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Review

Nighttime is associated with decreased survival for out of hospital cardiac arrests: A meta-analysis of observational studies

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ABSTRACT

Introduction: The relationship between time of day and the clinical outcomes of patients with out-of-hospital cardiac arrest (OHCA) remains inconclusive. We undertook a meta-analysis to assess the available evidence on the relationship between nighttime and prognosis for patients with OHCA.
Materials and methods: PubMed and EMBASE were searched through June 20, 2018, to identify all studies assessing the relationship between nighttime and prognosis for patients with OHCA. Random effects modes were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs).
Results: Eight observational studies met the inclusion criteria. Meta-analysis of 8 studies showed that compared with nighttime, the daytime OHCA patients had higher 1-month/in-hospital survival (OR, 1.25; 95% CI, 1.15–1.37; P = 0.00), with high heterogeneity among the studies (I^2 = 82.8%, P = 0.00).
Conclusions: Patients who experienced OHCA during the nighttime had lower 1-month/in-hospital survival than those with daytime OHCA. In addition to arrest event and pre-hospital care factors, patients' comorbidity and hospital-based care may also be responsible for lower survival at night.

1. Background

Out-of-hospital cardiac arrest (OHCA) is a public health problem worldwide and usually leads to death if not treated in the first few minutes [1]. Despite the improvements in the chain of survival, survival rates from OHCA remain poor (approximately 10%) [2]. Both pre-hospital and hospital-based care all have become widely accepted as important determinants of survival after OHCA, especially pre-hospital factors such as time from arrest to compressions and defibrillation [3]. However, the quality of OHCA management in pre-hospital and in-hospital settings varies according to the time of day [4]. Patients' biological differences, emergency medical services (EMS) and in-hospital personnel fatigue, staffing and operational factors, variation in the quality of cardiopulmonary resuscitation (CPR) parameters and response time likely contribute to the different quality of OHCA management by the time of day. The impact of time of OHCA occurrence has been extensively evaluated. A number of studies have demonstrated that there was a significant temporal difference in survival after OHCA and daytime OHCA was associated with significantly better resuscitation efforts than nighttime OHCA, such as the more prehospital return of spontaneous circulation (ROSC) and higher 1-month survival [5-7]. There are also some studies, however, that failed to demonstrate a temporal difference in survival [8,9].

Results from a single study may have been underpowered to detect statistically significant differences and there is no systematic review to assess the available evidence on the relationship between temporal variations and prognosis of OHCA. A better understanding of the relationship between temporal variations and prognosis after OHCA may be important in improving prevention and treatment strategies for increasing patient survival of OHCA. If there was indeed an increased risk of death for patients with nighttime OHCA, this might reflect differences in quality of care and would have important implications for health-care providers and health-care policy makers. The purpose of the current investigation is to compare the survival of patients with OHCA during nighttime and daytime.

2. Methods

2.1. Data sources and searches

We searched PubMed and Embase databases from inception through June 20, 2018, to identify all articles assessing the relationship between nighttime and prognosis for patients with OHCA, using the following keywords: out of hospital cardiac arrest, out of hospital heart arrest, temporal, nighttime, night, daytime and day. No publication type

Abbreviations: OHCA, out-of-hospital cardiac arrest; OR, odds ratio; RR, relative risk; CI, confidence interval; CPR, cardiopulmonary resuscitation; NOS, the Newcastle-Ottawa Scale; ROSC, return of spontaneous circulation; AED, automated external defibrillators; EMS, emergency medical services; COPD, chronic obstructive pulmonary disease.

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and language restrictions were applied. In addition, the reference lists of identified studies and the relevant review articles were checked manually to include other potentially eligible papers.

2.2. Study selection

Two investigators independently deleted duplicate records, screened all titles and abstracts of publications and excluded articles not meeting the inclusion criteria. In case of uncertainty, the full-text article was obtained to identify eligibility. Disagreements were resolved through consultation with a third author. Published studies meeting the following criteria were included: (1) Adult patients aged 18 years and older years who suffered an OHCA; (2) Studies that evaluated the association between nighttime OHCA and prognosis regardless of the different definition of nighttime; (3) Eligible studies had to report short-term mortality or survival (1-month, in-hospital or ICU survival/mortality), with adjustment for confounding factors. (4) We only included the origin studies, in which the definition of daytime and nighttime has been done by authors according to their EMS. We excluded studies that did not provide an adjusted odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI).

