	< 0.001
Male n (%)	651 (74)	129 (76)	34 (68)	0.492
History of HF n (%)	19 (2)	10 (7)	3 (6)	0.017
Hypertension n (%)	456 (52)	78 (45)	28 (56)	0.206
Diabetes mellitus n (%)	261 (30)	50 (30)	14 (28)	0.970
Hyperlipidemia n (%)	153 (17)	26 (15)	7 (14)	0.700
Current smoking n (%)	304 (35)	49 (29)	14 (28)	0.270
Previous CAD n (%)	251 (29)	44 (26)	19 (38)	0.257
Prior stroke/TIA n (%)	43 (5)	7 (4)	1 (2)	0.604
Type of ACS n (%)				0.320
STEMI	521 (59)	102 (60)	29 (58)	
NSTEMI	250 (28)	52 (31)	4 (28)	
UA	99 (11)	12 (7)	7 (14)	
ACS related coronary artery				0.381
LMCA n (%)	1 (0)	1 (1)	0 (0)	
LAD n (%)	407 (46)	64 (38)	17 (34)	
Cx n (%)	128 (15)	30 (18)	8 (16)	
RCA n (%)	283 (32)	64 (38)	19 (38)	
Others n (%)	61 (7)	12 (7)	5 (12)	
Multi-vessel disease n (%)	369 (42)	82 (49)	27 (54)	0.088
Major bleeding n (%)	23 (3)	7 (4)	2 (4)	0.497
Killip class ≥ 2 n (%)	72 (8)	16 (10)	14 (28)	< 0.001
Medication at discharge				
Beta-blocker n (%)	742 (85)	139 (82)	36 (72)	0.044
Statin n (%)	718 (82)	136 (81)	32 (64)	0.010
ACE-I/ARB n (%)	720 (82)	121 (72)	34 (68)	0.001
Outcomes				
In-hospital death n (%)	21 (2)	11 (7)	7 (14)	< 0.001
Stroke n (%)	22 (3)	6 (4)	3 (6)	0.285
HF admission n (%)	37 (4)	14 (8)	9 (18)	< 0.001
Myocardial reinfarction n (%)	78 (10)	13 (9)	5 (9)	0.870
TVR n (%)	85 (10)	13 (8)	4 (8)	0.689
30-day mortality n (%)	29 (3)	14 (8)	10 (20)	< 0.001
Cardiac death n (%)	42 (5)	18 (11)	14 (28)	< 0.001
All-cause death n (%)	135 (15)	46 (27)	26 (52)	< 0.001

HF: Heart failure, CAD: Coronary artery disease, TIA: Transient ischemic attack, ACE-I: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blocker, ACS: Acute coronary syndrome, UA: Unstable angina, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction.

Hospitalization for heart failure was significantly higher in the high-PT group. TVR, myocardial reinfarction and stroke/TIA rates were comparable in the groups.

In the multivariate Cox regression analysis, high-PT (HR: 2.648, 95% CI:1.590-4.410, p< 0.001), age, Killip class, LVEF, total bilirubin, serum creatinine, hemoglobin levels, WBC, histories of DM and stroke/TIA were independent predictors of long-term mortality (Table 3).

For long-term mortality, the AUC of a multivariable model that included age, WBC, creatinine, total bilirubin, hemoglobin, LVEF, Killip class, histories of DM and stroke/TIA was 0.820 (95% CI: 0.785-0.854, p< 0.001). When PT was added to a

Table 2. Laboratory results of the study groups

Variable	Low-group (n= 881)	Intermediate-group (n= 169)	High-group (n= 50)	p
SCr^*_{adm} (mg/dL)	0.83 (0.74-1.03)	0.88 (0.74-1.19)	0.90 (0.79-1.35)	0.105
WBC ($x10^3/mm^3$)	11 ± 4	12 ± 4	12 ± 5	0.004
Hemoglobin (g/dL)	12.7 ± 2	12.4 ± 2	11.9 ± 2	0.020
$Platelet_{adm}$ count ($x10^3/mm^3$)	252 ± 76	259 ± 83	235 ± 82	0.165
LVEF (%)	48 ± 10	43 ± 11	42 ± 12	< 0.01
ALT* (U/L)	29 (19-47)	35 (22-57)	36 (21-61)	0.132
AST* (U/L)	43 (24-96)	43 (25-124)	53 (34-121)	0.303
Total bilirubin* (mg/dL)	0.53 (0.40-0.71)	0.62 (0.43-0.99)	0.90 (0.55-1.2)	0.001
aPTT (second)	27.6 ± 7.8	29.7 ± 8.9	32.0 ± 8.9	< 0.01
PT (second)	11.2 ± 0.7	13.1 ± 0.4	15.2 ± 1.5	< 0.01

