

study versus 5% in our patients. In our study there was no significant correlation between TIMI risk score and long term mortality (TIMI score <4: 18.6% versus TIMI score \geq 4: 25.5%; $p=0.35$). Considering the fact that only 78 patients underwent long term follow up, we suppose that this finding should be evaluated at a larger series, but in present study, the explanation for this finding is related to the nature of parameters in TIMI risk score since parameters like systolic blood pressure, heart rate and Killip class may indicate to acute ischemia and acute left or right ventricular ischemia that resolves with routine treatments with no long term effect. Therefore, there is no place for increase in long term mortality with increase in TIMI risk score.

The RVI leads to significant increase in in-hospital mortality and morbidity of acute inferior wall infarction that can be predicted accurately with TIMI risk score system. Lack of early reperfusion therapy may lead to increased long term mortality of these patients, which could not be predicted accurately using this system.

Received 16th August 2005. Accepted for publication in final form 23rd January 2006.

Department of Cardiology, Madani Heart Hospital, Tabriz University of Medical Sciences, Tabriz, Iran. Address correspondence and reprint requests to Dr. Samad Ghaffari, Assistant Professor in Cardiology, Tabriz University of Medical Sciences, Tabriz, Iran. Tel. +98 (411) 3357770. Fax. +98 (411) 3344021. E-mail: ghaffaris@gmail.com

References

1. Gumina RJ, Wright RS, Kopecky SL, et al. Strong predictive value of TIMI risk score analysis for in-hospital and long term survival of patients with right ventricular infarction. *Eur Heart J* 2002; 23: 1678–1683.
2. Mehta S, Eikelboom J, Natarajan M, et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol* 2001; 37: 37–43.
3. Berger P, Ruocco N, Ryan T, et al. Frequency and significance of right ventricular dysfunction during inferior wall left ventricular myocardial infarction treated with thrombolytic therapy (results from the thrombolysis in myocardial infarction [TIMI] II trial). *Am J Cardiol* 1993; 71: 1148–1152.
4. Morrow D, Antman E, Parsons L, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA* 2001; 286: 1356–1359.
5. Ketikoglou DG, Karvounis HI, Papadopoulos CE, Zaglavara TA, Efthimiadis GK, Parharidis GE, et al. Echocardiographic evaluation of spontaneous recovery of right ventricular systolic and diastolic function in patients with acute right ventricular infarction associated with posterior wall left ventricular infarction. *Am J Cardiol* 2004; 93: 911–913.
6. Bowers TR, O'Neill WW, Grines C, Pica MC, Safi'an RD, Goldstein JA. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med* 1998; 338: 933–940.

An analysis of patients diagnosed with pulmonary embolism in terms of clinical and meteorological data

Ilker Ercan, MSc, PhD, Funda Coskun, MD, Sengul Cangur, BSc, MSc, Ahmet Ursavas, MD, Esra Uzaslan, MD, Ercument Ege, MD, Ismet Kan, MSc, PhD.

Pulmonary thromboembolism (PTE) is a major cause of morbidity and mortality. In this study, it is aimed to analyze the patients diagnosed with PTE through cluster analysis, a multivariate classification method, in order to establish whether there were classifications in terms of epidemiological, clinical, seasonal and meteorological variables.

Patients files of 49 patients diagnosed with PTE in our clinic between 1999 and 2003 were inspected retrospectively. Patients whose diagnose were confirmed with lung perfusion scintigraphy and contrast-enhanced spiral computed tomography were enrolled in the study. As the impact of meteorological factors was to be investigated, those coming from cities other than Bursa were excluded. All patients enrolled were evaluated for protein-C, protein-S, and antithrombin III values. They were also examined with Doppler ultrasonography with respect to deep vein thrombosis (DVT). Patients were also assessed in terms of PTE predisposition factors. Obesity (body mass index >28 kg/m²), major abdominal-pelvic surgery, knee-hip surgery, postoperative intensive care, pregnancy, postpartum period, use of oral contraceptives, acute myocardial infarct, congestive heart failure, malign diseases, history of trauma, and immobility were regarded to be predisposition factors. Patients with PTE were analyzed with respect to the months and seasons. In order to investigate the association between PTE and meteorological factors, data regarding temperature, humidity and air pressure were obtained from State Meteorological Services in Bursa for the days, which embolism events were observed.

