

RESEARCH REPORTS

IMPACT OF A NATIONWIDE NOTIFICATION PROMOTING EARLY ADRENALINE ADMINISTRATION ON TIME TO FIRST ADRENALINE IN OUT-OF-HOSPITAL CARDIAC ARREST IN JAPAN: AN INTERRUPTED TIME-SERIES ANALYSIS

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ABSTRACT

Purpose: This study evaluated whether the March 30, 2017, nationwide notification from the Fire and Disaster Management Agency (FDMA) shortened the time from patient contact to adrenaline administration (adrenaline time) for out-of-hospital cardiac arrest (OHCA).

Methods: We conducted an interrupted time-series (ITS) analysis using data from the All-Japan Utstein Registry (January 1, 2010–April 26, 2020). The study included OHCA patients who received adrenaline, with adrenaline time as the primary outcome. We estimated the immediate level change and post-intervention slope change, stratified by shockable and non-shockable rhythms. Ninety-five percent confidence intervals (CIs) and p values were Bonferroni-adjusted for the coprimary endpoints (level and slope change).

Results: We analyzed 18,412 patients in the shockable group and 160,013 in the non-shockable group. For the shockable group, the notification was not associated with a statistically significant level change (.19 minutes; 95% CI_{adj} [-0.33, 0.71]; $p_{adj} = .81$) or slope change (-0.01 minutes/30-day; 95% CI_{adj} [-0.03, 0.01]; $p_{adj} = .38$). Similarly, for the non-shockable group, no significant level change (-0.09 minutes; 95% CI_{adj} [-0.30, .11]; $p_{adj} = .59$) or slope change (-0.01 minutes/30-day; 95% CI_{adj} [-0.02, 0.00]; $p_{adj} = .10$) was observed.

Conclusion: The FDMA notification was not associated with an immediate or long-term reduction in adrenaline time, a clinically relevant prehospital process measure on the causal path to better outcomes.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) affects approximately 130,000 people annually in Japan (Fire and Disaster Management Agency, 2020a). As in other countries, OHCA remains an important public health challenge (Berdowski et al., 2010). In Japan's prehospital emergency care, intravenous adrenaline administration by emergency life-saving technicians (ELSTs) is standard

practice (Japan Resuscitation Council, 2016, 2021). A large randomized controlled trial and its long-term follow-up showed that adrenaline increased the return of spontaneous circulation and survival to hospital discharge but did not clearly improve favorable neurological outcomes (Haywood et al., 2021; Perkins et al., 2018). In recent years, it has been suggested that the timing of adrenaline administration, in addition to whether it is administered, can affect outcomes, with some reports indicating that early administration is associated with improved survival and favorable neurological outcomes (Okubo et al., 2021; Ran et al., 2020).

The Japan Resuscitation Council (JRC) Guidelines 2015 were the first to address the timing of adrenaline administration, recommending it as early as possible for non-shockable rhythms and proposing adrenaline administration for shockable rhythms after unsuccessful defibrillation (Japan Resuscitation Council, 2016). On March 30, 2017, the Fire and Disaster Management Agency (FDMA) issued a nationwide notification (FDMA Notification No. 41) as non-binding “technical advice” under Article 37 of the Fire Organization Act (Fire and Disaster Management Agency, 2017). Consistent with the JRC Guidelines 2015, it encouraged adrenaline administration as early as possible after patient contact in non-shockable cases; operational protocols were left to regional medical control (MC) councils, and no nationally mandated numerical time targets were specified. However, the extent to which this policy intervention shortened the time to adrenaline administration nationwide has not been systematically evaluated.

Earlier adrenaline is associated with improved survival and neurological outcomes (Nakagawa et al., 2023; Okubo et al., 2021; Ran et al., 2020), and shortening the time to adrenaline is a recognized quality goal; whether a national policy can achieve this has not been tested. In what is, to our knowledge, the first nationwide interrupted time-series evaluation of this policy, we therefore addressed a single question: Did the 2017 FDMA notification reduce the time from patient contact to first adrenaline administration (adrenaline time) nationwide? The study focused on whether the policy made prognosis-relevant early adrenaline achievable in practice rather than on patient prognosis itself; its outcome is a prehospital process measure (adrenaline time) not survival, and a rigorously estimated result—positive or null—informs how such policies should be designed.

METHODS

STUDY DESIGN

This observational study used an interrupted time-series (ITS) design with data from the All-Japan Utstein Registry. This study was designed and analyzed using established recommendations for interrupted time-series and segmented-regression analyses (Jandoc et al., 2015; Lopez Bernal et al., 2017; Penfold & Zhang, 2013; Wagner et al., 2002).

This study was approved by the Chuo University Ethics Committee (approval number 2025-076). The requirement for individual informed consent was waived because the study used de-identified registry data.

