lipid metabolism were relatively minimal because the number of patients with severe renal dysfunction (eGFR <30 mL/min) was small (41/513), especially among the patients with normoalbuminuria (7/305).

Our study is associated with several limitations. First, we used a cross-sectional analysis; therefore, a prospective study is needed to clarify whether RI without albuminuria increases the risk of CAD and PAD. Second, the number of participants was relatively small in epidemiological terms, suggesting that there may not have been a sufficient number of patients representing the whole range of the renal function. Third, the UAER was measured using only one urine sample in this study. Therefore, the evaluation of UAER performed in this study may be inaccurate compared to that observed in studies with two or three measurements, which is common practice. Fourth, it is possible that not all cases of asymptomatic CAD and CVD were detected since CT examinations and exercise electrocardiograms were not performed in all patients. Fifth, renal injury can be induced by contrast media in patients with CAD who have undergone coronary angiography. Therefore, we cannot rule out the possibility that the patients with RI had contrast nephropathy. Sixth, since we studied patients who were hospitalized for glycemic control, it is possible that the HbA1c levels were overestimated.

In conclusion, we demonstrated that RI without albuminuria is closely associated with peripheral artery atherosclerosis, thereby highlighting the importance of clinical screening of CAD and PAD in NA (RI+) patients. Furthermore, we demonstrated that the ApoB/LDL-C ratios and ApoC3 levels are significantly higher in patients with RI, thus suggesting that atherogenic dyslipidemia may underlie the association between RI and cardiovascular disease in patients with diabetes.

Conflicts of Interest

None to declare.

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シンポジウム 4　座長 柏木 厚典・山崎 義光

病因・病態から 新しい大血管症予防・治療法を考える

S4-1. 循環器病の危険因子としての糖尿病・メタボリックシンドローム

岡村 智教*　宮本 恵宏**

〔糖尿病合併症 27 (1)：89～93, 2013〕

循環器疫学研究における糖尿病の意義

糖尿病は，細小血管障害を通じて網膜症や腎症，神経障害の原因となるが，冠動脈疾患など循環器病の危険因子でもあり，これらは大血管障害と呼ばれている。欧米では，糖尿病は冠動脈疾患の非常に強い危険因子と考えられており，例えば Adult Treatment Panel (ATP) III では，糖尿病は冠動脈疾患を既にもっている患者と同等の二次予防相当のリスクとされている。欧米では循環器病の大部分は冠動脈疾患であるのに対し，本邦では脳卒中の発症率のほうがずっと高く，糖尿病と冠動脈疾患の関連についても未だ二次予防相当というエビデンスはない。日本動脈硬化学会の動脈硬化性疾患予防ガイドライン 2012 年版でも，糖尿病は二次予防相当ではなく，一次予防のハイリスク群（カテゴリー III）という扱いとされている。いずれにせよ日本人集団における糖尿病と循環器病の関連についての疫学研究をさらに進める必要がある。

疫学研究においては，多数の健常者を含む集団に対して糖尿病や耐糖能異常の評価を行う必要があり，評価指標は安価で簡便なものが望ましい。最近まで糖尿病の診断には糖負荷試験が用いられてきたが，これを地域の疫学研究に導入するのは困難であった。そのため多くの研究では糖負荷試験以外の手法で糖尿病のリスクを評価してきた。

血糖値と循環器病

図 1 に示すように，大阪府吹田市の住民基本台帳から無作為抽出した 5,321 人を 12 年間追跡した吹田研究の結果では[1]，正常型を基準 (1.00) とすると，脳卒中発症に対する糖尿病型の調整ハザード比 (HR) は，男性で 1.75，女性で 3.07 と有意に高かった（空腹時血糖が 100 mg/dl 未満を正常，100 mg/dl 以上 126 mg/dl 未満を境界型，Impaired Fasting Glucose，IFG，126 mg/dl 以上または糖尿病治療中を糖尿病と定義）。既存の疫学研究では，糖尿病の循環器病に対する相対危険度はほぼ 2～3 であること，男性に比し女性の相対危険度が大きいことが指摘されており，この結果はほぼそれを追認していた。一方，山形県の船形研究では IGT (Impaired Glucose Tolerance，75 グラム糖負荷試験で判定) および IFG と循環器病との関連を検討している[2]。この研究では IGT は循環器病の

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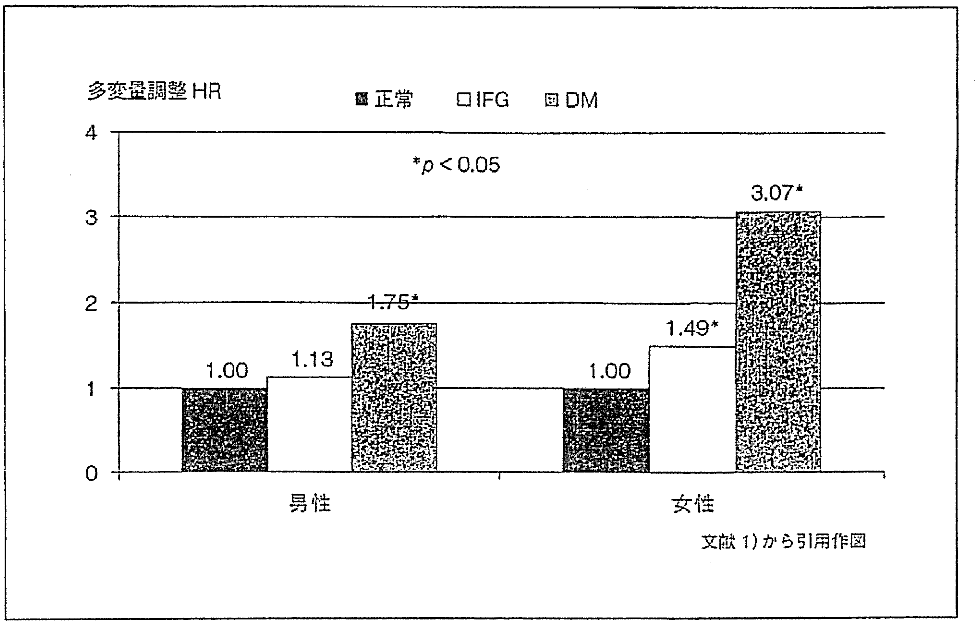


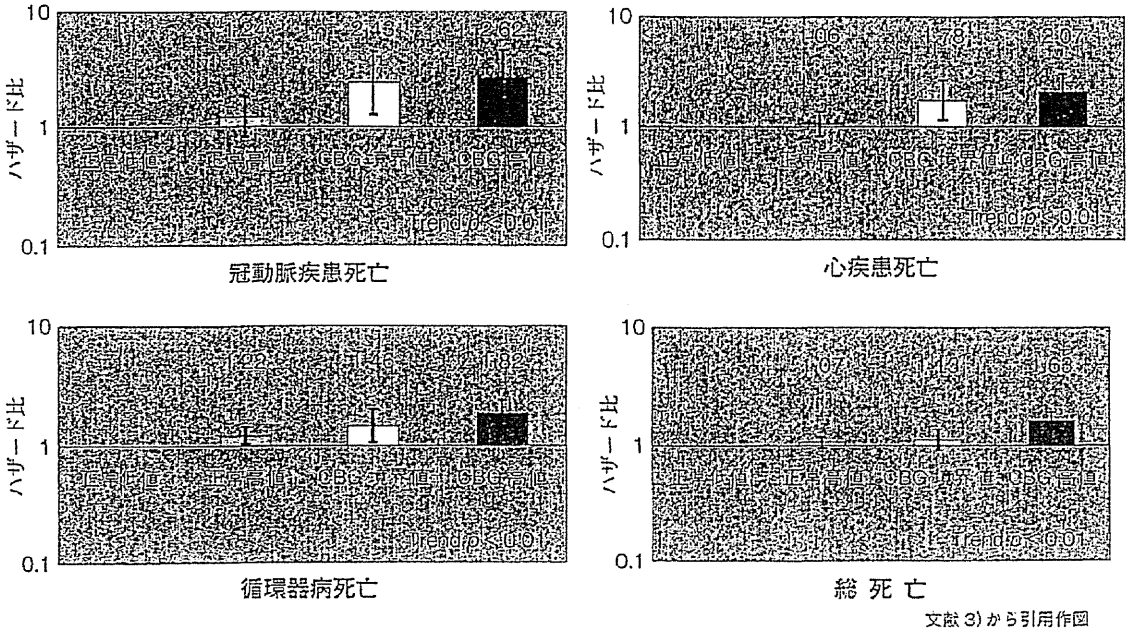
図1　空腹時血糖と循環器病の発症
—5,321人を12年間追跡（吹田研究）—

リスクを上昇させていたが，IFGでは有意なリスク上昇を認めなかった。これに対して吹田研究の女性ではIFGのHRは1.49であり，有意なリスク上昇を認めていた。空腹時血糖が糖尿病型の場合，本邦でも明らかに循環器病の危険因子となるが，糖尿病と正常の間の領域のリスクについてはエビデンスが乏しい。

一方，住民健診などでは血糖値の測定を随時で行わざるを得ない状況が多いが，その医学的評価はほとんどなされていない。厚生省（当時）の循環器疾患基礎調査の追跡調査であるNIPPON DATA80では[3]，19年追跡のデータで随時血糖（Casual Blood Glucose, CBG）は，冠動脈疾患，心疾患，循環器病，総死亡のいずれとも有意な正の関連を認めていた（図2：CBG 94，140，200 mg/d*l* で4群に分類）。随時血糖は食後高血糖を反映する指標とも考えられ，空腹時採血ができなかった場合でもスクリーニング指標として活用できる可能性が示唆された。

