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Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Evidence-Based Approach to Out-of-Hospital Cardiac Arrest

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Abbreviations *OHCA* out-of-hospital cardiac arrest · *CCL* cardiac cath lab · *PEA* pulseless electrical activity · *CAHP* cardiac arrest hospital prognosis · *ROSC* return of spontaneous circulation · *ECLS* extracorporeal life support · *AMI* acute myocardial infarction

Abstract

Purpose of review Out-of-hospital cardiac arrest (OHCA) is a leading cause of death. Despite improvements in the cardiac disease management, OHCA outcomes remain poor. The purpose of this review is to provide information on the management of OHCA survivors, evidence-based treatments, and current gaps in the knowledge.
Recent findings Most common cause of death from OHCA is neurological injury followed by shock and multiorgan failure. Prognostication tools are available to help with the clinical decision-making. Taking measures to improve EMS response time, encouraging bystander CPR, early defibrillation, and targeted temperature management are shown to improve survival. Early activation of cardiac catheterization lab for coronary angiography, hemodynamic assessment, and mechanical circulatory support should be considered in patients with shockable rhythm and presumed cardiac cause, those with ST elevation, ongoing ischemia, or evidence of hemodynamic and electrical instability. Randomized controlled trials are lacking in this field and benefits of interventions should be weighed against risk of pursuing a futile treatment. COVID-19 pandemic has added new challenges to the care of OHCA patients.

Summary Clinical decision-making to care for OHCA patients is challenging. There is a need for trials to provide evidence-based knowledge on the care of OHCA patients.

Introduction

Sudden cardiac arrest is a leading cause of death. Out-of-hospital cardiac arrest (OHCA) accounts for about 350,000 annual adults deaths in the USA [1–5]. Despite improvements in survival after OHCA, rate of survival to hospital discharge and survival with good neurological outcome remains less than 10% with significant variations in OHCA survival to discharge (3.4–22%) and survival with functional recovery (0.8–21%) across the US [2].

The goal of pre-hospital care for OHCA using what is referred to as the "chain of survival" concept is to improve the outcomes [6]. Encouraging and training bystander cardiopulmonary resuscitation (CPR), using automated external defibrillator (AED), high-quality CPR, and targeted temperature management (TTM) have been attributed to the improvements seen in OHCA survival [7, 8]. Notably, there are sex disparities in the OHCA outcomes. In a population-based study from Korea, survival rate and neurological recovery from cardiac arrest improved in both men and women from 2008 to 2015; however, the degree of improvement was lower in women [9].

Cause of death in two-thirds of patients hospitalized because of OHCA is neurological injury, while the rest of mortality is attributed to the shock and multiorgan failure [10, 11]. Withdrawal of life-sustaining treatment is the most common cause of in-hospital death for the survivors of cardiac arrest [4]. Cerebral Performance Category (CPC) scale is used to define neurological status of OHCA patients as following: level 1: good recovery; level 2: moderate disability; level 3: severe disability; level 4: vegetative state; and level 5: death. CPC levels 1 and 2 are considered the favorable neurological outcomes in the cardiac arrest studies [12].

Assessment and Risk Stratification

Accurate prognostication of OHCA survivors is important in order to inform family members, avoid futile treatments, and also avoid premature withdrawal of the care in those who may have a chance of meaningful recovery. Additionally, the prognostication tools are used to identify populations for research [4]. Multiple factors have been reported to be associated with poor outcome of OHCA patients. These include old age, unwitnessed cardiac arrest, lack of bystander CPR, achievement of return of spontaneous circulation (ROSC) after 30 min of CPR, initial non-shockable rhythm, elevated lactate level, and low pH (< 7.2) [13•]. The 3 most commonly used predictors of outcome are initial cardiac rhythm, age, and CPR duration [14]. Some of the predictive models used in clinical practice are discussed below.

OHCA score is a continuous score and was created based on a single-center study. Outcome predictors used in this study were shockable rhythm, duration of no-flow time (time from collapse to start of CPR), duration of low-flow time (time from CPR to ROSC), and admission levels of serum creatinine and lactate.