STUDY SETTING

As of 2020, Japan had a population of approximately 126 million and an area of 378,000 km². In Japan, emergency medical services (EMS) are provided around the clock by fire

departments (Okada et al., 2024). The system is single-tiered, with ambulances typically staffed by three emergency medical technicians (EMTs), at least one of whom is an ELST. Under the online medical direction of a physician, ELSTs are authorized to perform advanced life support (ALS) procedures such as establishing intravenous access, adrenaline administration, and advanced airway management (AAM) (e.g., supraglottic airway or endotracheal intubation). Within this scope, adrenaline is the only resuscitation drug that ELSTs are authorized to administer; antiarrhythmic agents are not legally authorized for administration by ELSTs, and physician-staffed ALS cases were excluded, so antiarrhythmic administration is structurally absent from this cohort. As a general rule, ELSTs administer adrenaline to cardiac-arrest patients aged 8 years or older, at a fixed dose of 1 mg irrespective of age or body weight; a small number of younger patients may receive adrenaline under exceptional circumstances (for example, when intravenous access has already been established), and all such cases were retained in the analysis. Adrenaline is administered intravenously using a 1-mg prefilled syringe, with repeat doses of 1 mg every 3-5 minutes. Although early adrenaline administration is a fundamental principle, transport to a medical facility may be prioritized over on-scene treatment depending on environmental factors and the estimated transport time. Consequently, adrenaline is sometimes not administered at the scene or is administered during transport to the hospital (e.g., inside an ambulance).

The intervention evaluated in this study was FDMA Notification No. 41, issued on March 30, 2017. It was distributed to fire departments nationwide as “technical advice” under Article 37 of the Fire Organization Act—an advisory instrument rather than a binding directive. In line with the JRC Guidelines 2015, the notification recommended earlier adrenaline administration for non-shockable rhythms; for shockable rhythms, adrenaline continued to follow unsuccessful defibrillation (approximately two minutes after the shock). Because the notification delegated implementation to regional MC councils and set no nationwide numerical time targets, its intensity and uniformity of implementation likely varied across regions—a feature central to interpreting our findings.

On April 27, 2020, the FDMA issued a nationwide notification to fire departments titled “Guidelines for the Response of Fire Departments to Patients with Cardiopulmonary Arrest Associated with Coronavirus Disease 2019 (COVID-19)” (Fire and Disaster Management Agency, 2020b). In addition to enforcing standard precautions, these guidelines emphasized infection-control measures for aerosol-generating resuscitation procedures and noted that early instrumented airway management (AAM) was desirable when it could be performed rapidly and reliably to minimize air leakage from patient exhalation. Because this may have increased the number of cases in which AAM was prioritized over adrenaline administration, this study used data from before the guidelines were issued.

In Japan, EMS personnel are typically not authorized to terminate resuscitation at the scene; thus, all patients for whom resuscitation is attempted are transported to the hospital. However, resuscitation attempts are not initiated in conditions such as severe torso trauma, traumatic brain injury with severe cerebral prolapse, skeletal remains, or early postmortem changes.

The ALS protocol in Japan is based on JRC guidelines, which are in accordance with the International Liaison Committee on Resuscitation Consensus. Furthermore, based on the

JRC guidelines, the FDMA notifies fire departments nationwide about its EMS protocols, allowing regional departments to establish their own protocols tailored to their local medical systems.

STUDY PARTICIPANTS

This study included patients with OHCA who were treated between January 1, 2010 and April 26, 2020 and received prehospital adrenaline. The exclusion criteria were: (1) receipt of physician-administered ALS, (2) EMS-witnessed cardiac arrest, (3) missing dispatcher-assistance data, (4) an unknown initial electrocardiogram (ECG) rhythm, (5) an adrenaline time of < 0 or > 40 minutes, and (6) a response time (emergency call to patient contact) of < 0 or > 20 minutes. Because the timing of adrenaline administration differs according to the initial ECG rhythm, the patients were divided into shockable and non-shockable groups, and each group was analyzed separately.

DATA COLLECTION AND QUALITY CONTROL

The All-Japan Utstein Registry, a nationwide OHCA registry, was established by the FDMA in January 2005. The registry records data in the international Utstein style. Utstein-style variables have been described previously (Jacobs et al., 2004; Okada et al., 2024). Time-related data were recorded by EMS personnel at the scene and compiled into a registry. These data included the times of emergency calls, ambulance dispatch, arrival at the scene, patient contact, adrenaline administration, and hospital arrival. The data were recorded in minutes (min).

OUTCOME

The primary outcome was the adrenaline time (min), defined as the interval from EMS patient contact to the first prehospital adrenaline administration.

STATISTICAL ANALYSIS

Because the timing and role of adrenaline differ fundamentally by initial rhythm—adrenaline is given as early as possible for non-shockable rhythms but only after unsuccessful defibrillation for shockable rhythms—all analyses were pre-specified to stratify by initial rhythm, modeling the shockable and non-shockable groups separately. We then summarized patient characteristics for the pre-intervention (January 1, 2010, to March 29, 2017) and post-intervention (March 30, 2017, to April 26, 2020) periods within each group. Categorical variables were presented as counts (percentages) and continuous variables as means (standard deviations). Imbalances between groups were assessed using the standardized mean difference (SMD).

In the ITS analysis, we defined the intervention date (March 30, 2017) as day 0. We then aggregated the data into 30-day intervals using the mean adrenaline time for each interval as a single time-series observation. An ITS segmented regression model was applied separately to the shockable and non-shockable rhythm groups to estimate the immediate-level and post-intervention slope changes associated with the intervention.

To assess the plausibility of the ITS design assumptions, we prospectively examined three conditions: (1) the assignment rule and threshold were clear, (2) the assignment variable (calendar date) was not subject to arbitrary manipulation, and (3) the assign-

ment variable did not affect other factors related to the outcome (Kontopantelis et al., 2015). Condition 1 was satisfied because the intervention date could be uniquely defined. Regarding condition 2, the intervention was a policy change based on a notification from the FDMA, making it practically impossible for providers in the field to manipulate the assignment variable. For condition 3, we tested for discontinuities at the intervention point by replacing the primary outcome in the ITS model with baseline covariates potentially associated with adrenaline time. These covariates included the day and time of OHCA onset, age, sex, etiology of arrest, witness status, bystander cardiopulmonary resuscitation (BCPR), public-access defibrillation (PAD), dispatcher assistance, EMS defibrillation, AAM before adrenaline administration, and response time. Only covariates that showed potential discontinuity were included in the final adjusted ITS model.

