

Association between atrial fibrillation and white blood cell count after the Great East Japan Earthquake

An observational study from the Fukushima Health Management Survey

Hitoshi Suzuki, MD, PhD^{a,b,*}, Tetsuya Ohira, MD, PhD^{b,c}, Yasuchika Takeishi, MD, PhD^a, Akira Sakai, MD, PhD^{b,d}, Mitsuaki Hosoya, MD, PhD^{b,e}, Seiji Yasumura, MD, PhD^{b,f}, Yukihiro Kawasaki, MD, PhD^{b,e,g}, Atsushi Takahashi, MD, PhD^{b,h}, Hironori Nakano, PhD^{b,c}, Kenji Kamiya, MD, PhD^b, for the Fukushima Health Management Survey Group

Abstract

We had earlier reported about the increase in the prevalence of atrial fibrillation (AF) among residents in the evacuation zone of Fukushima Prefecture after the Great East Japan Earthquake. In the present investigation, we explored the association between the prevalence of AF and white blood cell (WBC) count after the earthquake through an observational cross-sectional study.

A total of 14,800 participants (6427 men and 8373 women) were included in the Fukushima Health Management Survey. For the present study, 12-lead electrocardiogram tracings and the WBC count and its subtypes were obtained and analyzed. The odds ratios (ORs) of AF after the earthquake and the 95% confidence intervals (CIs) for one standard deviation of differential WBC count were calculated after adjustments for age and other potential confounding factors using the logistic regression model.

Our results revealed a prevalence of AF of 1.8% (269 participants) after the earthquake. Monocyte count and neutrophil/lymphocyte ratio exhibited a significant association with the prevalence of AF in the multivariable-adjusted model. The adjusted ORs of monocyte count and neutrophil/lymphocyte ratio for AF were 1.21 (95% CI, 1.05–1.40, $P = .01$) and 1.22 (95% CI, 1.01–1.44, $P < .05$), respectively.

The prevalence of AF was associated with increased monocyte count and neutrophil/lymphocyte ratio among residents in the evacuation zone in Fukushima Prefecture, suggesting that inflammation and psychological stress could be important factors mediating the development of AF after the earthquake.

Abbreviations: 2K-EDTA = ethylenediaminetetraacetic acid di-potassium, AF = atrial fibrillation, BMI = body mass index, BP = blood pressure, CHC = comprehensive health check, CIs = confidence intervals, ECG = electrocardiogram, FHMS = Fukushima Health Management Survey, ORs = odds ratios, WBC = white blood cell.

Keywords: atrial fibrillation, earthquake, white blood cell count

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia that causes substantial cardiovascular morbidity and mortality.^[1] Epidemiological studies have identified several risk factors for

AF, including hypertension, diabetes mellitus, heart failure, obesity, and heavy alcohol intake.^[2–4] Furthermore, the role of inflammation and psychological stress has been established in the development of AF.^[5,6] The white blood cell (WBC) count and its

Editor: Ardavan Khoshnood.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

^a Department of Cardiovascular Medicine, ^b Radiation Medical Science Center for the Fukushima Health Management Survey, ^c Department of Epidemiology, ^d Department of Radiation Life Sciences, ^e Department of Pediatrics, ^f Department of Public Health, Fukushima Medical University, Fukushima, ^g Department of Pediatrics, Sapporo Medical University, Sapporo, ^h Department of Gastroenterology, Fukushima Medical University, Fukushima, Japan.

* Correspondence: Hitoshi Suzuki, Department of Cardiovascular Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan (e-mail: shitoshi@fmu.ac.jp).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Suzuki H, Ohira T, Takeishi Y, Sakai A, Hosoya M, Yasumura S, Kawasaki Y, Takahashi A, Nakano H, Kamiya K. Association between atrial fibrillation and white blood cell count after the Great East Japan Earthquake: an observational study from the Fukushima Health Management Survey. *Medicine* 2021;100:6(e24177).

