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Seasonal variation in the occurrence of venous thromboembolism: A report from the Korean Venous Thromboembolism Working Party

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ABSTRACT

There have been conflicting results on seasonal variation in the occurrence of venous thromboembolism (VTE). It also has never been studied in Asian population. To address these issues, we investigated seasonal changes of the incidence of VTE in Korean population using 1,495 patients with VTE between January 2001 and December 2010. VTE occurred most frequently in the winter and least frequently in the summer ($\chi 2=11.83$, $P=0.008$). In the subset analyses, the same trend was shown in the PE ± DVT group, the unprovoked VTE group, and the VTE without malignancy group. The monthly occurrence rate peaked in December and was at its lowest in July ($P=0.004$). In conclusion, our study provides evidence that there is an increased risk for VTE in Korean population in the winter season.

Introduction

In contrast to arterial thrombotic events, there have been conflicting results regarding venous thromboembolism (VTE) in terms of seasonal variation. Recently, a meta-analysis demonstrated a significantly increased incidence of VTE in the winter [relative risk (RR) for a VTE in winter = 1.143], and this significantly increased risk was most evident in January, with the RR for VTE in January being 1.194 [1]. Based on these results, the effect of weather on VTE has been regarded as a risk factor for VTE albeit a relatively weak one.

Even though the meta-analysis supplied confirmatory evidence for seasonal variation in VTE, it had two limitations. First, few Asian patients were enrolled in the study (approximately 3% of the patient population) [1]. In term of ethnic differences, the incidence of VTE in the Asian population has been generally found to be lower than in whites, possibly because of genetic mutations [2]. There is evidence that genetic mutations, particularly those for clotting factor V (factor V Leiden) and factor II G20210A, are highly prevalent in the Caucasian population but virtually absent in the Asian population [3,4]. Second, the meta-analysis did not include a subgroup analysis of unprovoked VTE. Dentali et al. pointed out that no study has provided data regarding seasonal variation in the incidence of unprovoked VTE. To address these issues, we investigated whether seasonal variation affected the incidence of VTE in Koreans. The primary aim of the present study was to determine if there was any seasonal variation in the occurrence of VTE in the Korean population, and the secondary aim

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was to evaluate if such seasonal variation may be influenced by age, gender, and VTE risk factors.

Patients and Methods

Study population

The study consisted of patients with VTE who were registered with the VTE Registry of the Korean VTE Working Party (KVTEWP) between January 2001 and December 2010. During this period, 11 participating centers consecutively enrolled Korean VTE patients. VTE was confirmed by venography or compression ultrasonography for deep vein thrombosis (DVT) and by ventilation-perfusion lung scan or computed tomography for pulmonary embolism (PE). VTE was defined as provoked if the patient was found to have any of the following risk factors: recent surgery (<3 months), recent trauma/fracture (<3 months), immobilization (>7 days), malignancy, stroke, severe medical disease, autoimmune disease, pregnancy, use of oral contraceptives, and inherited thrombophilia. If a patient did not have any of these risk factors, the VTE was classified as unprovoked. The study protocol was approved by the Institutional Review Board of each participating hospital.

Data collection

Data were recorded on a computer-based case report form at each participating hospital and the forms were submitted to a centralized co-ordinating center through a Korean DVT registry website (http://kdvt.chamc.co.kr). Patients' identities remained confidential as they were identified by unique numbers assigned by the study coordinating center. The data on the computer-based case report forms included the age, sex, date of diagnosis, type of VTE, risk factors, management, and follow up of the patients, and we analyzed these variables in our data analysis. The date of VTE diagnosis was categorized both into twelve 1-month intervals and four 3-month intervals (Spring: March 1 – May 31; Summer: June 1 – August 31; Autumn: September 1 – November 30; Winter: December 1 – February 28) to evaluate monthly variation and seasonal variation.

Statistical analysis

The distribution of VTE onset within the four seasons was tested for homogeneity in the total VTE population and the various subsets by the chi-square test for goodness of fit with Bonferroni's correction. The chronobiological analysis of seasonal variation in VTE occurrence was performed by applying a partial Fourier analysis to the time series data in a harmonic regression model with SAS software version 9.1.3 (SAS Institute Inc., Cary, NC). This model selects the harmonic, or the combination of harmonics, that best explain the variance of data. The percentage of the overall variability of the data about the arithmetic mean that is attributable to the fitted rhythmic function (cosine curve by the method of least squares) estimates the goodness of fit of the approximating model, and the F-test statistic is used to test the zero-amplitude null hypothesis (absence of periodicity). The parameters calculated for the overall fit were the midline estimated statistic of rhythm (MESOR; the rhythm-adjusted mean over the time analyzed), the amplitude (half the distance between the absolute maximum and minimum of the fitted curve), and the peak (time of occurrence of absolute maximum), and the 95% confidence interval for each of these parameters was also determined. Bonferroni's correction was applied to multiple tests in the subgroup analysis. We described number of cases after mean-centering to adjust yearly variation. The number of cases after mean-centering was calculated using the formula total cases of each month minus mean cases of each year. A *P* value <0.05 was considered significant.

