Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

Procalcitonin as a prognostic marker for outcomes in post-cardiac arrest patients: A systematic review and meta-analysis

Hyungoo Shin[a,b,1], Jae Guk Kim[c,1], Wonhee Kim[c,d,*], Tae Ho Lim[e], Bo-Hyoung Jang[f], Youngsuk Cho[c,d], Kyu-Sun Choi[g], Chiwon Ahn[d,h], Juncheol Lee[i], Min Kyun Na[j]

[a] Department of Emergency Medicine, College of Medicine, Hanyang University Guri Hospital, Guri, Republic of Korea
[b] Department of Emergency Medicine, Graduate School of Medicine, Hanyang University, Seoul, Republic of Korea
[c] Department of Emergency Medicine, College of Medicine, Hallym University, Chuncheon, Republic of Korea
[d] Department of Biomedical Engineering, Graduate School of Medicine, Hanyang University, Seoul, Republic of Korea
[e] Department of Emergency Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea
[f] Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
[g] Department of Neurosurgery, College of Medicine, Hanyang University, Seoul, Republic of Korea
[h] Department of Emergency Medicine, Armed Forces Yangju Hospital, Yangju, Republic of Korea
[i] Department of Emergency Medicine, Armed Forces Capital Hospital, Seongnam, Republic of Korea
[j] Department of Neurosurgery, Brain Tumour Centre, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea

Abstract

Aim: This study aimed to seek evidence for the usefulness of the procalcitonin as a prognostic blood biomarker for outcomes in post-cardiac arrest patients.

Methods: We systematically searched MEDLINE, EMBASE, and the Cochrane Library (search date: 8 January, 2019). Studies on patients who experienced return of spontaneous circulation, who had out of hospital cardiac arrest and had their level of procalcitonin measured and outcomes assessed at and after hospital discharge, were included. We additionally performed subgroup analyses for confounding factors affecting patients' outcomes. To assess the risk of bias of each included study, the Quality in Prognosis Studies tool was used.

Results: A total of 1065 patients from 10 studies were finally included. Elevated procalcitonin level during hospital admission (at 0–24 h) was associated with in-hospital mortality (standardized mean difference (SMD) 0.64, 95% confidence interval (CI) 0.33–0.95, $I^2 = 26\%$). The elevation of procalcitonin level (at 0–48 h) was also associated with poor neurologic outcomes (at 0–24 h, SMD 0.61; 95% CI 0.44–0.79, $I^2 = 0\%$; at 24–48 h, SMD 0.58, 95% CI 0.35–0.82, $I^2 = 0\%$) as well as at 1–6 months (at 24–48 h, SMD 0.62; 95% CI 0.36–0.88, $I^2 = 0\%$).

Conclusions: Overall, the findings suggested that an elevated procalcitonin level measured at 0–48 h of post-cardiac arrest syndrome was associated with poor outcomes.

Keywords: Procalcitonin, Heart arrest, Patient outcome assessment

* Corresponding author at: Department of Emergency Medicine, College of Medicine, Hallym University, 1, Singil-ro, Yeongdeungpo-gu, Seoul 07441, Republic of Korea.
E-mail address: wonsee02@gmail.com (W. Kim).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.resuscitation.2019.02.041
Received 27 November 2018; Received in revised form 7 February 2019; Accepted 28 February 2019

Introduction

The post-cardiac arrest syndrome (PCAS) is a systemic inflammatory response syndrome observed in patients who experience return of spontaneous circulation (ROSC) following cardiac arrest (CA).[1] PCAS is associated with high morbidity and mortality,[1] and is increasingly recognized as an important determinant of outcomes following CA.[2,3] Thus, better diagnostic tools for predicting patient outcomes at early time-points following treatment are needed. Recent guidelines recommend using electroencephalography, somatosensory evoked potentials, brain imaging tests and blood markers as tools for assessing neurologic outcomes.[4] Blood markers including neuron specific enolase (NSE) and S-100B are unlikely to be affected by drugs such as sedatives and are easy to assess[5]; however, serum NSE and S-100B have low sensitivity and an inconsistent threshold for predicting neurologic outcomes after ROSC.[4,6–8]

The outcome of patients with PCAS is largely dependent on the duration of whole body ischemia and the subsequent release of inflammatory mediators during reperfusion.[9] The systemic ischemia/reperfusion of CA with associated oxygen deficiency causes immune system activation and coagulation pathways, increasing the risk of multiple organ failure and infection.[10] This state has many features in common with sepsis.[9]

Procalcitonin (PCT) can be used for recognition and severity stratification of PCAS. Previous studies also reported the prognostic value of PCT after ROSC and some found that an elevated PCT level was associated with poor outcomes.[11–20] Hence, we performed the first systematic review and meta-analysis to identify the impact of PCT as a prognostic biomarker for outcomes in post-cardiac arrest patients.

Methods

Our study was based on the principles outlined in the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[21] and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[22] The protocol was registered at http://www.crd.york.ac.uk/PROSPERO/ (CRD42019121329).

