Evidence synthesis on prognostic factors after cardiopulmonary resuscitation for in-hospital or out-of-hospital cardiac arrest

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1 Background

Every year, about 8000 people suffer from cardiac arrest in Switzerland, either during a hospitalisation (in-hospital setting) or outside (out-of-hospital setting)[17]. Despite the introduction of technology such as automated external defibrillators (AED) and standardized training in basic and advanced cardiac life support, the prognosis in most cases remains poor. Early decisions about the use of cardiopulmonary resuscitation (CPR) need to be informed by the available research evidence on prognosis.

In 2008 the Swiss Academy of Medical Sciences (SAMS) established a guideline for decisions about resuscitation, which was partly revised in 2013[16]. The present evidence synthesis was commissioned with the aim to review the current evidence on factors that are associated with the long-term prognosis of cardiac arrest after CPR in both the in-hospital and out-of-hospital setting. The results will be used to update the SAMS Guideline[16].

2 Methods

After consultation with members of the SAMS subcommittee in charge, we defined the inclusion criteria for this evidence synthesis as follows:

2.1 Population of interest

Adults and children.

2.2 Intervention

Cardiopulmonary resuscitation after cardiac arrest in the in-hospital or out-of-hospital setting.

2.3 Outcomes of interest

(1) Survival to hospital discharge and (2) survival with favourable neurological outcome (as defined by authors of the systematic reviews).

We took into account that the relevant literature uses a broad range of outcomes with a focus on short-term outcomes that are measurable during acute care. We deliberately restricted the scope of this evidence synthesis to two patient-relevant outcomes of interest. Prognostic factors associated with these two outcomes will be informative for the planned Guideline update.

2.4 Prognostic factors

Known patient characteristics or factors that can be measured immediately before, during or immediately after CPR for cardiac arrest (i.e. in the so-called pre-arrest, intra-arrest or post-arrest period).

2.5 Type of evidence

We used systematic reviews that were published in 2008 or later (i.e. the year of publication of the previous SAMS Guideline). Individual primary studies were not

considered. Reviews were only included if they provided adequate information in the Methods section to allow a judgement on whether it was systematically conducted. Only systematic reviews with a clear focus on prognostic factors were included. Those evaluating the effective-ness or safety of interventions used during or after CPR were excluded, as were systematic reviews on the diagnostic test accuracy of specific tests. Systematic reviews on very specific groups suffering from cardiac arrest (e.g. during submersion in water) were excluded because they would not be in-line with the broader scope of the Guideline.

2.6 Literature searches

We designed a systematic search strategy using Medical Subject Headings (MeSH) and free-text words (Appendices 7.1 and 7.2). Searches were adapted and run in Medline (accessed via PubMed) and the Cochrane Database of Systematic Reviews. The website of the European Network for Health Technology Assessment (EUnetHTA) was also searched for relevant health technology assessment reports. All searches were conducted in June 2018.

2.7 Selection of systematic reviews

The retrieved records were managed in a Reference Manager database. After deduplication, one assessor screened the titles and abstracts. A second assessor verified the decisions of the first. Of the retained references, we retrieved the full-text articles and decided on definitive inclusion. Again, a second assessor verified the decisions of the first.

2.8 Data extraction

Descriptive characteristics from each systematic review were extracted, as well as numerical information about the strength of association of prognostic factors with the outcomes of interest (e.g. odds ratios). If the definition of the outcome was different from ours (e.g. mortality instead of survival), we converted the extracted numeric values for both point estimates and limits of 95% confidence intervals. Whenever pooled results were not available, we extracted the narrative description of the results. Extracted data were entered in a Microsoft Excel spreadsheet, which was designed for this purpose. The data extraction of a random sample of 4 studies was checked in detail by a second assessor. As there were no major differences with the initial data extraction, the data extraction for the remaining studies was not re-checked.

2.9 Assessment of review quality

We chose an adapted version of the Risk of Bias in Systematic Reviews (ROBIS) tool, for the assessment of the methodological quality of the included systematic reviews. This provides detailed information on 21 key items in four domains and an overall assessment of risk of bias[23] . We accessed a specialized resource, the KSR Evidence database (https://ksrevidence.com) to retrieve available ROBIS assessments of included systematic reviews. Assessments that were not available in the database were then conducted by trained staff of Kleijnen Systematic Reviews Ltd. (York, United Kingdom), the producer of KSR Evidence.

