Original Article

Prognostic value of blood biomarkers in patients with unprovoked acute pulmonary embolism

Joo Hee Lee, Jin Won Huh, Sang-Bum Hong, Yeon-Mok Oh, Tae Sun Shim, Chae-Man Lim, Sang-Do Lee, Younsuck Koh, Woo Sung Kim, Jae Seung Lee

Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Address for correspondence:
Dr. Jae Seung Lee, Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 05505, Republic of Korea.
E-mail: jsdoc1186@hanmail.net

Submission: 15-02-2019
Accepted: 24-07-2019

Abstract:

BACKGROUND: Better outcomes have been observed in patients with acute unprovoked than provoked pulmonary embolism (PE). Prognostic biomarkers were studied in heterogeneous patient population and were not verified in patients with unprovoked PE.

METHODS: Patients diagnosed with unprovoked acute PE from 2010 to 2017 at Asan Medical Center, South Korea, were analyzed retrospectively. Adverse composite outcomes were defined as thrombolysis, thrombectomy, extracorporeal membrane oxygenation, or death. Venous blood samples were collected at the first visit before anticoagulant treatment. Biomarkers associated with composite outcomes were analyzed and compared with preexisting risk models.

RESULTS: This study included 265 patients (48.7% male) with a median age of 66.0 (interquartile range 52.0, 75.0) years. Composite outcomes occurred in 20 (7.5%) patients. Hemoglobin, uric acid, and glucose were significantly and independently associated with adverse composite outcomes. This biomarker model showed the highest prognostic accuracy for adverse composite outcomes, with an area under the curve of 0.806 (95% confidence interval: 0.702–0.911, $P < 0.001$), which was significantly better than that of PE severity index (PESI) or simplified PESI, and comparable to that of the European Society of Cardiology (ESC) risk classification.

CONCLUSIONS: The biomarker model including hemoglobin, uric acid, and glucose has good prognostic performance comparable to the ESC risk classification while PESI or simplified PESI score was not useful in unprovoked PE.

Keywords:

Biomarkers, glucose, hemoglobin, prognosis, pulmonary embolism, uric acid

Acute pulmonary embolism (PE) is a potentially life-threatening disease. Indeed, 30-day mortality rates in patients stratified by the European Society of Cardiology (ESC) classification into high-, intermediate–high-, and intermediate–low-risk groups were found to be 22%, 7.7%, and 6.0%, respectively.[1]

Early identification of patients at high risk of poor outcomes may improve the survival rate of patients with acute PE. Although the PE severity index (PESI) remains the most validated tool predicting short-term mortality in patients with acute PE, this index includes 11 variables and is somewhat complex to calculate, making it less useful in clinical practice. Moreover, patients with unprovoked PE were found to have a more favorable outcome than patients with provoked PE,[2,3] suggesting the need to validate risk classification systems in patients with unprovoked PE.

Biomarkers such as brain natriuretic peptide (BNP), troponin, and heart-type fatty acid-binding protein may help in

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.ATM_62_19

How to cite this article: Lee JH, Huh JW, Hong SB, Oh YM, Shim TS, Lim CM, *et al*. Prognostic value of blood biomarkers in patients with unprovoked acute pulmonary embolism. Ann Thorac Med 2019;14:248-53.

stratifying risk and determining prognosis in patients with acute PE. However, these biomarkers have been studied in highly heterogeneous patient populations with various provoking risk factors and have not been verified as useful in patients with unprovoked PE. This study therefore sought to identify blood biomarkers useful in assessing prognosis, including adverse outcomes, in patients with acute unprovoked PE.

Methods

This retrospective study included patients aged ≥18 years with unprovoked acute PE diagnosed from January 2010 to December 2017 at a 2700-bed university-affiliated tertiary referral center in Seoul, South Korea. Patients were diagnosed with unprovoked PE if they did not have known risk factors for PE. That is, patients with temporary (e.g., surgery, hospitalization due to acute illness, or cesarean section within 3 months; or estrogen therapy, pregnancy, or leg injury within 2 months) or persistent (cancer or inflammatory bowel disease) risk factors were excluded.[4] Patients who were referred to our hospital after the start of treatment at outside hospital were also excluded because it is difficult to review the initial manifestation. All clinical, radiologic, and laboratory data were retrospectively collected from medical records. PE was confirmed by spiral computed tomography or by ventilation–perfusion lung scanning, indicating a high probability of PE. Adverse composite outcomes included mortality and clinical conditions that would result in death unless treated with following strategies recommended by the ESC guidelines:[5] (1) thrombolysis, (2) thrombectomy, or (3) extracorporeal membrane oxygenation (ECMO).

