Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Impact of Cardiac Arrest Centers on the Survival of Patients With Nontraumatic Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis

Jun Wei Yeo;* Zi Hui Celeste Ng*; Amelia Xin Chun Goh*; Jocelyn Fangjiao Gao; Nan Liu, PhD; Shao Wei Sean Lam, PhD; Yew Woon Chia, MBBS, MMed; Gavin D. Perkins, MD; Marcus Eng Hock Ong, MBBS, MPH;† Andrew Fu Wah Ho, MBBS, MPH, MMed† for the National Targeted Temperature Management Workgroup;‡

BACKGROUND: The role of cardiac arrest centers (CACs) in out-of-hospital cardiac arrest care systems is continuously evolving. Interpretation of existing literature is limited by heterogeneity in CAC characteristics and types of patients transported to CACs. This study assesses the impact of CACs on survival in out-of-hospital cardiac arrest according to varying definitions of CAC and prespecified subgroups.

METHODS AND RESULTS: Electronic databases were searched from inception to March 9, 2021 for relevant studies. Centers were considered CACs if self-declared by study authors and capable of relevant interventions. Main outcomes were survival and neurologically favorable survival at hospital discharge or 30 days. Meta-analyses were performed for adjusted odds ratio (aOR) and crude odds ratios. Thirty-six studies were analyzed. Survival with favorable neurological outcome significantly improved with treatment at CACs (aOR, 1.85 [95% CI, 1.52–2.26]), even when including high-volume centers (aOR, 1.50 [95% CI, 1.18–1.91]) or including improved-care centers (aOR, 2.13 [95% CI, 1.75–2.59]) as CACs. Survival significantly increased with treatment at CACs (aOR, 1.92 [95% CI, 1.59–2.32]), even when including high-volume centers (aOR, 1.74 [95% CI, 1.38–2.18]) or when including improved-care centers (aOR, 1.97 [95% CI, 1.71–2.26]) as CACs. The treatment effect was more pronounced among patients with shockable rhythm (P=0.006) and without prehospital return of spontaneous circulation (P=0.005). Conclusions were robust to sensitivity analyses, with no publication bias detected.

CONCLUSIONS: Care at CACs was associated with improved survival and neurological outcomes for patients with nontraumatic out-of-hospital cardiac arrest regardless of varying CAC definitions. Patients with shockable rhythms and those without prehospital return of spontaneous circulation benefited more from CACs. Evidence for bypassing hospitals or interhospital transfer remains inconclusive.

Key Words: cardiac arrest ■ cardiac arrest center ■ heart arrest ■ resuscitation

Out-of-hospital cardiac arrest (OHCA) is the most time-critical medical emergency[1–3] and exerts a tremendous disease burden.[4] The post–cardiac arrest syndrome, a consequence of whole-body ischemia-reperfusion injury with devastating multiorgan involvement, is a significant contributor to poor outcomes among OHCA survivors, for which complex multidisciplinary care is required.[5–7] Postresuscitation

Correspondence to: Andrew Fu Wah Ho, MBBS, MPH, MMed, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608. E-mail: andrew.ho@duke-nus.edu.sg

*J. W. Yeo, Z. H. C. Ng, and A. X. C. Goh contributed equally as joint first authors.

†M. E. H. Ong and A. F. W. Ho contributed equally as joint last authors.

‡A complete list of the National Targeted Temperature Management Workgroup members can be found in the Appendix at the end of the article.

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023806

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- There is uncertainty over the role of cardiac arrest centers (CACs) in the care of out-of-hospital cardiac arrest (OHCA), and the 2020 International Liaison Committee on Resuscitation guidelines previously recommended with low certainty that patients with OHCA should be transported to a CAC, partly based on a systematic review on the topic.
- Treatment of nontraumatic patients with OHCA at CACs was associated with significantly improved survival and neurological outcomes, and these findings persisted even when using varying definitions of CAC (eg, high-volume centers).
- The treatment effect was more pronounced among patients with OHCA with shockable rhythm and those without prehospital return of spontaneous circulation.

What Are the Clinical Implications?

- The current updated systematic review and meta-analysis provided an upgraded level of evidence (Grading of Recommendations, Assessment, Development, and Evaluation level of evidence: moderate) in support of transport of nontraumatic patients with OHCA to CACs, and patients who would likely benefit most are those with shockable rhythms and those without prehospital return of spontaneous circulation.
- Regionalized care for patients with OHCA has the potential to improve outcomes, but transport policies that involve bypassing the nearest hospital for CACs or for interhospital transfer from non-CACs to CACs need further studies.

Nonstandard Abbreviations and Acronyms

CAC	cardiac arrest centers
OHCA	out-of-hospital cardiac arrest
ROSC	return of spontaneous circulation
TTM	targeted temperature management

care has been suggested to be the fifth link in the chain of survival concepts, and a component of an integrated emergency care network comprising community first responders, emergency medical services (EMS), and hospitals aiming to provide quality care to patients with OHCA. Despite advances in therapeutics such as targeted temperature management (TTM), mechanical circulatory support, and neuroprognostication, urgent questions remain pertaining to how best to organize hospitals and emergency care systems to improve access to quality care and clinical outcomes.[8]

The recent 2020 guidelines from the International Liaison Committee on Resuscitation recommended with low certainty[9–11] that patients with OHCA should be transported to cardiac arrest centers (CACs). CACs are specialized tertiary institutions, conceptually similar to level 1 trauma centers, and are often high-volume or regionalized centers treating patients with OHCA with the capability to organize postresuscitation care, including 24/7 access to a cardiac catheterization laboratory for coronary angiography and percutaneous coronary intervention (PCI), TTM, extracorporeal membrane oxygenation, and neuroprognostication among other interventions.[12–14] However, although there has been evidence for the effectiveness of each individual intervention in variable settings,[15–19] evidence for the benefit of CACs in treating patients with OHCA remain inconclusive. This is in part because CACs, which provide a complex bundle of interventions, have been poorly defined,[10,20] and similar institutions described in published literature may range from exhibiting only a few to many of the defining traits of a CAC. This brings about difficulties in statistical analysis and interpretation.

Furthermore, it is unknown which subpopulations benefit more from CACs, defined according to prehospital Utstein variables[21,22] such as the receipt of bystander cardiopulmonary resuscitation, initial shockable rhythm, or prehospital return of spontaneous circulation (ROSC). A recent cohort study by Chien et al[23] suggested that the presence of a shockable rhythm modified the benefits of CAC. Kajino et al[24] also showed significant benefit in patients without, but not for patients with, prehospital ROSC. This knowledge gap is especially pertinent because knowing which patients are likely to benefit from an expensive intervention can guide prioritization of scarce health care resources. This understanding also aids the rational ambulance diversion strategy to bring the right patients to the right destinations.[8,25]

Consequently, this systematic review aimed not only to provide urgently needed evidence for or against treating patients with OHCA at CACs, but also to analyze the impact within predefined subgroups.

METHODS

This systematic review and meta-analysis adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* guidelines (Table S3).[26,27] The study protocol had been published in the PROSPERO (International Prospective Register of Systematic Reviews; CRD42021260468). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Search Strategy

A systematic literature search was performed in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases from inception up to March 9, 2021. The search strategy was developed in consultation with a medical information specialist. Keywords and Medical Subject Headings terms such as "cardiac arrest center," "hospital volume," "postresuscitation care," "fifth link," "out-of-hospital cardiac arrest," and other synonyms were applied in the search strategy to identify relevant articles. Seventy-one references from the latest systematic review and meta-analysis on this topic,[10] including the review itself, were hand searched to identify additional relevant studies. The investigative team, which included several resuscitation scientists, were asked to ascertain if they were aware of additional relevant studies. This process did not surface any study that was not already captured in the search strategy. Articles were viewed through Endnote X9[28] (Clarivate, Philadelphia, PA) for an article sieve. The search was repeated on June 7, 2021 yielding no additional eligible articles. The detailed search strategy is available in Data S1.

Inclusion and Exclusion Criteria

An article sieve was conducted by 3 authors (J.W.Y., Z.H.C.N., A.X.C.G.) according to predefined criteria. Each article was reviewed by at least 2 authors blinded to each other's decision. Disputes were resolved through consensus from the senior author (A.F.W.H.). All studies were filtered through the following inclusion criteria: (1) studies with adult patients with OHCA of nontraumatic cause, (2) studies comparing CAC versus non-CAC, (3) studies comparing direct transport to CAC versus transfer to CAC, and (4) studies reporting outcomes of interest such as survival to 30 days or hospital discharge and survival to 30 days or hospital discharge with favorable neurological outcome. Good neurological outcome was defined as Cerebral Performance Category 1 or 2, or modified Rankin scale 0, 1, or 2. Both interventional studies, such as randomized clinical trials, and observational studies, such as retrospective or prospective cohorts, were included. Studies with only pediatric patients or with no control group were excluded. Review articles, meta-analyses, protocols, conference abstracts, letters, commentaries, and editorials were excluded from this review. We excluded studies that were not in the English language and were not accompanied by an English translation.

Definition of Cardiac Arrest Centers

There was a lack of consensus over the definition of a CAC in the literature.[7,10,12,20] For example, the Association for Acute CardioVascular Care of the European Society of Cardiology described cardiac arrest centers[12] as specialized institutions offering all recommended treatment options for patients with OHCA, including access to a coronary angiography laboratory with 24/7 PCI capability, TTM, extracorporeal membrane oxygenation, mechanical ventilation, and neurological prognostication. On the other hand, the German Resuscitation Council accreditation process required CACs to have standard operating procedures for communication with EMS and quality of care assessments in addition to 24/7 PCI, TTM, and intensive care capabilities.[29] Using a strict definition of CAC, only institutions with the capability for 2 or more of the above interventions and explicitly referred to by study authors as CACs or synonymous terms, such as critical care medical center, tertiary heart center, cardiac receiving center, and regional center, were accepted. PCI-capable hospital alone was not accepted as a term synonymous with CAC. Having the capability for only 1 of the above interventions was also considered insufficient, because a single intervention cannot constitute an intervention bundle. To account for differences in defining CACs, sensitivity analyses were conducted using less strict definitions, accepting terms like high-volume centers and centers with improved postresuscitation care including before-and-after study designs.

Statistical Analysis

Data on general article information (author, year, country), baseline demographics (age, sex, witnessed arrest, initial shockable rhythm, prehospital ROSC), and outcomes of interest (survival to 30 days or hospital discharge with good neurological outcome, survival to 30 days or hospital discharge) were abstracted by 3 authors (J.W.Y., Z.H.C.N., A.X.C.G.). The data abstraction process was blinded among the authors, who used a predetermined data collection form. Disputes were resolved through consensus from the senior author (A.F.W.H.). Adjusted odds ratio (aOR) and crude odds ratio (OR) for binary outcomes were abstracted from each article. Where incremental or hierarchical statistical models were presented, the OR adjusted for the maximum number of covariates was extracted. Where multiple statistical approaches were presented (eg, multivariable modeling and propensity-score matching) in the same study, we considered the approach used in the primary analysis. When unavailable, OR and 95% CI were calculated for articles reporting summary data using 2×2 contingency tables.

Conventional pairwise meta-analyses were performed. Given the high known concordance[30] between the outcomes of survival to 30 days and survival to hospital discharge, the decision was made in consensus with all study authors to pool both outcomes, which was deemed sufficient to demonstrate improvement in short-term OHCA outcomes, if any, consistent with

the Core Outcome Set for Cardiac Arrest.[31] The aORs were preferentially analyzed over ORs, because the estimates represent less bias caused by confounding. A DerSimonian-Laird random-effects model with inverse variance weights was applied regardless of heterogeneity because of expected between-study variations in population and interventions. Sensitivity analyses were performed for wider definitions of a CAC, including CACs defined as strictly explicit CACs and high-volume centers, or CACs and centers with improved postresuscitation care. Further sensitivity analyses applying fixed-effects models to the above were also performed. Heterogeneity was assessed using the I^2 statistic with 25%, 50%, and 75% thresholds for low, moderate, and high levels of heterogeneity, respectively. To account for heterogeneity, subgroup analyses were performed to compare studies measuring outcomes by hospital discharge versus 30 days, and also among all included studies for predefined, clinically important Utstein variables: initial shockable rhythm and presence of prehospital ROSC whenever possible. All analyses were performed using Review Manager (RevMan 5.4) software package[32] by the Cochrane Collaboration. Two-tailed statistical significance was set at $P<0.05$. Publication bias was assessed through visually inspecting funnel plots when 10 or more studies reported an outcome. The quality of observational studies was evaluated on the Newcastle-Ottawa scale,[33] and randomized clinical trial risk of bias was evaluated using the Cochrane Risk of Bias 2[34] tool. Two authors (J.W.Y., Z.H.C.N.) evaluated each article using the Newcastle-Ottawa scale or Cochrane Risk of Bias 2 tool, and disputes were resolved through consensus from the senior author (A.F.W.H.). The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach (Table S4) and the GRADEpro Guideline Development Tool (Evidence Prime, McMaster University).[35,36]

RESULTS

Literature Retrieval and Summary of Included Articles

The database search yielded 4544 articles. There were 1093 duplicate articles removed, and 3358 articles were excluded on the basis of their titles and abstracts. A further 54 articles were excluded upon full-text review. The κ value measuring interrater reliability was 0.75 when reviewing the title and abstracts and 0.9 for full-text review. Finally, 36 studies[20,23–25,37–68] qualified for analysis. The study selection process and reasons for excluding the 54 studies are illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-P 2020 flow diagram (Figure 1).

A total of 147 943 patients were included in the 36 studies. Two studies[55,67] were conducted in Australia, 1 in Canada[66], 1 in the Czech Republic,[60] 2 in Denmark,[47,53] 1 in France,[56] 5 in Japan,[24,44,50,58,64] 8 in South Korea,[40,42,46,48,49,51,62,63] 1 in Norway,[37] 4 in Taiwan,[23,45,65,68] 2 in the United Kingdom,[20,59] and 9[§] in the United States. Three articles reported data from the CARES (Cardiac Arrest Registry to Enhance Survival) registry, 2 articles from the CAVAS database (Cardiovascular Disease Surveillance), 2 articles from the NHIRD database (National Health Insurance Research), and 3 articles from the UOP (Utstein Osaka Project). Fifteen studies were prospective cohorts, 20 were retrospective cohorts, and 1 was a pilot study for a randomized clinical trial.

The characteristics and quality assessment of included studies are presented in Table S1. The figures for unadjusted analyses are presented in Figure S1. The summary of meta-analysis results is presented in Table.

Survival to 30 Days or Hospital Discharge With Good Neurological Outcome

Adjusted Analyses

Five studies[52,57,58,62,65] reported aORs for survival to 30 days or hospital discharge with good neurological outcome. Pooled analysis revealed significantly higher survival with good neurological outcome among patients treated at CACs (aOR, 1.85 [95% CI, 1.52–2.26]; Figure 2).[52,57,58,62,65] There was high between-study heterogeneity (I^2, 75%). This result remained significant when using a fixed-effects model (aOR, 1.67 [95% CI, 1.64–1.70]). On sensitivity analysis, pooled estimates also revealed a significant increase in this outcome among patients treated at CACs when including high-volume centers (aOR, 1.50 [95% CI, 1.18–1.91]; Figure 3A)[51,52,56–58,62,64,65] and also when including centers with improved postresuscitation care in the definition of CAC (aOR, 2.13 [95% CI, 1.75–2.59]; Figure 3B).[‖] When using fixed-effects models, these results remained significant when including high-volume centers (aOR, 1.67 [95% CI, 1.64–1.70]) or centers with improved postresuscitation care (aOR, 1.68 [95% CI, 1.65–1.71]). There was no publication bias observed on visual inspection of funnel plots (Figure S2).

