

META-ANALYSIS



Gasping as a predictor of short- and long-term outcomes in patients with cardiac arrest: a systematic review and meta-analysis

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Abstract

Aims: Cardiac arrest (CA), a worldwide health problem in the public, has a high mortality rate. While gasping has been associated with increased survival and Return of Spontaneous Circulation (ROSC) after cardiac arrest in some studies, more data is needed.

Data sources: The literature on cardiac arrest and gasping from Medline, PubMed, Embase, Cochrane, and Web of Science up to September 2020 were searched, categorized, and analyzed. The association of CA and gasping outcomes were assessed by risk ratios (RR) and 95% confidence intervals (CI). Heterogeneity, sensitivity analysis, and publication bias was discussed.

Results: 8 studies from 7 articles were included. A fixed-effect or random-effect model was applied to all the outcomes using estimate pooled risk ratios (RR). Patients suffering gasping during CA were 2.08 times more likely to have return of spontaneous ROSC compared with patients without gasping (RR = 2.08, 95% CI: 1.93-2.25, $P < 0.001$). There was a significant increase in the survival to discharge rate of the patients who gasped (RR = 3.75, 95% CI = 3.27-4.29, $P < 0.001$); along with a more favorable neurological 1-year survival (RR = 8.02, 95% CI: 5.56, 11.57; $P < 0.001$) and the presence of a shockable cardiac rhythm (RR = 2.82, 95% CI: 2.50, 3.18; $P < 0.001$).

Conclusions: The presence of agonal respirations is positively associated with ROSC, achieving a shockable cardiac rhythm, increasing survival rate to discharge, and a neurologically favorable 1-year survival. Gasping may play an important role in cardiopulmonary resuscitation (CPR) training.

Keywords

Gasping; Agonal respiration; Cardiac arrest; Cardiopulmonary resuscitation (CPR)

1. Introduction

Cardiac arrest is a worldwide public health problem, and is also a leading cause of death. Over 800,000 Europeans and North Americans suffer an out-of-hospital cardiac arrest (OHCA) every year, which is associated with high mortality [1]. Although significant efforts have been made, the outcomes are still poor with an overall survival averaging only 7.6% for the last 30 years [2, 3]. Post-resuscitation cerebral and myocardial dysfunction are the main causes of death following OHCA [4].

While several factors had been proven to affect the short and long-term outcomes of OHCA, such as the initial rhythm and the interval time to defibrillation, there is a growing interest in spontaneous respiratory activity during cardiac arrest or resuscitation. This gasping phenomenon has been associated with a greater chance of achieving Return of Spontaneous Circulation (ROSC), thus increasing the survival rate to discharge following OHCA, and preserving cerebral function after cardiopulmonary resuscitation (CPR) [5, 6].

Various terms have been used to describe this spontaneous respiratory activity, such as agonal breathing, agonal respirations, and abnormal breathing. Gasping has been defined by the Glossary Committee of the International Union of Physiological Sciences in 1973 as an abrupt, sudden and transient inspiratory effort [7]. Gasping after the onset of cardiac arrest (CA) has been reported to be associated with improved survival in animal models of cardiac arrest in previous studies [8–13]. A possible mechanism for the improved survival rate may be related to increased cardiac output and cerebral perfusion [10, 14].

While the observational short-term outcomes of ROSC and survival to discharge had been well studied in patients with gasping following OHCA, long-term outcomes such as cerebral function is still limited [15]. More in-depth analysis is needed to demonstrate the association of gasping and improved outcomes in OHCA patients.

A better knowledge of gasping is critical for both clinical

care and out-of-hospital CPR since it provides a better understanding of the physiology of cardiac arrest. The aim of this study is to further clarify and update the association of gasping associated with short and long-term outcomes following OHCA.

2. Methods

2.1 Search strategy

The literature of cardiac arrest and gasping from PubMed, Embase, Medline, Cochrane, and Web of Science up to September 2020 were searched, categorized, and analyzed with the search terms “cardiac arrest”, “CPR”, “heart arrest”, “out-of-hospital”, and “gasping”, “agonal breathing”, “agonal respiration”, “abnormal breathing”. In this analysis, only articles published in English were included.

