**Clinical Characteristics and Long-Term Outcomes of Patients with Acute Coronary Syndrome During Travel**

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**Summary**

Cardiovascular disease is a major cause of death among travelers, but the clinical characteristics and clinical outcomes of patients who develop acute coronary syndrome (ACS) while traveling have not been assessed. We evaluated 2548 patients with ACS who underwent primary percutaneous coronary intervention (PCI) between 1999 and 2015 and compared the incidences of all-cause and cardiac death during follow-up between travelers and locals. We assessed 192 (7.5%) patients who developed ACS while traveling. These patients were younger and had a higher prevalence of ST-elevation myocardial infarction than local patients. During a median follow-up period of 5.3 years, 632 (24.8%) all-cause deaths were identified, including 310 cardiac deaths (12.2%). Kaplan-Meier analysis revealed that the cumulative incidence of all-cause death was significantly lower among the travelers than locals ($P = 0.001$, log-rank test). Multivariate Cox hazard analysis revealed that travel was significantly associated with a lower rate of all cause death (hazard ratio, 0.53; 95% confidence interval, 0.33-0.80; $P = 0.002$). Cardiac mortality did not significantly differ between travelers and locals ($P = 0.29$). Patients with ACS treated with primary PCI while traveling had more favorable long-term clinical outcomes than local patients. Appropriate initial treatments and secondary preventions might improve the prognosis of travelers.

**Key words:** Travelers, Percutaneous coronary intervention

Acute coronary syndrome (ACS) is one of the leading causes of mortality worldwide. Primary percutaneous coronary intervention (PCI) is an established revascularization therapy for patients with ACS. Although early revascularization therapy and optimal medical treatment can improve the prognosis of patients with ACS, mortality associated with ACS has remained relatively high. The in-hospital mortality rate due to ACS in Asian countries has been reported to exceed 5%. The number of air travelers is increasing, particularly those aged > 60 years, who often have coronary risk factors. Cardiovascular disease is the leading cause of death among travelers. However, the clinical characteristics and outcomes of ACS onset while traveling have not been elucidated in detail. Our hospital in the eastern part of Shizuoka prefecture is located in a resort destination surrounded by Mount Fuji, the Pacific Ocean and the Izu Peninsula that is visited annually by more than 400,000 tourists. Therefore, we compared the clinical backgrounds and long-term mortality rates between patients who develop ACS while traveling and local patients.

**Methods**

**Study population and data collection:** This single-center, observational, retrospective cohort study initially evaluated 2548 consecutive patients with ACS (including ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], and unstable angina [UA]) who underwent primary PCI between 1999 and 2015 at our institution (Figure 1). Complete definitions for STEMI, NSTEMI and UA are provided in the PACIFIC Registry. To be diagnosed with STEMI, patients must have chest symptoms, ST segment elevation ≥ 1 mV in ≥ 2 limb leads, or ≥ 2 contiguous precordial leads or left bundle branch block, and elevated biochemical markers of myocardial necrosis (troponin T ≥ 0.1 ng/mL or creatine phosphokinase 2-fold above the normal range). For a diagnosis of NSTEMI, patients must have chest symptoms, ST-segment depression ≥ 0.05 mV or T-wave inversion ≥ 0.3 mV or transient < 0.05-mV ST-segment elevation, and elevated biochemical markers of myocardial necrosis (and no electrocardiogram...
abnormalities for STEMI). Patients with persistent pain at rest or nocturnal chest pain were diagnosed with UA.\textsuperscript{15} Demographic data and information about coronary risk factors, medications, revascularization procedure-related factors and comorbidities were collected to create a database. Patients who lived outside the eastern part of Shizuoka prefecture which is the medical area of our hospital and were listed as travelers in the medical records were defined as travelers.

Blood samples were collected and blood pressure (BP) was measured on admission. Patients with BP > 140/90 mmHg or those taking antihypertensive medication were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL, triglycerides (TG) ≥ 150 mg/dL or current treatment with statins and/or lipid-lowering agents.\textsuperscript{16} Diabetes mellitus was defined as either hemoglobin A1c (HbA1c) ≥ 6.5% or medication with insulin or oral hypoglycemic drugs. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/minute/1.73 m\textsuperscript{2} calculated using the modification of the diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine.\textsuperscript{17} A current smoker was defined as a person who smoked at the time of PCI or who had quit smoking within one year before PCI.\textsuperscript{15} We defined distance from our institution as the distance between our hospital and the place the patient suffered from ACS.

Written, informed consent was obtained from all patients before undergoing PCI. This study was conducted in accordance with the Declaration of Helsinki and with the approval of our institutional review board.

