REVIEW ARTICLE

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Cardiac arrest: an interdisciplinary scoping review of clinical literature from 2021

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Abstract

The Interdisciplinary Cardiac Arrest Research Review (ICARE) group was formed in 2018 to conduct an annual search of peer-reviewed literature relevant to cardiac arrest. Now in its fourth year, the goals of this review are to highlight annual updates on clinically relevant and impactful clinical and population-level studies in the interdisciplinary world of cardiac arrest research from 2021. To achieve these goals, a search of PubMed using keywords related to clinical research in cardiac arrest was conducted. Titles and abstracts were screened for relevance and sorted into seven categories: Epidemiology & Public Health; Prehospital Resuscitation; In-Hospital Resuscitation & Post-Arrest Care; Prognostication & Outcomes; Pediatrics; Interdisciplinary Guidelines; and Coronavirus disease 2019. Screened manuscripts underwent standardized scoring of methodological quality and impact by reviewer teams lead by a subject matter expert editor. Articles scoring higher than 99th percentile by category were selected for full critique. Systematic differences between editors' and reviewers' scores were assessed using Wilcoxon signed-rank test. A total of 4,730 articles were identified on initial search; of these, 1,677 were scored after screening for relevance and deduplication. Compared to the 2020 ICARE review, this represents a relative increase of 32% and 63%, respectively. Ultimately, 44 articles underwent full critique. The leading category was In-Hospital Resuscitation, representing 41% of fully reviewed articles, followed by Prehospital Resuscitation (20%) and Interdisciplinary Guidelines (16%). In conclusion, several clinically relevant studies in 2021 have added to the evidence base for the management of cardiac arrest patients including implementation and incorporation of resuscitation systems, technology, and quality improvement programs to improve resuscitation.

Keywords: Cardiopulmonary Resuscitation; Emergency Medical Services; Epidemiology; Heart Arrest; Out-of-Hospital Cardiac Arrest; Sudden Cardiac Death

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1. Introduction

1.1. Background

The annual incidence of adult out-of-hospital cardiac arrest (OHCA) is approximately 14-147 per 100,000 person-years worldwide, although there is considerable variability in incidence, survival, and access to prehospital care across these diverse geographic regions (1, 2). The average survival rate following adult OHCA is low at approximately 5-10% (1, 3). Ongoing improvements and novel approaches to care for these patients are continually being presented from clinical, social, and pharmacologic perspectives to reduce the signifi-

cant morbidity and mortality of cardiac arrest.

1.2. Importance

Given the broad scope and significant volume of cardiac arrest research across multiple disciplines, the Interdisciplinary Cardiac Arrest Research Review (ICARE) group was formed in 2018. This review, now in its fourth iteration, systematically gathers and summarizes articles from multiple disciplines with relevance or value to the realm of cardiac arrest research in keeping with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. As a scoping

review, rather than a systematic review focused on a specific research question, this review looks to serve as an annual update on clinically relevant cardiac arrest research.

1.3. Goals of this Investigation

This manuscript focuses on the major updates in epidemiologic and clinical cardiac arrest research. The intent of the ICARE review is to be a resource both for clinicians and researchers by referencing the most clinically relevant developments from the previous year.

2. Evidence acquisition

The methods for the 2021 ICARE edition are adopted from the Global Emergency Medicine Literature Review group's methodology and are consistent with PRISMA-ScR guidelines and the previously published annual reviews (4-7). Additional manual screening to prevent inadvertent omissions was also performed. The 2021 ICARE working group was comprised of 59 members; there were 46 reviewers and 13 editors, including one technical editor and a group of three senior editors. All editors have previously published peerreviewed cardiac arrest research. The ICARE group consists of physicians, scientists, medical students, and graduate students from multiple disciplines relevant to the field of cardiac arrest. All ICARE members are unpaid and selected through an application process prior to literature search. As a scoping review, this review was registered on OSFHome as protocol osf.io/g9whf.

2.1. Literature search

Publications pertaining to cardiac arrest were searched on PubMed in two phases: the first included publications between January and August 2021 and was conducted in October 2021, and the second included publications between September and December 2021 and was conducted in January 2022. Queries were limited to PubMed due to the clinical focus of PubMed and the sheer number of articles returned. To filter by article publication dates, both literature searches were performed using the "[PDAT]" PubMed/MEDLINE field description tag. Therefore, articles with either an 'Electronic Date of Publication' and/or 'Print Date of Publication' in 2021 were included.

Articles that were included in prior iterations were manually excluded by technical and section editors. Inclusion and exclusion criteria were consistent with previous ICARE reviews (4, 5, 7). Only articles that were available in English were included. Publications that were commentaries, editorials, case reports, study design protocols, data releases, and letters to the editor were excluded. We continued to use the search string employed in previous editions (4, 5, 7).

2.2. Article Screening

The titles and abstracts of identified articles were screened by the technical and section editors independently based on detailed inclusion and exclusion criteria employed in previous editions (4, 5, 7). The kappa statistic for agreement on article inclusion at this stage was calculated to determine consistency in the screening process. Articles selected for scoring were classified as either Original Research or Review according to the study design. The articles were classified into seven thematic categories: Epidemiology & Public Health; Prehospital Resuscitation, Technology & Care Processes; In-Hospital Resuscitation & Post-Arrest Care Processes; Prognostication & Outcomes; Pediatrics; Interdisciplinary Guidelines & Reviews; and the Coronavirus disease 2019 (COVID-19) pandemic. Results pertaining to basic science and pharmacology studies are being reported separately from this manuscript focused on clinical care.

2.3. Article Scoring

The scoring scale originally adapted from the annual Global Emergency Medicine Literature Review and utilized in prior ICARE reviews was again used according to the study type – original research or review (4-7). Each article was scored independently by reviewers, and scores were verified by each section editor. Scoring scales for original research and review articles are presented in tables 1 and 2, respectively. In addition to the reviewers' scoring, each article's "Impact" and "Importance" was graded independently by the section editor. Total scores ranged between 0-22 points and were calculated as a composite of the reviewer's "Clarity" and "Design" scores and the section editor's "Importance" and "Impact" scores. For quality control and to ensure scoring reliability among the ICARE group, random articles were selected, and reviewer and editor scores were compared. Systematic differences between editor and reviewer scores for each of the quality control articles were assessed using Wilcoxon signedrank test.