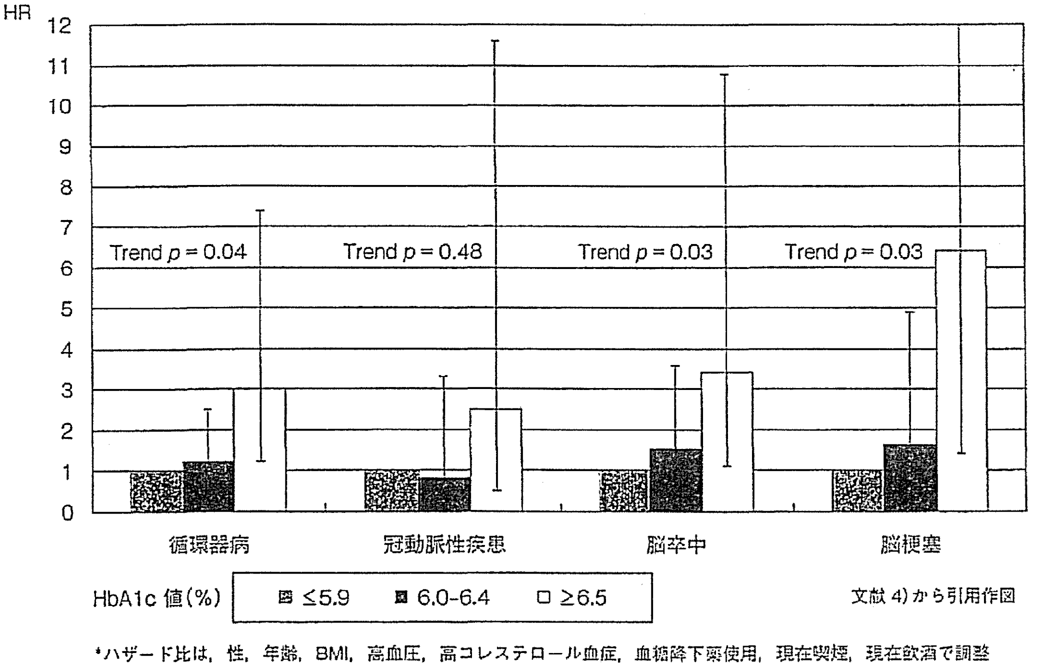
ヘモグロビンA1cと循環器病

わが国では平成20年度から特定健診（いわゆるメタボ健診）が開始され，糖尿病や循環器病の予防対策が行われている。特定健診では，空腹時血糖またはヘモグロビンA1cに基づいて受診者のリスクを階層化して特定保健指導を行うことになっている。しかしながらヘモグロビンA1cと循環器病のリスクについての疫学研究は少ない。吹田研究ではヘモグロビンA1c（NGSP値）と循環器病の発症について約13年の追跡調査の結果が報告されている（図3）。正常群（－5.9%）を基準として，境界群（6.0–6.4%），糖尿病群（6.5%以上）の循環器病発症のハザード比は，それぞれ1.2（95%信頼区間CI, 0.6–2.5），糖尿病群で3.0（95%CI, 1.2–7.4）であった[4]。この研究は吹田研究対象者のうち，サンプリングしてヘモグロビンA1cを測定した約4分の1の対象者の追跡結果である。境界群のリスク上昇が認められないのはサンプルサイズも影響している可能性があり，慎重な解釈が必要である。また保健指導の階層化の正常値（5.2%未満）の設定の妥当性についても，循環器病の観点からは裏づけとなるエビデンスが乏しい。



文献3)から引用作図

図2　随時血糖と死因別のハザード比
—9,444人を17.3年追跡（NIPPON DATA80）—



文献4)から引用作図

*ハザード比は，性，年齢，BMI，高血圧，高コレステロール血症，血糖降下薬使用，現在喫煙，現在飲酒で調整

図3　HbA1c（NGSP値）と循環器病発症リスク
—1,607人を12.7年間追跡（吹田研究）—

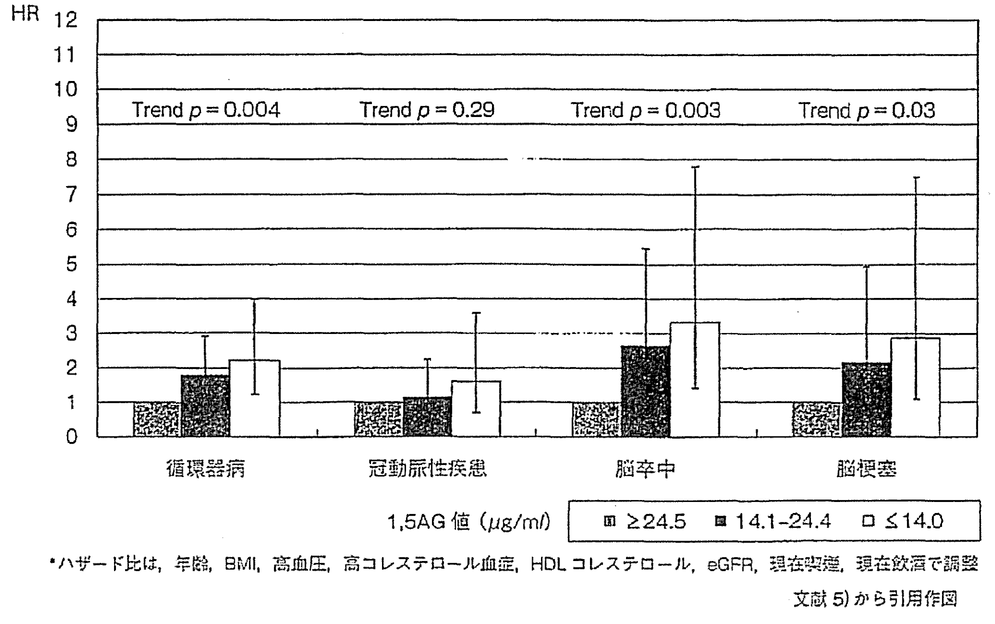


図4　血清 1,5-AG と循環器病発症リスク
—2,095 人を 11.7 年追跡（吹田研究）：男性の結果—

1,5 アンヒドログルシトール（1, 5AG）と循環器病

1,5AG は，ポリオール（多価アルコール）の一種であり，グルコースに似た構造を持ち体内に豊富に存在している。余分な 1,5AG は尿へ排泄され，腎臓でほとんどが再吸収される。しかし，血糖値が高い場合，グルコースの再吸収で競合阻害を受けるため尿中へ喪失され，結果としてその血中濃度は低下する。1,5AG は，採血前，数日間の血糖管理の状態を反映しており，食後高血糖の指標としても重要である。しかしながら新しい検査指標であり，循環器病との関連はほとんど検討されていなかった。

前述の吹田研究において，10 年以上前の凍結保存血清が存在していた 2,095 人（男性 991 人，女性 1,104 人）の 1,5AG を測定し，採血時点から最近までの循環器病発症との関連を検討した。図4に男性の結果を示したが，1,5AG の低下に伴って循環器病，冠動脈疾患，脳卒中，脳梗塞のいずれも発症リスクが上昇する傾向を示した[5]。冠動脈疾患だけは傾向性の検定（P for Trend）で有意差を認めていないが，これはイベント数が少ないためと考えられた（n=19）。

特定保健指導では，ヘモグロビン A1c を指導効果の判定指標としている場合が多いが，生活習慣の改善が検査値に反映されるまでに 1～2 か月のタイムラグがあるため，3～6 か月程度の保健指導で判定指標とするのは問題点が多い。今後，循環器病の予防という観点からは 1,5AG を保健指導の指標する方向性も検討されるべきであろう。なお 1,5AG と細小血管障害との関連については，さらなる疫学研究での検証が必要である。

おわりに

いずれの指標を用いても，明らかに「糖尿病」と診断できるカテゴリーでは循環器病のリスクが高いことがわかり，多くの研究を総合すると相対危険度は2～4の間であった。しかしながら正常と糖尿病の間の領域（IGTやIFG）が循環器病のリスクとなるかどうかは，研究ごとに，または男女別に結果が一定しておらず，日本人集団において更なる疫学研究知見の集積が必要である。

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Impact of the number of on-scene emergency life-saving technicians and outcomes from out-of-hospital cardiac arrest in Osaka City☆

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ABSTRACT

Backgrounds: In Japan, ambulance staffing for cardiac arrest responses consists of a 3-person unit with at least one emergency life-saving technician (ELST). Recently, the number of ELSTs on ambulances has increased since it is believed that this improves the quality of on-scene care leading to better outcomes from out-of-hospital cardiac arrest (OHCA). The objective of this study was to evaluate the association between the number of on-scene ELSTs and OHCA outcome.
Methods: This was a prospective cohort study of all bystander-witnessed OHCA patients aged ≥18 years in Osaka City from January 2005 to December 2007 using on an Utstein-style database. The primary outcome measure was one-month survival with favorable neurological outcome defined as a cerebral performance category ≤2. Multivariable logistic regression model were used to assess the contribution of the number of on-scene ELSTs to the outcome after adjusting for confounders.
Results: Of the 2408 bystander-witnessed OHCA patients, one ELST group was present in 639 (26.5%), two ELST were present in 1357 (56.4%), and three ELST group in 412 (17.1%). The three ELST group had a significantly higher rate of one-month survival with favorable neurological outcome compared with the one ELST group (8.0% versus 4.5%, adjusted OR 2.26, 95% CI 1.27–4.04), while the two ELST group did not (5.4% versus 4.5%, adjusted OR 1.34, 95% CI 0.82–2.19).
Conclusions: Compared with the one on-scene ELST group, the three on-scene ELST group was associated with the improved one-month survival with favorable neurological outcome from OHCA in Osaka City.

