Unique meteorological characteristics in the upper gastrointestinal bleeding by different etiologies in Beijing Area, China

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To the Editor: Upper gastrointestinal bleeding (UGIB) is a hemorrhage from mouth to the ligament of Treitz. Climatic condition affects the occurrence of many diseases as the variation on meteorological factors may influence blood pressure[1] and neuroendocrine factors.[2] The relationship between UGIB and meteorological factors remains controversial.[2,3] Such inconsistent conclusions may be related to the study area, etiology of UGIB and time period division. Beijing is a typical temperate monsoon climate with distinct seasons. We retrospectively reviewed patients admitted to our hospital from 2014 to 2018, whose UGIB was caused by peptic ulcer disease (PUD) or esophagogastric varices (EGV). As non-steroidal anti-inflammatory drugs (NSAIDs) are widely used and can cause gastrointestinal injuries, we separated PUD into non-NSAIDs-related ulcer (NSAIDs has never been used or has been discontinued for more than three months) and NSAIDs-related ulcer. Solar term is a special method created in ancient China. This time period division summarizes the influence of meteorological factors. Thus, frequency of UGIB was evaluated based on seasons, months and solar terms [Supplementary Table 1, http://links.lww.com/CM9/A356] in our study. This retrospective study was reviewed and approved by the Medical Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (No.2018-sci-200).

Statistical analyses were performed using R (3.6.0). χ^2 test and *t* test were used. Circular distribution test was applied to investigate UGIB occurrence in solar terms. $r = \sqrt{\left[\frac{\sum f_i \cos(\alpha_i)}{n}\right]^2 + \left[\frac{\sum f_i \sin(\alpha_i)}{n}\right]^2}$, $Z = nr^2$, $s = \frac{180^\circ}{n}\sqrt{-2\ln r}$ (f_i: cases of UGIB in i^{th} solar term, n: total cases of UGIB, α_i: angle corresponding to i^{th} solar term, r: angle dispersion index, Z: Rayleigh's Z [test statistic], s: circular standard deviation). $Z \geq Z_{0.05}$ indicates $\overline{\alpha}$ has a statistical meaning. Correlation between UGIB occurrence and meteorological factors were analyzed with Spearman correlation analysis and generalized additive models (GAMs): $log[E(Y_t|X_t)] = \beta_0 + \sum_{i=1}^{t} S_i(X_{t,i})$ (Y: UGIB occurrence, X: meteorological factors, s_i: a smooth, possibly non-linear, univariate function, t: UGIB onset time). $P < 0.05$ was statistically significant.

Six hundred and sixty-four patients (515 [77.56%] men and 149 [22.44%] women) who had UGIB caused by non-NSAIDs-related peptic ulcer (non-NSAIDs group, $n = 345$), NSAIDs-related peptic ulcer (NSAIDs group, $n = 161$) or EGV (EGV group, $n = 158$) were enrolled in the study. Diagnosis was confirmed by endoscopy and history of medication [Supplementary Figure 1, http://links.lww.com/CM9/A356]. We clarified the stability of meteorological factors from 2014 to 2018. Meteorological factors included daily average temperature [Figure 1A], atmosphere pressure, relative humidity, wind speed and daily temperature range [Supplementary Figure 2, http://links.lww.com/CM9/A356]. Meteorological factors had no significant changes in 5 years ($P > 0.05$). We could use the 5-year data in our study.

Seasons were divided as spring (March to May), summer (June to August), autumn (September to November) and winter (December to February). Significant seasonal variations were shown in non-NSAIDs group ($P = 0.014$), but not in NSAIDs and EGV groups ($P = 0.484$ and $P = 0.065$, respectively) [Figure 1B–D, Supplementary Table 2, http://links.lww.com/CM9/A356]. When the incidence was analyzed in 12 months, significant difference was found in non-NSAIDs group ($P = 0.004$). Both NSAIDs and EGV groups showed no significant variations ($P = 0.254$ and $P = 0.054$, respectively) [Figure 1E, Supplementary Table 3, http://links.lww.com/CM9/A356].