Unadjusted Analyses

Seven studies[23,53,57–59,62,65] reported ORs for survival to 30 days or hospital discharge with good neurological outcome. Pooled analysis revealed a significantly higher survival with good neurological outcome among patients treated at CACs (OR, 2.27 [95% CI, 1.58–3.25]). Pooled analysis also revealed a significant

[§]References 25, 38, 39, 41, 43, 52, 54, 57, 61.

[‖]References 25, 37, 44, 46, 48, 52, 54, 57, 58, 62, 65.

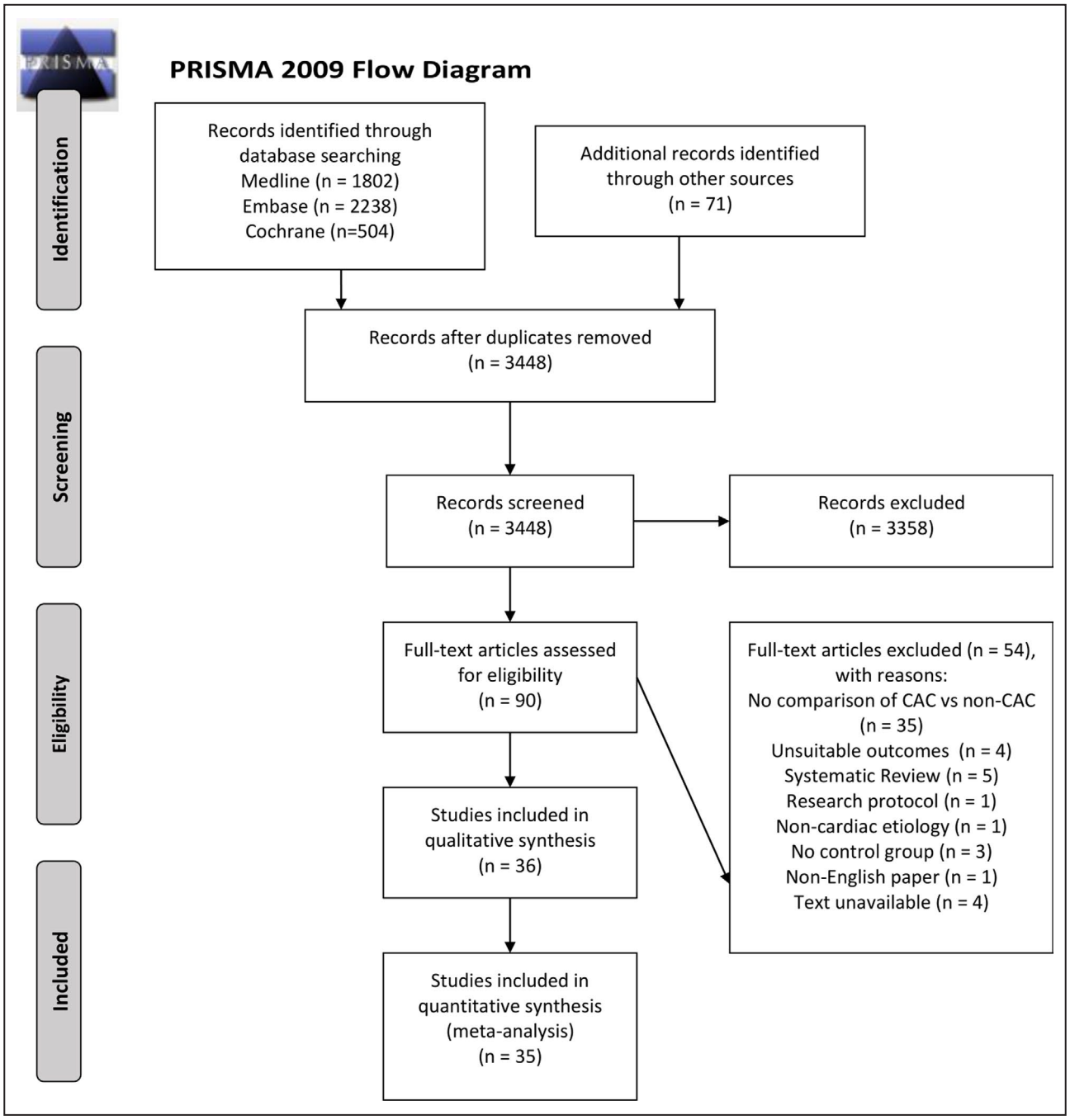


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.
CAC indicates cardiac arrest center.

increase in this outcome among patients treated at CACs when including high-volume centers (OR, 1.82 [95% CI, 1.35–2.46]) and also when including centers with improved postresuscitation care in the definition of CAC (OR, 2.16 [95% CI, 1.67–2.81]).

Subgroup Analysis

Subgroup analysis comparing patients with initial shockable or nonshockable rhythm (Figure 4)[23,25,44,50,65] revealed a significant increase in survival with good neurological outcome among patients with both shockable (OR, 2.31 [95% CI, 1.77–3.02]) and nonshockable rhythm (OR, 1.16 [95% CI, 0.73–1.84]) when treated at CACs. The treatment effect was significantly greater among patients with initial shockable compared with nonshockable rhythm (P=0.006). However, there was no significant difference in survival with good neurological outcome between patients with or without prehospital ROSC (P=0.09).

Table. Summary of Meta-Analysis Results

Outcomes	Studies	Sample size	Effect size, aOR (95% CI)	*P* value	I^2, %
Survival to discharge, 30 d with good neurological outcome					
Adjusted analyses					
CACs only	5	58 835	1.85 (1.52–2.26)	<0.00001*	75
CACs+high-volume centers	8	61 733	1.50 (1.18–1.91)	0.0008*	84
CACs+improved-care centers	11	65 292	2.13 (1.75–2.59)	<0.00001*	73
Unadjusted analyses					
CACs only	7	59 239	2.27 (1.58–3.25)	<0.00001*	90
CACs+high-volume centers	10	64 512	1.82 (1.35–2.46)	<0.00001*	92
CACs+improved-care centers	14	64 936	2.16 (1.67–2.81)	<0.00001*	84
Subgroup analyses					
Shockable/nonshockable	5	9129	…	0.006*	…
Prehospital ROSC/no ROSC	5	14 116	…	0.09	…
Survival to discharge, 30 d					
Adjusted analyses					
CACs only	7	25 895	1.92 (1.59–2.32)	<0.00001*	71
CACs+high-volume centers	9	31 406	1.74 (1.38–2.18)	<0.00001*	85
CACs+improved-care centers	12	27 762	1.97 (1.71–2.26)	<0.00001*	54
Unadjusted analyses					
CACs only	11	42 323	2.14 (1.75–2.61)	<0.00001*	89
CACs+high-volume centers	18	84 359	1.98 (1.63–2.40)	<0.00001*	93
CACs+improved-care centers	19	47 072	2.04 (1.72–2.43)	<0.00001*	84
Subgroup analyses					
Shockable/nonshockable	7	11 207	…	0.73	…
Prehospital ROSC/no ROSC	9	53 592	…	0.005*	…

aOR indicates adjusted odds ratio; CACs, cardiac arrest centers; and ROSC, return of spontaneous circulation.
*$P < 0.05$.

Survival to 30 Days or Hospital Discharge

Adjusted Analyses

Seven studies[20,45,57,62,65–67] reported aORs for survival to 30 days or hospital discharge. Pooled analysis revealed a significant increase in survival among patients treated at CACs (aOR, 1.92 [95% CI, 1.59–2.32]; Figure 5).[20,45,57,62,65–67] There was moderate between-study heterogeneity (I^2, 71%). This result remained significant when using a fixed-effects model (aOR, 1.92 [95% CI, 1.74–2.11]). On sensitivity analysis, pooled estimates also revealed a significant increase in this outcome among patients treated at CACs when including high-volume centers (aOR, 1.74 [95% CI, 1.38–2.18]; Figure 6A)[20,40,45,57,62,64–67] and also when including centers with improved postresuscitation care in the definition of CAC (aOR, 1.97 [95% CI, 1.71–2.26]; Figure 6B).¶ When using fixed-effects models, these results remained significant when including high-volume centers (aOR, 1.77 [95% CI, 1.63–1.92]) or centers with improved postresuscitation care (aOR, 1.95 [95% CI, 1.79–2.12]). There was no publication bias observed on visual inspection of funnel plots (Figure S2).

Unadjusted Analyses

Eleven studies# reported ORs for survival to 30 days or hospital discharge. Pooled analysis revealed a significant increase in survival among patients treated at CACs (OR, 2.14 [95% CI, 1.75–2.61]). Pooled analysis also revealed a significant increase in this outcome among patients treated at CACs when including high-volume centers (OR, 1.98 [95% CI, 1.63–2.40]) and also when including centers with improved postresuscitation care in the definition of CAC (OR, 2.04 [95% CI, 1.72–2.43]).

Subgroup Analysis

Subgroup analysis comparing patients with or without prehospital ROSC (Figure 7)[20,24,42,43,56,57,65–67] revealed a significant increase in survival among

¶References 20, 25, 39, 45, 46, 48, 54, 57, 62, 65–67.

#References 20, 24, 47, 53, 57, 59, 62, 65–68.

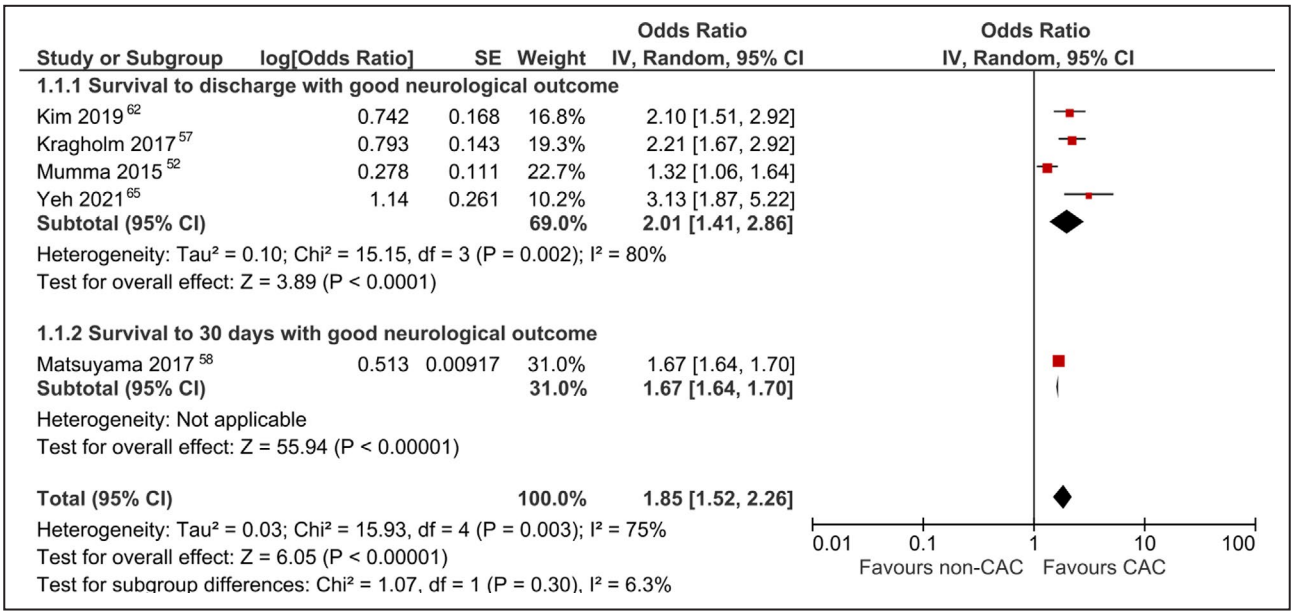


Figure 2. Forest plot for meta-analysis of adjusted analyses comparing survival with good neurological outcome between cardiac arrest centers (CACs) and non-CACs using a random-effects model and the strict definition of CACs.
IV indicates inverse variance.

patients with prehospital ROSC (OR, 1.46 [95% CI, 1.12–1.90]) as well as among patients without prehospital ROSC (OR, 2.52 [95% CI, 1.90–3.35]). The treatment effect was significantly greater among patients without prehospital ROSC (*P*=0.005). However, there was no significant difference in survival between patients with initial shockable or nonshockable rhythm (*P*=0.73).

Direct to CAC Versus Transfer to CAC

Only 2 studies[44,49] reported outcomes for patients directly transported to a CAC versus transferred to a CAC from another hospital. The studies were too heterogeneous to pool, but both reported no significant differences in survival or neurological outcomes between patients directly transported or transferred to a CAC.

DISCUSSION

The optimal CAC configuration and the benefit of CACs on the survival outcomes of patients with OHCA remain uncertain,[69] especially for predefined patient subgroups. Only low-certainty evidence for improved survival in CACs has been demonstrated by previous meta-analyses (Table S2),[7,10,70] which were limited by inconsistencies in CAC definitions and the reliance on before-and-after study designs vulnerable to inherent biases. This is, to our knowledge, the most up-to-date systematic review and meta-analysis on the topic, with 7 new studies since the last review by Yeung et al, and the first to demonstrate clearly improved survival among patients with OHCA treated in CACs compared with non-CACs. The results showed (1) significantly improved survival to 30 days or discharge with good neurological outcome and (2) improved survival to 30 days or discharge for patients with OHCA who received care at a CAC (main analysis), regardless of how strictly CACs were defined (sensitivity analyses). Additionally, subgroup analysis suggested that the treatment effect of CACs may be significantly better for patients with shockable rhythm and without prehospital ROSC. On the whole, only 6 studies using before-and-after designs were included in this review. These were excluded from the main analysis but included for the sensitivity and subgroup analyses. Taken together, these findings hold implications for the organization of emergency care systems and ambulance diversion strategies for patients with OHCA.

