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Clinical paper

Modulating effects of immediate neuroprognosis on early coronary angiography and targeted temperature management following out-of-hospital cardiac arrest: A retrospective cohort study

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Abstract

Aim: The simplified cardiac arrest hospital prognosis (sCAHP) score is a validated tool for predicting neurological outcomes after out-of-hospital cardiac arrest (OHCA). We used the sCAHP score to evaluate whether the effects of early coronary angiography (CAG) and targeted temperature management (TTM) for OHCA were modulated by immediate neuroprognosis.

Methods: This was a single-centre retrospective observational study. Consecutive OHCA patients were screened between 2011 and 2017. Multivariate logistic regression analysis and generalised additive models (GAMs) were used to examine the associations between independent variables and outcomes. Early CAG was defined as CAG performed within 24 h after return of spontaneous circulation (ROSC).

Results: A total of 412 patients were included in the study, and 94 (22.8%) patients had neurologically intact survival. The GAM plot identified a sCAHP score of 185 as the cut-off point to differentiate high-risk (sCAHP score $\geqq 185$) from low-risk (sCAHP score <185) patients. Regression models indicated that early CAG was significantly associated with favourable neurological [odds ratio (OR) 4.43, 95% confidence interval (CI) 2.28–8.60, $p < 0.001$] and survival outcomes (OR 3.47, 95% CI 1.93–6.25, $p < 0.001$), independent of the sCAHP score. Although TTM was associated with favourable neurological outcome only in low-risk patients (OR 2.13, 95% CI 1.10–4.13, $p = 0.02$), TTM was associated with improved survival for all patients (OR 2.66, 95% CI 1.54–4.59, $p < 0.001$), independent of the sCAHP score.

Conclusions: Early CAG and TTM should be considered for all OHCA patients as suggested by guidelines, irrespective of the immediately predicted neuroprognosis after ROSC.

Keywords: Out-of-hospital cardiac arrest, Coronary angiography, Percutaneous, Coronary intervention, Targeted temperature management, Neuroprognosis

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Introduction

Globally, out-of-hospital cardiac arrest (OHCA) strikes an estimated 28–44 people per 100,000 population annually.[1] In Asia, the overall survival rate to hospital discharge after OHCA was 5.4%, and the percentage of those recovering favourable neurological status was 2.7%.[2]

The post-resuscitation care includes early coronary angiography (CAG) and targeted temperature management (TTM).[3,4] Resuscitation guidelines[3,4] recommend early CAG along with percutaneous coronary interventions (PCI) if indicated for all OHCA patients with ST-segment elevation on post-resuscitation electrocardiogram; the guidelines also advocate early CAG for selected OHCA patients without ST-segment elevation on electrocardiogram.[5]

Analysis of a large registry[6] indicated that, in real-world practice, CAG was only performed in approximately one-third of OHCA patients arriving at PCI-capable centres. Lemiale et al.[7] reported that about 65% of OHCA patients died from neurological injuries when treated in intensive care units. This perceived medical futility may discourage clinicians or families from implementing early invasive procedures despite the fact that guidelines recommend patient selection for these procedures irrespective of neurological status.[3,4]

The cardiac arrest hospital prognosis (CAHP)[8] score uses variables that are immediately available on hospital admission, and displays excellent discriminatory performance in predicting neurological outcomes of OHCA patients. The CAHP score stratifies patients into three groups based on their risk and predicted outcomes: low risk, 40% of patients with unfavourable outcomes; medium risk, 80% of patients with unfavourable outcomes; and high risk, 95–100% of patients with unfavourable outcomes. Bougouin et al.[9] reported that early CAG was associated with better outcomes only in low-risk OHCA patients, and suggested that early CAG should focus on these patients with preserved neurological status.