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Institutional Review Board of Asan Medical Center (approval number: 2018-0201), which waived the requirement for informed consent due to the retrospective nature of the study. The study outcomes will not affect the future management of the patients, and the authors declare that the patient's personal data have been secured.

Risk groups based on early mortality rate were stratified according to the 2014 ESC guidelines and PESI and simplified PESI scores.[5,6] Patients were classified as being at high, intermediate–high, intermediate–low, or low risk, according to the ESC classification. Patients were classified by a numeric number and/or class from I to V (PESI alone) according to the PESI and simplified PESI. Risk-adjusted therapy was administered based on these risk classifications.

Venous blood samples were collected at the first visit to the clinic before anticoagulation was administered. Complete blood count was measured using a Sysmex XE-2100 automated hematology analyzer (Sysmex, Kobe, Japan). Plasma glucose was measured by the hexokinase method using an autoanalyzer (Toshiba, Tokyo, Japan). Serum uric acid was measured enzymatically using an automatic biochemistry analyzer (Cobas® 8000 modular analyzer series; Roche Diagnostics GmbH, Vienna, Austria). BNP concentration was estimated using a chemiluminescence immunoassay (ADVIA Centaur; Bayer Diagnostics, Tarrytown, NY, USA). Plasma D-dimer levels were determined by an enzyme-linked immunosorbent assay method using Asserachrom D-Di (Diagnostica Stago, Asnieres-sur-Seine, France). To identify blood biomarkers associated with high-risk PE, the levels of these biomarkers were compared in patients stratified according to the ESC risk classification and the occurrence or nonoccurrence of adverse composite outcomes.

Categorical variables were reported as *n* (%) and compared using the Chi-square test. Continuously measured parameters were reported as means ± standard deviation or median (interquartile range [IQR]) and were compared using Student's *t*-test or the Mann–Whitney U-test.

Risk factors associated with the adverse composite outcome were determined by logistic regression analysis using the backward stepwise conditional method. The variables assessed significant in univariate regression analysis were entered as independent variables in multivariate logistic regression model. Next, receiver operating characteristic (ROC) analysis was performed and the area under the curve (AUC) was determined to test the performance of blood biomarker model and preexisting risk model, with respect to predicting the likelihood of adverse composite outcomes. Statistical differences in AUC values among models were calculated using DeLong's test.[7]

All statistical analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium), with statistical significance defined as a $P < 0.05$.

Results

Between January 2010 and December 2017, 1561 patients were diagnosed with acute PE. Of these, 1210 patients with provoked PE and 86 with unprovoked PE who were referred to our hospital after the start of treatment at another hospital were excluded. This study therefore included 265 patients (48.7% male), of

median age 66.0 (IQR 52, 75) years, with unprovoked acute PE [Table 1]. Before being diagnosed with PE during this study period, 17 had a history of deep vein thrombosis (DVT) and 20 had a history of PE. DVT was evaluated in 87.5% of patients, with 57.4% confirmed as having DVT.

Table 2 compares blood biomarker levels in groups of patients categorized as being at low to intermediate–low risk and intermediate–high to high risk according to the ESC classification. White blood cell (WBC) counts and concentrations of uric acid, glucose, lactate dehydrogenase (LD), creatine kinase-muscle/brain (CK-MB), troponin I, and BNP were significantly higher in the intermediate–high- to high-risk group than in the low- to intermediate–low-risk group.

Adverse composite outcomes occurred in 20 (7.5%) patients; of these, 16 underwent thrombolysis, two underwent embolectomy, and two were supported with ECMO followed by thrombolysis or embolectomy. There were no in-hospital deaths. Patients who developed adverse composite outcome had significantly higher WBC counts and significantly higher concentrations of hemoglobin, uric acid, glucose, LD, troponin I, and BNP than patients who did not develop adverse composite outcomes [Table 3]. Univariate logistic regression analysis showed that hemoglobin, uric acid, glucose, CK-MB, and BNP concentrations were significantly associated with the adverse composite outcome. The ESC risk classification also showed significant relationship (odds ratio [OR]: 2.878, 95% confidence interval [CI]: 1.626–5.094, $P < 0.001$) with adverse