2.4. Formal article review

Articles scoring in the $99^{t\,h}$ percentile by category and type were evaluated for a formal review with accompanying summary. To reduce the likelihood of imperfect but high-impact articles unintentionally being excluded from formal summarization, articles that scored one point below the $99^{t\,h}$ percentile score were discussed in a committee consisting of three senior editors. Reviewers then summarized these articles with attention to the objective, key findings, and strengths/limitations of each study. Section editors then reviewed summaries for content, accuracy, and style according to each category.

3. Results

The screening, scoring, and full article review process is presented in figure 1. A total of 4,730 articles were identified on initial search; of these, 1,677 were scored after screening for relevance and deduplication, and 38 scored in the 99^{th} percentile for their respective sections and underwent full critique and summarization. A further 42 articles which scored one point below the 99^{th} percentile threshold for their given

Table 1 Scoring of original research articles

Quality measur	e Question	Points		
Design				
A	Descriptive studies (including case studies and case series, natural observation studies and descriptive surveys)	1 -or-		
Select One	Correlation studies (case control studies, prospective observational studies, retrospective studies)	2 -or-		
	Non-randomized or non-blinded experimental studies	3 -or-		
	Randomized, blinded experimental studies	4		
В	Study design is appropriate to answer the authors' hypothesis.	1		
C	Correct statistical tests are used to analyze the data.	1		
D	Results are presented accurately and without bias.	1		
E	Limitations are clearly described, and the conclusions are supported by data.	1		
Total		8 / Out of max		
		score 8		
Ethics				
A	The study was approved by an institutional review board (IRB)/institutional animal use and care	2		
	committee, ethics committee, community group, as required by local laws.			
В	Informed consent was obtained or consent was waived by the IRB (give point if not applicable, e.g.,			
	animal study).			
C	The authors declare their conflicts of interest or declare that none exist.	1		
Total		4 / Out of a max		
		of 4		
Importance				
A	The study results are not specific to one certain patient population but are broadly generalizable to a variety of settings.			
В	The topic being studied is an important one, in that it advances the field of cardiac arrest research or care.			
C	The study is clearly relevant to the realm of cardiac arrest research or care.	1		
Total	•	5 / Out of a max		
		of 5		
Impact*				
A	The findings or recommendations of this study may be feasibly implemented by practitioners* of cardiac arrest care.			
В	Practitioners* would likely change their practice if they were aware of this study.	2		
C	The authors of this study raise interesting questions that may stimulate further research.	1		
Total	, 01	5 / Out of a ma		
		of 5		

sections were also reviewed for inclusion and full review by the Editorial board; 6 additional articles were selected for full critique and summarization, for a total of 44 articles. Appendix 1 summarizes the articles reviewed. The scores for all Original Research and Review articles, and the full summaries of the top scoring cardiac arrest articles of 2021 identified by our review are available from the corresponding author upon request.

Inter-rater reliability between the screening editors revealed a Cohen's kappa score of 0.345 (95% CI: 0.021–0.67). Article scoring statistics for each category are summarized in table 3. The leading category was In-Hospital Resuscitation & Post-Arrest Care representing 41% (18/44) of fully reviewed articles. Among review articles, section editors scored a median 1 point (IQR: 0 – 3, p<0.001) less than reviewers. Among original research articles, section editors scored a median 2 points (IQR: 1 – 3, p<0.001) less than reviewers. The threshold for 99^{th} percentile for each section was a total score of 22 for Epidemiology & Public Health, 22 for Prehospital Resuscitation, Technology & Care Processes, 21 for In-Hospital

Resuscitation & Post-Arrest Care Processes, 21 for Prognostication & Outcomes, 21 for Pediatrics, 21 for Interdisciplinary Guidelines & Reviews, and 22 for COVID-19 related articles. The following sections highlight the critical findings of the top-scoring articles. More in-depth discussions and summaries of the data from each study are available upon request.

3.1. Epidemiology and public health initiatives (EPH)

Culic et al. identified daily life triggers that are associated with cardiac arrest and calculated their respective population attributable fractions (8). In order of highest to lowest risk, the triggers were: physical exertion, recent cocaine use, episodic alcohol consumption, recent amphetamine use, episodic coffee consumption, psycho-emotional stress within the previous month, influenza infection, and recent cannabis use. The relative risks of these triggers ranged from 1.10 to 4.98 (8).

In a study analyzing how cardiopulmonary resuscitation

Table 2 Scoring of review articles

Quality mea-	Question	Points
sure		
Clarity		
A	The review has a clearly stated hypothesis or purpose.	2
В	The authors provide sufficient background to put the results of the review into context.	1
C	The review can be understood by someone with general medical or public health training.	1
D	The authors use clear language and appropriate graphs, tables, and figures throughout the article.	1
Total		5 / Out of max score 5
Design		
A	This is a formal meta-analysis or a systematic review that only includes studies with a control	3
	group.	
В	There is a clear, reproducible method for the selection of studies included in this review.	2
C	Articles for this review were selected by at least two authors blinded to each other's selection.	1
D	The data was aggregated and/or analyzed appropriately.	1
Total		7 / Out of max score 7
Importance		
A	The review is not specific to one certain patient population but is broadly generalizable to a vari-	2
	ety of settings.	
В	The topic being reviewed is an important one, in that it advances the field of cardiac arrest re-	2
	search or care.	
C	This is clearly relevant to the realm of cardiac arrest research or care.	1
Total		5 / Out of max score 5
Impact*		
A	The findings or recommendations of this review appear to have applicability towards improving	2
	cardiac arrest research or care.	
В	Practitioners* would likely change their practice if they were aware of this review.	2
C	The authors of this review raise interesting questions that may stimulate further research.	1
Total		5 / Out of max score 5

Table 3 Summary statistics of reviewer scoring by category and article type

Article Category	Original Re	esearch (OR)	Review (RE)	
-	Count (%)	Median (IQR)	Count (%)	Median (IQR)
Basic Science & Pharmacology (BSP)	184 (13.4)	17 (15–18)	11 (3.6)	17 (16.5–21)
COVID-19 (COVID)	64 (4.7)	18 (15-20)	13 (4.2)	16 (15-19)
Epidemiology & Public Health (EPH)	324 (23.6)	16 (14-18)	51 (16.7)	16 (12-18)
Prehospital Resuscitation, Technology & Care Processes	184 (13.4)	18 (16-20)	26 (8.5)	18 (14.25-20.75
(PRE)				
In-Hospital Resuscitation & Post-Arrest Care Processes (IN)	305 (22.2)	18 (16-20)	54 (17.6)	16 (15-19)
Prognostication & Outcomes (PRO)	242 (17.7)	17 (14-18)	21 (6.9)	17 (16-19)
Pediatrics (PED)	68 (5.0)	18 (16-20)	16 (5.2)	16 (14.25-20.75
Interdisciplinary Guidelines & Reviews (GL)	-	-	114 (37.3)	16 (13-18)
Totals	1371 (100.0)	17 (15-19)	306 (100.0)	16 (14-19)

(CPR) coaches improve resuscitation team dynamics and communication, Jones et al. showed that CPR coaches improve overall team communication and adaptiveness as teams responded to their coach's feedback, while non-coached teams were not adaptive to feedback (9).

