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LETTER TO THE EDITOR

Seasonal variations of pulmonary embolism in hospitalized patients

In recent years, circannual variations in incidence and mortality for coronary artery diseases,[1] cerebrovascular diseases,[2,3] chronic obstructive pulmonary diseases[4] and venous thromboembolic diseases[5,6] have been demonstrated, with a peak in winter and a trough in summer, especially in elderly people. This could be explained by an increasing risk of thrombosis due to seasonal variations of environmental risk factors, diet, exercise, plasma lipids, haemorrheological and coagulation factors and seasonal variations of respiratory infections.[4]

Since there is little information about the circannual distribution of pulmonary embolism (PE) and its relation with weather conditions, we would like to submit to your attention the data of our study aimed at analysing the influence of changes in metereological parameters and seasonal variations in PE.

We observed the circannual distribution of 457 hospitalized patients, with mean age ± SD 71.68 ± 12.62 years, 51.7% males and 48.3% females, (324, 71% medical patients, 133, 29% surgical patients) discharged in a period 6 years long (1996–2001) from the Policlinico Le Scotte University Hospital of Siena, Italy, with diagnosis of PE (415.1 code of the International Classification of Diseases, 9th Clinical Modification ICD-9-CM). Of the patients, 358 (78.3%) were 65 years old and over, with mean age ± SD 77.51 ± 7.03 years, 49.1% males and 50.9% females.

We evaluated four metereological parameters: monthly mean temperature (°C), monthly mean excursion of temperature in a day (°C), monthly mean barometric pressure (millibar, mb) and monthly mean relative humidity (in percentage of water saturation, % saturation).

Moreover in a subgroup of elderly medical patients admitted in our Department, we analysed and compared the differences between cold and warm months of five laboratory parameters and commonest risk factors for PE: plasma D-Dimer levels (ng/ml, IL Test D-Dimer quantitative method, ACL Futura, Instrumentation Laboratory, Biokit S.A., Spain), plasma C-reactive protein (CRP, mg/dl, Dade/Behring Diagnostics, Marburg, Germany), plasma fibrinogen levels (Multifibren, Dade/Behring Diagnostics, Marburg, Germany, mg/dl), erythrocyte sedimentation rate (ESR, mm/h) and platelets count ($\times 10^6$/L).

For statistical analysis we used the *t*-test for the differences of the means of independent samples and the correlation index of Pearson (r^2) for the relation between meteorological parameters and number of cases of PE; $P<0.05$ and $r^2 \leqslant -0.5 \geqslant -1$ or $\geqslant 0.5 \leqslant 1$ were considered significant.

We noticed a weak percentage of PE in the cold months (October–March) than in the warm months (April–September) (54% vs. 46%, $P=$ ns), both in patients under 65 years old (56.5% vs. 43.5%, $P=$ ns) and in elderly patients (53.3% vs. 46.7%, $P=$ ns) and in the medical patients (cold months 49.8%, warm months 50.2%, $P=$ ns), while in the surgical patients there was a strong percentage in the cold months (61.5% vs. 38.5%, $P<0.05$).

Of the patients with PE, 24.2% died (24.4% in medical patients, 22.5% in surgical patients), 91% of them being elderly. Mortality for PE was strong in the cold months than in the warm months (64% vs. 36%, $P<0.05$), both in patients under 65 years (70% vs. 30%, $P<0.05$) and in elderly patients (63.4% vs. 36.6%, $P<0.05$). In medical patients mortality was 56.5% in cold months and 43.5% in warm months ($P<0.05$), in surgical patients mortality for PE was 60% in cold months and 40% in warm months ($P<0.05$).

Mean ± SD length of hospitalization (LOS) was 23.47 ± 18.73 days. Mean LOS in cold months was 23.57 ± 20.38 days, while in warm months was 23.38 ± 18.73 days ($P=$ ns). In medical patients mean ± SD LOS was 20.63 ± 15.81 days, while for surgical patients mean ± SD LOS was 30.20 ± 23.00 days ($P<0.05$).

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Table 1 shows the distribution of patients in the hospital wards with the seasonal variations. In medical patients we did not find strong differences for internal medicine and respiratory disease wards, while we found a strong difference for cardiology ward where PE was more frequent in warm months and for the other wards where PE was more frequent in cold months. In surgical patients we found a strong difference in the seasonal distribution of PE for general surgery and orthopedics wards, where PE was more frequent in cold moths. For the others surgical wards we did not find differences in seasonal distribution.