2.2 Selection criteria

The primary analysis of randomized trials or secondary analysis of observational cohort studies were eligible for inclusion by comparing clinical outcomes between patients with and without gasping during cardiac arrest. All the studies were selected by two independent reviewers based on the following criteria: (a) the subjects were human adults; (b) eligible clinical outcomes include ROSC, survival to discharge, survival to one-month, or Cerebral Performance Category (CPC) score; (c) sufficient published data for estimating the risk ratio (RR) with 95% CI. Studies were excluded if there was no sufficient data for pooling.

2.3 Quality assessment

The quality of a selected study was assessed by using a semi-quantification principle star system, consists of eight items in three forums including crowd selection, comparability, exposure assessment, and outcome evaluation utilizing the Newcastle-Ottawa scale [16].

2.4 Data extraction

Data was extracted by two independent reviewers from each eligible study. ROSC was the primary outcome variable, while survival to hospital discharge, survival to one-month, and one-year survival with Cerebral Performance Category (CPC) score ≤ 2 were the secondary outcome variables.

The study characteristics included the first author’s names, publication years, countries, type of recordings, study designs, and the total number of patients who suffered CA.

2.5 Statistical analysis

All analyses were conducted with Review Manager (version 5.3). Risk ratios (RR) and 95% CIs were calculated to determine the association of gasping and CA. The pooled RR and 95% CI were calculated by fixed-effect or random-effect model. If there was significant heterogeneity ($P < 0.05$, $I^2 > 50\%$), a random-effects model was adopted; otherwise, fixed-effects models were applied if there was no significant heterogeneity ($P \geq 0.05$, $I^2 \leq 50\%$). Heterogeneity was tested by the Q-test based on the Chi-square or I^2 statistic

test. Whenever heterogeneity was present, sensitivity analyses were performed by the absence of one trial in each turn to test the influence of a single study on the overall pooled estimate. Publication bias was evaluated by visually inspecting funnel plots.

3. Results

3.1 Study selection

Initially, the keywords search returned 407 records, of which 225 duplicated studies and 64 studies that referred to animals were excluded. After scanning the abstracts of the remaining potential eligible studies, 12 reviews, 5 case reports, and 83 irrelevant subjects of gasping and outcomes in patients with CA were further excluded. After full-text articles were assessed for eligibility, 11 studies were excluded, 5 of which failed to provide enough data and 6 reported no outcomes of interest. Finally, 8 studies from 7 articles [5, 6, 17–21], which involved patients who suffered a cardiac arrest, qualified for the inclusion criteria in the meta-analysis to estimate pooled data. Marterns *et al.* [18] reported two different databases (1983–1987 (1) and 1991–1993 (2)). The flow of studies, including the reasons for inclusion and exclusion of studies, is shown in Fig. 1.

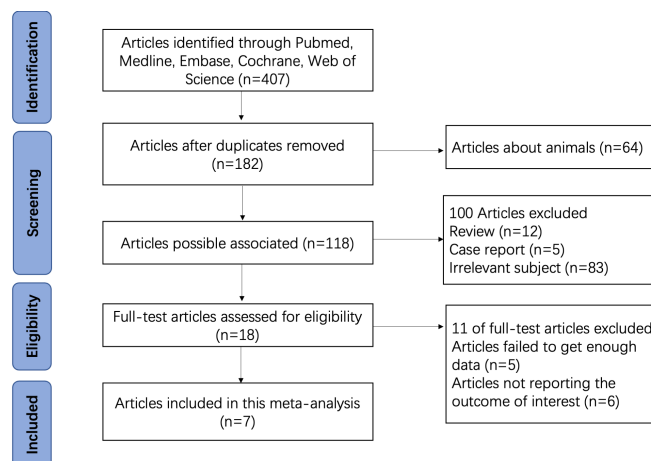


FIGURE 1. Selection of studies for the meta-analysis.

3.2 Study characteristic and validity assessment

The characteristics of the studies are shown in Table 1. All seven studies were observational, which included prospective [19–21] and retrospective cohort studies. Only one study [20] involved an in-hospital cardiac arrest, the others were out-of-hospital cardiac arrest. Among the seven cohorts, four studies from three articles reported the ROSC rate of gasping compared with no gasping patients, while six studies from five articles reported survival to hospital discharge, three studies reported favorable neurological outcomes, and four studies reported the relationship between gasping and cardiac rhythm during cardiac arrest. The quality assessments of the seven studies are shown in Table 2.

TABLE 1. Study characteristics.