High case volume and aggressive postresuscitation care have been shown to improve outcomes for OHCA, both of which are key features of CACs.[12,61,62] This analysis demonstrates improved survival and survival with good neurological outcomes both at discharge and 30 days for patients with OHCA treated at CACs, in contrast to a previous meta-analysis.[10,70] The quality of included articles using the strict definition of CAC was assessed to be high (≥7), and all were large cohort studies that comprehensively controlled for confounding and did not rely on study designs with historical controls. There was an observed decrease in benefit

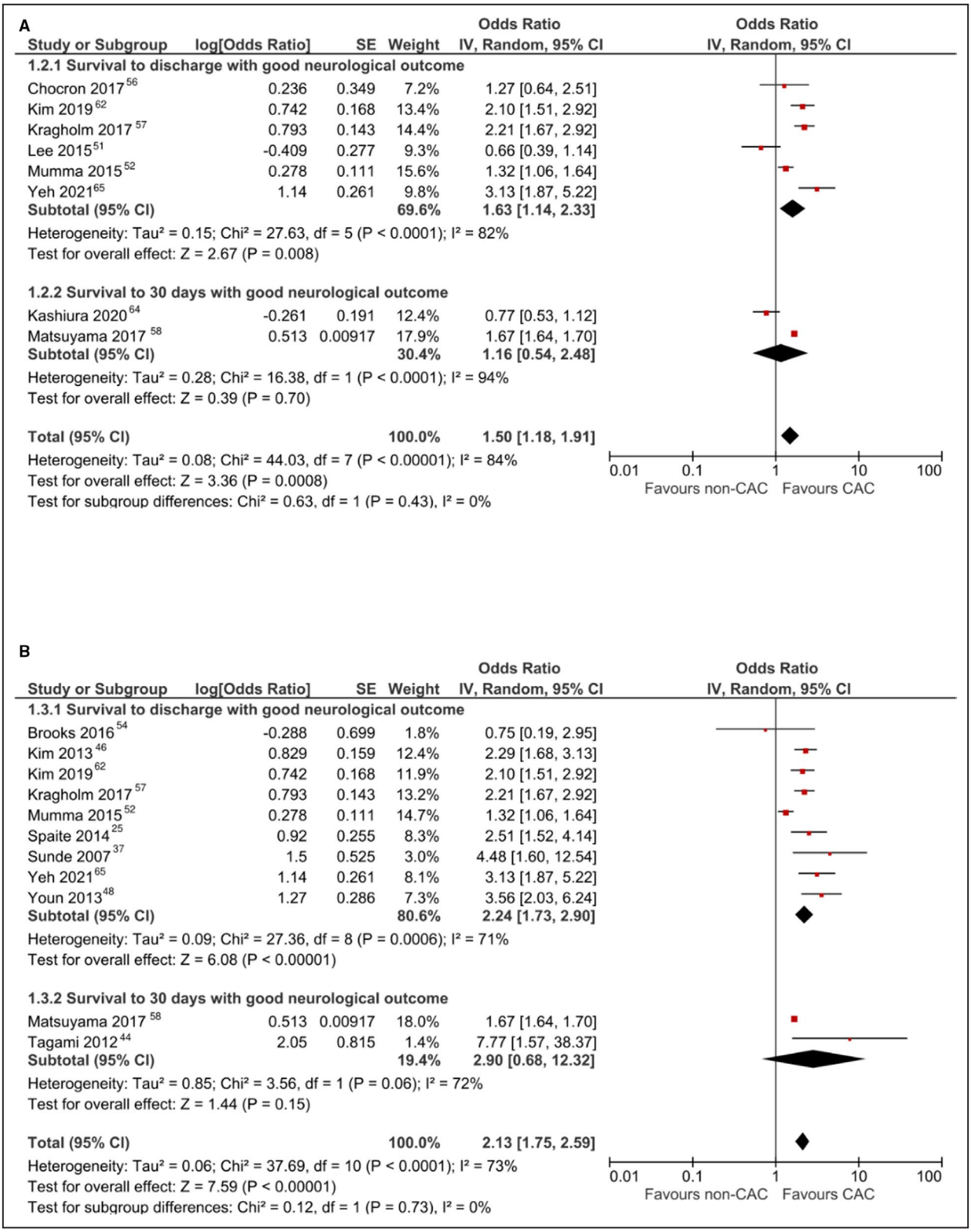


Figure 3. Sensitivity analyses for survival with good neurological outcome using less strict definitions of cardiac arrest centers (CACs).

A, Forest plot for meta-analysis of adjusted analyses comparing survival with good neurological outcome between CACs and non-CACs using a random-effects model and including high-volume centers. **B**, Forest plot for meta-analysis of adjusted analyses comparing survival with good neurological outcome between CACs and non-CACs using a random-effects model and including improved-care centers. IV indicates inverse variance.

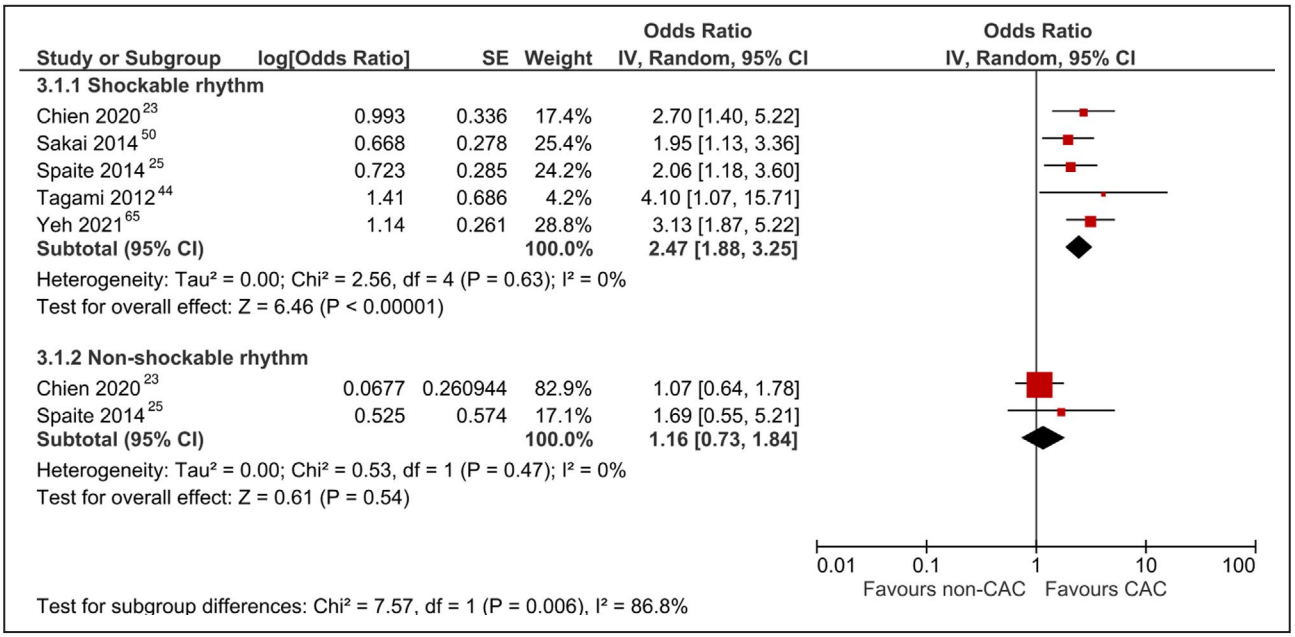


Figure 4. Forest plot for subgroup analysis comparing survival with good neurological outcome between cardiac arrest centers (CACs) and non-CACs within subgroups of patients with shockable and nonshockable rhythm.
IV indicates inverse variance.

when including high-volume centers as CACs as compared with including improved postresuscitation care centers as CACs, possibly suggesting the relatively higher contribution of postresuscitation interventions to the treatment effect, perhaps because cardiac causes of OHCA predominate in this study.[6,65] However, the consistency of significant benefit across all definitions of CAC indicates that patients should be transported to CACs or even hospitals exhibiting the variable features associated with CACs to improve outcomes.

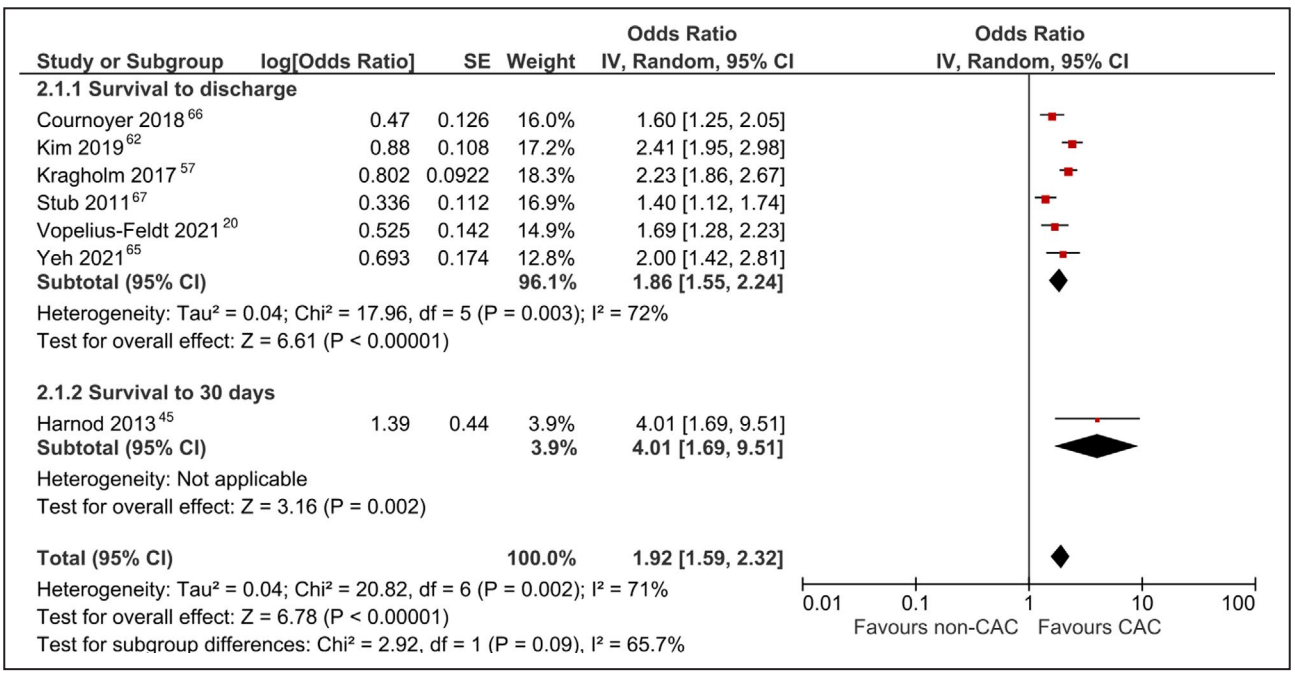


Figure 5. Forest plot for meta-analysis of adjusted analyses comparing survival between cardiac arrest centers (CACs) and non-CACs using a random-effects model and the strict definition of CACs.
IV indicates inverse variance.

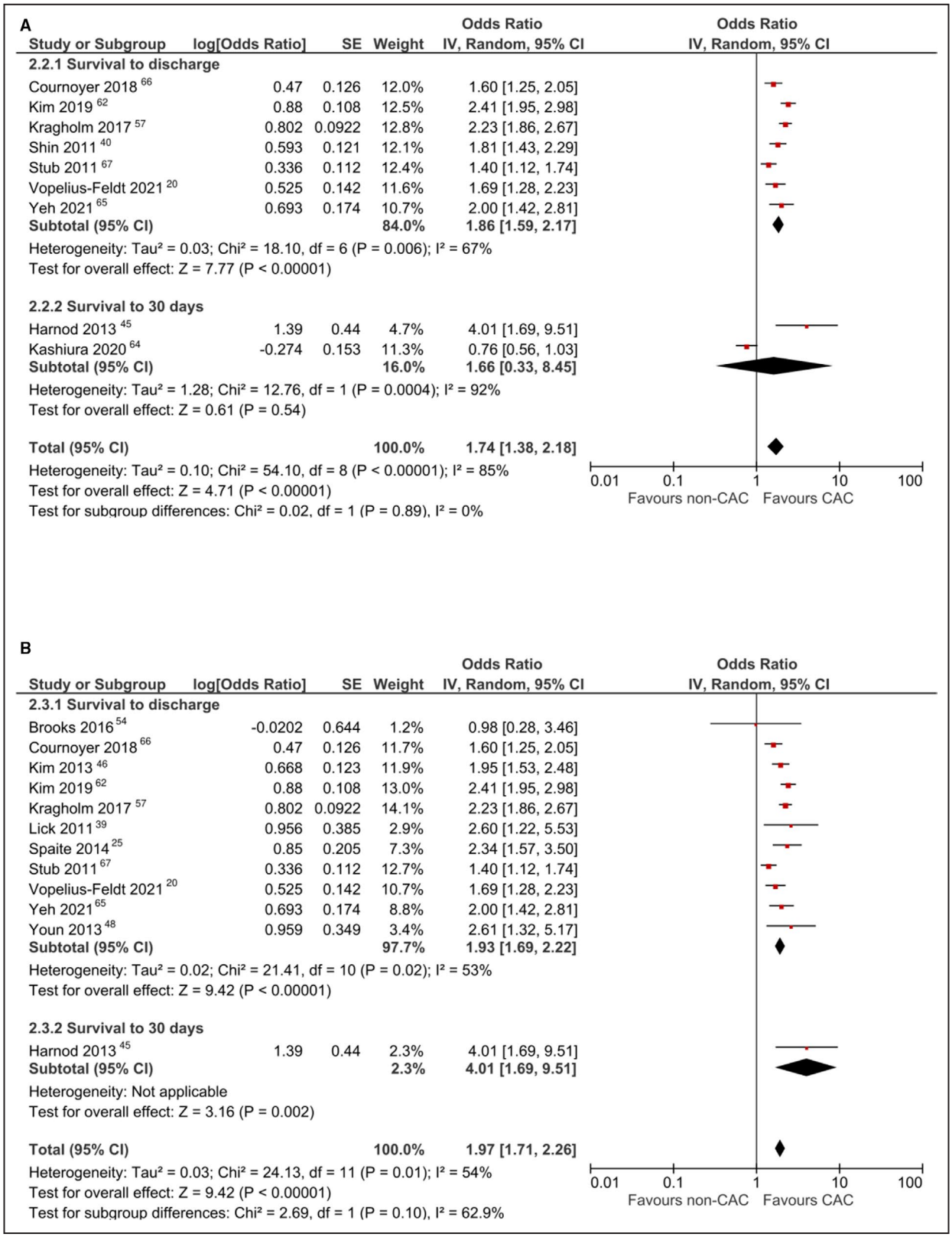


Figure 6. Sensitivity analyses for survival using less strict definitions of cardiac arrest centers (CACs).
A, Forest plot for meta-analysis of adjusted analyses comparing survival between CACs and non-CACs using a random-effects model and including high-volume centers. **B**, Forest plot for meta-analysis of adjusted analyses comparing survival between CACs and non-CACs using a random-effects model and including improved-care centers. IV indicates inverse variance.

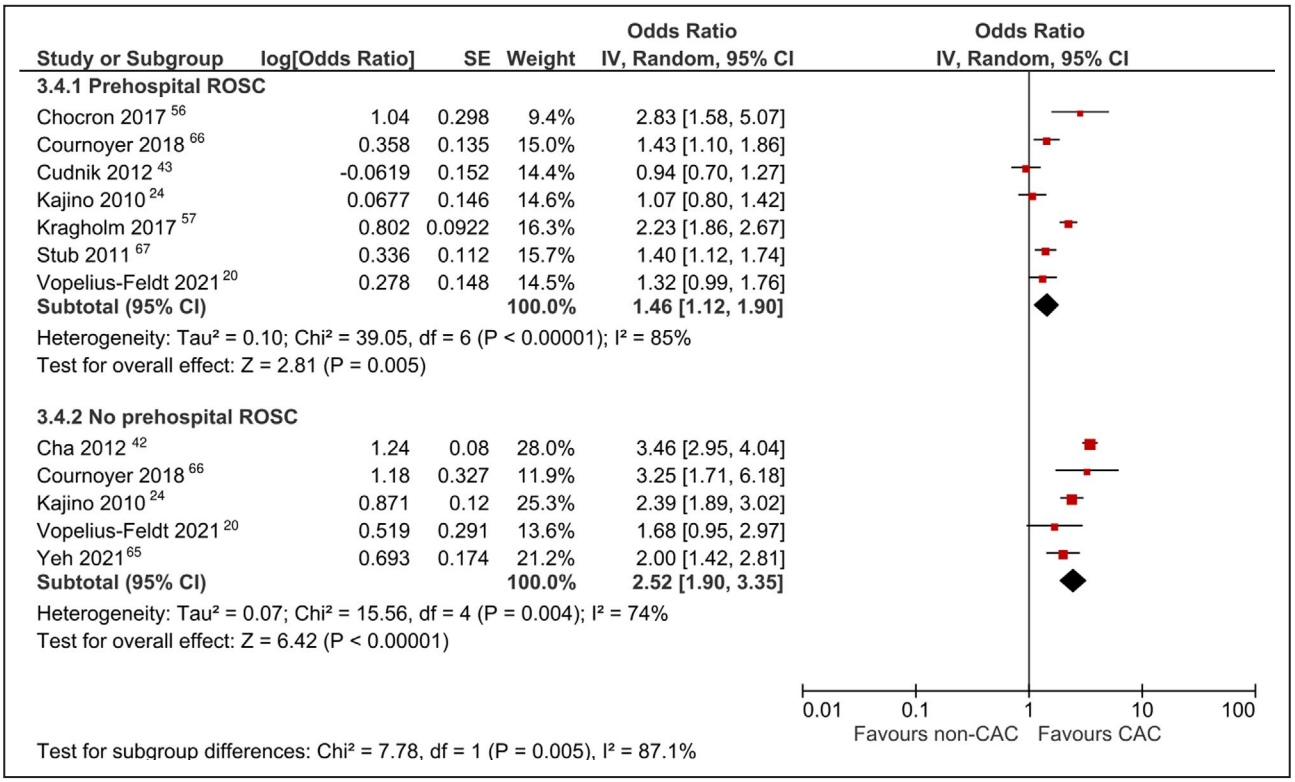


Figure 7. Forest plot for subgroup analysis comparing survival between cardiac arrest centers (CACs) and non-CACs within subgroups of patients with and without prehospital return of spontaneous circulation (ROSC).
IV indicates inverse variance.