To account for seasonality, we compared a model with no harmonic terms to models with harmonic terms ($k = 1-4$), assuming a 12-month cycle (Lopez Bernal et al., 2017). The final model for each group was selected using the Bayesian Information Criterion (BIC), which penalizes model complexity to avoid overfitting. Consequently, we adopted a model with $k = 1$ for the shockable group and $k = 2$ for the non-shockable group.

The effect of the intervention was estimated from the ITS models by calculating partial regression coefficients, Bonferroni-adjusted 95% confidence intervals (CIs), and Bonferroni-adjusted p -values. Because both level and slope changes were considered primary endpoints, we applied the Bonferroni method to adjust the significance level ($\alpha = 0.05/2 = 0.025$), controlling Type I error inflation from multiple comparisons.

Furthermore, we visualized the trend of the 30-day mean adrenaline time on a relative time axis. The observed 30-day averages are plotted as points in the figures. These points are overlaid with the fitted trend (solid line) and Bonferroni-adjusted 95% CI derived from the final ITS model. Additionally, the counterfactual trajectory, assuming the pre-intervention trend would have continued without the intervention, was extrapolated into the post-intervention period and displayed as a red dashed line with its corresponding 95% CI.

We conducted three sensitivity analyses to assess the robustness of the primary findings. First, we repeated the primary ITS analysis after excluding the initial 6 months following the intervention date. This accounts for a possible phased rollout of policies across different medical control (MC) regions. Second, we performed an ITS analysis with the pre-intervention period restricted to either the 24 or 36 months immediately preceding the intervention to evaluate the influence of long-term pre-intervention data on our estimates. Third, we conducted the primary analysis after excluding all data later than December 31, 2019—around the time the first COVID-19 cases were reported to the World Health Organization—to assess the potential impact of pandemic-related changes in the EMS system and operational procedures (World Health Organization, 2020). In all sensitivity analyses, we applied the same ITS model as in the primary analysis, with level and slope changes as endpoints.

Autocorrelation function plots of the residuals from our primary models showed no evidence of significant autocorrelation. The residuals satisfied the normality assumption. All statistical analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at .05 (two-tailed).

RESULTS

Figure 1 shows the patient selection flowchart. Of the 1,254,273 OHCA cases registered during the study period, 229,298 received adrenaline. After applying all eligibility criteria, 178,425 patients were included in the final analysis. This cohort consisted of 18,412 patients in the shockable rhythm group (pre-intervention, $n = 12,514$; post-intervention, $n = 5,898$) and 160,013 patients in the non-shockable rhythm group (pre-intervention, $n = 94,507$; post-intervention, $n = 65,506$).