The UGIB cases in 24 solar terms during the 5-year period are shown in Figure 1F. Significant difference was found in non-NSAIDs and EGV groups ($P = 0.013$ and $P = 0.008$,

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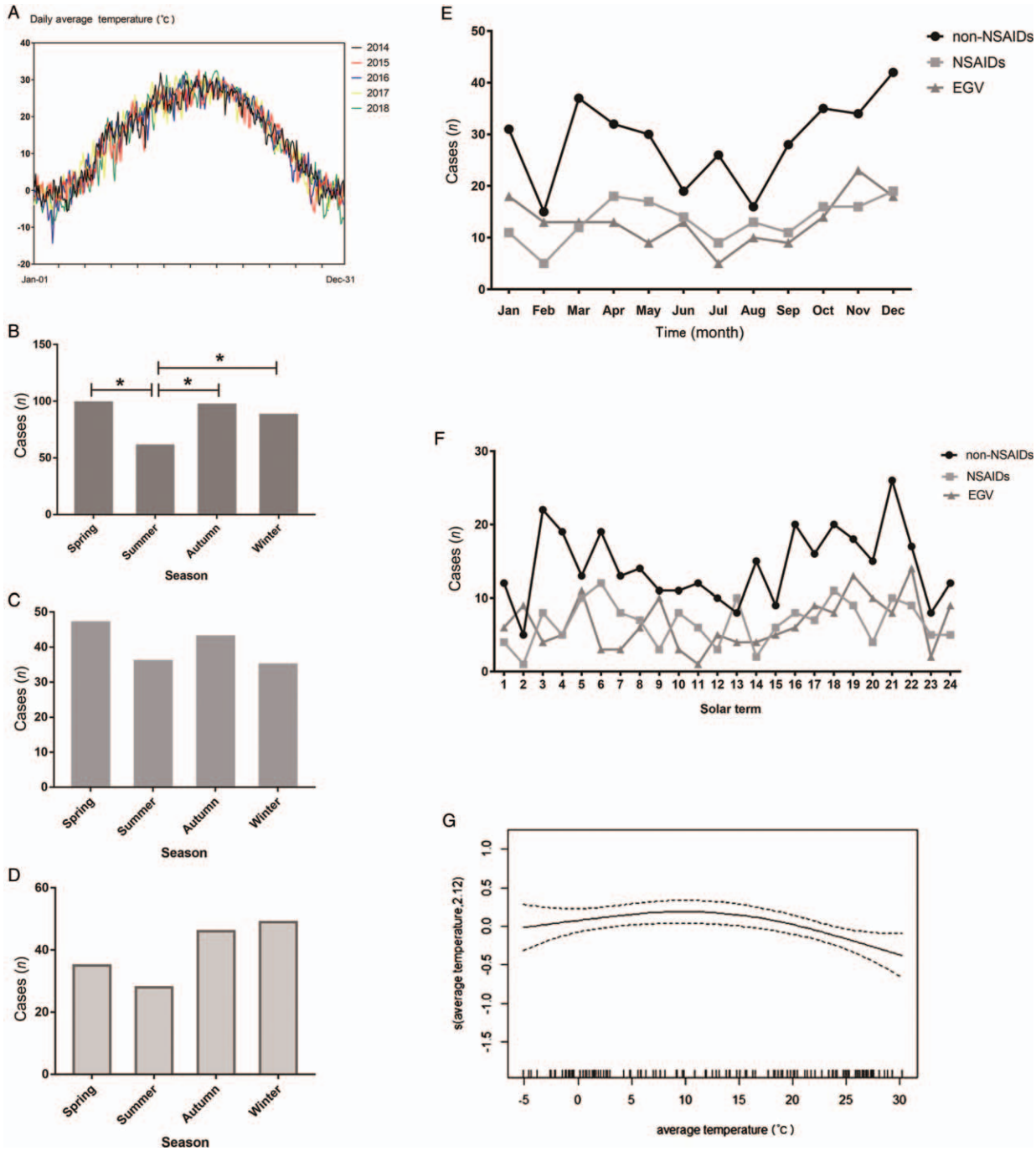

Figure 1: Daily data of average temperature from 2014 to 2018 (A). Seasonal variation in UGIB incidence caused by non-NSAIDs-related ulcer (B), NSAIDs-related ulcer (C), and gastroesophageal varices (D). UGIB incidence in 12 months (E) and 24 solar terms (F). Generalized additive model for non-NSAIDs-related ulcer bleeding and meteorological factors (G). NSAIDs: Non-steroidal anti-inflammatory drugs; EGV: Esophagogastric varices. $^{*}P < 0.05$.

respectively). Insignificant variance was found in the NSAIDs group ($P = 0.142$) [Supplementary Table 4, http://links.lww.com/CM9/A356]. To determine the specific onset pattern, circular distribution analysis was performed [Supplementary Table 5, http://links.lww.com/CM9/A356]. EGV group showed central trend on case occurrence ($Z = 6.64, Z > Z_{0.05}$). The peak period was from the Great Heat last year to the Spring Equinox this year. No central trend was found in non-NSAIDs group ($Z = 2.87$, $Z < Z_{0.05}$). Reviewing the incidence of each solar term in Figure 1F, the occurrence of non-NSAIDs-related peptic ulcer bleeding peaked in the Great Snow and the Waking of Insects.