Authors	Year	Country	Study design	Study Population	Type of patients	Totally Study Participants	Location	Outcome of interests
Bobrow	2008	USA	Retrospective cohort	Adult	Non-trauma	1218	Out-of-hospital	Survival to discharge, Shockable rhythm
Clark	1992	USA	Retrospective cohort	Adult, Infant	Non-trauma	445	Out-of-hospital	Survival to discharge
Martens	1995	Belgium	Retrospective cohort	Adult, Infant	Trauma, Non-trauma	(1) 3083; (2) 2127	Out-of-hospital	ROSC, Survival to discharge
Takei	2017	Japan	Retrospective cohort	Adult, Infant	Trauma, Non-trauma	9374	Out-of-hospital	Neurologically favorable 1 year survival, Shockable rhythm
Inaba	2015	Japan	Prospective cohort	Adult, Infant	Trauma, Non-trauma	7048	Out-of-hospital	Neurologically favorable 1 year survival, Shockable rhythm
Marengo	2018	Switzerla	Prospective Cohort	Adult, Infant	Trauma, Non-trauma	270	In Hospital	ROSC; Survival to discharge, Shockable rhythm
Debaty	2017	France	Prospective Cohort	Adult	Non-trauma	1888	Out-of-hospital	ROSC; Survival to discharge, Neurologically favorable 1 year survival, Shockable rhythm

TABLE 2. Assessment of the validity appraisal of the included seven studies.

	Bobrow	Clark	Martens	Takei	Inaba	Marengo	Debaty
Representativeness of the exposed cohort	*	*	*	*	*	*	*
Selection of the non-exposed cohort	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study	*	*	*	*	*	*	*
Comparability of cohorts on the basis of the design or analysis	**	-	**	**	**	**	**
Assessment of outcome	*	*	*	*	*	*	*
Was follow-up long enough for outcomes to occur	*	*	*	*	*	*	*
Adequacy of follow up of cohorts	*	*	*	-	-	-	*

3.3 Meta-analysis

3.3.1 ROSC

Four studies in three articles estimated the association of gasping with ROSC in patients suffering a cardiac arrest (Fig. 2). When low heterogeneity across the studies ($\text{Chi}^2 = 5.97$, $\text{df} = 3$, $P = 0.11$, $I^2 = 50.0\%$) was obtained, a fixed-effect model was applied to estimate a pooled RR of 2.08 (95% CI: 1.93-2.25), indicating that patients who suffered a cardiac arrest with gasping were 2.08 times more likely to develop ROSC compared to those without gasping. A funnel plot was utilized to assess the publication bias of all the studies (Fig. 3). We excluding a single study each time for sensitivity analysis. The result did not change the statistical outcome when the studies were excluded.

3.4 Survival to discharge

In six studies involving 8746 patients after cardiac arrest, 331 out of 1464 patients (22.6%) survived to hospital discharge in

the gasping group, while 432 out of 7282 patients (5.9%) in no gasping group survived to discharge. In view of the very low heterogeneity among these studies ($\text{Chi}^2 = 3.23$, $\text{df} = 5$, $P = 0.66$, $I^2 = 0\%$) the fixed-effects model was then adopted. A pooled analysis indicated that there was a significant difference of survival to discharge between the patients who gasped during cardiac arrest compared with those who did not (RR = 3.75, 95% CI = 3.27-4.29, $P < 0.001$) (Fig. 2). As shown in Fig. 3, a funnel plot was used to assess the publication bias of all studies; the points representing the evaluated studies in the funnel plot were concentrated at the top, indicating that the studies had high precision and large sample sizes. A sensitivity analysis was performed by the same method above which excluding every single study each time and the results did not change the outcome statistically by excluding any studies, indicating that the outcome showed a high stability.