We devised a question based on population, intervention, comparison, and outcome (PICO). We performed a literature search on critical assessments and summarized the eligible studies; their outcomes were then evaluated in a meta-analysis. The PICO question was as follows: population (P) = post-cardiac arrest adult patients after ROSC; intervention (I) = serum PCT level; comparator (C) = none; outcome (O) = outcomes.

Search strategy

We performed an extensive database search for studies evaluating the prognostic impact of PCT in adult patients with cardiac arrest. A literature search was performed by two experienced reviewers (H. Shin and J. Kim) on 8 January, 2019. The search encompassed the MEDLINE and EMBASE databases via the Ovid interface, and the Cochrane library without language restriction. Additionally, we manually checked the references of eligible studies to find related studies.

Search terms included "cardiac arrest" or "cardiopulmonary resuscitation" or "CPR" or "return of spontaneous resuscitation" or "ROSC" or "advanced cardiac life support" and "PCT" (Supplementary Table 1). We included all articles that reported any prospective or retrospective cohort studies that addressed our PICO question.

Study selection

Two reviewers (H. Shin and J. Kim) checked the title, abstract, and type of each article and independently selected all studies on the basis of predefined selection criteria.

The exclusion criteria were as follows: irrelevant populations (patients without sustained ROSC, and patients with sepsis or bacterial infection), irrelevant outcomes, duplicate data or studies, reviews, case reports, editorials, letters, comments, or meta-analyses, animal studies, and studies on paediatric populations. We excluded duplicate articles after comparing the title, authors, and year of publication of all identified studies. In case of disagreement between the two reviewers, a third reviewer (W. Kim) intervened, and differences were discussed until a consensus was reached. After eliminating the excluded abstracts, we acquired the full-texts of the selected articles, which were then rescreened and evaluated more thoroughly for eligibility using the same inclusion and exclusion criteria.

Ultimately, our selected studies included (1) adult patients with ROSC (2) those whose PCT levels were examined and (3) those who had neurologic outcomes recorded during admission or after discharge and in-hospital mortality.

Data extraction

Two reviewers (H. Shin, J. Kim) independently extracted the relevant data regarding patients in the included studies. Discrepancies between reviewers were discussed and resolved by consensus. The following variables were extracted: the first author's name, year of publication, country in which the study was conducted, inclusion period, study type, sample size, cardiac arrest type (out-of-hospital CA; OHCA vs. in-hospital CA; IHCA), number of patients with in-hospital mortality and poor neurologic outcome (PNO), equipment used for PCT measurement, PCT sampling time (at 0–24 h vs. at 24–48 h), tool (Glasgow Outcome Scale; GOS and Cerebral Performance Category Scale; CPC), time points of outcome measurement (at 0–1 month: within 1 month, at 1–6 months: not include 1 month but include 6 months, at 6–12 months: not include 6 months but include 12 months), and mean (±SD) PCT level. If the latter was not available, estimated mean (±SD) values were calculated from the median values with interquartile ranges using the method of Wan et al.[23] The neurologic outcome scores were divided into good or poor based on the GOS (4–5: good outcome; 1–3: poor outcome) and CPC (1–2: good outcome; 3–5: poor outcome). Some studies that did not meet these criteria are represented in Table 1. If none of these variables were described in the studies, we sent relevant questions to the corresponding authors via email.

Risk of bias in individual studies

The methodological quality of eight identified studies were independently assessed by two reviewers (H. Shin and J. Kim) with blinding to authorship and journal using the Quality in Prognosis Studies (QUIPS) tool, with values of 2, 1, and 0 considered to be low, unclear, and high risk, respectively.[24] We categorized a study as high quality if it achieved a score of nine or more points in the sum of each seven-item

Table 1 – Study characteristics.

