

Lymphedema as a Meteoropathic Disease Based on a Retrospective Study in a Single Institute: a Preliminary Report

Motomu Suzuki

Yokohama City University

Koukichi Koukichi

Yokohama City University

Taro Mikami (✉ zeong3@mac.com)

Chigasaki Municipal Hospital

Yuichiro Yabuki

Yokohama City University

Saori Asano

Yokohama City University

Shinya Kitayama

Yokohama City University

Shintaro Kagimoto

Yokohama City University

Toshinori Iwai

Yokohama City University

Satomi Sugiyama

Yokohama City University

Kazunori Yasumura

Kanagawa Children's Medical Center

Jiro Maegawa

Yokohama City University

Research Article

Keywords: Lymphedema, meteoropathic disease, single institute, preliminary report, cellulitis

Posted Date: January 5th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1218610/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Since cellulitis is one of the most important factors for the prognosis of lymphedema, the prevention and prediction of cellulitis are considered to be critical in controlling lymphedema. We hypothesized that patients with lymphedema might show meteoropathy, as abdominal aortic aneurysm ruptures are considered to be influenced by climatic conditions, and the lymphatic system is one of the circulation systems. Thus, we aimed to determine if the onset of cellulitis in limbs affected by lymphedema is related to climatic conditions. We reviewed the clinical records of patients with lymphedema admitted for cellulitis at our institute between January 2007 and December 2017. We identified 40 patients, 25 of whom lived in the same area. We examined the association between the number of patient admissions according to season and meteorological data obtained from the Japan Meteorological Agency database. Thirteen of 25 patients were admitted in summer, whereas only one patient was admitted in winter. Both higher temperature and lower atmospheric pressure around the day of admission were associated with the occurrence of cellulitis. Lymphedema may be regarded as a meteoropathic disease, as climatic conditions were shown to be associated with cellulitis in limbs affected by lymphedema.

Introduction

Most of the activities of living organisms are considerably affected by changes in the climate. Global surface temperatures have been rising for the past 50 years. From 2007 to 2017, the global temperatures increased by 0.26 °C, while the levels of atmospheric carbon dioxide (CO₂), one of the greenhouse gases, increased from 382.7 ppm to 407.5 ppm (<https://climate.nasa.gov/vitalsigns/global-temperature/>).

Cellulitis is well known as one of the most important factors for the prognosis of both primary and secondary lymphedema^[1]. Patients with lymphedema with cellulitis often relapse, leading to subcutaneous tissue damage, including lymph vessel damage, followed by scar formation and fibrosis, which accelerate the deterioration in lymphedema. Accordingly, the prevention and prediction of cellulitis are both considered important in controlling lymphedema^[2].

Furthermore, disorders, such as migraine, pain associated with past trauma, and some infectious diseases are considered to be influenced by climatic conditions^[3-5]. Meteoropathy refers to diseases with an occurrence deeply associated with meteorological conditions^[3, 4]. Even abdominal aortic aneurysm rupture, a severely critical disease, has been reported to be related to changes in atmospheric pressure^[6, 7]. We hypothesized that lymphedema might also show meteoropathy, as the lymphatic system is one of the circulation systems. In the present study, we reviewed the admission records of patients in our institute to determine if the onset of cellulitis in limbs affected by lymphedema is related to climatic conditions, such as atmospheric pressure and temperature.

Methods

The participants comprised patients who were admitted to the Department of Plastic and Reconstructive Surgery at Yokohama City University Hospital from January 2007 to December 2017 for cellulitis in a limb affected by lymphedema. The computerized medical record system was used to identify candidates diagnosed with “lymphedema,” whose reason for admission was cellulitis. Among the identified patients, we selected the largest group of patients who indicated the same city (Yokohama City) as their place of residence on the day of admission for a detailed analysis in order to control for geographical conditions and climate factors, such as temperature and atmospheric pressure. The admission date was classified into the following periods based on the four seasons: spring (March to May), summer (June to August), autumn (September to November), and winter (December to February)^[6, 7].

Meteorological data were obtained from the Japan Meteorological Agency database (<https://www.data.jma.go.jp/obd/stats/etrn/index.php>). The 15-day centralized moving averages (CMAs) of the temperature and atmospheric pressure were calculated from 15 days before admission to the day before admission (Supplementary Fig. S1). The data were compiled using Microsoft 365 Excel (Microsoft Japan Co., Ltd., Tokyo, Japan).

Statistical analysis

Data normality was evaluated using the Shapiro-Wilk test. For non-normally distributed data, and in cases in which the number of samples did not exceed 5, the Kruskal-Wallis test was used for statistical analysis. For normally distributed data, the t-test was used. Statistical analysis was performed using R for Windows (x64 3.1.3, <https://cran.r-project.org/bin/windows/base/>). A *p*-value <0.05 was considered to be statistically significant.

Ethical considerations

This study was approved by the ethics board of Yokohama City University Hospital (Research No. B180400056) and conformed to the guidelines stipulated in the 2013 revision of the Declaration of Helsinki. Informed consent was obtained from the patients through an opt-out approach on the website of Yokohama City University Hospital; none of the patients rejected participation.