1. Introduction

Sudden cardiac arrest (SCA) is one of the leading causes of death and an important public health problem in the industrialized world.[1,2] In Japan, approximately 60,000 out-of-hospital cardiac arrests (OHCAs) of cardiac origin occur every year, and this number has been steadily increasing.[3] Despite continuous improvements

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in the "chain of survival," survival from OHCA remains low.[1–4]

In Japan, the Emergency Medical Service (EMS) system response mostly consists of a single tiered ambulance system that is dispatched to the scene of all OHCA. Each ambulance is staffed with a 3-person unit including at least one emergency life-saving technician (ELST). ELST are trained to perform advanced airway management and may also administer adrenaline under on-line medial command.[5] The number of trained ESLTs has been steadily increasing in Japan,[5] which might improve the quality of care delivered on scene and lead to improved outcomes from OHCA. However, the benefits of having multiple higher trained providers on critical EMS calls for OHCA patients remain controversial.[6,7]

In 1998, the Osaka Municipal Fire Department launched a population-based registry of OHCA in Osaka City, a large urban community with approximately 2.7 million inhabitants. Using this database, we collected approximately 2400 bystander-witnessed OHCAs from January 1st, 2005 to December 31st, 2007. The aim of this study was to evaluate the association between the number of ELSTs on scene and outcomes from OHCA.

2. Methods

2.1. Study design, population, and setting

The present study was carried out within the Utstein Osaka Project, a prospective, population-based cohort study of all persons with OHCA treated by EMS personnel in Osaka prefecture, Japan. This study included all OHCA patients in Osaka City aged 18 years or older who were presumed to be of cardiac and non-cardiac origin, witnessed by bystanders, and transported to medical institutions from January 1, 2005 through December 31, 2007. Osaka City is the third largest city in Japan with a population of 2.7 million residents (2005) in an area of 222 km^2.[8] Cardiac arrest was defined as the cessation of cardiac mechanical activities as confirmed by the absence of signs of circulation.[9,10] An arrest was presumed to be of cardiac etiology unless it was caused by trauma, drowning, drug overdose, asphyxia, exsanguination, or by any other non-cardiac causes determined clinically by a physician in charge, working in collaboration with the EMS.

This study was approved by the Ethics Committees of the Kyoto University Graduate School of Medicine. The requirement to obtain individual informed consent for the review of patient outcome was waived by the Personal Information Protection Law and the National Research Ethics Guidelines of Japan.

2.2. The EMS system in Osaka City

The municipal EMS system is the same as in other areas of Osaka Prefecture, and has been described previously.[4,11,12] The EMS system is operated by the Osaka Municipal Fire Department and is activated by dialing 119 on the telephone. During the study period, there were 25 fire stations (60 ambulances) and a single dispatch center in Osaka City.[13] Life support is available there 24 h every day.

Each fire ambulance has three EMS personnel with at least one ELST, a highly-trained prehospital emergency care provider. ELSTs are authorized to use an automated external defibrillator, to insert an intravenous line, and to place advanced airway management devices for OHCA patients under on-line medical control direction. Specially trained ELSTs have been permitted to insert tracheal tubes since July 2004 and to administer intravenous epinephrine since July 2006. In Japan, EMS personnel are not permitted to terminate resuscitation in the field and all patients on whom resuscitation is attempted are transported to the hospital. Until September 2006, all EMS providers performed CPR according to the Japanese Guidelines based on the American Heart Association, European Resuscitation Council, and the International Liaison Committee on Resuscitation 2000 Guidelines using a 15:2 compression-to-ventilation ratio. After September 2006, they switched to a ratio of 30:2 based on the 2005 Guidelines.[14] Public-access defibrillation programs have been promoted in Japan since July 2004.[14]

2.3. ELST certification

There are two options to becoming certified as an ELST in Japan.[11] The first is through the educational system within the fire department itself. To become an Emergency Medical Technician (EMT), all fire department personnel are required to have received fundamental medical education in emergency care for 250 h through a training academy. After being actively engaged in pre-hospital setting as an EMT for more than 5 years or 2000 h, EMTs must pass the national examination of ELST after having received at least one additional year of medical education and training at the fire academy. The second way is through the education system in an accredited EMT school or college. To become an ELST, candidates must pass the national examination of ELST after receiving medical education and training in emergency care at the certified EMT school or college for at least two years. The cumulative number of ELSTs has increased gradually in Osaka City and reached to 508 in 2007 since the ELST system started in 1991.[13]

2.4. Data collection and processing

Data were prospectively collected using a data collection tool designed by the project steering committee. Included were all core data elements recommended in the Utstein style for OHCA,[9,10] including age, sex, etiology, first documented rhythm, resuscitation time-course, bystander-initiated CPR, location of arrest, advanced airway placement, adrenaline administration, year, field return of spontaneous circulation (ROSC), total ROSC, hospital admission, and one-month survival and neurological status at one month after the event as well as the number of on-scene ELSTs. Resuscitation time-course included a series of EMS-related times such as call, the initiation of CPR, departure at the scene, and hospital arrival. ROSC was defined as the restoration of a sustained spontaneous perfusing rhythm.[9,10] The data sheet was filled out by the EMS personnel in cooperation with the physicians in charge of the patient. It was then transferred to the Information Center for Emergency Medical Services of Osaka and reviewed by the investigators. If the information provided on the data sheet was unclear or incomplete, it was returned to the appropriate EMS personnel for completion.

2.5. Methods of measurement

All survivors were followed for up to one month after the event, and the neurological outcomes were determined by the physician responsible for the care of the patient. Neurological status was determined using the Cerebral Performance Category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death.[9,10] Neurologically favorable survival was defined as a CPC category 1 or 2.[9,10] The primary outcome measure was one-month survival with favorable neurological outcome. Secondary outcomes included field ROSC, total ROSC, hospital admission, and one-month survival.

2.6. Primary data analysis

Patient characteristics, EMS characteristics, and outcomes among bystander-witnessed OHCA patients were evaluated after grouping the EMS scene personnel based on the number of ELSTs

(One ELST plus two EMTs, two ELSTs and one EMT, or three ELSTs [no EMT]). Patient characteristics were compared using chi-square test for categorical variables and one-way analysis of variance for numerical variables. EMS characteristics such as procedures and care time intervals by EMS were tested with univariable regression models for categorical variables and linear tests for numerical variables. Multivariable logistic regression models were used to assess the contribution of the number of on-scene ELSTs to the outcomes referring to one ELST. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated after adjusting for potential confounding factors that were biologically essential and considered to be associated with outcomes were included in the multivariable analysis. Those factors included age (for one year old increase), sex (male or female), etiology (presumed cardiac or non-cardiac), first documented rhythms (VF or others), location of arrest (public or not), bystander CPR (yes or no), advanced airway management (yes or no), epinephrine administration (yes or no), and the time interval from call to CPR by EMS (for one minute increase), and year (for one year increase). All statistical analyses were performed using SPSS statistical package ver16.0J (SPSS, Inc., Chicago, IL). All tests were 2-tailed, and P values of <0.05 were considered statistically significant

3. Results

3.1. Overview of OHCA patients in Osaka City

During these 3 years, a total of 6942 OHCA patients were registered (Fig. 1). Of them, 6849 were adults aged ≥18 years old, and 6461 were attempted resuscitation by EMS. A total of 2408 bystander-witnessed OHCA patients were eligible for our analyses excluding 487 patients witnessed by EMS and 3566 patients without witness. Among these patients, 639 (26.5%) received basic life support (BLS) or advanced life support (ALS) procedures by one ELST on the scene, 1357 (56.4%) two ELSTs, and 412 (17.1%) three ELSTs, respectively. The proportion of on-scene three ELSTs did not significantly increased during the study period.

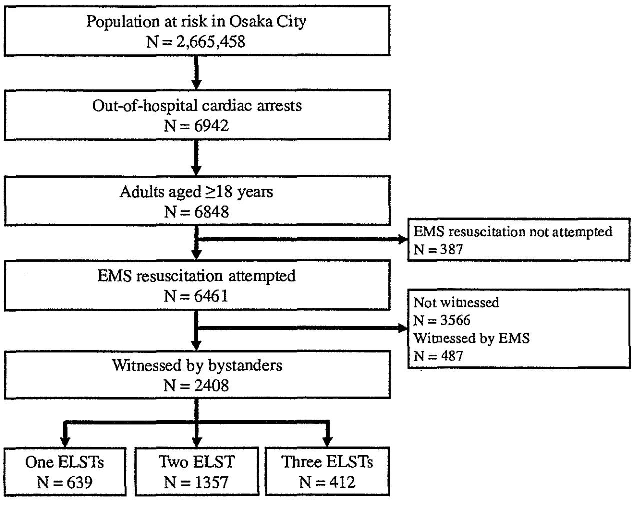

Fig. 1. Overview of out-of-hospital cardiac arrests with an abridged Utstein template from January 1, 2005 through December 31, 2007. EMS, emergency medical service; ELST, emergency life-saving technician.

3.2. Patient characteristics by the number of on-scene ELSTs

Table 1 shows the patient characteristics of bystander-witnessed OHCA by the number of on-scene ELSTs. Mean age and the proportion of male, public places, VF as first documented rhythm, and presumed cardiac etiology were similar between the three groups. The proportion of patients with bystander CPR was significantly different between the groups ($P = 0.036$).

3.3. EMS characteristics by the number of on-scene ELSTs

EMS advanced interventions and activity times of bystander-witnessed OHCA by the number of on-scene ELSTs are noted in Table 2. The proportion of adrenaline administration (from 4.7% in the one ELST group to 14.1% in the three ELST group, P for trend <0.001) and advanced airway management (from 78.2% in the one ELST group to 83.5% in the three ELST group, P for trend = 0.003) was significantly higher as the number of on-scene ELSTs increased. The EMS scene time also increased with the presence of more ELSTs (from 12.4 minutes in the one ELST group to 13.5 minutes in the three ELST group, P for trend = 0.001) whereas the time interval from 119 call to CPR initiation by EMS remained the same.