Table 1: Baseline characteristics of patients with unprovoked acute pulmonary embolism

Characteristics	Values
Number of patients	265
Age, years	66.0 (52,75)
Male sex, *n* (%)	129 (48.7)
Body mass index, kg/m^2	25.0±4.0
Ever-smoker, *n* (%)	78 (29.4)
Time from onset to visit clinic, days (*n*=246)	6 (2, 14)
History of DVT, *n* (%)	17 (6.4)
History of PE, *n* (%)	20 (7.5)
Diagnosis, *n* (%)	
PE only	80 (30.2)
PE with DVT	152 (57.4)
Proximal DVT	33 (12.5)
Proximal and distal DVT	86 (32.5)
Distal DVT	33 (12.5)
DVT not evaluated	33 (12.5)
ESC Risk Classification, *n* (%): Low/intermediate-low/intermediate-high/high	76 (28.7)/126 (47.5)/53 (20)/10 (3.8)
PESI score, points	79.1±25.7
PESI score, class, *n* (%): Class I/II/III/IV/V	78 (29.4)/99 (37.4)/55 (20.8)/24 (9.1)/9 (3.4)
Simplified PESI score, *n* (%): 0/1/2/3/4/5	152 (57.4)/86 (32.5)/17 (6.4)/9 (3.4)/1 (0.4)/0 (0)

All values are presented as *n* (%) and means±SD or median [interquartile range]. SD=Standard deviation, DVT=Deep vein thrombosis, PE=Pulmonary embolism, ESC=European Society of Cardiology, PESI=Pulmonary embolism severity index

Table 2: Blood biomarker levels at patient admission according to the European Society of Cardiology Classification

Characteristics	Total	Low and intermediate-low (*n*=202)	Intermediate-high and high (*n*=63)	*P*
White blood cell,/uL	8910.3±3182.5	8582.3±2994.6	9961.9±3546.8	0.003
Hemoglobin, g/dL	13.8±1.9	13.8±1.8	13.7±2.2	0.681
Platelet, ×10^3/uL	210.4±67.6	207.8±66.4	218.6±71.4	0.270
CRP, mg/dL	1.6±2.5	1.7±2.7	1.4±1.8	0.469
Uric acid, mg/dL	5.6±2.0	5.3±1.7	6.5±2.6	0.003
Glucose, mg/dL	137.0±56.5	132.3±51.7	151.9±68.1	0.008
LD, IU/L (*n*=201)	319.8±236.5	289.8±98.7	397.3±411.6	0.001
CK, IU/L (*n*=220)	153.6±388.8	133.8±381.1	206.4±407.3	0.567
CK-MB, ng/mL (*n*=215)	2.9±3.7	2.1±2.5	4.9±5.1	<0.001
Troponin I, ng/mL (*n*=218)	0.2±0.7	0.1±0.6	0.4±0.9	<0.001
BNP, pg/mL (*n*=212)	246.9±528.0	121.6±286.8	543.3±790.7	<0.001
D-dimer, ug/ml FEU	8.9±11.0	8.1±8.0	11.5±17.3	0.056

All values are presented as means±SD. SD=Standard deviation, CRP=C-reactive protein, LD=Lactate dehydrogenase; CK=Creatine kinase, BNP=Brain natriuretic peptide, FEU=Fibrinogen equivalent unit

composite outcome. Multivariate analysis showed that hemoglobin, uric acid, and glucose were significantly and independently associated with adverse composite outcomes [Table 4]. By contrast, PESI score (OR: 1.009, 95% CI: 0.993–1.026, P = 0.261) and simplified PESI score (OR: 1.495, 95% CI 0.920–2.431, P = 0.105) were not significant predictors of adverse composite outcomes in univariate logistic regression analysis.

The ability of each prognostic model to predict adverse composite outcomes is shown in Table 5 and Figure 1. The ROC curve for a biomarker model including hemoglobin, uric acid, and glucose concentrations showed the highest prognostic accuracy for adverse composite outcomes, with an AUC of 0.806 (95% CI: 0.702–0.911, P < 0.001), which was significantly better than that of PESI (AUC: 0.517, 95% CI: 0.376–0.657, P = 0.0001) or simplified PESI (AUC: 0.598, 95% CI: 0.467–0.728, P = 0.0009), and similar to that of ESC risk classification (AUC: 0.686, 95% CI: 0.548–0.824, P = 0.0659).