* These values were described by median with inter-quartile range (25^{th} and 75^{th} percentile).
SCr: Serum creatinine at admission, WBC: White blood cell, LVEF: Left ventricular ejection fraction, ALT: Alanine transaminase, AST: Aspartat transaminase, aPTT: Activated partial thromboplastin time, PT: Prothrombin time.

Table 3. Independent predictors of all-cause mortality

	Univariate			Multivariate		
Variable	HR	95% CI	p	HR	95% CI	p
Age (per 1 year)	1.051	1.039-1.064	< 0.001	1.022	1.007-1.035	0.004
Male	0.679	0.507-0.907	0.009	-		
Diabetes mellitus	1.903	1.444-2.509	< 0.001	1.410	1.019-1.952	0.038
Hipertension	1.217	0.922-1.606	0.165	-		
Stroke history	2.349	1.464-3.768	< 0.001	2.056	1.252-3.375	0.004
Multi-vessel disease	1.975	1.498-2.604	< 0.001	-		
Killip class ≥ 2	5.742	4.224-7.806	< 0.001	3.806	2.588-5.596	< 0.001
LVEF (per 1% change)	0.951	0.939-0.963	< 0.001	0.974	0.961-0.988	< 0.001
Creatinine (per 1 mg/dL)	1.332	1.240-1.431	< 0.001	1.234	1.110-1.372	< 0.001
Hemoglobin (per 1 mg/dL)	0.784	0.734-0.838	< 0.001	0.847	0.779-0.922	< 0.001
WBC (per 10^3/L)	1.082	1.046-1.119	< 0.001	1.082	1.040-1.126	< 0.001
Total bilirubin (per 1 mg/dL)	2.137	1.549-2.949	< 0.001	2.043	1.361-3.066	0.001
Beta-blocker use at follow-up	0.574	0.417-0.791	0.001			
ACE-I/ARB use at follow-up	0.437	0.327-0.585	< 0.001			
TVR	0.424	0.237-0.760	0.004	-		
aPTT (sec)	0.984	0.947-1.023	0.414	-		
Low-PT group (reference)	1	1	1			
Intermediate-PT group	1.926	1.1374-2.701	< 0.001	-		
High-PT group	4.447	2.920-6.773	< 0.001	2.648	1.590-4.410	< 0.001

HR: Hazard ratio, CI: Confidence interval, LVEF: Left ventricular ejection fraction, WBC: White blood cell, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, ACE-I/ARB: Angiotensin-converting enzyme inhibitors/angiotensin-receptor blocker, TVR: Target vessel revascularization.

multivariable model, the AUC was 0.833 (95% CI: 0.799-0.867, difference p= 0.0398, Figure 2). Moreover, the addition of PT to a multivariable model was associated with a significant NRI estimated at 26.7% (p< 0.001) and an integrated discrimination improvement of 0.022 (p= 0.001) (Table 4). Figure 3 shows the Kaplan-Meier survival curves. In addition, we performed a landmark analysis in these patients. Even after performing a landmark analysis at day-30 after the diagnosis of ACS, the high-PT group had a lower survival rate both during the first 30-days and after 30-days (Figures 4A, and B).

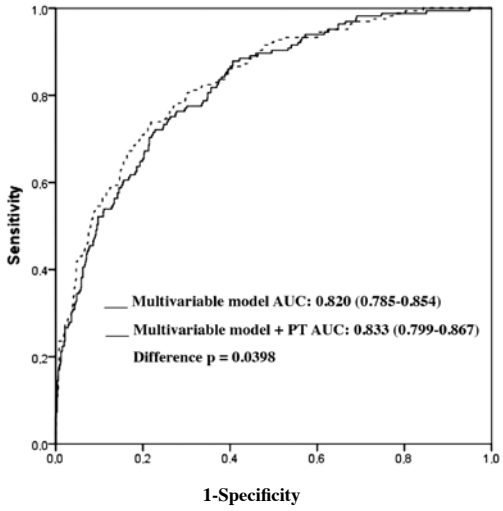

Figure 2. Receiver operating characteristic (ROC) curves for the multivariable model and multivariable model plus prothrombin time (PT) for predicting all-cause total mortality.