Results

Baseline characteristics

A total of 1,495 cases of VTE were registered in the study period. The mean age of the patients was 60 (SD 16) years, and 43.2% were male. Of the VTE patients, 746 (49.9%) patients were diagnosed as having an isolated DVT, whereas 749 (50.1%) were diagnosed with PE with or without DVT. VTE was unprovoked in 412 (27.5%) patients and provoked in 1,083 (72.4%) patients. Among the provoked VTE cases, VTE was related to malignancy (n = 434), recent surgery (n = 292), immobilization (n = 231), trauma/fracture (n = 125), severe medical disease (n = 160), inherited thrombophilia (n = 89), stroke (n = 88), pregnancy/post-partum (n = 21), use of oral contraceptives (n = 12), and autoimmune disease (n = 8).

Seasonal distribution of venous thromboembolism

Of the 1,495 patients with VTE, the diagnosis was established in the spring in 392 patients (26.2%), in the summer in 317 patients (21.2%), in the autumn in 385 patients (25.7%), and in the winter in 401 patients (26.8%) (Table 1). VTE occurred most frequently in the winter and least frequently in the summer ($\chi2 = 11.83$, $P = 0.008$). In the subset analyses, the same trend was shown in the PE ± DVT group ($\chi2 = 13.63$, $P = 0.007$), symptomatic PE group ($\chi2 = 16.77$, $P = 0.002$), the unprovoked VTE group ($\chi2 = 17.80$, $P = 0.001$), and the VTE without malignancy group ($\chi2 = 12.53$, $P = 0.012$). Alternatively, the elderly (≥60 yr) group and the VTE with malignancy group had the most VTE occurrences in autumn.

Monthly distribution of venous thromboembolism

The monthly distribution of VTE is shown in Fig. 1. The monthly occurrence rate peaked in December and was at its lowest in July ($P = 0.004$) (Table 2). In addition, similar trends were found in subset analyses of men (peak in December, $P = 0.014$), the elderly group (peak in December, $P = 0.034$), the PE ± DVT group (peak in November, $P = 0.001$), symptomatic PE group (peak in November, $P = 0.001$), the

Table 1
Seasonal Variation of onset of venous thromboembolism: Conventional χ2 Statistics.

	Total	Spring	Summer	Autumn	Winter	χ2	*P* value
Total	1,495	392 (26.2%)	317 (21.2%)	385 (25.7%)	401 (26.8%)	11.8334	0.008
Gender*							
Men	646	168	134	168	176	6.5077	0.179
Women	849	224	183	217	225	5.5536	0.271
Age*							
<60 yr	639	160	142	151	186	6.7653	0.160
≥60 yr	856	232	175	234	215	10.4953	0.030
VTE type*							
DVT only	746	183	168	205	190	3.8016	0.567
Proximal DVT	671	162	153	182	174	2.9374	0.803
PE ± DVT	749	209	149	180	211	13.6328	0.007
Symptomatic PE	655	183	125	155	192	16.7740	0.002
VTE cause*							
Unprovoked	412	110 (7.3%)	83 (5.5%)	84 (5.6%)	135 (9.0%)	17.8058	0.001
Provoked	1,083	282 (18.9%)	234 (15.6%)	301 (20.1%)	266 (17.8%)	8.9187	0.061
Cancer*							
Yes	434	107	90	136	101	10.6636	0.027
No	1,061	285	227	249	300	12.5344	0.012

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.
* After Bonferroni's correction due to subgroup analysis.

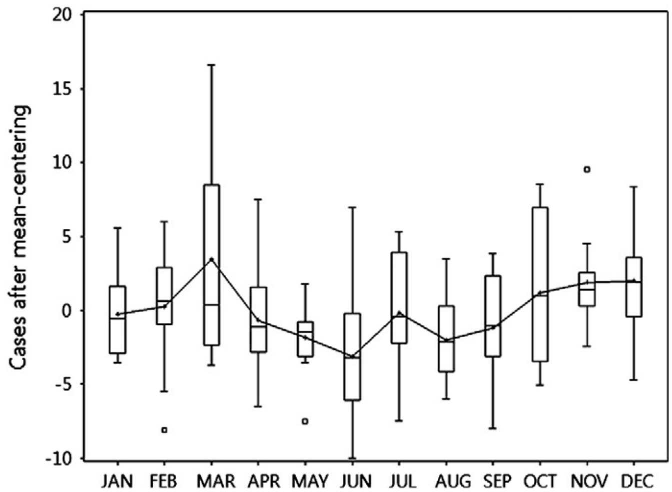

Fig. 1. Monthly distribution of venous thromboembolism. Results are expressed as cases after mean-centering with box-and-whisker plot. Results represent the monthly occurrence rate peaked in December (95% CI: November – January, $P=0.004$).