3 Results

3.1 Literature searches

Our searches identified 669 potentially relevant records after removal of duplicates (see PRISMA flow diagram, Appendix 7.3). Title and abstract screening excluded 524 records.; of those, we kept the records of 116 guideline documents, which were not assessed futher at this stage. The full text of 145 records was assessed for inclusion; of which 124 records were excluded for various reasons (for details see Prisma Flow Diagram, Appendix 7.3). As a result 21 systematic reviews were included in this report[1-15,18-22,24].

3.2 Characteristics of included reviews

Of the 21 included systematic reviews, 17[1-11,13,15,18,20-22] focused on adults and one on children[14] (Table 1). One was mainly on studies in adults but probably included some studies in children, as well[24]. Two systematic reviews[12,19] did not specify the population they focused on, and we grouped them with the ones focusing on adults. Three systematic reviews[3,5,22] reported prognostic factors for cardia arrest in in-hospital settings and nine[1,4,6,7,9,15,18,21,24] in out-of-hospital settings; the remaining reviews[2,8,10-14,20] reported results for both. Of note, one review[19] did not specify the setting and is reported together with the reviews reporting results for both in- and out-of-hospital settings. The number of included studies per systematic review ranged from 5 to 79. The total number of included patients per systematic review ranged from 841 to 1,108,281. Nineteen[1-3,5-15,18,20-22,24] systematic reviews reported survival to hospital discharge and 13[2-4,6-12,14,19,21] survival with favourable neurological outcome. For further details, see Table 1.

3.3 Quality of included reviews

In the overall assessment of methodological quality, two[1,2] of the 21 included reviews had low risk of bias and one[18] had unclear risk of bias. The remaining 18 reviews were fraught with high risk of bias.

The detailed assessments by ROBIS domain and review are included in the Supplementary Table S1 (Appendix 7.4). With regard to aspects of study eligibility (ROBIS domain 1), nine reviews had low risk of bias, three unclear risk of bias and nine high risk of bias. When considering aspects of identification and selection of studies for inclusion in the systematic review (ROBIS domain 2), four reviews had low risk of bias, two had unclear risk of bias and 15 had high risk of bias. In data collection and appraisal of the included studies (ROBIS domain 3), five reviews had low risk of bias, three had unclear risk of bias and 13 had high risk of bias. With regard to synthesis and presentation of findings (ROBIS domain 4), seven reviews had low risk of bias, two had unclear risk of bias and twelve had high risk of bias.

3.4 Association with prognostic factors

Results are presented separately for adults and children in a table format, as well as for the in-hospital, out-of-hospital and mixed setting. Each table is split into: part (a) for the outcome “Survival to hospital discharge” and part (b) for the outcome “Favourable neurological outcome”. There were differences in how each systematic review defined “good” or “favourable” neurological outcome (see footnotes in each table). We catego-

rised prognostic factors as “pre-arrest”, “intra-arrest” and “post-arrest” using available information from the systematic reviews.

3.4.1 Adults experiencing in-hospital cardiac arrest

In five systematic reviews[3,5,8,10,22] we identified 26 prognostic factors for survival to hospital discharge (Table 2a). In two[3,8] systematic reviews three prognostic factors for favourable neurological outcome were identified. (Table 2b).
The following factors reported a statistically significant association with survival to hospital discharge: younger age, cardiac aetiology of cardiac arrest, lower blood creatinine level, overweight resp. obesity (BMI 25-29.9 resp. >30 vs. 18.5 to 24.9), shockable cardiac rhythm, shorter low-flow time (i.e. time until extracorporeal CPR was started), shorter total cardiac arrest time, lower blood lactate level before CPR, duration of chest massage of less than five minutes, lower blood lactate on ICU admission, and lower creatinine level within 24 hours after ICU admission. The following factors reported a statistically significant inverse association with survival to hospital discharge: known metastatic malignancy, known dependency, haematocrit < 0.35, presence of more than two acute diseases, higher SOFA score and higher (modified) PAM scores.
The following factors reported a statistically significant association with favourable neurological outcomes: overweight (BMI 25 to 29.9 vs. 18.5 to 24.9), shorter low-flow time and lower blood lactate level.

