Table 1
Baseline characteristics and survival rate at discharge of total 1282 cases.

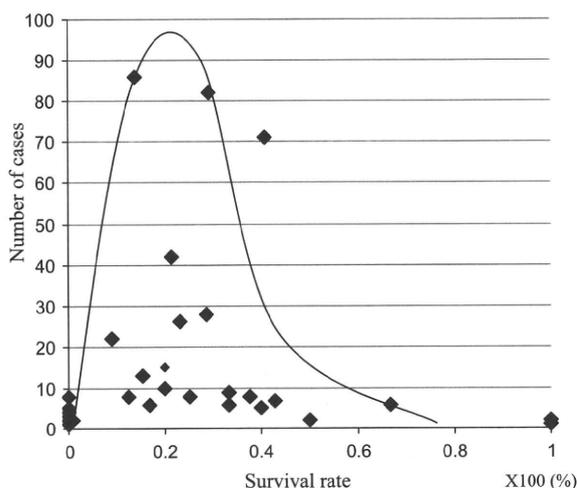| Characteristic		n
Age—year	51 (4–88)	722
Males—no. (%)	419 (75.9)	552
Witnessed arrest—no. (%)	333 (90.7)	367
Bystander CPR—no. (%)	234 (71.8)	326
Cardiac aetiology—no. (%)	621 (48.4)	930
Survival rate at discharge—no. (%)		
Simple average (%)	42.9 ± 1.5	991
Overall rate (=total survival cases/total cases) (%)	29.1 ± 1.4	991
Overall rate (=total survival cases/total cases) (%) excluding hypothermia cases	26.7 ± 1.4	516

Fig. 2. The number of cases and the survival rate at discharge in each of 44 case series (Funnel plot method).

3. Results

The baseline characteristics of cases, which included descriptions of specific elements, were as follows: the average age was 51 years (range, 4–88 years) in 722 cases; 419 patients (75.9%) were male and 133 (24.1%) were female in 552 cases; witnessed arrest was 90.7% (333 cases) of 367 cases; bystander CPR was performed in 234 (71.8%) of 326 cases; and cardiac aetiology was verified in 621 (48.4%) of 930 cases (Table 1).

As many as 54 papers, with the exception of 43 case reports presenting only one case, provided 991 cases with clearly described outcomes. The simple average survival rate at discharge was 42.9 ± 1.5%. Overall survival rate at discharge (=total survival cases/total cases) was 29.1 ± 1.4%. Excluding accidental hypothermia cases, overall survival rate at discharge of 516 cases was 26.7 ± 1.4%. When the relationship between the number of cases and the survival rate at discharge in each of 44 case series was subjected to the funnel plot, the data presented the reverse-

Table 2
Baseline characteristics and survival rate at discharge in the in-depth review and additional pre-/in-hospital data.

Characteristic		n
Age—average year (min–max)	45 (4–88)	130
Males—no. (%)	94 (67.6)	
Females—no. (%)	38 (27.3)	
Not recorded—no. (%)	7 (5.0)	
Witnessed arrest—no. (%)	72 (51.8)	
Non-wittnessed arrest—no.(%)	7 (5.0)	
Not recorded—no. (%)	60 (43.2)	
Bystander CPR—no. (%)	44 (31.7)	
	20 (14.4)	
Not recorded—no. (%)	75 (54.0)	
Initial rhythm		
Shockable rhythm (VF, pulseless VT)—no. (%)	23 (16.5)	
Non-shockable rhythm (asystole/PEA)—no. (%)	11 (7.9)	
Not recorded—no. (%)	105 (75.5)	
Rhythm on admission of ED		
Shockable rhythm (VF, pulseless VT)—no. (%)	25 (18.0)	
Non-shockable rhythm (asystole, PEA)—no. (%)	21 (15.1)	
Not recorded—no. (%)	93 (66.9)	
Rhythm before introduction of ECPR		
Shockable rhythm (VF, pulseless VT)—no. (%)	44 (31.6)	
Non-shockable rhythm (asystole, PEA)—no. (%)	22 (15.8)	
Not recorded—no. (%)	73 (52.5)	
Aetiology		
Cardiac aetiology—no. (%)	88 (63.3)	
Non-cardiac aetiology—no. (%)	46 (33.1)	
Not recorded—no. (%)	5 (3.6)	
Collapse—ECPR interval (min)	52.0 [33.3, 70]*	37
Admission on ER—ECPR interval (min)	32.0 [20.0, 60.0]*	30
Duration of ECPR (h)	48.0 [20.3, 48.0]*	57
Hospitalization (day)	16.5 [3.0, 47.0]*	38
CAG—yes/no/not recorded	31/12/96	
PCI—yes/no/not recorded	22/19/98	
IABP—yes/no/not recorded	37/11/91	
Therapeutic hypothermia—yes/no/not recorded	20/8/111	
Complication related to ECPR		
Bleeding	4	
Ischemia of lower extremity	2	
Malposition	2	
No complications	3	
Not recorded	128	

* Median value [25% tile, 75% tile].

funnel type that centred on the average survival rate of all cases (Fig. 2).