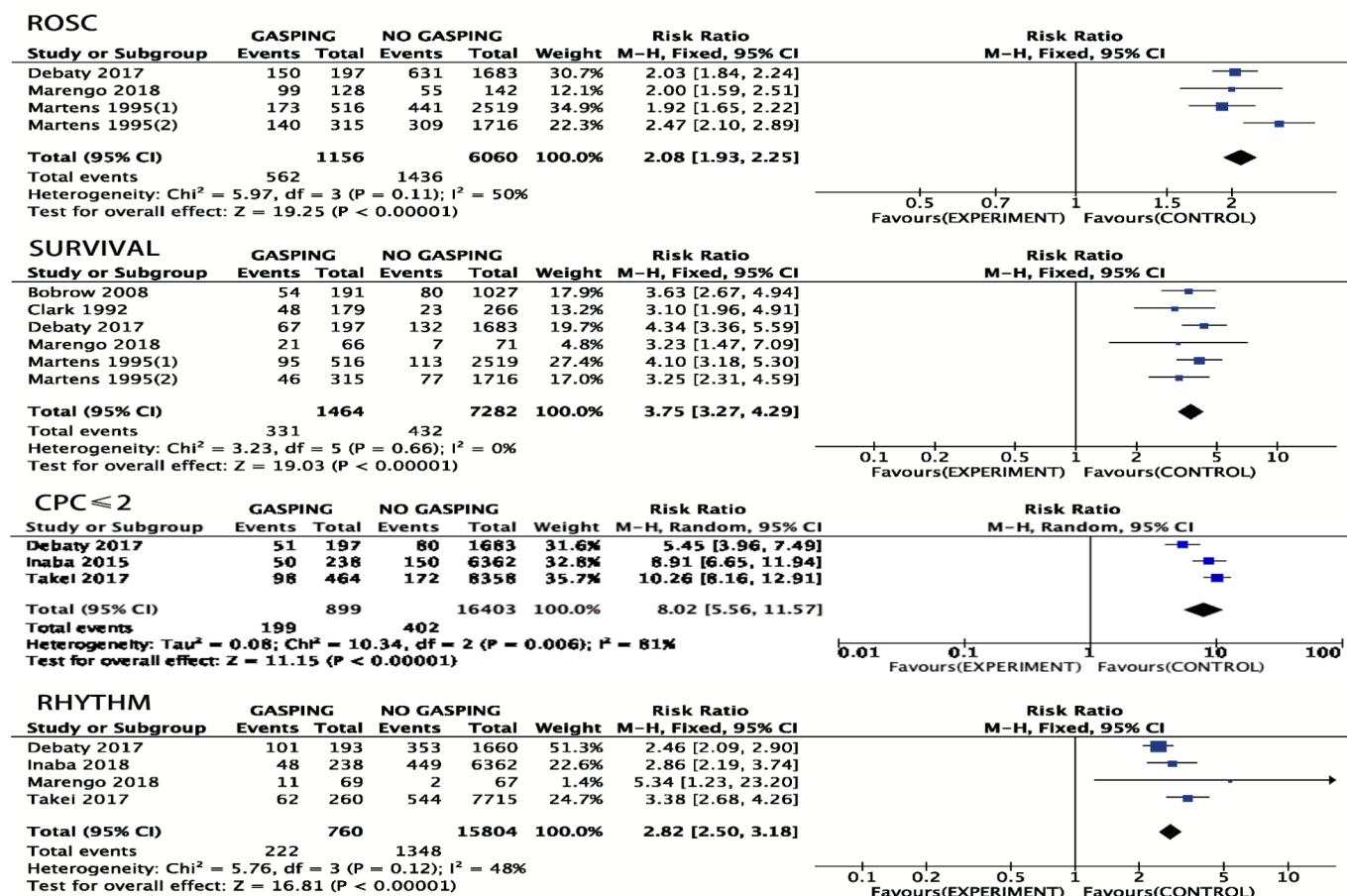


FIGURE 2. Forrest plot showing the pooled estimate of the effect between gasping and no gasping. OR, risk ratio; CI, confidence limit; M-H: Mantel Haenszel method.

3.5 CPC ≤ 2

Only three studies showed outcomes on the association of gasping with neurologically favorable one-year survival. These cohort studies were included to estimate the pooled RR of 8.02 (95% CI: 5.56, 11.57; $P < 0.001$) (Fig. 2). Although the pooled result of the trials showed a significantly increased chance to achieve a good neurological outcome when patients gasped during cardiac arrest, the association of gasping and CPC ≤ 2 was highly heterogeneous ($\chi^2 = 10.34$; $df = 2$; $P = 0.006$; $I^2 = 81\%$). The funnel plots depicted in Fig. 3 were generally asymmetrical, indicating the presence of publication bias. Although only three observational studies were involved in this analysis, sensitivity analysis demonstrated that the absence of any study each time did not influence the outcome of the statistics, indicating that the outcome was stable.