3.4.2 Adults experiencing out-of-hospital cardiac arrest

In ten systematic reviews[1,6-10,15,18,21,24] we identified 14 prognostic factors for survival to hospital discharge (Table 3a) and in five systematic reviews [4,6-9] ten prognostic factors for favourable neurological outcome (Table 3b).
The following factors reported a statistically significant association with survival to hospital discharge: female gender, younger age, race (white vs. black), cardiac arrest witness by bystander / emergency medical service, bystander CPR, presenting cardiac rhythm (ventricular fibrillation / tachycardia), gasping, and return to sponta-neous circulation. The following two factors reported a statistically significant inverse association with survival to hospital discharge: nursing home residency and asystole.
The following factors reported a statistically significant association with favourable neurological outcomes: initial shockable cardiac rhythm, conversion to sponta-neous shockable rhythm, shorter low-flow time, increased arterial pH on admission, and lower blood lactate level.

3.4.3 Adults experiencing either in-hospital or out-of-hospital cardiac arrest

In six systematic reviews[2,8,10,12,13,20] we identified four prognostic factors for survival to hospital discharge (Table 4a) and in six systematic reviews[2,8,10-12,19] six prognostic factors for favourable neurological outcome (Table 4b).
The following factors reported a statistically significant association with survival to hospital discharge: underweight (BMI < 18.5) resp. overweight (BMI 25-29.9), better cerebral oxygenation as measured by near-infrared spectroscopy (NIRS) saturation, higher end-tidal carbon dioxide ($EtCO_2$) level, and lower arterial carbon dioxide tension ($PaCO_2$).

The following factors reported a statistically significant association with favourable neurological outcomes: overweight (BMI 25.0-29.9), better cerebral oxygenation as measured by near-infrared spectroscopy (NIRS) saturation, (severe) rebound hyperthermia, lower arterial carbon dioxide tension ($PaCO_2$), increased neuron-specific enolase and decreased S-100B marker. The following factors reported a statistically significant inverse association with favourable neurological outcomes: rebound hyperthermia and severe rebound hyperthermia (>38.5°C).

3.4.4 Children experiencing either in- or out-of-hospital cardiac arrest

In one systematic review[14] we identified four prognostic factors for survival to hospital discharge (Table 5a) and in the same review seven prognostic factors for favourable neurological outcome (Table 5b). The following two factors reported a statistically significant association with survival to hospital discharge: initially shockable rhythm and shorter duration of resuscitation. For The following factors reported a statistically significant association with favourable neurological outcomes: age above one year, initially shockable rhythm, any CPR by bystander, daytime (vs. night), working week day (vs. weekend/holiday) and CPR instructions to bystander via telephone.

4 Discussion

We identified 21 systematic reviews that were published over the past ten years and matched with our inclusion criteria. We identified only one systematic review with a clear focus on children. Although this review included data from more than 18,000 patients from 16 primary studies, the evidence on prognostic factors after CPR in children (as compared to adults) is not well established.

Overall, most of the included systematic reviews were of low methodological quality. Methodological shortcomings were present in all four domains defined by the ROBIS tool and included a lack of transparency about study populations (e.g. whether analysed datasets included children), setting in which cardiac arrest occurred (in-hospital or out-of-hospital), and definitions of outcomes. We assume that some of these problems are due to the poor reporting quality of the included primary studies. Several reviews provided only narrative accounts of which factors were found to be associated with the outcomes of interest in the included studies. We did not verify such information systematically by retrieving and checking the primary studies as this was beyond the scope of this work.

The analysed systematic reviews do not suggest that there is a clear pattern of factors that are associated with survival to hospital discharge or with favourable neurological outcome after CPR. One may regard as the more robust prognostic factors those that were associated in both settings (i.e. in-hospital and out-of-hospital). For survival to hospital discharge (in adults) such factors were younger age and absence of functional dependency/nursing home residency. For survival with favourable neurological outcome (in adults), such factors were shorter low-flow time (time until extracorporeal CPR was started) and lower blood lactate level. A more in-depth analysis and interpretation would need to take into account additional aspects such as generalizability of results, strength of association and dose-response relationships. Any conclusion on prognostic factors in children will need to take into account that only one systematic review reported on paediatric populations.

