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Research paper

Three-year follow-up of the impact of Kumamoto Earthquake on acute myocardial infarctions: An interrupted time series analysis

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ABSTRACT

Study objective: This study aimed to investigate whether the incidence of acute myocardial infarction (AMI) and subsequent outcomes over the three years after the Kumamoto earthquake differed from the underlying trend before the earthquake.
Design: Quasi-experimental design.
Setting: Twenty-one institutions participating from the Kumamoto Prefecture and capable of receiving AMI patients and performing coronary angiography and interventions.
Participants: In total 6553 consecutive patients with AMI between 2013 and 2019 were included in this study.
Interventions: Interrupted time series analysis.
Main outcome measure(s): AMI incidence and following cardiac events after the earthquake.
Results: The rate ratio (RR) for AMI incidence after the earthquake was 1.12 (95 % confidence interval [CI]: 1.00–1.25) with reference to that before the earthquake. AMI rates increased among people with diabetes mellitus (RR: 1.20, 95 % CI: 1.01–1.44), those with current smoking (RR: 1.27, 95 % CI: 1.03–1.56), and those with a body mass index >25 kg/m^2 (RR: 1.27, 95 % CI: 1.06–1.52). Increased number of AMI patients with onset-to-door time >12 h (RR: 1.46, 95 % CI: 1.02–2.08), a high Killip class on hospital admission (RR: 1.37, 95 % CI: 1.13–1.67), and unperformed emergent coronary angiography (RR: 1.40, 95 % CI: 1.02–1.91) were frequently observed after the earthquake, which may affect following in-hospital cardiac events (RR: 1.49, 95 % CI: 1.03–2.15).
Conclusions: The Kumamoto earthquake had an impact on the increase in the incidence of AMI and the following in-hospital cardiac outcomes. Emergency medical care should be ensured in such a way that high-risk patients are managed as usual, especially immediately after earthquake.

1. Introduction

Beginning in April 2016, a series of powerful shallow earthquakes, including numerous aftershocks, struck the Kumamoto area of central Kyushu in Southwest Japan. The Kumamoto Prefecture has an area of 7400 km^2 and a stable population of approximately 1.7 million, according to the Kumamoto Prefectural Government Office records [1]. The Kumamoto Acute Coronary Events (KACE) study is a multicenter observational study, with 21 participating institutions from the Kumamoto Prefecture that are capable of receiving acute myocardial infarction (AMI) patients and performing coronary angiography and interventions [2]. Most patients with AMI in the Kumamoto Prefecture are transported to one of these participating institutions.

An interrupted time series (ITS) is an important observational design used to examine exposure effects [3]. When an exposure such as an earthquake occurs at a known time, postexposure trends can be examined for distinct changes from preexisting trends, thus serving as the counterfactual [3]. However, to the best of our knowledge, no study has reported on the incidence of AMI before and after the earthquake using ITS analysis. Therefore, this study aimed to investigate whether the incidence of AMI and subsequent outcomes over the three years after the Kumamoto earthquake differed from the underlying trend before the

Abbreviations: AMI, acute myocardial infarction; ITS, interrupted time series; KACE, Kumamoto Acute Coronary Events; RR, rate ratio.

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earthquake, using ITS analysis.

2. Materials and methods

We used an ITS design to compare the incidence and subsequent event rates of AMI before and after the Kumamoto earthquake in April 2016. Data on the monthly total incidence of AMI occurring in Kumamoto between 2013 and 2019 were extracted from the KACE study database [2] in the form of anonymous individual records that included age, sex, date and time of AMI onset, coronary risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, and chronic kidney disease), culprit vessels, Killip classification, in-hospital mortality and cardiac events which were defined as a composite of cardiac death, non-fatal recurrent myocardial infarction, unstable angina, and exacerbation of heart failure. AMI was diagnosed according to the universal definition of myocardial infarction proposed by the Joint European Society of Cardiology/American Heart Association/World Heart Federation Task Force [4]. This study was approved by the Ethics Committee of the Sakurajyuji Hospital, who waived the requirement for patient written informed consent, as only deidentified data were used. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Human Research Committee of the institution.