Areas under the receiver operating characteristics curve (AUC) used in the development and validation cohorts were 0.82 and 0.88, respectively [15].

Cardiac Arrest Hospital Prognosis (CAHP) score includes seven variables of age, non-shockable rhythm, no-flow time, low-flow time, location of cardiac arrest, the amount of epinephrine used during CPR, and pH. CAHP score identifies three groups based on their risk of poor neurological outcome: low risk (40% risk of unfavorable outcome), medium risk (80% risk of unfavorable outcome), and high risk (95–100% risk of unfavorable outcome). This score has *C*-statistics of 0.93 in the development cohort and 0.91 in the validation cohort [16].

Target Temperature Management score stratifies patients based on outcomes at 6 months. Ten predictors of poor neurological outcome (CPC 3–5) are old age, arrest at home, non-shockable rhythm, longer duration of no-flow and low-flow, higher amount of epinephrine use, bilateral absence of corneal and pupillary reflexes, Glasgow Coma Scale (GCS) motor response of 1, pH, and PaCO2. The median AUC was 0.84 [17].

Most recently, $MIRACLE_2$ score was created based on a single-center study of 373 patients. Predictors of poor outcome (CPC 3–5) at 6 months were unwitnessed arrest, non-shockable rhythm, non-reactivity of pupils, age, changing intra-arrest rhythm, low pH (<7.2), and higher amount of epinephrine administration. The AUC was 0.9 in the development and 0.84/0.91 in the validation cohorts [18].

Risk assessment tools have several limitations. For example, estimates of no-flow and low-flow times are known to be inaccurate [15]. American Heart Association (AHA) reports that the overall quality of prognostication studies and degree of confidence in predictors are low, and therefore, it has called for improvements in these studies [4]. Initial evaluation of patients with OHCA includes focused history and physical examination, and diagnostic tests such as brain imaging which helps to both diagnose the cause of cardiac arrest and also for prognostication.

Considering heterogeneity of patients with OHCA and their dynamic clinical course, excessive reliance on a risk assessment tool may lead to inaccurate neurological prognostication. Society for Cardiovascular Angiography and Intervention (SCAI) expert consensus statement [13•] recommends against decision-making based on only one indicator and instead suggesting to implement a dynamic decision-making strategy based on "situational awareness and assessment" of all relevant clinical factors observed at any encounter during the care of comatose OHCA patients.

Activation of Cardiac Catheterization Lab

Coronary artery disease is the most common cause of OHCA [19]; therefore, patients who have retained consciousness after successful resuscitation are treated similar to patients with acute coronary syndrome [20]. Based on 2015 AHA guidelines [21], coronary angiography (CAG) is recommended in selected OHCA patients with suspected cardiac origin and ST elevation on ECG (class I, LOE B-NR). However, the decision to perform early CAG in OHCA comatose patients with ST elevation should be based not only on the post-ROSC ECG findings but also on overall clinical findings and presentation [13•], including evaluation of their neurological prognosis [16].

In the absence of ST elevation on ECG, noninvasive tests are not sensitive enough in assessing ongoing ischemia in the OHCA comatose patients [12]. An observational study showed a reduction of about 25% in left ventricular systolic function revealed by performing echocardiogram within 72 h of inpatient cardiac arrest [22]. However, it is not clear whether post-ROSC left ventricular systolic dysfunction detected by echocardiogram has a prognostic impact and whether it indicates ongoing ischemia. Given limitations of noninvasive testing in this setting, decision-making in these patients regarding CAG and its timing can be challenging.

SCAI expert consensus statement prefers use of "activation of cardiac catherization lab" terminology, instead of CAG and percutaneous coronary intervention (PCI), because it would also entail the potentially required hemodynamic assessment and use of mechanical circulatory support. Additionally, a "Definite or Defer" approach of cardiac catheterization lab activation is recommended at the initial and any subsequent stage of post-cardiac arrest care (Fig. 1) [13•].