Received: 24 May 2020 / Received in final form: 14 October 2020 / Accepted: 10 December 2020

<http://dx.doi.org/10.1097/MD.00000000000024177>

subtypes are considered as markers of inflammation and stress in various diseases, which is because neutrophils represent activated nonspecific inflammation and lymphopenia represents a marker of poor general health and psychological stress. Therefore, several studies have examined the association between WBC count and the prevalence of AF.^[7–10]

We had recently reported about the increased prevalence of AF among residents in the evacuation zone in Fukushima Prefecture after the Great East Japan Earthquake that occurred on March 11, 2011, with excess alcohol intake and obesity being associated with an increased risk for AF.^[11] The Great East Japan Earthquake, the subsequent tsunami, and the Fukushima nuclear accident had resulted in physical and psychological stress among the residents of Fukushima Prefecture, which may have had an impact on the AF rate in the population.^[12,13] Those results suggested that health-related behaviors involving psychological stress and inflammation could be important factors mediating the development of AF after the disaster. The present study was conducted to investigate the association between WBC count and the prevalence of AF among the residents in the evacuation zone in Fukushima Prefecture after the Great East Japan Earthquake.

2. Methods

2.1. Study population

The Comprehensive Health Check (CHC) is one of the detailed surveys of the Fukushima Health Management Survey (FHMS). A previous study has described the detailed methods of the CHC and the FHMS.^[12] The subjects of the CHC consisted of Japanese men and women of all age groups living in the evacuation area specified by the government after the accident at the Fukushima Daiichi Nuclear Power Plant in Fukushima Prefecture, including Tamura City, Minamisoma City, Kawamata-machi, Hironomachi, Naraha-machi, Tomioka-machi, Kawauchi-mura, Okuma-machi, Futaba-machi, Namie-machi, Katsurao-mura, Iitate-mura, and part of Date City, with a total of 210,189 subjects. Of these subjects, 28,170 men and women aged 20 to 89 years participated in the CHC from June 2011 (5 months after the disaster) to the end of March 2012. If the participants underwent ≥ 2 examinations during the period, the earlier data were used in the analysis. We excluded the residents whose WBC count and electrocardiogram (ECG) data were unavailable, and the remaining data of 14,800 participants (6427 men and 8373 women) were used for analyses.

Informed consent was obtained from community representatives to conduct an epidemiological study based on the guidelines of the Council for International Organizations of Medical Science, and the study was approved by the Ethics Committee of Fukushima Medical University (#1319 and #1916).

2.2. Measurements

Based on the 12-lead ECG tracings obtained from subjects in the supine position, AF was diagnosed if the P-wave activity was not evident and the ventricular response was irregular. Venous blood was collected from the subjects using ethylenediaminetetraacetic acid di-potassium (2K-EDTA) as an anticoagulant for measuring the WBC count. The counts of total WBCs, lymphocytes, monocytes, neutrophils, eosinophils, and basophils were determined using an automated cell counter. Diabetes mellitus was defined as a fasting glucose level of at least 126 mg/dL

(7.0 mmol/L), an HbA1c level of at least 6.1%, and/or the use of medications for diabetes mellitus.

Height in stocking feet and weight in light clothing were measured, and the body mass index (BMI) was calculated as weight (kg)/height (m²). Overweight was defined as a BMI ≥ 25 kg/m². Systolic and diastolic blood pressure (BP) values were measured by trained technicians using a standard mercury sphygmomanometer on the right arm of participants in the seated position. Readings were made to the nearest 2 mmHg, and diastolic BP was taken at the phase V Korotkoff sound. Hypertension was defined as a systolic BP ≥ 140 mmHg, a diastolic BP ≥ 90 mmHg, or the use of antihypertensive medications.

An interviewer collected details regarding the history of cigarette smoking and weekly alcohol intake in units of “go,” a traditional Japanese unit of volume corresponding to 22 g of ethanol, which was subsequently converted into g/day. One go equates to 180 mL of sake and corresponds to one bottle (500 mL) of beer, two single shots (60 mL) of whiskey, or two glasses (240 mL) of wine. Participants who consumed ≥ 2 go (≥ 44 g ethanol) per day were classified as being current excessive drinkers.

2.3. Statistical analysis

Differences in mean values or proportions of potential risk factors between participants with AF and those without AF were analyzed for statistical significance using *t* test for continuous variables and the chi-square test for dichotomous variables. The odds ratios (ORs) of AF after the disaster and the 95% confidence intervals (CIs) for one standard deviation of differential WBC count were calculated after adjustments for age and other potential confounding factors using the logistic regression model. Age, sex, excess ethanol intake, smoking, being overweight, hypertension, and diabetes mellitus were the potential confounding factors. These analyses were also conducted stratified by sex. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). All probability values for statistical tests were two-tailed, with *P* values $< .05$ considered as statistically significant.

