

Does time of day influences outcome in out-of-hospital cardiac arrest patients?

A meta-analysis of cohort studies

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Abstract

Background: Whether time of day has impact on outcomes after out-of-hospital cardiac arrest (OHCA) remains controversial. However, there are no evidence syntheses describing the impact of time differences on outcomes from OHCA.

Methods: A meta-analysis of cohort studies exploring the association between time of day and survival in patients with OHCA was performed. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled using a random-effects model.

Results: Ten studies involving 252,848 patients and 24,646 survivals were included. Patients with night-time OHCA had significantly lower short-term survival compared to patients with daytime OHCA (OR, 1.20; 1.07–1.36; $P < .001$). The relationship between temporal differences and survival was consistent in most subgroups. For long-term survival, it remained unclear whether night-time was associated with reduced OHCA survival at 12 months (OR, 1.47; 0.71–3.06; $P < .001$). Three studies including 183,129 patients examined the association between weekend and survival in OHCA patients. Survival did not differ on weekends compared to weekdays (OR, 1.00; 0.97–1.04; $P = .918$).

Conclusions: Night-time is associated with a lower survival in OHCA patients. However, similar findings are not observed in OHCA patients on weekends. Caution is required in interpretation of these results accounting for high level of heterogeneity and large, well designed, randomized trials are warranted.

Abbreviations: AED = automated external defibrillator, ALS = advanced life support, CI = confidence interval, CPR = cardiopulmonary resuscitation, EMS = emergency medical service, NOS = Newcastle-Ottawa Scale, OHCA = out-of-hospital cardiac arrest, OR = odds ratio, PRISMA = the Preferred Reporting Items for Systematic Reviews and Meta-Analysis, ROSC = return of spontaneous circulation.

Keywords: meta-analysis, out-of-hospital cardiac arrest, resuscitation, survival

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1. Introduction

Out-of-hospital cardiac arrest (OHCA) remains a major public health issue globally.^[1–2] Despite ongoing efforts to improve the management, survival outcomes in such patients are still unsatisfactory.^[1,3,4] A key concept in the beneficial treatment of patients with OHCA is the strategy known as the “chain of survival,” which emphasizes a coordinated set of actions that includes the immediate recognition of cardiac arrest and activation of the emergency-response system; cardiopulmonary resuscitation (CPR); defibrillation; and advanced life support and integrated care after cardiac arrest.^[5] Besides, research in cardiac arrest resuscitation has embraced that the most important links in the chain of survival are the earliest ones — recognition of cardiac arrest and initiation of CPR.^[6] All these vary according to time of day. Shift work disrupts circadian rhythms, causing health risks and deterioration in the healthcare workers ability and attention, motivation, and decision -making.^[7,8] Therefore, night-time circumstances may have an effect on the resuscitation efforts performed by health-care providers when OHCA occurs.

Recent studies have reported significant differences in return of spontaneous circulation (ROSC) for patients with OHCA at night compared to daytime.^[9,10] However, the result remains controversial. Night-time treatment of OHCA is associated with poorer outcomes than day-time treatment, with this difference

being potentially attributed to the reduced quality of treatment and the lower frequencies of witnessed cardiac arrest and bystander CPR rates.^[11] A comprehensive understanding of the potential effect of time differences on outcomes of out-of-hospital cardiac arrest definitely could provide valuable information to health policy-makers and hospital managers. But to date, no syntheses of studies have been published to assess, with precision, the associations between time differences and OHCA outcomes through the decades. Thus, given existing controversy whether time of day affects outcomes after OHCA we performed this meta-analysis to pool the available data and to investigate the associations between time differences and clinical outcomes of patients with OHCA.

2. Methods

2.1. Data sources and search strategy

Independently, 2 authors (W.-L.J. and W.-X.Q.) undertook the searches, without any restrictions, of the PubMed, Embase from inception to 21 February 2020. A combination of medical subject headings (MESH) terms and key words was used while searching. The search terms were related to those, including “night-shift”, “night”, “night-time”, “out-of-hours”, “evening”, “off-hour”, “after-hours”, “time” and “heart arrest”, “cardiac arrest”, “cardiopulmonary resuscitation”, “out of hospital cardiac arrest”, “survival”, “outcome”. Previous review articles and the reference lists of the original studies were also manually searched to identify all potentially eligible studies. Moreover, conference abstracts for unpublished work were also checked to include available studies.

The present meta-analysis was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).^[12]

2.2. Study selection criteria

Cohort studies were included if: they aimed to investigate whether outcomes after OHCA differ during night-time and weekends compared with daytime and weekdays; study participants were mainly adults; and the study reported available adjusted data to obtain a summary result.