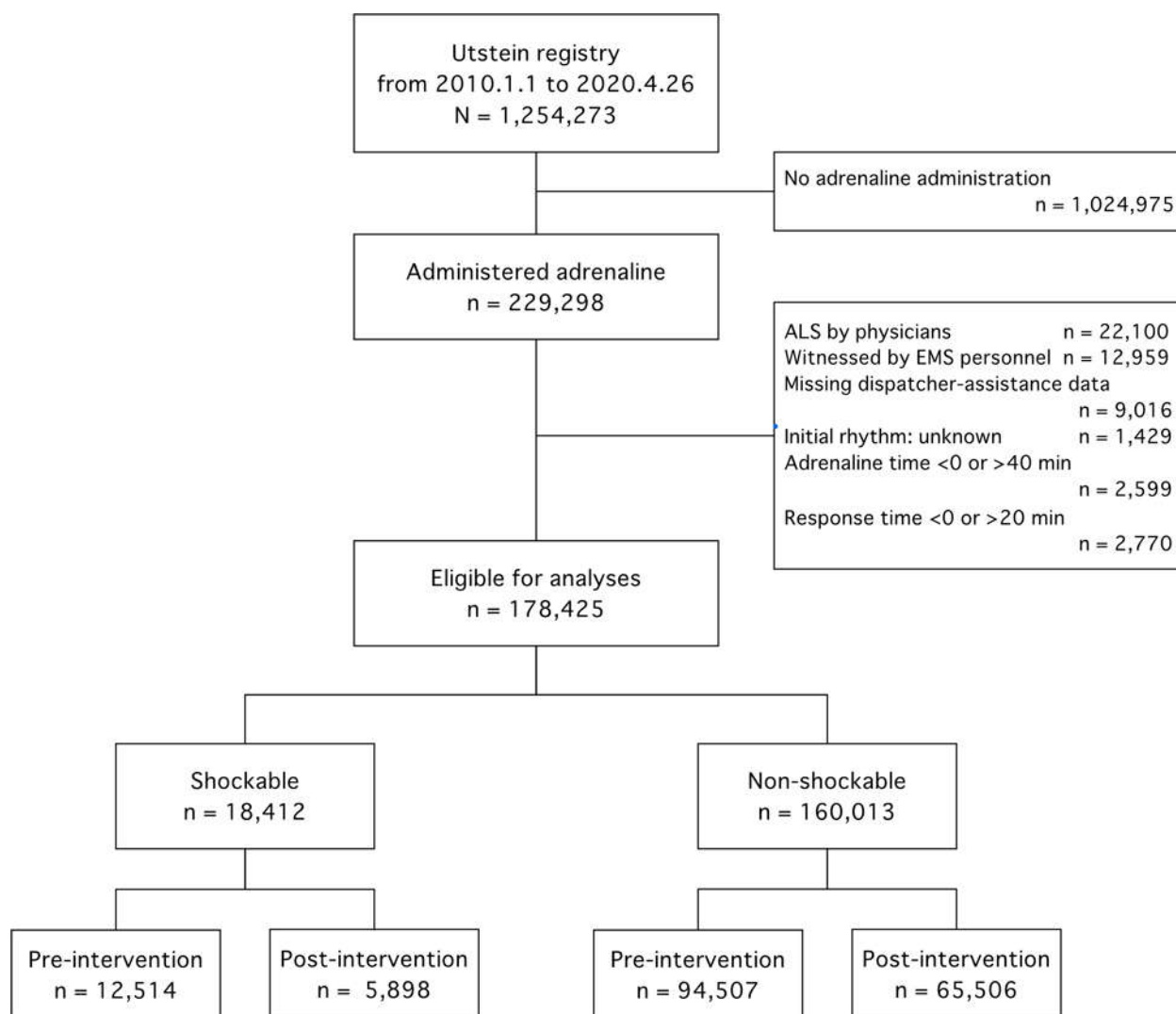


Figure 1. Patient selection flowchart.

Abbreviations: ALS, advanced life support; EMS, emergency medical service.)

Patient characteristics are summarized in Table 1. In the shockable rhythm group, the mean patient age was 67.1 years, and 80.0% were male. The age distribution was overwhelmingly adult: the median age was 69 years (interquartile range [IQR], 58-78; range, 8-105), and pediatric patients (< 16 years) accounted for only 0.1%. Bystander CPR (62.8% vs. 55.6%; SMD = 0.15), dispatcher assistance (68.1% vs. 58.9%; SMD = 0.19), and defibrillation by EMS (98.2% vs. 95.5%; SMD = 0.17) were all more frequent in the post-intervention period, as was AAM before adrenaline administration (50.1% vs. 36.7%; SMD = 0.27).

The mean response time was slightly longer in the post-intervention period (8.0 vs. 7.7 min; SMD = 0.10), whereas the mean time to adrenaline administration was longer in the pre-intervention period (14.2 vs. 13.5 min; SMD = 0.12).

Characteristic	Shockable				Non-Shockable			
	Overall	Pre-Inter- vention	Post-Inter- vention	SMD	Overall	Pre-Inter- vention	Post-Inter- vention	SMD
<i>n</i> (%)	<i>n</i> = 18,412	<i>n</i> = 12,514	<i>n</i> = 5,898		<i>n</i> = 160,013	<i>n</i> = 94,507	<i>n</i> = 65,506	
Occurrence date				0.006				0.004
Weekday	12,904 (70.1)	8,759 (70.0)	4,145 (70.3)		112,999 (70.6)	66,670 (70.5)	46,329 (70.7)	
Weekend	5,508 (29.9)	3,755 (30.0)	1,753 (29.7)		47,014 (29.4)	27,837 (29.5)	19,177 (29.3)	
Occurrence time frame				0.01				0.02
Daytime	8,389 (45.6)	5,689 (45.5)	2,700 (45.8)		68,145 (42.6)	40,674 (43.0)	27,471 (41.9)	
Nighttime	10,023 (54.4)	6,825 (54.5)	3,198 (54.2)		91,868 (57.4)	53,833 (57.0)	38,035 (58.1)	
Age, mean (SD), y	67.1 (15.2)	66.9 (15.3)	67.5 (15.1)	0.04	76.3 (14.6)	75.9 (14.8)	76.9 (14.3)	0.07
Age, median [IQR] (range), y	69 [58–78] (8–105)	68 [58–78] (8–103)	69 [58–79] (9–105)		80 [70–86] (0–110)	79 [69–86] (0–107)	80 [70–87] (0–110)	
Age group, n (%)				0.05				0.07
<16 y	19 (0.1)	16 (0.1)	3 (0.1)		217 (0.1)	138 (0.1)	79 (0.1)	
16–64 y	7,069 (38.4)	4,879 (39.0)	2,190 (37.1)		27,165 (17.0)	17,015 (18.0)	10,150 (15.5)	
≥65 y	11,324 (61.5)	7,619 (60.9)	3,705 (62.8)		132,631 (82.9)	77,354 (81.9)	55,277 (84.4)	
Sex, male	14,728 (80.0)	10,004 (79.9)	4,724 (80.1)	0.004	94,279 (58.9)	55,765 (59.0)	38,514 (58.8)	0.004
Cardiogenic	16,626 (90.3)	11,215 (89.6)	5,411 (91.7)	0.07	98,440 (61.5)	56,924 (60.2)	41,516 (63.4)	0.07
Witnessed	4,631 (25.2)	3,168 (25.3)	1,463 (24.8)	0.002	27,298 (17.1)	16,686 (17.7)	10,612 (16.2)	0.04
Bystander CPR performed	10,660 (57.9)	6,958 (55.6)	3,702 (62.8)	0.15	86,803 (54.2)	49,219 (52.1)	37,584 (57.4)	0.11
Public access defibrillation	794 (4.3)	523 (4.2)	271 (4.6)	0.02	1,885 (1.2)	1,101 (1.2)	784 (1.2)	0.003
Dispatcher-assistance	11,391 (61.9)	7,375 (58.9)	4,016 (68.1)	0.19	101,913 (63.7)	57,852 (61.2)	44,061 (67.3)	0.13
Defibrillation by EMS	17,746 (96.4)	11,952 (95.5)	5,794 (98.2)	0.17	11,934 (7.5)	7,389 (7.8)	4,545 (6.9)	0.02
AAM before adrenaline administration	7,548 (41.0)	4,594 (36.7)	2,954 (50.1)	0.27	78,649 (49.2)	41,596 (44.0)	37,053 (56.6)	0.25
Response time, mean (SD), min	7.8 (2.8)	7.7 (2.8)	8.0 (2.7)	0.10	8.0 (2.9)	7.9 (2.9)	8.1 (2.9)	0.07
Time from EMS contact to adrenaline administration, mean (SD), min	14.0 (6.3)	14.2 (6.4)	13.5 (6.1)	0.12	14.9 (6.5)	15.1 (6.7)	14.4 (6.3)	0.11