The simplified CAHP (sCAHP) score removes the no-flow interval [i.e., the time from arrest to initiation of cardiopulmonary resuscitation (CPR)], and was recently validated with excellent discriminatory performance in an East Asian cohort.[10] In current analysis, we used the sCAHP score to evaluate whether the therapeutic effects of early CAG and TTM would be modulated by immediate neuroprognosis after OHCA in East Asian patients.

Materials and methods

Setting

This observational study was performed by retrospectively analysing the prospectively-collected OHCA database of the National Taiwan University Hospital, which is a tertiary medical centre. Patients or their surrogates gave written informed consent to be include into the database. Our hospital has 2600 beds, including 220 beds in intensive care units, and there are approximately 100,000 patient visits to our emergency department each year. The study was conducted in accordance with the Declaration of Helsinki, and was approved by institutional research ethics committee (reference number: 201708013RIND).

CPR and post-resuscitation care for OHCA were performed as recommended by guidelines.[3,4] If indicated, CAG, PCI, TTM, and extracorporeal CPR were initiated at any time when needed on a 24 h/7 day basis. The decision to perform CAG and PCI was left to the discretion of the on-duty cardiologist. TTM was applied to patients who remained comatose after return of spontaneous circulation (ROSC).[11,12] Our TTM protocol was published previously.[11,12] Briefly, a peripheral cooling device was applied to achieve the targeted temperature of 33 °C within 4–6 h after ROSC. The targeted temperature was maintained for 24 h. The protocol for extracorporeal CPR has been described elsewhere.[13,14] Briefly, the extracorporeal CPR would be initiated for patients who did not have ROSC after 10 min of CPR if the cause of collapse was assumed to be of cardiac origin.[13,14]

If ROSC was achieved, neuroprognosis was estimated based on daily assessments of brainstem reflexes along with electroencephalography on days 3 and 7. Withdrawal of life-sustaining therapy for post-ROSC patients was not permitted by law in Taiwan until 2015.

Patients

Consecutive OHCA patients were screened between January 2011 and March 2017, and those who met the following criteria were included in the study: (1) age 18 years or older; (2) non-traumatic cardiac arrest; (3) no documentation of a do-not-resuscitate order before cardiac arrest; and (4) sustained ROSC after CPR, which was defined as ROSC lasting for at least 20 min without resumption of chest compressions. If multiple cardiac arrest events occurred in a single patient, only the first event was recorded.

Data collection and outcome measures

Details of the OHCA events were extracted from the electronic ambulance and medical records. Study data for each patient included age, sex, comorbidities, variables derived from the Utstein template,[15] initial post-ROSC electrocardiogram findings, and laboratory results on admission to the intensive care units. The sCAHP score[10] was calculated using the same method as the original CAHP[8] score (Supplemental Table S1), except that the no-flow interval was omitted because the time of arrest was not routinely recorded according to the Utstein template.[15] The low-flow interval was defined as the interval from the initiation of CPR to ROSC, and early recovery of consciousness was defined as appropriate response to verbal commands within the first 4 h after ROSC. The diagnosis of ST-segment elevation myocardial infarction was made by on-duty cardiologists. Early CAG or PCI was defined as CAG or PCI performed within 24 h of ROSC.[16]

The primary outcome was favourable neurological status at hospital discharge, defined as Cerebral Performance Category 1 or 2.[17] The secondary outcome was survival to hospital discharge.

Statistical analysis

Data were analysed using R 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria). Categorical data were expressed as counts and proportions, and continuous data were expressed as means and standard deviations. Categorical variables were compared using Fisher's exact test, and continuous variables were examined using Wilcoxon's rank-sum test. A two-tailed p-value of <0.05 was considered as statistically significant.

The odds ratio (OR) was selected as the outcome measure, and multivariate logistic regression analyses were performed to examine the associations between the independent variables and outcomes.

All available independent variables were considered in the regression model regardless of whether they were identified as significant by the univariate analysis. The stepwise variable selection procedure (with iterations between the forward and backward steps) was applied to obtain the final regression model. Significance levels for entry and stay were set at 0.15 to avoid exclusion of potential candidate variables. The final regression model was identified by sequentially excluding individual variables with a p-value >0.05 until all regression coefficients were statistically significant.