3.2. Prehospital resuscitation, technology and care processes (PRE)

Several prehospital studies attempted to identify modifiable factors within the chain of survival to improve survival and good neurological outcome. These studies ranged from patient-level interventions to systemic practice changes. High-quality CPR and early defibrillation are basic life sup-

port (BLS) skills and mainstays in the chain of survival. Two studies sought to improve the delivery of these fundamental interventions. De Graaf et al. evaluated a new automated external defibrillator (AED) algorithm ("cprINSIGHT") that analyzes cardiac rhythm while chest compressions are ongoing (10). This new algorithm demonstrated a similar sensitivity (96%) and specificity (98%) as a conventional AED, while decreasing CPR interruptions and median pre-shock delay (8 s vs. 22 s, p<0.001) and increasing median chest compression fraction (CCF) (86% vs. 80%, p<0.001). Although 30% of analyses ultimately required a pause in CPR, this new algorithm shows significant improvement in CCF. Another study emphasized the importance of BLS skills by demonstrating the

effectiveness and safety of bag-valve-mask (BVM), as compared to laryngeal mask airway (LMA), ventilation during continuous CPR in a simulated setting (11). Dundar et al. found that LMAs were associated with larger volume and faster ventilation, as compared to BVM ventilation (11). Passive leg raise (PLR) is a simple, rapid, minimally invasive diagnostic modality that provides a fluid challenge and assesses fluid responsiveness, as is performed in sepsis patients (12). In early CPR guidelines, PLR was included to augment venous return and coronary perfusion pressure, although this recommendation was later removed. Azeli et al. performed a randomized controlled trial (RCT) evaluating the rates of survival-to-discharge with favorable neurological outcome, survival-to-admission, and complications between patients resuscitated in the PLR versus flat position (13). Though underpowered, the study found no difference in outcomes or complications between the two resuscitation strategies, and further studies were recommended.

Recently, there has been growing interest in the use of highperformance CPR teams to improve the time-sensitive delivery of interventions and to minimize delays. Although such teams have been varied in their approach, definition, configuration, and context, their common goal is to deliver quality resuscitative efforts by focusing on skill delivery and seamless coordination. The first meta-analysis investigating the impact of teams on patient outcomes found that they improved the rates of prehospital return of spontaneous circulation (ROSC), survival-to-discharge, and favorable neurological outcomes (14). Given the variability in clinical contexts worldwide, the ideal strategy for a given locale must be tailored to local capabilities.

Other studies sought to describe vascular access, medication administration, and hospital interventions for OHCA patients. A meta-analysis by Hsieh et al. showed there was no significant difference between IV and IO vascular access on neurological outcomes (OR=0.60, I²=95%) and survival-to-discharge (OR=0.66, I²=89%) for OHCA patients (15). Although this meta-analysis is limited by confounding factors related to obesity, time to intervention, rather than access type, was identified as an important modifier, which stresses the importance of timely interventions. Another meta-analysis found that sodium bicarbonate did not improve survival-to-discharge (OR=0.66, p=0.53) or ROSC (OR=1.54, p=0.54), consistent with AHA guidelines (16, 17). Nas et al. found that shock-resistant ventricular fibrillation (VF) or ventricular tachycardia (VT) (defined as requiring more than three defibrillation attempts) was associated with significantly lower rates of 24-hour survival (75% vs. 93%, p<0.001) and survival-to-discharge (61% vs. 78%, p=0.002), while having higher rates of intubation, mechanical CPR, antiarrhythmic administration, and acute coronary occlusions (41% vs. 26%, p=0.006) (18). Downing et al. performed a meta-analysis evaluating the survival benefit of extracorporeal cardiopulmonary resuscitation (ECPR) for OHCA and found that 60% of OHCA patients had VF/VT arrest; of OHCA patients treated with ECPR, 24% survived to discharge, and 18% had favorable neurological function at discharge (19). Several recently published studies, including two randomized trials (COACT and PEARL), have found that early coronary angiography (CAG) is not beneficial for patients without post-ROSC ST-elevation (20-23); however, in the context of these two studies, patients with persistent VT/VF are at high risk for acute coronary occlusions and may be excellent candidates for ECPR despite not meeting ST-elevation criteria (18).

From a systems-level approach to OHCA, Nehme et al. found improved survival-to-discharge, event survival, and ROSC after a state-wide quality improvement (QI) program was implemented in Victoria, Australia (24). The QI program included a resuscitation checklist and team leader, resuscitation choreography, on-screen rhythm analysis, manual mode defibrillations, preemptive monitor charging, pulse checks for appropriate rhythms, real-time CPR feedback, and post-event debrief, which are all components of high-performance teams that focus on the chain of survival.

3.3. In-hospital resuscitation and post-arrest care (IN)

The in-hospital literature centered around a systems-based approach to cardiac arrest resuscitation. Other common themes included the integration of technology with resuscitation, and medication and procedural interventions during and after cardiac arrest.

Using the risk factors defined by the American College of Cardiology for post-resuscitation angiography, Harhash et al. evaluated the association between the number of simultaneous risk factors and the likelihood of poor survival (25). They found eight characteristics that were individually associated with poor survival: >85 years of age, time-to-ROSC >30 min, non-shockable rhythm, no bystander CPR, lactate >7, unwitnessed arrest, pH <7.2, and CKD. The presence of any 3 or more risk factors was associated with <40% survival; the presence of ≥6 risk factors or the simultaneous presence of the three most significant risk factors in a post-arrest patient was associated with 10% survival-to-discharge.

Centers of excellence have been shown to improve outcomes for stroke, STEMI, and trauma (26-30). The same concept has been proposed for cardiac arrest resuscitation. Similar to high-performance teams that deliver expedient, accurate, choreographed care in the prehospital setting, hospitals designated as cardiac arrest centers (CACs) achieved a nearly two-fold improvement in survival-to-discharge and 30-day survival with favorable neurologic outcome, as compared to hospitals without CAC designation (31). Similarly, hospitals that appointed physician resuscitation champions had a 29.5% survival-to-discharge, as compared to hospitals with non-physician champions (26.7%) or hospitals with no champions (26.3%). Hospitals with active physician champions were 4 times more likely to be in the top survival quintile (32).