3. Results

3.1. Characteristics of the study population

Among the 14,800 men and women, AF was confirmed in 269 participants (1.8%) after the disaster. The mean values of age, monocyte count, and neutrophil/lymphocyte ratio and the proportion of people with overweight, hypertension, diabetes mellitus, and current excessive drinkers were higher among participants with AF than among participants without AF (Table 1).

3.2. WBC and its subtypes associated with AF

Table 2 shows the age-adjusted and multivariable-adjusted ORs and 95% CIs of AF for one standard deviation of differential WBCs count among men and women. A significant association was detected between monocyte count and neutrophil/lymphocyte ratio and the prevalence of AF in the multivariable-adjusted model. The adjusted ORs of monocyte count and neutrophil/lymphocyte ratio for AF were 1.21 (95% CI, 1.05–1.40, *P* = .01)

Table 1
Means or proportions of characteristics of participants with atrial fibrillation and those without atrial fibrillation after the Great East Japan Earthquake.

	Atrial fibrillation	No atrial fibrillation	P value
n	269	14,531	
Age, y	63.6	60.5	<.0001
Men, %	49.0	40.0	<.0001
Overweight (body mass index ≥ 25 kg/m ²), %	49.4	34.0	<.0001
Hypertension, %	77.3	54.5	<.0001
Diabetes mellitus, %	13.8	10.1	<.05
Current smokers, %	13.8	13.7	.96
Current excessive drinkers*, %	10.0	4.7	<.0001
White blood cell, /mm ³	6038	5891	.14
Neutrophil, /mm ³	3356	3244	.14
Lymphocyte, /mm ³	2144	2141	.94
Monocyte, /mm ³	356	320	<.0001
Eosinophil, /mm ³	153	156	.67
Neutrophil/Lymphocyte ratio	1.75	1.63	.02

* Ethanol intake 44g \geq /day.

and 1.22 (95% CI, 1.01–1.44, $P < .05$), respectively. Further analysis of the associations stratified by sex revealed similar relationships in both men and women.

4. Discussion

The present study has demonstrated that the prevalence of AF was associated with an increased neutrophil/lymphocyte ratio and monocyte count among residents in the evacuation zone in Fukushima Prefecture after the Great East Japan Earthquake. This finding suggests that inflammation and psychological stress could be important factors mediating the development of AF after a disaster.

Previous studies have demonstrated that inflammation and psychological stress are associated with increased risk of AF.^[5,6]

WBC count and its subtypes have been found to be markers of inflammation and stress in various cardiovascular diseases, including AF. Neutrophils represent activated nonspecific inflammation, and lymphopenia is a marker of poor general health and psychological stress. Therefore, the neutrophil/lymphocyte ratio provides information about both the inflammatory environment and the stress response.^[7–10] Gibson et al^[7] reported that an elevated neutrophil/lymphocyte ratio found before and after coronary artery bypass grafting was associated with an increased prevalence of AF after the operation. Im et al^[8] demonstrated that the neutrophil/lymphocyte ratio after radiofrequency catheter ablation for AF was a predictor for the early recurrence of AF. In addition to selected patient samples, Misialek et al^[9] investigated a large population-based cohort of 14,500 American individuals who underwent longitudinal annual health examinations (ARIC study) and observed that a higher neutrophil/lymphocyte ratio was associated with AF risk. The results of our study, which was conducted after a disaster, are comparable to the results of the abovementioned previous studies. The mental health and lifestyle survey in the FHMS revealed that those who evacuated in response to governmental directions after the Great East Japan Earthquake tended to perform less physical activity, had trouble sleeping, and felt more psychological stress.^[14] Therefore, we considered that various factors, including psychological stress, may influence the neutrophil/lymphocyte ratio, resulting in the prevalence of AF after the disaster.