2.3. Data extraction

The following data were extracted from each included articles: first author, publication year, study region, sample size, definitions of night or weekend, study design, major clinical outcome, adjustments. Two independent authors (W.-L.J. and W.K.) performed the data extraction and any disagreement was resolved using discussion. We pooled the short-term survival (in-hospital or 30-day survival) and long-term survival (12-months survival) with the adjusted data. Meanwhile, the supplementary files were checked for data extraction and study authors were contacted where necessary.

2.4. Quality assessment

Studies were evaluated for quality assessment by using the Newcastle–Ottawa Scale,^[13] which awards a maximum of 9 stars for selection and comparability and outcome. We judged studies with a score of 7 to 9, 4 to 6, and 0 to 3 to be at high, moderate, and low quality of studies, respectively.

2.5. Statistical analysis

To present a summary odds ratio (OR), multivariate OR with 95 CIs were pooled by using a random-effects model, accounting for significantly clinical heterogeneity. Between-study statistical heterogeneity was evaluated using the Cochran Q statistic and quantified with the I^2 statistic.^[14] $P < .100$ and an I^2 value greater than 50% were considered to denote the statistical significance of heterogeneity. We also carried out predefined subgroup analyses to study the effect of temporal difference in OHCA patients. To test the influence of a single study on the overall estimates, a sensitivity analysis was performed by omitting 1 study in turn. Funnel plots and Eggers linear regression tests were taken to assess publication bias.^[15] All statistical analyses were undertaken using STATA, version 12.0 (Stata Corporation, College Station, Texas).

2.6. Ethics approval

Ethics declarations and consent to participate are not applicable for meta-analysis.

3. Results

3.1. Study identification

The detailed procedure of literature search and selection is summarized in Figure 1. Our initial search strategy identified 11,541 hits. After removal of duplicates, 7941 hits remained. After reviewing the full text of manuscripts, 10 publications met the inclusion criteria and were included in the qualitative synthesis.^[10,16,17,18–24] Thirty papers that were excluded for the following reasons: 10 were reviews or editorial articles, 5 had an eligible population, 5 provided insufficient data, 1 was a duplicate study, and 9 were excluded because they were unrelated.

3.2. Description of studies

Characteristics of the included studies are shown in Table 1. The ten articles were all published in English between 2010 and 2019. Among the included publications, 2 of 10 were prospective studies,^[16,22] and 6 of 10 were multicenter studies.^[16,17,18,19,22,23] Three studies (including 855,031 patients) were performed in the North America.^[10,18,19] Additionally, 4 studies were performed in Europe,^[20–22] and the other 3 were performed in Asia.^[16,17,18,23] This meta-analysis consisted of 252,848 patients and 24,646 survivals. The number of patients ranged from 1059 to 173,137. In addition, the definitions of night-time or weekend showed variability in the 10 studies.

3.3. Risk of bias assessment

The Newcastle–Ottawa Scale was used to assess the methodological quality of the included studies. The scale, properly speaking, assigned up to 9 points for selection and comparability of cohorts and assessment of outcome. Details of the quality assessment are depicted in Table 2. The average score of the included studies was 7.8, and the NOS score for each study was 7 or above, suggesting that all the studies were of high quality.

3.4. Relationship between night-time and outcome

Data on survival was available in all included studies, 9 as short-term survival, 1 as long-term survival, and in 1 manuscript a