We used generalised additive models (GAMs)[18] to examine the nonlinear effects of continuous variables and, if necessary, to identify the appropriate cut-off point(s) for dichotomising a continuous variable during the variable selection procedure. The interaction between the sCAHP score and early invasive procedures (CAG, PCI, TTM, and extracorporeal CPR) was assessed during the model-fitting process. In the sensitivity analysis, early PCI was used to replace early CAG during the model-fitting process. We assessed the goodness-of-fit of the fitted regression model using c statistics, adjusted generalised R^2, and the Hosmer–Lemeshow goodness-of-fit test.

Results

A total of 936 adult non-traumatic OHCA patients were sent to our emergency department during the study period, and resuscitation efforts resulted in sustained ROSC in 412 patients who were included in the analysis. As shown in Table 1, the mean age of the patients was 65.2 years (standard deviation: 16.8 years). The majority (74.0%) of the arrests were witnessed, and most of the initial rhythms were non-shockable (69.9%). The mean duration of the low-flow interval was 33.9 min (standard deviation: 22.8 min). The mean sCAHP score was 186.3 (standard deviation: 49.9). There were 49 patients (11.9%) diagnosed as ST-segment elevation myocardial infarction. There were 103 patients receiving early CAG and 51 patients receiving early PCI. A total of 94 patients (22.8%) survived to hospital discharge with favourable neurological status.

The GAM plot revealed a linear association of logit (p) with sCAHP score, where p represented the probability for favourable neurological status at hospital discharge (Supplemental Fig. S1). If logit (p) was greater than zero, the odds for favourable neurological status were greater than one. Therefore, sCAHP score of 185 was selected as the cut-off point to differentiate high-risk (sCAHP score $\geq$185) from low-risk (sCAHP score $<$185) patients.

We included all independent variables listed in Table 1 in the regression analysis for variable selection. Regression models with and without interaction terms were built for neurological and survival outcomes, respectively. As shown in Tables 2 and 3, Model 1a/2a indicated that early CAG was significantly associated with favourable neurological [OR 4.43, 95% confidence interval (CI) 2.28–8.60, $p<0.001$] and survival (OR 3.47, 95% CI 1.93–6.25, $p<0.001$) outcomes when the effects of sCAHP score and early recovery of consciousness were adjusted. Model 1b indicated that TTM was associated with favourable neurological outcome only in low-risk patients (OR 2.13, 95% CI 1.10–4.13, $p=0.02$), whereas Model 2a indicated that TTM was associated with improved survival for all patients (OR 2.66, 95% CI 1.54–4.59, $p<0.001$). The outcome proportions stratified by early CAG/TTM and sCAHP score are presented as stereoscopic bar graph in Figs. 1 and 2.

As indicated by the sensitivity analyses (Supplemental Tables S2 and S3), the associations between early PCI and favourable outcomes were also independent of sCAHP score.

Discussion

Main findings

In this study, we first used a validated tool, i.e. sCAHP score, to stratify OHCA patients into different risks of poor neurological outcome. We then used multivariate regression analyses to study the associations between early CAG or TTM and OHCA outcomes. The results indicated that early CAG was associated with improved neurological and survival outcomes across different risk strata. By contrast, TTM seemed to be more effective only in low-risk patients for improving neurological outcome but consistently effective across all risk strata for improving survival. Finally, in the sensitivity analysis, early PCI was demonstrated to improve outcomes independent of the neuro-prognosis by sCAHP score, which may explain the reason why early CAG may benefit OHCA patients. Our results corroborated the guideline recommendations[3,4] that the decision to perform emergent CAG or TTM should be based on a cluster of considerations rather than solely on predicted neuroprognosis.