The 2020 International Liaison Committee on Resuscitation statement also noted that evidence for CACs among subgroups of patients remain inconclusive.[69] This analysis contributes to this active debate by demonstrating that survival with good neurological outcomes was more pronounced among patients with shockable rhythm and that survival was more pronounced among patients without prehospital ROSC when comparing transport to CACs and non-CACs. Patients with shockable rhythm have also been associated with OHCA of cardiac causes and may benefit the most from early access to PCI[71,72] and intensive cardiac care.[65] Increased benefit in patients without ROSC also partially supports the view favoring quicker transport of patients with refractory OHCA to a hospital[73–76] instead of prolonging on-scene resuscitation,[77] allowing patients to access advanced critical care and extracorporeal membrane oxygenation. These findings should be interpreted with caution, because the studies included for subgroup analysis were vulnerable to bias but offer preliminary evidence that EMS may consider prioritizing patients with shockable rhythm or without prehospital ROSC for transport to CACs. It should also be considered that patients with nonshockable rhythms inherently have poorer survival and neurological outcomes compared with those with shockable rhythms, which may have contributed to findings of poorer survival and neurological outcomes among such patients regardless of the effect of CACs in relation to non-CACs. In addition, because patients with nonshockable rhythms still significantly benefited from a CAC albeit to a lesser extent, this analysis does not support depriving these patients from CAC care, but rather, warrants further examination of the associated incremental cost-effectiveness.

Although transport to a CAC improves outcomes, it remains unclear if EMS should bypass the nearest emergency departments in favor of CACs.[57,78] It has been suggested that the increase in transport time caused by bypassing the nearest hospital does not substantially affect outcomes after transport to CACs.[23,42,57,76,79] Other options include initial transport to a non-CAC with eventual interhospital transfer to a CAC, which seemed to have similar outcomes in this review,[44,49] but more definitive evidence is required to confirm this finding, in the form of an interventional trial comparing ambulance diversion strategies.

Strengths and Limitations

This is the largest systematic review and meta-analysis of evidence for the benefits of CACs conducted to date, involving OHCA registries and databases from

various nations and a sample size of 147 943 patients. However, differences across geographical regions may have led to the high statistical heterogeneity encountered in various analyses. Outcomes at both 30 days and at discharge were pooled, also contributing to heterogeneity, because time points for discharge may differ based on health system. However, we found that our results remained consistent both on pooling survival at 30 days with survival at discharge, and also when examining each of these separately. Another limitation is that the included studies used largely similar but not identical covariates for the adjustment of ORs, which may lead to residual confounding. As a whole, the interpretation of our results should also consider that specific levels of care at non-CAC hospitals were inconsistently defined.

Subgroup analyses should be interpreted carefully given existing selection bias by EMS and smaller sample sizes. The conclusion that patients with shockable rhythms do better when transported to CACs may have been driven by a higher proportion of ST-segment–elevation myocardial infarction within this group, hence accounting for better outcomes thanks to the presence of cardiac catheterization laboratories in CACs. Furthermore, observational studies are inherently susceptible to selection and observation biases. High-quality randomized clinical trials are therefore urgently needed to confirm present findings. Evidence for direct transport or transfer to a CAC was inconclusively assessed. Non-English language articles were also excluded.

CONCLUSIONS

CACs improved survival and neurological outcomes at discharge or 30 days among patients with OHCA, regardless of how CACs were defined. There was preliminary evidence for EMS to consider transport to CACs, especially for patients with shockable rhythm or patients without prehospital ROSC. High-quality data are needed to confirm these findings and conclusively assess whether patients should bypass the nearest hospital to be transported to a CAC versus transferred to a CAC from the nearest hospital.

APPENDIX

The National TTM Workgroup, which is part of the Unit for Prehospital Emergency Care, Ministry of Health, Singapore, currently consists of: Shiang-Hu Ang, Ruth Weixian Chen, Yew Woon Chia (chairperson), Enoch Hin Kei Chan, Ee Ling Goh, Andrew Fu Wah Ho, Vui Kian Ho, Hong Khai Lau, Eng Kiang Lee, Benjamin Sieu-Hon Leong, Jia Hao Lim, Shir Lynn Lim, Julian Kenrick Xingyuan Loh, Jimmy Heng Ann Ong, Marcus Eng Hock Ong, Kah Hua Peck, Daniel Yong Jing Quek, Christopher Ying Hao Seet, Shobbit Swarup, and Thon Hon Yong.

ARTICLE INFORMATION

Received September 8, 2021; accepted November 9, 2021.

Affiliations

Yong Loo Lin School of Medicine, (J.W.Y., Z.H.N., A.X.G., J.F.G.) and Centre for Quantitative Medicine, Duke-NUS Medical School (N.L.), National University of Singapore, Singapore (N.L.); Health Services Research Centre, SingHealth Duke-NUS Academic Medical Centre, Singapore (S.W.L.); Department of Cardiology, Tan Tock Seng Hospital, Singapore (Y.W.C.); Warwick Medical School, University of Warwick, Coventry, United Kingdom (G.D.P.); Department of Emergency Medicine, Singapore General Hospital, Singapore (M.E.O., A.F.H.); Health Services & Systems Research (M.E.O.) and Pre-Hospital and Emergency Research Centre, Health Services and Systems Research (A.F.W.H.), Duke-NUS Medical School, Singapore.

Sources of Funding

Dr Ho was supported by the Estate of Tan Sri Khoo Teck Puat (Khoo Clinical Scholars Programme), Khoo Pilot Award (KP/2019/0034), Duke-NUS Medical School, and National Medical Research Council (NMRC/CS_Seedfd/012/2018). This study was conducted as part of the National TTM Workgroup, a unit under the Unit for Prehospital Emergency Care, Ministry of Health, Singapore.

Disclosures

Dr Ong reports funding from the Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices and an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S4
Figures S1–S2

REFERENCES

1. Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. *Lancet*. 2018;391:980–988. doi: 10.1016/S0140-6736(18)30316-7
2. Lotfi A, Klein LW, Hira RS, Mallidi J, Mehran R, Messenger JC, Pinto DS, Mooney MR, Rab T, Yannopoulos D, et al. SCAI expert consensus statement on out of hospital cardiac arrest. *Catheter Cardiovasc Interv*. 2020;96:844–861. doi: 10.1002/ccd.28990
3. Kiguchi T, Okubo M, Nishiyama C, Maconochie I, Ong MEH, Kern KB, Wyckoff MH, McNally B, Christensen EF, Tjelmeland I, et al. Out-of-hospital cardiac arrest across the world: first report from the International Liaison Committee on Resuscitation (ILCOR). *Resuscitation*. 2020;152:39–49. doi: 10.1016/j.resuscitation.2020.02.044
4. Coute RA, Nathanson BH, Panchal AR, Kurz MC, Haas NL, McNally B, Neumar RW, Mader TJ. Disability-adjusted life years following adult out-of-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12:e004677. doi: 10.1161/CIRCOUTCOMES.118.004677
5. Myat A, Song K-J, Rea T. Out-of-hospital cardiac arrest: current concepts. *Lancet*. 2018;391:970–979. doi: 10.1016/S0140-6736(18)30472-0
6. Hassager C, Nagao K, Hildick-Smith D. Out-of-hospital cardiac arrest: in-hospital intervention strategies. *Lancet*. 2018;391:989–998. doi: 10.1016/S0140-6736(18)30315-5
7. Storm C, Leithner C, Krannich A, Suarez JI, Stevens RD. Impact of structured pathways for postcardiac arrest care: a systematic review and meta-analysis. *Crit Care Med*. 2019;47:e710–e716. doi: 10.1097/CCM.0000000000003827
8. Ho AFW, Ong MEH. Transportation during and after cardiac arrest: who, when, how and where? *Curr Opin Crit Care*. 2021;27:223–231. doi: 10.1097/MCC.0000000000000816

9. Soar J, Berg KM, Andersen LW, Böttiger BW, Cacciola S, Callaway CW, Couper K, Cronberg T, D'Arrigo S, Deakin CD, et al. Adult advanced life support: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation*. 2020;156:A80–A119. doi: 10.1016/j.resuscitation.2020.09.012
10. Yeung J, Matsuyama T, Bray J, Reynolds J, Skrifvars MB. Does care at a cardiac arrest centre improve outcome after out-of-hospital cardiac arrest?—a systematic review. *Resuscitation*. 2019;137:102–115. doi: 10.1016/j.resuscitation.2019.02.006
11. Czarnecki A, Qiu F, Koh M, Cheskes S, Dorian P, Scales DC, Ko DT. Association between hospital teaching status and outcomes after out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005349. doi: 10.1161/CIRCOUTCOMES.118.005349
12. Sinning C, Ahrens I, Cariou A, Beygui F, Lamhaut L, Halvorsen S, Nikolaou N, Nolan JP, Price S, Monsieurs K, et al. The cardiac arrest centre for the treatment of sudden cardiac arrest due to presumed cardiac cause—aims, function and structure: position paper of the Association for Acute Cardiovascular Care of the European Society of Cardiology (AVCV), European Association of Percutaneous Coronary Interventions (EAPCI), European Heart Rhythm Association (EHRA), European Resuscitation Council (ERC), European Society for Emergency Medicine (EUSEM) and European Society of Intensive Care Medicine (ESICM). *Eur Heart J Acute Cardiovasc Care*. 2020;9:S193–S202. doi: 10.1177/2048872620963492
13. Elmer J, Callaway CW, Chang C-C, Madaras J, Martin-Gill C, Nawrocki P, Seaman KAC, Sequeira D, Traynor OT, Venkat A, et al. Long-term outcomes of out-of-hospital cardiac arrest care at regionalized centers. *Ann Emerg Med*. 2019;73:29–39. doi: 10.1016/j.annemergmed.2018.05.018
14. Donnino MW, Rittenberger JC, Gaieski D, Cocchi MN, Giberson B, Peberdy MA, Abella BS, Bobrow BJ, Callaway C. The development and implementation of cardiac arrest centers. *Resuscitation*. 2011;82:974–978. doi: 10.1016/j.resuscitation.2011.03.021
15. Girotra S, Chan PS, Bradley SM. Post-resuscitation care following out-of-hospital and in-hospital cardiac arrest. *Heart*. 2015;101:1943. doi: 10.1136/heartjnl-2015-307450
16. Nikolaou NI, Netherton S, Welsford M, Drennan IR, Nation K, Belley-Cote E, Torabi N, Morrison LJ, Belley-Cote E, Drennan I, et al. A systematic review and meta-analysis of the effect of routine early angiography in patients with return of spontaneous circulation after out-of-hospital cardiac arrest. *Resuscitation*. 2021;163:28–48. doi: 10.1016/j.resuscitation.2021.03.019
17. Debaty G, Babaz V, Durand M, Gaide-Chevronnay L, Fournel E, Blancher M, Bouvaist H, Chavanon O, Maignan M, Bouzat P, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. *Resuscitation*. 2017;112:1–10. doi: 10.1016/j.resuscitation.2016.12.011
18. Avalli L, Maggioni E, Formica F, Redaelli G, Migliari M, Scanziani M, Celotti S, Coppo A, Caruso R, Ristagno G, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. *Resuscitation*. 2012;83:579–583. doi: 10.1016/j.resuscitation.2011.10.013
19. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, Collins G, Zhang L, Kalra R, Kosmopoulos M, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet*. 2020;396:1807–1816. doi: 10.1016/S0140-6736(20)32338-2
20. von Vopelius-Feldt J, Perkins GD, Benger J. Association between admission to a cardiac arrest centre and survival to hospital discharge for adults following out-of-hospital cardiac arrest: a multi-centre observational study. *Resuscitation*. 2021;160:118–125. doi: 10.1016/j.resuscitation.2021.01.024
21. Navab E, Esmaeili M, Poorkhorshidi N, Salimi R, Khazaei A, Moghimbeigi A. Predictors of out of hospital cardiac arrest outcomes in pre-hospital settings; a retrospective cross-sectional study. *Arch Acad Emerg Med*. 2019;7:36–36. doi: 10.22037/aaem.v7i1.370
22. Barnard EBG, Sandbach DD, Nicholls TL, Wilson AW, Ercole A. Prehospital determinants of successful resuscitation after traumatic and non-traumatic out-of-hospital cardiac arrest. *Emerg Med J*. 2019;36:333. doi: 10.1136/emermed-2018-208165
23. Chien C-Y, Tsai S-L, Tsai L-H, Chen C-B, Seak C-J, Weng Y-M, Lin C-C, Ng C-J, Chien W-C, Huang C-H, et al. Impact of transport time and cardiac arrest centers on the neurological outcome after out-of-hospital cardiac arrest: a retrospective cohort study. *J Am Heart Assoc*. 2020;9:e015544. doi: 10.1161/JAHA.119.015544
24. Kajino K, Iwami T, Daya M, Nishiuchi T, Hayashi Y, Kitamura T, Irisawa T, Sakai T, Kuwagata Y, Hiraide A, et al. Impact of transport to critical care medical centers on outcomes after out-of-hospital cardiac arrest. *Resuscitation*. 2010;81:549–554. doi: 10.1016/j.resuscitation.2010.02.008
25. Spaite DW, Bobrow BJ, Stolz U, Berg RA, Sanders AB, Kern KB, Chikani V, Humble W, Mullins T, Stapczynski JS, et al. Statewide regionalization of postarrest care for out-of-hospital cardiac arrest: association with survival and neurologic outcome. *Ann Emerg Med*. 2014;64:496–506.e491. doi: 10.1016/j.annemergmed.2014.05.028
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PG. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Phys Ther*. 2009;89:873–880. doi: 10.1093/ptj/89.9.873
27. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. doi: 10.1136/bmj.n160
28. The EndNote Team. Endnote. 2013;Endnote X9.
29. Rott N, Scholz KH, Busch HJ, Frey N, Kelm M, Thiele H, Böttiger BW. Cardiac arrest center certification for out-of-hospital cardiac arrest patients successfully established in Germany. *Resuscitation*. 2020;156:1–3. doi: 10.1016/j.resuscitation.2020.08.007
30. Majewski D, Ball S, Bailey P, McKenzie N, Bray J, Morgan A, Finn J. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. *Resuscitation*. 2021;166:43–48. doi: 10.1016/j.resuscitation.2021.07.023
31. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Circulation*. 2018;137:e783–e801. doi: 10.1161/CIR.0000000000000562
32. Collaboration TC. Review manager (RevMan). 2020.
33. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2000.
34. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898
35. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, deBeer H, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394. doi: 10.1016/j.jclinepi.2010.04.026
36. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490. doi: 10.1136/bmj.328.7454.1490
37. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73:29–39. doi: 10.1016/j.resuscitation.2006.08.016
38. Gaieski DF, Band RA, Abella BS, Neumar RW, Fuchs BD, Kolansky DM, Merchant RM, Carr BG, Becker LB, Maguire C, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation*. 2009;80:418–424. doi: 10.1016/j.resuscitation.2008.12.015
39. Lick CJ, Aufderheide TP, Niskanen RA, Steinkamp JE, Davis SP, Nygaard SD, Bemenderfer KK, Gonzales L, Kalla JA, Wald SK, et al. Take Heart America: a comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. *Crit Care Med*. 2011;39:26–33. doi: 10.1097/CCM.0b013e3181fa7ce4
40. Shin SD, Suh GJ, Ahn KO, Song KJ. Cardiopulmonary resuscitation outcome of out-of-hospital cardiac arrest in low-volume versus high-volume emergency departments: an observational study and propensity score matching analysis. *Resuscitation*. 2011;82:32–39. doi: 10.1016/j.resuscitation.2010.08.031
41. Walters EL, Morawski K, Dorotta I, Ramsingh D, Lumen K, Bland D, Clem K, Nguyen HB. Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after