The association between early CAG and survival to hospital discharge was assessed in an observational study, using CAHP score [16]. In this study, patients with low-risk CAHP score (score < 150) were more likely to undergo early CAG compared with medium-risk (score 150–200) and high-risk (score > 200) groups (86%, 66%, and 47%, respectively). This reflects selection bias in the observational studies. Additionally, early CAG strategy was independently associated with better survival only in the low-risk group (odds ratio: 2.3). Overall, 41% of this study's patients had ST elevation MI (STEMI) and survival to hospital discharge in these patients was better than those without STEMI (44% versus 27%, $p < 0.001$). Based on these findings, one can argue that an early CAG strategy should be considered for eligible patients with presumed cardiac cause and low-risk CAHP score, even in the absence of STEMI.

The decision to perform early CAG in post-OHCA patients with suspected cardiac origin (initial shockable rhythm) and no evidence of STEMI is more complex. The reported prevalence of culprit lesions in this population is variable. Based on one report, about 33% of the patients who underwent CAG had a culprit lesion and occluded vessel was found in about 23% of patients [23]. Previous meta-analysis studies [24, 25] have suggested improved survival using early CAG; however, observational studies are limited due to selection bias. There are several ongoing randomized trials comparing immediate versus delayed CAG in OHCA patients without STEMI [13•, 26•]. COACT trial is one of those published randomized studies [27••].

COACT trial [27••] investigated the impact of immediate versus delayed CAG and PCI in 522 OHCA patients without ST elevation on post-ROSC ECG. This study excluded some patients, for example, those with shock. The primary outcome of 90-day survival was not significantly different between the two groups (64.5% in immediate and 67.2% in the delayed CAG group; $p = 0.51$). An acute unstable lesion was reported in 13.6% of immediate group and 16.9% of delayed group. Acute thrombotic occlusion was seen in 3.4% and 7.6% of immediate and