Author	Year published	Country	Inclusion period	Study type	Sample size, CA type	PNO, n (%)	In-hospital mortality[a], n (%)	PCT detection method	PCT sampling time	Outcome measurement	
										Assessment tool[b]	Time point
Adib-conquy	2007	France	–	–	54 OHCA	40 (74.1)	40 (74.1)	Lumitest Brahms	0–24 h 24–48 h	Survival/Death	3 days
Annborn	2013	Sweden	2003–2007	sPOS	84 (73 OHCA + 11 IHCA)	42 (50.0)	41 (48.8)	BRAHMS sensitive LIA	0–24 h 24–48 h	CPC (1–2/3–5)	6 months
Engel	2013	Switzerland	2009–2012	sPOS	100 (90 OHCA + 10 IHCA)	52 (52.0)	46 (46.0)	VIDAS BRAHMS	24–48 h	CPC (1–2/3–5)	3 months
Fries	2003	Germany	–	sROS	23 OHCA	16 (69.6)	9 (39.1)	LIAISON	0–24 h 24–48 h	GOS (4–5/1–3)	2 weeks
Isenschmid	2018	Switzerland	2012–2017	sPOS	321 CA	186 (57.9)	186 (57.9)	–	0–24 h	Survival/Death	At hospital discharge
Krzych[c]	2017	Poland	–	sPOS	70 (33 OHCA + 37 IHCA)	38 (54.3)	21 (30.0)	LIAISON BRAHMS	0-24 h	GOS (4–5/1–3)	At hospital discharge
Ok	2016	Turkey	2012–2013	sPOS	30 IHCA	11 (36.7)	9 (30.0)	Cobas e411, Roche	0-24 h 24–48 h	GOS (1–3/4–5)	At hospital discharge
Pekkarinen	2018	Europe	2010–2011	mPOS	275 OHCA	142 (51.6)	132 (48.0)	LIAISON BRAHMS	0–24 h	CPC (1–2/3–5)	1 year
Stammet	2011	Luxembourg	2008–2010	sROS	53 (40 OHCA + 13 IHCA)	26 (49.1)	–	ECLIA BRAHMS	24–48 h	CPC (1–2/3–5)	6 months
Varon	2015	USA Spain	2013–2014	mROS	55 OHCA	34 (61.8)	0	Thermo Scientific BRAHMS and LUMItest	0-24 h	CPC (1–2/3–5)	0–2 weeks

Abbreviations: CA = cardiac arrest; PNO = poor neurologic outcome; PCT = procalcitonin; OHCA = out-of-hospital cardiac arrest; h = hour; ICU = intensive care unit; sPOS = single-center prospective observational study; IHCA = in-hospital cardiac arrest; CPC = cerebral performance categories; sROS = single-center retrospective observational study; GOS = Glasgow outcome scale; mPOS = multi-center prospective observational study; mROS = multi-center retrospective observational study.

[a] Number of patients with death (CPC 5 or GOS 1; GOS 5 in the study by Ok et al.).

[b] The neurologic outcome was evaluated by dividing into two groups (good versus poor). The scoring system was based on the CPC (1–2: good; 3–5: poor) and GOS (4-5: good; 1–3: poor), however, GOS scoring system was inversely used in the study by Ok et al. likewise (GOS 1–3: good outcome/GOS 4-5: poor outcome).

[c] Abstract only.

score. Unresolved disagreements between reviewers were resolved by discussion or review by the third author.

Statistical analysis

In the main analysis, we examined the association between the PCT level and outcomes among patients with ROSC. The strength of association between elevated PCT level and poor outcomes (in-hospital mortality and PNO) was measured by the standardized mean differences (SMD) using a random effects model.[25] This model was also used to synthesize the individual data of included studies considering the diversity of countries, medical systems, and inclusion periods. PCT levels across comparison groups were extracted as mean differences with 95% confidence intervals (CIs).

To measure heterogeneity, I^2 statistics were used to estimate the proportion of between-study inconsistency due to the true differences between studies (rather than differences due to random error or chance), with values of 25%, 50%, and 75% considered to be low, moderate, and high, respectively.[26]

We performed planned subgroup analyses for the following confounders: in-hospital mortality (≥40% vs. <40% vs. unknown); PNO (≥50% vs. <50%); sample size (≥60 vs. <60); OHCA (100% vs. <100%); Age (≥65 years vs. <65 years); male (≥70% vs. <70%); shockable rhythm (≥60% vs. <60% vs. unknown); therapeutic hypothermia (TTM) (100% vs. <100% vs. unknown), severity score (Acute Physiology and Chronic Health Evaluation [APACHE] II vs. Simplified Acute Physiology Score [SAPS] II vs. unknown); cumulative vasopressor dose (reported vs. unknown); and study quality (low vs. high). For specific confounders such as in-hospital mortality, PNO, sample size, male, and shockable rhythm, the calculated median value from all studies was used as a reference to perform subgroup analysis for neurologic outcome.

We used Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK) to perform the statistical analysis, and a P-value <0.05 was considered statistically significant. Identification of publication bias was also performed by the R packages 'meta' (R version 3.3.2). Publication bias was assessed using a funnel plot and Egger's test. The asymmetry of the funnel plot and P-value (<0.05) using Egger's test indicated that bias existed.

Results

Study selection and characteristics of included studies

A total of 408 records were identified through database searching (Fig. 1). After removing 51 duplicates, the titles and abstracts for 357 records were screened for eligibility. Of these, 42 records were identified as being potentially relevant, and full-text articles were retrieved for a more thorough review. After excluding 32 manuscripts following full-text assessment of the articles, ten studies, which enrolled 1065 patients, were included in the meta-analysis. Nine were full publications and one was a conference abstract.