Results

In total, 40 patients diagnosed with lymphedema were admitted to our hospital during the 11-year study period; among these, 25 lived in the same city (Yokohama City). None of the patients were admitted two or more times during the study period. Most of the patients were regarded as having cancer-related lymphedema, and none of the patients had lipolymphedema (Table 1, Fig. 1, Supplementary Table S1, Supplementary Fig. S2). Most of the patients were classified as having clinical stage 2 according to the scale of the International Society of Lymphology^[8]. All of the 40 patients, except for two patients, owned garments or elastic bandages and two of these patients lived in Yokohama City.

Table 1
Background characteristics of the included patients

Age (years)	56.1±18.6 (15-79)
Sex	Male: 7, female: 33
Affected limbs	Upper limb: 8, lower limb: 32
Body mass index (kg/m ²)	25.4±4.70 (18.6-35.5)
Type of lymphedema	Primary: 13, secondary: 27
Primary diseases of secondary lymphedema	Uterine body cancer: 14, uterine cervix cancer: 7, breast cancer: 3, cancer of the caput pancreatis: 1, ovarian cancer: 1, sarcoma in the abdomen: 1
Severity of lymphedema (clinical stage on the International Society of Lymphology scale)	Stage 1: 1, Stage 2: 30, Stage 3: 9
Total N=40; Data are presented as the mean ± standard deviation or as the number of cases	

Among all 40 patients, 20 were admitted from June to August, whereas 20 were admitted from September to May (Supplemental Fig. S3). Among the 25 patients from Yokohama City, 13 were admitted from June to August and 12 were admitted from September to May. In terms of seasons, 6 patients were admitted in spring, 13 in summer, 5 in autumn, and 1 in winter (Fig. 1).

The mean temperature and atmospheric pressure during the observation period are shown in Figure 2. The atmospheric pressure showed a downward slope from spring to summer and an upward slope from summer to winter. The 15-day CMAs of the temperature and atmospheric pressure from 14 days before admission to the admission day showed seasonal differences among the three seasons from spring to autumn (Table 2, Fig. 3). The mean change in temperature from 4 days before admission to the day before admission was 0.36 °C in spring, 0.12 °C in summer, 0.30 °C in autumn, and 0.10 °C in winter. The amount of change in temperature around the admission day was relatively large in spring and autumn compared to that in summer and winter. Similar findings were observed for the atmospheric pressure. The mean change in atmospheric pressure from 4 days before admission to the day before admission was 0.55 hPa in spring, 0.39 hPa in summer, 0.63 hPa in autumn, and 0.47 hPa in winter (Table 3, Fig. 4). Although the variation in atmospheric pressure before the admission day was lower in summer than in spring and autumn, the seasonal differences failed to reach statistical significance ($p=0.147$, Fig. 4).

Table 2

Results of the statistical analysis of the meteorological data before the admission day in 25 patients

	CMA ₁₅ (0) temperature [°C]			CMA ₁₅ (0) atmospheric pressure [hPa]		
	Spring	Summer	Autumn	Spring	Summer	Autumn
Mean	10.5	24.9	21.8	1010.8	1003.2	1008.4
Median	10.6	25.3	23.6	1012.5	1002.0	1007.0
Number of samples	6	13	5	6	13	5
SD	2.36	2.36	5.62	3.54	2.97	4.45
Shapiro-Wilk test	0.744	0.345	0.053	0.138	0.045	0.777
Kruskal-Wallis test	$p = 0.0016$			$p = 0.0018$		
CMA ₁₅ (0) temperature: centralized moving average of the temperature for 15 days, from 14 days before admission to the admission day						
CMA ₁₅ (0) atmospheric pressure: centralized moving average of the atmospheric pressure for 15 days, from 14 days before admission to the admission day						

Table 3

The differences in the CMA of the temperature or atmospheric pressure from 4 days before admission to the day before admission and those of the day before admission

		Spring	Summer	Autumn	Winter
$\Delta T(D15)$	Mean	0.36	0.12	0.30	0.10
	SD	0.15	0.07	0.06	0
	Shapiro-Wilk test	0.925	0.086	0.147	NA
$\Delta P(D15)$	Mean	0.55	0.39	0.63	0.47
	SD	0.27	0.22	0.31	0
	Shapiro-Wilk test	0.237	0.364	0.083	NA
CMA, centralized moving average					
mean $\Delta T(D15) = (CMA_{15}(-3) + CMA_{15}(-2) + CMA_{15}(-1)) - CMA_{15}(0) \times 3 / 3$					
SD $\Delta T(D15) =$ standardized difference of $\Delta T(D15)$					
NA: not applicable					

Discussion

We conducted the present study based on previous literature suggesting the relevance of low atmospheric pressure to abdominal aortic aneurysm ruptures^[6, 7]. We applied a similar approach to the lymphatic system and its disorder, lymphedema, and hypothesized a relationship between climatic conditions and the occurrence of cellulitis in lymphedema, which is of relevance considering the unusual weather patterns in recent years, such as global warming. As a result, we found that cellulitis in patients with limb lymphedema is meteoropathic in nature, as in previous studies, including a systematic review^[9, 10]. Accordingly, patients with limb lymphedema may need to take special care to avoid developing cellulitis in summer or in seasons with lower atmospheric pressure.