2.3. Data abstraction

Using a pre-defined standardized data extraction form, two authors independently extracted data in a blinded fashion from eligible studies. Collected data included the following: first author, publication year, study type, country, the definition of nighttime, outcome measures, study quality or risk of bias, and study results including a number of patients in each group, survival in each group, and adjusted OR for survival with corresponding 95%CI.

2.4. Quality assessment (risk of bias)

The Newcastle-Ottawa Scale (NOS) was used to evaluate the selection, comparability, and outcome of observational studies included in our meta-analysis. The maximum score a study can receive is nine, with higher scores representing better study design. Five or fewer points indicated poor quality [10]. The quality assessment was not conducted for articles published as abstracts, due to the lack of information.

2.5. Data analysis

In our current meta-analysis, we pooled individual study data (adjusted OR and 95%CI), performed the meta-analysis by means of a random effects model, and reported the pooled OR for survival with corresponding 95% CI. For the purpose of this meta-analysis, the adjusted OR in the individual study was calculated with nighttime OHCA as the reference. If a study reported the adjusted OR and CI calculated with daytime OHCA as the reference or a study presented the pooled OR and CI for mortality instead of survival, we took the inverse of both the OR and the CI to make the combination of data consistent. If a study reported the adjusted RR and CI, the RRs were transformed into ORs using the formula $OR = (1- Po) RR/(1- Po \times RR)$, in which Po is the incidence of the outcome of interest in the reference group [11]. Heterogeneity between studies was measured by the chi-squared test and quantified with I^2 statistic. I^2values of 0–24.9%, 25–49.9%,50–74.9%, and 75–100% were considered as none, low, moderate, and high thresholds for statistical heterogeneity. Sensitivity analyses were performed to explore the influence of a single study on the overall pooled estimate by omitting one study at a time. All statistical analysis was performed using Stata (version12.0, Stata Corporation, USA), and a P value <0.05 was considered statistically significant.

3. Results

3.1. Search and selection

The initial search yielded 671 potentially articles. After removing duplicates and screening the titles and abstracts, 33 articles were potentially eligible and were reviewed in full text. Three studies assessed survival to hospital discharge based on working hours versus off-hours were excluded [12-14]. Two studies were excluded because they divided the hours of the day into four-time blocks (00:00–05:59, 06:00–11:59, 12:00–17:59 and 18:00–23:59) instead of daytime versus nighttime [15,16]. One study was excluded because they did not provide an adjusted OR or RR [17]. One study was also excluded because they included OHCA patients who were under 18 years of age [18]. Wallace et al. performed a retrospective study to evaluate the association between time of day and 30-day survival after OHCA. The adjusted RR in the study was transformed into OR and the study was finally included in our current meta-analysis [5]. Ultimately, 8 studies that met our eligibility criteria were included in our meta-analysis [5-9,19-21]. The details of study selection and exclusion at each stage of review are shown in Fig. 1.

3.2. Characteristics of studies

The eight included studies were published between 2011 and 2018. Seven were published in peer-reviewed journals and one as conference abstract [8]. Furthermore, seven were retrospective observational studies and one was a prospective observational study [7]. Six studies reported 1-month survival and two studies reported in-hospital mortality among the included studies [9,19]. Time of day was divided into two time periods (daytime and nighttime) in five studies [5,8,9,20,21], while patients were assigned to three categories according to the time of OHCA (daytime, evening and nighttime) in the other three studies [6,7,19].

The main characteristics, and bias and quality assessments of the studies included in this meta-analysis are presented in Table 1. The Newcastle-Ottawa scale was used to assess the quality of seven studies and the remaining one study could not be assessed since it was only in abstract form [8]. Among the seven studies, five studies scored 7 points and two studies scored 6 points. The main reasons for the loss of scores in the quality assessment were lack of representativeness of the sample population and the comparability of baseline characteristics between cohorts.