Table 1. Baseline patients' characteristics stratified by initial rhythm and pre-/post-intervention periods.

Notes: Pre-intervention: cardiac arrests before the FDMA notification (2010-01-01 to 2017-03-29). Post-intervention: on/after the notification (2017-03-30 to 2020-04-26). Data are *n* (%) unless otherwise indicated.

Abbreviations: SMD, standardized mean difference between pre- and post-intervention groups (continuous variables: standardized difference of means; the age-group categorical SMD uses the multinomial [Yang–Dalton] method). SD, standard deviation; IQR, interquartile range; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; AAM, advanced airway management.

In the non-shockable rhythm group, the mean patient age was 76.3 years, and 58.9% were male. The median age was 80 years (IQR, 70–86; range, 0–110), and pediatric patients (< 16 years) accounted for 0.1% of the group. Bystander CPR (57.4% vs. 52.1%; SMD = 0.11), dispatcher assistance (67.3% vs. 61.2%; SMD = 0.13), and AAM before adrenaline administration (56.6% vs. 44.0%; SMD = 0.25) were all more frequent in the post-intervention period.

As in the shockable group, the mean time to adrenaline administration was longer in the pre-intervention period (15.1 vs. 14.4 min; SMD = 0.11).

Table 2 shows the assessment of discontinuities in baseline covariates at the intervention point. In the shockable group, a significant discontinuity was observed in the proportion of patients receiving AAM before adrenaline administration (coefficient [95% CI], 0.04 [0.01, 0.07], $p = .02$). In the non-shockable group, significant discontinuities were identified in witness status (coefficient [95% CI], -0.03 [-0.04, -0.02], $p < .001$) and response time (coefficient [95% CI], 0.08 [0.02, 0.14], $p = 0.01$). Therefore, these variables were included in the final ITS model for adjustment.

Variable	Shockable			Non-Shockable		
	Coefficient	95% CI	p -value	Coefficient	95% CI	p -value
Occurrence date	-0.02	(-0.05 to 0.01)	0.13	0.01	(-0.00 to 0.02)	0.19
Occurrence time frame	0.02	(-0.01 to 0.05)	0.19	-0.01	(-0.02 to 0.00)	0.08
Age	0.72	(-0.23 to 1.68)	0.14	-0.06	(-0.36 to 0.24)	0.68
Sex	-0.02	(-0.04 to 0.01)	0.12	0.00	(-0.01 to 0.01)	0.50
Cardiogenic	0.01	(-0.01 to 0.02)	0.50	0.01	(-0.00 to 0.02)	0.21
Witness status	-0.02	(-0.05 to 0.01)	0.20	-0.03	(-0.04 to -0.02)	<.001
Bystander CPR performed	0.00	(-0.03 to 0.03)	0.90	0.00	(-0.01 to 0.01)	0.93
Public access defibrillation	0.00	(-0.02 to 0.01)	0.79	0.00	(-0.00 to 0.00)	0.88
Dispatcher-assistance	0.02	(-0.01 to 0.05)	0.30	0.00	(-0.01 to 0.01)	0.63
Defibrillation by EMS	0.00	(-0.01 to 0.00)	0.31	0.00	(-0.01 to 0.00)	0.35
AAM before adrenaline administration	0.04	(0.01 to 0.07)	0.02	-0.01	(-0.02 to 0.00)	0.09
Response time	0.09	(-0.08 to 0.27)	0.31	0.08	(0.02 to 0.14)	0.01

Table 2. Validity check of the interrupted time-series design: assessment of discontinuities in baseline covariates at the intervention point.

Note: This analysis was a necessary step to identify which baseline covariates required adjustment—only covariates showing a discontinuity were included in the adjusted model—and it does not estimate the intervention effect on adrenaline time, which is reported in Table 3. Each baseline covariate was substituted as the outcome to test for a level discontinuity at the intervention date.

Abbreviation: CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; AAM, advanced airway management.

The results of the primary ITS models are presented in Table 3 and illustrated in Figure 2. In the shockable group, no statistically significant immediate level change (0.19; 95% CI_{adj} [-0.33, 0.71]; $p_{adj} = .81$) or subsequent slope change (-0.01; 95% CI_{adj} [-0.03, 0.01]; $p_{adj} = .38$) was observed following the intervention. Similarly, in the non-shockable group, no significant changes were observed for either the level (-0.09; 95% CI_{adj} [-0.30, 0.11]; $p_{adj} = .59$) or the slope (-0.01; 95% CI_{adj} [-0.02, 0.00]; $p_{adj} = .10$).