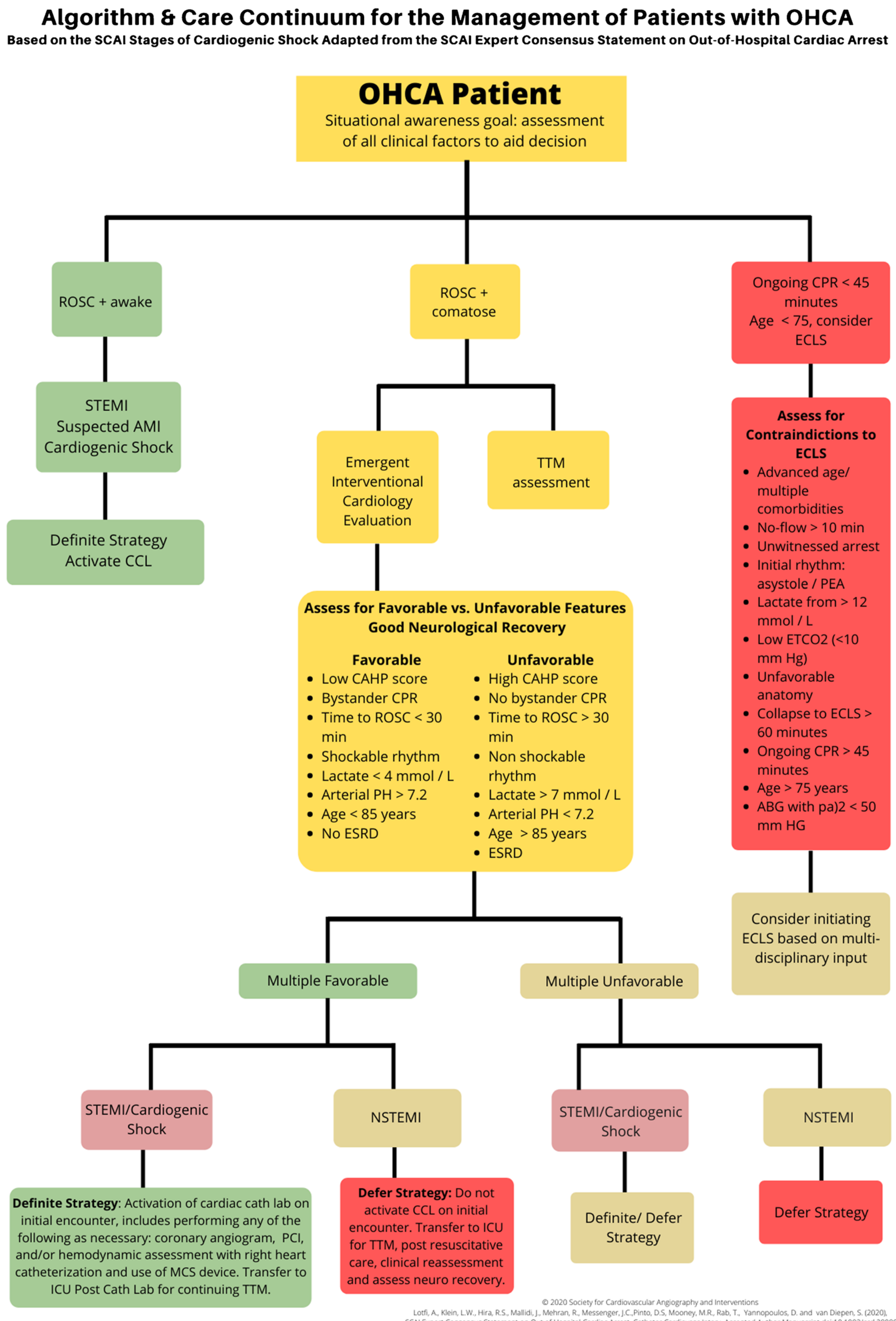

Fig. 1. Algorithm of clinical factors available to aid in decision-making along the continuum of care of patients with out-of-hospital cardiac arrest. Obtained with permission from publisher of *Catheterization and Cardiovascular Interventions* [13•].

delayed groups, respectively. PCI was performed in 33.0% versus 24.2%, and CABG was performed in 6.2% versus 8.7% of the immediate and delayed groups, respectively.

In COACT trial, there was also no difference in the secondary outcomes including survival with good cerebral function, recurrence of ventricular tachycardia requiring defibrillation, markers of shock, duration of mechanical ventilation or inotropic support, and TTM. However, immediate strategy affected some aspects of the care including later target temperature achievement, less use of oral antiplatelets, and more use of glycoprotein IIb/IIIa inhibitors compared with the delayed CAG group [27••]. One-year follow-up of COACT trial showed similar results with no significant difference in survival between the immediate group (61.4%) and delayed group (64.0%) [28•].

A recent systematic review and meta-analysis [26•] of 11 studies, including 3581 OHCA patients without ST elevation, had findings similar to COACT trial. This study found no significant difference in 30-day mortality, neurological outcome, or rate of PCI, in those received early versus delayed CAG. The definition of early CAG varied among studies and ranged from less than 2 h (immediate) to within 24 h or while the patient was still comatose. Overall, 42% had early CAG, 58% had delayed CAG, and 24% of patients underwent PCI.

Studies have shown that patients with non-shockable initial rhythm have worse prognosis than those with a shockable rhythm [5, 29]. Patients with initial non-shockable rhythm and subsequent conversion to shockable rhythm have lower survival compared with those with initial shockable rhythm [30], although those showing conversion to shockable rhythm and cardiac arrest due to cardiac causes may have a better prognosis [31].

In addition to investigating the cause of cardiac arrest, post-cardiac arrest care includes measures to reduce brain injury and to optimize cardiac function, among other supportive cares. Post-cardiac arrest shock has been reported in 68% of OHCA patients and is the cause of mortality in about a third of them while in the intensive care unit [11]. Treatment of cardiogenic shock (CS) post-OHCA is challenging and limited studies are available. Early PCI of culprit lesion in the setting of acute myocardial infarction (AMI) and CS has shown to improve the outcomes [32•] and patients with CS are more likely to have multivessel coronary artery disease [33].