The main characteristics of the 10 eligible studies are shown in Table 1. In addition, patients' baseline characteristics are provided in Supplementary Table 2. Two studies reported in-hospital mortality as patients' outcome. Eight studies focused on ROSC after CA and had neurologic outcomes as the main outcome measurements. Eight studies were single centre studies conducted in Europe and two were multinational studies. Four studies included only OHCA patients, one study included only IHCA patients, and four studies included both OHCA and IHCA patients. PCT was measured at 0–24 h in eight studies, at 24–48 h in six studies. In four studies, PCT was measured both at 0–24 h and at 24–48 h. Five studies assessed neurologic

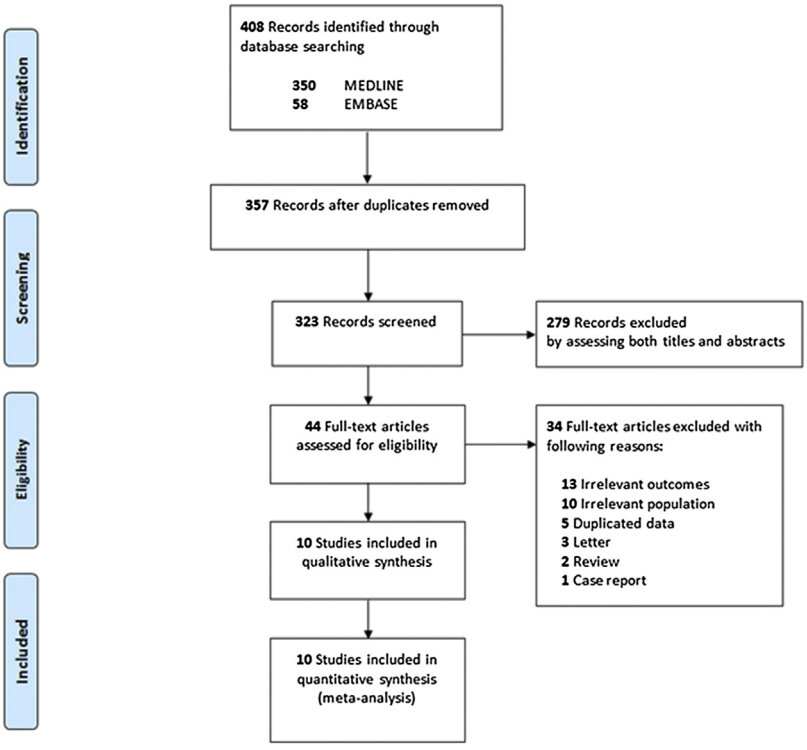

Fig. 1 – Flow diagram of studies included in the meta-analysis.

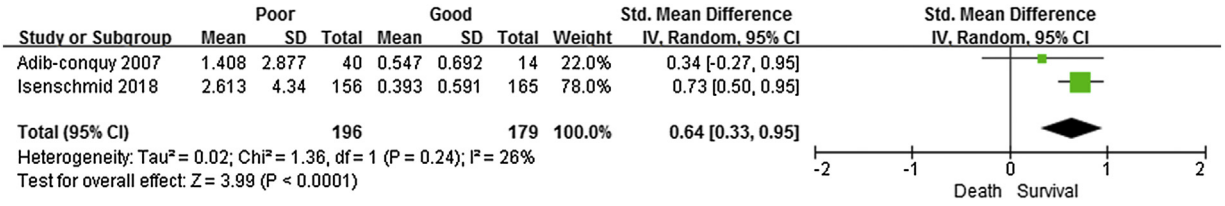

Fig. 2 – Forest plot of the effect of elevated PCT level at 0-24 h and in-hospital mortality.

outcomes according to the CPC, and considered a CPC of 3–5 as a poor neurologic outcome. Three studies evaluated patients using the GOS, and a score of 1–3 was considered a poor neurologic outcome. OK et al. divided patients into two groups (GOS 1–3: good outcome/ GOS 4–5: poor outcome).[16] Assessment tool and time point of outcome measurement at discharge or after hospital discharge are recorded in Table 1.

Quality of the included studies

Among the 10 studies that were included in this present study, using the quality scoring system, three out of 10 studies were rated as low-quality.[11,13,16] The following major factors affected the study quality: selection bias by random sequence generation, attrition bias by incomplete outcomes data and reporting bias by selective reporting bias. The summary of our risk of bias assessment of the studies included is shown in Supplementary Fig. 1.

Main analysis

Ten relevant studies including 1065 patients were analysed. Two studies reported differences in PCT level between the survivors and non-survivors. Eight studies reported differences in PCT level between the GNO group and the PNO group.

The value of PCT measured at 0–24 h for predicting in-hospital mortality

The PCT level measured at 0–24 h during hospital admission was relatively higher in non-survivors than survivors, demonstrating a positive association with an overall SMD [(mean value in the non-survivors– mean value in survivors)/pooled SD] of 0.64 (95% CI, 0.33–0.95; $I^2 = 26\%$; $P < 0.001$, Fig. 2).

