Seasonal Variation in Critical Limb Ischemia Requiring Endovascular Therapy: An Analysis of a Multicenter Database of Japanese Patients with Critical Limb Ischemia Undergoing Endovascular Therapy

Mitsuyoshi Takahara1, Osamu Iida2, Yoshimitsu Soga3, Keisuke Hirano4, Terutoshi Yamaoka5, Daizo Kawasaki6, Kenji Suzuki7, Nobuhiro Suematsu8, Yoshiaki Shintani9, Yusuke Miyashita10, Hideaki Kaneto1 and Iichiro Shimomura1

1Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Suita, Japan
2Cardiovascular Center, Kansai Rosai Hospital, Amagasaki, Japan
3Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan
4Department of Cardiology, Saiseikai Yokohama City Eastern Hospital, Yokohama, Japan
5Department of Vascular Surgery, Matsuyama Red Cross Hospital, Matsuyama, Japan
6Cardiovascular Division, Hyogo College of Medicine, Nishinomiya, Japan
7Department of Cardiology, Sendai Kosei Hospital, Sendai, Japan
8Department of Cardiology, Fukuoka Red Cross Hospital, Fukuoka, Japan
9Department of Cardiology, Shin Koga Hospital, Kurume, Japan
10Department of Cardiovascular Medicine, Shinshu University Hospital, Matsumoto, Japan

Aim: We investigated whether any seasonal variation is observed in the incidence, severity and prognosis of critical limb ischemia (CLI) requiring endovascular therapy.

Methods: We analyzed a multicenter database of 1,568 consecutive CLI cases undergoing primary endovascular therapy for infrainguinal lesions between July 2004 and June 2011. The monthly incidence was assessed according to the cumulative number of cases in each month, using a simple moving average. The data were fitted to a nonlinear regression model with a cosine function. The monthly proportion of cases in each Rutherford classification among the overall CLI population was assessed using a multinomial logistic regression model. The monthly risk of major amputation was evaluated using a Cox proportional hazard regression model.

Results: Significant seasonal variation was observed in the incidence of CLI ($p<0.01$). It was higher in the period from winter to spring, with a peak in March, and lower in the period from summer to autumn, with a trough in September; the fold difference between the peak and trough was 2.2. The seasonal variation was more markedly observed in the cases with a more severe Rutherford class. The proportion of cases in each Rutherford classification among the overall CLI population also exhibited significant seasonal variation ($p<0.01$). In addition, the risk of major amputation demonstrated significant seasonal variation ($p=0.03$); however, the statistical significance was lost following adjustment for the Rutherford classification ($p=0.10$).

Conclusions: Seasonal variation is observed in the incidence and severity of CLI. The seasonality of the limb prognosis is likely explained by that of the CLI severity.


Key words: Seasonal variation, Critical limb ischemia, Rutherford classification

Address for correspondence: Mitsuyoshi Takahara, Department of Metabolic Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: takahara@endmet.med.osaka-u.ac.jp
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Introduction

Critical limb ischemia (CLI) represents the most advanced stage of peripheral arterial disease (PAD)
and is characterized by chronic ischemic rest pain or tissue loss, including either ulcers or gangrene\(^3\). CLI patients have an extremely poor prognosis, and urgent revascularization is often indicated in clinical practice\(^3\).

A number of previous studies have investigated the seasonal variation of the incidence of other cardiovascular diseases, such as ischemic heart disease and stroke\(^2\)\(^-\)\(^7\). In addition, some reports have demonstrated that the severity and prognosis of these diseases also vary with the season\(^3\)\(^,\)\(^8\)\(^,\)\(^9\). However, the seasonal variation of CLI remains unknown.

**Aim**

The aim of the current study was to examine whether seasonal variation is present in the incidence, severity and prognosis of CLI requiring endovascular therapy.

**Methods**

We evaluated a multicenter database of 1,568 consecutive cases with CLI undergoing primary endovascular therapy for infrarigual arterial lesions at nine participating cardiovascular and vascular centers in Japan (see Footnote A) between July 2004 and June 2011. All patients with chronic ischemic rest pain and/or foot ulcers or gangrene were evaluated for limb ischemia using angiography. The diagnosis and management of CLI were compliant with the Transatlantic Inter-Society Consensus (TASC)\(^10\) or its revised version, the TASC II\(^1\). Once the patients were diagnosed with CLI, endovascular therapy was employed as the first-line procedure for revascularization according to the recommendations in the TASC (II). The indications for endovascular therapy were judged according to consensus among vascular specialists, including vascular surgeons.