In the present study, conducted in Japan, the number of admitted patients was about two times higher in summer than in other seasons (Supplementary Fig. S2). Moreover, when the analysis was limited to patients living in Yokohama City (removing the influence of geographical environment factors), the same tendency was observed; most of the 25 patients were admitted during the months and days with higher temperature and lower atmospheric pressure. Thus, severe cellulitis may be more apt to occur in patients with limb lymphedema on days with higher temperature or lower atmospheric pressure (e.g. summer in Japan).

In addition, the average change in the temperature or atmospheric pressure around the time of admission was higher in spring and autumn than in summer, at least when considering the period from 4 days before admission to the day before admission. However, because the present study utilized 15-day CMA data, the development of cellulitis might have been influenced by climatic conditions during the prior 2 weeks.

Based on the abovementioned study results, there seems to be a seasonal occurrence of cellulitis in patients with limb lymphedema. A higher temperature or lower atmospheric pressure conceivably contributes to the development of cellulitis. Moreover, cellulitis in patients with limb lymphedema might be caused by a continuous higher temperature, rather than by daily and random changes in weather conditions.

Furthermore, if limb lymphedema is categorized as a meteoropathic disease, limb lymphedema conditions may be controlled by medication, as with migraine, rheumatoid arthritis, and bronchial asthma^[11–13]. In fact, some previous studies have suggested that ketoprofen might be effective in secondary lymphedema^[14–16]. Based on histopathology, the end stage of lymphedema shows fibrosis and fat deposition in the subcutaneous tissue^[17–20]. Thus, lymphedema can be regarded as a type of chronic inflammatory disease that is meteoropathic in nature^[14, 21].

The limitations of the present study are as follows. First, this study was a retrospective single-center study with only 25 cases. Second, this study did not include patients with cellulitis who were not admitted during the study period. Moreover, we could not evaluate cases with limb lymphedema that had not progressed to cellulitis during the study period. Third, the reasons for admission were varied; the only unanimous finding of the admitted patients was severe redness at the affected site. Thus, the evaluation

criteria of admission were obscure. Fourth, data regarding the compliance of the patients in using elastic garments or bandages from the medical records was of poor quality. Given the high temperature in summer in Japan, many patients with limb lymphedema are apt to neglect the garments although they understand the importance of the garments in managing lymphedema. Furthermore, a previous study in Japan indicated that wearing garments in summer is a risk factor of cellulitis for lower limb lymphedema^[9]. Additionally, the 15-day CMAs of the temperature and atmospheric pressure might not entirely represent the climatic conditions of the 2 weeks before admission; however, 15 days was defined and hypothesized as a valid number of days by the authors. Prospective cohort and multi-institutional joint research with unified inclusion criteria for admission and consideration of the patient background, such as age, sex, and site of affected limbs, is desirable for the further elucidation of the meteoropathic nature of lymphedema.

Conclusions

Lymphedema may be regarded as a meteoropathic disease, as climatic conditions were shown to be associated with cellulitis in limbs affected by lymphedema. Severe cellulitis may be apt to occur in patients with limb lymphedema on days with higher temperature or lower atmospheric pressure. Accordingly, patients with limb lymphedema may need to take extra precautions, or even medication, to avoid developing cellulitis in summer or in seasons with lower atmospheric pressure.

Declarations

Acknowledgments:

We thank Mr. Takuya Kaga and Ms. Minami Tada for encouraging us to proceed with this research. We also thank Editage (www.editage.jp) for English language editing.

Author Contributions:

MS, TM, and JM planned the study and drafted the manuscript. MS and KH collected the meteorological data and performed the data analysis. SA, SK, TI, SS, and KY collected and managed the patient data. TM and KY arranged and revised the figures. All of the authors consented to this submission.

Competing interests:

The authors declare no competing interests.

Funding:

Not applicable

Data availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Pappalardo, M. *et al.* Staging and clinical correlations of lymphoscintigraphy for unilateral gynecological cancer-related lymphedema. *J. Surg. Oncol.* **121**, 422–434 (2020). [10.1002/jso.25817](https://doi.org/10.1002/jso.25817), Pubmed:[31875981](https://pubmed.ncbi.nlm.nih.gov/31875981/).
2. Mihara, M. *et al.* Lymphaticovenular anastomosis to prevent cellulitis associated with lymphoedema. *Br. J. Surg.* **101**, 1391-1396 (2014). [10.1002/bjs.9588](https://doi.org/10.1002/bjs.9588), Pubmed:[25116167](https://pubmed.ncbi.nlm.nih.gov/25116167/).
3. Licanin, I., Fisekovic, S. & Babić, S. Admission rate of patients with most common psychiatric disorders in relation to seasons and climatic factors during 2010/2011. *Mater. Sociomed* **24**, 94-99 (2012). [10.5455/msm.2012.24.94-99](https://doi.org/10.5455/msm.2012.24.94-99), Pubmed:[23922518](https://pubmed.ncbi.nlm.nih.gov/23922518/).
4. Okuma, H., Okuma, Y. & Kitagawa, Y. Examination of fluctuations in atmospheric pressure related to migraine. *Springerplus* **4**, 790 (2015). [10.1186/s40064-015-1592-4](https://doi.org/10.1186/s40064-015-1592-4), Pubmed:[26702379](https://pubmed.ncbi.nlm.nih.gov/26702379/).
5. Loth, F. L. *et al.* What makes patients aware of their artificial knee joint? *BMC Musculoskelet. Disord.* **19**, 5 (2018). [10.1186/s12891-017-1923-4](https://doi.org/10.1186/s12891-017-1923-4), Pubmed:[29310652](https://pubmed.ncbi.nlm.nih.gov/29310652/).
6. Smith, R. A., Edwards, P. R. & Da Silva, A. F. A. F. Are periods of low atmospheric pressure associated with an increased risk of abdominal aortic aneurysm rupture? *Ann. R. Coll. Surg. Engl.* **90**, 389-393 (2008). [10.1308/003588408X285892](https://doi.org/10.1308/003588408X285892), Pubmed:[18634734](https://pubmed.ncbi.nlm.nih.gov/18634734/).
7. Kordzadeh, A., Askari, A. & Panayiotopoulos, Y. Atmospheric pressure and infra-renal abdominal aortic aneurysm rupture: a single observational study and a comprehensive review of literature. *Int. J. Surg.* **11**, 458-462 (2013). [10.1016/j.ijvsu.2013.04.008](https://doi.org/10.1016/j.ijvsu.2013.04.008), Pubmed:[23619334](https://pubmed.ncbi.nlm.nih.gov/23619334/).
8. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. *Lymphology* **36**, 84-91 (2003). Pubmed:[12926833](https://pubmed.ncbi.nlm.nih.gov/12926833/).
9. Dai, M., Minematsu, T., Nakagami, G., Sugama, J. & Sanada, H. Awareness and attitudes of lymphoedema patients toward compression stockings in the summer: a cross-sectional questionnaire survey. *J. Lymphoedema* **15** (2020).
10. Witt, S., Watt, B., Gordon, S. & Piller, N. Climate change and climatic variation impact on chronic oedemas: a systematic review. *J. Lymphoedema* **16** (2021).
11. Eyigor, S., Karapolat, H. & Kirazli, Y. Efficacy of etanercept and complete decongestive physical therapy in bilateral lower-limb lymphoedema associated with rheumatoid arthritis: a case report. *Adv. Ther.* **25**, 23-28 (2008). [10.1007/s12325-008-0006-1](https://doi.org/10.1007/s12325-008-0006-1), Pubmed:[18227980](https://pubmed.ncbi.nlm.nih.gov/18227980/).
12. Tong, D., Eather, S. & Manolios, N. Psoriatic arthritis and chronic lymphoedema: treatment efficacy by adalimumab. *Clin. Rheumatol.* **28**, 1349-1350 (2009). [10.1007/s10067-009-1259-z](https://doi.org/10.1007/s10067-009-1259-z), Pubmed:[19693641](https://pubmed.ncbi.nlm.nih.gov/19693641/).

13. Lekpa, F. K., Economu-Dubosc, A., Fevre, C., Claudepierre, P. & Chevalier, X. Efficacy of etanercept in lymphedema associated with psoriatic arthritis. *J. Rheumatol.* **36**, 207-208 (2009). [10.3899/jrheum.080453](https://doi.org/10.3899/jrheum.080453), Pubmed:19208540.
14. Rockson, S. G. *et al.* Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema. *JCI Insight* **3** (2018). [10.1172/jci.insight.123775](https://doi.org/10.1172/jci.insight.123775), Pubmed:30333315.
15. Tian, W. *et al.* Leukotriene B4 antagonism ameliorates experimental lymphedema. *Sci. Transl. Med.* **9** (2017). [10.1126/scitranslmed.aal3920](https://doi.org/10.1126/scitranslmed.aal3920), Pubmed:28490670.
16. Nakamura, K., Radhakrishnan, K., Wong, Y. M. & Rockson, S. G. Anti-inflammatory pharmacotherapy with ketoprofen ameliorates experimental lymphatic vascular insufficiency in mice. *PLOS ONE* **4**, e8380 (2009). [10.1371/journal.pone.0008380](https://doi.org/10.1371/journal.pone.0008380), Pubmed:20027220.
17. Brorson, H., Ohlin, K., Olsson, G. & Karlsson, M. K. Breast cancer-related chronic arm lymphedema is associated with excess adipose and muscle tissue. *Lymphat. Res. Biol.* **7**, 3-10 (2009). [10.1089/lrb.2008.1022](https://doi.org/10.1089/lrb.2008.1022), Pubmed:19231988.
18. Brorson, H., Ohlin, K., Olsson, G. & Nilsson, M. Adipose tissue dominates chronic arm lymphedema following breast cancer: an analysis using volume rendered CT images. *Lymphat. Res. Biol.* **4**, 199-210 (2006). [10.1089/lrb.2006.4404](https://doi.org/10.1089/lrb.2006.4404), Pubmed:17394403.
19. Kataru, R. P. *et al.* Fibrosis and secondary lymphedema: chicken or egg? *Transl. Res.* **209**, 68-76 (2019). [10.1016/j.trsl.2019.04.001](https://doi.org/10.1016/j.trsl.2019.04.001), Pubmed:31022376.
20. Schaverien, M. V., Munnoch, D. A. & Brorson, H. Liposuction treatment of lymphedema. *Semin. Plast. Surg.* **32**, 42-47 (2018). [10.1055/s-0038-1635116](https://doi.org/10.1055/s-0038-1635116), Pubmed:29636653.
21. Asano, S. *et al.* Preliminary Report. The relevance of tumor necrosis factor-alpha in acquired primary lymphedema-A histopathological investigation. *Lymphat. Res. Biol.* **18**, 232-238 (2020). [10.1089/lrb.2019.0046](https://doi.org/10.1089/lrb.2019.0046), Pubmed:31750769.