unprovoked VTE group (peak in November, $P=0.001$), and the VTE without malignancy group (peak in December, $P=0.001$).

Discussion

The weather of South Korea is characterized by four distinct seasons, spring, summer, autumn and winter, and the contrast between winter and summer is striking. Winter is bitterly cold, whereas summer is hot and humid. The transitional seasons, spring and autumn, are sunny and generally dry. Based on these environmental conditions, we investigated seasonal variations in the VTE Registry of 11 Korean teaching hospitals. Our study demonstrated a significant seasonal variation in VTE in Korean patients that was characterized by a peak in the winter and a nadir in the summer. This study represents the largest national epidemiologic study of seasonal variation in VTE in Asia. The results will provide a better insight into and a fuller understanding of VTE pathophysiology in Asia.

Many studies about the seasonal variation of VTE have been reported over the last three decades, but these studies are not always in agreement [5–11]. Differences in geographical area, ethnicity, and ambient temperature all could lead to contradictory results regarding seasonal variation in VTE. Of these studies, many were conducted by Italian groups. In a prospective study, Galleerani et al. reported significant seasonal variation in the occurrence of DVT with a peak in winter [7]. Recently, a study of the MASTER registry, which is composed of the data of patients from 25 Italian hospitals, found a similar seasonal pattern [10]. However, in contrast to the Italian studies, a large population-based study that used the National Hospital Discharge Survey of the United States did not show a seasonal pattern in the diagnosis of PE among hospitalized patients [11]. Several factors, such as the definition of season and the statistical analysis used, may partially explain the results, but study population, climate conditions, and geographic location might be the most likely explanations for these contradictory results. Korea and Italy have seasons with similar characteristics, and therefore our results should be more congruent with the results of the MASTER registry study than the study in the United States. Hence, our study demonstrating a significant seasonal variation in VTE was as expected. Interestingly, when our study population was stratified into subgroups, this trend was observed in unprovoked VTE patients, but the provoked group failed to show any seasonal variation. This is likely because seasonal variation is only a weak risk factor for VTE, and thus would only have a prominent role in the etiology of unprovoked VTE (i.e., when the stronger risk factors are not present) . Recently, Dentali et al. demonstrated confirmatory evidence for seasonal variation in VTE. According to a meta-analysis that included 17 studies, these results showed that winter was associated with a 14% risk for VTE [1]. Although the meta-analysis provided strong evidence for the seasonal variation of VTE, we should also consider ethnic differences in the occurrence of VTE. In this regard, our results might support the notion that the meta-analysis results can be generalized to all populations regardless of ethnic differences.

Although the mechanism of seasonal variation in VTE has not been elucidated, possible mechanisms have been reported that could explain this association. First, hemostatic alterations have been suggested as the most plausible explanation for seasonal variation in VTE. Keatinge et al. demonstrated that mild surface cooling increased the packed cell volume, the platelet count, and usually the mean platelet volume to produce a 15% increase in the fraction of plasma volume occupied by platelets [12]. In addition, Woodhouse et al. reported that the clotting activities of plasma fibrinogen and factor VII (FVIIc) were greater in the winter with the estimated winter-summer differences being 0.13 g/L for fibrinogen and 4.2% of the standard for FVIIc [13]. Although the seasonal differences in

Table 2
Monthly Variation of VTE: Chronobiological analysis.