3.1. In-depth review

An in-depth review of 139 cases demonstrated that the cause of arrest was cardiac in 88 cases (63.3%). The average age was 45 years (range, 4–88) in 130 cases, with 67.6% male (94/132). Witnessed arrest was 91.1% (72/79). Bystander CPR was performed in 68.8% (44/64) (Table 2). There were 60 cases of shockable rhythm on the electrocardiogram (ECG) either at the scene or on arrival at the ED or just before introduction of ECPR.

There was no significant difference in survival rate at discharge between the cases with cardiac aetiology and those with non-cardiac aetiology (59.1% vs. 79.2%, odds ratio=0.73, 95%

Table 3
Comparison of survival-to-hospital discharge between cases with cardiac and non-cardiac aetiology, and comparison between cases with shockable and non-shockable rhythm in the in-depth review.

	Survival	n	OR [lower 95%, higher 95%]	p
Cardiac aetiology—no. (%)	43 (59.1)	76	0.73 [0.29, 1.87]	0.51
Non-cardiac aetiology—no. (%)	16 (79.2)	25		
Total	59 (58.4)	101		
Shokable rhythm (VF, pulseless VT)	33 (70.2)	47	4.02 [1.32, 12.41]	0.01
Non-shockable rhythm (asystole, PEA)	7 (36.8)	19		
Total	40 (60.6)	66		

Table 4
Aetiology and neurological outcome in the in-depth review.

Etiology	n	(%)	Outcome at discharge (Glasgow Outcome Scale)						GR of GOS (%)		Favourable outcome of GOS (GR or MD) (%)	
			GR	MD	SD	VS	D	Not recorded*	Exclude*	Include*	Exclude*	Include*
ACS	43	30.9	18		1	2	19	3	41.9	45.0	41.9	45.0
Arrythmia	22	15.8	13	1			8		59.1	59.1	63.6	63.6
Hypothremia	19	13.7	12		1		5	1	63.2	66.7	63.2	66.7
Overdose	10	7.2	9				1		90.0	90.0	90.0	90.0
Myopathy	8	5.8	3	1			3	1	37.5	42.9	50.0	57.1
Trauma	3	2.2	1				2		33.3	33.3	33.3	33.3
Myocarditis	7	5.0	2	1		1	3		28.6	28.6	42.9	42.9
PE	4	2.9	1				2	1	25.0	33.3	25.0	33.3
Asthma	2	1.4	1				1		50.0	50.0	50.0	50.0
Renal failure	2	1.4	1				1		50.0	50.0	50.0	50.0
Drowning	2	1.4	1			1			50.0	50.0	50.0	50.0
Neck hanging	1	0.7	1						100.0	100.0	100.0	100.0
AAD	1	0.7					1		0.0	0.0	0.0	0.0
SAH	1	0.7					1		0.0	0.0	0.0	0.0
Unknown	2	1.4			1		1		0.0	0.0	0.0	0.0
No description	12	8.6	4	1			4	3	33.3	44.4	41.7	55.6
Total	139	100	67	4	3	4	52	9	48.2	51.5	51.1	54.6

* "Exclude" means "% calculated by excluding the number of not-recorded cases from a population". "Include" means "% calculated by including the total number of cases in a population".

confidence interval (CI): 0.29–1.87, $p = 0.51$). Excluding cases of accidental hypothermia and cases with no records of cardiac rhythm/aetiology, survival rate at discharge of the cases with shockable rhythm on the initial ECG or during transport or after admission was statistically higher than that of non-shockable rhythm in this population (70.8% vs. 36.8%, odds ratio = 4.02, 95% CI: 1.32–12.4, $p = 0.01$) (Table 3).

The rates of good recovery, moderate disability, severe disability, vegetative state, death at hospital discharge and non-recorded cases were 48.2%, 2.9%, 2.2%, 2.9%, 37.4% and 6.4%, respectively. The main outcomes of patients receiving ECPR were good recovery or death (Table 4).