Figures

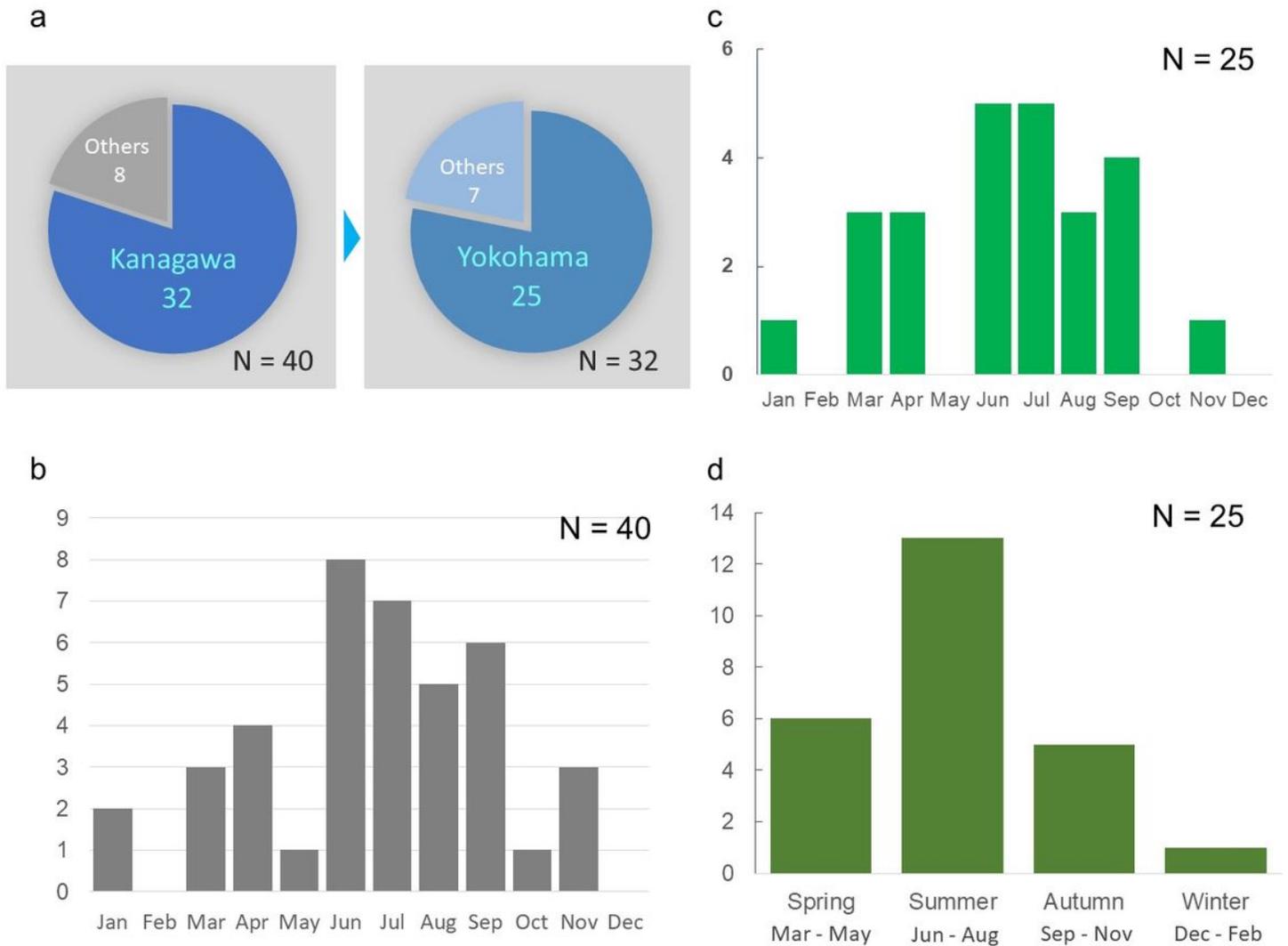


Figure 1

Background characteristics of all patients (N=40) and the distribution of patients who lived in Yokohama City according to the date of the admission (N=25).

a. Number of patients according to residential area. Thirty-two of 40 patients lived in Kanagawa prefecture; of these, 25 resided in Yokohama City.

b. Number of patients stratified by the month of the admission day.

c. Number of patients who lived in Yokohama City according to the month of admission.

d. Number of patients who lived in Yokohama City according to the season in which they were admitted.