3.4. Outcomes by the number of ELSTs

Table 3 shows the outcomes from bystander-witnessed OHCA by the number of on-scene ELSTs. The three ELST group had a significantly higher rate of one-month survival with favorable neurological outcome compared with the one ELST group (8.0% versus 4.5%, adjusted OR 2.26, 95% CI 1.27–4.04). However, the two ELST group did not (5.4% versus 4.5%, adjusted OR 1.34, 95% CI 0.82–2.19). However, increasing the number of on-scene ELSTs did not significantly improve field ROSC, total ROSC, hospital admission, and one month survival after OHCA.

3.5. Factors associated with favorable neurological outcome

In the multivariable analysis, factors associated with one-month survival with favorable neurological outcome are shown as a forest plot in Fig. 2. Younger age (adjusted OR for one year old increase 0.99, 95% CI 0.97–0.99), presumed cardiac etiology (adjusted OR 2.24, 95% CI 1.25–4.02), VF as first documented rhythm (adjusted

Table 1
Patient characteristics of bystander-witnessed out-of-hospital cardiac arrest by the number of ELSTs.

	The number of on-scene ELSTs			
	One ELST ($N = 639$)	Two ELSTs ($N = 1357$)	Three ELSTs ($N = 412$)	P value
Age, year, mean (SD)	68.9 (17.4)	69.8 (16.8)	68.7 (17.2)	0.950
Men, n (%)	423 (66.2)	840 (61.9)	272 (66.0)	0.101
Cardiac etiology, n (%)	414 (64.8)	927 (68.3)	284 (68.9)	0.231
VF as first documented rhythm, n (%)[a]	109 (17.1)	227 (16.8)	70 (17.1)	0.981
Public location, n (%)	138 (21.6)	288 (21.2)	82 (19.9)	0.794
Bystander CPR, n (%)	214 (33.5)	428 (31.5)	158 (38.3)	0.036

ELST denotes emergency life-saving technician; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; SD, standard deviation.
[a] Data on VF were missing for 14 (0.6%) patinets.

Table 2
EMS characteristics of bystander-witnessed out-of-hospital cardiac arrest by the number of ELSTs.

	The number of on-scene ELSTs			
	One ELST (*N* = 639)	Two ELSTs (*N* = 1357)	Three ELSTs (*N* = 412)	*P* for trend
Adrenaline, *n* (%)	30 (4.7)	136 (10.0)	58 (14.1)	<0.001
Advanced airway, *n* (%)	500 (78.2)	1099 (81.0)	44 (83.5)	0.003
EMS care interval, min, mean (SD)				
Call to EMS CPR start	8.3 (3.4)	8.0 (3.0)	8.1 (3.4)	0.171
EMS scene time	12.4 (5.1)	12.9 (5.2)	13.5 (5.5)	0.001

ELST denotes emergency life-saving technician; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; SD, standard deviation.

Table 3
Outcomes from bystander-witnessed out-of-hospital cardiac arrest by the number of ELSTs.

		The number of on-scene ELSTs		
	Total (*N* = 2408)	One ELST (*N* = 639)	Two ELSTs (*N* = 1357)	Three ELSTs (*N* = 412)
Field ROSC, *n* (%)	318 (13.2)	75 (11.7)	175 (12.9)	68 (16.5)
Adjusted OR (95% CI)		Reference	1.07 (0.78–1.45)	1.41 (0.96–2.07)
Total ROSC, *n* (%)	1030 (42.8)	265 (41.5)	77 (42.5)	188 (45.6)
Adjusted OR (95% CI)		Reference	1.03 (0.84–1.25)	1.17 (0.90–1.51)
Hospital admission, *n* (%)	57 (35.6)	212 (33.2)	488 (36.0)	157 (38.1)
Adjusted OR (95% CI)		Reference	1.14 (0.93–1.40)	1.24 (0.95–1.62)
One-month survival, *n* (%)	281 (11.7)	69 (10.8)	160 (11.8)	52 (12.6)
Adjusted OR (95% CI)		Reference	1.15 (0.84–1.59)	1.24 (0.82–1.87)
CPC 1 or 2, *n* (%)	135 (5.6)	29 (4.5)	73 (5.4)	33 (8.0)
Adjusted OR (95% CI)		Reference	1.34 (0.82–2.19)	2.26 (1.27–4.04)

ELST, denotes emergency life-saving technician; ROSC, return of spontaneous circulation; CPC, cerebral performance category; OR, odds ratio; CI, confidence interval. ORs were calculated after adjusting for age, gender, etiology, first documented rhythm, location, bystander CPR, advanced airway management, epinephrine admistration, call to CPR time by EMS, and year.

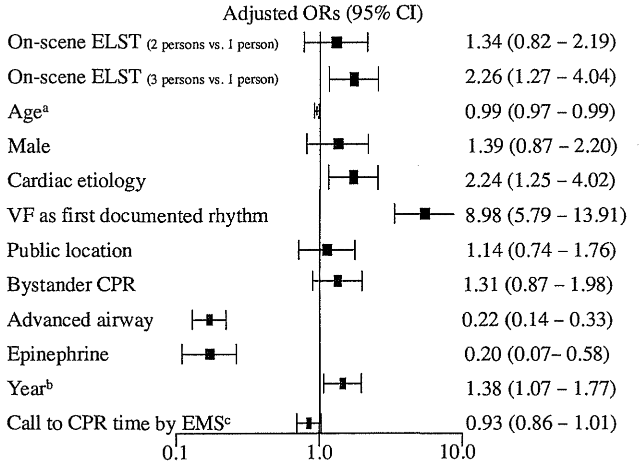

Fig. 2. Multivariable-adjusted odds ratios for one-month neurologically favorable survival. OR, odds ratio; CI, confidence interval; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation; ELST, emergency life-saving technician; EMS, emergency medical service. [a]OR for one year old increase, [b]OR for one year increase, [c]OR for one minute increase.

OR 8.98, 95% CI 5.79–13.91), and year (adjusted OR for one year increase 1.38, 95% CI 1.07–1.77) were also associated with a better neurological outcome. Advanced airway management (adjusted OR 0.22, 95% CI 0.14–0.33) and epinephrine administration (adjusted OR 0.20, 95% CI 0.07–0.58) were associated with a worse outcome.

4. Discussion

From this large, prospective registry in Osaka City, we demonstrated that the three on-scene ELST group was associated with the improved one-month survival with favorable neurological outcome from OHCA compared with the one on-scene ELST group. Since ELST program started in 1991, the Fire and Disaster Management Agency of Japan has recommended that each ambulance be staffed with a 3-person unit including at least one ELST. The cumulative number of certified ELSTs in Japan was reported to be 21,268 in 2010.[5] However, the impact of increasing the number of on-scene ELSTs has been insufficiently investigated to date. The results from this study will provide additional useful information on the design and structure of EMS systems in Japan and elsewhere.

Why did on-scene participation of three ELSTs contribute to improving favorable neurological outcome from OHCA? Although the proportion of advanced airway management and adrenaline administration increased with increasing the number of on-scene ELSTs in this target area, these treatment factors did not contribute to improving one-month survival with favorable neurological outcome from OHCA in the multivariable analysis. Far from it, they seemed to be associated with a worse outcome like some previous observational studies suggested.[15,16] However, we consider that there should be an inversion phenomenon of cause-and-effect and it would be difficult to assess the effect of ALS measures in this observational study, because EMS personnel in Japan could provide advanced life support measures only for OHCA patients who did not get ROSC by basic life support such as chest compressions and defibrillations. The adjustment in the multivariable analysis for epinephrine administration and use of advanced airways procedures which were used more extensively when there were more trained EMS personnel might be questioned, but the analysis without these variables also produced the same conclusions. Previous observational studies showed that the procedural experience of paramedics was associated with the improved outcome after prehospital cardiac arrests.[17–19] Of note, that paper also showed no effect of the years of treatment decision making on outcomes from cardiac arrest.[19] Because ELSTs in Japan are well-trained and have accumulated their on-scene experience to obtain the certification as described in the Methods, on-scene participation of the multiple ELSTs with more clinical experience might lead to better CPR quality and improve team dynamics and crew resource management, and resulted in better outcomes from OHCA.

While favorable neurological outcome significantly differed by the number of ELSTs, there were no significant associations between the ELST groups and other outcomes, although all adjusted ORs were greater than one. Our previous report suggesting the effectiveness of CPR by bystanders also showed significant difference only in neurological outcome while there were no difference in other outcomes.[20] Different from advanced treatments like epinephrine admistration,[12,15] the effectiveness of CPR or the CPR quality might tend to be greater in neurological function rather than other outcomes, and this discrepancy also might suggest that on-scene participation of the multiple ELSTs contribute better neurological outcomes by improving CPR quality. In addition, the improvement in favorable neurological outcome during the study period could be partially explained by the changes of the CPR guideline,[21] which might contribute to improve the CPR quality by EMS. Unfortunately, we did not have detailed information on CPR quality measures or team dynamics between ELSTs. We are now prospectively collecting these data in the designated target area and hope to address this issue in a future study.

Other published observational studies have not been able to demonstrate the benefits from having additional advanced trained providers such as paramedics on scene on survival or resuscitation process measures.[6,7] One study demonstrated decreased survival rates as the number of on-scene paramedics increased,[6] and suggested that the CPR quality was more important than the number of paramedics themselves. If so, both this study and our study, which look like different results, might suggest the same thing (i.e., importance of improving the CPR quality). In addition, there are several reasons why these findings are different from ours. This study used an OHCA data registry from a two tiered EMS system. Osaka has a single tier EMS system and is one of the most advanced areas of prehospital cares and has a considerable high rate of favorable neurological outcome.[4] These differences in EMS system might affect the effect of the number of EMS personnel. Although a previous report showed that two tiered system are more effective that single tiered systems with regards to improved survival from OHCA,[22] such systems might reduce the effectiveness of the having a higher number of trained personnel on scene.