3.3. Meta-analysis

Eight studies (a total of 214,001 patients) evaluated daytime/nighttime OHCA were included in our pooled analysis (Table 2). Compared with nighttime, the daytime OHCA patients had higher 1-month/in-hospital survival (OR, 1.25; 95% CI, 1.15–1.37; $P = 0.00$), with high heterogeneity among the studies ($I^2 = 82.8\%$, $P = 0.00$) (Fig. 2).We conducted sensitivity analysis by omitting one study at a time, generating the pooled estimates and comparing with the original estimates. Omitting any one of eight studies had no dramatic influence on the original pooled ORs with newly pooled OR ranging from 1.20 (95%CI, 1.12–1.29; $I^2 = 73.5\%$) to 1.29 (95% CI 1.17–1.41; $I^2 = 82.6\%$).

To further explore possible reasons for a high statistical heterogeneity and verify the robustness of our results, we conducted a post hoc subgroup analysis stratifying studies according to the number of time periods that time of day was divided into (two time periods(daytime and nighttime) versus three time periods (daytime, evening and nighttime)). The daytime OHCA patients were associated with a significant increase in 1-month/in-hospital survival in both subgroups. The adjusted OR of 1-month/in-hospital survival in two time periods subgroup and three time periods subgroup was 1.16 (95% CI, 1.09–1.25; $I^2 = 72.7\%$) and 1.60 (95% CI, 1.17–2.19; $I^2 = 86\%$), respectively (Fig. 3).

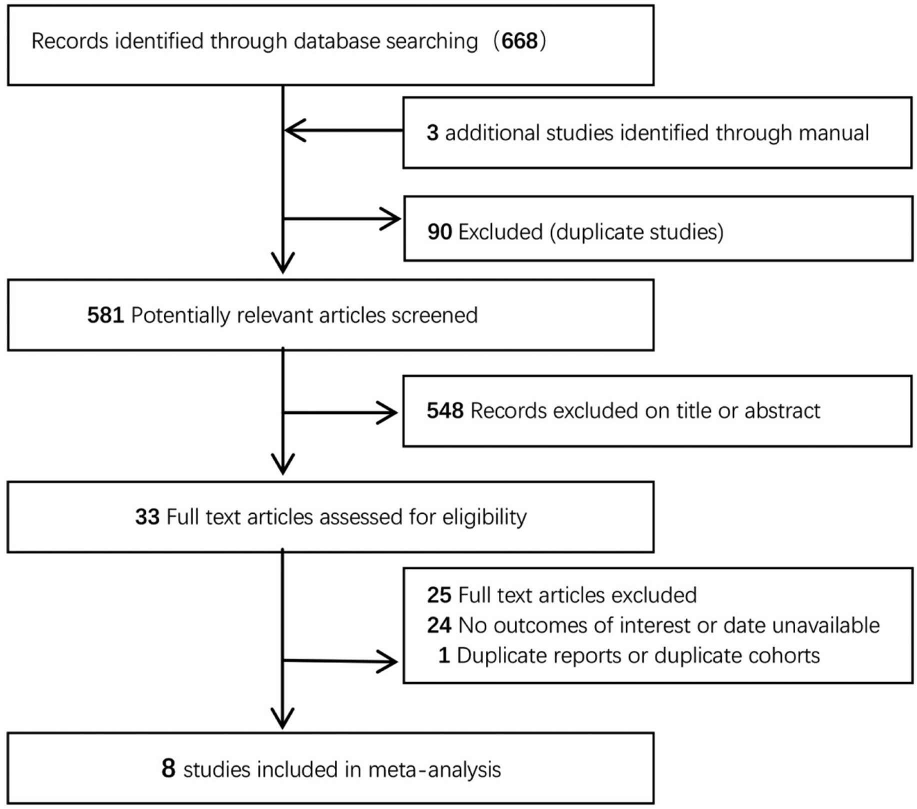

Fig. 1. Study flow diagram.

4. Discussion

To our knowledge, this article reports the first meta-analysis of observational studies of the association between temporal differences and clinical outcomes of patients with OHCA. We found evidence of a 1.25-fold increase in the adjusted odds of 1-month/in-hospital survival in persons with daytime OHCA when compared with nighttime OHCA. The results of this meta-analysis, however, should be interpreted with caution because of significant heterogeneity among studies and a small number of studies included.