out-of-hospital cardiac arrest: a feasibility study. *Shock*. 2011;35:360–366. doi: 10.1097/SHK.0b013e318204c106
42. Cha WC, Lee SC, Shin SD, Song KJ, Sung AJ, Hwang SS. Regionalisation of out-of-hospital cardiac arrest care for patients without prehospital return of spontaneous circulation. *Resuscitation*. 2012;83:1338–1342. doi: 10.1016/j.resuscitation.2012.03.024
43. Cudnik MT, Sasson C, Rea TD, Sayre MR, Zhang J, Bobrow BJ, Spaite DW, McNally B, Denninghoff K, Stolz U. Increasing hospital volume is not associated with improved survival in out of hospital cardiac arrest of cardiac etiology. *Resuscitation*. 2012;83:862–868. doi: 10.1016/j.resuscitation.2012.02.006
44. Tagami T, Hirata K, Takeshige T, Matsui J, Takinami M, Satake M, Satake S, Yui T, Itabashi K, Sakata T, et al. Implementation of the fifth link of the chain of survival concept for out-of-hospital cardiac arrest. *Circulation*. 2012;126:589–597. doi: 10.1161/CIRCULATIONAHA.111.086173
45. Harnod D, Ma MH-M, Chang WH, Chang R-E, Chang C-H. Mortality factors in out-of-hospital cardiac arrest patients: a nationwide population-based study in Taiwan. *Int J Gerontol*. 2013;7:216–220. doi: 10.1016/j.ijge.2013.08.001
46. Kim JY, Shin SD, Ro YS, Song KJ, Lee EJ, Park CB, Hwang SS. Post-resuscitation care and outcomes of out-of-hospital cardiac arrest: a nationwide propensity score-matching analysis. *Resuscitation*. 2013;84:1068–1077. doi: 10.1016/j.resuscitation.2013.02.010
47. Søholm H, Wachtell K, Nielsen SL, Bro-Jeppesen J, Pedersen F, Wanscher M, Boesgaard S, Møller JE, Hassager C, Kjaergaard J. Tertiary centres have improved survival compared to other hospitals in the Copenhagen area after out-of-hospital cardiac arrest. *Resuscitation*. 2013;84:162–167. doi: 10.1016/j.resuscitation.2012.06.029
48. Youn CS, Kim SH, Oh SH, Kim YM, Kim HJ, Park KN. Successful implementation of comprehensive packages of postcardiac arrest care after out-of-hospital cardiac arrest: a single institution experience in South Korea. *Ther Hypothermia Temp Manag*. 2013;3:17–23. doi: 10.1089/ther.2012.0018
49. Kang MJ, Lee TR, Shin TG, Sim MS, Jo IJ, Song KJ, Jeong YK. Survival and neurologic outcomes of out-of-hospital cardiac arrest patients who were transferred after return of spontaneous circulation for integrated post-cardiac arrest syndrome care: the another feasibility of the cardiac arrest center. *J Korean Med Sci*. 2014;29:1301–1307. doi: 10.3346/jkms.2014.29.9.1301
50. Sakai T, Kitamura T, Iwami T, Hayashi Y, Rinka H, Ohishi Y, Mohri T, Kishimoto M, Kawaguchi R, Kajino K, et al. Actual treatments for out-of-hospital ventricular fibrillation at critical care medical centers in Osaka: a pilot descriptive study. *Acute Med Surg*. 2014;1:150–158. doi: 10.1002/ams2.27
51. Lee SJ, Jeung KW, Lee BK, Min YI, Park KN, Suh GJ, Kim KS, Kang GH. Impact of case volume on outcome and performance of targeted temperature management in out-of-hospital cardiac arrest survivors. *Am J Emerg Med*. 2015;33:31–36. doi: 10.1016/j.ajem.2014.10.003
52. Mumma BE, Diercks DB, Wilson MD, Holmes JF. Association between treatment at an ST-segment elevation myocardial infarction center and neurologic recovery after out-of-hospital cardiac arrest. *Am Heart J*. 2015;170:516–523. doi: 10.1016/j.ahj.2015.05.020
53. Søholm H, Kjaergaard J, Bro-Jeppesen J, Hartvig-Thomsen J, Lippert F, Køber L, Nielsen N, Engsig M, Steensen M, Wanscher M, et al. Prognostic implications of level-of-care at tertiary heart centers compared with other hospitals after resuscitation from out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2015;8:268–276. doi: 10.1161/CIRCOUTCOMES.115.001767
54. Brooks SC, Scales DC, Pinto R, Dainty KN, Racz EM, Gaudio M, Amaral ACKB, Gray SH, Friedrich JO, Chapman M, et al. The postcardiac arrest consult team: impact on hospital care processes for out-of-hospital cardiac arrest patients. *Crit Care Med*. 2016;44:2037–2044. doi: 10.1097/CCM.0000000000001863
55. Schober A, Sterz F, Laggner AN, Poppe M, Sulzgruber P, Lobmeyr E, Datler P, Keferböck M, Zeiner S, Nuernberger A, et al. Admission of out-of-hospital cardiac arrest victims to a high volume cardiac arrest center is linked to improved outcome. *Resuscitation*. 2016;106:42–48. doi: 10.1016/j.resuscitation.2016.06.021
56. Chocron R, Bougouin W, Beganton F, Juvin P, Loeb T, Adnet F, Lecarpentier E, Lamhaut L, Jost D, Marijon E, et al. Are characteristics of hospitals associated with outcome after cardiac arrest? Insights from the Great Paris registry. *Resuscitation*. 2017;118:63–69. doi: 10.1016/j.resuscitation.2017.06.019
57. Kragholm K, Malta Hansen C, Dupre ME, Xian Y, Strauss B, Tyson C, Monk L, Corbett C, Fordyce CB, Pearson DA, et al. Direct transport to a percutaneous cardiac intervention center and outcomes in patients with out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003414. doi: 10.1161/CIRCOUTCOMES.116.003414
58. Matsuyama T, Kiyohara K, Kitamura T, Nishiyama C, Nishiuchi T, Hayashi Y, Kawamura T, Ohta B, Iwami T. Hospital characteristics and favourable neurological outcome among patients with out-of-hospital cardiac arrest in Osaka, Japan. *Resuscitation*. 2017;110:146–153. doi: 10.1016/j.resuscitation.2016.11.009
59. Patterson T, Perkins GD, Joseph J, Wilson K, Van Dyck L, Robertson S, Nguyen H, McConkey H, Whitbread M, Fothergill R, et al. A randomised trial of expedited transfer to a cardiac arrest centre for non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest: the ARREST pilot randomised trial. *Resuscitation*. 2017;115:185–191. doi: 10.1016/j.resuscitation.2017.01.020
60. Seiner J, Polášek R, Lejsek J, Strýček M, Karásek J. Cardiac arrest center—one-year experience of the Regional Hospital Liberec. *Cor Vasa*. 2018;60:e234–e238. doi: 10.1016/j.crvasa.2017.08.002
61. Balian S, Buckler DG, Blewer AL, Bhardwaj A, Abella BS. Variability in survival and post-cardiac arrest care following successful resuscitation from out-of-hospital cardiac arrest. *Resuscitation*. 2019;137:78–86. doi: 10.1016/j.resuscitation.2019.02.004
62. Kim JY, Moon S, Park JH, Cho HJ, Song JH, Jeon W, Chang H, Ro YS, Shin SD. Effect of transported hospital resources on neurologic outcome after out-of-hospital cardiac arrest. *Signa Vitae*. 2019;15:51–58. doi: 10.22514/sv151.042019.7
63. Park JH, Lee SC, Shin SD, Song KJ, Hong KJ, Ro YS. Interhospital transfer in low-volume and high-volume emergency departments and survival outcomes after out-of-hospital cardiac arrest: a nationwide observational study and propensity score-matched analysis. *Resuscitation*. 2019;139:41–48. doi: 10.1016/j.resuscitation.2019.03.044
64. Kashiura M, Amagasa S, Moriya T, Sakurai A, Kitamura N, Tagami T, Takeda M, Miyake Y, Inokuchi S, Masui Y, et al. Relationship between institutional volume of out-of-hospital cardiac arrest cases and 1-month neurologic outcomes: a post hoc analysis of a prospective observational study. *J Emerg Med*. 2020;59:227–237. doi: 10.1016/j.jemermed.2020.04.039
65. Yeh C-C, Chang C-H, Seak C-J, Chen C-B, Weng Y-M, Lin C-C, Huang C-H, Tseng H-J, Ng C-J, Tsai L-H. Survival analysis in out-of-hospital cardiac arrest patients with shockable rhythm directly transport to heart centers. *Signa Vitae*. null:1–8. doi: 10.22514/sv.2021.084
66. Cournoyer A, Notebaert É, de Montigny L, Ross D, Cossette S, Londei-Leduc L, Iseppon M, Lamarche Y, Sokoloff C, Potter BJ, et al. Impact of the direct transfer to percutaneous coronary intervention-capable hospitals on survival to hospital discharge for patients with out-of-hospital cardiac arrest. *Resuscitation*. 2018;125:28–33. doi: 10.1016/j.resuscitation.2018.01.048
67. Stub D, Smith K, Bray JE, Bernard S, Duffy SJ, Kaye DM. Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest. *Heart*. 2011;97:1489–1494. doi: 10.1136/hrt.2011.226431
68. Lai CY, Lin FH, Chu H, Ku CH, Tsai SH, Chung CH, Chien WC, Wu CH, Chu CM, Chang CW. Survival factors of hospitalized out-of-hospital cardiac arrest patients in Taiwan: a retrospective study. *PLoS One*. 2018;13:e0191954. doi: 10.1371/journal.pone.0191954
69. Greif R, Bhanji F, Bigham BL, Bray J, Breckwoldt J, Cheng A, Duff JP, Gilfoyle E, Hsieh M-J, Iwami T, et al. Education, implementation, and teams: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2020;142:S222–S283. doi: 10.1161/CIR.0000000000000896
70. Lipe D, Giwa A, Caputo ND, Gupta N, Addison J, Cournoyer A. Do out-of-hospital cardiac arrest patients have increased chances of survival when transported to a cardiac resuscitation center? *J Am Heart Assoc*. 2018;7:e011079. doi: 10.1161/JAHA.118.011079
71. Garcia S, Drexel T, Bekwelem W, Raveendran G, Caldwell E, Hodgson L, Wang Q, Adabag S, Mahoney B, Frascone R, et al. Early access to the cardiac catheterization laboratory for patients resuscitated from cardiac arrest due to a shockable rhythm: the Minnesota Resuscitation Consortium Twin Cities Unified Protocol. *J Am Heart Assoc*. 2016;5:e002670. doi: 10.1161/JAHA.115.002670
72. Tsai SL, Chaou CH, Huang CH, Tzeng IS, Kuo CW, Weng YM, Chien CY. Features of hospital and emergency medical service in out-of-hospital cardiac arrest patients with shockable rhythm. *Am J Emerg Med*. 2017;35:1222–1227. doi: 10.1016/j.ajem.2017.03.032

73. Shanmugasundaram M, Lotun K. Refractory out of hospital cardiac arrest. *Curr Cardiol Rev*. 2018;14:109–114. doi: 10.2174/1573403X14666180507155622
74. Sonneville R, Schmidt M. Extracorporeal cardiopulmonary resuscitation for adults with refractory out-of-hospital cardiac arrest. *Circulation*. 2020;141:887–890. doi: 10.1161/CIRCULATIONAHA.119.044969
75. Matsuyama T, Irisawa T, Yamada T, Hayakawa K, Yoshiya K, Noguchi K, Nishimura T, Ishibe T, Yagi Y, Kiguchi T, et al. Impact of low-flow duration on favorable neurological outcomes of extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest. *Circulation*. 2020;141:1031–1033. doi: 10.1161/CIRCULATIONAHA.119.044285
76. Park HA, Ahn KO, Lee EJ, Park JO; On Behalf Of The Korean Cardiac Arrest Research Consortium Ko CI. Association between survival and time of on-scene resuscitation in refractory out-of-hospital cardiac arrest: a cross-sectional retrospective study. *Int J Environ Res Public Health*. 2021;18. doi: 10.3390/ijerph18020496
77. Gregers E, Kjærgaard J, Lippert F, Thomsen JH, Køber L, Wanscher M, Hassager C, Søholm H. Refractory out-of-hospital cardiac arrest with ongoing cardiopulmonary resuscitation at hospital arrival—survival and neurological outcome without extracorporeal cardiopulmonary resuscitation. *Crit Care*. 2018;22:242. doi: 10.1186/s13054-018-2176-9
78. Karasek J, Seiner J, Renza M, Salanda F, Moudry M, Strycek M, Lejsek J, Polasek R, Ostadal P. Bypassing out-of-hospital cardiac arrest patients to a regional cardiac center: impact on hemodynamic parameters and outcomes. *Am J Emerg Med*. 2021;44:95–99. doi: 10.1016/j.ajem.2021.01.080
79. Geri G, Gilgan J, Wu W, Vijendira S, Ziegler C, Drennan IR, Morrison L, Lin S. Does transport time of out-of-hospital cardiac arrest patients matter? A systematic review and meta-analysis. *Resuscitation*. 2017;115:96–101. doi: 10.1016/j.resuscitation.2017.04.003

SUPPLEMENTAL MATERIAL

Data S1. Detailed Search Strategy.