Furthermore, differences in the prehospital emergency systems between Japan and western countries might also have affected the differences in the effects seen from having a higher number of more trained providers on scene. Unlike paramedics from western countries, highly-trained ELSTs in Japan are only permitted to perform ALS procedures during resuscitation efforts.[11,23] In addition, EMS providers were not permitted to terminate resuscitation in the field.[3,24] These differences in the training levels of ELST vs. paramedics from western countries require further study.

Importantly, the number of ELSTs needed within EMS in Japan deserves discussion, even if the increased number of on-scene ELSTs contributed to improving the outcome from OHCA in this study. Potential disadvantages of having more ELSTs on the scene include decreased procedural experience per ELST. It is also very expensive to train and maintain the skills of EMS personnel[11] and the cost-effectiveness of any EMS system structure changes should be considered as well. Clearly, more studies are needed to assess the association between the increased number of on-scene ELSTs, the skills performed and the OHCA outcome to better understand how to best deploy the most efficient and cost-effective emergency medical system.

This study has some inherent limitations, however. First, we did not obtain data on the ELST certification basis (college training vs. practice pathway) or experience level, both of which could have an influence on the outcomes. In addition, we were not able to classify the exact ELST level (additional certification is required for endotracheal intubation or/and adrenaline administration). Secondly, CPR quality measures which have been associated with outcomes from OHCA (compression rate, compression depth, CPR fraction, peri-shock pauses and ventilation rate) were not available for analysis in this study.[25,26] Third, our data does not address potential impact of post-resuscitation care within hospitals (hemodynamic support, induced hypothermia, and coronary interventional therapies).[27] Fourth, CPC scores might be biased due to physician's invested interest in the patient's outcome. Finally, this was not a randomized controlled trial and although we adjusted for Utstein confounding variables in the multivariable analysis, other unknown confounding factors might exist which may have affected our findings.

5. Conclusions

Compared with the one on-scene ELST group, the three on-scene ELST group was associated with the improved one-month survival with favorable neurological outcome from OHCA in Osaka City. Additional studies are required to further understand these findings.

Conflict of interest

There are no conflicts of interest to declare.

Role of funding source

This work was supported by a grant from the Fire Disaster Management Agency (for studies concerning a strategy for applying the results of the Utstein report to the improvement of emergency service).

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Regional Variation in Survival Following Pediatric Out-of-Hospital Cardiac Arrest

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Background: Although regional variation in outcome after adult out-of-hospital cardiac arrest (OHCA) is known, no clinical studies have assessed this in pediatric OHCA.

Methods and Results: This nationwide, prospective, population-based observation of the whole of Japan included consecutive OHCA patients with resuscitation attempt from January 2005 through December 2009. Primary outcome was 1-month survival with neurologically favorable outcome. Japan was divided into the following 7 regions as the largest administrative units: Hokkaido-Tohoku, Kanto, Tokai-Hokuriku, Kinki, Chugoku, Shikoku, and Kyushu-Okinawa. The outcome of pediatric OHCA was then compared between the regions. Multiple logistic regression analysis was used to adjust for other factors that were considered to influence the relationship between region and outcome. A total of 8,240 pediatric OHCA patients were registered during the study period. One-month survival with neurologically favorable outcome significantly differed by region: 2.5% (24/967) in Hokkaido-Tohoku (adjusted odds ratio [AOR], 1.65; 95% confidence interval [CI]: 0.94–2.90), 2.9% (47/1614) in Tokai-Hokuriku (AOR, 2.06; 95% CI: 1.28–3.31), 2.1% (26/1239) in Kinki (AOR, 1.45; 95% CI: 0.84–2.51), 3.4% (16/465) in Chugoku (AOR, 3.11; 95% CI: 1.62–6.00), 1.5% (4/259) in Shikoku (AOR, 0.79; 95% CI: 0.26–2.43), and 2.8% (27/974) in Kyushu-Okinawa (AOR, 2.15; 95% CI: 1.24–3.74) referred to Kanto (1.4%, 37/2722).

Conclusions: According to Japanese nationwide OHCA registry data there are significant regional variations in the outcome of pediatric OHCA.

Key Words: Cardiopulmonary resuscitation; Children; Out-of-hospital cardiac arrest; Regional variation; Utstein

Approximately 2,000 out-of-hospital cardiac arrests (OHCAs) occur annually among children in Japan.[1,2] Recently, some studies have reported that the characteristics and outcomes of pediatric OHCA differ from those of adults,[3–6] and children are more likely to survive an OHCA than adults, although the proportion is still low.[7] There might be some child-specific circumstances and countermeasures.

Editorial p ????

The preceding studies found that OHCA outcome varied by geographic region for adults.[8–11] Difference in the quality and quantity of the emergency medical service (EMS) systems might be a possible explanation for the regional variation.[8,9] For children, regional variation in OHCA outcome might be greater because treatment for pediatric OHCA is more specific and more complicated, and require much greater expertise than for adult OHCA,[12] but no clinical studies have addressed these questions.

The All-Japan Utstein Registry is a large prospective population-based cohort study of OHCA in Japan, which was launched in 2005 and covers approximately 127 million residents.[1,2,13] During the 5 years beginning 2005, there have been approximately 10,000 resuscitated OHCAs in children. Using this nationwide database, we evaluated regional variations in outcome of pediatric OHCA.

Methods

Study Design and Settings

The All-Japan Utstein registry of the Fire and Disaster Management Agency (FDMA) is a prospective, nationwide, pop-

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ulation-based registry system of OHCA in adults and children, with Utstein-style data collection.[14,15] This study enrolled all adult and pediatric patients who had an OHCA, were treated by EMS personnel, and were transported to medical institutions from 1 January 2005 through 31 December 2009. The research protocol was approved by the Ethics Committee of Kyoto University Graduate School of Medicine, and the requirement of informed consent was waived according to the national ethics guidelines for epidemiological studies established by the Japanese government.

Cardiac arrest was defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.[14,15] The arrest was presumed to be of cardiac origin unless it was caused by cerebrovascular disease, respiratory disease, malignant tumor, external causes including trauma, hanging, drowning, drug overdose, and asphyxia, or any other non-cardiac cause. Diagnosis of presumed cardiac or non-cardiac origin was clinically made by the physician in charge, in collaboration with the EMS personnel.

Do-not-resuscitate orders or living wills are generally not accepted in Japan, and EMS providers are not legally permitted to terminate resuscitation in the field. Therefore, most patients with OHCA treated by EMS personnel were transported to hospital and registered in this cohort. The cohort excluded cases of obvious signs of death on EMS arrival such as decapitation, incineration, decomposition, rigor mortis, or dependent lividity.

EMS Systems in Japan

Japan had a population of approximately 127 million in 2005, 21.3 million of whom were <18 years of age in an area of approximately 378,000 km^2 (inhabited area, 121,000 km^2).[16] EMS is provided by municipal governments through a fire department model. There were 804 fire departments with a respective dispatch center in 2009. Usually, a fire department ambulance has a crew of 3 emergency providers, including at least 1 emergency life-saving technician (ELST). ELSTs are trained to insert an i.v. line, place an adjunct airway, and use a semi-automated external defibrillator. Under online medical control, specially trained ELSTs have also been able to insert an endotracheal tube, and give i.v. epinephrine since April 2006.[17] Citizen use of automated external defibrillator (AED) has been legally permitted since July 2004 in Japan.[18] All EMS providers perform cardiopulmonary resuscitation (CPR) according to the Japanese CPR guidelines, which are based on the European Resuscitation Council and American Heart Association guidelines, and the International Liaison Committee on Resuscitation (ILCOR) recommendations.[3–6] In Japan, approximately 2 million citizens per year participate in community CPR programs, which includes training in chest compression, mouth-to-mouth ventilation, and use of AED.[1]

Data Collection and Quality Control

Data were collected with the use of a form based on the Utstein-style guidelines for reporting OHCA,[14,15] and included details on sex, age, witness status, first recorded cardiac rhythm, time course of resuscitation, bystander-initiated CPR, public-access AED use, advanced airway management, i.v. epinephrine, as well as pre-hospital return of spontaneous circulation (ROSC), 1-month survival, and neurological status 1 month after the event. The time course of resuscitation included details on the time of call received, vehicle arrival at the scene, contact with patient, initiation of CPR, defibrillation by EMS, and hospital arrival. First documented rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene. When laypersons delivered shocks using a public-access AED, the victims' first documented rhythm was regarded as ventricular fibrillation (VF). Both bystander-initiated chest compression-only and conventional CPR with rescue breathing were considered as bystander CPR. The time of collapse and initiation of bystander CPR was obtained by EMS interview with the bystander before leaving the scene. The time of defibrillation by EMS personnel was recorded in the semi-automated defibrillator. All survivors were evaluated 1 month after the event for their neurological function by the EMS personnel in charge.

The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the FDMA database server. They were logically checked by the computer system and were confirmed by the implementation working group. If the data form was incomplete, the FDMA returned it to the respective fire station for completion.

Key Regional Definition and Demographic Data

To assess regional variations in OHCA, we divided Japan into the following 7 regions as the largest administrative units in Japan: Hokkaido-Tohoku, Kanto, Tokai-Hokuriku, Kinki, Chugoku, Shikoku, and Kyushu-Okinawa, which are commonly used in administrative surveys.[19] We obtained the following information by region: pediatric and adult population and the densities (per 1,000 km^2 inhabited area) of pediatricians, emergency pediatricians, hospitals, EMS personnel, and ambulances calculated from Japanese administrative materials.[1,20]

Main Outcome Measure

Neurological outcome was assessed with the Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale as: 1, good performance; 2, moderate disability; 3, severe cerebral disability; 4, coma/vegetative state; and 5, death. The primary outcome measure was 1-month survival with favorable neurological outcome, defined as CPC category 1 or 2.[2,14,15] Secondary outcome measures included pre-hospital ROSC and 1-month survival.