3.6 Shockable rhythm

Meta-analysis of four studies showed a significant increase in a shockable cardiac rhythm during cardiac arrest in gasping patients compared with patients with no gasping. A fixed-effect model estimated the pooled RR as 2.82 (95% CI: 2.50, 3.18; $P < 0.001$) with low heterogeneity ($\chi^2 = 5.76$; $df = 3$; $P = 0.12$; $I^2 = 48\%$) (Fig. 2). The patients were much more likely to have a shockable cardiac rhythm during cardiac arrest who were gasped. A funnel plot was used to assess the publication bias of all studies. The funnel plot (Fig. 3) was

almost symmetrical, indicating that publication bias may exist but was not apparent. A sensitivity analysis was performed as the same method above. The results showed a decreased heterogeneity ($I^2 = 95\%$ to $I^2 = 48\%$) and higher RR (2.04 to 2.82) when excluding the study of Bobrow2018 [6]. Since the data from the Bobrow2018 study only referred to ventricular fibrillation (VF) but not a totally shockable rhythm, we deleted the data from this study. However, the absence of any study data did not change the outcome statistically since the affected quantity was small.

4. Discussion

In this meta-analysis, we reviewed the studies regarding the outcomes of patients gasping during CPR. The pooled results suggested that the present of gasping significantly improve the short- and long-term outcomes in cardiac arrest patients.

Despite the widespread use of automated external defibrillators (AED), survival to hospital discharge remains poor following OHCA [2]. Several methods to assess neurological prognosis in patients after cardiac arrest who are successfully resuscitated include neurological examination, EEG, biomarkers and neuroimaging studies [22]. However, none of the above modalities has shown to predict neurological recovery. Therefore, other parameters are required for assessment of the long-term neurological function after CA. Results from a survey of survivors of OHCA in Japan showed that 30-day neu-