A foreshock (seismic scale: 7) of a 6.5 magnitude earthquake occurred on April 14, 2016, in Kumamoto, and a subsequent mainshock of magnitude 7.3 occurred on April 16, 2016 (seismic scale: 7). Thereafter, 22 of the 25 following earthquakes during April 2016 measured ≥5 on the 7-stage seismic scale (88 %) [5]. Therefore, we defined April 2016 as the exposure period and excluded patients who developed AMI between April 1 and April 30, 2016, from the statistical analyses.

We applied a generalized linear model based on the Poisson distribution of AMI monthly counts and subsequent in-hospital cardiac events and explored whether the AMI trend after the earthquake differed from that before the earthquake, after adjusting for seasonality and long-term trends [6]. We adjusted for seasonal variations in hospital AMI admissions by including two sine/cosine pairs [7]. Residual autocorrelation was negligible after checking the plot of the model residuals and the partial autocorrelation function. The monthly AMI cases per 10,000 age-standardized population were counted, and the rate ratio (RR) was calculated by comparing the post-earthquake trend in AMI with the pre-earthquake trend that would have continued in the absence of the earthquake. Stratified analyses were conducted to investigate whether the Kumamoto earthquake may have had a differential impact according to the patient background. We also explored AMI characteristics and procedures to speculate the relationships with in-hospital outcomes. Data were analyzed using STATA version 16, and all tests were two-sided and performed at a 5 % level of statistical significance.

3. Results

A total of 6553 consecutive patients who developed AMI between January 1, 2013, and December 31, 2019, were enrolled. The 74 patients who developed AMI during April 2016 were excluded from the statistical analyses. Finally, the study included 6479 patients (4646 men and 1833 women). The number of patients before the Kumamoto earthquake (January 2013–March 2016) was 2978 (n = 902 [January to December in 2013], n = 900 [January to December in 2014], n = 902 [January to December in 2015], n = 274 [January to March in 2016]), and the number after the earthquake (May 2016–December 2019) was 3501 (n = 646 [May to December in 2016], n = 1012 [January to December in 2017], n = 922 [January to December in 2018], n = 921 [January to December in 2019]).

Age-standardized onset rates and the predicted regression curve are shown in Fig. 1. We observed a significant increase in the rate of AMI after the earthquake ($p = 0.049$). Table 1 demonstrates the monthly cases and RRs before and after the Kumamoto earthquake. The mean number of AMI onset cases was 0.43 per 10,000 age-standardized population per month before the earthquake and 0.45 after the earthquake. The RR after the earthquake compared with that before the earthquake was 1.12 (95 % confidence interval [CI]:1.00–1.25). The RR for in-hospital mortality (RR: 1.10, 95 % CI: 0.78–1.56) was not different; however, in-hospital cardiac events were significantly more frequent after the Kumamoto earthquake (RR: 1.49, 95 % CI: 1.03–2.15, $p = 0.035$) (Fig. 2).

Stratified analyses were performed to explore the factors that influence AMI incidence. Age ≥ 65 years (RR: 1.12, 95 % CI: 0.99–1.26) and male sex (RR: 1.21, 95 % CI: 0.96–1.53) did not show a risk increase after the earthquake. Regarding coronary risk factors, AMI rates