The application of technology to resuscitation was an area of focus in this year's cardiac arrest literature. It has been suggested that audiovisual devices improve CPR quality (33-36), although its survival benefit was unclear; Goharani et al. elucidated the survival benefit in patients for whom an audiovisual device is used during CPR (time ratio [TR]=1.31, p<0.001) (37). Besides the delivery of high-quality CPR, Advanced Cardiac Life Support (ACLS) calls for an algorithmic approach that incorporates the timely delivery of medications and electricity. During this high-intensity clinical scenario, Grundgeiger et al. advocates the use of cognitive aid applications to further coordinate resuscitation teams (38). The composite CPR performance score was significantly higher in teams that utilized a cognitive aid (mean difference=0.23, p=0.002). Similarly, Crabb et al. showed that a clinical decision display significantly improved the timing of rhythm checks, defibrillation, and medication administration (39).

Resuscitation does not end at ROSC. Jang et al. found that prolonged emergency department (ED) length-of-stay (LOS) is associated with poorer outcomes (40). Therefore, although hospitals suffer from ED overcrowding and emergency physicians are skilled in resuscitation, patients are best served in the intensive care unit (ICU) where comprehensive postarrest care can be delivered. In the post-ROSC phase, there was significantly more false-positive electrocardiograms if obtained 7 minutes after ROSC (41).

Similar to previous literature, a randomized, multicenter trial of 530 patients and a meta-analysis of more than 34,000 patients continued to show no survival benefit for early CAG in the absence of ST-elevation (23, 42). Nonetheless, Harhash et al. demonstrated that in OHCA patients without ST-elevation and with non-shockable rhythms, CAG revealed acute coronary culprits for 1 in 4 patients (25). As discussed above, acute coronary syndrome (ACS) may not always present with ST-elevation; the clinician must have a high index of suspicion for coronary disease, even if an emergent CAG may not be required. Kuroki et al. performed a multicenter, cohort study of 935 propensity-score matched post-arrest patients to evaluate the difference in neurologic outcome between ECPR alone vs. ECPR with intra-aortic balloon pump (IABP) and found that the ECPR+IABP group showed significantly better neurologic outcome than the ECPR alone group (35% vs. 25%, p<0.001) (43). Further subgroup analysis showed this neurologic benefit applied to the ACS group, rather than the non-ACS group.

Previous literature suggests patients who receive corticosteroids after ROSC have improved survival (44, 45), and a meta-analysis analyzing the use of steroids during cardiac arrest found that steroid administration was associated with increased rates of survival-to-discharge, sustained ROSC, and favorable neurologic outcome (46). After ROSC, a retrospective study showed the use of high-dose benzodiazepines was associated with a delay in regaining consciousness (47).

In a post hoc analysis evaluating the quality of targeted tem-

perature management (TTM) delivery with neurologic outcome, the quality of TTM was given a composite score. De Fazio et al. found that high-quality TTM was delivered to a small proportion of patients, and TTM quality was not associated with neurologic outcome (48). Although the authors mention limitations such as underpowered studies, unreliable reporting, arbitrarily chosen TTM components, variable sites of temperature measurement, among others, and hypothesized pathophysiological explanations, clinicians should still attempt to deliver TTM as precisely as possible. Morris et al. found that women were significantly less likely to receive TTM than men (41.6% vs. 46.4%, p<0.001) (49). The major driver of this disparity was due to early restrictions on care (e.g., DNR orders, family requests) and non-shockable rhythms. Although it is unclear why women are more prone to have early DNR orders, this is consistent across various medical illnesses (50, 51); therefore, it is important for clinicians to educate patient's families regarding TTM and the difficulty in prognostication during the early post-arrest phase.

Although the literature has not demonstrated an outcome benefit for mechanical CPR, it has significant staff and resource advantages (52, 53). Fuest et al. performed a RCT to identify the optimal ventilation strategy during mechanical CPR. They found that tidal volume was significantly lower with continuous positive airway pressure (CPAP), as compared to bilevel positive airway pressure (BPAP) (p<0.05), suggesting BPAP might be the superior alternative currently (54).

3.4. Prognostication and outcomes (PRO)

Early and accurate prognostication is important as additional high-tech, resource-intensive, and expensive therapeutic procedures may be employed for patients who are likely to have neurologic recovery. Various diagnostic modalities, such as magnetic resonance imaging, electroencephalogram (EEG), and lab biomarkers, have been proposed as prognostic methods to determine the likelihood of neurologic recovery after cardiac arrest (55-59). While EEG and somatosensory evoked potentials (SSEP) are among the most reliable prognosticating indices for predicting outcomes, these studies were performed 6-to-12 hours after cardiac arrest (60-62). A retrospective study evaluated the prognostic accuracy of EEG and SSEP patterns during the early period after cardiac arrest by performing a clinical evaluation (GCS, pupillary exam) and neurophysiological studies (EEG, SSEP) within six hours post-arrest (63). Specific EEG and SSEP background patterns were associated with particular neurological outcomes. Continuous, or nearly continuous, EEG patterns correlated with favorable prognoses with very high reliability even at an early post-arrest stage, and were never associated with bilaterally absent SSEPs. Bilaterally absent SSEPs were always associated with poor outcome. Burst-suppression, suppression, and discontinuous EEG patterns were usually associated with higher degrees of hypoxicischemic encephalopathy, although some patients had consciousness recovery (63).

A systematic review of the association between BMI and outcomes after OHCA found that underweight patients had higher rates of in-hospital mortality and poor neurological outcomes compared to patients with normal weight (64). Underweight patients were thought to have a poorer prognosis because of aging, poorer nutritional status, impaired wound healing, and higher risk of infection and complications (64). While obese patients also had higher rates of inhospital mortality, there was no change in neurological outcome when compared to normal-weight patients. Several previous studies have found that higher BMI had no impact on prognosis or that patients with higher BMI had better outcomes (65-67). This phenomenon, termed the "obesity paradox," remains controversial; it is intuitive that obese patients are at increased risk for comorbidities and worse outcomes after cardiac arrest, although these independent variables are subject to confounding factors and difficult to analyze, and studies evaluating these factors are complicated by data collection errors (64).