The main finding of our meta-analysis seems to support the view that outcomes from cardiac arrest which occurs at night have worse outcomes. The results of the sensitivity analysis and subgroup analyses did not draw different conclusions, indicating that our main finding was robust. It is widely accepted that less bystander-witnessed arrest, less shockable heart rhythm, late and less bystander resuscitation (bystander automated external defibrillators (AED) and CPR), longer time from 9-1-1 call received to EMS arrival at scene, private arrest location and other survival-related risk factors during night significantly decreased resuscitation efforts and led to a lower prehospital ROSC and survival in patients with OHCA compared to daytime. In our meta-analysis, however, we noticed that the survival also remained lower at night even if we pooled the adjusted ORs, which adjusting for survival-related risk factors mentioned above. Remarkably, the adjusted factors were mostly arrest event and pre-hospital care factors. Moreover, Karlsson et al. found that 30-day and 1-year survival was also significantly lower in patients with nighttime OHCA compared to the patients with daytime OHCA when limiting the analysis to patients arriving at the hospital with ROSC [6]. In addition to arrest event and pre-hospital care factors, therefore, other unadjusted factors may also be responsible for lower survival at night, such as patients' comorbidity and hospital-based care.

Three recent studies found that most of the comorbidity conditions were associated with increased mortality in patients with OHCA, such as renal disease, diabetes with/without complications, metastatic carcinoma, chronic obstructive pulmonary disease (COPD), asthma, heart failure, cerebrovascular disease and peripheral vascular disease [9,22,23]. Furthermore, a previous prospective population-based cohort study (The Rotterdam study) also revealed that COPD was significantly associated with an increased risk of dying due to sudden cardiac death

Table 1
The main characteristics of the studies included in the meta-analysis

Study/year	Dates	Country	Study type	Nighttime definition	Outcome	Quality assessment (NOS)
Koike/2011	2005–2008	Japan	Retrospective cohort	17:00 PM- 08:59 AM	1-month survival	High quality (6 points)
Bagai/2013	2005–2010	America	Retrospective cohort	23:01 PM-07:00 AM[a]	in-hospital survival	High quality (7 points)
Wallace/2013	2008–2012	America	Retrospective cohort	20:00 PM-07:59 AM	1-month survival	High quality (7 points)
Karlsson/2014	2001–2010	Denmark	Retrospective cohort	23:00 PM-06-59 AM[a]	1-month survival	High quality (7 points)
Matsuyama/2016	2005–2012	Japan	Retrospective cohort	17:00 PM-09:00 AM	1-month survival	High quality (7 points)
Matsumura/2016	2012–2013	Japan	Prospective cohort	23:00 PM-07:00 AM[a]	1-month survival	High quality (7 points)
Schriefl/2017	2013–2015	Vienna	Retrospective cohort	19:00 PM-07:00 AM	1-month survival	NA
Couper/2018	2003–2015	Britain	Retrospective cohort	20:00 PM-08:00 AM	in-hospital survival	High quality (6 points)

NA: not available, NOS: The Newcastle-Ottawa Scale.
[a] Patients were assigned to three categories according to the time of OHCA in the origin study: daytime, evening and nighttime.

Table 2
Number of patients and survival percentage per group, adjusted OR with 95% CI and possible confounding factors