Search strategy for Medline

1: Cardiac Care Facilities/
2: Cardiology Service, Hospital/
3: Regional Medical Programs/
4: ((heart or cardi*) adj3 (attack or arrest) adj3 (centre* or center*)).ab,kf,ti.
5: (cardiac resuscitation center* or cardiac resuscitation centre* or regional cardiac resuscitation).ab,kf,ti.
6: (regional system* or network or hospital volume or patient volume).ab,kf,ti.
7: (Cardiac Receiving Center* or Cardiac Receiving Centre*).ab,kf,ti.
8: "Cardiac Care Facilit*".ab,kf,ti.
9: (Cardi* adj2 (Centre* or Center*)).ab,kf,ti.
10: (Cardiology adj1 (Service or care) adj2 Hospital).ab,kf,ti.
11: cardiac catheterisation laboratory.ab,kf,ti.
12: (CAC or CACs).ab,kf,ti.
13: ((post cardiac arrest or postcardiac arrest) adj1 (care or treatment)).ab,kf,ti.
14: ((post resuscitation or postresuscitation) adj1 (care or treatment)).ab,kf,ti.
15: fifth link.ab,kf,ti.
16: Tertiary Care Centers/
17: (Tertiary adj1 (care or Center* or Centre*)).ab,kf,ti.
18: Cardiac Arrest Registry.ab,kf,ti.
19: ("Critical care medical center*" or "Critical care medical centre*").ab,kf,ti.
20: ("critical care centre*" or "critical care center*").ab,kf,ti.
21: or/1-20
22: exp heart arrest/
23: cardiopulmonary resuscitation/ or advanced cardiac life support/
24: Out of Hospital Cardiac Arrest.ab,kf,ti.
25: OHCA.ab,kf,ti.
26: return of spontaneous circulation.ab,kf,ti.
27: ROSC.ab,kf,ti.
28: ((heart or cardiac or cardiovascular) adj1 arrest).ab,kf,ti.
29: asystole.ab,kf,ti.
30: pulseless electrical activity.ab,kf,ti.
31: Advanced Cardiac Life Support.ab,kf,ti.
32: ACLS.ab,kf,ti.

33: Ventricular Fibrillation/
34: (cardiopulmonary arrest or cardiopulmonary resuscitation).ab,kf,ti.
35: (cardio-pulmonary arrest or cardio-pulmonary resuscitation or CPR) .ab,kf,ti.
36: code blue.ab,kf,ti.
37: or/22-36
38: and/21,37
39: exp Organ Transplantation/ or “transplant”.ab,kf,ti.
40: 38 not 39
41: Animals/ not (Animals/ and Humans/)
42: 40 not 41
43: (exp Pediatrics/ or exp CHILD/) not exp Adult/
44: 42 not 43
45: (letter or comment or editorial or note or news).pt.
46: 44 not 45
47: Case Reports/ or (case report or case series).ti.
48: 46 not 47
49: remove duplicates from 48

Search strategy for Embase

1: ‘heart center’/de
2: ‘cardiology service’/de
3: ‘regional medical program*’:ab,ti,kw
4: ((heart or cardi*) NEAR/3 (attack OR arrest) NEAR/3 (centre* or center*)):ab,ti,kw
5: ‘cardiology service*’:ab,ti,kw
6: ‘cardiac resuscitation center*’:ab,ti,kw OR ‘cardiac resuscitation centre*’:ab,ti,kw OR ‘regional cardiac resuscitation’:ab,ti,kw
7: ‘regional system*’:ab,ti,kw OR ‘network’:ab,ti,kw OR ‘hospital volume’:ab,ti,kw OR ‘patient volume’:ab,ti,kw
8: ‘cardiac receiving center*’:ab,ti,kw OR ‘cardiac receiving centre*’:ab,ti,kw
9: ‘cardiac care facilit*’:ab,ti,kw
10: (cardi* NEAR/2 (centre* or center*)):ab,ti,kw
11: (cardiology NEAR/1 (service OR care) NEAR/2 hospital):ab,ti,kw
12: cardiac AND catheterisation AND laboratory:ab,ti,kw
13: ‘cardiac catheterisation laboratory’:ab,ti,kw
14: cac:ab,ti,kw OR cacs:ab,ti,kw
15: ((‘post cardiac arrest’ OR ‘postcardiac arrest’) NEAR/1 (care OR treatment)):ab,ti,kw
16: ((‘post resuscitation’ OR ‘postresuscitation’) NEAR/1 (care OR treatment)):ab,ti,kw
17: ‘fifth link’:ab,ti,kw

18: ‘tertiary care center’/de
19: (tertiary NEAR/1 (care OR center* OR centre*)):ab,ti,kw
20: ‘cardiac arrest registry’:ab,ti,kw
21: ‘critical care medical center*’:ab,ti,kw OR ‘critical care medical centre*’:ab,ti,kw
22: ‘critical care centre*’:ab,ti,kw OR ‘critical care center*’:ab,ti,kw
23: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24: ‘heart arrest’/exp
25: ‘cardiac life support’:ab,ti,kw
26: ‘ohca’:ab,ti,kw
27: ‘return of spontaneous circulation’/de
28: ((heart OR cardiac OR cardiovascular) NEAR/1 arrest):ab,ti,kw
29: asystole:ab,ti,kw
30: ‘pulseless electrical activity’:ab,ti,kw
31: acls:ab,ti,kw
32: ‘heart ventricle fibrillation’/de
33: ‘cardiopulmonary arrest’:ab,ti,kw OR ‘cardiopulmonary resuscitation’:ab,ti,kw
34: ‘cardio-pulmonary arrest’:ab,ti,kw OR ‘cardio-pulmonary resuscitation’:ab,ti,kw OR ‘cpr’:ab,ti,kw
35: ‘code blue’:ab,ti,kw
36: #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
37: #23 AND #36
38: ‘organ transplantation’/exp OR ‘transplant’:ab,ti,kw
39: #37 NOT #38
40: ‘animal’/exp NOT (‘animal’/exp AND ‘human’/exp)
41: #39 NOT #40
42: (‘pediatrics’/exp OR ‘child’/exp) NOT ‘adult’/de
43: #41 NOT #42
44: ‘article’/it
45: #43 AND #44
46: ‘case report’/de OR ‘case study’/de OR ‘case study’:ti OR ‘case series’:ti
47: #45 NOT #46

Search strategy for Cochrane CENTRAL

1: MeSH descriptor: [Cardiac Care Facilities] this term only
2: MeSH descriptor: [Cardiology Service, Hospital] this term only
3: MeSH descriptor: [Regional Medical Programs] this term only
4: ((heart or cardi*) NEAR/3 (attack or arrest) NEAR/3 (centre* or center*)):ti,ab,kw

5: (cardiac resuscitation center* or cardiac resuscitation centre* or regional cardiac resuscitation):ti,ab,kw
6: (regional system* or network or hospital volume or patient volume):ti,ab,kw
7: (Cardiac Receiving Center* or Cardiac Receiving Centre*):ti,ab,kw
8: ("Cardiac Care Facility" or "Cardiac Care Facilities"):ti,ab,kw
9: (Cardi* NEAR/2 (Centre* or Center*)):ti,ab,kw
10: (Cardiology NEAR/1 (Service or Care) NEAR/2 Hospital):ti,ab,kw
11: (cardiac catheterisation laboratory):ti,ab,kw
12: (CAC or CACs):ti,ab,kw
13: (("post cardiac arrest" or "postcardiac arrest") NEAR/1 (care or treatment)):ti,ab,kw
14: (("post resuscitation" or "postresusciation") NEAR/1 (care or treatment)):ti,ab,kw
15: (fifth link):ti,ab,kw
16: MeSH descriptor: [Tertiary Care Centers] this term only
17: (Tertiary NEAR/1 (Care or Center* or Centre*)):ti,ab,kw
18: (Cardiac Arrest Registry):ti,ab,kw
19: ("Critical care medical center*" or "Critical care medical centre*"):ti,ab,kw
20: ("critical care center*" or "critical care centre*"):ti,ab,kw
21: #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
22: MeSH descriptor: [Heart Arrest] explode all trees
23: MeSH descriptor: [Cardiopulmonary Resuscitation] this term only
24: MeSH descriptor: [Advanced Cardiac Life Support] this term only
25: (Out of Hospital Cardiac Arrest):ti,ab,kw
26: OHCA:ti,ab,kw
27: (return of spontaneous circulation):ti,ab,kw
28: ROSC:ti,ab,kw
29: ((heart or cardiac or cardiovascular) NEAR/1 arrest):ti,ab,kw
30: asystole:ti,ab,kw
31: (pulseless electrical activity):ti,ab,kw
32: (Advanced Cardiac Life Support):ti,ab,kw
33: ACLS:ti,ab,kw
34: MeSH descriptor: [Ventricular Fibrillation] this term only
35: (cardiopulmonary arrest or cardiopulmonary resuscitation):ti,ab,kw
36: (cardio-pulmonary arrest or cardio-pulmonary resuscitation or CPR):ti,ab,kw
37: (code blue):ti,ab,kw
38: #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
39: #21 and #38
40: MeSH descriptor: [Organ Transplantation] explode all trees
41: #40 or transplant:ti,ab,kw
42: #39 not #41
43: MeSH descriptor: [Animals] this term only

44: MeSH descriptor: [Humans] this term only
45: #43 not (#43 and #44)
46: #42 not #45
47: MeSH descriptor: [Pediatrics] explode all trees
48: MeSH descriptor: [Child] explode all trees
49: MeSH descriptor: [Adult] explode all trees
50: (#47 or #48) not #49
51: #46 not #50
52: (article):pt
53: #51 and #52
54: MeSH descriptor: [Case Reports] this term only
55: #54 or (case report):ti or (case series):ti
56: #53 not #55

Table S1. Summary of Included Studies

Author	Country	Study Design	Comparison	Sample size	Age (mean SD)	Male	CAC description	NOS
Balian 2019	USA	Retrospective cohort	High volume centres	613	65 +/- 23	354	High volume center (84-205 cases/5 years)	7
			Low volume centres	577	64 +/- 22	371		
Brooks 2016	USA	Prospective cohort	Improved care centres	151	64.7 +/- 16	117	Post-arrest consult team: PCI, TTM, NP	7
			Usual care	855	65.3 +/- 16.6	567		
Cha 2012	South Korea	Retrospective cohort	High volume centres	11777	65 (51-75)*	7742	High volume center (>33 cases/year)	7
			Low volume centres	15885	66 (53-76)*	10438		
Chien 2020	Taiwan	Prospective cohort	CACs	2578	69.4 +/- 16.9	1782	CAC: 24/7 PCI, TTM, ECMO	7
			Non-CACs	2578	69.3 +/- 17	1757		
Chocron 2017	France	Retrospective cohort	High volume centres	917	60.1 +/- 15.4	658	High volume center (>/=1000 ICU/year, >/= 15 cases/ year): 24/7 PCI, TTM, CAG	7
			Low volume centres	91	66.6 +/- 16.6	56		
Cournoyer 2018	Canada	Retrospective cohort	CACs	2389	67.1 +/- 16.4	1629	PCI-capable STEMI center: 24/7 PCI, CAG	7
			Non-CACs	2533	67.4 +/- 16.8	1608		
Cudnik 2012	USA			928	62.6	566		7

		Prospective cohort	High volume centres Low volume centres	697	63.7	397	High volume center (>40 cases/year): 24/7 PCI, TTM	
Gaieski 2009	USA	Prospective cohort	Improved care centres Usual care	18 18	57 (20-86)* 67 (35-87)*	12 9	Post-resuscitation algorithm: TTM, PCI, EGDHO	7
Harnod 2013	Taiwan	Retrospective cohort	CACs Non-CACs	435 457			Critical care medical center	9
Kajino 2010	Japan	Prospective cohort	CACs Non-CACs	2881 7502		1781 4179	Critical care medical center	8
Kang 2014	South Korea	Retrospective cohort	Transferred to CAC Direct transport to CAC	41 50	54.6 +/- 17.6 48.9 +/- 16.9	27 28	CAC: PCI, CAG, TTM	8
Kashiura 2020	Japan	Retrospective cohort	High volume centres Low volume centres	912 889	71 (60-81)* 71 (60-82)*	577 575	High volume centre (79-118 cases/15 months)	8
Kim 2013	South Korea	Retrospective cohort	Improved care centres Usual care	678 678	57.6 +/- 14.7 57.1 +/- 15.7	520 511	Active post-resuscitation care: TTM, PCI, CABG	8
Kim 2019	South Korea	Retrospective cohort	CACs Non-CACs	4036 5876	68 (54-79)* 72 (57-81)*	2632 3654	Cardiac resuscitation centre: 24/7 PCI, TTM	7
Kragholm 2017	USA	Prospective cohort	CACs Non-CACs	1359 148	65 (55-75)* 67 (56-78)*	827 83	PCI center: 24/7 PCI, TTM	7
Lai 2018	Taiwan		CACs	2255			Critical care medical center	9

		Retrospective cohort	Non-CACs	2353				
Lee 2015	South Korea	Retrospective cohort	High volume centres	289	58 (47-70)*	201	High volume center (>15.5 cases/year): TTM	7
			Low volume centres	289	58 (48-69.5)*	200		
Lick 2011	USA	Prospective cohort	Improved care centres	247	62 +/- 15.6	173	CAC: PCI, TTM, ICD	7
			Usual care	106	68 +/- 14.6	75		
Matsuyama 2017	Japan	Retrospective cohort	CACs	15118			Critical care medical center: 24/7 PCI, ECMO	8
			Non-CACs	24847				
Mumma 2015	USA	Retrospective cohort	CACs	3340	65 (53-77)*	1956	STEMI centers: 24/7 PCI, TTM	7
			Non-CACs	2523	68 (55-79)*	1379		
Park 2019	South Korea	Retrospective cohort	High volume centres	1200		804	High volume center (>100 OHCA cases/ year): PCI, TTM, ECMO	7
			Low volume centres	2608		1760		
Patterson 2017	UK	Randomised controlled trial	CACs	18			CAC: 24/7 PCI, TTM, CAG	Some concerns[†]
			Non-CACs	15				
Sakai 2014	Japan	Prospective cohort	CACs	112		91	Critical care medical center: PCI, TTM, ECMO	7
			Non-CACs	140				
Schober 2016	Austria	Prospective cohort	High volume centres	378	60 (49-70)*	276	High volume center (>100 OHCA cases/ year): 24/7 CAG, TTM	8
			Low volume centres	269	66 (52-75)*	181		
Seiner 2018				61		46		6

	Czech Republic	Prospective cohort	Improved care centres Usual care	147		117	After designation as CAC, post-cardiac arrest treatment: PCI, TTM, MV, ICD	
Shin 2011	South Korea	Retrospective cohort	High volume centres Low volume centres	3533 3533	60.9 +/- 19.4 60.5 +/- 18.6	2270 2322	High volume center (>68 OHCA cases/ 2 years)	7
Soholm 2013	Denmark	Retrospective cohort	CACs Non-CACs	761 457	 68 +/- 14	581 278	Tertiary centre: PCI, TTM, CAG	8
Soholm 2015	Denmark	Prospective cohort	CACs Non-CACs	586 492	63 +/- 15 68 +/- 14	433 303	Tertiary centre: PCI, TTM, ICD, EGDHO	6
Spaite 2014	USA	Prospective cohort	Improved care centres Usual care	1737 440	63 (62.2-63.8)* 63.9 (62.4-65.4)*	1132 280	After receiving designation as cardiac receiving center: PCI, CAG, TTM	7
Stub 2011	Australia	Retrospective cohort	CACs Non-CACs	1816 890	 	1294 571	Cardiac centre: 24/7 PCI and interventional cardiac services	7
Sunde 2007	Norway	Prospective cohort	Improved care centres Usual care	61 58	63 +/- 14 68 +/- 12	50 46	Standardised treatment protocol: PCI, TTM, MV, EGDHO	7
Tagami 2012	Japan	Prospective cohort	Improved care centres Usual care	712 770	76.3 +/- 13.9 75.3 +/- 14.5	397 458	Post-resuscitation care bundle: TTM, CAG, ECMO	8
	UK		CACs	2184	72 (60-82)*	1374	24/7 PCI centres: TTM	7