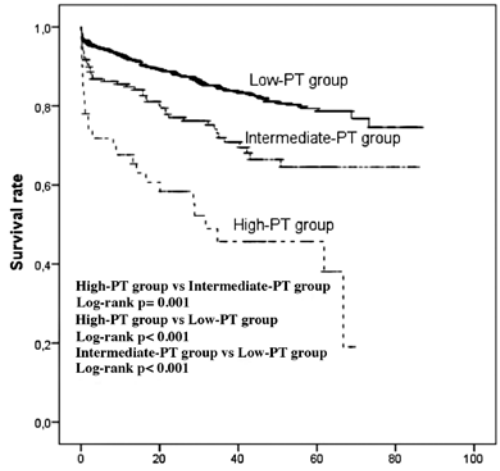

Figure 3. Kaplan-Meier survival curves for all-cause mortality.

Table 4. Statistics for model improvement with the addition of PT

Continous NRI	26.7%	p< 0.001
IDI statistics	0.022	p= 0.001
AUC		
Multivariable model	0.820	p< 0.001
Multivariable model plus PT	0.833	p< 0.001
Difference p		0.0398

Multivariable model includes the following variables: White blood cell count, age, history of diabetes mellitus, stroke, creatinine, hemoglobin, left ventricular ejection fraction, total bilirubin, and Killip class.
PT: Prothrombin time, NRI: Net reclassification index, IDI: İntegrated discrimination index.

DISCUSSION

This is the first study to investigate the association of admission PT level in the absence of previous anticoagulant therapy with all-cause total mortality in ACS patients who were treated with PCI. We observed that prolonged PT was associated with increased all-cause mortality in those patients who did not receive anticoagulant therapy during the median follow-up of 30.5 months.

The increased PT in ACS patients may be due to several mechanisms. The activation of inflammatory and coagulation pathways plays an important role in the pathogenesis of vascular diseases. There is growing evidence of cross-talk relation between these two systems; that is, one can trigger the other[16]. Inflammation and neurohormonal activity have been shown to activate the coagulation system[17-20]. The activation of the coagulation system and increased inflammation may cause consumptive coagulopathy. Moreover, systemic coagulation pathways are hyperactive or stimulated, and additional injury is a potent trigger resulting in markedly increased thrombin formation and platelet activation in ACS[21]. Thrombin itself has a proinflammatory effect in acute thromboembolic events[22]. Elevated levels of prothrombin fragment, which is a circulating thrombin marker, and thrombin-antithrombin complexes (TAT) triggered by vascular injury have been observed in ACS patients[23-26]. Although TAT and prothrombin fragment levels were not measured in our study, there was a positive correlation between WBC count as an index of inflammation and PT. We believe that prolonged PT is related to inflammation, which contributes to the consumptive coagulopathy.

Since coagulation factors are synthesized in the liver, hepatic injury or failure may lead to a decrease in plasma coagulation factors. Alehagen et al. showed that coagulation factors such as II, VII, and XI can be decreased in heart failure patients[27]. That decrease was not related to the level of ALT, which is one of the most sensitive enzymes indicating liver disease in that study. In another study, an improvement in the factor II, V, VII, and IX levels was observed in heart failure patients after implantation of an LV assist device, regardless of hepatic dysfunction (e.g., ALT > 60 U/L)[28]. LVEF was lower in the high-PT group in the present study. On the other hand, total bilirubin, which is a nonspecific marker of liver damage, was positively and a weak correlated with PT in the current study. Thus, we believe that hepatic dysfunction is partially responsible for the prolongation of PT.