Statistical Analysis

The characteristics of patients and prehospital care in pediatric OHCA were compared among the 7 regions using analysis of variance for numerical variables, and chi-squared test or Fisher's exact test for categorical variables. Multivariate analysis was used to assess the regional variation for 1-month survival with favorable neurological outcome; adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcome were used in multivariate analysis. These variables included age (infants aged <1 year; children aged 1–17 years); sex (male, female); origin of arrest (cardiac, non-cardiac); type of bystander witness (none, family members and others); first documented rhythm (VF, non-VF); type of bystander-initiated CPR (none, any CPR); time interval from call to CPR by EMS personnel (for 1-min increments); and year of arrest (for 1-year increments). In addition, we calculated the AORs of OHCA children for neurologically favorable outcome referring to adults in the respective region by multivariate logistic regression analysis.

All of the tests were 2-tailed and $P<0.05$ was considered statistically significant. All statistical analysis was done using SPSS version 16.0J (SPSS, Chicago, IL, USA).

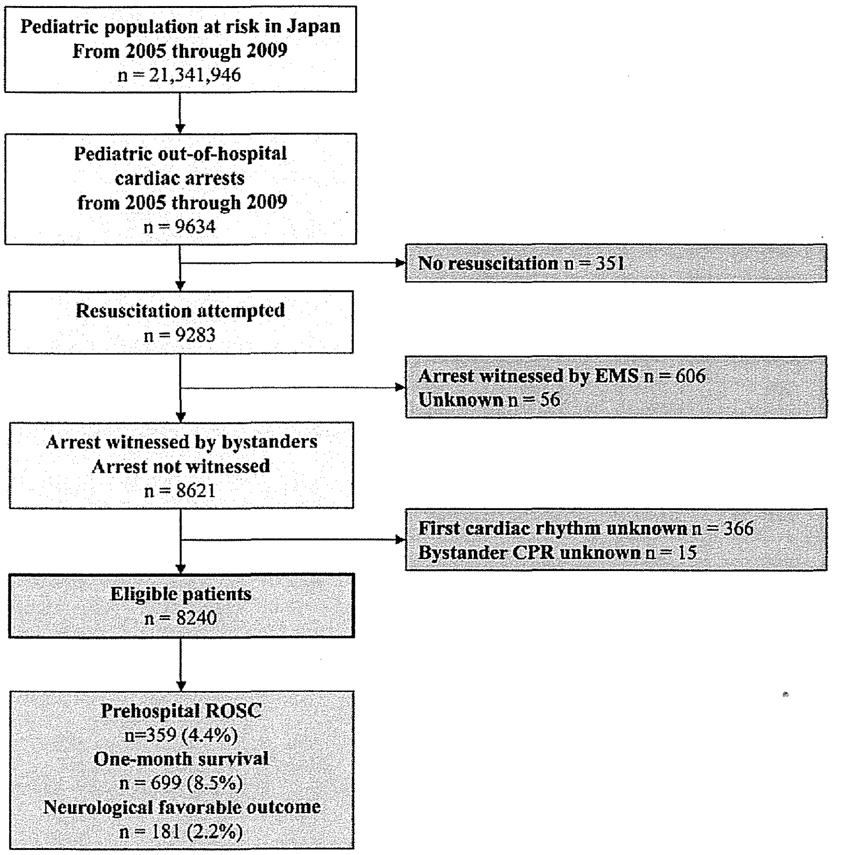

Figure 1. Study flow of pediatric out-of-hospital cardiac arrest cases with an abridged Utstein template from 1 January 2005 through 31 December 2009. CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ROSC, return of spontaneous circulation.

Table 1. Pediatric OHCA Demographic Characteristics by Region in Japan

	Hokkaido-Tohoku	Kanto	Tokai-Hokuriku	Kinki	Chugoku	Shikoku	Kyushu-Okinawa
Pediatric population (×1,000)	2,540	6,542	4,120	3,514	1,299	675	2,651
Population density†	60	361	180	415	155	139	161
Density‡ of							
Pediatricians	34.7	272.8	105.4	299.6	109.0	101.2	106.4
Emergency physicians	27.8	180.8	70.3	212.7	72.7	63.9	91.4
Hospitals	12.9	55.8	29.5	78.4	36.1	37.1	32.6
EMS personnel	256.7	675.8	592.9	946.7	619.5	456.6	415.5
Ambulances	23.7	80.9	52.3	96.7	56.6	52.5	45.7
Incidence§ (95% CI)							
Age 0–17 years	7.6 (6.3–8.9)	8.3 (6.8–9.8)	7.8 (6.7–8.9)	7.1 (6.7–7.4)	7.2 (6.3–8.0)	7.7 (6.1–9.3)	7.4 (6.9–7.8)
Age 1–17 years	4.8 (4.1–5.0)	4.6 (3.9–4.7)	4.6 (4.1–4.7)	4.6 (4.1–4.6)	4.7 (3.9–5.0)	4.9 (4.2–5.2)	4.8 (4.2–5.0)
Age <1 year	67.6 (43.8–91.2)	77.4 (45.6–109.2)	69.2 (45.5–92.9)	54.3 (50.9–57.7)	55.9 (44.4–67.4)	63.7 (35.7–91.7)	57.8 (43.5–72.1)

†No. children per 1 km² inhabited area; ‡No. per 1,000 km² inhabited area; §mean annual incidence per 100,000 population. CI, confidence interval; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.

Results

A total of 9,634 pediatric OHCAs were documented during these 5 years in Japan (**Figure 1**). Out of 9,283 patients with resuscitation attempt, 8,240 who had suffered cardiac arrest before EMS arrival were enrolled in the present analysis, excluding patients with missing data on first documented rhythm (n=366) and bystander CPR (n=15). The proportion of prehospital ROSC among the eligible patients was 4.4%, 1-month survival 8.5%, and 1-month survival with neurologically favorable outcome, 2.2%.

Table 1 lists the demographic characteristics of pediatric OHCA by region. The population density and the densities of pediatricians, emergency pediatricians, hospitals, EMS personnel, and ambulances substantially differed among the 7 regions. The annual incidence of pediatric OHCA per 100,000

Table 2. Pediatric OHCA Patient and EMS Characteristics by Region in Japan

	Hokkaido-Tohoku (n=967)	Kanto (n=2,722)	Tokai-Hokuriku (n=1,614)	Kinki (n=1,239)	Chugoku (n=465)	Shikoku (n=259)	Kyushu-Okinawa (n=974)	P-value‡
Age (years)	2 (0–12)	1 (0–9)	1 (0–11)	2 (0–11)	2 (0–11)	2 (0–12)	2 (0–11)	<0.001
Infant aged <1 year	391 40.4 (37.3–43.6)	1,310 48.1 (46.2–50.0)	707 43.8 (41.4–46.3)	477 38.5 (35.8–41.3)	177 38.1 (33.6–42.7)	101 39.0 (33.0–45.2)	369 37.9 (34.8–41.0)	<0.001
Male	605 62.6 (59.4–65.6)	1,647 60.5 (58.6–62.4)	998 61.8 (59.4–64.2)	746 60.2 (57.4–63.0)	280 60.2 (55.6–64.7)	142 54.8 (48.6–61.0)	597 61.3 (58.2–64.4)	0.390
Type of origin								<0.001
Cardiac origin	301 31.1 (28.2–34.2)	1,013 37.2 (35.4–39.1)	510 31.6 (29.3–33.9)	407 32.8 (30.2–35.5)	98 21.1 (17.5–25.1)	92 35.5 (29.7–41.7)	195 20.0 (17.6–22.7)	
Non-cardiac origin	666 68.9 (65.9–71.8)	1,709 62.8 (60.9–64.6)	1,104 68.4 (66.1–70.7)	832 67.2 (64.5–70.0)	367 78.9 (74.9–82.6)	167 64.5 (58.3–70.3)	779 80.0 (77.3–82.5)	
Type of bystander-witnessed status								0.086
No witness	696 72.0 (69.0–74.8)	2,005 73.7 (72.0–75.3)	1,175 72.8 (70.6–75.0)	923 74.5 (72.0–77.0)	348 74.8 (70.6–78.7)	192 74.1 (68.4–79.4)	720 73.9 (71.0–76.7)	
Family	170 17.6 (15.2–20.1)	431 15.8 (14.5–17.3)	271 16.8 (15.0–18.7)	172 13.9 (12.0–15.9)	59 12.7 (9.8–16.1)	36 13.9 (9.9–18.7)	157 16.1 (13.9–18.6)	
Others	101 10.4 (8.6–12.6)	286 10.5 (9.4–11.7)	168 10.4 (9.0–12.0)	144 11.6 (9.9–13.5)	58 12.5 (9.6–15.8)	31 12.0 (8.3–16.6)	97 10.0 (8.2–12.0)	
Type of bystander-initiated CPR								<0.001
No CPR	461 47.7 (44.5–50.9)	1,523 55.9 (54.1–57.8)	800 49.6 (47.1–52.0)	634 51.2 (48.4–54.0)	244 52.5 (47.8–57.1)	134 51.8 (45.5–58.0)	428 44 (40.8–47.1)	
Chest compression-only CPR	231 23.9 (21.1–26.7)	555 20.4 (18.9–22.0)	402 24.9 (22.8–27.1)	194 15.7 (13.7–17.8)	86 18.5 (15.1–22.3)	40 15.4 (11.3–20.4)	237 24.3 (21.7–27.2)	
Conventional CPR with rescue breathing	275 28.4 (25.6–31.4)	644 23.7 (22.1–25.3)	412 25.5 (23.4–27.7)	411 33.2 (30.6–36.0)	135 29.0 (24.9–33.4)	85 32.8 (27.1–38.9)	309 31.7 (28.8–35.0)	
Type of first recorded rhythm								0.263
VF	58 6.0 (4.6–7.7)	120 4.4 (3.7–5.3)	96 6.0 (4.8–7.2)	56 4.5 (3.4–5.8)	30 6.5 (4.4–9.1)	18 7.0 (4.2–10.8)	53 5.4 (4.1–7.1)	
PEA	135 14 (11.8–16.3)	388 14.3 (13.0–15.6)	252 15.6 (13.9–17.5)	187 15.1 (13.1–17.2)	67 14.4 (11.3–17.9)	32 12.4 (8.6–17.0)	134 13.8 (11.7–16.1)	
Asystole	774 80 (77.4–82.5)	2,214 81.3 (80.0–82.8)	1,266 78.4 (76.4–80.4)	996 80.4 (78.1–82.6)	368 79.1 (75.2–82.8)	209 80.6 (75.4–85.3)	787 80.8 (78.2–83.2)	
Public-access AED use	3 0.3 (0.1–0.9)	17 0.6 (0.40–1.0)	12 0.7 (0.4–1.3)	5 0.4 (0.1–0.9)	2 0.4 (0.1–1.5)	0 0.0	2 0.2 (0.0–0.7)	0.336
Shocks by EMS†	45 4.7 (3.4–6.2)	90 3.3 (2.7–4.1)	69 4.3 (3.3–5.4)	42 3.4 (2.5–4.6)	17 3.7 (2.1–5.8)	14 5.4 (3.0–8.9)	39 4.0 (2.9–5.4)	0.383
Epinephrine use	25 2.6 (1.7–3.8)	56 2.1 (1.6–2.7)	31 1.9 (1.3–2.7)	13 1.0 (0.6–1.8)	4 0.9 (0.2–2.2)	1 0.4 (0.0–2.1)	2 0.2 (0.0–0.7)	<0.001
Intubation	13 1.3 (0.7–2.3)	64 2.4 (1.8–3.0)	32 2.0 (1.4–2.8)	24 1.9 (1.3–2.9)	5 1.1 (0.4–2.5)	5 1.9 (0.6–4.5)	16 1.6 (0.9–2.7)	<0.001
Time course by EMS (min)								
Call to CPR by EMS	9.7 (6–10)	8.9 (6–10)	9.3 (7–11)	8.3 (6–10)	9.3 (6–11)	9.1 (6–10)	9.4 (6–11)	<0.001
Call to hospital arrival	30.7 (20–37)	31.0 (23–36)	29.2 (20–34)	27.8 (20–32.5)	28.6 (19–33)	27.8 (18–32)	26.7 (18–31)	<0.001