**Primary endpoint:** The primary endpoint was all-cause death during follow-up. Clinical follow-up included a review of medical charts, telephone contact and questionnaires sent to patients or their families. Mortality data were collected from the medical records of patients who died or who were treated at our institution, and details and causes of death were obtained from other hospitals to which patients had been admitted.

**Statistical analysis:** Quantitative data are presented as the mean ± standard deviation (SD) or median with interquartile ranges (IQR). Categorical data are expressed as counts and ratios (%), and were compared using unpaired t tests and Chi-squared tests. Unadjusted cumulative event rates between the two groups were compared using Kaplan-Meier curves and log-rank tests.

Associations between travel and the primary endpoint were determined using multivariate Cox proportional hazard regression analysis. Multivariate models were adjusted for age, sex, hypertension, statins, chronic kidney disease, current smoking, multivessel disease, BMI, prior MI, atrial fibrillation, final TIMI3, and Killip class. Factors that significantly differed in univariate analyses were entered into multivariate analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. All statistical analyses were carried out using JMP version 14.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

**Results**

**Patient background:** We analyzed data from 2,548 patients with ACS treated by primary PCI between 1999 and 2015 at our institution. Among them, 192 (7.5%) were traveling at the time of ACS onset. Table I shows the clinical and procedural characteristics of the patients. The travelers were significantly younger and had a higher prevalence of males, STEMI, and elevated white blood cell (WBC) counts and Hb values. The ratio of door-to-balloon time < 90 minutes was significantly higher for the travelers than the locals (75.3% versus 66.5%). The prevalence of hypertension, diabetes, dyslipidemia, CKD, medication, or TIMI3 and Killip 3-4 did not significantly differ between the groups.

**Clinical outcomes:** The median follow-up period was 5.3 (IQR, 1.6-10.0) years. Overall, 632 (24.8%) all-cause deaths were identified during follow-up, including 310 (12.2%) cardiac deaths. Table II shows the causes of death. There was a significant difference in all cause death and unknown death between locals and travelers. Figure 2 shows Kaplan-Meier curve for all-cause death between the two groups. The mortality was significantly higher among the locals than the travelers (51.2% versus 26.6%; $P = 0.001$, log-rank test). In contrast, the incidence of cardiac deaths did not significantly differ between the groups (23.6% versus 12.5%; $P = 0.29$, log-rank test) (Figure 3).

Table III shows the results of the Cox proportional hazard regression analysis of all-cause deaths. All-cause death was significantly associated with the travelers group compared with the locals group (HR, 0.53; 95% CI, 0.33-0.80; $P = 0.002$), even after adjustment for other risk factors. Multivariate Cox hazard analysis also showed that age, CKD, BMI, statin use, and Killip 3-4 were independent predictors of all-cause mortality among patients with ACS.

**Discussion**

The major findings of the present study were as follows: (1) 7.5% of ACS patients were travelers, (2) travelers were younger with higher prevalences of males and STEMI, the prevalence of coronary risk factors did not significantly differ, (3) the incidence of all-cause mortality was significantly lower among the travelers than the locals and the incidence of cardiac death was not significantly different between the two groups, and (4) travel was an
Table I. Patient Background