There are no studies to compare single-vessel versus multivessel PCI for treatment of post-OHCA patients with CS. CULPRIT-SHOCK trial assessed the effect of culprit-only PCI versus immediate multivessel PCI on the outcomes of 706 patients with multivessel disease, AMI, and CS [32•]. At 1 month, there was no difference in the composite primary outcome of death or renal replacement therapy (45.9% in culprit-only group and 55.4% in multivessel group, relative risk: 0.83; 95% confidence interval [CI], 0.71 to 0.96; $p = 0.01$) and 30-day mortality from any cause was lower in the culprit-only group. In this study, approximately 62% of patients had STEMI and 28% required mechanical circulatory support [32•]. Furthermore, at 1-year follow-up, there was no significant difference in mortality between the culprit-only and multivessel PCI groups (50.0% in culprit-only group and 56.9% in multivessel group, relative risk: 0.88; 95% CI: 0.76 to 1.01) [33]. Based on the findings of this study, culprit-vessel PCI in patients with CS and AMI should be the default strategy. It is noteworthy that about 53% of patients randomized in the CULPRIT-SHOCK trial [32•] had resuscitation before randomization and about one third of the patients received mild hypothermia.

Mechanical Circulatory Support

There are no large randomized controlled trials investigating outcomes of mechanical circulatory support in OHCA patients. Intraaortic balloon pump (IABP), Impella (Abiomed, Danvers, MA), and extracorporeal membrane oxygenation (ECMO) have been used for management of CS. Table 1 summarizes data on use of IABP and Impella in IABP-SHOCK II trial [34] and IMPRESS in Severe Shock trial [35]. In observational studies, the use of ECMO in dedicated centers has been reported to improve survival of cardiac arrest patients. It can be used as part of extracorporeal CPR (ECPR) for refractory CPR or for profound CS post CPR (ECS) [36–38]. Main objectives of ECPR are to optimize organ perfusion and provide neuroprotection, although achievement of ROSC and defibrillation would also be more successful after adequate coronary perfusion has been established [39].

Suitable candidates for ECPR may be patients without major prior comorbidities, less than 5 min no-flow time, end-tidal CO_2 of >10 mmhg, and refractory shockable rhythm. ECPR is time-critical and recommended to be initiated within 60 min of cardiac arrest. Since longer duration of conventional CPR is associated with worse prognosis, therefore, it may only be practical in dedicated centers. International consensus guidelines recommend ECPR

Table 1. Mechanical circulatory support in cardiogenic shock

	Methods	Outcome	Results
IABP-SHOCK II [34]	600 patients Randomized, multicenter CS and AMI IABP vs. no IABP CPR before randomization: 42.2% (IABP) and 47.8% (control) Left ventricular ejection fraction: 35% Early revascularization with primary PCI: 95.8%	Primary: 30-day all-cause mortality Secondary: Reinfarction, stent thrombosis, stroke, bleeding, peripheral complications, sepsis	Primary: IABP group: 39.7% Control group: 41.3% RR: 0.96; 95% CI: 0.79 to 1.17; p=0.69 No difference is secondary outcomes
IMPRESS in Severe Shock [35]	48 patients Randomized, multicenter Severe CS and AMI Impella CP vs. IABP CPR before randomization: 100% (Impella) and 83% (IABP) Therapeutic hypothermia: 75% Left ventricular ejection fraction <40%: 68% (Impella) and 77% (IABP) PCI: 98%	Primary: 30-day all-cause mortality Secondary: 6-month mortality	Primary: IABP: 50% Impella CP: 46% Hazard ratio: 0.96; 95% CI: 0.42 to 2.18; p=0.92 Secondary: 50% mortality in both groups

IABP, intraaortic balloon pump; *CS*, cardiogenic shock; *AMI*, acute myocardial infarction; *PCI*, percutaneous coronary interventions; *RR*, relative risk; *CI*, confidence interval cannulation within 20 min of arrest for eligible patients. To maintain high-quality CPR, use of an automated mechanical chest compression has been recommended [39]. There are ongoing studies to assess the effect of ECPR in cardiac arrest [13•]. Based on 2019 AHA focused update, there is insufficient evidence to recommend routine use of ECPR. In selected patients, ECPR can be considered a rescue therapy, if it can be implemented expeditiously and managed by skilled providers (class 2b, LOE C-limited data) [40].