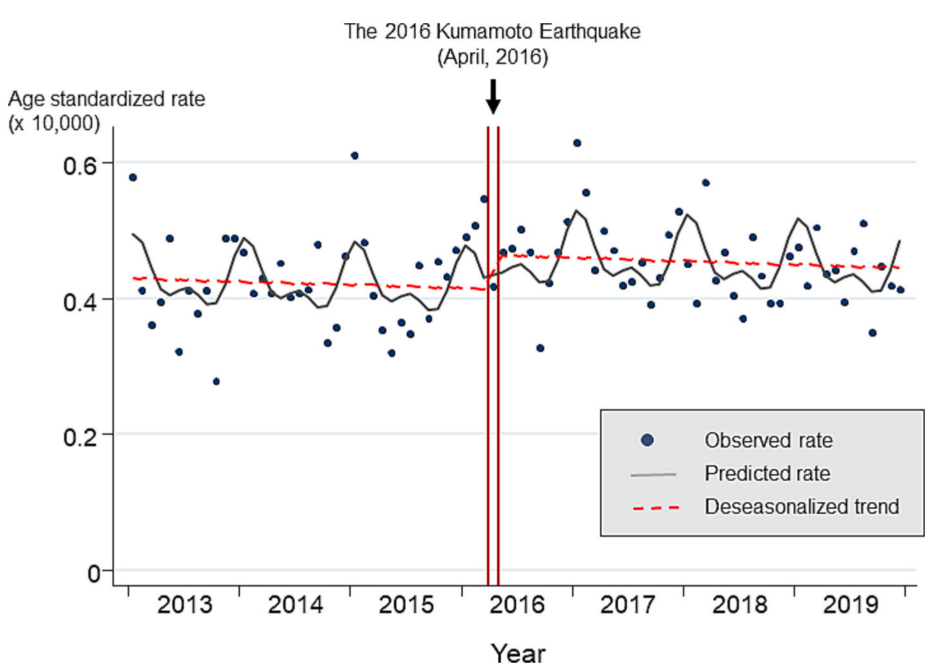

Fig. 1. Monthly AMI cases in Kumamoto, Japan, between 2013 and 2019.

Table 1
Background of AMI patients before and after the Kumamoto earthquake.

	Before earthquake	After earthquake	p-Value
	January 2013 to March 2016	May 2016 to December 2019	
	n = 2978	n = 3501	
Age ≥ 65 years	52.7 ± 9.5	57.3 ± 7.5	
	0.29 ± 0.05	0.33 ± 0.04	
		1.12 (0.99–1.26)	0.065
Men	54.8 ± 10.2	56.8 ± 7.9	
	0.31 ± 0.06	0.32 ± 0.04	
		1.21 (0.96–1.53)	0.212
Current smoking	21.4 ± 6.5	23.9 ± 4.9	
	0.12 ± 0.04	0.14 ± 0.03	
		1.27 (1.03–1.56)	0.027
Hypertension	55.4 ± 10.6	59.9 ± 8.3	
	0.31 ± 0.06	0.34 ± 0.05	
		1.12 (0.99–1.28)	0.081
Hyperlipidemia	41.5 ± 9.7	46.0 ± 7.2	
	0.23 ± 0.05	0.26 ± 0.04	
		1.04 (0.89–1.22)	0.627
Diabetes	27.7 ± 6.2	31.0 ± 6.1	
	0.16 ± 0.04	0.18 ± 0.04	
		1.20 (1.01–1.44)	0.038
Chronic kidney disease	33.3 ± 7.3	36.6 ± 5.7	
	0.19 ± 0.04	0.21 ± 0.03	
		1.09 (0.94–1.27)	0.248
Body mass index ≥25 kg/m^2	22.3 ± 5.0	24.6 ± 5.2	
	0.12 ± 0.03	0.14 ± 0.03	
		1.27 (1.06–1.52)	0.010

Top: monthly cases (mean ± standard deviation); middle: monthly cases per 10,000 age-standardized population (mean ± standard deviation); bottom: rate ratio (95 % confidence interval).
Chronic kidney disease is defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

increased after the earthquake among people with diabetes mellitus (RR: 1.20, 95 % CI: 1.01–1.44), those with current smoking (RR: 1.27, 95 % CI: 1.03–1.56), and those with a body mass index >25 kg/m^2 (RR: 1.27, 95 % CI: 1.06–1.52), whereas no significant trend change was noted among people with hypertension (RR: 1.12, 95 % CI: 0.99–1.28), hyperlipidemia (RR: 1.04, 95 % CI: 0.89–1.22) and chronic kidney disease (RR: 1.09, 95 % CI: 0.94–1.27) (Table 1).