Immediate post-resuscitation neuroprognosis

Maupain et al.[8] used the Paris OHCA registry to develop the CAHP score and defined the risk groups by splitting the scoring system into terciles of patients. Categorizing a continuous variable without knowing the relationship between independent and dependent variables may lead to loss of information and statistical power.[19] Therefore, we used a GAM plot (Supplemental Fig. S1) to identify the optimal cut-off point differentiating high-risk from low-risk patients. As we had removed the no-flow interval from the calculation of the sCAHP score, our cut-off point (sCHAP score = 185) may be essentially the same as the one used by Maupain et al.[8] to define high-risk patients (CAHP score = 200).

Immediate neuroprognosis and effects of CAG

Bougouin et al.[9] also used the same registry as Maupain et al.[8] and reported that there were no significant associations between early CAG or TTM and favourable outcomes for all OHCA patients. They did report an association between early CAG and favourable outcomes among low-risk patients (CAHP score $<$150).[9] By contrast, our analysis indicated that early CAG was associated with favourable outcomes for all OHCA patients, independent of post-ROSC neurological status (i.e., early recovery of consciousness) and independent of the predicted neuroprognosis according to the sCAHP score.

Our study cohort included more patients stratified as the high-risk group than the Bougouin et al.[9] study, with the proportion of high-risk patients at 55% versus 19%, respectively. This difference may be caused by the lower proportions of witnessed arrest (74% versus 96%, respectively) and shockable rhythms (30% versus 50%, respectively) in our cohort. The survival rates of high-risk patients also differed substantially between our study (37/226, 16.4%) and the the study by Bougouin et al.[9] (7/274, 2.6%). Because the proportion and survival of high-risk patients were low in the study by Bougouin et al.,[9] it may lack the statistical power to detect the effects of early CAG in the high-risk subgroup.

Table 1 – Baseline characteristics of study patients.

Variable	All patients (n=412)	sCAHP score <185 (n=186)	sCAHP score ≥185 (n=226)	p-Value
Age, years (SD)	65.2 (16.8)	57.2 (16.1)	71.8 (14.4)	<0.001
Male, n (%)	282 (68.4)	135 (72.6)	147 (65.0)	0.11
Comorbidities, n (%)				
Diabetes mellitus	135 (32.8)	56 (30.1)	79 (35.0)	0.34
Hypertension	207 (50.2)	78 (41.9)	129 (57.1)	0.003
Coronary artery disease	133 (32.3)	54 (29.0)	79 (35.0)	0.21
Heart failure	37 (9.0)	19 (10.2)	18 (8.0)	0.49
Arrhythmia	37 (9.0)	16 (8.6)	21 (9.3)	0.86
Chronic obstructive pulmonary disease or asthma	25 (6.1)	5 (2.7)	20 (8.9)	0.01
End-stage renal disease	30 (7.3)	14 (7.5)	16 (7.1)	1
Cirrhosis	11 (2.7)	6 (3.2)	5 (2.2)	0.55
Stroke	30 (7.3)	9 (4.8)	21 (9.3)	0.09
Malignancy	68 (16.5)	25 (13.4)	43 (19.0)	0.14
Witnessed arrest, n (%)	305 (74.0)	153 (82.3)	152 (67.3)	<0.001
Arrest at home, n (%)	191 (46.4)	38 (20.4)	153 (67.7)	<0.001
Shockable rhythms, n (%)	124 (30.1)	89 (47.8)	35 (15.5)	<0.001
Adrenaline dose, n (%)				<0.001
0	87 (21.1)	71 (38.2)	16 (7.1)	
1–2 mg	105 (25.5)	61 (32.8)	44 (19.5)	
≥3 mg	220 (53.3)	54 (29.0)	166 (73.5)	
Time from CPR to ROSC (min) (SD)	33.9 (22.8)	22.2 (17.3)	43.5 (22.4)	<0.001
Laboratory tests (SD)				
pH	7.1 (0.2)	7.2 (0.2)	7.0 (0.2)	<0.001
$PaCO_2$ (mmHg)	63.3 (28.3)	52.0 (23.9)	72.6 (28.3)	<0.001
HCO_3^- (mmol/L)	19.6 (6.2)	19.2 (5.7)	19.9 (6.6)	0.46
Lactate (mmol/L)	10.1 (4.6)	9.0 (4.6)	11.0 (4.5)	<0.001
Creatinine (mg/dL)	2.5 (3.0)	2.4 (2.9)	2.6 (3.1)	0.009
sCAHP score	186.3 (49.9)	142.0 (32.0)	222.7 (27.5)	<0.001
Early recovery of consciousness following ROSC, n (%)	33 (8.0)	27 (14.5)	6 (2.7)	<0.001
STEMI	49 (11.9)	17 (9.1)	32 (14.2)	0.13
Post-ROSC interventions, n (%)				
TTM	139 (33.7)	81 (43.5)	58 (25.7)	<0.001
ECPR	88 (21.4)	44 (23.7)	44 (19.5)	0.33
Early CAG	103 (25.0)	64 (34.4)	39 (17.3)	<0.001
Early PCI	51 (12.4)	34 (18.3)	17 (7.5)	0.001
Survival to hospital discharge, n (%)	145 (35.2)	108 (58.1)	37 (16.4)	<0.001
Favourable neurological outcome at hospital discharge, n (%)	94 (22.8)	80 (43.0)	14 (6.2)	<0.001