Spring: March to May; Summer: June to August; Autumn: September to November; Winter: December to February

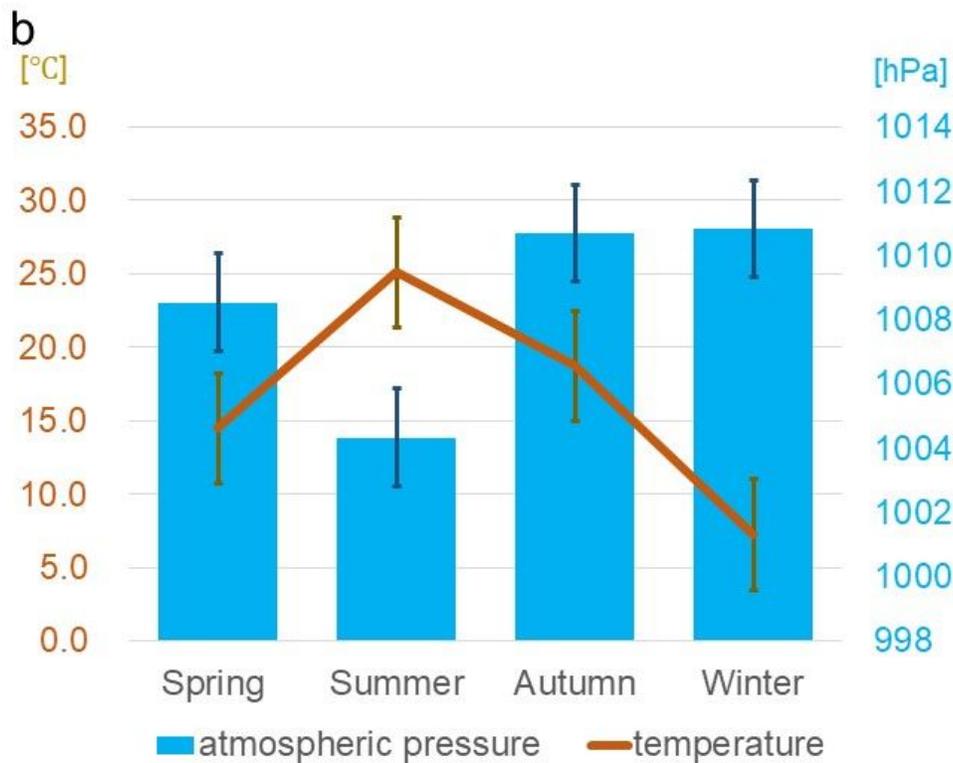
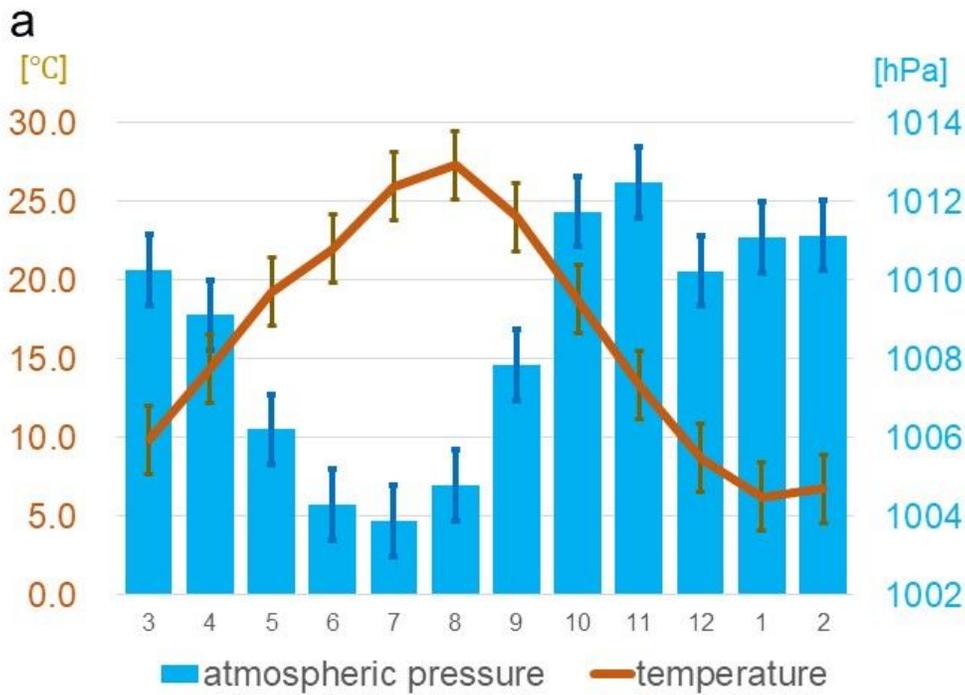


Figure 2

Mean temperature and atmospheric pressure during the observation period.

a. Monthly data. The atmospheric pressure gradually decreased from spring to summer and the temperature simultaneously increased. In contrast, as the temperatures fell from summer to winter, the atmospheric pressure increased.

b. Seasonal data. The difference in atmospheric pressure between autumn and winter was not as obvious as that in temperature.