Table 3: Comparison of blood biomarkers in patients with and without the adverse composite outcome*

Characteristics	Composite outcome		*P*
	No (*n*=245)	Yes (*n*=20)	
White blood cell,/uL	8640.1±2862.4	12220.0±4800.0	0.001
Hemoglobin, g/dL	13.7±1.8	15.1±2.2	0.001
Platelet, ×10³/uL	210.2±67.2	212.2±75.0	0.903
CRP, mg/dL	1.6±2.5	2.4±2.4	0.157
Uric acid, mg/dL	5.5±2.0	7.1±2.2	0.001
Glucose, mg/dL	134.9±53.7	162.1±80.5	0.038
LD, IU/L (*n*=201)	303.8±131.5	518.1±724.5	0.049
CK, IU/L (*n*=220)	152.2±397.1	166.9±300.9	0.873
CK-MB, ng/mL (*n*=215)	2.7±3.2	4.8±6.9	0.364
Troponin I, ng/mL (*n*=218)	0.2±0.6	0.5±1.5	0.024
BNP, pg/mL (*n*=212)	220.4±465.8	516.9±932.2	0.006
D-dimer, ug/ml FEU	8.7±11.1	11.5±9.4	0.265

All values are presented as mean±SD. *Including thrombolysis, embolectomy, ECMO, or death. SD=Standard deviation, CRP=C-reactive protein, LD=Lactate dehydrogenase, CK=Creatine kinase, BNP=Brain natriuretic peptide, FEU=Fibrinogen equivalent unit

Table 4: Risk factors for the adverse composite outcome*

Variables	OR (95% CI)	*P*
Hemoglobin, g/dL	1.627 (1.165-2.272)	0.004
Uric acid, mg/dL (*n*=261)	1.342 (1.077-1.674)	0.009
Glucose, mg/dL (*n*=260)	1.008 (1.001-1.015)	0.019
Female sex	2.631 (0.839-8.256)	0.097

*Including thrombolysis, embolectomy, ECMO, or death. ECMO=Extracorporeal membrane oxygenation, OR=Odds ratio, CI=Confidence interval, CK=Creatine kinase; BNP=Brain natriuretic peptide

Discussion

Few studies to date have evaluated the ability of blood biomarkers to predict risk and outcome in patients with unprovoked acute PE. This study found that, in addition to BNP and troponin I concentrations, WBC counts, and hemoglobin, uric acid, glucose, and LD concentrations were useful in predicting adverse composite outcomes in patients with unprovoked acute PE. The biomarker model including hemoglobin, uric acid, and glucose had the highest prognostic performance comparable to ESC risk classification while PESI or simplified PESI score was not useful in unprovoked PE.

PESI and simplified PESI score were failed to predict adverse composite outcomes in unprovoked PE patients. There could be several reasons. Unprovoked PE patients have less comorbidities compared with provoked PE patients which are included in PESI and simplified PESI scoring system. Other factors (age and sex) may also have not had a significant impact on determining thrombolysis, thrombectomy, or ECMO. On the other hand, ESC risk classification includes right ventricular

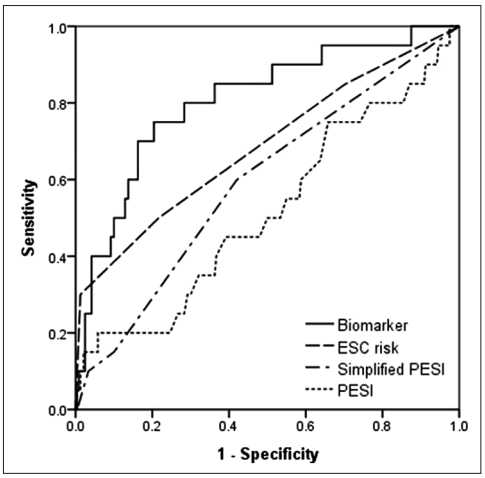

Figure 1: The receiver operating characteristics curve of each risk prediction models with respect to predicting adverse composite outcomes*. *Including thrombolysis, embotectomy, ECMO, or death. Biomarker model means "hemoglobin + uric acid + glucose" model. ESC = European Society of Cardiology, PESI = Pulmonary embolism severity index