CAG = coronary angiography; CPR = cardiopulmonary resuscitation = ECPR, extracorporeal cardiopulmonary resuscitation; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation; sCAHP = simplified cardiac arrest hospital prognosis score; SD = standard deviation; STEMI = ST-segment elevation myocardial infarction; TTM = targeted temperature management.

Although subgroup analysis has been used as a simple and intuitive way to analyse heterogeneous subjects, its validity is inevitably jeopardized by the insufficiency of statistical power due to the reduction of sample size in each subgroup. Thus, subgroup analyses are conducted primarily for an exploratory purpose, and the discovered heterogeneity in effects across subgroups should be confirmed or falsified by a regression analysis including the corresponding interaction terms along with the full sample size to maximise the statistical estimation efficiency.[20–22] This is the procedure that was conducted in our analysis.

Patient selection for early CAG in OHCA survivors

Previous studies reported that patients with history of coronary arterial disease, initial shockable rhythms, or ST-segment elevation on post-ROSC electrocardiogram were more likely to receive early CAG, probably because these factors suggested a higher probability of coronary lesions amenable to PCI.[6,23] In addition to these considerations, the decision to perform CAG may be outcome-driven. Rab et al.[24] developed a risk-stratifying algorithm for OHCA survivors to identify those who were less likely to benefit from an early invasive strategy. The suggested unfavourable factors[24] included unwitnessed arrest, initial non-shockable rhythms, no bystander CPR, CPR duration >30 min., ongoing CPR, pH < 7.2, lactate level >7 mmol/L, age > 85 years, end-stage renal disease, and non-cardiac causes. If OHCA survivors had multiple unfavourable factors, early CAG may be considered futile and not suggested.[24] Nonetheless, most of the unfavourable factors identified by Rab et al.[24] were included in our analysis, which indicated that the therapeutic effects of CAG were independent of these factors. Sunde and Andersen[25] remarked that these scoring systems or prediction algorithms should not be used for individual decision-making because they could lead to inappropriate withdrawal of life-sustaining therapy, with self-fulfilling prophecy.

Table 2 – Multiple logistic regression model with favourable neurological outcome at hospital discharge as the dependent variable.