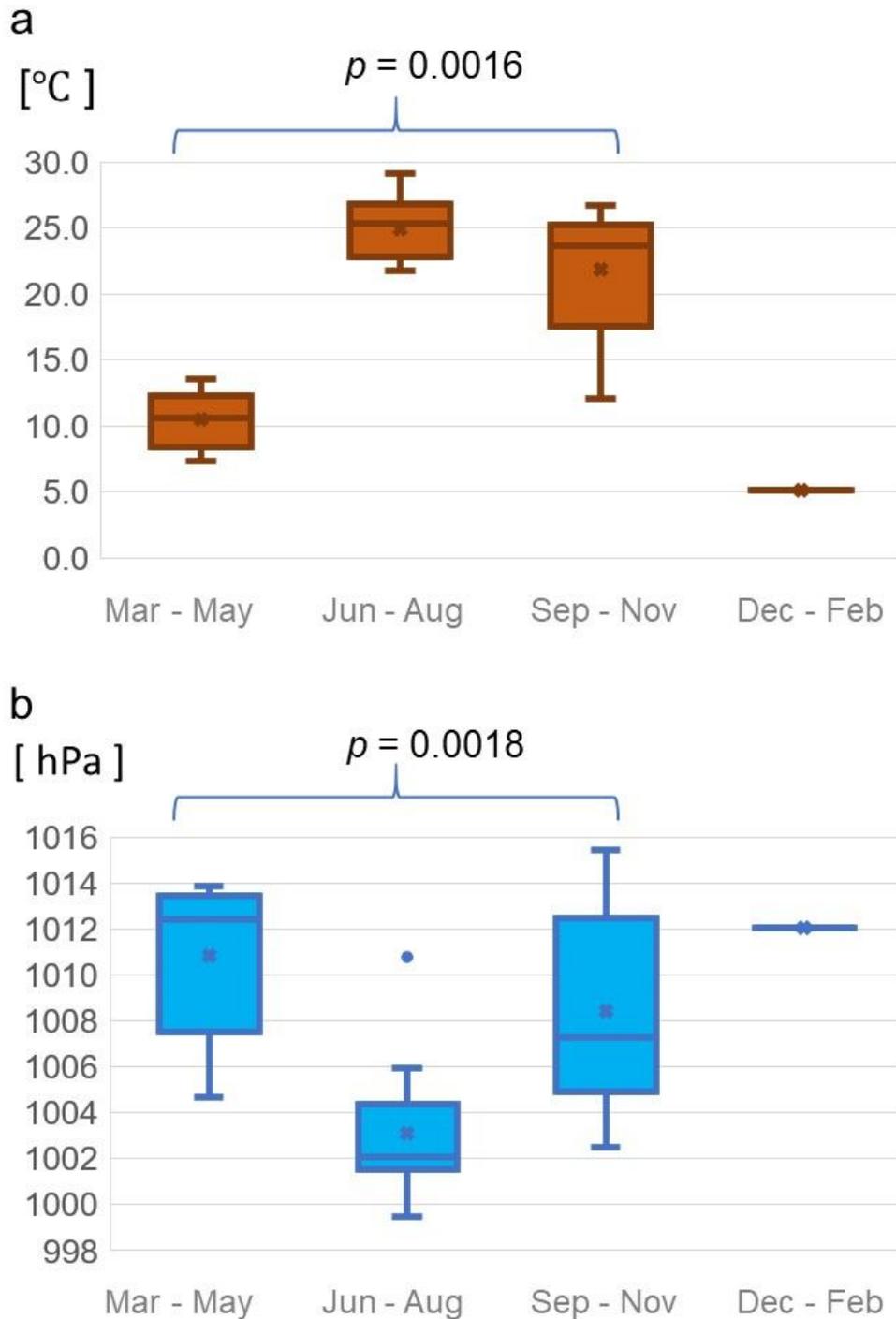


Figure 3

Box-and-whisker plots of the meteorological data around the admission day for the 25 residents of Yokohama City, shown according to season. Since winter had a sample size of only one, statistical

analysis was performed with the other three seasons (spring, summer, and autumn) (see Table 2).

a. Centralized moving average of the temperature for 15 days, from 14 days before admission to the admission day. The Shapiro-Wilk test indicated that the data were normally distributed for all seasons. However, since autumn had a sample size of only five, the Kruskal-Wallis test was applied, which indicated statistically significant differences among the three seasons ($p=0.0016$).

b. Centralized moving average of the atmospheric pressure for 15 days, from 14 days before admission to the admission day. The Shapiro-Wilk test indicated that the data was not normally distributed for summer, and autumn had a sample of only five; thus, the Kruskal-Wallis test was applied, which indicated statistically significant differences among the three seasons ($p=0.0018$).