Targeted Temperature Management

Most common cause of death following OHCA is neurological injury [10]. Hypothermia and prevention of hyperthermia have been shown to improve post-cardiac arrest survival and neurological outcome [41, 42]. In a trial of 939 post-OHCA unconscious patients (GCS 3) with presumed cardiac cause, effects of targeted temperatures of 33 °C and 36 °C were compared. Additionally, active prevention of post-cardiac arrest fever was implemented in all patients for 3 days. Investigators found no difference between the groups in overall mortality at the end of trial, or combined outcome of death and poor neurological function at 180 days. In this study, a shockable rhythm was present in about 80%, STEMI was present in about 40%, and CS was present in about 15% of patients [43]. Another study investigated long-term cognitive function and quality of life in OHCA patients who received TTM at 33 °C versus 36 °C. This study showed no significant difference between the two groups [44]. Based on a systematic review and meta-analysis of 6 RCTs, there is an overall 30% survival benefit when applying hypothermia [45].

The 2015 International Consensus guidelines [21] recommend TTM of 32 to 36 °C for OHCA patients presenting with initial shockable rhythm (strong recommendation, low quality evidence), and non-shockable rhythm (weak recommendation, very low-quality evidence) cases who remain unresponsive after ROSC. Primary outcome of survival with favorable neurological outcome at 90 days was higher in OHCA patients with non-shockable rhythm when treated with TTM compared with no TTM [46]. Pre-hospital cooling by infusing up to 2 l of 4 °C normal saline has not been shown to improve survival to hospital discharge, or neurologic outcomes. Instead, pre-hospital cooling was associated with higher risk of re-arrest in the field, increased chance of pulmonary edema, and used of more diuretics [47].

Community Response

Highest survival of OHCA patients with shockable rhythm is when bystander starts CPR and attempts defibrillation within 3–5 min of collapse. Indeed, the significant variability in survival of OHCA has been mostly attributed to differences in bystander response [2]. However, the rate of bystander defibrillation remains low [1, 48]. In a prospective multicenter cohort study of 56,765 OHCA cases in the Asia-Pacific, modifiable factors that were associated with improved OHCA survival were bystander CPR, out-of-hospital defibrillation, and response time less than or equal to 8 min [49]. Citizen responder system as a supplement to the emergency medical services (EMS) has been organized in some societies to improve use of public access AEDs, including in residential areas. An RCT has been initiated to study the effects of citizen responder system in Denmark [48, 50]. In Singapore, there is a centralized protocol for dispatch-assisted CPR, CPR training programs, and a first-responder mobile application [8]. These public health interventions have shown to improve bystander CPR rate and survival to hospital discharge.

New technological initiatives, such as use of smartphone application to increase bystander CPR, have been implemented with some success [51]. In a prospective observational study in the Capital Region of Denmark, activation of voluntary citizen responders through smartphone application had promising results. The primary outcome of this study was the rate of bystander CPR and defibrillation. Out of 819 suspected cases, 53.5% had confirmed cardiac arrest, one citizen responder arrived before EMS in 42% of cases, and this increased the odds for bystander CPR to 1.7 and for bystander defibrillation to 3.7, respectively [48].

Pre-hospital Use of Mobile Application

Managing patients with OHCA is highly time sensitive to ensure rapid assessment and appropriate care. We use General Devices e-Bridge mobile telemedicine application (https://general-devices.com/innovations/mobiletelemedicine/) for early triage of OHCA patients brought to the Emergency Department (ED) of Baystate Medical Center in Springfield, MA. This application is compliant with the Health Insurance Portability and Accountability Act and allows EMS to provide ED with the patient characteristics, direct communication, ECGs, pictures, video,

Table 2. Mobile e-Bridge OHCA application

Variables			
Witnessed arrest	Yes	No	Unknown
Shockable rhythm	Yes	No	Unknown
Location	Home	Public	
Bystander CPR	Yes	No	Unknown
Received shock	Yes	No	Unknown
Epinephrine dose (mg)	0	1–2	3+
Patient intubated	Yes	No	
Pre-arrest ECG STEMI	Yes	No	Unknown
Post-arrest ECG STEMI	Yes	No	Unknown
History of CAD	Yes	No	Unknown
History of cardiomyopathy	Yes	No	Unknown
History of dementia	Yes	No	Unknown
Collapse to BLS	0–5 min	5–10 min	Other
BLS to ROSC	0–20 min	20–30 min	Other
Vital signs, blood glucose, ETCO2, GCS, heart rhythm			