In a recent study, prolonged PT and an increased INR in the absence of anticoagulant therapy were associated with six-month mortality in patients with acute pulmonary embolism[8]. INR >

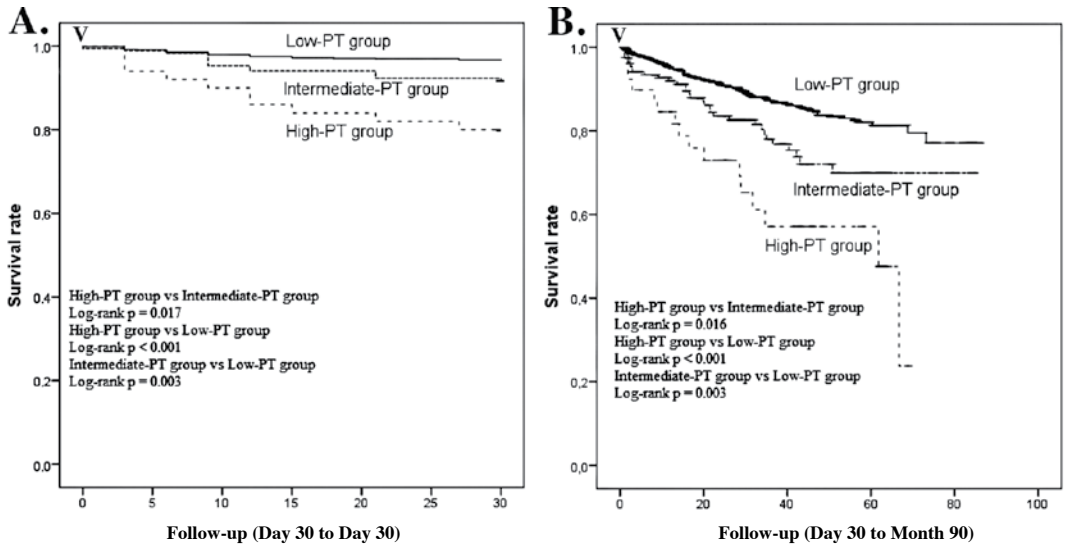

Figure 4. Landmark analysis: cumulative survival rate during the first 30 days after diagnosis of acute coronary syndrome (A) and after 30 days (B).

1.2 was independent predictor of mortality in those patients. Moreover, per 1-sec increase in PT on admission was related to mortality in those patients[8]. Fei et al. reported that PT was significantly more prolonged in non-survivors than in survivors who were hospitalized in an intensive care unit[29]. They also found that PT of 12 sec was a cut-point for predicting in-hospital mortality, with a sensitivity of 83% and a specificity of 51%.

Hannan et al. showed prolonged PT was independently associated with mortality in patients underwent coronary artery bypass grafting (CABG)[9]. In their study, patients with PT ≥ 14 sec had a 1.86 fold increased risk of 30-day mortality in these patients. Tamayo et al. revealed that there was a relationship between high INR and 90- day mortality in Post Cardiac Surgery (POCAS) Scale in patients who were treated with CABG[30]. In a prospective, multicenter observational cohort study, it was observed that, of the 1,923 patients admitted to the ICU, 30% developed abnormal INR values (defined as an INR > 1.5)[31]. Most of the INR abnormalities were minor and short-lived (73% of the worst INR values 1.6 to 2.5). In all the regression models, there was a strong independent association between abnormal INR values and greater ICU mortality (p< 0.0001), particularly when the INR increased after ICU admission[31]. Similar to the above-mentioned studies, prolonged PT in the absence of anticoagulant therapy was independently associated with long-term mortality in ACS patients underwent PCI in our study.

Acute traumatic coagulopathy (ATC), as defined by an elevated INR, is a well-studied and increasingly well-defined entity in adults after injury, and it was associated with mortality[32-35]. Coagulopathy was also identified as an independent risk factor for acute renal failure and multiorgan failure[36]. PT was found to be the independent predictor of long-term mortality in patients undergoing carotid stenting[37]. In that study, PT remained a significant predictor for mortality after excluding patients with (stopped) oral anticoagulation. We demonstrated the association of PT with mortality by also performing landmark analysis in present study. Moreover, we found that high-PT group had a lower survival rate even after the first 30-day. Although increased PT is treated with fresh frozen plasma, it is unclear whether the long-term risk associated with increased PT may be modified by treatment. It has been shown that there was not an association of transfusion with correction of PT/INR or improved survival[38]. Furthermore, studies in both adults and children showed that plasma transfusions to correction for mildly higher PT/INR routinely fail to normalize this value and expose patients to unnecessary risk and delays[39-41]. The major bleeding rates were similar between the groups in the present study. In addition, none of patients in our study received fresh frozen plasma. An elevated INR/PT may likely serve as a marker of systemic coagulation and inflammatory dysregulation rather than as a treatment target[38].