Vopelius-Feldt 2021		Retrospective cohort	Non-CACs	2184	73 (62-82)*	1430		
Walters 2011	USA	Prospective cohort	Improved care centres	29	62 +/- 10	19	Care bundle: PCI, TTM, EGDHO	7
			Usual care	26	64 +/- 15	18		
Yeh 2021	Taiwan	Retrospective cohort	CACs	1222	62.61 +/- 15.67	926	Heart centre: 24/7 PCI, TTM	7
			Non-CACs	366	61.95 +/- 16.19	288		
Youn 2013	South Korea	Retrospective cohort	Improved care centres	168	62.3 +/- 19.3	111	Post-cardiac arrest care package: PCI, TTM, MV, EGDHO, NP	7
			Usual care	149	65 +/- 14.4	106		

CAC: Cardiac arrest centre; NOS: Newcastle-Ottawa score; STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; CAG: Coronary artery angiography; TTM: targeted temperature management; ECMO: extracorporeal membrane oxygenation, MV: mechanical ventilation, NP: neuroprognostication, EGDHO: early goal-directed hemodynamic optimization, ICD: implantable cardioverter defibrillator
*Median, IQR, †Cochrane Risk of Bias 2 Tool

Table S2. Summary of Pre-existing Meta-Analyses

Author	Year	Comparison	Definition of CAC	Findings
Yeung et al	2019	CAC vs non-CAC	Accepted 'cardiac arrest centre' or 'regionalized cardiac arrest care' or 'high case volume centres' of similar description in the literature.	Very low certainty evidence suggests that post-cardiac arrest care at cardiac arrest centres is associated with improved survival with favourable neurological outcome at hospital discharge and improved survival to hospital discharge. Care at CACs did not improve survival to 30 days with favourable neurological outcome and survival to 30 days. There remains a need of high quality data individual patient data meta-analysis and or data from randomised trials to fully elucidate the impact of CAC.
Lipe et al	2018	CAC vs non-CAC	To be considered a cardiac resuscitation center, a hospital was required to have both PCI capability and TTM capability as defined by the American Heart Association.	Adult patients suffering from an OHCA transported to cardiac resuscitation centers seem to have better outcomes than their counterparts. It is reasonable to transport these patients directly to cardiac resuscitation centers (class IIa, level of evidence B-nonrandomized). Future studies should further clarify how long a bypass time is tolerable for these patients, especially for the subpopulation of patients not having experienced prehospital ROSC.
Storm et al	2019	Structured pathways of care vs usual care	Studies implemented a structured care pathway, defined as an organized treatment protocol which was determined a priori, implemented postcardiac arrest and during the acute hospitalization, and had more than one intervention (e.g., PCI and TTM).	Our findings support a highly organized approach to postcardiac arrest care, in which a cluster of evidence-based interventions are delivered by a specialized interdisciplinary team. Given the overall low certainty of evidence, however, definitive recommendations will depend on confirmation in additional high-quality studies. Additionally, results presented here provide the rationale for future studies which will test optimal combinations and timing of interventions, and which will integrate a structured approach to neurologic prognostication with the goal of further ameliorating care and outcomes in this population. There is also a need for new research which accounts for heterogeneity inherent in this population and validates personalized approaches based on biological subtypes.

CAC: Cardiac arrest centers; PCI: Percutaneous coronary intervention; TTM: Targeted temperature management

Table S3. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 8-9
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 9
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 10; Supp Material 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 12-14
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 12
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 12; Table 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 13-14
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 12-13
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 11-12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	Page 12-13

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 13
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 12-13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 13
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 13
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 13
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 13-14
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Supp Material 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp Material 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp Material 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 16-19; Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 16-19
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 16-18
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supp Material 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supp Material 7
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 20-22
	23b	Discuss any limitations of the evidence included in the review.	Page 22-23
	23c	Discuss any limitations of the review processes used.	Page 22-23
	23d	Discuss implications of the results for practice, policy, and future research.	Page 20-22
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 10
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 10
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 10
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 23-24
Competing interests	26	Declare any competing interests of review authors.	Page 23-24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 10

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S4. GRADE Evidence Table

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Care at CACs**	**Care at non-CACs**	**Relative (95% CI)**	**Absolute (95% CI)**		
Survival with good neurological outcome												Critical
5	Observational cohort studies	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding reduces demonstrated effect*	1561 / 21735 (7.2%)	480 / 31237 (1.5%)	**OR 1.85** (1.52 to 2.26)	13 more per 1,000 (from 8 more to 19 more)	⊕⊕⊕◯ Moderate	
Survival with good neurological outcome, shockable rhythm subgroup												Critical
5	Observational cohort studies	Serious†	Not serious	Not serious	Not serious	Strong association‡	213 / 1376 (15.5%)	54 / 544 (9.9%)	**OR 2.47** (1.88 to 3.25)	115 more per 1,000 (from 72 more to 164 more)	⊕⊕◯◯ Low	
Survival with good neurological outcome, nonshockable rhythm subgroup												Critical
2	Observational cohort studies	Serious†	Not serious	Not serious	Not serious	-	-	-	**OR 1.43** (1.04 to 1.98)	-	⊕◯◯◯ Very low	
Survival												Critical
7	Observational cohort studies	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding reduces demonstrated effect*	2536 / 13441 (18.9%)	987 / 12454 (7.9%)	**OR 1.92** (1.59 to 2.32)	63 more per 1,000 (from 41 more to 87 more)	⊕⊕⊕◯ Moderate	
Survival, prehospital ROSC subgroup												Critical
7	Observational cohort studies	Serious†	Not serious	Not serious	Not serious	-	2065 / 6200 (33.3%)	817 / 2601 (31.4%)	**OR 1.46** (1.12 to 1.90)	87 more per 1,000 (from 25 more to 151 more)	⊕◯◯◯ Very low	
Survival, no prehospital ROSC subgroup												Critical
5	Observational cohort studies	Serious†	Not serious	Not serious	Not serious	Strong association‡	412 / 3895 (10.6%)	176 / 8929 (2.0%)	**OR 2.52** (1.90 to 3.35)	29 more per 1,000 (from 17 more to 43 more)	⊕⊕◯◯ Low	

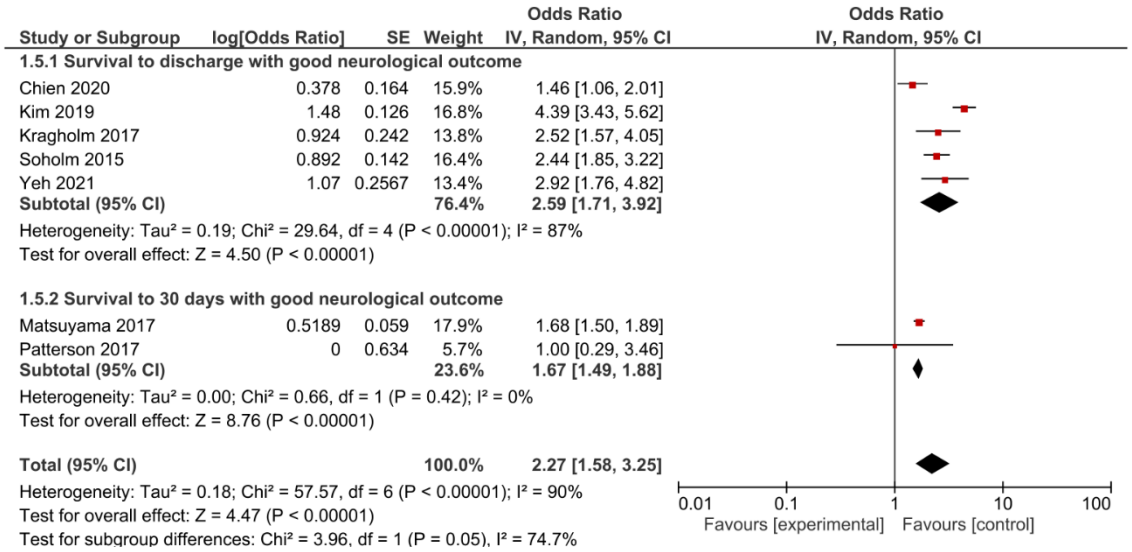
CAC: Cardiac arrest centre; OR: Odds ratio; CI: Confidence interval; ROSC: Return of spontaneous circulation

* Some studies (e.g., Mumma. et al, Harnod. et al) did not adjust for certain prehospital variables, leading to residual confounding. However, it is likely that emergency medical services transported sicker patients who had more severe prehospital characteristics to CACs for advanced care. This was expected to diminish the intervention effect.

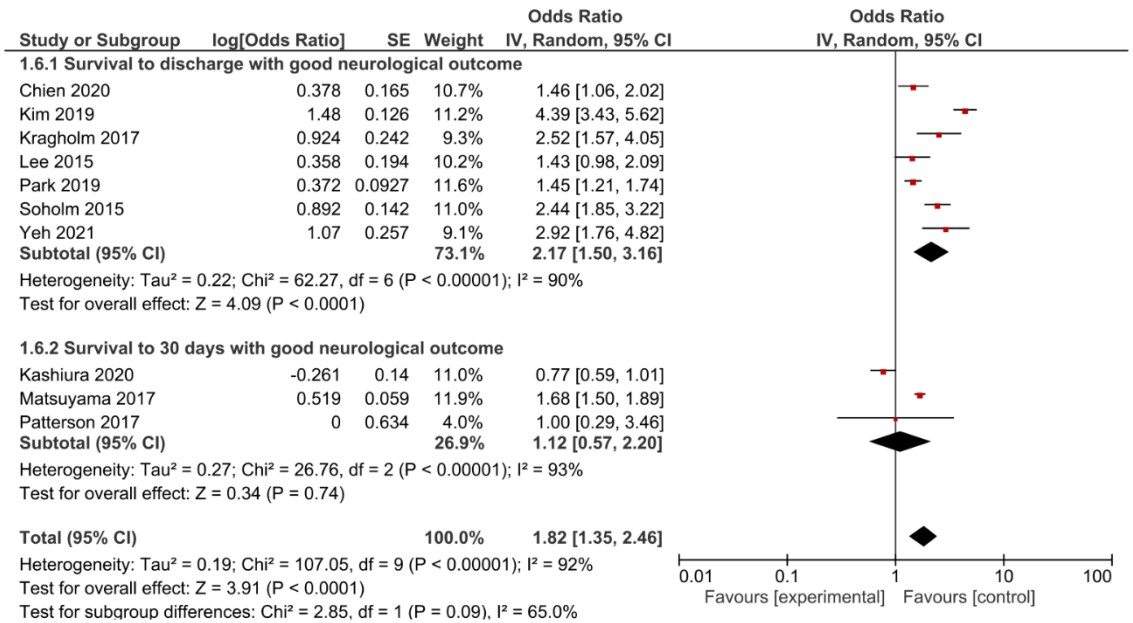
† Inclusion of before-and-after study designs ‡ RR > 2.0 from direct evidence

Figure S1. Forest Plots for Meta-Analyses of Unadjusted Odds Ratios

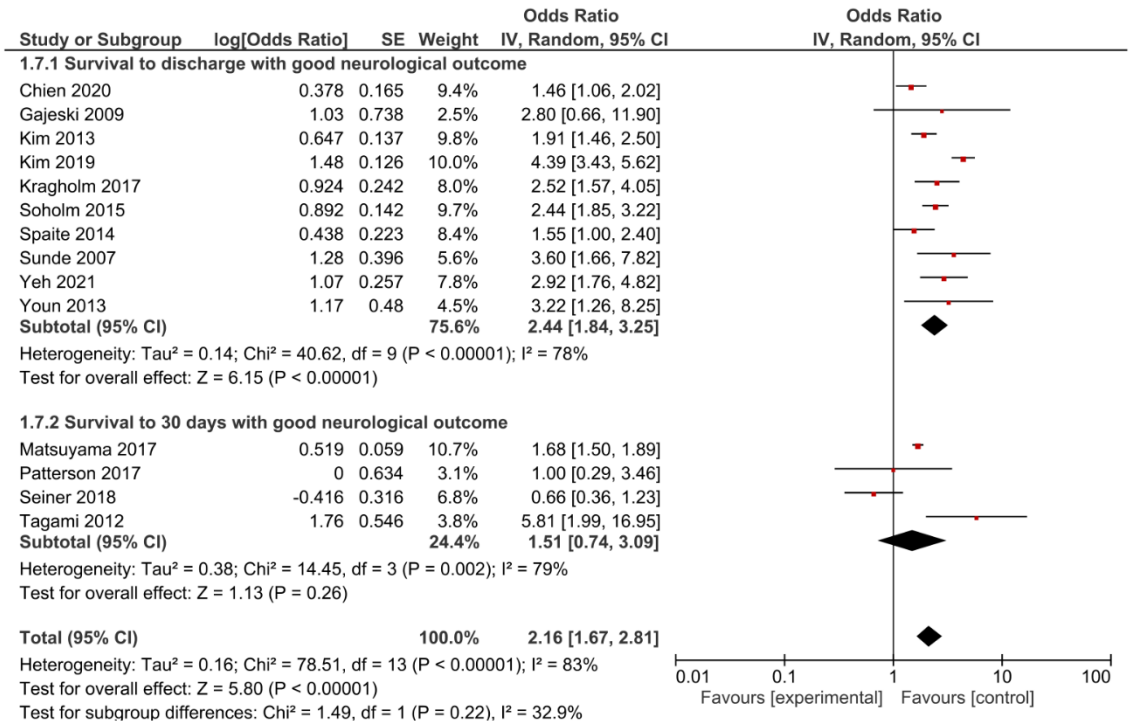
1: Forest plot for meta-analysis of unadjusted analyses comparing survival with good neurological outcome between CACs and non-CACs, using a random effects model and the "strict" definition of CACs