Factors that affect in-hospital prognosis were also examined. The number of patients with morning onset (RR: 1.23, 95 % CI: 1.02–1.50), onset-to-door time >12 h (RR: 1.46, 95 % CI: 1.02–2.08), and a high Killip class on hospital admission (RR: 1.37, 95 % CI: 1.13–1.67) was significantly higher after the earthquake than before the earthquake. Unperformed procedures including emergent coronary angiography (RR: 1.40, 95 % CI: 1.02–1.91), intra-aortic balloon pumping (RR: 1.12, 95 % CI: 1.00–1.26), and percutaneous cardiopulmonary support (RR: 1.13, 95 % CI: 1.01–1.27) were frequently observed (Table 2).

4. Discussion

The number of patients with AMI significantly increased after the earthquake in the Kumamoto Prefecture with the monthly AMI incidence increasing by 12 %. This equates to 100 more AMI patients in the first year after the earthquakes. We found a significant increase in the frequency of AMI-related risk factors, such as diabetes mellitus, active smoking, and obesity, with these rates being over 20 %.

The incidence of AMI after the earthquake has been previously reported [8]. Deleterious effects of stress may yield alterations in cardiac regulation by the sympathetic nervous system as well as in hemostasis, leading to the onset of AMI [9]. However, significant increases in AMI admissions after a major earthquake have not been consistent [8], possibly due to several varying factors, such as earthquake type, magnitude, region, onset time, and season, which may have different and serious impacts on stress. The deleterious effects of coronary risk factors may be amplified as a consequence of the earthquake. This study discovered that the earthquake contributed to considerable lifestyle changes; moreover, increased prevalence of diabetes, active smoking, and obesity led to increased risk of AMI.

Previous observational studies used a “before and after” study design, specifically comparing AMI mortality between several years before and after the earthquake. Moreover, the use of the mean number of AMI cases or deaths in the same periods of the previous years as a

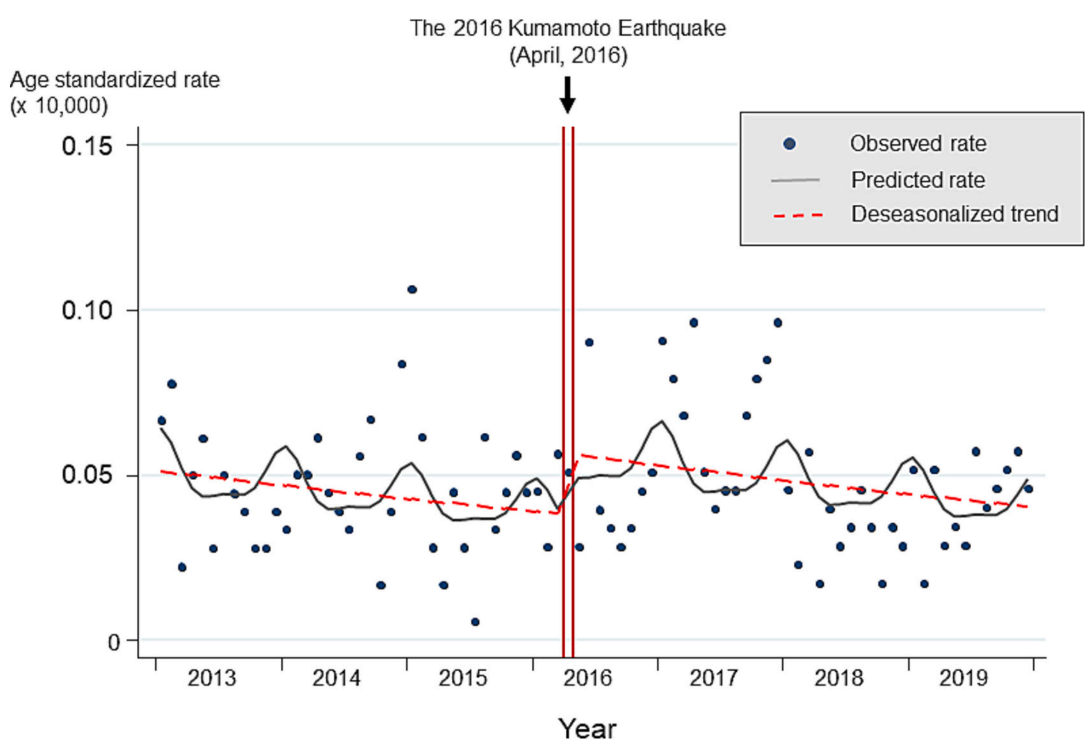

Fig. 2. Monthly in-hospital cardiac events in AMI cases in Kumamoto, Japan, between 2013 and 2019.