The monthly distribution of PE revealed a peak in March and a trough in August, for all the considered patients and for the group of elderly patients. The seasonal distribution of the cases was: Winter 134 (elderly 100), Spring 127 (elderly 93), Summer 97 (elderly 72), Autumn 109 (elderly 82).

We found a strong inverse correlation between mean monthly temperature and barometric pressure and number of cases affected by PE ($r^2 = -0.66$ and -0.61, respectively, see Fig. 1), while we found a weak inverse correlation between mean monthly excursion of temperature in a day and humidity and PE ($r^2 = -0.42$ and -0.38, respectively).

Considering separately medical and surgical patients, we found many weak peaks of occurrence of PE during the year in medical patients, while in surgical patients a strong peak of occurrence in March was found. In medical patients only weak

Table 1 Wards of hospital admission and seasonal variations.

Hospital wards	Patients number	Cold months (October–March)	Warm months (April–September)	*P*
Medical patients				
Internal medicine	188	90	98	ns
Respiratory disease	59	30	29	ns
Cardiology	32	13	19	<0.05
Other wards*	35	21	14	<0.05
Surgical patients				
General Surgery	65	40	25	<0.05
Orthopedics	38	25	13	<0.05
Other wards†	30	15	15	ns

*Geriatrics 13, Oncology 5, Infettivology 4, Haematology 2, Neurology 8, Intensive Care 7.
†Heart Surgery 4, Neurosurgery 13, Urology 9, Vascular Surgery 4.

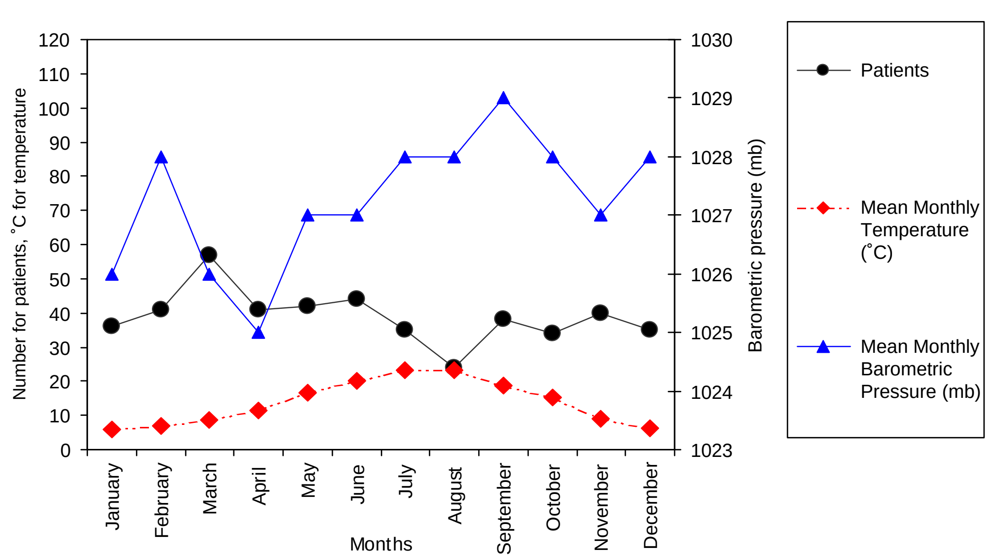

Figure 1 Circannual distribution of PE and metereological variations.

inverse correlations between number of cases and weather parameters were found (monthly mean temperature $r^2 = -0.25$, barometric pressure $r^2 = -0.08$, mean monthly excursion $r^2 = -0.03$, mean humidity $r^2 = -0.38$). Instead in surgical patients we found a strong inverse correlation with barometric pressure ($r^2 = -0.83$), while for the other parameters we found a weak correlation (mean monthly temperature $r^2 = -0.41$, mean monthly excursion $r^2 = -0.11$, humidity $r^2 = -0.36$). Figure 2 shows medical and surgical patients and the strong correlation for surgical patients.

The subgroup of elderly patients admitted in our Department and considered for the biochemical analysis were 75 with mean age$\pm$SD 78.5$\pm$7.5 years. Of them, 44 were admitted in the cold months and 31 in the warm months. We noticed strong mean levels of CRP (6.6 vs. 4.3 mg/dl, $P<0.05$), D-Dimer (1856 vs. 1690 ng/ml, $P<0.05$) and platelets (251.5 vs. 189.4×10^3/l, $P<0.05$) in the group admitted in the cold months, while we observed weak differences in fibrinogen (491.4 vs. 469.0 mg/dl, $P = $ ns) and ESR (33.80 vs. 34.03 mm/h, $P = $ ns).