In the light of these findings, we speculate that prolonged PT is a result of underlying patient comorbidities (e.g., hepatic dysfunction, heart failure, DM, stroke/TIA). Moreover, it may be a marker of severity of ACS (e.g., higher Killip class). It may also reflect hemostatic imbalance and systemic inflammation.

Study Limitations

Our study has several limitations. First, it is a retrospective and non-randomized study. Thus, it is likely subject to selection bias. However, we were careful to enroll consecutive patients. We did not routinely measure commonly used inflammatory markers such as C-reactive protein and interleukins. Thus, PT was not compared with these inflammatory markers. Moreover,

we did not measure the level of specific coagulation factors such as factor II, VII, and IX in these patients.

CONCLUSION

Our findings suggest that prolonged initial PT in the absence of anticoagulant use may be an independent predictor of all-cause mortality in ACS patients undergoing PCI. It may be associated with inflammation, lower EF, and hepatic insufficiency. Furthermore, ACS patients with prolonged PT may require close care for clinical events such as death and heart failure at follow-up. Large prospective studies are required to evaluate the exact prognostic impact of PT in these patients.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: TK

Analysis/Interpretation: TK, SY, SV

Data Acquisition: TK, AÇ, EV

Writting: TK

Critical Revision: CN, MK, MSB

Final Approval: All of authors

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
2. Fenning RS, Wilensky RL. New insights into the vulnerable plaque from imaging studies. Curr Atheroscler Rep 2014;16:397.
3. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852-66.
4. Capodanno D, De Caterina R. Bivalirudin for acute coronary syndromes: premises, promises and doubts. Thromb Haemost 2015;113:698-707.
5. Fuhrmann V, Kneidinger N, Herkner H, Heinz G, Nikfardjam M, Bojic A, et al. Hypoxic hepatitis: Underlying conditions and risk factors for mortality in critically ill patients. Intensive Care Med 2009;35:1397-405.
6. Raurich JM, Llompart-Pou JA, Ferreruela M, Colomar A, Molina M, Royo C, et al. Hypoxic hepatitis in critically ill patients: Incidence, etiology and risk factors for mortality. J Anesth 2011;25:50-6.
7. Okada A, Sugano Y, Nagai T, Takashio S, Honda S, Asaumi Y, et al; NaDEF Investigators. Prognostic value of prothrombin time international normalized ratio in acute decompensated heart failure - a combined marker of hepatic insufficiency and hemostatic abnormality. Circ J 2016;80:913-23.
8. Wong CC, Ng AC, Lau JK, Chow V, Chen V, Ng AC, et al. High mortality in patients presenting with acute pulmonary embolism and elevated INR not on anticoagulant therapy. Thromb Haemost 2016;115:1191-9.
9. Hannan EL, Qian F, Pine M, Fry DE, Whitman K, Dennison BA. The value of adding laboratory data to coronary artery bypass grafting registry data to improve models for risk-adjusting provider mortality rates. Ann Thorac Surg 2015;99:495-501.
10. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.
11. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999-3054.
12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
15. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11-21.
16. Levi M, van der Poll T, Buller HR. Bidirectional relation between inflammation and coagulation. Circulation 2004:109;2698-704.
17. Sbarouni E, Bradshaw A, Andreotti F, Tuddenham E, Oakley CM, Cleland JG. Relationship between hemostatic abnormalities and neuroendocrine activity in heart failure. Am Heart J 1994;127:607-12.
18. Marcucci R, Gori AM, Giannotti F, Baldi M, Verdiani V, Del Pace S, et al. Markers of hypercoagulability and inflammation predict mortality in patients with heart failure. J Thromb Haemost 2006;4:1017-22.
19. Chin BS, Blann AD, Gibbs CR, Chung NA, Conway DG, Lip GY. Prognostic value of interleukin-6, plasma viscosity, fibrinogen, von Willebrand factor, tissue factor and vascular endothelial growth factor levels in congestive heart failure. Eur J Clin Invest 2003;33:941-8.
20. Undas A, Szułdrzyński K, Brummel-Ziedins KE, Tracz W, Zmudka K, Mann KG. Systemic blood coagulation activation in acute coronary syndromes. Blood 2009;113:2070-8.
21. Giannitsis E, Mair J, Christersson C, Siegbahn A, Huber K, Jaffe AS, et al; Biomarker Study Group of the European Society of Cardiology (ESC) Acute Cardiovascular Care Association (ACCA). How to use D-dimer in acute cardiovascular care. Eur Heart J Acute Cardiovasc Care 2017;6:69-80.
22. Merlini PA, Ardissino D, Oltrona L, Broccolino M, Coppola R, Mannucci PM. Heightened thrombin formation but normal plasma levels of activated factor VII in patients with acute coronary syndromes. Arterioscler Thromb Vasc Biol 1995;15:1675-9.
23. Hoffmeister HM, Ehlers R, Buttcher E, Steinmetz A, Kazmaier S, Helber U, et al. Relationship between minor myocardial damage and inflammatory acute-phase reaction in acute coronary syndromes. J Thromb Thrombolysis 2003;15:33-9.
24. Merlini PA, Bauer KA, Oltrona L, Ardissino D, Cattaneo M, Belli C, et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. Circulation 1994;90:61-8.
25. Hoffmeister HM, Jur M, Wendel HP, Heller W, Seipel L. Alterations of coagulation and fibrinolytic and kallikrein-kinin systems in the acute and postacute phases in patients with unstable angina pectoris. Circulation 1995;91:2520-7.
26. Golino P, Ravera A, Ragni M, Cirillo P, Piro O, Chiariello M. Involvement of tissue factor pathway inhibitor in the coronary circulation of patients with acute coronary syndromes. Circulation 2003;108:2864-9.
27. Ardissino D, Merlini PA, Bauer KA, Galvani M, Ottani F, Franchi F, et al. Coagulation activation and long-term outcome in acute coronary syndromes. Blood 2003;102:2731-5.