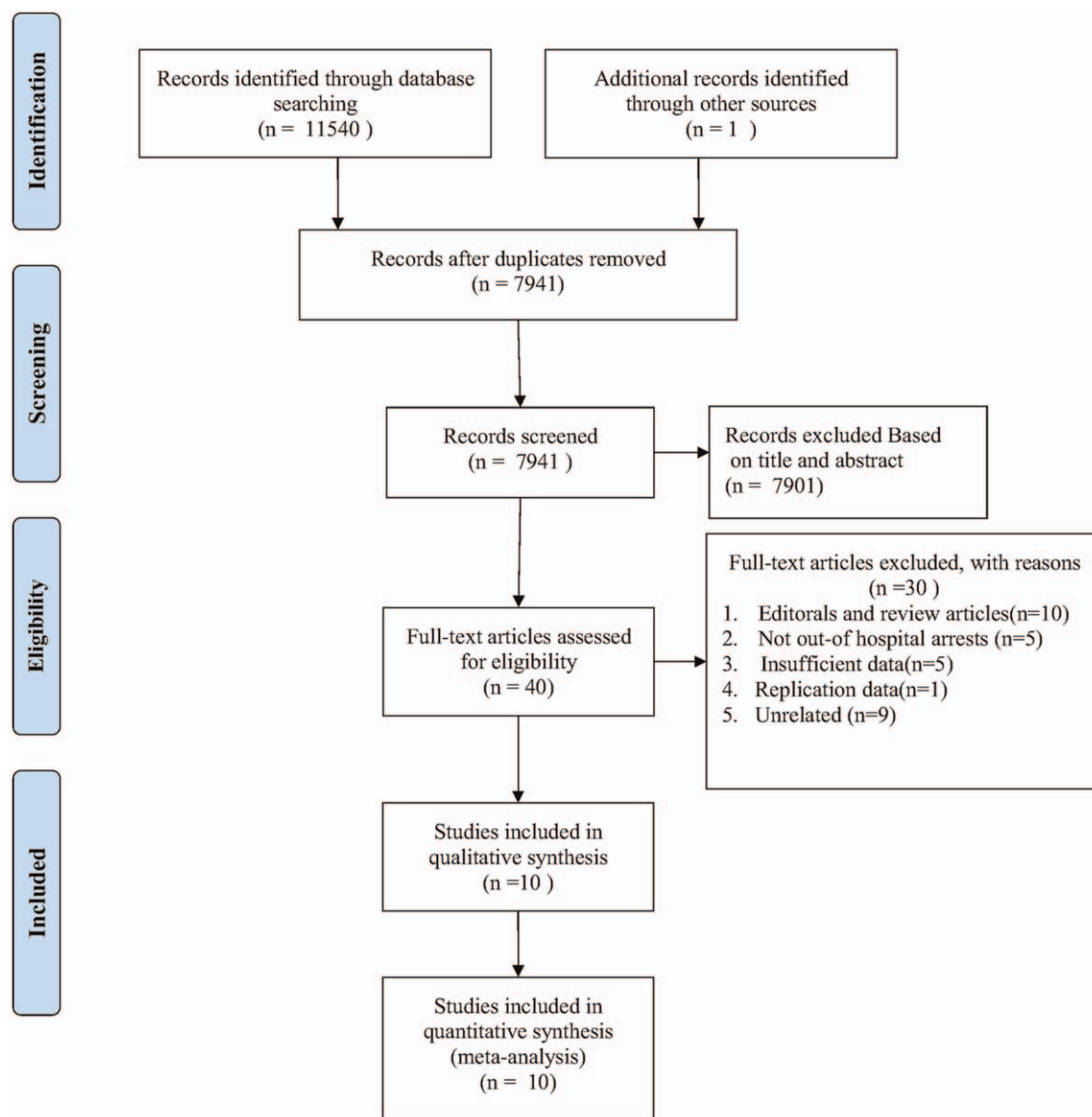


Figure 1. Flow diagram of article selection.

composite of both outcomes was presented. There was a significant temporal difference in short-term survival after OHCA; that is, night-time OHCA patients had significantly lower short-term survival (OR, 1.20; 95% CI, 1.07 to 1.36; $P < .001$); Fig. 2), with significant heterogeneity ($I^2 = 95.0\%$). For long-term survival, there was not enough evidence to support that OHCA survival at 12 months differ between night and day (OR, 1.47; 95% CI, 0.71 to 3.06; $I^2 = 93.8\%$; $P < .001$) (Fig. 3). Considering only 2 studies were included in testing the relationship between time and OHCA survival at 12 months, and therefore, further evidence on this topic is urgently required.

3.5. Relationship between weekend and outcome

Three studies including 183,129 patients explored the association between weekend and survival in OHCA patients. Survival did not differ on weekends compared to weekdays (OR, 1.00; 95% CI, 0.97–1.04; $I^2 = 0\%$; $P = .918$) (Fig. 4).

3.6. Subgroup analyses and sensitivity analysis

To investigate the possible source of between-study heterogeneity, we performed several pre-specified subgroup analyses according to the definition of night (23:00–07:00 vs 17:00–8:59), geographic region (Asia vs North America vs Europe), sample size (≤ 10000 vs > 10000), study design (Prospective cohort vs Retrospective cohort), adjusted for comorbidities (yes vs no), type of survival (1-month survival vs in-hospital survival). Variations in geographic region, number of populations and type of survival may be the main cause of the between-study heterogeneity. It is noteworthy that the overall heterogeneity was significantly reduced in the subgroup of region (North America), sample size (≤ 10000) and in-hospital survival. The relationship between temporal differences and survival was consistent in most subgroups. Details can be shown in Table 3. In addition, our sensitivity analyses suggested that the overall combined OR did not meaningfully alter by exclusion of any

Table 1
Characteristics of included studies.