The present study also demonstrated the association between monocyte count and the prevalence of AF. Monocyte activation plays a vital role in chronic inflammation and cardiovascular diseases, including AF, in which monocytes and differentiated macrophages participate in the inflammatory response and tissue remodeling.^[15,16] Fontes et al^[15] initially showed that a higher circulating monocyte ratio was associated with postoperative AF in cardiac surgery. Later, Gurses et al^[16] found that peripheral toll-like receptors on monocytes were independent predictors of AF recurrence after cryoablation. The exact mechanism

Table 2
Multivariable-adjusted odds ratios and 95% confidence intervals of atrial fibrillation for one standard deviation of differential leukocytes count among men and women after the Great East Japan Earthquake.

	Crude OR		Age- and sex-adjusted OR		Multivariable-adjusted* OR	
Total						
Neutrophil, /mm ³	1.09	0.97–1.22	1.04	0.92–1.17	0.79	0.63–0.98
Lymphocyte, /mm ³	1.00	0.89–1.13	0.98	0.88–1.10	1.04	0.88–1.22
Monocyte, /mm ³	1.32	1.19–1.46	1.14	1.02–1.28	1.21	1.05–1.40
Eosinophil, /mm ³	0.97	0.86–1.11	0.89	0.77–1.03	0.86	0.74–1.01
Neutrophil/Lymphocyte ratio	1.13	1.02–1.24	1.08	0.97–1.20	1.22	1.01–1.48
Men						
Neutrophil, /mm ³	0.95	0.82–1.09	0.97	0.84–1.12	0.78	0.60–1.03
Lymphocyte, /mm ³	0.96	0.84–1.10	1.01	0.89–1.14	1.02	0.85–1.23
Monocyte, /mm ³	1.13	0.99–1.28	1.12	0.98–1.27	1.22	1.04–1.44
Eosinophil, /mm ³	0.81	0.68–0.97	0.85	0.71–1.01	0.81	0.68–0.97
Neutrophil/Lymphocyte ratio	1.03	0.91–1.17	1.03	0.91–1.17	1.13	0.89–1.44
Women						
Neutrophil, /mm ³	1.21	0.98–1.48	1.23	1.00–1.51	0.81	0.53–1.25
Lymphocyte, /mm ³	0.96	0.75–1.23	0.93	0.73–1.19	1.03	0.72–1.48
Monocyte, /mm ³	1.26	1.00–1.58	1.24	0.98–1.57	1.18	0.88–1.60
Eosinophil, /mm ³	1.02	0.80–1.30	1.04	0.81–1.32	1.03	0.78–1.35
Neutrophil/Lymphocyte ratio	1.25	1.06–1.47	1.26	1.07–1.48	1.41	0.99–2.00

OR = odds ratio.

* Adjusted for age, sex, excess ethanol intake, current smoking, overweight, hypertension, and diabetes mellitus, and other leukocytes counts.

underlying the association between inflammation and AF risk after the disaster is unknown. However, our study findings may indicate that chronic inflammation plays an important role in the prevalence of AF caused by the disaster.

Our study has some limitations. First, the observational cross-sectional design of the study identifies only an association and not the causality because WBC count and its subtypes had not been examined at annual checkups in most of the areas before the disaster. Second, subjects living in the nonevacuation zone were not included in the study. It is necessary to examine cohorts in areas not affected or less affected by the disaster who underwent checkups to evaluate the influence of the disaster. Third, in the present study, because AF was defined by evaluating 12-lead ECG tracings only, we could not distinguish the AF forms: paroxysmal, persistent, long-term persistent, and permanent. Therefore, the findings of the present study are not generally applicable to all AF types because etiologies and risk factors may be different. Fourth, we did not consider the effects of radiation exposure on the association between WBC counts and AF although lymphocytes are susceptible to damage from radiation. However, a previous study showed that there were no marked effects of radiation exposure on the WBC counts, including neutrophil and lymphocyte counts, within 1 year after a nuclear accident in an evacuation area.^[17] Finally, the association between WBC count and AF risk might be confounded by various factors that were not measured in this study. We cannot rule out the possibility of residual confounding factors, including socioeconomic aspects and biological inflammatory markers, after the disaster.

In conclusion, the prevalence of AF was associated with an increased monocyte count and neutrophil/lymphocyte ratio among residents in the evacuation zone in Fukushima Prefecture, suggesting that inflammation and psychological stress could be important factors mediating the development of AF after the earthquake.

Acknowledgments

The National Health Fund for Children and Adults Affected by the Nuclear Incident supported this survey. The authors would like to thank Enago (www.enago.jp) for the English language review. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Fukushima Prefecture government.