Data given as median (IQR), or n % (95% CI). †Calculated only for VF cases. ‡Calculated to test the homogeneity among the 7 regional groups. AED, automated external defibrillation; CPR, cardiopulmonary resuscitation; IQR, interquartile range; PEA, pulseless electrical activity; VF, ventricular fibrillation. Other abbreviations as in Table 1.

Table 3. Pediatric OHCA Outcome by Region in Japan

	Hokkaido-Tohoku (n=967)	Kanto (n=2,722)	Tokai-Hokuriku (n=1,614)	Kinki (n=1,239)	Chugoku (n=465)	Shikoku (n=259)	Kyushu-Okinawa (n=974)
Prehospital ROSC, n (%)	47 (4.9)	108 (4.0)	77 (4.8)	54 (4.3)	21 (4.5)	9 (3.5)	43 (4.4)
Crude OR (95% CI)	1.24 (0.87–1.76)	Reference	1.21 (0.90–1.64)	1.10 (0.79–1.54)	1.14 (0.71–1.85)	0.87 (0.44–1.74)	1.11 (0.78–1.60)
Adjusted OR (95% CI)	1.08 (0.75–1.57)	Reference	1.07 (0.78–1.46)	0.97 (0.68–1.37)	1.02 (0.62–1.68)	0.71 (0.34–1.45)	0.96 (0.66–1.40)
One-month survival, n (%)	82 (8.5)	158 (5.8)	146 (9.0)	118 (9.5)	52 (11.2)	24 (9.3)	119 (12.2)
Crude OR (95% CI)	1.51 (1.14–1.99)	Reference	1.61 (1.28–2.04)	1.71 (1.33–2.19)	2.04 (1.47–2.84)	1.66 (1.06–2.60)	2.26 (1.76–2.90)
Adjusted OR (95% CI)	1.42 (1.06–1.89)	Reference	1.54 (1.21–1.97)	1.62 (1.25–2.10)	2.0 (1.41–2.82)	1.53 (0.95–2.45)	2.16 (1.66–2.80)
Neurologically favorable 1-month survival, n (%)	24 (2.5)	37 (1.4)	47 (2.9)	26 (2.1)	16 (3.4)	4 (1.5)	27 (2.8)
Crude OR (95% CI)	1.85 (1.10–3.10)	Reference	2.18 (1.41–3.36)	1.56 (0.94–2.58)	2.60 (1.43–4.69)	1.14 (0.40–3.22)	2.07 (1.25–3.42)
Adjusted OR (95% CI)	1.65 (0.94–2.90)	Reference	2.06 (1.28–3.31)	1.45 (0.84–2.51)	3.11 (1.62–6.00)	0.79 (0.26–2.43)	2.15 (1.24–3.74)

ORs were adjusted for sex, age, origin of arrest, type of bystander witness, type of bystander CPR, first recorded rhythm, time interval from call to CPR by EMS, and year of arrest. OR, odds ratio; ROSC, return of spontaneous circulation. Other abbreviations as in Tables 1,2.

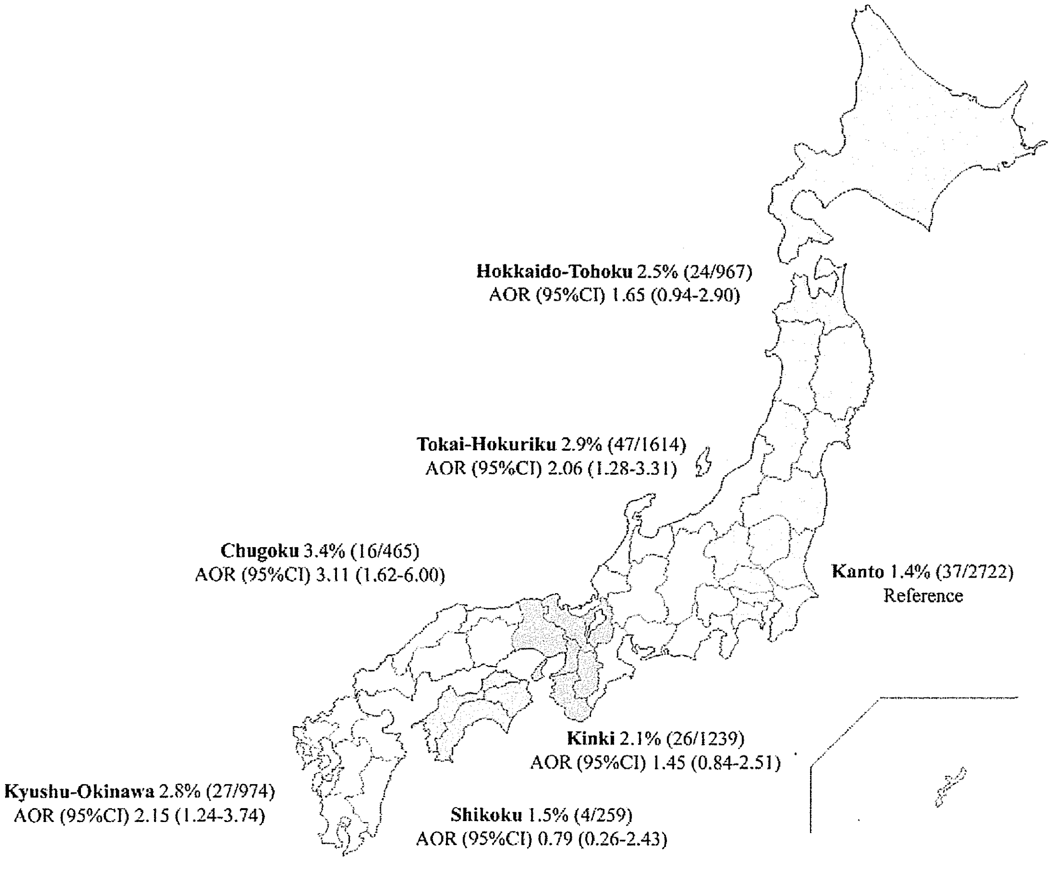

Figure 2. Proportion of neurologically favorable 1-month survival after pediatric out-of-hospital cardiac arrest in Japan according to region. Adjusted odds ratios (AORs) and 95% confidence intervals (95% CIs) compared with Kanto were calculated. ORs were adjusted for sex, age, origin of arrest, type of bystander witness, type of bystander cardiopulmonary resuscitation (CPR), first recorded rhythm, time interval from call to CPR by the emergency medical service, and year of arrest.