Study/year	Region	Population, n	Definition of night or weekend	Study design	Major clinical outcome	OR and 95% CIs	Adjustments
Matsumura et al/2016	67 EMS in Japan	Adult, 13780	Night-time (23:01–07:00)	Prospective cohort	1-month survival	1.66 (1.34–2.07)	Age, sex, witnessed arrest, bystander CPR, call-response interval per minute and initial shockable rhythm
Koike et al/2011	1 national registry in Japan	Adult, 173137	night-time (17:00–8:59)weekend (Sat Sun and national holidays)	Retrospective cohort	1-month survival	Night (1.26;1.22–1.31), weekend 1 (0.96–1.04)	Age, sex, bystander CPR, public AED, initial rhythm, adrenaline, call-to-hospital admission interval and time of admission
Wallace et al/2013	EMS in US	Adult, 4789	Night-time (20:00–07:59)	Retrospective cohort	30-day survival	1.10 (1.02–1.18)	Age, sex, race, presenting rhythm field termination status, duration of call, dispatch-to-scene interval, AED application, bystander CPR, and arrest location
Brooks et al/2010	EMS within 9 US and 1 Canadian sites	Adult, 9667	night-time (00:01–06:00), weekend (Sat Sun)	Retrospective cohort	in-hospital survival	Night 1.08 (0.84–1.54), weekend 0.99 (0.82,1.19)	Age, sex, initial rhythm, witness status, bystander CPR, bystander automated external defibrillator use, EMS response time and ROC site
Bagai et al/2013	>70 EMS and 340 hospitals in US	Adult, 18588	night-time (23:01–07:00)	Retrospective cohort	in-hospital survival	1.23 (1.05–1.43)	Age, sex, race, witness status, layperson resuscitation, first monitored cardiac rhythm, and EMS response time
Uray et al/2015	EMS in Vienna	Adult, 1059	Night-time (04:01–7:59)	Retrospective cohort	12-months survival	1.01 (0.76–1.31)	Age, sex, initial rhythm, arrest location, and comorbid conditions
Karam et al/2017	EMS in Paris	Adult, 9834	night-time (18:00–8:00),weekend (Sat Sun and public holidays)	Retrospective cohort	in-hospital survival	0.85 (0.69–1.06)	Age, sex, time of occurrence, shockable initial rhythm, bystander initiated CPR, and OHCA location
Karlsson et al/2014	Denmark	Adult, 18929	night-time (23:00–06:59)	Retrospective cohort	30-day, 1-year survival	30-day 2.08 (1.64–2.63), 1-year 2.13 (1.67–2.70)	Age, sex, calendar year, first recorded heart rhythm, civil status, location, witnessed, bystander CPR, AED use, time interval and comorbidities
Schrieffl C et al/2019	EMS in Vienna	Adult, 1811	night-time (19:00–07:00), weekend (Sat Sun)	Prospective cohort	30-day survival	Night (1.1;0.9–1.3), weekend 1.1 (1.0–1.4)	age, sex and initial rhythm
Takayama W et al /2019	2 critical care centres in Japan	Adult, 1254	night-time (23:00–06:59)	Retrospective cohort	in-hospital survival	1.0 (0.98–1.03)	age, sex, witnessed, bystander CPR, initial rhythm, the cause of cardiac arrest.

AED = automatic external defibrillator, CI = confidence interval, CPR = cardiopulmonary resuscitation, EMS = emergency medical systems, OHCA = out-of-hospital cardiac arrest, OR = odds ratio, US = United States.

individual study, with a range from 1.16 (95% CI, 1.03–1.31 to 1.25 (95% CI, 1.10–1.42).

3.7. Publication bias

The existence of publication bias was judged by funnel plots and Eggers test. Although the Egger test did not reveal any significant evidence of publication bias (short-term survival for night-time

studies, $P = .319$), it is challenging to rule out the possibility of publication bias by visual inspection of the funnel plot since only 7 studies were included (Fig. 5).

4. Discussion

The principal finding of this study is that night-time is significantly associated with lower survival in OHCA patients.

Table 2
Quality assessment with Newcastle-Ottawa Scales.

Study	Selection				Comparability	Outcome			Total score
	Exposed Cohort	Nonexposed Cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Matsumura, 2016	*	*	*	*	**	*	*	—	8
Koike, 2011	*	*	*	*	**	*	*	—	8
Wallace, 2013	*	*	*	*	**	*	*	—	8
Brooks, 2010	*	*	*	*	**	*	*	—	8
Bagai, 2013	*	*	*	*	**	*	*	—	8
Uray, 2015	*	*	*	*	*	*	*	—	7
Karam, 2017	*	*	*	*	**	*	*	—	7
Karlsson, 2014	*	*	*	*	**	*	*	—	8
Schrieffl C, 2019	*	*	*	*	**	*	*	—	8
Takayama W, 2019	*	*	*	*	**	*	*	—	8