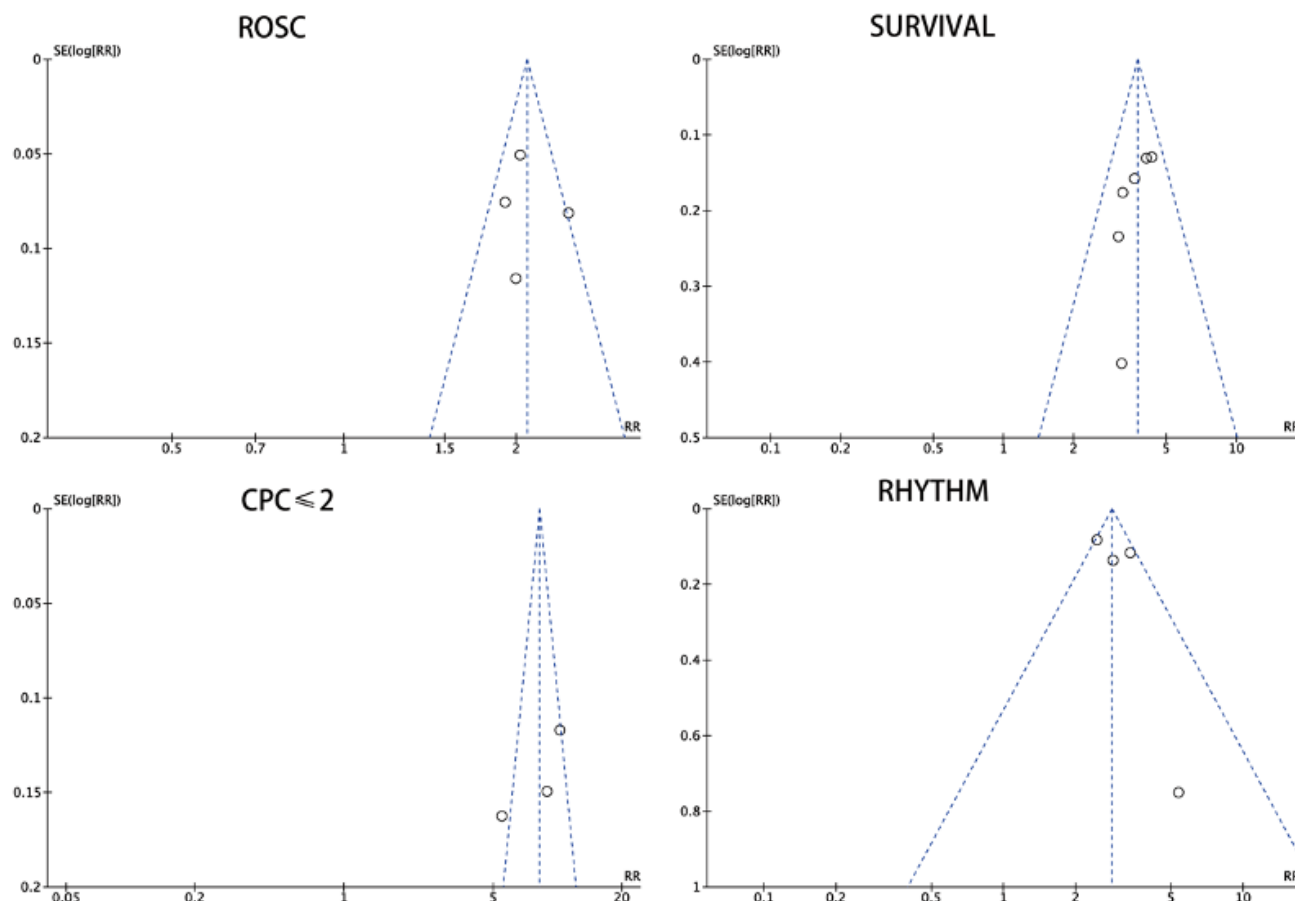


FIGURE 3. Funnel plot of pooling of gasping effect on different outcome. The hollow dots and dotted line indicate individual studies and 95% confidence intervals, respectively.

rologic outcomes were more favorable in patients who gasped [23], suggesting that gasping may be a more reliable tool to predict neurologic outcomes in these patients. Clarification of the relationship between gasping and prognosis during or after CPR, will allow us to better understand the underlining mechanisms of CPR.

Favorable initial rhythms, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), are well-known as factors associated with decreased mortality. Nearly thirty years ago, the presence of gasping during CPR was found to be more likely associated with a shockable cardiac rhythm and improved hospital survival to discharge [5]. Subsequent studies found that gasping during cardiopulmonary resuscitation was common in both animals and humans [6, 13]. The incidence of gasping before the arrival of emergency medical personal has been shown to be 55% [5]. Our previous studies in animals also demonstrated that the gasping during cardiac arrest exactly improved cardiac output, maintained more optimal amplitudes of VF waveforms, enhanced cerebral blood flow, and decreased intracranial pressure (ICP) [10, 24]. The study by Debaty2017 [21] found that gasping during CPR was a “natural biomarker for the presence of brainstem activity”, and strongly demonstrated its association with better long-term survival with good brain function.

Researchers have previously shown that gasping is generated by the intrinsic neuronal activities located in the medulla oblongata [25–27]. Gasping has been demonstrated to be

an auto-resuscitative phenomenon in human infants [28]. A gasping-like behavior is almost always present in terminally ill adult patients dying from a variety of causes.

It is important to recognize that gasping, has been mistaken for life signs that may result in the abandonment of attempts for resuscitation by a bystander in some, but not all studies [29, 30]. The ability to recognize gasping improves the diagnostic accuracy of a OHCA and should be included in all cardiopulmonary resuscitation training programs.

Our findings demonstrated that patients who suffered gasping during cardiac arrest were more likely to achieve ROSC, and significantly increased the survival to discharge with no heterogeneity. Moreover, gasping significantly increased the chance for the presence of a shockable cardiac rhythm during cardiac arrest and is a favorable factor for a better neurological one-year survival.

There are some limitations with our study. Randomized control trails (RCT) studies were not included in this meta-analysis, since only observational studies have been reported for OHCA. Only three studies were qualified for reporting neurological outcomes, leading to a highly heterogeneous group of patients. Most of the studies provided no details about the frequency of gasping, the depth of gasping or the timing of gasping in relation to OHCA.

In conclusion, we found that the presence of agonal respirations is positively associated with achievement of ROSC, shockable cardiac rhythms, increased survival to discharge,

and neurologically favorable one-year survival. Therefore, gasping needs be emphasized in CPR training, and should be recognized by bystanders or medical workers as soon as possible, to achieve the most favorable outcomes following OHCA.

AUTHOR CONTRIBUTIONS

Qinyue Guo conceived and designed the study; Qinyue Guo and Jing Xu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Qinyue Guo drafted the manuscript and made the statistical analysis, Qindong Shi revised it, all authors critically reviewed the manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest to disclose for all authors of this study.

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