The three sensitivity analyses are presented in Table 4. In the model excluding the initial 6 months post-intervention, the estimated level change for the shockable group was -0.16 (95% CI_{adj} [-0.69, 0.37]; $p_{adj} = 1.00$). Although not statistically significant, the direction of this effect differs from that in the primary model. For the non-shockable group, however, this analysis showed a statistically significant level change of -0.35 (95% CI_{adj} [-0.59, -0.10]; $p_{adj} = .004$). The remaining sensitivity analyses showed no statistically significant associations.

	Shockable ^a			Non-Shockable ^b		
	Coefficient	Bonferroni adj. 95 % CI ^c	Bonferroni adj. <i>p</i> ^c	Coefficient	Bonferroni adj. 95 % CI ^c	Bonferroni adj. <i>p</i> ^c
Level change	0.19	-0.33 to 0.71	0.81	-0.09	-0.30 to 0.11	0.59
Slope change	-0.01	-0.03 to 0.01	0.38	-0.01	-0.02 to 0.00	0.10

Table 3. Interrupted time-series model estimates of the level and slope changes in adrenaline time.

^a Shockable: pre-intervention intercept = 14.7, pre-intervention slope = -0.01, post-intervention slope = -0.02. Covariates: advanced airway management before adrenaline administration. Seasonality modeled by harmonic regression (12-month period, 1 harmonic). No multicollinearity among variables.

^b Non-shockable: pre-intervention intercept = 13.2, pre-intervention slope = -0.01, post-intervention slope = -0.02. Covariates: witness status and response time. Seasonality modeled by harmonic regression (12-month period, 2 harmonics). No multicollinearity among variables.

^c Bonferroni correction applied for the two primary comparisons ($\alpha = 0.025$). CI, confidence interval.

DISCUSSION

This study employed an ITS design with the All-Japan Utstein Registry to analyze changes in adrenaline time following the March 30, 2017, notification from the FDMA. Our results demonstrated no statistically significant immediate level change or post-intervention slope change. The significant level change in the non-shockable group, seen only after excluding the first 6 months (-0.35 min), suggests that the policy's effects may become apparent only after a phased implementation period. However, these findings suggest that any changes had limited clinical significance.

The FDMA notification likely failed to reduce adrenaline administration time nationwide because it was a low-intensity policy that granted broad discretion for implementation. As an advisory instrument based on the JRC Guidelines 2015, it relied on regional MC councils to develop operational protocols and lacked specific national targets. Consequently, implementation varied widely by region, likely diluting any local effects on the national average. Framed this way, a rigorously estimated null result is itself an actionable finding: an advisory notification that merely communicates a recommendation on paper—without embedded numerical time targets—did not shorten adrenaline time nationally.

Aichi Prefecture, which has a short adrenaline administration time, uses a specific time-based protocol for adrenaline administration (Aichi Council for the Advancement of Ambulance Services, n.d.; Ueta et al., 2023). This protocol codifies clear temporal goals—such as establishing intravenous access within 4 min of contact, the first adrenaline dose within the next 2 min, AAM within another 2 min, and the second adrenaline dose 2 min later, creating a shared operational standard (Table 5). Our findings suggest that a national notification without process-level details is unlikely to reduce adrenaline time nationwide. Aichi additionally operates its own regional certification system with intensive, standardized crew training, reinforcing these time targets in practice (Kitagawa & Saito, 2018). This implies that achieving a meaningful nationwide reduction requires a more specific policy that defines and embeds temporal goals into practice, supported by training and certification (Ueta et al., 2023). Similar time-target-based quality improvement frameworks have improved time-sensitive care in other emergency conditions (Fonarow et al., 2011).

The primary strength of this study is its quasi-experimental ITS design. This approach allowed us to estimate policy effects using continuous observational data from the