In this study, the data were analyzed using the cluster analysis method. The data set included mixed type measures. Therefore, Gower similarity coefficient was used to compute the similarity between individuals. Single linkage method was used for merging clusters. After description of the clusters, for determining the variables, which make the difference in the formation of the clusters, Mann-Whitney U test and Fisher's exact test were used. Statistical significance was set as

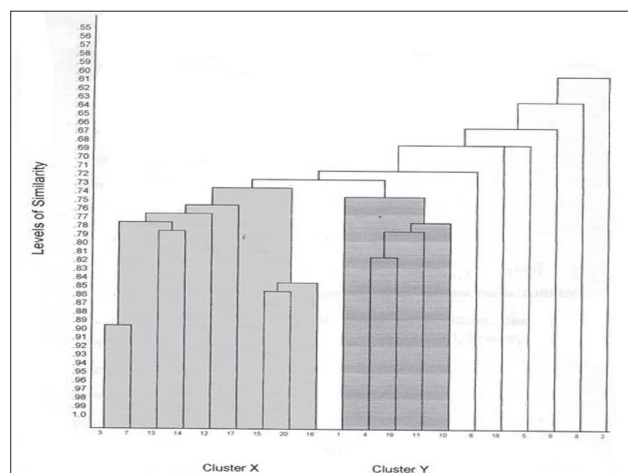


Figure 1 - Dendrogram indicating classification of patients regarding levels of similarity.

$\alpha=0.05$. In order to statistically evaluate the patients through clustering method, 20 patients possessing all pre-disposition factors of pulmonary embolism were enrolled in the study. Of these, 14 (70%) were males, 6 (30%) were females, with a mean age of 49.30 ± 3.53 (mean \pm SEM) years. A total of 2 clusters were established at a similarity level of 0.723. Of the 20 patients, 14 (70%) were formed into clusters. The remaining 6 (30%) patients were regarded to be controversial units. The dendrogram indicating the classification of the patients in terms of their levels of similarity is given in **Figure 1**. No significant differences were established between the clusters in terms of protein-C, protein-S and antithrombin III values ($p>0.05$). One patient in each cluster was observed with DVT and therefore, no significant difference was established between the clusters in terms of DVT ($p>0.05$). Of the patients in cluster X, 3 patients were established with predisposition factors. However, no statistically significant differences were observed between the clusters with respect to predisposition factors ($p>0.05$). All the patients in this present study were assessed regarding the factors known to lead to pulmonary embolism. Statistical analysis revealed that patients were similar and were formed into 2 groups. While age, protein-C, protein-S, antithrombin III, gender, predisposition factors (prolonged bed rest, obesity, long journey, anamnesis, and so forth) and DVT were observed to have no impact on the formation of cluster X, consisting of 9 patients, and cluster Y, consisting of 5 patients; season, month, temperature, and air pressure were noted to have been effective. While the mean temperature was $21.46 \pm 1.85^\circ\text{C}$ in cluster X at the time of embolism

diagnosis, it was $4.38 \pm 0.85^\circ\text{C}$ in cluster Y ($p<0.01$). The mean value for air pressure was 999.84 ± 0.98 Mb for cluster X, ($p<0.05$), and 1007.04 ± 2.29 Mb for cluster Y, ($p<0.05$). Distribution of the patients with respect to months demonstrated a significant difference for the month of January ($p<0.001$). All of the embolism cases in cluster X had occurred in the months other than January. Similarly, 4 (80%) out of the 5 patients in cluster Y had been diagnosed with embolism in January. When embolism cases were analyzed regarding the seasons, it was noted that all the patients in cluster X had experienced embolism in seasons other than winter; all the patients in cluster Y had experienced embolism in winter ($p<0.001$).

Our study established that seasonal variations in temperature and air pressure had an impact on pulmonary embolism incidence. It was observed that patients with pulmonary embolism had been grouped into 2 clusters, which had no differences in terms of age, gender, severity and predisposition factors. The determinant factors in the clusters were demonstrated to be the differences in temperature and air pressure. Seasonal variations in venous thromboembolic diseases have often been associated with meteorological variables such as temperature, humidity and air pressure. The increase observed in venous thromboembolism is attributed to hypercoagulation induced by cold weather; peripheral vasoconstriction and limited mobility in winter months. The incidences of aortic dissection, sudden cardiac death, stroke, and venous thromboembolic diseases have been reported to be subject to seasonal variations.^{1,2} The increase in venous thromboembolic diseases in winter months has been stated in various studies. A study conducted in France, evaluating nationwide hospital records between 1995 and 1998, assessed 65,081 DVT and 62,237 PTE cases. The study revealed a significant increase in DVT and PTE incidences in winter.³ Similarly, Sharma et al⁴ reported 2.9 times higher incidence of non-fatal PTE in autumn and winter than summer and spring in their study evaluating 248 non-fatal PTE patients. In this present study, it was observed that all of the patients in cluster Y had experienced embolism in winter. The most extensive study on seasonal variations in venous thromboembolism was carried out on 2,457,000 PTE and 5,767,000 DVT cases between 1979 and 1999 in the USA. The study which reviewed all hospital records nationwide reported that there were no significant differences in terms of seasons or months.⁵

Clauss et al⁶ investigated the influence of environmental factors such as temperature, vapor pressure, air pressure, rainfall, and humidity on

pulmonary embolism incidence. They reported that pulmonary embolism incidence was correlated positively with vapor pressure and rainfall. Our study did not take rainfall, but air pressure was observed to be a factor with an impact on pulmonary embolism incidence, consistent with the above mentioned study. Various proposals have been made to explain the association between venous thromboembolism and seasonal factors. Patients in this study were observed to have formed 2 similar clusters. Temperature and air pressure were the differences between the clusters. We established that predisposition factors to pulmonary embolism did not differ between the clusters. The number of patients in our study was limited since we enrolled only the patients who possessed all predisposition factors.