Independent variable[a]	Odds ratio	95% confidence interval	*p*-Value
Model 1a: Regression model without interaction terms[b]			
sCAHP score	0.97	0.96–0.98	<0.001
Early recovery of consciousness following ROSC	10.95	3.89–30.86	<0.001
Early CAG	4.43	2.28–8.60	<0.001
Arrythmia	5.72	1.91–17.07	0.002
HCO_3^- >25 (mmol/L)	2.37	1.08–5.20	0.03
Lactate (mmol/L)	0.92	0.85–1.00	0.04
Model 1b: Regression model with interaction terms[c]			
Early recovery of consciousness following ROSC	14.20	5.21–38.73	<0.001
sCAHP score ≥185 * no early CAG	0.13	0.05–0.34	<0.001
Lactate (mmol/L)	0.88	0.82–0.95	0.001
sCAHP score <185 * early CAG	3.25	1.58–6.67	0.004
Arrythmia	4.00	1.44–11.15	0.008
Creatinine ≤1.5 (mg/dL)	2.12	1.12–3.99	0.02
sCAHP score <185 * TTM	2.13	1.10–4.13	0.02

CAG = coronary angiography; ROSC = return of spontaneous circulation; sCAHP score = simplified cardiac arrest hospital prognosis score.
[a] Independent variables are arranged in order of ascending *p*-values.
[b] Model 1a, goodness-of-fit assessment: $n = 412$; adjusted generalized $R^2 = 0.54$; *c* statistic = 0.90 (95% confidence interval 0.86–0.94); and Hosmer–Lemeshow goodness-of-fit chi-squared test $p = 0.24$.
[c] Model 1b, goodness-of-fit assessment: $n = 412$; adjusted generalized $R^2 = 0.48$; *c* statistic = 0.88 (95% confidence interval 0.84–0.92); and Hosmer–Lemeshow goodness-of-fit chi-squared test $p = 0.20$.

Table 3 – Multiple logistic regression model with survival to hospital discharge as the dependent variable.

Independent variable[a]	Odds ratio	95% confidence interval	*p*-Value
Model 2a: Regression model without interaction terms[b]			
sCAHP score	0.98	0.97–0.99	<0.001
Early CAG	3.47	1.93–6.25	<0.001
Early recovery of consciousness following ROSC	7.97	2.73–23.24	<0.001
TTM	2.66	1.54–4.59	<0.001
Stroke	4.58	1.71–12.23	0.002
Creatinine ≤1.8 (mg/dL)	2.49	1.34–4.60	0.004
Lactate ≤6.5 (mmol/L)	2.12	1.18–3.81	0.01
Witnessed arrest	2.01	1.04–3.90	0.04
Model 2b: Regression model with interaction terms[c]			
sCAHP score ≥185 * no early CAG	0.21	0.11–0.39	<0.001
Early recovery of consciousness following ROSC	9.27	3.25–26.38	<0.001
TTM	3.03	1.78–5.18	<0.001
Creatinine ≤1.8 (mg/dL)	2.74	1.49–5.02	0.001
sCAHP score <185 * early CAG	3.25	1.58–6.67	0.001
Lactate ≤6.5 (mmol/L)	2.32	1.30–4.13	0.004
Stroke	3.89	1.44–10.54	0.008
Witnessed arrest	2.27	1.19–4.34	0.01

CAG = coronary angiography; ROSC = return of spontaneous circulation; sCAHP score = simplified cardiac arrest hospital prognosis score; TTM = targeted temperature management.
[a] Independent variables are arranged in order of ascending *p*-values.
[b] Model 2a, goodness-of-fit assessment: $n = 412$; adjusted generalized $R^2 = 0.50$; *c* statistic = 0.87 (95% confidence interval 0.84–0.91); and Hosmer–Lemeshow goodness-of-fit chi-squared test $p = 0.27$.
[c] Model 2b, goodness-of-fit assessment: $n = 412$; adjusted generalized $R^2 = 0.47$; *c* statistic = 0.86 (95% confidence interval 0.83–0.90); and Hosmer–Lemeshow goodness-of-fit chi-squared test $p = 0.90$.