Table 5: The performance of each risk prediction models with respect to predicting adverse composite outcomes*

Predictors	AUC (95%CI), *P*	*P* value compared to biomarker model
PESI	0.517 (0.376-0.657), 0.802	0.0001
Simplified PESI	0.598 (0.467-0.728), 0.147	0.0009
ESC Risk Classification	0.686 (0.548-0.824), 0.006	0.0659
Hemoglobin + uric acid + glucose	0.806 (0.702-0.911), <0.001	Index

*Including thrombolysis, embolectomy, ECMO, or death. ECMO=Extracorporeal membrane oxygenation, AUC=Area under the curve, CI=Confidence interval, PESI=Pulmonary embolism severity index, ESC=European Society of Cardiology

function and cardiac biomarkers, which may better reflect hemodynamic significance that is important in determining thrombolysis, thrombectomy, or ECMO.

Venous thromboembolism (VTE) and cardiovascular disease have been found to share common risk factors.[8] For example, elevated uric acid concentration and hyperglycemia are risk factors for several cardiovascular diseases and may also be risk factors for VTE. Several studies report that the development of VTE is associated with uric acid levels or gout,[9,10] possibly due to the pro-oxidant and pro-inflammatory effects of uric acid and its induction of endothelial dysfunction.[11] Previous studies have also reported that elevated uric acid was predictive of PE severity[12] and short-term mortality.[13] Uric acid, a byproduct of purine catabolism, is increased under the hypoxic conditions associated with diseases, such as obstructive sleep apnea, chronic obstructive pulmonary disease, and congestive heart failure.[14-16] In addition, uric acid levels may correlate negatively with cardiac output and positively with mean pulmonary arterial pressure in patients with PE and primary pulmonary hypertension.[12,17] These findings suggest that hypoxia, pulmonary hypertension, and decreased cardiac output in PE may elevate uric acid level, which correlates with the severity of PE.

Hyperglycemia was another cardiovascular risk factor found in this study to be a significant risk factor for adverse composite outcome. Several studies have reported relationships between hyperglycemia and acute PE development or mortality,[18,19] with mortality rates higher in individuals without than with diabetes.[19] Hyperglycemia can activate the coagulation system, reduce fibrinolysis, and reduce the protective glycocalyx layer by directly affecting the endothelium; this, in turn, is often accompanied by hyperinsulinemia, resulting in an even stronger hypercoagulable state.[20] Hyperglycemia may also result from the release of stress hormones, such as catecholamines, growth hormone, and cortisol in acute stress conditions. Determining the causal relationship between hyperglycemia and PE requires a determination of the history of previous diabetes mellitus (DM) and long-term blood glucose levels before and after the acute stage of PE.

Hemoglobin was significantly higher (15.1 ± 2.2 g/dL) in patients with adverse composite outcomes and had an OR of 1.438 for the development of adverse outcomes. Increases in hematocrit may increase blood viscosity,[21] platelet function (adhesiveness and reactivity),[22,23] and thrombin activity and concentration.[24] Although there was an opposite result that low hemoglobin concentration was associated with high mortality rates in patients with PE,[25] the cohort in that study was heterogeneous, with many patients in the low hemoglobin group having cancer, surgery, or bleeding, and the possible causes of anemia were not evaluated.

This study had several limitations. First, it was a retrospective observational study in a single tertiary center. All data were collected from patients' medical records, making them susceptible to bias in data selection and analysis. Second, we cannot explain why patients with unprovoked PE had a better prognosis and different risk factors than patients with provoked PE. The absence of several comorbidities in patients with unprovoked PE may have contributed to their better prognosis. In addition, advanced treatments, such as thrombolysis, embolectomy, and ECMO, were readily available to patients in our medical center but may be less available to patients in primary and secondary care hospitals. Finally, we could not determine whether the above-described biomarkers are causes or effects of PE. Further studies are needed to validate these biomarkers.

Conclusions

The biomarker model including hemoglobin, uric acid, and glucose has good prognostic performance comparable to ESC risk classification while PESI or simplified PESI score was not useful in unprovoked acute PE. Measurement of these biomarkers is very useful in real clinical practice, as these assays are relatively noninvasive, cost-effective, and easily available.