3.5. Pediatrics (PED)

A systematic review found that sodium bicarbonate administration during resuscitation was associated with significantly lower survival-to-discharge (68). A large prospective cohort study examined 2 airway management strategies (ETI vs. SGA) during pediatric OHCA and found that ETI was associated with lower 30-day survival and worse neurologic outcome (69). Similar to the adult literature's emphasis on implementing technology during resuscitation, Siebert et al. performed a multicenter RCT evaluating a pediatric digital assistance application's effect on the rate of medication errors, time to medication preparation, and time to medication delivery (70). The group using the application experienced a decrease in medication errors, time to drug preparation, and time to drug delivery.

The International Liaison Committee on Resuscitation (IL-COR) Pediatric Core Outcome Set for Cardiac Arrest (P-COSCA) consisted of a multidisciplinary group that developed a core outcome set (COS) specific to pediatric cardiac arrest with the goal of standardizing assessment and outcome reporting to improve comparability across studies, reduce bias, and allow for meta-analyses. The COS prioritized survival-to-discharge and one-year survival; neurologic function at discharge; and neurologic, cognitive, and physical function at one year (71).

Morgan et al. found that children with an active diagnosis of pulmonary hypertension prior to in-hospital cardiac arrest were less likely to survive to discharge compared to children without pulmonary hypertension (72).

3.6. Interdisciplinary guidelines and reviews (GL)

The European Resuscitation Council (ERC) guidelines for BLS are largely informed by the ILCOR 2020 International Consensus on CPR and Emergency Cardiovascular Care Consensus on Science with Treatment Recommendations (CoSTR). While the goal of guideline review committees is to produce systematic review recommendations, the guideline committees acknowledge that the guidelines are largely based on low-certainty data.

The 2021 ERC BLS update advocates for the initiation of CPR for any unresponsive individual with absent or abnormal (e.g., agonal) respirations; data demonstrates poor sensitivity for identifying pulselessness by laypersons and medical providers and should be deferred (73, 74). Activation of the emergency response system should occur concurrently with CPR; the use of a mobile device with a handsfree option allows a lone rescuer to request EMS while initiating CPR contemporaneously (73). A meta-analysis of 5 RCTs failed to demonstrate improved outcomes from CPR preceding defibrillation; therefore, rhythm analysis and early defibrillation should occur as soon as an AED is available without additional delay for CPR (73). The ERC recommends EMS transport of OHCA patients to dedicated CACs that can provide interventional cardiology and critical care services (74, 75). The ERC updates also focus on education, technology, and endeavors to monitor resuscitation systems. ERC advocates for the employment of large-scale registries to capture data on epidemiology, treatment, and outcomes of cardiac arrest, the continuous monitoring of resuscitation systems, and the development of strategies to enhance performance (74, 75). Moreover, technology can be employed for simulation exercises and the engagement of community members through social media or mobile apps. Finally, school children and families can be instructed through instructor-led trainings and mass media campaigns (75-77). The ERC recommends tailoring educational competencies towards different target audiences (i.e., laypersons vs. healthcare providers), while emphasizing critical technical skills (e.g., high-quality CPR) (76). Although technology and simulation exercises have the potential to enhance learning and skill acquisition, their objective impact has not yet been fully quantified (76).

The annual ILCOR CoSTR update addressed several key topics pertaining to cardiac arrest via systematic review. Based on this 2021 update, prehospital dispatchers should follow a standardized algorithm for determining whether a patient is in cardiac arrest during an emergency call (75, 77). CAG should be considered in patients achieving ROSC; in particular, early CAG should be performed in patients with ST-elevation (77). CPR in the prone position may be reasonable if an advanced airway is in place and defibrillation can be attempted in this position (77).

A systematic review of 17 RCTs that examined TTM after cardiac arrest found that TTM was not associated with improved survival or favorable neurologic outcome when compared to

normothermia (78). Rather, prevention of hyperthermia may be protective.

3.7. COVID-19 and cardiac arrest (COV)

During the COVID pandemic, CPR continued to be recommended for cardiac arrest patients, although healthcare workers were advised to wear N95 masks (77). While offering protection, these masks limit cardiopulmonary capacity and the ability to complete physical activity. In a randomized controlled simulation, Cekmen et al. evaluated whether changing rescuers every one minute, as opposed to the AHA-recommended 2-minute interval improved compression depth (79). Although mean compression depth did not change, there was less variation in compression depth when CPR rescuers changed every minute. Although the authors proposed changing rescuers every one minute, further studies will have to evaluate its impact on CCF, the critical metric of high-quality CPR.

4. Discussion

Cardiac arrest remains a leading cause of morbidity and mortality worldwide. Advances in research continuously attempt to improve our understanding and therapeutic approach to the multi-faceted field of cardiac arrest that spans multiple disciplines. Therefore, as our understanding of cardiac arrest becomes more robust, the ability to stay current given the growing amount of literature published annually becomes increasingly time- and resource-intensive.

General trends in clinical cardiac arrest research in the year 2021 focused on the integration of technology with all aspects of resuscitation, continued efforts to clarify timing for post-arrest CAG, and implementation of centers of excellence and quality improvement programs to improve outcomes. The application of technology was studied from multiple arenas of cardiac arrest care.

From a community level, the ERC recommended engaging and instructing school children, families, staff, and communities using social media, mobile apps, mass media campaigns, and simulation exercises (75-77). The annual ILCOR CoSTR update recommended the implementation of standardized algorithms for prehospital dispatchers to remotely determine if a patient is in cardiac arrest and to provide prearrival instructions for laypersons (75, 77). During resuscitation, the integration of cognitive aid applications, clinical decision display systems, and audiovisual feedback devices can help offload mental tasks, improve high-quality CPR, and improve survival (37-39). There were numerous calls to implement quality improvement programs and additional largescale registries to capture data to monitor resuscitation systems and develop strategies to enhance performance (24, 71, 74, 75). Taken altogether, the authors believe that physician champions should play an integral role in CACs that focus on the timely delivery of appropriate interventions in the resuscitation and post-arrest phases. Cognitive aids and decision tools should be used to help offload cognitive demand and ensure timeliness of interventions.

The appropriate patient population and timing for CAG continues to be an area of focus. Although the literature continues to show that early CAG for non-ST-elevation has no survival benefit, culprit lesions were found in 1 of 4 post-arrest patients without ST-elevation and without a shockable rhythm (25). The subset of patients with refractory VT/VF may be appropriate for immediate CAG, although future studies will need to be conducted.