Study/year	Total No. (survival,%)	Day No. (survival,%)	Night No. (survival,%)	Adjusted OR (95% CI)	Possible confounding factors
Koike/2011	106,577 (8.8)	42,546 (10.2)	64,031 (7.9)	1.26 (1.22–1.31)	Gender, age, bystander CPR, public AED use, Arrest presenting rhythm, adrenaline, and call-to-hospital admission interval.
Bagai/2013	18,588 (10.1)	7503 (10.8)	4202 (7.1)	1.23 (1.06–1.43)	Age, sex, race, first monitored cardiac rhythm, witness status, layperson resuscitation, and EMS response time.
Wallace/2013	4789 (9.92)	2827 (10.9)	1962 (8.56)	1.11 (1.02–1.21)	Age, sex, race, presenting rhythm, field termination status, total duration of call, time interval from dispatch to arrival at the scene, AED application by a bystander or first responder, bystander CPR performance, and location of the arrest
Karlsson/2014	18,929 (7.8)	8280 (7.8)	3893 (3.1)	2.08 (1.61–2.63)	Age, sex, year, initial rhythm, civil status, location, witnessed status, bystander CPR, AED, time interval and some basic diseases.
Matsuyama/2016	44,474 (NA)	15,798 (NA)	28,676 (NA)	1.18 (1.11–1.26)	Age, sex, good activities of daily living, location, aetiology of arrest, bystander witness, bystander CPR, and first documented rhythm.
Matsumura/2016	13,780 (7.6)	5474 (7.6)	2970 (4.9)	1.66 (1.34–2.07)	Age, sex, witness status, bystander CPR, call response interval, and initial shockable rhythm
Schriefl/2017	1817 (NA)	NA	NA	1.06 (0.77–1.47)	Age, sex, initial rhythm, arrest location, witness status, layperson resuscitation and EMS response time
Couper/2018	5047 (NA)	3399 (NA)	1648 (NA)	1.09 (0.99–1.20)	Many clinically relevant predictor variables as possible. Such as age, sex, cardiac arrest location, arrest presenting rhythm, etc.

NA: not available, OR: odds ratio. CPR: cardiopulmonary resuscitation, AED: automated external defibrillators, EMS: emergency medical services.

(HR 1.34, 95% CI 1.06–1.70) [24]. In our current meta-analysis, only one study compared patients' comorbidities and found that nighttime patients were more associated with a history of COPD [6]. Therefore, the poor prognosis of patients at night may be partly due to more comorbidities in nighttime patients. However, there are only limited studies comparing patients' baseline comorbidities difference between day and night. Knowing whether survival difference caused by unmodifiable factors is important for health-care providers and policymakers, so further exploration of the effect of pre-arrest comorbidities difference between day and night on the survival of OHCA may be warranted.

Approximately a quarter of patients successfully resuscitated from OHCA and admitted to hospital [25]. The level of post-resuscitation treatment provision has been presuming to be related to prognosis [26]. Matsumura et al. found that there are significantly reduced resuscitation efforts (less in-hospital intubation and blood gas analysis) by in-hospital healthcare providers during the nighttime compared with daytime [7]. Accordingly, a difference in terms of the level of hospital-based care between day and night may also be responsible for the temporal difference in survival after OHCA. A recent systematic review found no association between in-hospital nighttime intensivist staffing and intensive care unit mortality [27]. The study, however, included mixed intensive care unit populations included medical and surgical patients. Further study is needed to determine the effect of nighttime intensivist staffing on OHCA patient populations. Furthermore, heavy workload during shifts and in-hospital personnel fatigue at night may strongly influence patients' outcome. Since this information was not available, it remains a matter of speculation.

Future studies should pay more attention to the following points. First, it is necessary to determine to whether pre-arrest comorbidities