Table 2 shows risk factors for PE found in this subgroup of patients with the seasonal variations. We found a strong difference for deep vein thrombosis (DVT), immobility (bed rest over 4 days), fractures and recent surgery that were more frequent in warm months and for heart failure that was more frequent in cold months; we observed a weak difference for COPD, cancer and leg extremity paralysis.

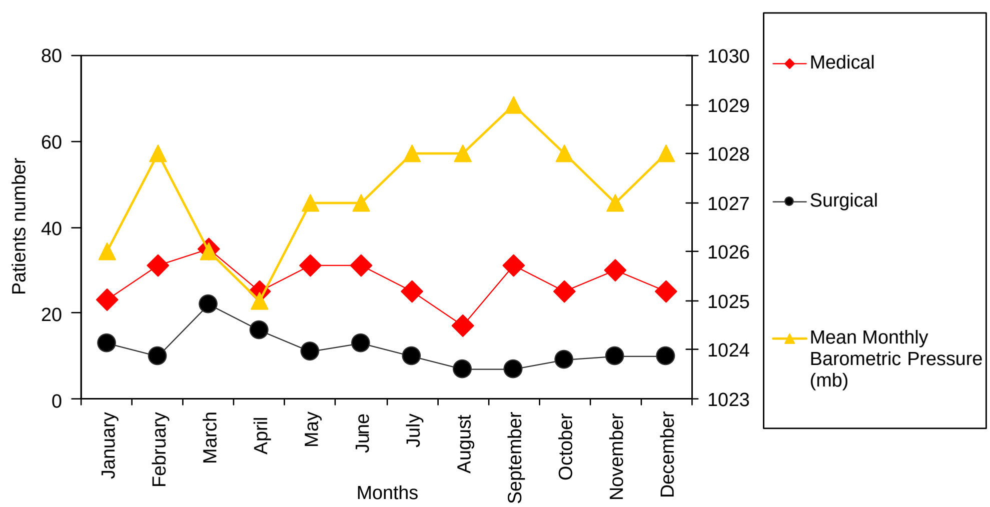

Figure 2 Seasonal variations in medical and surgical patients and weather's changes.

Table 2 Risk factors for PE and seasonal variations.

Risk factor	Patients number	Cold months (October–March)	Warm months (April–September)	P
	75	44(58.6%)	31(41.4%)	<0.05
DVT	28(37.3%)	13(29.5%)	15(48.3%)	<0.05
Cancer	11(14.6%)	6(13.6%)	5(16.1%)	ns
COPD	14(18.6%)	7(15.9%)	7(22.5%)	ns
Heart failure	22(29.3%)	16(36.3%)	6(19.3%)	<0.05
Immobility	44(58.6%)	23(52.2%)	21(67.7%)	<0.05
Fractures	5(6.6%)	2(4.5%)	3(9.6%)	<0.05
Recent surgery	5(6.6%)	2(4.5%)	3(9.6%)	<0.05
Leg extremity paralysis	12(16%)	6(13.6%)	6(19.3%)	ns

DVT = deep vein thrombosis; COPD = chronic obstructive pulmonary disease.

In agreement with the studies that observe a seasonal variation in occurrence[5,7,8] and mortality for PE[9–15] with a prevalence in autumn and/or winter, our findings, with the limitation of the retrospective studies, demonstrate a weak seasonal difference in the occurrence of PE in surgical patients and a strong seasonal difference for mortality of PE both in medical and in surgical patients, with a peak of cases in winter (January–March) and a trough in the warm months.

Moreover our study could add information about the role of some metereological parameters in seasonal variations of incidence and mortality of PE. When we consider all patients, mean monthly temperature and barometric pressure could have a role on seasonal distribution of PE, while when we consider separately medical and surgical patients, only barometric pressure seems to influence PE occurrence in surgical patients.