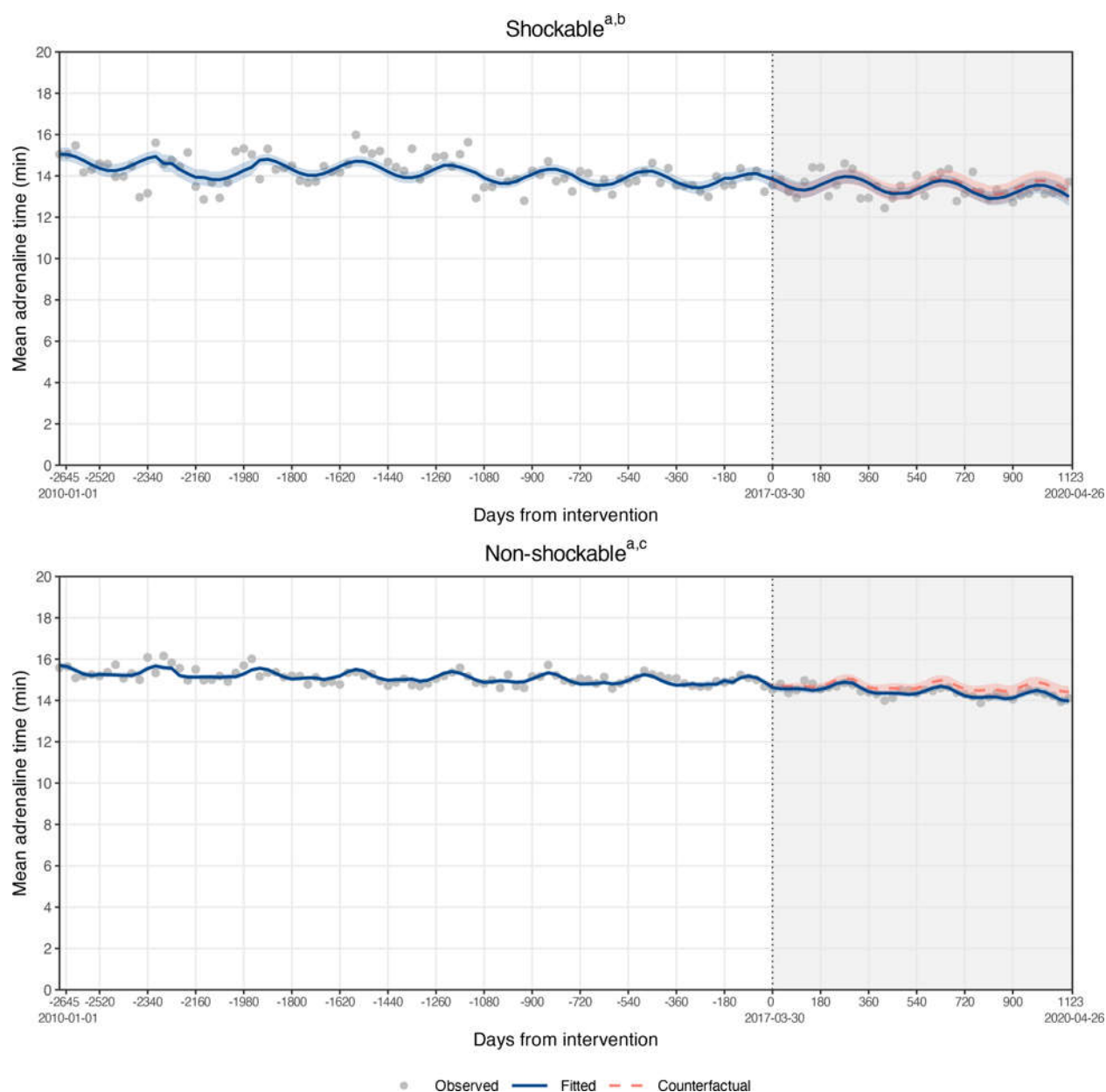


Figure 2. Trends in adrenaline time with interrupted time-series analysis.

Abbreviation: adrenaline time, time from emergency medical service contact to adrenaline administration.

^a Bonferroni-adjusted 95% confidence intervals ($\alpha = 0.025$ for two primary comparisons).

^b Covariates for shockable group include advanced airway management (AAM) before adrenaline administration; seasonality modeled using harmonic regression (12-month period, 1 harmonic). No multicollinearity was observed.

^c Covariates for non-shockable group include witness status and response time; seasonality modeled using harmonic regression (12-month period, 2 harmonics). No multicollinearity was observed.

All-Japan Utstein Registry with a clearly defined intervention date (Lopez Bernal et al., 2017; Penfold & Zhang, 2013). The ITS design is a robust method for evaluating policy interventions in which randomization is not feasible. It offers higher internal validity than simple pre-post comparisons because it separates immediate-level changes from post-intervention slope changes (Wagner et al., 2002). Furthermore, its ability to explicitly model pre-intervention trends and seasonality makes it a particularly suitable framework for analyzing nationwide EMS data (Lopez Bernal et al., 2017). Our study adhered to best practices for ITS implementation to ensure the reliability of our findings. We prospec-

tively checked for discontinuities in the baseline covariates at the intervention point. We selected the final model after comparing multiple candidates for seasonality adjustment. These rigorous steps ensure a robust and reliable policy evaluation.

	Shockable			Non-Shockable		
	Coefficient	Bonferroni adj. 95 % CI ^a	Bonferroni adj. <i>p</i> ^a	Coefficient	Bonferroni adj. 95 % CI ^a	Bonferroni adj. <i>p</i> ^a
Excluding first 6 months post-intervention ^b						
Level change	-0.16	-0.69 to 0.37	1.00	-0.35	-0.59 to -0.10	0.004
Slope change	-0.002	-0.027 to 0.024	1.00	-0.005	-0.016 to 0.006	0.70
Pre-intervention period limited to 24 months ^c						
Level change	0.30	-0.31 to 0.91	0.53	-0.03	-0.23 to 0.16	1.00
Slope change	0.001	-0.035 to 0.036	1.00	0.001	-0.013 to 0.015	1.00
Pre-intervention period limited to 36 months ^d						
Level change	0.13	-0.41 to 0.67	1.00	-0.13	-0.32 to 0.07	0.29
Slope change	-0.01	-0.04 to 0.01	0.47	-0.009	-0.020 to 0.003	0.18
Excluding data after Dec 31, 2019 (before COVID-19) ^e						
Level change	0.20	-0.32 to 0.73	0.79	-0.08	-0.30 to 0.13	0.74
Slope change	-0.01	-0.04 to 0.01	0.50	-0.01	-0.02 to 0.002	0.15

Table 4. Results of sensitivity analyses.

^a Bonferroni correction applied for two primary comparisons ($\alpha = 0.025$).

^b Shockable: Pre-intervention, $n = 12,667$ (89 points); Post-intervention, $n = 4,938$ (31 points). Non-shockable: Pre-intervention, $n = 95,693$ (89 points); Post-intervention, $n = 57,423$ (31 points).