In the recently published multicentre, randomized Coronary Angiography after Cardiac Arrest (COACT) trial, Lemkes et al.[26] reported that for OHCA patients with initial shockable rhythms but without ST-segment elevation on post-ROSC electrocardiogram, a strategy of immediate CAG did not result in higher 90-day survival than a strategy of delayed CAG (64.5% versus 67.2%). However, these actual high survival rates were far beyond those used in the sample-size calculation. Therefore, a 27% benefit or a 38% harm of immediate CAG for 90-day survival could not be excluded based on the COACT trial.[26] An appropriate strategy of patient selection may maximize the benefits of early CAG for OHCA patients.

In the sensitivity analysis, early PCI was demonstrated to improve outcomes independent of the neuroprognosis by sCAHP score, which suggested that revascularization may be the main driver of the

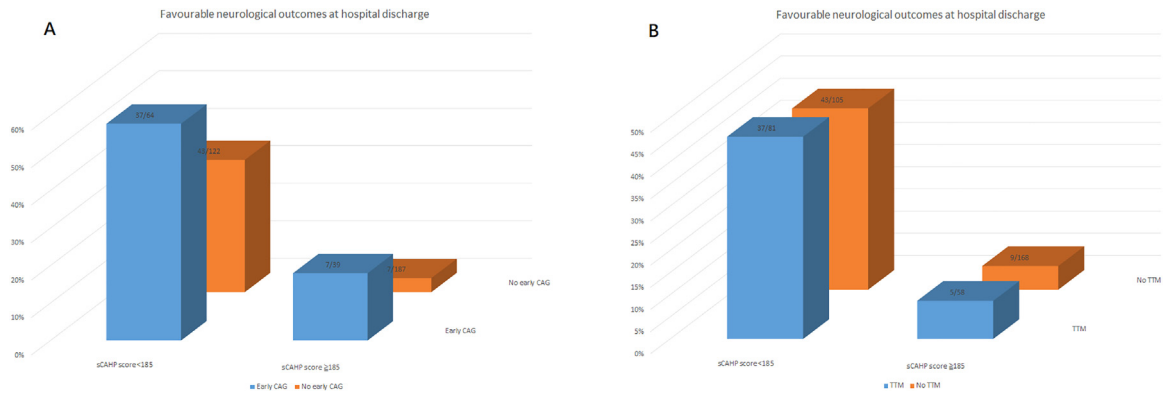

Fig. 1 – Stereoscopic bar graph for proportions of favourable neurological outcome at hospital discharge of patients stratified by sCAHP score and early CAG (panel A) or by sCAHP score and TTM (panel B). The numbers of outcomes/patients in each subgroup are expressed on top of each bar. sCAHP score = simplified cardiac arrest hospital prognosis score; CAG = coronary angiography; TTM = targeted temperature management.