In disagreement with our results was a previous study of Stein et al. considering a period of about 20 years (1979–1999) where a difference was not found in seasonal incidence for PE in the entire United States (US) and in the single regions of US, clearly different for climatic conditions,[16] and another 5 years long (1996–2001) retrospective study conducted in Spain where, although a peak of occurrence of PE was noticed in autumn and winter, the higher mortality for PE was observed in spring.[17]

It was already demonstrated by Bull et al.[18] and Keatinge et al.[19] that haemostatic and haemorrherologic parameters could be increased with low temperature, providing a probable explanation for rapid increases in coronary and cerebral thrombosis in cold weather. Our study could suggest that the haemostatic factors are higher in the cold months in patients with PE although the commonest risk factors for venous thromboembolic disease were not more frequent in these months. This mayor status of blood agreeability probably could explain the more severe episodes of pulmonary embolism in winter, responsible for higher mortality and could add data to a previous study of Manfredini et al.[8] in which the winter peak of PE should be not influenced by underlying clinical conditions, suggesting that seasonality of PE could be due to endogenous variations.

Our study could be considered a pilot sudy: future prospective studies could establish the exact influence of weather on circannual variations of PE and haemostasis.

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References

1. Pell JP, Cobbe SM. Seasonal variations in coronary heart disease. *Q J Med* 1999;**92**:689–96.
2. Hong YC, Rha JH, Lee JT, Ha EH, Kwon HJ, Kim H. Ischemic stroke associated with decrease in temperature. *Epidemiology* 2003;**14**:473–8.
3. Passero S, Reale F, Ciacci G, Zei E. Differing temporal patterns of onset in subgroups of patients with intracerebral hemorrhage. *Stroke* 2000;**31**:1538–44.
4. The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart diseases, cerebrovascular disease, respiratory diseases, and all causes in warm and cold regions of Europe. *Lancet* 1997;**349**:1341–6.
5. Boulay F, Berthier F, Schoukroun G, Raybaut C, Gendreike Y, Blaive B. Seasonal variations in hospital admission for deep vein thrombosis and pulmonary embolism: analysis of discharged data. *Br Med J* 2001;**323**:601–2.
6. Gallerani M, Boari B, de Toma D, Salmi R, Manfredini R. Seasonal variation in the occurence of deep vein thrombosis. *Med Sci Monit* 2004;**10**:CR191–6.
7. Sharma GV, Frisbie JH, Tow DE, Yalla SV, Khuri SF. Circadian and circannual rhythm of nonfatal pulmonary embolism. *Am J Cardiol* 2001;**87**:922–4.
8. Manfredini R, Gallerani M, Boari B, Salmi R, Metha RH. Seasonal variation in onset of pulmonary embolism is indipendent of patients' underlyng risk comorbid conditions. *Clin Appl Thromb Hemost* 2004;**10**:39–43.
9. Allan TM, Douglas AS. Seasonal variation in deep vein thrombosis. Fatal pulmonary embolism is increased in both autumn and winter. *Br Med J* 1996;**312**:1227.
10. Silcocks P. Seasonal variation in numbers of necropsies with pulmonary embolism. *J Clin Pathol* 1994;**47**:478–9.
11. Manfredini R, Gallerani M, Salmi R, Zamboni P, Fersini C. Fatal pulmonary embolism in hospitalized patients: evidence for a winter peak. *J Int Med Res* 1994;**22**:85–9.
12. Green J, Edwards C. Seasonal variation in the necropsy incidence of massive pulmonary embolism. *J Clin Pathol* 1994;**47**:58–60.
13. Gallerani M, Manfredini R, Ricci L, Grandi E, Cappato R, Calo G, Pareschi PL, Fersini C. Sudden death from pulmonary thromboembolism: chronobiological aspects. *Eur Heart J* 1992;**13**:661–5.
14. Wroblewski BM, Siney PD, White R. Fatal pulmonary embolism after total hip arthroplasty. Seasonal variation. *Clin Orthop Relat Res* 1992;**276**:222–4.
15. Colantonio D, Casale R, Natali G, Pisqualetti P. Seasonal periodicity in fatal pulmonary thromboembolism. *Lancet* 1990;**335**:56–7.
16. Stein P, Kayali F, Olson RE. Analysis of occurrence of venous thromboembolic disease in the four seasons. *Am J Cardiol* 2004;**93**:511–3.
17. Montes Santiago J, Rey Garcia G, Mediero Dominguez A. Seasonal variations in morbidity and mortality for pulmonary embolism in Galicia, Spain. *Ann Med Interna* 2003;**20**:457–60.
18. Bull GM, Brozovic M, Chakrabarti R, Meade TW, Morton J, North WR, Stirling Y. Relationship of air temperature to various chemical, haematological, and haemostatic variables. *J Clin Pathol* 1979;**32**:16–20.
19. Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. *Br Med J* 1984;**289**:1405–8.

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