Author contributions

Conceptualization: Hitoshi Suzuki, Tetsuya Ohira, Akira Sakai, Mitsuaki Hosoya, Seiji Yasumura, Yukihiko Kawasaki, Atsushi Takahashi, Kenji Kamiya.

Data curation: Hitoshi Suzuki, Tetsuya Ohira, Akira Sakai, Mitsuaki Hosoya, Seiji Yasumura, Yukihiko Kawasaki, Atsushi Takahashi, Hironori Nakano, Kenji Kamiya.

Formal analysis: Tetsuya Ohira, Hironori Nakano.

Funding acquisition: Kenji Kamiya.

Supervision: Yasuchika Takeishi, Seiji Yasumura, Kenji Kamiya.

Writing – original draft: Hitoshi Suzuki, Tetsuya Ohira.

Writing – review & editing: Yasuchika Takeishi, Akira Sakai, Mitsuaki Hosoya, Seiji Yasumura, Yukihiko Kawasaki, Atsushi Takahashi, Hironori Nakano, Kenji Kamiya.

References

- Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001;285:2370–5.
- Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840–4.
- Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: The Niigata Preventive Medicine Study. *Circulation* 2008;117:1255–60.
- Sano F, Ohira T, Kitamura A, et al. Heavy alcohol consumption and risk of atrial fibrillation: The Circulatory Risk In Communities Study (CIRCS). *Circ J* 2014;78:955–61.
- Li J, Solus J, Chen Q, et al. Role of inflammation and oxidant stress in atrial fibrillation. *Heart Rhythm* 2010;7:438–44.
- Svensson T, Kitlinski M, Engström G, et al. Psychological stress and risk of incident atrial fibrillation in men and women with known atrial fibrillation genetic risk scores. *Sci Rep* 2017;7:42613.
- Gibson PH, Cuthbertson BH, Groat BL, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. *Am J Cardiol* 2010;105:186–91.
- Im SI, Shin SY, Na JO, et al. Usefulness of neutrophil/lymphocyte ratio in predicting early recurrence after radiofrequency catheter ablation in patients with atrial fibrillation. *Int J Cardiol* 2013;168:4398–400.
- Misialek JR, Bekwelem W, Chen LY, et al. Association of white blood cell count and differential with the incidence of atrial fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study. *PLoS One* 2015;10:e0136219.
- Shao Q, Chen K, Rha SW, et al. Usefulness of neutrophil/lymphocyte ratio as a predictor of atrial fibrillation: a meta-analysis. *Arch Med Res* 2015;46:199–206.
- Suzuki H, Ohira T, Takeishi Y, et al. Fukushima Health Management Survey Group. Increased prevalence of atrial fibrillation after the Great East Japan Earthquake: Results from the Fukushima Health Management Survey. *Int J Cardiol* 2015;198:102–5.
- Yasumura S, Hosoya M, Yamashita S, et al. Fukushima Health Management Survey Group. Study protocol for the Fukushima Health Management Survey. *J Epidemiol* 2012;22:375–83.
- Harasawa K, Tanimoto T, Kami M, et al. Health problems in the temporary housing in Fukushima. *Lancet* 2012;379:2240–1.
- Yabe H, Suzuki Y, Mashiko H, et al. Mental Health Group of the Fukushima Health Management Survey. Psychological distress after the Great East Japan Earthquake and Fukushima Daiichi Nuclear Power Plant accident: results of a mental health and lifestyle survey through the Fukushima health management survey in FY2011 and FY2012. *Fukushima J Med Sci* 2014;60:57–67.
- Fontes ML, Mathew JP, Rinder HM, et al. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Atrial fibrillation after cardiac surgery/cardiopulmonary bypass is associated with monocyte activation. *Anesth Analg* 2005;101:17–23.
- Gurses KM, Kocyigit D, Yalcin MU, et al. Monocyte toll-like receptor expression in patients with atrial fibrillation. *Am J Cardiol* 2016;117:1463–7.
- Sakai A, Ohira T, Hosoya M, et al. White blood cell, neutrophil, and lymphocyte counts in individuals in the evacuation zone designated by the government after the Fukushima Daiichi Nuclear Power Plant accident: the Fukushima Health Management Survey. *J Epidemiol* 2015;25:80–7.