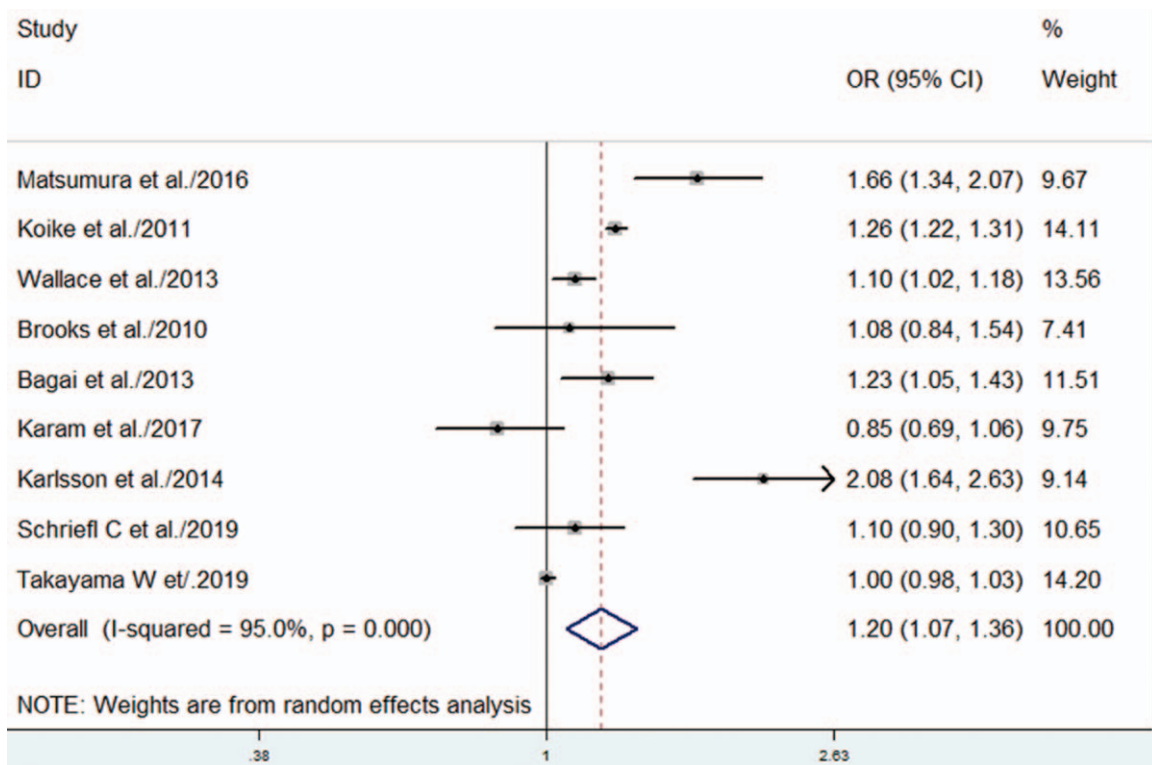


Figure 2. Forest plot showing the effect of night-time on short-term survival after OHCA. OR = odds ratio.

The relationship between short-term survival and night-time seems to be consistent in most subgroup analyses. Besides, there exists a high degree of statistical heterogeneity in our analyses. This is probably owing to the very different geographic region, number of populations, type of survival and definitions of

night-time used in included studies. Caution should be therefore required in interpretation of these findings.

Our meta-analysis suggests that an association seems to exist between time of day and OHCA outcomes. However, the underlying factor of this difference has not been fully understood