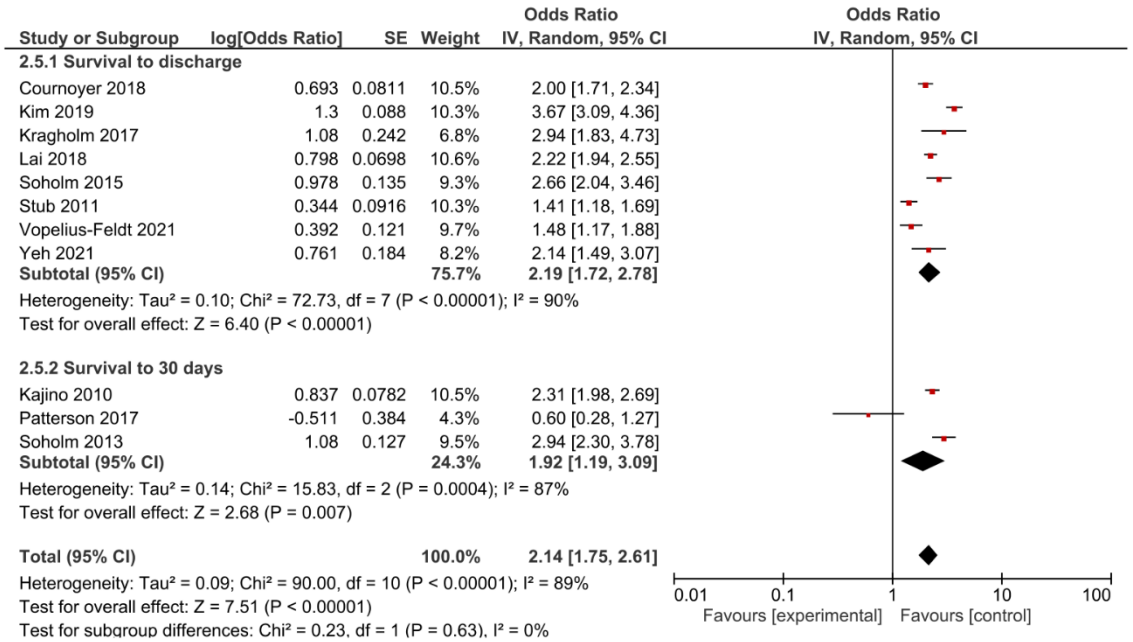
2: Forest plot for meta-analysis of unadjusted analyses comparing survival with good neurological outcome between CACs and non-CACs, using a random effects model and including high volume centres



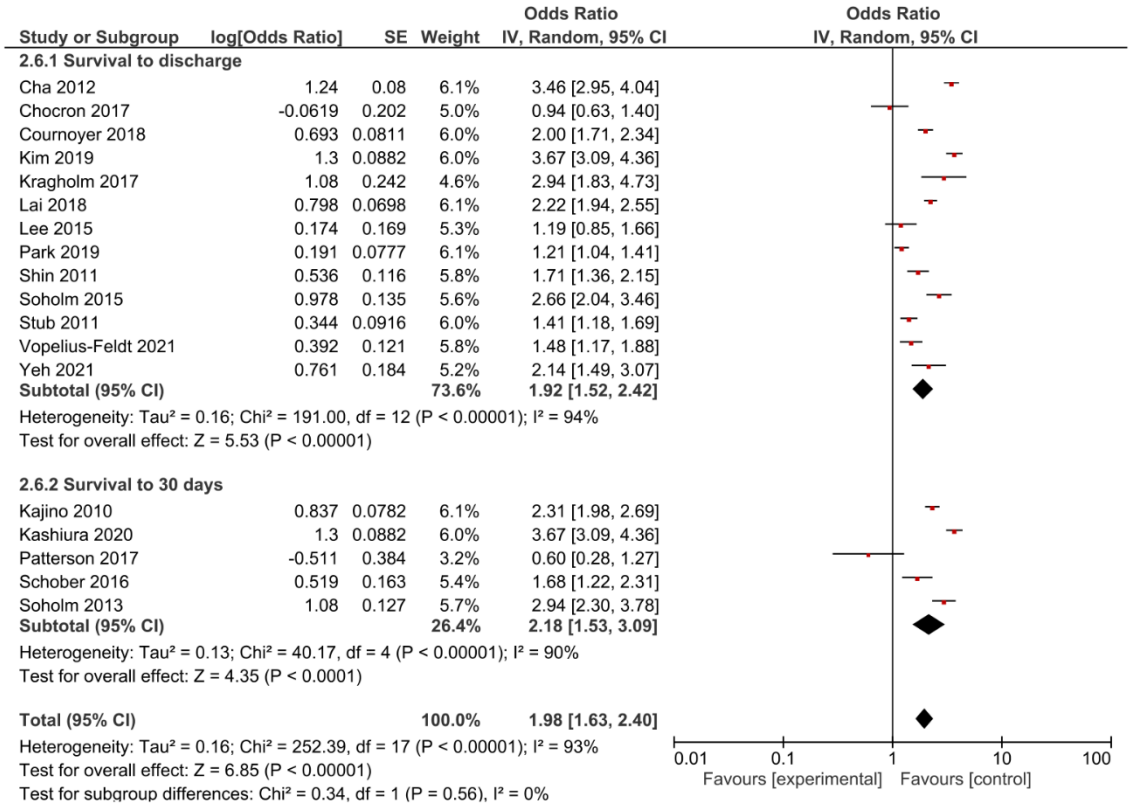
3. Forest plot for meta-analysis of unadjusted analyses comparing survival with good neurological outcome between CACs and non-CACs, using a random effects model and including improved care centres



4. Forest plot for meta-analysis of unadjusted analyses comparing survival between CACs and non-CACs, using a random effects model and the “strict” definition of CACs



5. Forest plot for meta-analysis of unadjusted analyses comparing survival between CACs and non-CACs, using a random effects model and including high volume centres



6. Forest plot for meta-analysis of unadjusted analyses comparing survival between CACs and non-CACs, using a random effects model and including improved care centres

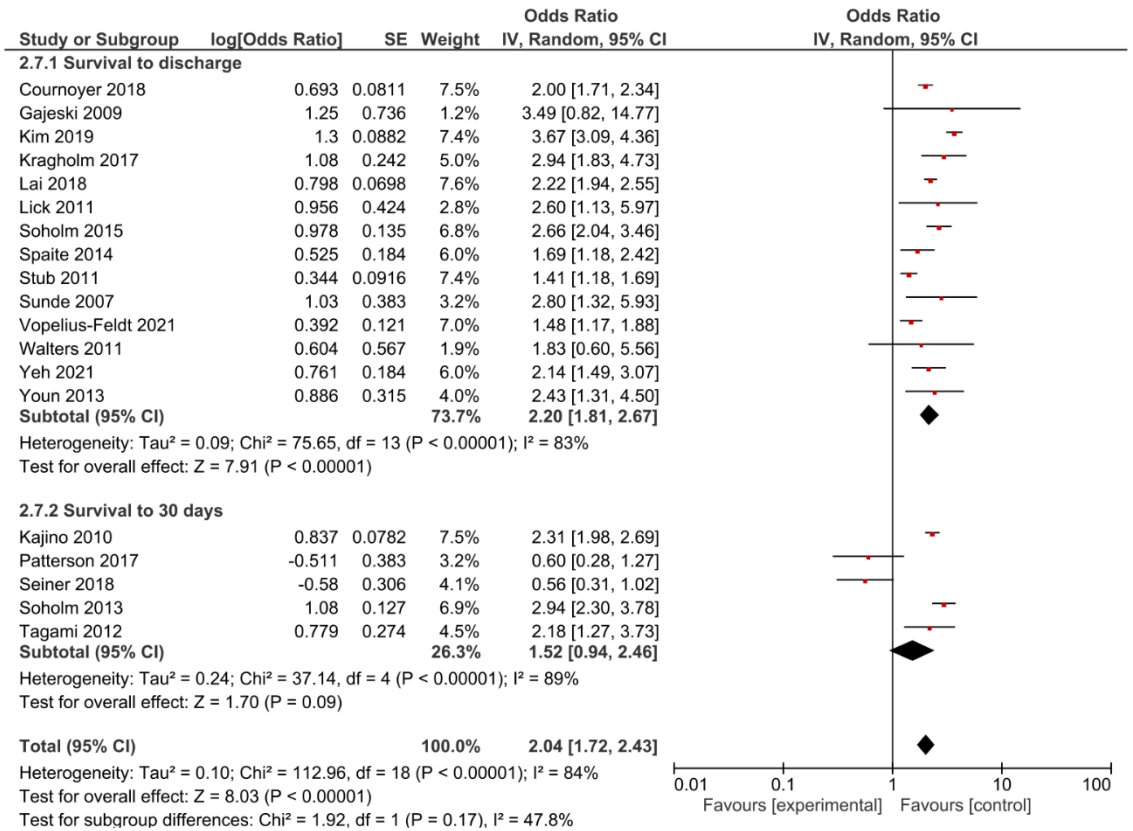
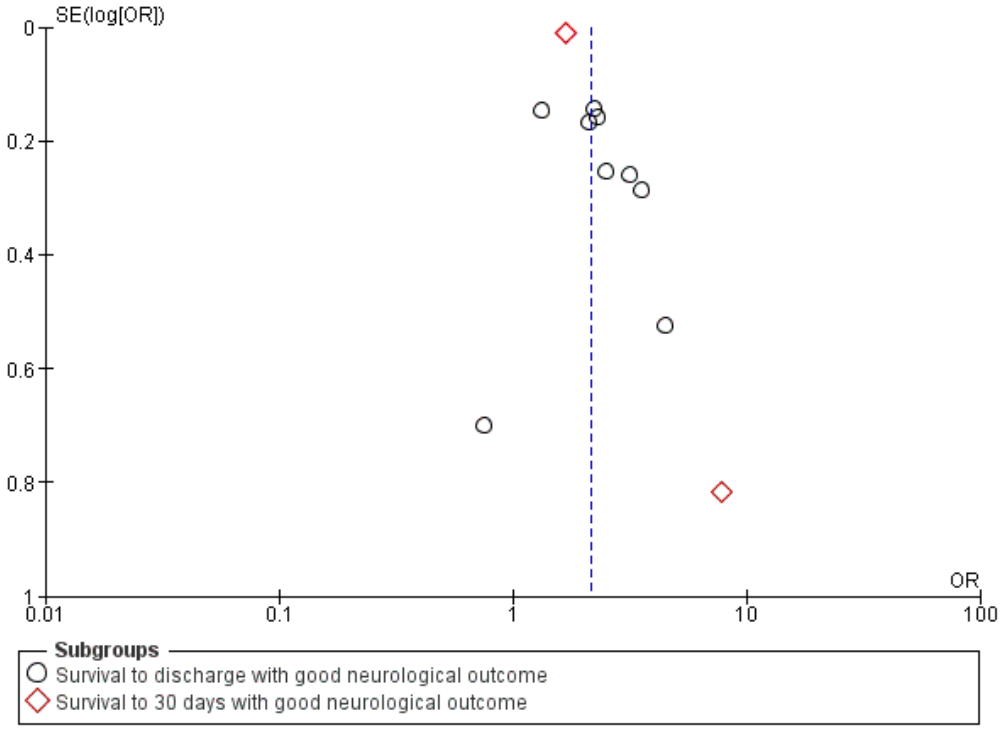
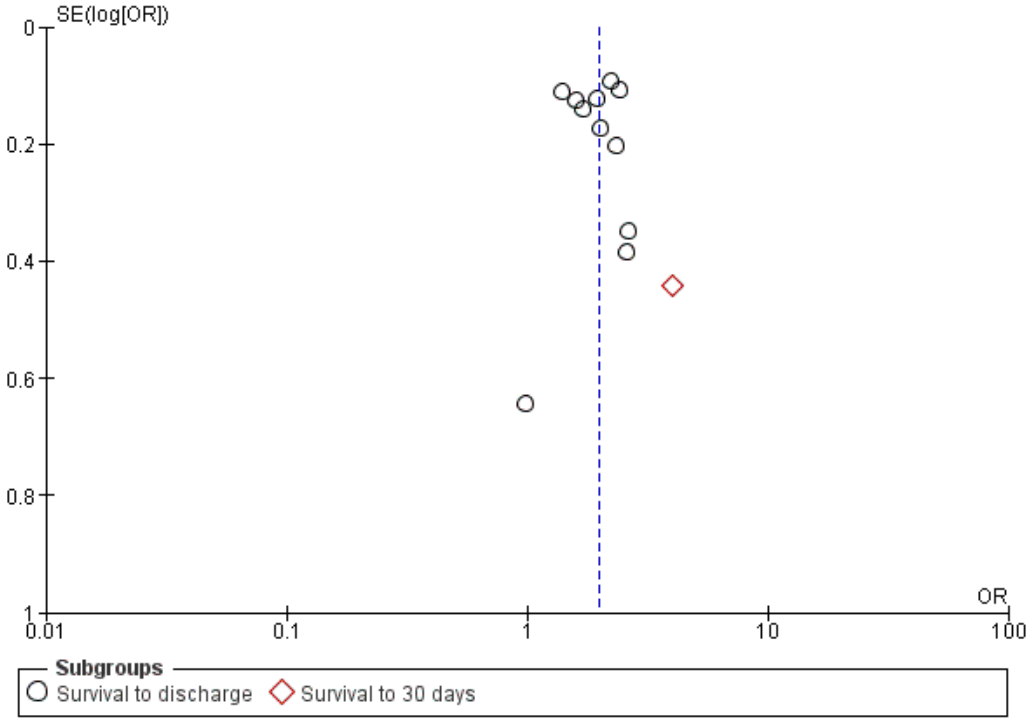

Study or Subgroup
log[Odds Ratio]
SE
Weight
Odds Ratio
IV, Random, 95% CI
Odds Ratio
IV, Random, 95% CI
2.7.1 Survival to discharge
Cournoyer 2018 0.693 0.0811 7.5% 2.00 [1.71, 2.34]
Gajeski 2009 1.25 0.736 1.2% 3.49 [0.82, 14.77]
Kim 2019 1.3 0.0882 7.4% 3.67 [3.09, 4.36]
Kragholm 2017 1.08 0.242 5.0% 2.94 [1.83, 4.73]
Lai 2018 0.798 0.0698 7.6% 2.22 [1.94, 2.55]
Lick 2011 0.956 0.424 2.8% 2.60 [1.13, 5.97]
Soholm 2015 0.978 0.135 6.8% 2.66 [2.04, 3.46]
Spaite 2014 0.525 0.184 6.0% 1.69 [1.18, 2.42]
Stub 2011 0.344 0.0916 7.4% 1.41 [1.18, 1.69]
Sunde 2007 1.03 0.383 3.2% 2.80 [1.32, 5.93]
Vopelius-Feldt 2021 0.392 0.121 7.0% 1.48 [1.17, 1.88]
Walters 2011 0.604 0.567 1.9% 1.83 [0.60, 5.56]
Yeh 2021 0.761 0.184 6.0% 2.14 [1.49, 3.07]
Youn 2013 0.886 0.315 4.0% 2.43 [1.31, 4.50]
Subtotal (95% CI) 73.7% 2.20 [1.81, 2.67]
Heterogeneity: Tau² = 0.09; Chi² = 75.65, df = 13 (P < 0.00001); I² = 83%
Test for overall effect: Z = 7.91 (P < 0.00001)
2.7.2 Survival to 30 days
Kajino 2010 0.837 0.0782 7.5% 2.31 [1.98, 2.69]
Patterson 2017 -0.511 0.383 3.2% 0.60 [0.28, 1.27]
Seiner 2018 -0.58 0.306 4.1% 0.56 [0.31, 1.02]
Soholm 2013 1.08 0.127 6.9% 2.94 [2.30, 3.78]
Tagami 2012 0.779 0.274 4.5% 2.18 [1.27, 3.73]
Subtotal (95% CI) 26.3% 1.52 [0.94, 2.46]
Heterogeneity: Tau² = 0.24; Chi² = 37.14, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.70 (P = 0.09)
Total (95% CI) 100.0% 2.04 [1.72, 2.43]
Heterogeneity: Tau² = 0.10; Chi² = 112.96, df = 18 (P < 0.00001); I² = 84%
Test for overall effect: Z = 8.03 (P < 0.00001)
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 47.8%
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Figure S2. Funnel Plots

1: Survival to discharge or 30 days with good neurological outcome (CACs and improved care centers)



2: Survival to discharge or 30 days (CACs and improved care centers)


SE(log[OR])
0
0.2
0.4
0.6
0.8
1
0.01
0.1
1
10
100
OR
Subgroups
Survival to discharge
Survival to 30 days