28. Alehagen U, Dahlstrom U, Lindahl TL. Low plasma concentrations of coagulation factors II, VII and XI indicate increased risk among elderly with symptoms of heart failure. Blood Coagul Fibrinolysis 2010;21:62-9.

29. Fei A, Lin Q, Liu J, Wang F, Wang H, Pan S. The relationship between coagulation abnormality and mortality in ICU patients: a prospective, observational study. Sci Rep 2015;5:9391.

30. Tamayo E, Fierro I, Bustamante-Munguira J, Heredia-Rodríguez M, Jorge-Monjas P, Maroto L, et al. Development of the Post Cardiac Surgery (POCAS) prognostic score. Crit 2013;17:R209.

31. Walsh TS, Stanworth SJ, Prescott RJ, Lee RJ, Watson DM, Wyncoll D; Writing Committee of the Intensive Care Study of Coagulopathy Investigators. Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in United Kingdom intensive care units. Crit Care Med 2010;38:1939-46.

32. Cohen MJ, Call M, Nelson M, Calfee CS, Esmon CT, Brohi K, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg 2012;255:379-85.

33. Cohen MJ, Kutcher M, Redick B, Nelson M, Call M, Knudson MM, et al. Clinical and mechanistic drivers of acute traumatic coagulopathy. J Trauma Acute Care Surg 2013;75:S40-7.

34. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127-30.

35. Peltan ID, Vande Vusse LK, Maier RV, Watkins TR. An international normalized ratio–based definition of acute traumatic coagulopathy is associated with mortality, venous thromboembolism, and multiple organ failure after injury. Crit Care Med 2015;43:1429-38.

36. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127-30.

37. Hoke M, Ljubuncic E, Steinwender C, Huber K, Minar E, Koppensteiner R, et al. A validated risk score to predict outcomes after carotid stenting. Circ Cardiovasc Interv 2012;5:841-9.

38. Leeper CM, Kutcher M, Nasr I, McKenna C, Billiar T, Neal M, et al. Acute traumatic coagulopathy in a critically injured pediatric population: Definition, trend over time, and outcomes. J Trauma Acute Care Surg 2016;81:34-41.

39. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. Am J Clin Pathol 2006;126:133-9.

40. Soundar EP, Besandre R, Hartman SK, Teruya J, Hui SK. Plasma is ineffective in correcting mildly elevated PT-INR in critically ill children: a retrospective observational study. J Intensive Care 2014;2:64.

41. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion 2006;46:1279-85.