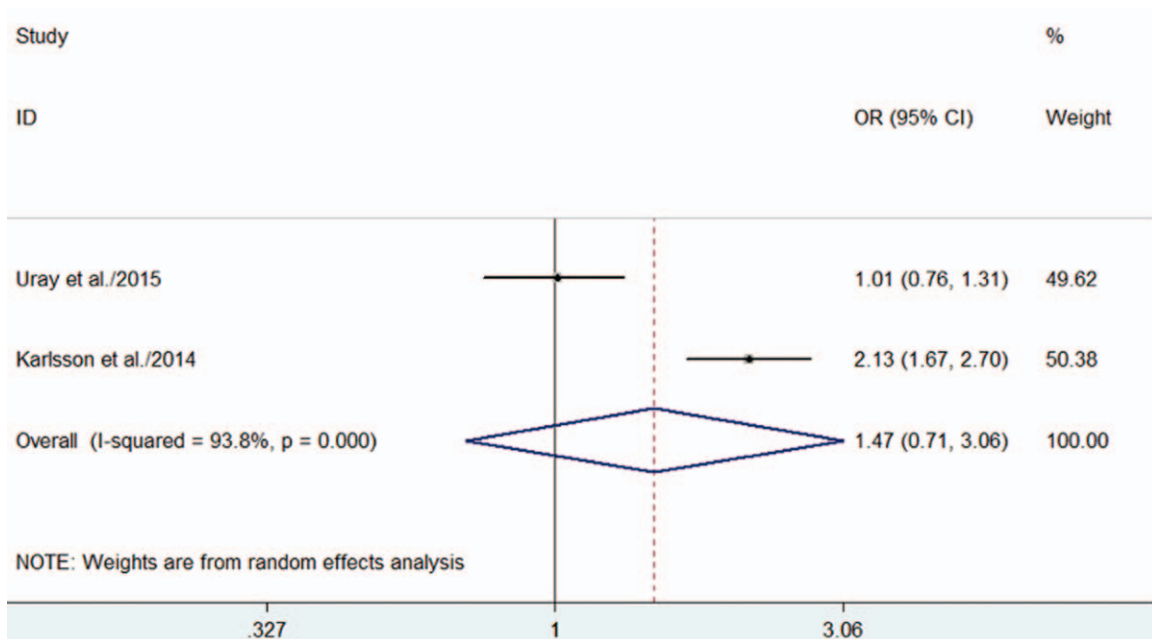


Figure 3. Forest plot showing the effect of night-time on long-term survival after OHCA. OR = odds ratio.

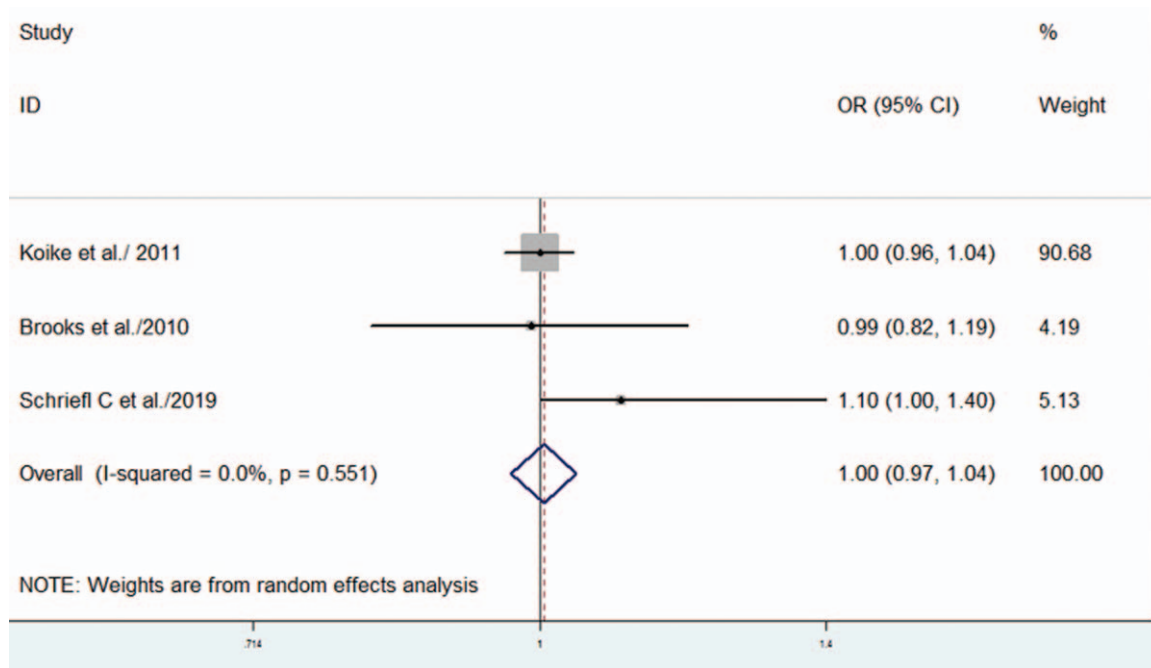


Figure 4. Forest plot showing the effect of weekend on OHCA survival. OR = odds ratio.

and requires additional research to explore. To date, there are several potential mechanisms for elaboration the effect of temporal difference in OHCA patients. First, physiological factors: several potential triggers for cardiac arrest have demonstrated circadian variability, such as physical activity, psychological stress, increases in blood pressure, heart rate and sympathetic tone, increased platelet aggregation, and decreased fibrinolytic activity.^[2,5] Second, night-time treatment of OHCA is associated with worse outcomes than day-time treatment, with

this difference being potentially attributed to the reduced frequencies of bystander CPR and witnessed cardiac arrest.^[8] On the basis of some researches, fewer staff who were fatigued and not motivated during night-time shifts might decrease the quality of treatment. Last but not least, recent work has supported that OHCA patients who were treated at night-time had an increased risk of CPR-related chest injuries.^[2,3] The lower rates of ROSC could be partially explained for a higher incidence of chest injuries, as failure of thoracic compliance (e.g., because of

Table 3
Subgroup analyses of relationship between night-time and short-term survival in OHCA.