Table 2
AMI characteristics and unperformed procedures before and after the Kumamoto earthquake.

	Before earthquake	After earthquake	p-Value
	January 2013 to March 2016	May 2016 to December 2019	
	n = 2978	n = 3501	
Characteristics			
Onset time 6:00 to 11:59 a.m.	19.6 ± 5.0	23.2 ± 4.4	
	0.11 ± 0.03	0.13 ± 0.03	
		1.23 (1.02–1.50)	0.033
Onset-to-door time >12 h	9.6 ± 3.4	7.3 ± 3.8	
	0.05 ± 0.02	0.04 ± 0.02	
		1.46 (1.02–2.08)	0.040
STEMI	56.3 ± 9.9	57.6 ± 8.7	
	0.31 ± 0.05	0.32 ± 0.04	
		1.14 (0.99–1.32)	0.072
Killip II + III + IV	21.3 ± 5.2	23.6 ± 5.8	
	0.12 ± 0.03	0.13 ± 0.03	
		1.37 (1.13–1.67)	0.001
Culprit LAD region	25.9 ± 5.7	31.1 ± 6.8	
	0.14 ± 0.03	0.18 ± 0.04	
		1.06 (0.88–1.28)	0.520
Unperformed procedures			
Emergent CAG	15.7 ± 4.9	10.5 ± 5.4	
	0.09 ± 0.03	0.06 ± 0.03	
		1.40 (1.02–1.91)	0.035
Coronary revascularization	19.7 ± 5.3	13.6 ± 5.8	
	0.11 ± 0.03	0.08 ± 0.03	
		1.28 (0.98–1.66)	0.066
IABP	66.0 ± 11.1	71.0 ± 9.3	
	0.37 ± 0.06	0.40 ± 0.05	
		1.12 (1.00–1.26)	0.046
PCPS	74.7 ± 12.5	77.4 ± 10.4	
	0.42 ± 0.07	0.44 ± 0.06	
		1.13 (1.01–1.27)	0.034

Top: monthly cases (mean ± standard deviation); middle: monthly cases per 10,000 age-standardized population (mean ± standard deviation); bottom: rate ratio (95 % confidence interval).
Emergent CAG is defined as that performed <24 h from AMI onset.
AMI, acute myocardial infarction; CAG, coronary angiography; IABP, intra-aortic balloon pumping; LAD, left anterior descending branch; PCPS, percutaneous cardiopulmonary support; STEMI, ST-elevation myocardial infarction.

control might have been unable to fully account for the underlying trends of AMI onset. As there may be a nonuniform distribution in the number of AMI cases during the control period, seasonal variation and unknown chronobiological factors may mask the true effects of the earthquake on AMI incidence. In the present study, we introduced an ITS design that was superior to the “before and after” designs, in that it avoided threats to internal validity, such as short-term fluctuations, secular trends, and regression to the mean [3].

Since the 1990s, Japan has experienced several major earthquakes (the Great Hanshin-Awaji earthquake in 1995 [10], the Niigata-Chuetsu earthquake in 2004 [11], and Great East Japan Earthquake in 2011 [12–15]), including the Kumamoto earthquake in 2016. The reported results of earthquake impact on AMI incidence and subsequent outcomes are conflicting, which may be due to heterogeneous data and different statistical methods. However, a systematic review reported a possible impact of the earthquake on the incidence of acute coronary syndrome and cardiac mortality [16]. The present study failed to show a significant increase in mortality due to AMI as only cases with a definite diagnosis were included, and cases with no clear cause or suspected AMI, such as out-of-hospital cardiac arrest of presumed cardiac origin, were excluded from the KACE study.