Spearman correlation analysis showed the relationship between UGIB occurrence and single meteorological factor. Solar term average of the above-mentioned meteorological factors were included. The onset of EGV

bleeding was associated with temperature ($r_s = -0.442$, $P = 0.031$) and atmospheric pressure ($r_s = 0.490$, $P = 0.015$) [Supplementary Table 6, http://links.lww.com/CM9/A356]. Actual environment is influenced by multiple meteorological factors which interact with each other. To determine the most influential factors, we used GAMs, which allowed non-linear relations between the response variable and each explanatory variable, and added interaction between variables to further analyze the data. The optimal model, which had the minimum AIC value, consisted of time and average temperature. Non-NSAIDs-related peptic ulcer bleeding had peak onset when the average temperature reached 10°C, then turned into a descending trend when temperature got higher [Figure 1G]. As for EGV bleeding, the model with the minimum AIC for EGV bleeding contained average temperature and relative humidity. When the average relative humidity of solar term was constant, the incidence increased by 3% when the average temperature decreased by 1°C, and when the average temperature was constant, the average relative humidity increased by 1%, the incidence increased by 1.3%. The incidence of NSAIDs group showed no correlations with meteorological factors, so further analysis of the GAMs was not performed.

In this study, UGIB by different etiologies showed different onset rhythms. Episodes of non-NSAIDs-related peptic ulcer bleeding showed seasonal variations with the lowest frequency in summer, and a peak onset in December among 12 months. NSAIDs-related peptic ulcer bleeding, however, showed no significant variations among seasons and month. The occurrence of PUD is related to the imbalance between invasion and defense factors. In cold season, the thickness of gastric mucus became thinner, the expression of heat shock protein (HSP)70 decreased, and gastric acid increased.[4] The change of gastric mucosal function affects the occurrence of PUD. As PUDs are related to season and climate, UGIB caused by PUD may also show the same trend. NSAIDs can cause gastrointestinal injuries through sustained local and systemic effects. The long-term effect of drugs may conceal the influence of meteorological factors. Thus, clinicians should pay attention to PUD and timely treatment of PUD can avoid UGIB, especially that caused by non-NSAIDs-related ulcer. *H. pylori (HP)* is an important cause of PUD.[5] However, most patients enrolled in this study were from Department of Emergency, and were lack of *HP* test results. Further studies are needed to clarify the effect of *HP*.

Cold exposure is likely to increase blood pressure and cardiac output, and lead to peripheral vasoconstriction, resulting in an increase in portal tension and portal venous flow.[2] The onset of EGV bleeding showed a seasonal pattern in previous studies.[3] However, we came to the opposite outcome. Seasons and months cannot reflect the climatic characteristics of different regions accurately. So we need a more appropriate divisional system to describe the influence of meteorological factors. Solar terms are spaced 15° apart along the ecliptic, and reflect the changes in climate and natural phenomena, suggest the climate and disease pathogenesis. Our study showed the presentation of non-NSAIDs-related peptic ulcer bleeding had no central trend, but with peak onset at the Great Snow and the Waking of Insects. The onset of EGV bleeding showed no seasonal pattern, but it showed a central trend with a peak period from the Great Heat last year to the Spring Equinox this year. Fast changes of meteorological factors can be seen in these terms, which may lead to frequent changes in neuroendocrine factors. We further analyzed the relationship between UGIB onset and meteorological factors. Peak onset of UGIB caused by non-NSAIDs-related peptic ulcer can be seen when the solar term average temperature reached 10°C. For EGV bleeding, the incidence was not only associated with temperature, but also with relative humidity, but this possible mechanism needs further study. Above all, solar terms may play a role in the incidence of UGIB.

In conclusion, UGIB caused by different etiologies has various onset regularities. Determining the correlation between UGIB and meteorological factors can aid in improving prevention and therapeutic strategies.

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Conflicts of interest

None.

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