The monthly incidence of CLI was assessed according to the cumulative number of cases in each month, which was corrected for a standard month of 30 days. A simple moving average, calculated by averaging the number of cases in the month of interest, the previous month and the following month, was used to smooth random variation. In addition, a mathematical model of seasonality was developed based on the cosine function, a simple curve of cyclic periodicity, using the nonlinear least squares method\(^5\) (see Footnote B). We also divided the study population according to clinical severity, based on the Rutherford classification, and assessed the respective monthly incidence in each subgroup.

We subsequently investigated whether the severity of CLI varies with the season. The seasonality was assessed using the cosine function in a multinomial logistic regression model whose dependent variable was the Rutherford classification. With respect to the regression analysis, the cosine function with an unknown horizontal shift was transformed into the sum of the sine and cosine functions with no horizontal shift, and the regression coefficients were estimated\(^11\) (see Footnote B).

Finally, we examined whether the prognosis of CLI varies with the season. The prognostic outcome measure was a major amputation within six months. A Cox hazard regression analysis was performed. The seasonality was again assessed using the sum of the sine and cosine functions (see Footnote B).

In the current study, we additionally performed a linear regression analysis to evaluate whether any metabolic parameters in the study population exhibit seasonal variation using the sum of the sine and cosine functions (see Footnote B). Note that these parameters had some missing data. We also investigated whether the city size, assessed according to the log-transformed city population, affects the amplitude of the seasonal variation (see Footnote C). The data regarding the city population were obtained from the national population census\(^12\).

The data are presented as the mean and standard deviation (SD) for continuous variables or as percentages for discrete variables, if not otherwise specified. A \(p\) value of \(<0.05\) was considered to be statistically significant, and 95% confidence intervals (CIs) are reported when necessary. All statistical analyses were performed using the SPSS Statistics Version 19 software package (SPSS Inc.).

**Footnote A**

The participating centers were: Cardiovascular center, Kansai Rosai Hospital, Amagasaki; Department of Cardiology, Kokura Memorial Hospital, Kitakyushu; Department of Cardiology, Saiseikai Yokohama City Eastern Hospital, Yokohama; Department of Cardiology, Shin Koga Hospital, Kurume; Department of Cardiovascular Medicine, Shinshu University Hospital, Matsumoto; Department of Cardiology, Sendai Kosei Hospital, Sendai; Cardiovascular Division, Hyogo College of Medicine, Nishinomiya; Department of Cardiology, Fukuoka Red Cross Hospital, Fukuoka; Department of Vascular Surgery, Matsuyama Red Cross Hospital, Matsuyama.

**Footnote B**

The seasonality of the incidence of CLI was
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Sex: Male / Female</th>
<th>976 (62%) / 592 (38%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1097 (70%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1225 (78%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>650 (41%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>352 (22%)</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>799 (51%)</td>
</tr>
<tr>
<td>Rutherford classification</td>
<td></td>
</tr>
<tr>
<td>Class 4</td>
<td>420 (27%)</td>
</tr>
<tr>
<td>Class 5</td>
<td>886 (56%)</td>
</tr>
<tr>
<td>Class 6</td>
<td>262 (17%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
</tr>
<tr>
<td>Femoropopliteal lesions</td>
<td>866 (55%)</td>
</tr>
<tr>
<td>Isolated infrapopliteal lesions</td>
<td>702 (45%)</td>
</tr>
</tbody>
</table>

The data are presented as the mean ± SD or numbers (percentages).

Table 2. Seasonal variation in metabolic parameters

<table>
<thead>
<tr>
<th>No of data available</th>
<th>Distribution</th>
<th>Seasonal variation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>$R^2$ ($p$ value)</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>1484</td>
<td>21.5 ± 3.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>298</td>
<td>143 ± 27</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>1414</td>
<td>6.8 ± 1.5</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>1274</td>
<td>47 ± 18</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mg/dl)</td>
<td>1231</td>
<td>121 ± 38</td>
</tr>
</tbody>
</table>

The seasonal variation in metabolic parameters was assessed using the linear regression models in which the sum of the sine and cosine functions was entered (see Footnote B). The hemoglobin A1c levels were converted to National Glycohemoglobin Standardization Program equivalent values using the conversion equation reported by the Japan Diabetes Society. HDL, high-density lipoprotein.