Subgroup	Reference	Studies, n	Test of interaction		Test of heterogeneity	
			OR (95% CI)	P value	I ² , %	P value
Total	[10,17,18–24]	9	1.20 (1.07–1.36)	.001	95.0	<.0001
The definition of night						
23:00–07:00	[17,19,20,22,24]	5	1.35 (1.03–1.77)	<.0001	93.6	<.0001
17:00– 8:59	[10,18,21,23]	4	1.10 (0.96–1.25)	<.0001	86.9	<.0001
Geographic region						
Asia	[10,17,19,24]	3	1.24 (1.01–1.52)	.036	98.4	.014
North America	[18–20]	3	1.12 (1.05–1.20)	.001	0	.427
Europe	[21–23]	3	1.24 (0.77–2.02)	.375	93.7	<.0001
Sample size						
≤ 10000	[18,19,21,23,24]	5	1.03 (0.96–1.11)	.427	57.4	.052
> 10000	[10,17,20,22]	4	1.48 (1.21–1.81)	<.0001	86.8	<.0001
Study design						
Prospective cohort	[17,23]	2	1.35 (0.90–2.01)	.149	87.5	.005
Retrospective cohort	[10,18–22,24]	7	1.17 (1.03–1.34)	.018	95.9	<.0001
Adjusted for comorbidities						
YES	[22,24]	2	1.43 (0.70–2.93)	.330	97.3	<.0001
NO	[7–22,24]	7	1.17 (1.05–1.30)	.004	80.9	<.0001
Type of survival						
1-month survival	[10,17,18,22,23]	5	1.34 (1.16–1.56)	<.0001	89.5	<.0001
in-hospital survival	[19–21,24]	4	1.03 (0.90–1.18)	.63	67.6	.026

NA = not applicable, OR = odds ratio.

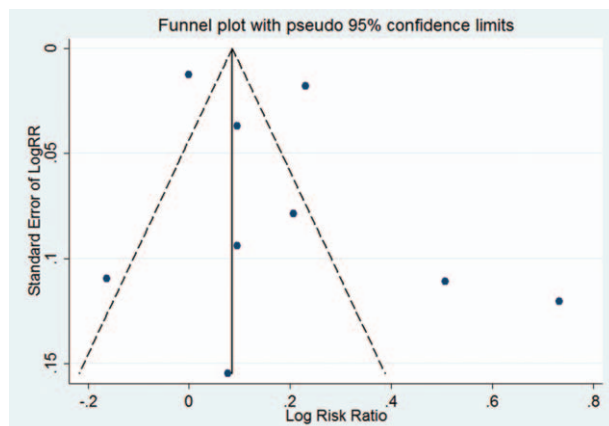


Figure 5. Funnel plot for publication bias of the relationship between night-time and short-term survival after OHCA. OR = odds ratio.

pneumothorax or fractured bones) might interrupt the cycle of positive and negative pressure, which could cause ineffective chest compressions.^[26] Furthermore, we should note that a causal relationship between night-time and worse OHCA outcomes could not be established in some subgroup, because of differences in outcome measures, definitions of night-time and so on. It is reasonable to speculate that there are several other factors which exert a stronger effect, such as bystander CPR and initial defibrillation.^[27–29] And thus the negative impact of night-time may have been masked especially when the observed association is not strong. One possible hypothesis may be that a linear association may not exist between time difference and survival; however, a threshold “late” night-time that is associated with worse outcomes may exist in OHCA patients. Therefore, more intensive resuscitation efforts may improve patient survival when OHCA occurs in a special threshold night-time.

Pre-hospital mortality is related to cardiac arrest characteristics and pre-hospital healthcare providers response, in-hospital mortality is associated with subsequent ischemia-reperfusion injury causing both organ failure and anoxic brain injury.^[30–33] Thus, out-of-hospital cardiac arrest, as a devastating medical globally, would certainly benefit more from increasing the resuscitation efforts by bystanders and in-hospital healthcare providers during the night-time. Strengthening of the early links in the chain of survival (i.e., cardiac arrest recognition, call for assistance, bystander CPR performance, and bystander AED application) has the greatest potential to improve survival. If return of spontaneous circulation occurs, the focus shifts from resuscitation to stabilization and transfer to a specialist facility. Nevertheless, the detection and treatment of patients may be less effective on the basis of differences in event characteristics, participant characteristics, and therapeutic measures when OHCA occurs at night. This meta-analysis showed that there was a relationship between time of day and survival from OHCA. Our findings suggest that more intensive resuscitation efforts during the night-time may mean better outcomes in case of OHCA. If out-of-hospital cardiac arrests are more common or survival is worse at night-time, any such association may have important implications for hospital staffing, training, care delivery processes, and equipment decisions. Physicians have a role in helping to make the public aware of the importance of effective treatment contribution to favorable outcomes.