5. Limitation

The 2021 ICARE is not without limitations. First, the conclusions presented are descriptive of the current evidence for various aspects of cardiac arrest research but should not be considered comprehensive. The aim of this literature review is to highlight advances in the various fields of cardiac arrest medicine on an annual basis. An intrinsic shortcoming of this approach is that it does not provide focused context, as may be seen in a systematic review, nor does it fully account for differences in systems of care. To address this concern, article summaries and full commentaries for additional context can be provided by the corresponding author upon request. There is potential for bias in the inherently subjective 'Impact' and 'Importance' categories, although articles are screened and reviewed by multiple study team members to mitigate this risk. Additionally, while the methodology used to screen, select, and score articles is designed to capture the most relevant research, it is possible that other highquality publications may be inadvertently omitted. Lastly, to remain objective in this literature search, this review did not include letters to the editor, commentaries, and other editorials which can provide additional context when interpreting the impact of large studies.

6. Conclusion

In the first 3 iterations of ICARE reviewing cardiac arrest literature published in 2018-2020, our group reviewed an average of 1,201 papers annually. In this fourth iteration, we reviewed 1,747 manuscripts. The continually increasing volume of literature concerning cardiac arrest medicine is indisputable, and a real need exists for a holistic overview that addresses trends without being limited to the narrow focus of a systematic review. ICARE seeks to provide such a broad, multidisciplinary review of clinically relevant research articles that serves as an accessible guide and reference for clinicians and scientists to be aware of the latest and most impactful updates. For 2021, ICARE fully summarized 44 articles in seven different categories. The top-scoring articles were focused on the implementation and incorporation of technology, education, and quality improvement to influence outcomes following cardiac arrest.

7. Declarations

7.1. Acknowledgments

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7.2. Authors' contributions

The project was conceptualized by TKB. Data was collected by the ICARE group. Data analysis was performed by CWH, TWM, and FH. The primary authorship of the manuscript was by CWH and TWM. All authors participated in reviewing and editing of the paper. **CWH and TWM contributed equally and both place as the first author in this paper.**

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7.4. Conflict of interest

The authors do not have any conflicts of interest to report.

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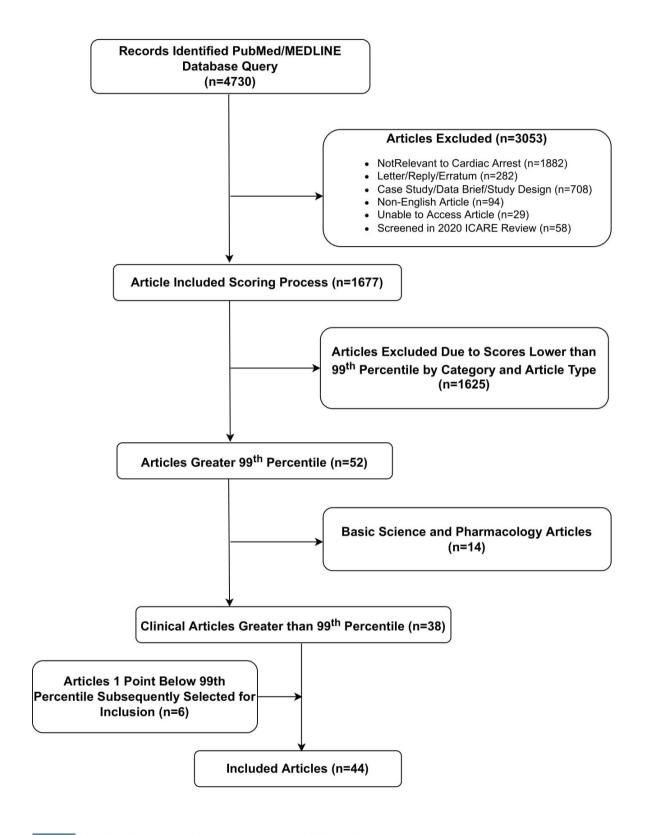


Figure 1 Flowchart demonstrating the screening, scoring, and full article review process

First author, Journal	Title	Туре	e Summary
Prehospital resuscita	tion, technology and care processes		
	Analyzing the heart rhythm during chest compressions: performance and clinical value of a new AED algorithm	OR	A novel AED algorithm ("cprINSIGHT") demonstrated greater chest compression fractions and shorter delay in identifying out-of-hospital cardiac arrest (OHCA) patients' heart rhythms with a similar sensitivity and specificity as the traditional AED algorithm.
Ng Q, J Clin Med	A systematic review and meta-analysis of the implementation of high-performance car- diopulmonary resuscitation on out-of-hospital cardiac arrest outcomes	RE	This seven-study meta-analysis found that the application of high-performance CPR (HP CPR) increases the probability of return of spontaneous circulation (ROSC) survival to hospital discharge, and favorable neurologica status at discharge in patients with out-of-hospital cardiac arrest (OHCA).
	Intraosseous versus intravenous vascular access during cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a systematic review and meta-analysis of observational studies	RE	This nine-study meta-analysis found that there was no significant difference in the discharge neurologic statu-or survival of patients with out-of-hospital cardiac arres (OHCA) associated with the vascular access, either intra venous (IV) or intraosseous (IO), placed during cardiopul monary resuscitation (CPR).
Dundar ZD, Prehosp Disaster Med	Bag-Valve-Mask versus Laryngeal Mask Airway Ventilation in Cardiopulmonary Resuscitation with Continuous Compressions: A Simulation Study	OR	
Alshahrani M, Int J Emerg Med	Use of sodium bicarbonate in out-of-hospital cardiac arrest: a systematic review and meta-analysis	RE	This meta-analysis compared studies testing the benefits of using sodium bicarbonate during adult cardiac life support (ACLS). Based on the studies reviewed, there is no benefit to using sodium bicarbonate for out-of-hospital cardiac arrest (OHCA) patients.
Nas J, Resuscitation	Coronary angiography findings in patients with shock-resistant ventricular fibrillation cardiac arrest	OR	For out-of-hospital cardiac arrest patients with ventric ular fibrillation, there are more acute coronary occlu sions and an overall worse outcome when the patient ha shock-resistant ventricular fibrillation versus those tha were not shock-resistant.
Azeli Y, Crit Care	Clinical outcomes and safety of passive leg raising in out-of-hospital cardiac arrest: a randomized controlled trial	OR	In this randomized controlled trial evaluating resuscitation in the passive leg raise (PLR) position versus the flat position, no improved survival-to-hospital discharge was seen; no evidence of adverse events was found.
Nehme Z, Resuscitation	Effect of a resuscitation quality improvement programme on outcomes from out-of-hospital cardiac arrest	OR	This time-series analysis found improved patient out comes following out-of-hospital cardiac arrest (OHCA) of medical etiology after a state-wide implementation of resuscitation quality improvement program.
Emerg Med	How effective is extracorporeal cardiopul- monary resuscitation (ECPR) for out-of- hospital cardiac arrest? A systematic review and meta-analysis	RE	Extracorporeal cardiopulmonary resuscitation (ECPR) is a promising intervention for out-of-hospital cardiac arrest (OHCA). This meta-analysis found increased rates of survival to discharge and favorable neurologic outcomes fo OHCA patients treated with ECPR compared to traditional CPR.
	tion and post-arrest care processes		
tation	Women receive less targeted temperature management than men following out-of-hospital cardiac arrest due to early care limitations – A study from the CARES Investigators		A correlation has shown that women are less likely to receive targeted temperature management (TTM) compared to men due to limitations earlier in their care and a prevalence of non-shockable rhythms.
Levito MN, Resuscitation	Impact of benzodiazepines on time to awakening in post cardiac arrest patients	OR	Post cardiac arrest, comatose patients who received high dose benzodiazepines exhibited a delay in awakening.
Desch S, N Engl J Med	Angiography after Out-of-Hospital Cardiac Arrest without ST-Segment Elevation	OR	Based on study results there were no significant benefits to performing an angiography earlier in care for patients with resuscitated out-of-hospital cardiac arrest (OHCA without ST-segment elevation.
Baldi E, JAMA Netw Open	Association of Timing of Electrocardiogram Acquisition After Return of Spontaneous Circulation With Coronary Angiography Findings in Patients With Out-of-Hospital Cardiac Arrest	OR	Early acquisition of electrocardiogram (EKG) after return of spontaneous circulation (ROSC) from out-of-hospita cardiac arrest (OHCA) is associated with a higher false positive rate than if obtained greater than 8 minutes after ROSC.