| Baseline characteristic                        | Overall (n = 2,548) | Travelers (n = 192) | Locals (n = 2,356) | P     |
|-----------------------------------------------|---------------------|---------------------|--------------------|-------|
| Age, years                                    | 68.0 ± 11.8         | 65.6 ± 10.7         | 68.2 ± 11.9        | 0.004 |
| Male, n (%)                                   | 1869 (73.4)         | 154 (80.2)          | 1715 (72.8)        | 0.02  |
| Hypertension, n (%)                           | 1706 (67.0)         | 125 (65.1)          | 1581 (67.1)        | 0.57  |
| Diabetes, n (%)                               | 942 (37.0)          | 78 (40.6)           | 864 (36.7)         | 0.28  |
| Dyslipidemia, n (%)                           | 1378 (54.1)         | 101 (52.6)          | 1277 (54.2)        | 0.67  |
| CKD, n (%)                                    | 929 (36.5)          | 70 (36.5)           | 859 (36.5)         | 0.98  |
| Current smoker, n (%)                         | 1106 (43.5)         | 91 (47.6)           | 1015 (43.1)        | 0.23  |
| Family history, n (%)                         | 456 (18.3)          | 38 (20.1)           | 418 (18.1)         | 0.50  |
| Multivessel coronary disease, n (%)           | 1114 (43.7)         | 76 (39.8)           | 1038 (44.1)        | 0.25  |
| Body mass index, kg/m²                        | 23.8 ± 3.7          | 24.2 ± 3.6          | 23.8 ± 3.7         | 0.18  |
| TC, mg/dL                                     | 187.7 ± 44.3        | 186.3 ± 44.9        | 187.8 ± 44.3       | 0.67  |
| LDL-C, mg/dL                                  | 117.2 ± 37.0        | 112.7 ± 38.3        | 117.5 ± 36.9       | 0.26  |
| HDL-C, mg/dL                                  | 46.2 ± 13.3         | 44.7 ± 14.6         | 46.3 ± 13.2        | 0.11  |
| TG, mg/dL                                     | 76 [48, 119]        | 74 [48, 113]        | 76 [48, 119]       | 0.18  |
| FBG, mg/dL                                    | 174.8 ± 82.7        | 185.7 ± 86.2        | 173.9 ± 82.4       | 0.06  |
| HbA1c, %                                      | 6.4 ± 1.4           | 6.7 ± 1.5           | 6.3 ± 1.4          | 0.25  |
| White blood cells, 1000/μL                    | 10000 [12800, 7900] | 11000 [13500, 9100] | 10000 [12775, 7800] | < 0.0001 |
| Hemoglobin, g/dL                              | 13.4 ± 3.0          | 14.1 ± 8.1          | 13.3 ± 2.1         | 0.0007 |
| eGFR, mL/minute/1.73 m²                       | 66.0 ± 17.5         | 66.7 ± 16.7         | 66.0 ± 17.6        | 0.61  |
| Hemodialysis, n (%)                           | 66 (2.6)            | 2 (1.1)             | 64 (2.7)           | 0.12  |
| LVEF, %                                       | 59.1 ± 11.5         | 58.7 ± 12.5         | 59.2 ± 11.4        | 0.66  |
| Medications                                   |                     |                     |                    |       |
| ACE-I/ARB, n (%)                               | 1763 (69.2)         | 124 (64.6)          | 1639 (69.6)        | 0.15  |
| β-blocker, n (%)                              | 901 (35.4)          | 59 (30.7)           | 842 (35.8)         | 0.16  |
| Insulin, n (%)                                | 90 (3.5)            | 6 (3.13)            | 84 (3.57)          | 0.75  |
| OHA, n (%)                                    | 418 (16.4)          | 37 (19.5)           | 381 (16.2)         | 0.27  |
| Statin, n (%)                                 | 1702 (66.9)         | 126 (66.0)          | 1576 (66.7)        | 0.78  |
| ACS nature, n (%)                             | 1960 (77.0)         | 165 (86.4)          | 1797 (76.3)        | 0.0004|
| STEMI                                         | 203 (8.0)           | 14 (7.3)            | 189 (8.0)          |       |
| NSTEMI                                        | 382 (15.0)          | 12 (6.3)            | 370 (15.7)         |       |
| DTB in STEMI, minutes                         | 95.1 ± 79.5         | 79.9 ± 49.9         | 96.6 ± 81.7        | 0.01  |
| DTB in STEMI (< 90 minutes)                   | 1287 (67.2)         | 122 (75.3)          | 1165 (66.5)        | 0.02  |
| Distance from our institution (km)            | 27.1 ± 0.4          | 30.1 ± 1.4          | 26.8 ± 0.4         | 0.02  |
| Prior MI, n (%)                               | 175 (6.9)           | 17 (8.9)            | 158 (6.7)          | 0.27  |
| Prior PCI, n (%)                              | 192 (7.6)           | 20 (10.5)           | 172 (7.3)          | 0.13  |
| Prior CABG, n (%)                             | 49 (1.9)            | 3 (1.6)             | 46 (2.0)           | 0.70  |
| Atrial fibrillation, n (%)                    | 110 (4.3)           | 9 (4.7)             | 101 (4.3)          | 0.80  |
| Final TIMI, n (%)                             | 2448 (96.5)         | 182 (97.3)          | 2266 (96.5)        | 0.52  |
| Killip 3-4, n (%)                             | 219 (8.6)           | 21 (11.1)           | 198 (8.4)          | 0.22  |

ACE-I indicates angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; CAGB, coronary artery bypass grafting; CKD, chronic kidney disease; DTB, door to balloon time; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; OHA, oral hypoglycemic agents; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TC, total lipoprotein cholesterol; TG, triglycerides; TIMI, thrombolysis in myocardial infarction; and UAP, unstable angina pectoris