The value of PCT measured at 0–24 h for predicting neurologic outcomes according to the time points for measuring neurologic outcome (at hospital discharge vs. at 0–1 month vs. at 1–6 months vs. at 6–12 months)

In our meta-analysis, the PCT level at 0–24 h during hospital admission was found to be significantly elevated in the PNO group compared to the GNO group, demonstrating a positive association with an overall SMD [(mean value in the PNO group– mean value in the GNO group)/pooled SD] of 0.61 (95% CI, 0.44–0.79; $I^2 = 0\%$; $P < 0.001$, Fig. 3). In the analysis for predicting neurologic outcome at hospital discharge, the PCT level in the PNO group was relatively

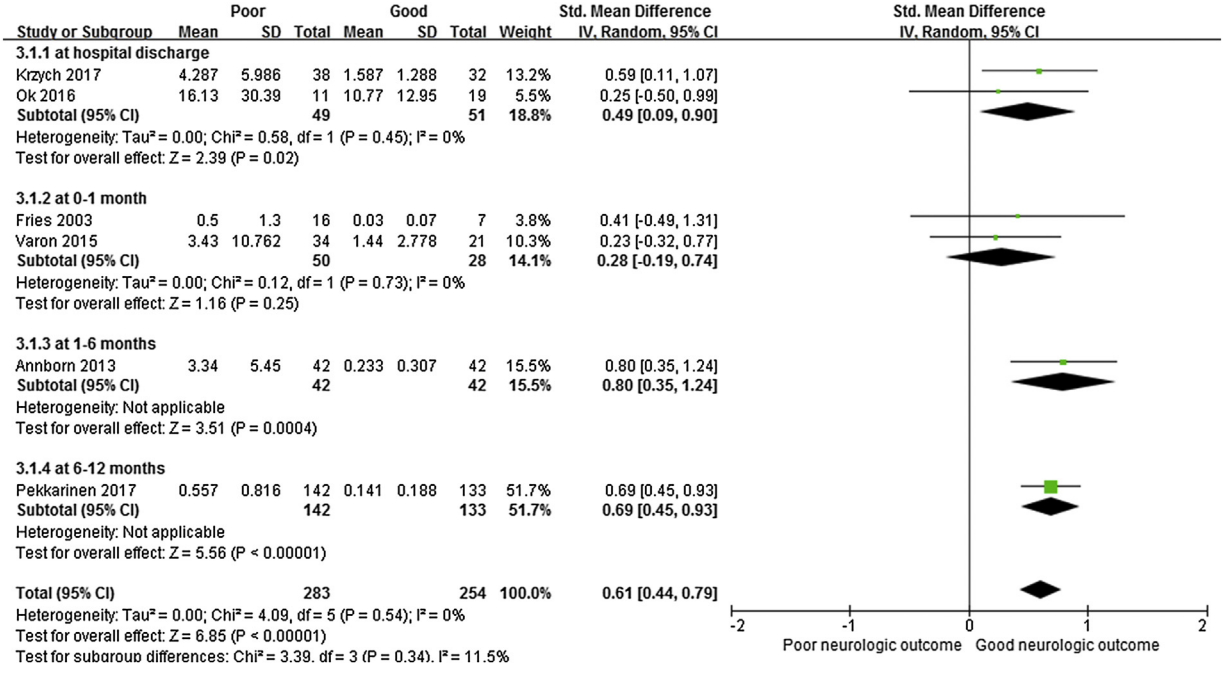

Fig. 3 – Forest plot of the effect of elevated PCT level at 0-24 h and poor neurologic outcome.

higher than that of the GNO group (2 studies; SMD, 0.49; 95% CI, 0.09–0.90; $I^2 = 0\%$; $P = 0.02$). There was no statistically significant difference in PCT level for predicting neurologic outcomes at 0–1 month between the PNO and GNO groups.

The value of PCT measured at 24–48 h for predicting neurologic outcomes according to the time points for measuring neurologic outcome (at hospital discharge vs. at 0–1 month vs. at 1–6 months vs. at 6–12 months)

The PCT level measured at 24–48 h during hospital admission was also found to be significantly higher in the PNO group than in the GNO group, demonstrating a positive association with an overall SMD [(mean value in the PNO group – mean value in the GNO group)/pooled SD] of 0.58 (95% CI, 0.35–0.82; $I^2 = 0\%$; $P < 0.001$, Fig. 4). In the analysis of time points for measuring neurologic outcome at 1–6 months, the PCT level in the PNO group was relatively higher than that of the GNO group (3 studies; SMD, 0.62; 95% CI, 0.36–0.88; $I^2 = 0\%$; $P < 0.001$).

Subgroup analysis

Subgroup analyses were performed to identify the following confounders: in-hospital mortality, PNO, sample size, OHCA, age, sex, shockable rhythm, TTM, severity score, cumulative vasopressor dose, and study quality. As a result, there were no significant changes in heterogeneities and the results of subgroup analyses are provided in Supplementary Table 3.

Publication bias

There was no definite asymmetry in the forest plot. No significant bias existed statistically in the assessment based on Egger's regression test when the PCT sampling time was analysed (at 0–24 h, $P = 0.14$; at 24–48 h, $P = 0.71$) (Fig. 5).