Most of the core hospitals in Kumamoto Prefecture were not affected by the Kumamoto earthquake and were able to accept and treat AMI patients. Nevertheless, the poor prognosis of patients after hospitalization may have resulted in part from the delayed arrival of AMI patients and the inability to provide aggressive treatments after the earthquake. It is possible that the victims were unable to visit a hospital, making it difficult for them to continue taking their oral medications. The exacerbation of the risks may have led to the onset of AMI. Although these points need to be verified further, we believe that there is a critical need to establish a medical emergency system urgently. The government must actively inform high-risk victims that they will continue to receive treatments following an earthquake.

4.1. Limitations

This study has several limitations. First, although almost all AMI patients were transferred to participating core hospitals capable of performing coronary angiography and coronary intervention in the Kumamoto Prefecture [2], not all patients may have been registered in the KACE registry, especially during the earthquake period, as AMI patients might be transported to smaller facilities other than the core hospitals. Second, psychological stress could not be assessed for AMI incidence after the Kumamoto earthquake. However, there is an enormous amount of literature on psychological stress and cardiovascular disease [9]. Mental and physical stress after the Kumamoto earthquake may have had some influence on the onset of AMI as many buildings and houses collapsed and people in the affected areas were forced to live as evacuees in temporary housing. A previous study reported that emotional stress levels increased after the Great Hanshin-Awaji earthquake by using the post-traumatic stress disorder reaction index score and elucidated that AMI could be triggered by severe emotional stress due to an earthquake [17]. However, there may be numerous factors besides mental and physical stress caused by earthquakes that could be difficult to assess. Third, the ITS designs lack control for other environmental exposures that might affect the natural trend of AMI onset. Several large-seismic scale earthquakes occurred during the study period (2013–2019) in Japan. In September 2018, Hokkaido experienced a seismic scale 7 earthquake (Hokkaido Eastern Iburi earthquake), which was equivalent to the Kumamoto earthquake. Previous reports have shown a positive relationship between the disaster area near the epicenter and cardiovascular mortality [10,11]. However, as Kumamoto and Hokkaido are approximately 1400 km apart and the Hokkaido Eastern Iburi earthquake did not directly cause any damage in the Kumamoto Prefecture, it is unlikely that this earthquake had a significant impact on the results of this study. At the end of 2019, the novel coronavirus first appeared in Wuhan, China; however, it was not identified in Japan until January 2020 [18].

5. Conclusions

The Kumamoto earthquake had an impact on the increase in the incidence of AMI and following in-hospital cardiac events. Emergency medical care should be ensured in a way that high-risk patients are treated and managed as usual, especially immediately after the earthquake.

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Disclaimers

Not applicable.

Meeting/presentation

Not applicable.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A

The KACE study investigators are listed below in alphabetical order.

Amakusa Medical Center: Naritsugu Sakaino; Arao City Hospital: Ichiro Kajiwara; Aso Medical Center: Shinzo Miyamoto; Japan Community Health Care Organization Hitoyoshi Medical Center: Hirofumi Kurokawa; Japan Community Health Care Organization Kumamoto General Hospital: Shunichi Koide; Japanese Red Cross Kumamoto Hospital: Ryusuke Tsunoda; Kamiamakusa General Hospital, Genki Moriguchi; Kumamoto Central Hospital, Kenji Morihisa; Kumamoto City Hospital, Ikuo Misumi; Kumamoto Kenhoku Hospital: Masakazu Matsukawa; Kumamoto Kinoh Hospital: Eisaku Harada; Kumamoto Regional Medical Center: Nobutaka Hirai; Kumamoto Saishunso National Hospital: Jun Hokamaki; Kumamoto Rosai Hospital: Toshiyuki Matsumura; Kumamoto University Hospital: Kenichi Tsujita; Minamata City General Hospital and Medical Center: Toyoki Hirose; National Hospital Organization Kumamoto Medical Center: Kazuteru Fujimoto; Saiseikai Kumamoto Hospital, Tomohiro Sakamoto; Sugimura Hospital, Hiroshi Matsuda; Taragi Municipal Hospital, Tomio Wakita; Ueki Hospital: Seiji Hokimoto.

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