In conclusion, this present study which is aimed to analyze the patients with pulmonary embolism through cluster analysis, a multivariate classification method, revealed that clinical variables did not have an impact on the formation of the clusters and seasonal factors were associated with the classification of patients with pulmonary embolism, and that these factors may have an impact on clinical variables.

Received 27th September 2005. Accepted for publication in final form 31st December 2005.

From the Department of Biostatistics (Ercan, Cangur, Kan) and the Department of Chest Diseases and Tuberculosis (Coskun, Ursavas, Uzaslan, Ege), Uludag University Medical School, Bursa, Turkey. Address correspondence and reprint requests to: Dr. Ilker Ercan, Department of Biostatistics, Uludag University Medical School, Gorukle 16059, Bursa, Turkey. Tel. +90 (224) 4428200 Ext. 21028. Fax. +90 (224) 4428666. E-mail: ercan@uludag.edu.tr

References

1. Mehta RH, Manfredini R, Hassan F, Sechtem U, Bossone E, Oh JK, et al. Chronobiological patterns of acute aortic dissection. *Circulation* 2002; 106: 1110-1115.
2. Casetta I, Granieri E, Portaluppi F, Manfredini R. Circadian variability in hemorrhagic stroke. *JAMA* 2002; 287: 1266-1267.
3. Boulay F, Berthier F, Schoukroun G, Raybaut C, Gendreike Y, Blaive B. Seasonal variations in hospital admission for DVT and pulmonary embolism: analysis of discharge data. *BMJ* 2001; 323: 601-602.
4. Sharma GV, Frisbie JH, Tow DE, Yalla SV, Khuri SF. Circadian and circannual rhythm of nonfatal pulmonary embolism. *Am J Cardiol* 2001; 87: 922-924.
5. Stein PD, Kayali F, Olson RE. Analysis of occurrence of venous thromboembolic disease in the four seasons. *Am J Cardiol* 2004; 93: 511-513.
6. Clauss R, Mayes J, Hilton P, Lawrenson R. The influence of weather and environment on pulmonary embolism: pollutants and fossil fuels. *Med Hypotheses* 2005; 64: 1198-1201.

Busulfan induced myoclonus

David J. Denison, MD,
Asem A. Alghzaly, MRCP(UK).

Busulfan is an alkylating chemotherapeutic agent. In combination with other chemotherapeutic drugs, it is an acceptable preparative (conditioning) agent before bone marrow and peripheral blood stem cell transplantation. Busulfan rapidly enters the central nervous system (CNS) and may cause seizures when used in a high dose.¹ Consequently, patient should receive prophylactic phenytoin (with therapeutic level) to begin before busulfan and continued for 24 hours after the last dose. There is a wide intra- and interindividual variation of absorption and metabolism of busulfan. In addition, pharmacokinetic differences exist between age groups.

Our patient is a 16-year-old Omani lady with precursor B cell acute lympholytic leukemia, diagnosed on September 2004. She has an unremarkable medical history. She was started on chemotherapy. As cytogenetic study showed Philadelphia chromosome positive, that put her at a high risk of relapse, it was decided to proceed to allogeneic bone marrow transplantation as early as possible in the first remission. She was admitted to bone marrow transplantation unit on April 2005, her body weight was 39 kg, height 154.6 cm and body surface area 1.3 m.² The preparative regimen consisted of fludarabine and busulfan.³ Aiming at decreasing the regimen related to toxicity, a busulfan pharmacokinetic study was performed.² Two days before starting the regimen, a study was carried out using a busulfan test dose as a guide to the appropriate actual dose. This was followed by monitoring of the serum busulfan level throughout the regimen.⁴ Phenytoin was started before the Busulfan (BU) test dose, continued through the regimen and until 24 hours after the last dose of BU. She received an oral stat dose of phenytoin 300 mg, followed by 100 mg tid oral. Serum free phenytoin level before starting BU was 3.5 umol/l (therapeutic range 3.3-9.6). The 4th day regimen consisted of a single daily intravenous (iv) dose of BU and fludarabine. On the first and second days she received daily 140 mg BU, while on the third and fourth she received daily 160 mg, guided by the prior regimen study and serum level monitoring. After receiving the last dose of BU, she developed for a few second a generalized myoclonus. Again and after the fourth hour of this episode, she