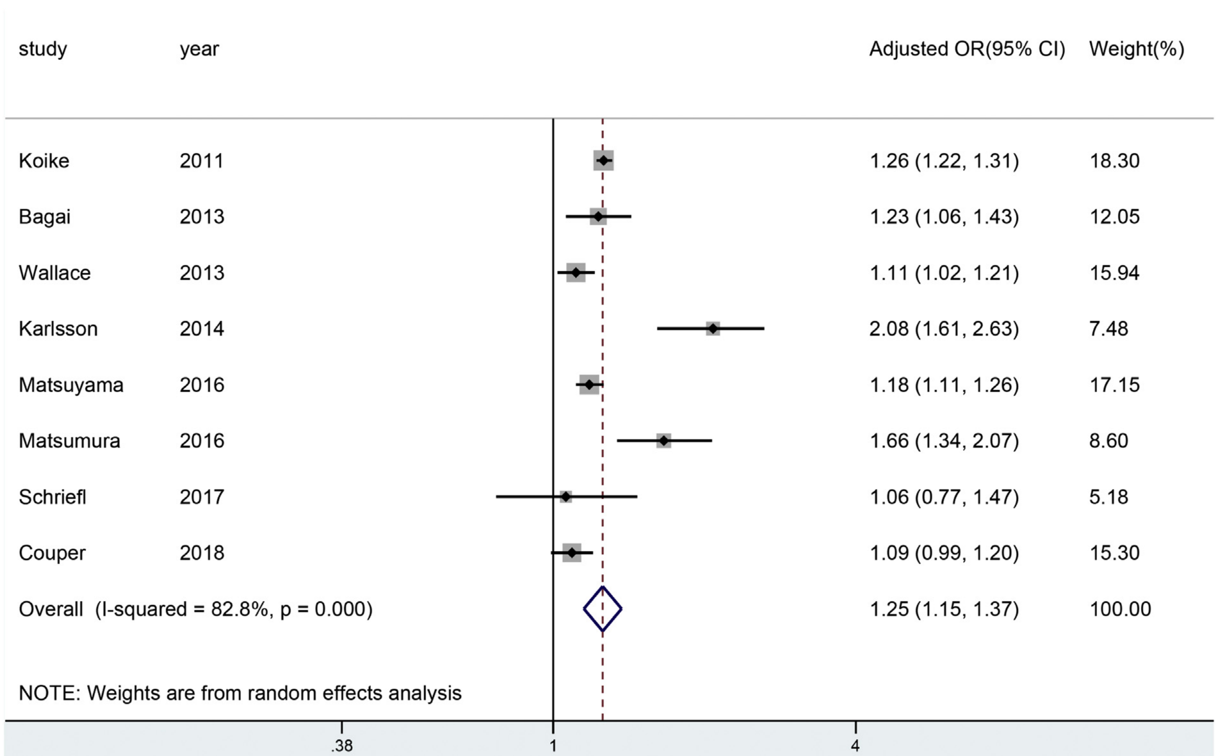

Fig. 2. Forest plot showing the adjusted effect of daytime versus nighttime OHCA on 1-month/in-hospital survival. CI confidence interval.