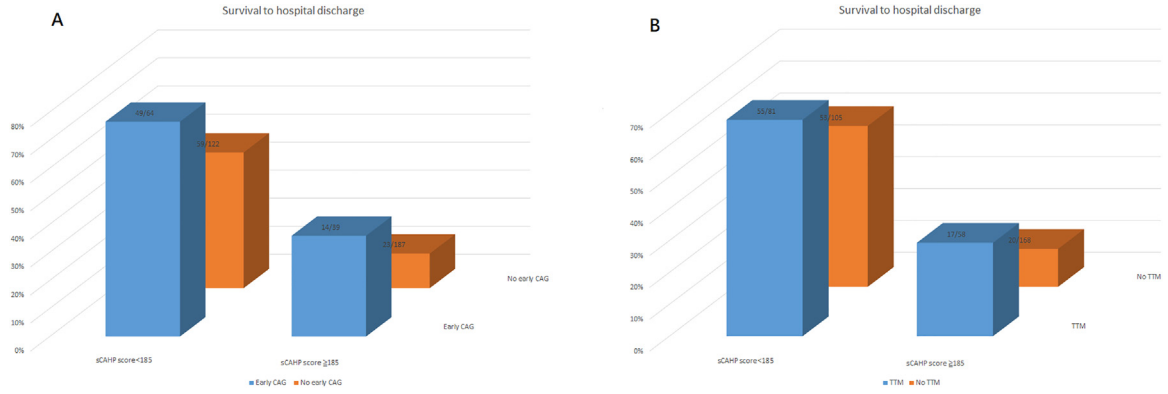

Fig. 2 – Stereoscopic bar graph for proportions of survival to hospital discharge of patients stratified by sCAHP score and early CAG (panel A) or by sCAHP score and TTM (panel B). The numbers of outcomes/patients in each subgroup are expressed on top of each bar. sCAHP score = simplified cardiac arrest hospital prognosis score; CAG = coronary angiography; TTM = targeted temperature management.

association between early CAG and improved outcomes. Ischemic heart disease was the most common cause of OHCA[27]; therefore, early CAG and PCI if indicated may improve the post-ROSC circulatory status, reduce the need for high-dose vasopressors, and prevent secondary cerebral ischemic injuries, leading to improved neurological outcomes.

Immediate neuroprognosis and effects of TTM

Resuscitation guidelines recommended that TTM is performed for all comatose OHCA survivors.[3,4] However, the guidelines also noted that it was unknown whether certain OHCA subgroups benefitted from lower (32–34 °C) or higher (36 °C) temperatures.[3,4] In our hospital, the target temperature was maintained at 33 °C for 24 h, and current analysis suggested that TTM was more effective in low-risk patients. Previous studies reported that age[28] and time to ROSC[29] were inversely associated with post-TTM neurological outcomes. Kjaergaard et al.[29] reported that the effects of TTM at different temperatures were not modulated by the time to ROSC; that is, TTM did not appear to be more effective for patients achieving ROSC within a certain time period. Therefore, using composite scoring systems such as the CAHP/sCAHP score may be more efficient for identifying subgroups that would most benefit from TTM. The brain is more sensitive to reduced blood supply than the myocardium, and the time window before the onset of irreversible damage is shorter in the brain than in myocardium.[30] This may explain why early CAG was effective independent of sCAHP score, whereas TTM was more effective in low-risk patients only. Nevertheless, TTM should still be performed for all OHCA patients as suggested by guidelines[3,4] as its benefit for survival was independent of sCAHP score.

Study limitations

First, although multivariate analysis was used to adjust the effects of existing variables, the effects of unmeasured confounding factors could not be adjusted. Despite that the discriminatory performance of sCAHP score had been validated,[10] the no-flow time may still be a significant confounding factor in the analysis for the witnessed patients. Second, although the sCAHP score was not used in clinical practice, its components were well-known to predict OHCA outcomes, and it may influence the decision-making process. Withdrawal of life-sustaining therapy was not legal in Taiwan until 2015, which may

reduce the possible bias of self-fulfilling prophecy. Third, Early CAG was defined as CAG performed within 24 h of ROSC. During this period, information that could influence the decision to perform CAG was not analysed. The definition of early CAG was consistent with that used in previous studies.[16] This inherent limitation of the observational study design could only be resolved by conducting randomized controlled trials.

Conclusions

Early CAG was associated with improved neurological and survival outcomes of OHCA, irrespective of the immediate neuroprognosis predicted by sCAHP score. By contrast, when OHCA patients were stratified by sCAHP score, TTM appeared to be more effective in improving neurological outcome only for low-risk OHCA patients (patients with sCAHP score <185). The beneficial effects of TTM for survival were consistent for all OHCA patients, independent of the sCAHP score. Therefore, early CAG, PCI and TTM should be considered for all OHCA patients as suggested by guidelines, irrespective of the immediately predicted neuroprognosis.

Conflicts of interests

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.08.014.

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