Table II. The Cause of Death

| overall (n = 2,548) | travelers (n = 192) | locals (n = 2,356) | P     |
|---------------------|---------------------|--------------------|-------|
| All cause death, n (%) | 632 (24.8)          | 32 (16.7)          | 600 (25.4) | 0.004 |
| Cardiac death, n (%)  | 310 (12.2)          | 20 (10.4)          | 290 (12.3) | 0.43  |
| Cancer death, n (%)   | 90 (3.5)            | 4 (2.1)            | 86 (3.7)  | 0.21  |
| Infectious death, n (%)| 68 (2.7)            | 2 (1.0)            | 66 (2.8)  | 0.10  |
| Cerebrovascular death, n (%) | 42 (1.6) | 3 (1.6) | 39 (1.7) | 0.92  |
| Unknown death, n (%)  | 122 (4.8)           | 3 (1.6)            | 119 (5.1) | 0.01  |
A previous study has shown ACS is a major cause of death among travelers\(^\text{14}\) and previous reports have suggested that elderly travelers should receive risk assessment and guidance before travelling.\(^\text{18,19}\) Gidron, \textit{et al.} showed that emotional and physical changes during travel are associated with an increased risk of adverse cardiac events among patients.\(^\text{20}\) Therefore, people at high risk for cardiovascular disease (CVD) or with a history of CVD should be very careful while traveling. In addition, travelers might not receive timely treatment compared with locals due to insurance issues, unclear medical information, and lack of information from medical institutions at travel destinations.

In our study, travelers were at significantly lower risk for all-cause death than locals. There were several possible reasons for this result. First, we inferred that the travelers were less frail and had higher activities of daily living (ADL) levels than the locals, because travelers had higher BMI than locals. Weight loss is one of the criteria for frailty.\(^\text{21}\) Some studies have found that frailty independently predicts all-cause mortality and adverse events (nonfatal myocardial reinfarction, major bleeding) among elderly ACS patients.\(^\text{22,23}\) We considered that lower frailty or higher ADL levels influenced the prognosis of the travelers. Second, most travelers were admitted to our institution while traveling from urban areas, and a health dispar-
The current ESC guideline recommended that treatment of coronary revascularization for patients with ACS. Primary PCI has been established as an effective therapy (OMT), is important for the prognosis of patients who develop ACS while traveling. For such patients, hospitals where initial treatment and secondary prevention are administered can be quite far apart.

Some limitations need to be acknowledged. Unknown confounders might have affected outcomes regardless of analytical adjustments due to the single-center, observational study of a small patient cohort. In addition, confounding bias might exist that could be difficult to assess. This study included patients with bare metal stents.

**Conclusions**

The long-term clinical outcomes of ACS treated by primary PCI were more favorable for travelers compared with local patients. One reason for this might be differences in patient background, such as low frailty and high ADL levels. Travel is a risk factor for patients with cardiovascular disease, but appropriate initial treatment and secondary prevention might further improve the prognosis of travelers.

**Disclosure**

Conflicts of interest: The authors have no conflicts of interest to disclose.

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| Table III. Cox Proportional Hazard Models for All-Cause Death |
|---------------------------------|
| Variable | HR (95% CI) | p-Value | HR (95% CI) | p-Value |
|---------|------------|--------|------------|--------|
| Travel  | 0.56 (0.38-0.79) | 0.006 | 0.53 (0.33-0.80) | 0.002 |
| Age     | 1.07 (1.06-1.08) | <0.0001 | 1.06 (1.05-1.07) | <0.0001 |
| Male    | 0.69 (0.58-0.81) | <0.0001 | 0.93 (0.77-1.14) | 0.5 |
| Hypertension | 1.33 (1.12-1.58) | 0.001 | 1.08 (0.90-1.31) | 0.41 |
| Diabetes | 0.95 (0.81-1.12) | 0.57 |
| Dyslipidemia | 0.59 (0.50-0.70) | <0.0001 |
| CKD     | 2.41 (2.05-2.82) | <0.0001 | 1.35 (1.12-1.62) | 0.002 |
| Current smoker | 0.59 (0.51-0.71) | <0.0001 | 1.03 (0.84-1.25) | 0.79 |
| Multivessel coronary disease | 1.55 (1.32-1.82) | <0.0001 | 1.05 (0.77-1.37) | 0.58 |
| Body mass index | 0.91 (0.89-0.93) | <0.0001 | 0.2 (0.05-0.76) | 0.02 |
| Statin  | 0.31 (0.27-0.37) | <0.0001 | 0.42 (0.35-0.50) | <0.0001 |
| STEMI   | 1.09 (0.98-1.21) | 0.12 |
| Prior MI | 1.54 (1.18-1.97) | 0.002 | 1.29 (0.96-1.69) | 0.09 |
| Atrial fibrillation | 1.94 (1.39-2.64) | 0.0002 | 1.11 (0.77-1.55) | 0.58 |
| Final TIMI3 | 0.55 (0.39-0.79) | 0.002 | 0.89 (0.58-1.36) | 0.59 |
| Killip 3-4 | 5.76 (4.72-6.97) | <0.0001 | 4.31 (3.43-5.42) | <0.0001 |

HR indicates Hazard ratio; CI, confidence interval; CKD, chronic kidney disease; MI, myocardial infarction; STEMI, ST elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.
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