^c Shockable: Pre-intervention, $n = 3,854$ (25 points); Post-intervention, $n = 5,745$ (37 points). Non-shockable: Pre-intervention, $n = 31,880$ (25 points); Post-intervention, $n = 64,320$ (37 points).

^d Shockable: Pre-intervention, $n = 5,630$ (37 points); Post-intervention, $n = 5,745$ (37 points). Non-shockable: Pre-intervention, $n = 45,706$ (37 points); Post-intervention, $n = 64,320$ (37 points).

^e Shockable: Pre-intervention, $n = 12,667$ (89 points); Post-intervention, $n = 5,120$ (33 points). Non-shockable: Pre-intervention, $n = 95,693$ (89 points); Post-intervention, $n = 56,309$ (33 points).

Step	Procedure	Target After Preceding Step	Cumulative Time from Contact
1	Secure intravenous (IV) access	Within 4 min of patient contact	≤ 4 min
2	First adrenaline (1 mg) administration	Within the next 2 min	≤ 6 min
3	Advanced airway management (AAM)	Within another 2 min	≤ 8 min
4	Second adrenaline (1 mg) administration	Within the next 2 min	≤ 10 min

Table 5. Time-targeted field protocol for administration used in Aichi Prefecture, Japan.

Note: The protocol codifies sequential time targets, measured from the moment of patient contact, that allow two adrenaline doses to be administered within 10 min in the field. Reproduced from the Aichi Prefecture ambulance cardiopulmonary resuscitation and pre-cardiac-arrest protocols; the same target sequence is described in Ueta et al. (2023).

Abbreviations: AAM, advanced airway management; IV, intravenous. In a nationwide analysis using the All-Japan Utstein Registry, Aichi Prefecture recorded the shortest mean time from patient contact to first adrenaline administration among Japanese prefectures (9.0 ± 4.6 min) and the highest proportion of patients receiving adrenaline within 10 min of contact (75.1%), compared with a national mean of 15.4 ± 6.3 min (Ueta et al., 2023). Crew adherence is reinforced through the prefecture's regional certification and standardized re-education system, administered by the district medical control councils (Kitagawa & Saito, 2018).

Protocol source: Aichi Council for the Advancement of Ambulance Services [Aichi Prefectural Medical Control Council]. (n.d.). Aichi Prefecture ambulance cardiopulmonary resuscitation protocol and pre-cardiac-arrest protocol (16th ed.) [in Japanese]. Nagoya, Japan: The Council. The same four-step target sequence is described in Ueta, H., Tanaka, H., Takyu, H., et al. (2023). Journal of EMS Medicine, 2(1), 31–38. <https://doi.org/10.35616/jemsm.2021.00080>. Certification and standardized-training system: Kitagawa, Y., & Saito, H. (2018). Current status of the medical control system in Aichi Prefecture [in Japanese]. FY2018 National Medical Control Council Liaison Conference, Fire and Disaster Management Agency. https://www.fdma.go.jp/singi_kento/kento/items/kento233_03_shiryo-2.pdf

LIMITATIONS

This study has several limitations. First, because this was an observational study using secondary data from the All-Japan Utstein Registry, the influence of unmeasured confounders could not be completely ruled out. Factors such as the resuscitation skills of the EMTs or specific on-scene circumstances may have influenced the time to adrenaline administration. In particular, the All-Japan Utstein Registry does not record indicators of cardiopulmonary resuscitation quality (e.g., chest compression depth or rate). In addition, although the time to defibrillation is recorded, it is defined only for patients who actually received defibrillation; because most non-shockable arrests—and a minority of shockable arrests—do not, this interval is missing for a large proportion of the cohort, so we did not include it as a covariate to avoid the resulting missing data and selection problems. Residual confounding by these unmeasured or only partially observed process factors cannot be excluded. Second, the ITS design assumes the absence of concurrent events that can systematically affect outcomes (Lopez Bernal et al., 2018). We cannot entirely rule out residual time-varying confounding factors such as nationwide operational changes, equipment updates, or shifts in public behavior regarding emergency calls. Third, our analysis does not estimate regional heterogeneity in policy implementation; our model did not account for potential implementation lags or variations in adherence. Fourth, we modeled seasonality using harmonic terms in the order selected by BIC. Our model may not perfectly capture the underlying seasonal patterns, which may have influenced our estimates (Bhaskaran et al., 2013). Fifth, although aggregating data into 30-day intervals mitigates the influence of weekly variations and outliers, it may mask sharp short-term changes in outcomes (Alarcon Falconi et al., 2020). Sixth, the end of the study period coincided with the beginning of the COVID-19 pandemic and the resulting changes in emergency demand and operational procedures may have affected our estimates (Fire and Disaster Management Agency, 2020b; World Health Organization, 2020). Finally, our findings are specific to the Japanese EMS context (e.g., the scope of practice for ELSTs, the MC system, and the prevalence of dispatcher-assisted CPR and PAD). Therefore, the transportability of the findings to other countries or EMS systems may be limited.

CONCLUSION

Using a nationwide interrupted time-series analysis, we found that the 2017 FDMA notification was not associated with a statistically significant immediate or sustained reduction in adrenaline time for either shockable or non-shockable rhythms. Our conclusions are restricted to this prehospital process measure and make no claim about patient survival. The findings indicate that an advisory notification without embedded temporal targets is insufficient on its own; future efforts should codify explicit time targets at the MC level, together with crew training, implementation support, and procedural refinement.

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