Fig. 1. Monthly incidence of cases of CLI requiring endovascular therapy

The monthly incidence of cases of CLI requiring endovascular therapy per the annual number of cases was calculated using the simple moving average method (bar graph). Significant monthly variation was observed ($p<0.01$). The error bars represent 95% CIs. The solid line represents the cosine function estimated according to the nonlinear regression model, while the dotted line represents the annual average.
Therefore, both the amplitude $B$ and the month of the peak $T$ were derived from $\beta_1$ and $\beta_2$. 

**Footnote C**

To assess the influence of the city size on the seasonality of the incidence of CLI, we developed the following nonlinear regression model and estimated the regression parameters according to the least squares method: $Y = \alpha + \gamma \times C + \beta \times \cos(2\pi(t-t_0)/12)$, where the dependent variable $Y$ is the estimated monthly prevalence per annual cases, $t$ is the month, $C$ is the decadic logarithm of the city population and the other variables are the regression parameters to be estimated. A value of $\gamma$ that is significantly larger or smaller than 0 indicates that a ten-fold increase in the city population is associated with $\gamma/100$ percent increase or $-\gamma/100$ percent decrease, respectively, in the amplitude of the seasonality.

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**Fig. 2.** Rutherford classification and seasonal variation

A to C: The monthly incidences of cases of Rutherford class 4 (A), class 5 (B) and class 6 (C) per the annual number of cases were calculated using the simple moving average method (bar graph). Significant monthly variation was observed in every Rutherford classification (all $p<0.01$). The error bars represent 95% CIs. The solid line represents the cosine function estimated according to the nonlinear regression model, while the dotted line represents the annual average. D: The monthly proportions of cases in Rutherford class 4 (light gray), class 5 (dark gray) and class 6 (black) among the overall CLI population were analyzed using a multinomial logistic regression model. Significant seasonal variation was observed ($p<0.01$).
Rutherford Classification and Seasonal Variation

Fig. 2A to C show the respective monthly incidence in each Rutherford class. Although every Rutherford class exhibited seasonal variation and was well fitted to a cosine function ($R^2 = 0.89, 0.95, \text{ and } 0.96$ in Rutherford classes 4, 5 and 6; all $p<0.01$), the amplitude differed among Rutherford classes. The fold difference in the monthly number between the peak and trough was calculated to be 1.7 (95% CI: 1.5 to 2.0) in Rutherford class 4, 2.2 (95% CI: 1.9 to 2.6) in Rutherford class 5 and 3.8 (95% CI: 2.9 to 5.2) in Rutherford class 6, thus indicating that the more severe the Rutherford class the more marked the seasonality. A subsequent multinomial logistic regression analysis showed that the proportion of cases in each Rutherford class among the overall CLI population exhibited statistically significant seasonal variation ($p<0.01$) (Fig. 2D). The seasonal variation was not influenced by the city size ($p=0.84$).

CLI Prognosis and Seasonal Variation

As shown in Fig. 3, the risk of major amputation demonstrated significant seasonal variation ($p=0.03$). The unadjusted hazard ratio of the peak relative to the trough was calculated to be 1.7 (95% CI: 1.5 to 2.0) in Rutherford class 4, 2.2 (95% CI: 1.9 to 2.6) in Rutherford class 5 and 3.8 (95% CI: 2.9 to 5.2) in Rutherford class 6, thus indicating that the more severe the Rutherford class the more marked the seasonality. A subsequent multinomial logistic regression analysis showed that the proportion of cases in each Rutherford class among the overall CLI population exhibited statistically significant seasonal variation ($p<0.01$) (Fig. 2D). The seasonal variation was not influenced by the city size ($p=0.84$).

Results

The baseline characteristics of the cases are shown in Table 1. They were $73 \pm 10$ years of age, and 62% were male. A total of 420 cases (27%) were categorized as Rutherford class 4 (i.e., ischemic rest pain without tissue loss), while 886 (56%) and 262 (17%) were categorized as Rutherford class 5 (minor tissue loss) and 6 (major tissue loss), respectively. A total of 113 cases underwent major amputation within six months. No significant seasonal variation in metabolic parameters was observed in the current population (Table 2).

CLI Incidence and Seasonal Variation

The monthly incidence of CLI is shown in Fig. 1. Seasonal variation was observed, with a peak in March and a trough in September; 12% (95% CI: 10% to 13%) of the annual cases were observed in March, while 5% (95% CI: 4% to 6%) were observed in September. The nonlinear regression analysis showed that the data were well fitted to the cosine function with annual periodicity ($R^2 = 0.97, p<0.01$). The fold difference between the peak and trough reached 2.2 (95% CI: 2.0 to 2.5). No significant influence of city size on the seasonality of the severity and prognosis of CLI by assessing the interaction effects between the log-transformed city population and the seasonality.