4. Discussion

In our study, the survival rate at discharge was higher than that presented in the annual data in the official report of the Ambulance Service of the Fire Department in 2006 in Japan. The survival rate at 1 month was 8.5% of 18,320 cases of witnessed and cardiac-verified out-of-hospital cardiac arrest. Of these cases, the survival rate of patients of VF/pulseless VT was 20.5% (1049/5113). Although there might be different characteristics in each case included in the analysis, results from the funnel plot demonstrated low publication bias in this population. Therefore, these results suggest that ECPR may provide a higher survival rate than conventional CPR. However, patient selection bias, for example, a tendency to use ECPR in younger patients, remains a limitation. Recently, several reports described the efficacy of ECPR on the outcome of cases of in-hospital cardiac arrest,[9,10] cardiogenic shock[10] or paediatric cases.[11] Chen and his colleagues reported in their prospective cohort study that ECPR provided better outcomes for in-hospital cardiac arrest patients than conventional CPR.[9] Nichol et al. systematically reviewed a large number of case series studies of cardiogenic shock and cardiac arrest. The survival-to-hospital discharge rate was 44.9 ± 6.7% of 1494 cases in 84 reports.[10] Another meta-analysis of 288 paediatric cases reported the rate as 39.6%.[11]

Most neurological outcomes in the GOS at discharge were good recovery or death, and there were very few cases of mild disability, severe disability and vegetative state in this in-depth review of cases, regardless of the cause of cardiac arrest. The principal component of the ECPR was a heparin-bonded surface circuit including a centrifugal pump and hollow-fibre oxygenator. In general, the pump can immediately generate sufficient blood flow in adult patients after the introduction of the artificial circulation. On the other hand, closed chest compression results in a cardiac output of 25–30% of normal when performed under optimal conditions.[1] Thus, cerebral blood flow may be adequately maintained during ECPR, and may be one of the reasons for a good neurological outcome in patients receiving ECPR. In addition, the circuit of the ECPR can be easily connected to a temperature controller, which is able to perform therapeutic hypothermia. In our few cases with documentation, therapeutic hypothermia was actually combined with ECPR in 71.4% (20/28) of the patients. In the metabolic phase of a three-phase time-sensitive model after cardiac arrest, a possible protective mechanism against reperfusion cellular injury may involve hypothermia-mediated attenuation of the rapid oxidant burst.[12] Nagao et al. described that ECPR for induction of hypothermia has been shown to improve survival rates in a small study of patients, who arrived at the ED in cardiac arrest and failed to respond to standard advanced cardiac life-support techniques.[13] A previous report described that more rapid introduction of hypothermia can contribute to a better neurological outcome.[6] Unfortunately, we could not collect detailed data on the association with therapeutic hypothermia, but a rapid induction of hypothermia could also explain the better neurological outcome of patients receiving ECPR where it was applied.

The establishment of a technique for immediate corrective intervention with the ECPR circuit is one of the future problems to be resolved. It is very difficult to access the large vessels during CPR. The CoSTR 2005 stated that ECPR is a difficult technique because experienced staff is required to perform it safely and quickly. Rapid placement of arterial and venous cannulae in the circuit is a key intervention for successful ECPR. Delayed placement prevents patients from obtaining the full performance capability of ECPR. Although an echo-guide technique or surgical approach has been introduced, a standard method has not yet been established. Further study will determine a standard procedure for its rapid and safe replacement. Other problems are lack of a standard method of weaning, complications related to haemorrhage with the use of anticoagulants and the cost.

In this study, there were a number of causes of cardiac arrest and no significant differences in the outcomes between cases with car-

diac and non-cardiac aetiology. Many of the cases in this population were witnessed and received bystander CPR. Comparing survival rates at discharge between the cases with shockable and non-shockable rhythm, a statistically significant higher survival rate was found in the cases with shockable rhythm. Based on these findings, inclusion criteria for a multicentre, prospective non-randomised cohort study were established. The 'SAVE-J: Study of advanced life support for ventricular fibrillation with extracorporeal circulation in Japan' was launched and has been ongoing since October 2008 to compare the proportion of patients with a favourable neurological outcome by intention-to-treat in an ECPR group with a non-ECPR group. The key inclusion criteria were as follows: (1) shockable rhythm on the initial ECG; (2) cardiac arrest on arrival at hospital regardless of the presence of recovery of spontaneous circulation before arrival; (3) arrival at hospital within 45 min of the call for an ambulance or cardiac arrest; and (4) cardiac arrest remaining for more than 15 min after arrival at hospital. The result of SAVE-J will determine the efficacy of ECPR and the indication criteria.

5. Conclusion

The study found that the influence of publication bias in published case series of ECPR in Japan was relatively low. The analysis indicated that ECPR could provide a higher survival rate with favourable neurological outcome in cases of out-of-hospital cardiac arrest.

Conflict of interest statement

No conflict of interests to declare.

Acknowledgements

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