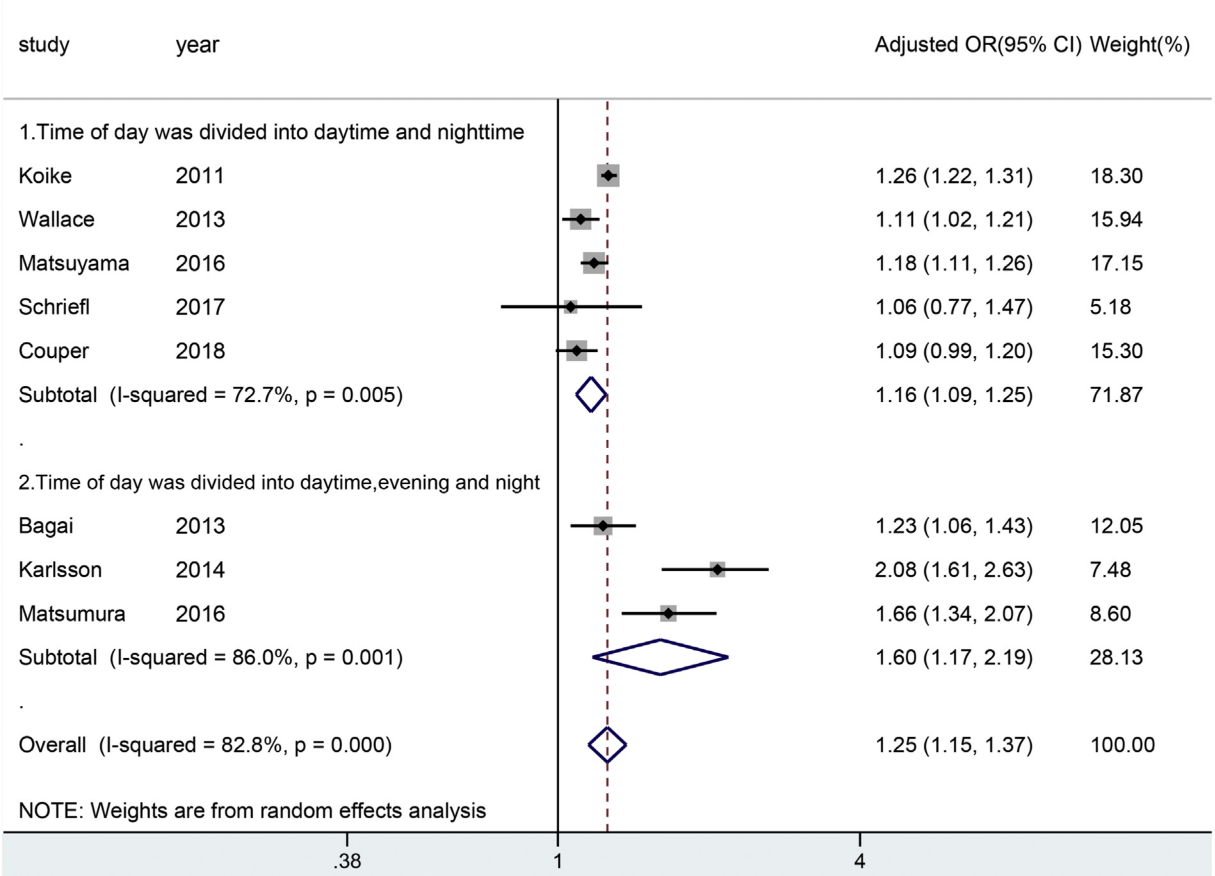

Fig. 3. Forest plot showing subgroup analysis stratifying studies according to the number of time periods that time of day was divided into (two time periods versus three time periods). CI confidence interval.

difference between day and night can affect patients' outcome. This may be feasible if future studies provide a more detailed description of patients' comorbidities. Second, future studies should continue to explore the relationship between hospital-based care in ICU and/or general wards during daytime and nighttime and patient outcomes, such as patients to doctor/nurse ratios, workload (such as the turnover of patients), and the frequency of post-resuscitation care (such as ventilatory support, percutaneous coronary intervention capability, vasopressor medications and blood gas analysis). Finally, further studies also should focus on EMS and in-hospital personnel fatigue at night by filling out relevant questionnaires.

Statistical heterogeneity was high in our study. Subgroup analyses also showed high heterogeneity in both subgroups ($I^2 = 72.7\%$ in two time periods subgroup, $I^2 = 86.0\%$ in three time periods subgroup). The high heterogeneity may have resulted from (1) different definitions were used for nighttime. Among the eight studies included, time of day was divided into two time periods (daytime versus nighttime) in five studies and the definition of nighttime differ between studies. While in the other three studies, patients were assigned to three categories (daytime versus evening versus nighttime) in three studies and nighttime was roughly defined as 23:00 PM-07:00 AM. Although inconsistent, investigators may differ in nighttime definitions on account of differences in what time services change in their EMS. Varied definitions of nighttime may lead to methodological heterogeneity among the included studies. (2) the heterogeneous study population. Koike et al. only included OHCA patients who were witnessed by bystanders [20]. Couper et al. included exclusively adult patients who had a first OHCA attributable to the acute coronary syndrome and who admitted to hospital following successful resuscitation [9]. (3) different study setting. There is no doubt that the quality of medical care systems and available health resources differ between countries and regions. As the number of studies included was small, we did not perform subgroup analysis based on different study setting. Different research populations and settings among studies may lead to clinical heterogeneity.

Our study has several potential limitations that need to be considered. First, studies included in the analysis were all observational studies because there is no way to randomize day versus nighttime care. Meta-analysis of observational studies cannot avoid undetected biases and confounding factors inherent in the original studies though we sought to control for bias by systematically assessing study quality. Second, there was significant statistical heterogeneity among studies and a small number of studies included. The sensitivity analysis and subgroup analyses did not clarify the source of the heterogeneity observed in this study, which may affect the validity of our results and limit the general application of our findings.

5. Conclusion

In conclusion, the current meta-analysis indicated that patients who experienced OHCA during the nighttime had lower survival than those with daytime OHCA. In addition to arrest event and pre-hospital care factors, patients' comorbidity and hospital-based care may also be responsible for lower survival at night.

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Declarations of interest

None.

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