CPR, cardiopulmonary resuscitation; *STEMI*, ST elevation myocardial infarction; *CAD*, coronary artery disease; *BLS*, basic life support; *ROSC*, return of spontaneous circulation; *ETCO2*, end-tidal CO2; *GCS*, Glasgow Coma Scale and live streaming information. Table 2 includes the data that are transferred by this mobile application. Based on these data, ED clinician can activate the appropriate resources prior to the patient arrival. Our goals are to implement this OHCA application and assess its efficacy in improving OHCA patients care.

OHCA and Coronavirus Pandemic

Global pandemic of highly transmissible coronavirus disease which started in 2019 (COVID-19) has added important challenges to rescuers providing CPR. Approximately 3 to 6% of COVID-19 patients become critically ill and are at risk of cardiac arrest [52]. Data from Italy showed 58% increase in OHCA in a 40-day period during the February and March 2020 compared with similar period in 2019. Additionally, EMS arrived 3 min later, bystander CPR was 15.6% lower, and out-of-hospital death in those received CPR by EMS was 14.9% higher in 2020 compared with 2019 [53] .

EMS staff work near each other and there is risk of lapses in infection control strategies while caring for critically ill patient. Additionally, the administration of CPR includes procedures such as chest compression, airway management, and ventilation which may be associated with aerosol generation, although an effect has not been demonstrated in the limited evidence available [54]. Covering patient's mouth and nose while performing defibrillation and chest compression may increase the safety [55]. AHA consensus report provides recommendations for CPR including considering resuscitation appropriateness, use of personal protection equipment, limiting personnel number, clear communication, using bag-mask device with filter and tight seal, using mechanical CPR device, and early intubation techniques with cuffed tube [52]. In a study from Washington State, COVID-19 was diagnosed in less than 10% of OHCA cases during January and April 2020 [56]. In the communities with low transmission rate of COVID-19, most of the cardiac arrest cases are likely not due to the coronavirus infection [55].

COVID-19 pandemic has clearly added more complexity to the "chain of survival" process. EMS rescuers, already critically needed due to the pandemic demand, are at risk of acquiring infection especially in the settings of shortage of personal protective equipment. EMS providers must be instructed about the community transmission rate and also be equipped with the appropriate equipment and training to reduce the risk of contracting infection. Balancing the risk of infection against appropriateness of CPR while caring for OHCA patients highlights some of the ethical dilemmas that medial staff are currently dealing with during the COVID era.

Predictors of Future Cardiac Arrest

There have been efforts to study the biomarkers related to the sudden cardiac death. In a study done by Everett et al. [57•], total to high-density lipoprotein cholesterol ratio, high-sensitivity troponin I, N-terminal pro-B-type natriuretic peptide, and high-sensitivity C-reactive protein had significant, independent, and additive association with the risk of sudden cardiac death. These associations were independent of the preexisting cardiovascular disease. According to the authors, these markers may be useful in identifying asymptomatic individuals at risk of sudden cardiac death. This is especially important given that majority of sudden cardiac deaths happen in individuals with no prior diagnosis of cardiovascular or structural heart disease. Moreover, based on these findings, lipid metabolism disorders, myocardial injury, myocardial strain, and vascular inflammation may be related to the underlying pathophysiological mechanisms of sudden cardiac death.

Conclusion

OHCA is associated with poor outcome in majority of patients. Based on the current evidence, effective strategies to improve outcome include chain of survival, bystander CPR, defibrillation, and TTM. Neurological prognostication of comatose patients remains challenging and requires further research. Additionally, evidence-based knowledge regarding the treatment of post-cardiac arrest shock, cardiac catheterization lab activation, and mechanical circulatory support is lacking. Currently, several ongoing trials on OHCA are in progress. An individualized decision-making, led by a multidisciplinary team and based on relevant clinical data, is required to provide the appropriate care for the OHCA patients.

Supplementary Information

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Compliance with Ethical Standards

Conflict of Interest
Mohammad Amin Kashef declares that he has no conflict of interest. Amir Lotfi declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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