First author, Journal		Type	Summary
	tion, technology and care processes		
Fuest K, Resuscitation	Comparison of volume-controlled, pressure- controlled, and chest compression-induced ventilation during cardiopulmonary resuscita- tion with an automated mechanical chest com- pression device: A randomized clinical pilot study	OR	In patients who are undergoing cardiopulmonary resuscitation, biphasic positive airway pressure (BPAP) deliver larger tidal volumes, but all examined modes gave ade quate minute ventilation.
Nikolaou NI, Resus- citation		RE	After formal systematic review and meta-analysis, the data does not support routine early coronary angiograph in adult patients who survive out of hospital cardiac arrest (OHCA).
Kuroki N, Resuscita- tion	Combined use of venoarterial extracorporeal membrane oxygenation and intra-aortic bal- loon pump after cardiac arrest	OR	The addition of an intra-aortic balloon pump to veno arterial extracorporeal membrane oxygenation in post arrest survivors is associated with better neurological out comes, as compared to the use of veno-arterial extracorporeal membrane oxygenation alone.
Harhash AA, J Am Coll Cardiol	Risk Stratification Among Survivors of Cardiac Arrest Considered for Coronary Angiography	OR	The presence of six or more risk factors in cardiac arressurvivors was associated with ≤10% survival to discharge Simultaneous presentation with the three strongest risl factors (>85 years, time-to-ROSC >30 min, and non shockable rhythm) predicted similarly poor outcomes.
Chan JL, J Am Heart Assoc	Association Between Hospital Resuscitation Champion and Survival for In-Hospital Cardiac Arrest	OR	Hospitals with active physician resuscitation champion were 4 times more likely to achieve better survival o cardiac arrest patients compared to hospitals with non physician champions or no champions.
Yeo JW, J Am Heart Assoc	Impact of Cardiac Arrest Centers on the Survival of Patients With Nontraumatic Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis	RE	Hospitals with Cardiac Arrest Centers (CACs) achieved better survival to discharge and survival to 30 days with favorable neurological outcomes for patients experiencing out-of-hospital cardiac arrest (OHCA) as compared to hospitals without CACs.
-	Clinical benefits of corticosteroid administra- tion during adult cardiopulmonary resuscita- tion: A systemic review and meta-analysis	RE	Administration of corticosteroids during resuscitation fol lowing a cardiac arrest resulted in improved likelihood of sustained return of spontaneous circulation (ROSC), fa vorable neurological outcomes, and survival to discharge
Harhash AA, Resuscitation	Incidence of cardiac interventions and associated cardiac arrest outcomes in patients with non-shockable initial rhythms and no ST elevation post resuscitation	OR	Out-of-hospital cardiac arrest (OHCA) survivors with non shockable rhythms and no ST-elevation have a poor prog nosis and are often not managed with coronary angiography. This study demonstrates a significant association olikely culprit coronary lesions at post-resuscitation coronary angiography within this population.
susc Plus	The use of a cognitive aid app supports guideline-conforming cardiopulmonary resuscitations: A randomized study in a high-fidelity simulation		Cognitive aids supplement the learning and performance in high-crisis events that require significant timing and coordination. This study demonstrates how these tool decrease mental and physical demand to achieve the same quality performance of guideline-conforming cardiopulmonary resuscitation.
tation	Quality of targeted temperature management and outcome of out-of-hospital cardiac arrest patients: A post hoc analysis of the TTH48 study		get temperature management (TTM) as a means of neuroprotection after reperfusion in out-of-hospital cardia arrest (OHCA) patients. This study demonstrates that the quality of TTM was not associated with patients' outcomor with the duration of TTM.
Emerg Med	Innovation In Resuscitation: A Novel Clinical Decision Display System For Advanced Cardiac Life Support		arrest resuscitation improved adherence to ACLS guide lines and achieved provider satisfaction.
Med	gency department and outcomes in out-of-hospital cardiac arrest		Longer emergency department lengths of stay after successful cardiac arrest resuscitation are associated with worse neurologic outcomes.
Podsiadło P, Resuscitation	Impact Of Rescue Collapse On Mortality Rate In Severe Accidental Hypothermia: A Matched- Pair Analysis	OR	Cardiac arrest occurring during resuscitation of sever accidental hypothermia significantly increases mortality rate.