	Total	MESOR ± SE; 95% CI	AMPL ± SE; 95% CI	Peak; 95% CI	Trough; 95% CI	PR (%)	*P* value
Total	1495	−0.02 ± 0.37, (−0.74, 0.71)	1.75 ± 0.52, (0.74, 2.76)	Dec, (Nov, Jan)	Jul, (Jun, Aug)	8.02	0.004
Gender*							
Men	646	−0.01 ± 0.20, (−0.46, 0.44)	0.91 ± 0.28, (0.28, 1.54)	Dec, (Nov, Jan)	Jul, (Jun, Aug)	7.91	0.014
Women	849	−0.02 ± 0.25, (−0.58, 0.54)	0.84 ± 0.35, (0.05, 1.63)	Dec, (Oct, Feb)	Jul, (May, Sep)	4.15	0.130
Age*							
<60 yr	639	−0.03 ± 0.19, (−0.46, 0.41)	0.68 ± 0.27, (0.08, 1.29)	Nov, (Oct, Jan)	Aug, (Jun, Sep)	4.98	0.088
≥60 yr	856	0.01 ± 0.28, (−0.62, 0.63)	1.15 ± 0.40, (0.26, 2.04)	Dec, (Nov, Feb)	Jul, (May, Aug)	6.51	0.034
VTE type*							
DVT only	746	0.00 ± 0.23, (−0.52, 0.52)	0.76 ± 0.33, (0.03, 1.49)	Jan, (Nov, Mar)	Jun, (Apr, Aug)	4.05	0.148
Proximal DVT	671	0 ± 0.21, (−0.47, 0.46)	0.63 ± 0.29, (−0.02, 1.29)	Jan, (Nov, Mar)	Jun, (Apr, Aug)	3.55	0.213
PE ± DVT	749	−0.05 ± 0.23, (−0.56, 0.47)	1.26 ± 0.32, (0.54, 1.98)	Nov, (Oct, Dec)	Aug, (Jul, Sep)	11.55	0.001
Symptomatic PE	655	−0.05 ± 0.22, (−0.54, 0.44)	1.3 ± 0.3, (0.62, 1.98)	Nov, (Oct, Dec)	Aug, (Jul, Sep)	13.48	0.001
VTE cause*							
Unprovoked	412	−0.04 ± 0.19, (−0.48, 0.39)	1.20 ± 0.27, (0.60, 1.81)	Nov, (Oct, Dec)	Aug, (Jul, Sep)	15.60	0.001
Provoked	1,083	0.00 ± 0.31, (−0.70, 0.71)	0.95 ± 0.44, (−0.05, 1.94)	Jan, (Nov, Mar)	Jun, (Apr, Aug)	3.35	0.223
Cancer*							
Yes	434	0.00 ± 0.21, (−0.47, 0.47)	0.67 ± 0.30, (0.01, 1.33)	Feb, (Jan, Apr)	May, (Mar, Jun)	3.94	0.214
No	1,061	−0.02 ± 0.28, (−0.65, 0.60)	1.57 ± 0.39, (0.69, 2.45)	Nov, (Oct, Dec)	Aug, (Jul, Sep)	10.98	0.001

MESOR, midline estimated statistic of rhythm; AMPL, 1-half the difference between the absolute maximum and minimum of the fitted curve; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.
* After Bonferroni's correction due to subgroup analysis.

fibrinogen concentration found in previous studies ranged from 0.13 g/L to 0.78 g/L, these studies confirmed that plasma fibrinogen did vary by season and had a winter peak and a summer nadir [13–15]. Interestingly, this variation correlated significantly with inflammatory makers such as C-reactive protein and α1-antichymotrypsin. In this respect, hemostatic alteration can be explained by the high incidence of acute respiratory infections in winter. However, this hypothesis has not been confirmed. Moreover, seasonal variation in fibrinogen did not show any correlation with other inflammatory markers, including white cell count, interleukin-6, and soluble P-selectin [14,16]. Second, limited physical activity during cold weather could explain the seasonal variation of VTE. As VTE is a multifactorial disease driven by environmental/acquired risk factors, cold weather might have more of an impact on a subject who already had other VTE risk factors (e.g., old age, malignancy, and inherited thrombophilia). In addition to hemostatic alterations and limited physical activity, many other factors, including air pollution, respiratory infection, and atmospheric pressure, have been proposed. However, the influences of these factors on VTE remain controversial [17–19].

This study has several potential limitations. First, we did not divide the seasons exactly by day but instead categorized the seasons by quarter of the year. Thus, there is a possibility that a few patients were categorized incorrectly. However, because the study duration is so broad and we categorized the season based on mean temperature by month, the likelihood that we misclassified the number of VTE events that would sufficiently interfere with our findings is very low. Second, we defined the occurrence of VTE based on the date of diagnosis, and there is the possibility that there was a substantial interval between the onset of symptoms and the date of diagnosis. However, because VTE was usually diagnosed at maximum 6–12 days after clinical presentation, the influence on our results is likely low. Third, since all participating hospitals are teaching hospitals, the cases were mostly hospitalized cases in our registry. Thus, the present data should be interpreted with caution because over 90% of VTE patients were hospitalized cases. Our results may not adapt to the seasonal variation of the outpatient cases.

In conclusion, our study provides evidence that there is an increased risk for VTE, particularly unprovoked VTE, in Korean population in the winter season.

Conflict of Interest Statement

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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