Discussion

This systematic review and meta-analysis showed that an elevated PCT level measured at 0–24 h during hospital admission was associated with in-hospital mortality. It further showed that the elevation of PCT level measured at 0–48 h during hospital admission was also associated with poor neurologic outcomes. To the best of our knowledge, this is the first meta-analysis to demonstrate that elevation of serum PCT could be associated with poor outcomes.

PCT has been shown to be a specific marker of bacterial infection in patients with sepsis. PCT is also a predictor of sepsis-associated mortality and a valuable tool to guide antibiotic therapy.[27–29] However, PCT levels may be increased in patients who do not have bacterial infection or sepsis.[30] Elevated PCT levels were found in patients who died from circulatory shock[31] and PCT levels increased significantly in those with cerebral ischemic stroke.[32] During cerebral ischemia/reperfusion, the calcitonin gene-related peptide (CGRP) level in the brain tissue neurons was relatively increased.[33] PCT in endocrine cells is induced by CALC-1 by elevated CGRP.[34]

Several studies have shown that during the early post resuscitation phase following CA, the diagnostic value of PCT to assess infection is poor.[35,36] In one meta-analysis, the PCT in critically ill patients showed low sensitivity and low specificity for infection.[37] Annborn et al. suggested that elevated PCT levels after CA represent a nonspecific inflammatory response, rather than a specific response to infection, and PCT levels were robustly associated with time to ROSC, a surrogate marker for duration of ischemia.[12] Engel et al. suggested that early elevated PCT levels after CA might identify patients at higher risk for cardio-circulatory failure, PCAS-related organ dysfunction and death; furthermore, elevated PCT levels are unreliable for predicting early-onset infections after CA.[13] Another previous study reported that elevated PCT levels were unrelated to infection, indicating an inflammation-related induction of PCT.[38] However, severe infection or sepsis could affect the prognosis of the patients. Coba et al. showed that OHCA adults with bacterial infection had significantly increased short-term mortality.[39] Bacterial infection including early onset pneumonia, which is common after cardiac arrest, leads to elevated PCT levels.[40] Further studies excluding patients with associated bacterial infection or sepsis in CPR are needed to identify the prognostic impact of PCT in post-cardiac arrest patients.

The 2015 AHA guidelines recommend that comatose adult patients with ROSC after CA undergo therapeutic temperature management (TTM).[4] TTM may reduce the harmful effects of ischemia by decreasing the body's need for oxygen and also help

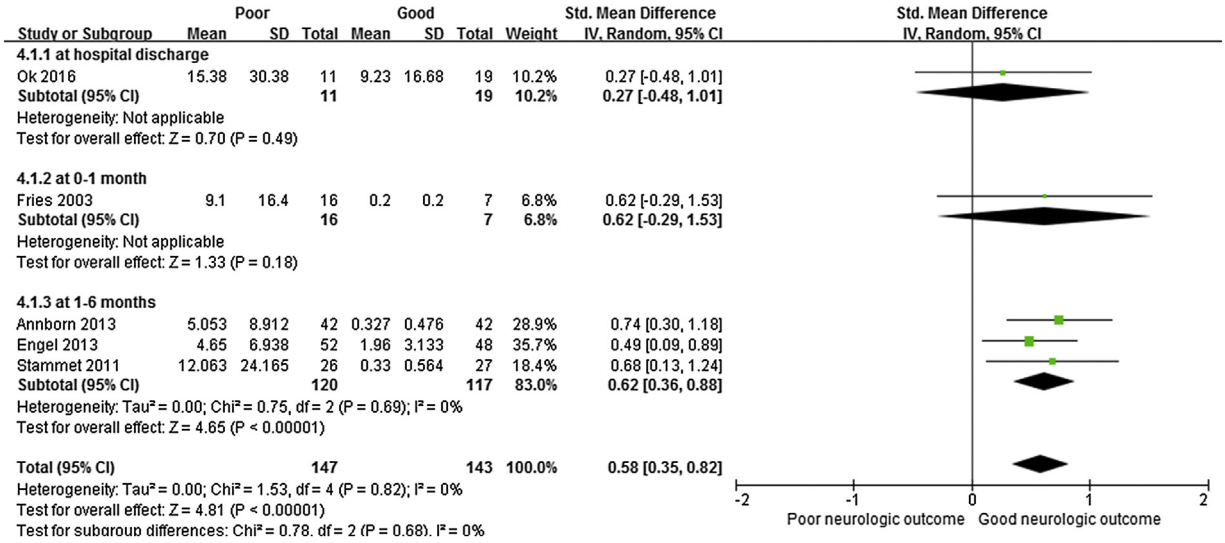

Fig. 4 – Forest plot of the effect of elevated PCT level at 24–48 h and poor neurologic outcome.