Table 4. One-Month Survival With Neurologically Favorable Outcome After OHCA by Region in Japan

	Hokkaido-Tohoku	Kanto	Tokai-Hokuriku	Kinki	Chugoku	Shikoku	Kyushu-Okinawa
Children	2.5 (24/967)	1.4 (37/2,722)	2.9 (47/1,614)	2.1 (26/1,239)	3.4 (16/465)	1.5 (4/259)	2.8 (27/974)
Adults	1.3 (840/64,137)	1.1 (1,773/155,389)	1.4 (1,333/95,589)	1.9 (1,338/70,714)	1.3 (343/27,100)	1.1 (171/15,080)	1.6 (798/48,986)
Crude OR (95% CI)	1.92 (1.27–2.89)	1.19 (0.86–1.66)	2.12 (1.58–2.85)	1.11 (0.75–1.65)	2.78 (1.67–4.63)	1.37 (0.50–3.71)	1.72 (1.17–2.54)
Adjusted OR (95% CI)	2.95 (1.87–4.65)	1.81 (1.28–2.56)	3.23 (2.32–4.49)	1.77 (1.16–2.72)	5.51 (3.10–9.80)	1.62 (0.56–4.68)	2.98 (1.94–4.57)

OR is for children vs. adults. ORs were adjusted for sex, age, origin of origin, type of bystander witness, type of bystander CPR, first recorded rhythm, time interval from call to CPR by EMS, and year of arrest. Abbreviations as in Tables 1–3.

Table 5. Contributing Factors to Favorable Neurological 1-Month Survival After Pediatric OHCA in Japan

	Adjusted OR (95% CI)	P-value
Male (vs. female)	0.75 (0.54–1.05)	0.099
Age 1–17 years (vs. infant aged <1 year)	1.65 (1.11–2.44)	0.012
Cardiac origin (vs. non-cardiac origin)	1.55 (1.07–2.23)	0.019
VF (vs. non-VF)	10.24 (7.04–14.91)	<0.001
Bystander-witnessed status (vs. no witness)	5.15 (3.52–7.54)	<0.001
Bystander CPR (vs. no CPR)	1.63 (1.16–2.30)	0.005
Region		
Hokkaido-Tohoku	1.65 (0.94–2.90)	0.083
Kanto	Reference	
Tokai-Hokuriku	2.06 (1.28–3.31)	0.003
Kinki	1.45 (0.84–2.51)	0.186
Chugoku	3.11 (1.62–6.00)	0.001
Shikoku	0.79 (0.26–2.43)	0.686
Kyushu-Okinawa	2.15 (1.24–3.74)	0.006
Call to CPR by EMS (for 1-min increment)	0.90 (0.85–0.95)	<0.001
Year (for 1-year increment)	1.14 (1.01–1.29)	0.030

Abbreviations as in Tables 1–3.

population ranged from 7.1 to 8.1 throughout Japan. Although the incidence was similar among the regions (4.6–4.9) for children aged 1–17 years, it varied by region (54.3–77.4) for infants aged <1 year.

The characteristics of patients and prehospital care in pediatric OHCA are noted by region in **Table 2**. Whereas the proportions of infant (37.9–48.1%) and cardiac origin (20.0–37.2%) were significantly different by region, those of witness status, VF as first recorded rhythm, public-access AED use, and shocks by EMS were similar. In contrast, the proportion of bystander CPR (44.1–56.0%) and the mean time interval from collapse to CPR by EMS (8.3–9.7 min) and to hospital arrival (26.7–31.0 min) significantly differed by region. After categorizing the data according to age group (infants aged <1 year and children aged 1–17 years; **Table S1**), there were similar regional variations in the characteristics of patients and prehospital care.

Table 3 lists the outcomes of pediatric OHCA by region. We found no significant differences in AORs for pre-hospital ROSC by region, but 1-month survival with neurologically favorable outcome was very heterogeneous (**Figure 2**), that is, significantly greater in Tokai-Hokuriku (2.9%, 47/1614; AOR, 2.06; 95% CI: 1.28–3.31), Chugoku (3.4%, 16/465; AOR, 3.11; 95% CI: 1.62–6.00), and Kyushu-Okinawa (2.8%, 27/974; AOR, 2.15; 95% CI: 1.24–3.74) compared with Kanto (1.4%, 37/2722), even adjusting for potential confounding factors. Again, after analyzing the data according to age group (infants aged <1 year and children aged 1–17 years; **Table S2**), AOR among children aged 1–17 years was significantly greater in Chugoku (AOR, 4.17; 95% CI: 1.99–8.73) and Kyushu-Okinawa (AOR, 1.98; 95% CI: 1.02–3.85) compared with Kanto. There were no significant regional differences in 1-month survival with neurologically favorable outcome after OHCA among infants aged <1 year.

The ratio of 1-month survival with neurologically favorable OHCA outcome between children and adults was compared among regions (**Table 4**). The ratios of children vs. adults were considerably different by region: 5.51 (95% CI: 3.10–9.80) in Chugoku, 3.23 (95% CI: 2.32–4.49) in Tokai-Hokuriku, 2.98 (95% CI: 1.94–4.57) in Kyushu-Okinawa, 2.95 (95% CI: 1.87–4.65) in Hokkaido-Tohoku, 1.81 (95% CI: 1.28–2.56) in Kanto, 1.77 (95% CI: 1.16–2.72) in Kinki, and 1.62 (95% CI: 0.56–4.68) in Shikoku.

On multivariate analysis (**Table 5**), compared with infants aged <1 year, children aged 1–17 years had a significantly better neurological outcome (AOR, 1.65; 95% CI: 1.11–2.44). VF as first documented rhythm (AOR, 10.24; 95% CI: 7.04–14.91), bystander-initiated CPR (AOR, 1.63; 95% CI: 1.16–2.30), and earlier CPR time by EMS (AOR for 1-min increase, 0.90; 95% CI: 0.85–0.95) were associated with better neurological outcome.

Discussion

Using the nationwide registry of OHCA in Japan, we have found that there are significant regional variation in characteristics and outcome of pediatric OHCA. In particular, we found more than 3-fold differences in neurologically favorable survival by region even considering potential known prognostic factors. In contrast to the underpowered previous studies, the present sufficiently large study has clearly identified these important regional variations in pediatric OHCA outcome. To our knowledge, this is the first report to assess the regional variation of pediatric OHCA survival.

In this study, neurologically favorable outcome significantly differed by region, whereas pre-hospital ROSC did not. This discrepancy presumably resulted from the difference in intensive care after hospital arrival. The performance and the quality of advanced life-saving treatment after hospital arrival would be the most plausible explanation for this regional variation in pediatric OHCA outcome. Recently, some studies reported that post-resuscitation care such as therapeutic hypothermia, extracorporeal CPR, and percutaneous coronary intervention might be effective for pediatric cardiac arrest.[21–24]

Differences in OHCA outcome in children were larger than those in adults. Regional variations in the pediatric health-care system such as an unbalanced density of pediatricians might be a possible reason for the regional variation. Furthermore, the pre-hospital care protocol for OHCA patients provided by the FDMA was developed mainly for adults and not for children. Given that pediatric OHCA is far less frequent than adult OHCA, then it might be difficult for both EMS personnel and physicians to accumulate sufficient experience to hone their skills for pediatric cardiac arrest. The child-specific life support system and technique should be developed and distributed.

Present multivariate analysis showed that bystander CPR was associated with better neurological outcome, and this would be a possible explanation for the poor outcome observed in the Kanto area, where the prevalence of bystander CPR was relatively low. Furthermore, the present study has shown that there were great differences in the prevalence of bystander CPRs and the resuscitation time course by the EMS by region, both of which are other key factors for OHCA survival. Many previous studies have shown that bystander CPR improved survival after pediatric and adult OHCA.[3–6,13,25,26] The difference in the prevalence of bystander CPR in this study might be derived from the difference in social activities to promote citizen CPR by region. It is well known that early CPR by EMS personnel and early access to hospitals improve survival after OHCA.[25,27] The present data showing marked regional variations in EMS response time should be discussed to establish more effective and efficient EMS systems.

Importantly, the proportion of neurologically favorable survival after pediatric OHCA remained low regardless of geographical region. Because bystander CPR and public-access AED use are not sufficiently frequent (approximately 50% and <1%, respectively) in any region, further efforts to spread CPR and AED use in communities are needed. In addition, improvements in advanced treatment for pediatric OHCA are needed. Although we previously indicated that the transportation of OHCA patients to the governmentally deployed critical care medical centers (CCMCs) contributed to improving outcome for adult OHCA,[28] it is not clear that this knowledge would be applicable to pediatric OHCA. Some reports found that transportation of OHCA children to pediatric intensive care unit (PICU) could improve their survival.[29,30] In Japan, however, most OHCA children are transported to adult CCMCs or ordinary hospitals rather than PICU. An integrated system to provide intensive care for OHCA children and an evaluation of its effectiveness are matters of urgency.

In this study, the incidence of infant OHCA and the ratio of cardiac/non-cardiac origins differed by region. Regional variations in the incidence of adult OHCA are partly explained by the regional variations in risk factors such as medication for hypertension and dyslipidemia.[8,9] A preventive approach to pediatric OHCA is important,[4] and further effort should be made to facilitate prevention of pediatric cardiac arrest.

Study Limitations

This observational study has several inherent limitations. First, we did not obtain detailed demographic and socioeconomic status, which would influence regional variations in OHCA,[31,32] and there might be unmeasured confounding factors that might have influenced the association between region and outcome. Second as with all epidemiologic studies, the integrity and validity of the data, as well as ascertainment bias, are potential limitations of the study. The use of uniform data collection based on Utstein-style guidelines for reporting cardiac arrest, the large sample size, and the population-based design should minimize these potential sources of bias.

In future studies, we will investigate detailed data including regional and social conditions such as education for citizen and hospital information in order to assess clearly the causes of the regional variations in survival following pediatric OHCA.

Conclusions

This nationwide population-based observational study has shown that there are significant regional variations in 1-month survival with neurologically favorable outcome in pediatric OHCA. To evaluate factors contributing to better outcome, further study including data on both pre- and in-hospital advanced care, and emergency transportation systems are needed.

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