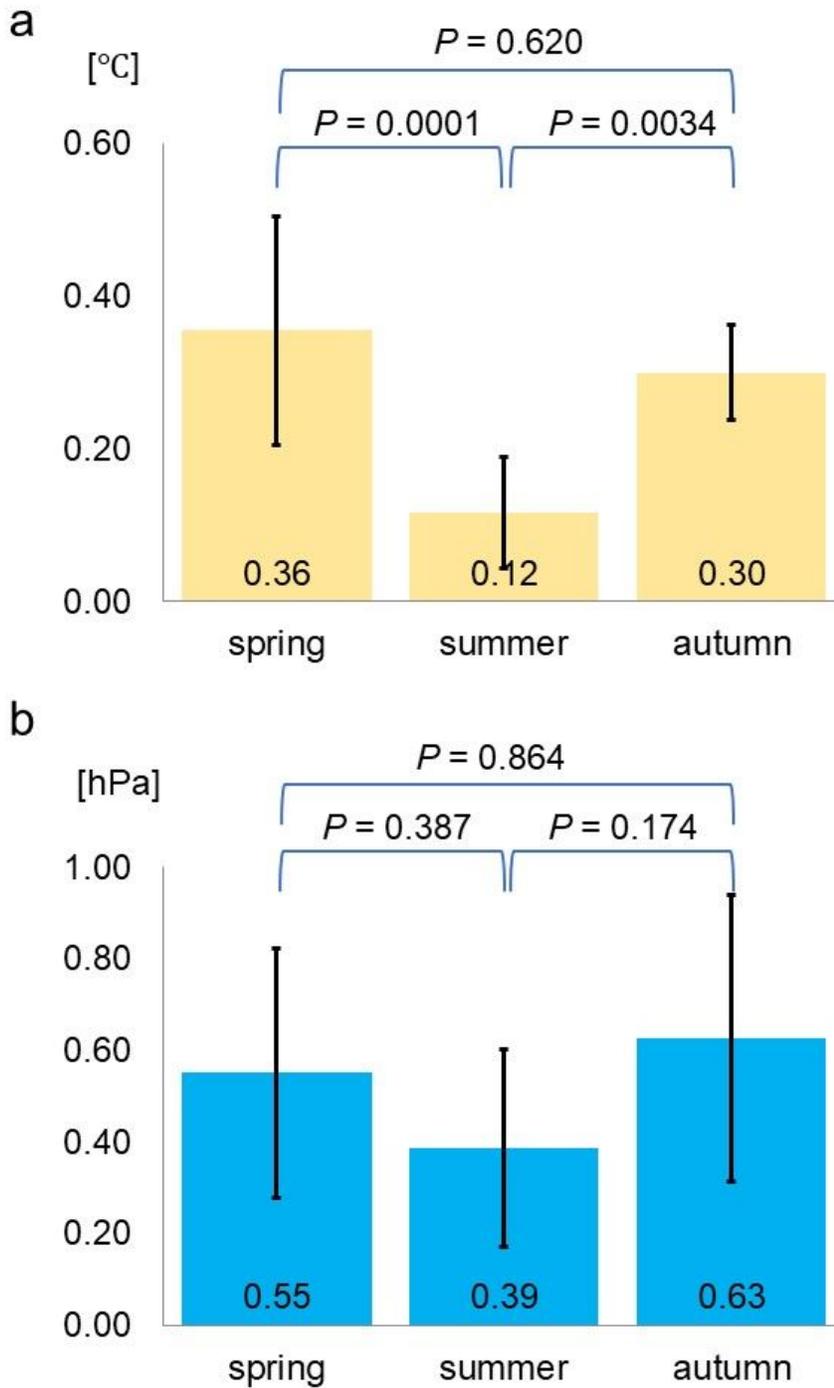


Figure 4

The difference in the centralized moving averages of the temperature or atmospheric pressure from 4 days before admission to the day before admission, as well as those for the day before admission. Since winter had a sample size of only one, statistical analysis was performed with the other three seasons (spring, summer, and autumn) (see Table 3).

a. Differences in temperature. As the Shapiro-Wilk test indicated normality of the data for each season, an analysis of variance (ANOVA) was applied, which indicated statistically significant differences among the seasons ($p < 0.0001$). Turkey's HSD test indicated significant differences between spring and summer ($p = 0.0001$) and between summer and autumn ($p = 0.0034$), but not between spring and autumn ($p = 0.620$).

b. Differences in atmospheric pressure. As the Shapiro-Wilk test indicated normality of the data for each season, an ANOVA was applied. Although the mean atmospheric pressure was lower in summer than in spring and autumn, the ANOVA failed to reach statistical significance ($p = 0.147$). The results of Turkey's HSD test are shown.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SuzukiMeteoropathySupplementaryDATABind.pdf](#)