CLI Prognosis and Seasonal Variation

The monthly risk of major amputation was analyzed using a Cox proportional hazard regression model. The data represent the unadjusted hazard ratios relative to the annual average risk with 95% CIs.
impairs the peripheral microvascular blood flow\textsuperscript{14, 15}).

studies reported that a cold environment more severely
deteriorate limb ischemia. Indeed, a few previous
influence of ambient temperature on the progression
namic mechanism. One possible explanation is the
Cold stimuli would cause vasoconstriction
in cases with more severe CLI (Fig. 2A to C), and the
proportion of cases in each Rutherford class among
the overall CLI population also varied across the sea-
sons (Fig. 2D). These findings indicate that the sea-
sonal variation of CLI is considerable and cannot be
ignored in clinical practice.

The current study demonstrated that there was
significant seasonal variation in the incidence of CLI
(Fig. 1). The fold difference between the peak and
trough reached as high as 2.2. Furthermore, seasonal
variation was more markedly observed among the
cases with more severe CLI (Fig. 2A to C), and the
proportion of cases in each Rutherford class among
the overall CLI population varied across the seas-
ses (Fig. 2D). These findings indicate that the sea-
sonal variation of CLI is considerable and cannot be
ignored in clinical practice.

The underlying pathogenesis of the observed sea-
sonal variation remains unknown. Given that similar
patterns of seasonality are observed in other cardiovas-
cular diseases\textsuperscript{2-9)}, there may be a common hemody-
namic mechanism. One possible explanation is the
influence of ambient temperature on the progression
of CLI. Cold stimuli would cause vasoconstriction
and deteriorate limb ischemia. Indeed, a few previous
studies reported that a cold environment more severely
impairs the peripheral microvascular blood flow\textsuperscript{14, 15}).
However, there remain questions regarding the influ-
ence of cold temperatures on the peripheral macrovas-
cular blood flow\textsuperscript{16}). Future studies are needed to inves-
tigate the underlying pathogeneses.

Other possible explanations include the influence
of metabolic profiles and social factors. It has been
generally reported that metabolic profiles worsen in
winter, which may increase the risk of cardiovascular
disease\textsuperscript{17}). In addition, metabolic abnormalities are
substantially associated with lifestyle and social fac-
tors, whose trends vary according to the region, es-
specially between large cities and other areas. These fac-
tors may therefore affect the seasonality of cardiovas-
cular diseases. However, in the current study popula-
tion, no significant seasonal variation was observed in
metabolic parameters. In addition, the city size did
not significantly influence the seasonality of CLI.
These findings indicate that the seasonality of CLI
might be unrelated to metabolic profiles and regional
backgrounds in Japan.

In addition to demonstrating the seasonality of
the incidence and severity of CLI, the current study
showed that the risk of major amputation exhibited
significant seasonal variation (Fig. 3). However, this
seasonal variation lost statistical significance when
adjusted for the Rutherford classification. These find-
ings indicate that the seasonal variation of the progno-
sis of CLI would be explained by that of the severity
of CLI.

There are several limitations to the current study.
First, the current study was based on a database of
CLI patients undergoing primary endovascular ther-
apy. It remains to be revealed whether a similar pat-
tern of seasonal variation is observed in CLI patients
undergoing open bypass surgery. Second, the current
study recruited only Japanese patients. Another clin-
ic point of interest is whether there are ethnic differ-
ences in the seasonal variation of CLI. Third, the cur-
tent database was imperfect with respect to metabolic
profiles, with some missing data. In addition, we did
not take into consideration any medications that
might substantially influence the patients’ metabolic
profiles. These imperfections may result in nonsignifi-
cance of the metabolic seasonality. Fourth, the assess-
ment of geographic characteristics might be insuffi-
cient. We used the city size, assessed according to the
population of the city in which revascularization was
performed. However, this city was not always the same
city in which the patient lived. Furthermore, the city
population itself may not appropriately reflect the
characteristics of the geographic region. Future
detailed studies are therefore needed to validate the
current findings.

Conclusion

Seasonal variation was observed in the incidence
and severity of CLI requiring endovascular therapy.
The apparent seasonality of the limb prognosis was
likely explained by that of the severity of CLI. Future
studies are needed to investigate the underlying patho-
genesis of the seasonal variation in the incidence and
severity of CLI.

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**Notice**

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**Conflicts of Interest**

None.

**References**