Acknowledgments

This study was supported by University of Ulsan College of Medicine, Seoul, Republic of Korea.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Becattini C, Agnelli G, Lankeit M, Masotti L, Pruszczyk P, Casazza F, *et al*. Acute pulmonary embolism: Mortality prediction by the 2014 European society of cardiology risk stratification model. Eur Respir J 2016;48:780-6.
2. Klok FA, Zondag W, van Kralingen KW, van Dijk AP, Tamsma JT, Heyning FH, *et al*. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med 2010;181:501-6.
3. Stoeva N, Kirova G, Staneva M, Lekova D, Penev A, Bakalova R. Recognition of unprovoked (idiopathic) pulmonary embolism-prospective observational study. Respir Med 2018;135:57-61.
4. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA, *et al*. Categorization of patients as having provoked or unprovoked venous thromboembolism: Guidance from the SSC of ISTH. J Thromb Haemost 2016;14:1480-3.
5. Konstantinides SV, Torbicki A, Agnelli G, Danchin N,

Fitzmaurice D, Galiè N, *et al.* 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033-69.
6. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, *et al.* Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9.
7. 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.
8. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherosclerosis: A PRISMA-compliant systemic review and meta-analysis. Medicine (Baltimore) 2016;95:e4495.
9. Kubota Y, McAdams-DeMarco M, Folsom AR. Serum uric acid, gout, and venous thromboembolism: The atherosclerosis risk in communities study. Thromb Res 2016;144:144-8.
10. Yamada N, Ota S, Liu Y, Crane MM, Chang CM, Thaker S, *et al.* Risk factors for nonfatal pulmonary embolism in a Japanese population: A hospital-based case-control study. Angiology 2010;61:269-74.
11. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol 2005;25:39-42.
12. Shimizu Y, Nagaya N, Satoh T, Uematsu M, Kyotani S, Sakamaki F, *et al.* Serum uric acid level increases in proportion to the severity of pulmonary thromboembolism. Circ J 2002;66:571-5.
13. Ozsu S, Çoşar AM, Aksoy HB, Bülbül Y, Oztuna F, Karahan SC, *et al.* Prognostic value of uric acid for pulmonary thromboembolism. Respir Care 2017;62:1091-6.
14. Saito H, Nishimura M, Shibuya E, Makita H, Tsujino I, Miyamoto K, *et al.* Tissue hypoxia in sleep apnea syndrome assessed by uric acid and adenosine. Chest 2002;122:1686-94.
15. Ozanturk E, Ucar ZZ, Varol Y, Koca H, Demir AU, Kalenci D, *et al.* Urinary uric acid excretion as an indicator of severe hypoxia and mortality in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. Rev Port Pneumol (2006) 2016;22:18-26.
16. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: Insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. Circulation 2003;107:1951-3.
17. Nagaya N, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, *et al.* Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. Am J Respir Crit Care Med 1999;160:487-92.
18. Hermanides J, Cohn DM, Devries JH, Kamphuisen PW, Huijgen R, Meijers JC, *et al.* Venous thrombosis is associated with hyperglycemia at diagnosis: A case-control study. J Thromb Haemost 2009;7:945-9.
19. Scherz N, Labarère J, Aujesky D, Méan M. Elevated admission glucose and mortality in patients with acute pulmonary embolism. Diabetes Care 2012;35:25-31.
20. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: A prothrombotic factor? J Thromb Haemost 2010;8:1663-9.
21. Wells RE Jr., Merrill EW. Influence of flow properties of blood upon viscosity-hematocrit relationships. J Clin Invest 1962;41:1591-8.
22. Santos MT, Valles J, Marcus AJ, Safier LB, Broekman MJ, Islam N, *et al.* Enhancement of platelet reactivity and modulation of eicosanoid production by intact erythrocytes. A new approach to platelet activation and recruitment. J Clin Invest 1991;87:571-80.
23. Valles J, Santos MT, Aznar J, Marcus AJ, Martinez-Sales V, Portoles M, *et al.* Erythrocytes metabolically enhance collagen-induced platelet responsiveness via increased thromboxane production, adenosine diphosphate release, and recruitment. Blood 1991;78:154-62.
24. Horne MK 3rd, Cullinane AM, Merryman PK, Hoddeson EK. The effect of red blood cells on thrombin generation. Br J Haematol 2006;133:403-8.
25. Jiménez D, Escobar C, Martí D, Díaz G, César J, García-Avello A, *et al.* Association of anaemia and mortality in patients with acute pulmonary embolism. Thromb Haemost 2009;102:153-8.