First author, Journal	Title	Туре	Summary
Prehospital resuscita	tion, technology and care processes		
Goharani R, ESC Heart Fail	Survival To Intensive Care Unit Discharge Among In-Hospital Cardiac Arrest Patients By Applying Audiovisual Feedback Device	OR	Use of a chest compression audiovisual feedback device was associated with improved rates of survival.
Prognostication and	outcomes		
Lee H, Int J Environ Res Public Health	Association between Body Mass Index and Outcomes in Patients with Return of Spontaneous Circulation after Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis	RE	Body mass index (BMI) is a known factor that can af fect morbidity and mortality after an out-of-hospital car diac arrest (OHCA) with return of spontaneous circulation (ROSC). This meta-analysis concluded that underweigh patients had worse neurological outcomes, and both un derweight and obese patients had lower survival rates in patients with ROSC after OHCA.
Carrai R, Clinical Neurophysiology	Are neurophysiologic tests reliable, ultra-early prognostic indices after cardiac arrest?	OR	Electroencephalography (EEG) and somatosensory evoked potentials (SSEP) have the potential to be useful predictors of good outcome following cardiac arrest when obtained in the first 6 hours following cardiac arrest.
Pediatrics			
tion	Sodium bicarbonate administration during in- hospital pediatric cardiac arrest: a systematic review and meta-analysis		Routine sodium bicarbonate (SB) use during pediatric resuscitation has diminished over time following the 2010 change in American Heart Association (AHA) guidelines however, significant clinical usage persists. This review bolsters support for the AHA recommendation to avoid routine use of SB administration in pediatric cardiac arrest, yet leaves undefined the clinical situations in which it may still be beneficial.
Le Bastard Q, Resuscitation	Endotracheal intubation versus supraglottic procedure in paediatric out-of-hospital cardiac arrest: a registry-based study	OR	A large prospective cohort study examined two airway management strategies during pediatric out-of-hospita cardiac arrest (OHCA) and found that 30-day surviva rates and good neurologic outcome were better in those patients undergoing a supraglottic procedure rather than endotracheal intubation.
Topjian AA, Resuscitation	P-COSCA (Pediatric Core Outcome Set for Car- diac Arrest) in children: an advisory statement from the International Liaison Committee on Resuscitation	RE	The P-COSCA is an initiative designed to standardize pre- arrest baseline and post-arrest assessment of outcomes in pediatric survivors of cardiac arrest.
tation	Pulmonary hypertension among children with in-hospital cardiac arrest: a multicenter study		Children who had an active diagnosis of pulmonary hy pertension prior to an in-hospital cardiac arrest had de creased rates of survival to discharge compared to chil dren who did not have documented pulmonary hyperten sion prior to an in-hospital cardiac arrest.
Netw Open	Effect of a mobile app on prehospital medication errors during simulated pediatric resuscitation: a randomized clinical trial	OR	Use of a mobile application during simulated medication preparation and administration to a toddler under going resuscitation resulted in significantly reduced rate of medication errors and reduced the time to administration of the drug to the patient.
Epidemiology and pu			
	Public health impact of daily life triggers of sud- den cardiac death: A systematic review and comparative risk assessment	RE	The most important daily life triggers of sudden cardiac death are episodic alcohol consumption, physical exer- tion, consumption of cocaine, and consumption of coffee
Jones KA, AEM Educ	Train Using natural language processing to compare task-specific verbal cues in coached versus noncoached cardiac arrest teams during simulated pediatrics resuscitation	OR	Natural language processing verbal cues by coached car- diac teams experienced significantly fewer total questions asked and had greater amounts of positive and directiona utterances for rate and depth of CPR during simulated pe- diatric cardiac arrest.

First author, Journal	Title	Туре	Summary
Interdisciplinary guid	delines and review		
Olasveengen TM, Resuscitation	European Resuscitation Council Guidelines 2021: Basic Life Support. Resuscitation	RE	The 2021 update to the European Resuscitation Council Guidelines on Basic Life Support, based on the International Liaison Committee on Resuscitation (ILCOR) 2020 recommendations, recommend initiation of cardiopulmonary resuscitation (CPR) for all individuals unresponsive and with absent or abnormal breathing. The benefits of early CPR as well as automated external defibrillator use by laypersons outweighs the risk of harm to individuals receiving CPR.
Wyckoff MH, Circula- tion	2021 International Consensus on Cardiopul- monary Resuscitation and Emergency Cardio- vascular Care Science With Treatment Recom- mendations	RE	This summary of the International Liaison Committee on Resuscitation (ILCOR) International Consensus or Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) addresses fourteen key topics pertaining to cardiopulmonary resuscitation (CPR) via systemic review, highlighting key recommendations pertaining to basic and advanced life support, pediatric and neonatal life support, education and implementation, and firs aid, with additional focus on areas for future research.
	The Effect of Therapeutic Hypothermia after Cardiac Arrest on the Neurological Outcome and Survival—A Systematic Review of RCTs Published between 2016 and 2020	RE	Therapeutic hypothermia is used after cardiopulmonary arrest, though its effectiveness remains controversial This article did systematic review of the literature, finding that although it is safe, it has not improved survivarates or neurological status.
Wyckoff ML, Resuscitation	2021 International Consensus on Cardiopul- monary Resuscitation and Emergency Cardio- vascular Care Science With Treatment Recom- mendations	RE	In its 5th annual summary of cardiopulmonary resuscitation and emergency cardiovascular science, the International Liaison Committee on Resuscitation (ILCOR) assesses the most recent systematic reviews on numerous domains within resuscitation care—including basic life support, advanced life support, and pediatric and neonatal life support— with treatment recommendations and areas of knowledge gaps for further research also highlighted.
Perkins G, Resuscitation	European Resuscitation Council Guidelines 2021: Executive summary	RE	This executive summary from the European Resuscitation Council highlights the most recent and practical guidelines for resuscitation protocols in Europe. By employing both systematic and scoping reviews, these guidelines encompass recommendations across numerous domains pertaining to cardiopulmonary resuscitation (CPR) including epidemiology, systems care, basic and advanced life support, post-resuscitation care neonatal and pediatric life support, and education.
	European Resuscitation Council Guidelines 2021: Education for resuscitation		The 2021 education guidelines from the European Resuscitation Council provide general guidance to both laypersons and healthcare professionals about improving the survival of patients after cardiac arrest. Educational initiatives should be tailored toward the target audience and should emphasize the components of high-quality resuscitation.
tation	European Resuscitation Council Guidelines 2021: Systems saving lives	RE	The Systems Saving Lives chapter of the European Resuscitation Council guidelines describes several multidisciplinary factors that can improve cardiac arrest management and outcomes, emphasizing the roles of individuals and groups across the chain of survival.
Cekmen B, Am J Emerg Med	Chest compression quality during CPR of potential contagious patients wearing personal protection equipment	OR	Changing the rescuer performing cardiopulmonary resuscitation (CPR) compressions while wearing an N95 mask every 1 minute instead of the standard 2 minutes prevents variations in the quality of CPR compressions with time.