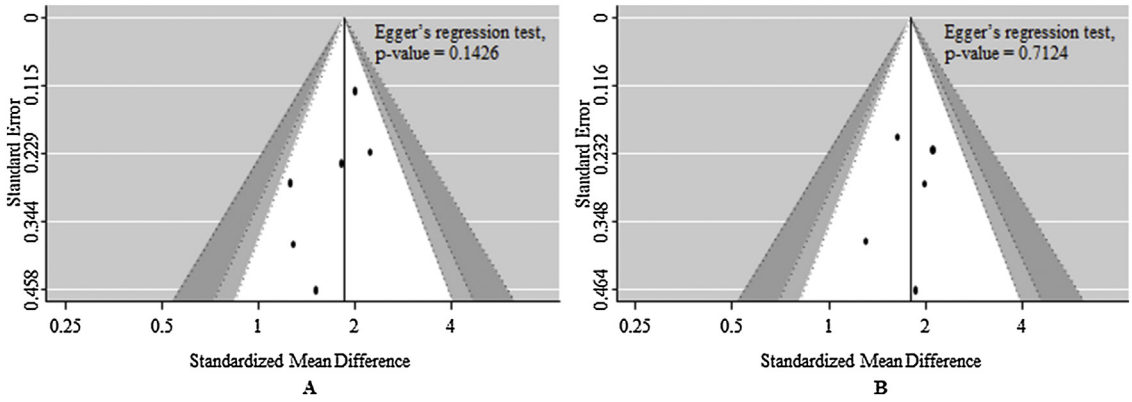

Fig. 5 – Funnel plot and Egger's regression test to assess for publication bias.
(A) Publication bias for an elevated PCT level at 0-24 h and poor neurologic outcome.
(B) Publication bias for an elevated PCT level at 24-48 h and poor neurologic outcome.

to reduce reperfusion injury, damage caused by oxidative stress when the blood supply is restored to tissue after a period of ischemia.[41] The systemic ischemia/reperfusion of CA with associated oxygen deficiency causes activation of immune system and coagulation pathways, increasing the risk of multiple organ failure and infection.[42] This condition has many features in common with sepsis.[9] PCT levels may be affected by the application and timing of induction TTM. TTM was performed in some of the patients included in this meta-analysis. Although Bro-Jeppesen et al. showed that the level of TTM did not modify the level of inflammatory markers including PCT and there were no differences in PCT levels at any time points,[43] additional studies are needed to identify the impact of TTM on PCT levels.

This meta-analysis has several limitations. First, all included studies in this meta-analysis were confined to Europe (except one multinational study including USA), and only two studies were multicentre studies. For more generalizable findings, data from other races or countries are required. Second, heterogeneity existed in patient characteristics, places of cardiac arrest (OHCA vs. IHCA), initial rhythm (shockable vs. non-shockable), and PCT sampling time (at 0–24 h vs. at 24–48 h). Although performed planned subgroup analyses and used SMD for the strength of association between elevated PCT level and poor outcomes and a random effects model, the selection bias in observational studies in this meta-analysis could not be sufficiently resolved. To address this heterogeneity, further studies should be conducted with more details, and categorized by location. Third, early CPC measured at discharge could change up until 6 months suggesting the results may have differed if a long-term CPC measurement after 6 months was used.[44] Thus, we tried to further analyse the value of PCT level for predicting neurologic outcomes according to the time points for measuring neurologic outcome (at hospital discharge vs. at 0–1 month vs. at 1–6 months vs. at 6–12 months). Fourth, we could not analyse prognostic accuracy of PCT using a summary receiver operating characteristics curve analysis for predicting poor neurologic outcomes of patients with ROSC after CA due to lack of data.

Conclusion

An elevated PCT level at an early phase of PCAS is associated with poor outcomes. On the basis of these findings, the measurement of PCT levels in adult patients with ROSC could be a valuable marker for prognosis.

Author contributions

J. Kim, H. Shin and W. Kim conceived the study, and designed the review. C. Ahn, J. Lee and M. Na performed the searches and screened studies for eligibility. T. Lim, B. Jang, Y. Cho, and K.-S. Choi assessed the quality of the papers and performed statistical analysis. J. Kim and H. Shin drafted the manuscript, and T. Lim, B. Jang, and K.-S. Choi contributed substantially to its revision. W. Kim takes responsibility for the paper as a whole.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.041.

REFERENCES

1. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350–79.

2. Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J 2006;27:2840–5.
3. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004;30:2126–8.
4. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S465–82.
5. Sandroni C, D'Arrigo S, Nolan JP. Prognostication after cardiac arrest. Crit Care 2018;22:150.
6. Pfeifer R, Börner A, Krack A, Sigusch HH, Surber R, Figulla HR. Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation 2005;65:49–55.
7. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation 2014;85:1779–17899.
8. Grubb NR, Simpson C, Sherwood RA, et al. Prediction of cognitive dysfunction after resuscitation from out-of-hospital cardiac arrest using serum neuron-specific enolase and protein S-100. Heart 2007;93:1268–73.
9. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002;106:562–8.
10. Adams JA. Endothelium and cardiopulmonary resuscitation. Crit Care Med 2006;34:S458–65.
11. Adib-Conquy M, Monchi M, Goulenok C, et al. Increased plasma levels of soluble triggering receptor expressed on myeloid cells 1 and procalcitonin after cardiac surgery and cardiac arrest without infection. Shock 2007;28:406–10.
12. Annborn M, Dankiewicz J, Erlinge D, et al. Procalcitonin after cardiac arrest – an indicator of severity of illness, ischemia-reperfusion injury and outcome. Resuscitation 2013;84:782–7.
13. Engel H, Ben Hamouda N, Portmann K, et al. Serum procalcitonin as a marker of post-cardiac arrest syndrome and long-term neurological recovery, but not of early-onset infections, in comatose post-anoxic patients treated with therapeutic hypothermia. Resuscitation 2013;84:776–81.
14. Fries M, Kunz D, Gressner AM, Rossaint R, Kuhlen R. Procalcitonin serum levels after out-of-hospital cardiac arrest. Resuscitation 2003;59:105–9.
15. Isenschmid C, Kalt J, Gamp M, et al. Routine blood markers from different biological pathways improve early risk stratification in cardiac arrest patients: results from the prospective, observational COMMUNICATE study. Resuscitation 2018;130:138–45.
16. Krzych ŁJ, Gołąb K, Pstraś J, Knapik P. Predicting outcome after cardiac arrest with serum S-100B protein and procalcitonin: a prospective observational study. Eur J Anaesthesiol 2017;34:846–8.
17. Ok G, Aydın D, Erbüyün K, et al. Neurological outcome after cardiac arrest: a prospective study of the predictive ability of prognostic biomarkers neuron-specific enolase, glial fibrillary acidic protein, S-100B, and procalcitonin. Turk J Med Sci 2016;46:1459–68.
18. Pekkarinen PT, Ristagno G, Wilkman E, et al. Procalcitonin and presepsin as prognostic markers after out-of-hospital cardiac arrest. Shock 2018;50:395–400.
19. Stammet P, Devaux Y, Azuaje F, et al. Assessment of procalcitonin to predict outcome in hypothermia-treated patients after cardiac arrest. Crit Care Res Pract 2011;2011:631062.
20. Varon J, Anda-Izaguirre ID, Fernandez-Hernandez S, et al. Procalcitonin levels as predictors of neurological outcome in patients with cardiac arrest treated with mild therapeutic hypothermia: a retrospective study. Crit Care Shock 2015;18:97–103.
21. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
24. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280–6.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
27. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
28. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001;164:396–402.
29. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med 2006;34:2596–602.
30. Meisner M. Update on procalcitonin measurements. Ann Lab Med 2014;34:263–73.
31. Adib-Conquy M, Monchi M, Goulenok C, et al. Increased plasma levels of soluble triggering receptor expressed on myeloid cells 1 and procalcitonin after cardiac surgery and cardiac arrest without infection. Shock 2007;28:406–10.
32. Tian D, Zhang S, He X, Liu H. Serum procalcitonin as a diagnostic marker in acute ischemic stroke. Neuroreport 2015;26:33–7.
33. Yang SI, Yuan Y, Jiao S, Luo QI, Yu J. Calcitonin gene-related peptide protects rats from cerebral ischemia/reperfusion injury via a mechanism of action in the MAPK pathway. Biomed Rep 2016;4:699–703.
34. Vijayan AL, Vanimaya, Ravindran S, et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care 2017;5:51.
35. Mongardon N, Lemiale V, Perbet S, et al. Value of procalcitonin for diagnosis of early onset pneumonia in hypothermia-treated cardiac arrest patients. Intensive Care Med 2010;36:92–9.
36. Schuetz P, Affolter B, Hunziker S, et al. Serum procalcitonin, C-reactive protein and white blood cell levels following hypothermia after cardiac arrest: a retrospective cohort study. Eur J Clin Invest 2010;40:376–81.
37. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 2007;7:210–7.
38. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care 2004;8: R234–42.
39. Coba V, Jaehne AK, Suarez A, et al. The incidence and significance of bacteremia in out of hospital cardiac arrest. Resuscitation 2014;85:196–202.
40. Tsai MS, Chiang WC, Lee CC, et al. Infections in the survivors of out-of-hospital cardiac arrest in the first 7 days. Intensive Care Med 2005;31:621–6.
41. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008;371:1955–69.
42. Cerchiari EL, Safar P, Klein E, Diven W. Visceral, hematologic and bacteriologic changes and neurologic outcome after cardiac arrest in dogs. The visceral post-resuscitation syndrome. Resuscitation 1993;25:119–36.
43. Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. The inflammatory response after out-of-hospital cardiac arrest is not modified by targeted temperature management at 33 °C or 36 °C. Resuscitation 2014;85:1480–7.
44. Scheel M, Storm C, Gentsch A, et al. The prognostic value of gray-white-matter ratio in cardiac arrest patients treated with hypothermia. Scand J Trauma Resusc Emerg Med 2013;21:23.