Furthermore, although physicians are not directly involved in early pre-arrival measures to cardiac arrest, they should know how to support these resuscitation efforts, inspire proper education for lay providers, and advocate for placement of automated external defibrillators (AEDs) for public access. In other words, health policy-makers and hospital administrators can make evidence-based decisions about the hospital equipment arrangement and scheduling systems in different time period, which may play a substantial role in improving OHCA survival. With high volumes of OHCA occurring every year, even a low rate of avoidable harm will be associated with many preventable deaths. Finding a clear risk factor, even if the effect were small or indirect, would represent a great improvement in treating this deadly and costly condition accordingly.

Accounting for the existing controversies and challenges, additional researches on exploring the association between the time of day and outcomes after OHCA are still warranted. First, continued exploration into potential mechanisms is needed. Successful resuscitation efforts require implementing a “chain of survival” with both pre-hospital and hospital-based links, including activation of emergency medical service (EMS), early cardiopulmonary resuscitation, appropriate defibrillation, advanced cardiovascular life support, post-resuscitation care in the hospital and these vary according to time of day. At present it is difficult for us to precisely determine which elements are mainly responsible for the variable outcomes, accounting for the impact of off-hours (night-time and weekends) on OHCA survival. Therefore, a better understanding of temporal differences in OHCA survival certainly will hold important implications for developing preventative strategies and utmost optimization of systems for care. Second, standardizing the definition of night-time or weekend and the end points are necessary. To some extent, statistical heterogeneity could be reduced significantly. Through the standardization, it will become possible to manage data and then translate the evidence into clinical practice. However, it is interesting that patients who receive night-time treatment after OHCA have a lower survival rate compared with day-time in our predefined subgroup analyses with low heterogeneity. This is likely due to different bystander CPR rates and advanced life support (ALS) performance provided by EMS personnel considering time of the day. In addition, we did not confirm an association between weekend and OHCA survival or find the effect of night-time on OHCA survival at 12-months, although between-study heterogeneity may be a question. The principal reason is lacking of available data in this field. Thus, it is important to conduct larger, well designed studies on these topics. Finally, the relationships between temporal difference and neurological outcome or resuscitation efforts are also important issues in patients of OHCA. To date, evidence is limited and continued exploration is still needed in the future.

The strength of this meta-analysis is that there was an exhaustive search without any language restrictions and using the PRISMA guidelines as our systematic review methods. Additionally, the existing trials were rigorously judged for methodological quality, and high quality studies were included in our analysis. This analysis also has several caveats to take into account when interpreting the findings, the principal 1 being the high level of between-study heterogeneity. Perhaps unsurprisingly, this heterogeneity likely exists because of the variety of data source, populations studied, definitions for night-time and weekend, adjustment for confounding factors, and study design. Accordingly, the pool result was obtained through a random-effects

model, which could reduce the bias. Second, although more and more evidence emphasizes the potential impact of temporal difference in outcomes of patients with OHCA, no randomized trials were conducted to explore their relationship currently. Considering the characteristics of cohort study, we should acknowledge selection bias and potential confounding. In practice, just like any observational and descriptive study, it is impossible to totally exclude confounding factors, especially when the observed association is not strong. Last, current guidelines recommend testing for funnel plot asymmetry in the basis of more than 10 identified studies.^[34] Therefore, although a comprehensive search of literature was performed in our meta-analysis, it remains hard to rule out the existence of publication bias since only 9 studies were included.

In summary, the present meta-analysis revealed that nighttime have the potential to significantly decrease the likelihood of meaningful survival in patients after OHCA. Therefore, health policy-makers and hospital administrators can make evidence-based decisions about the hospital equipment arrangement and scheduling systems in different time period, which may play a substantial role in improving OHCA outcomes. However, it is interesting to note that similar findings are not founded between weekend and survival rates from OHCA. Accounting for high heterogeneity between the included studies and the lack of large, well designed, randomized studies on this topic, further evidence for improving our understanding of the effect of temporal difference on survival in OHCA patients is needed.

Author contributions

Conceived and designed the experiments: WLJ GXQ WXQ WK CLY. Performed the experiments: WLJ WXQ. Analyzed the data: WLJ WK. Contributed reagents/materials/analysis tools: CLY. Wrote the paper: WLJ GXQ WZ YH CLY. All authors have read and approved the final manuscript.

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Resources: Kai Wang.

Software: Kai Wang.

Writing – original draft: Lijun Wang, Xiaoqin Gan, Hong Yan, Zhen Wang, Li yong Chen.

Writing – review & editing: Lijun Wang, Xiaoqin Gan, Li yong Chen.

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