5 Tables

Table 1: Characteristics of included systematic reviews (NR=not reported)

Review	Population	In-/Out-of-hospital setting	Number of included studies/ datasets	Number of included patients	Survival to hospital discharge	Survival with favourable neurological outcome	Risk of bias (ROBIS)
Bougouin 2015[1]	Adults	Out	13	409,323	Yes	No	Low
Cournoyer 2016[2]	Adults	Both	20	2,436	Yes	Yes	Low
D'Arrigo 2017[3]	Adults	In	11	856	Yes	Yes	High
Debaty 2017[4]	Adults	Out	15	841	No	Yes	High
Ebell 2011[5]	Adults (>14 y.)	In	35	96,499	Yes	No	High
Geri 2017[6]	Adults	Out	9	46,417	Yes	Yes	High
Hasan 2014[7]	Adults	Out	11	548,440	Yes	Yes	High
Kakavas 2018[8]	Adults (based on mean age)	Both[a]	7	24,651	Yes	Yes	High
Luo 2017[9]	Adults	Out	12	1,108,281	Yes	Yes	High
Ma 2018[10]	Adults	Both[a]	7	25,035	Yes	Yes	High
Makker 2017[11]	Adults (at least in 4/6 studies)	Both	6	950	Yes[b]	Yes	High
McKenzie 2017[12]	Not specified[c]	Both	9	23,434	Yes	Yes	High
Paiva 2018[13]	Adults	Both	17	6,198	Yes	No	High
Phillips 2015[14]	Children (0-18 y.)	Both	16 (in 21 publ.)	>18,000	Yes	Yes	High
Sasson 2010[15]	Adults	Out	79	142,740	Yes	No	High
Shah 2012[18]	Adults	Out	15	107,426	Yes	No	Unclear
Shinozaki 2009[19]	Not specified[c]	Not specified	24	NR	No	Yes	High
Touma 2013[20]	Adults	Both	23	NR	Yes	No	High
van de Glind 2013[21]	Adults (>70 y.)	Out	23	44,582	Yes	Functional and cognitive status	High
van Gijn 2014[22]	Adults (>70 y.)	In	29	417,190	Yes	No	High
Zhao 2015[24]	Adults[d]	Out	5 (in 4 publ.)	10,797	Yes	No	High

[a] Results reported also separately for in- and out-of-hospital cardiac arrest; presented in the relevant tables.
[b] One of 6 studies reported 30-day mortality.
[c] Results are presented together with the reviews reporting on adults.
[d] Three of 5 studies likely included children.

Table 2a: Prognostic factors assessed for survival to discharge in adults experiencing in-hospital cardiac arrest (MD=Mean Difference; OR=Odds Ratio; BMI=Body Mass Index; VF/VT=Ventricular Fibrillation/pulseless Ventricular Tachycardia; ICU=Intensive Care Unit; SOFA=Sequential Organ Failure Assessment; PAR=Prognosis After Resuscitation; PAM=Pre-Arrest Morbidity)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
Age	1[3]	MD −2.33 years (−5.98 to 1.31)
Age >75 years (vs. below)	1[5*]	OR 0.35 (0.16 to 0.80)**
Age >80 years (vs. below)	1[5*]	OR 0.37 (0.16 to 0.88)**
Gender (women vs. men)	1[3]	OR 1.12 (0.76 to 1.67)**
Cardiac aetiology	1[3]	OR 1.90 (1.03 to 3.52)
Blood creatinine level	1[3]	MD −0.41 mg/ml (−0.67 to −0.14)
Cardiac arrest was anticipated	1[5*]	OR 0.05 (0.00 to 1.25)**
Haematologic malignancy (co-morbidity)	1[5*]	OR 0.26 (0.04 to 1.67)**
Metastatic malignancy (co-morbidity)	1[5*]	OR 0.21 (0.07 to 0.63)**
Dependency (any location)	1[5*]	OR 0.16 (0.06 to 0.39)**
Independent function level	1[22]	1 study reported not significant association with survival
Normal mental status	1[22]	1 study reported not sign. association
Haematocrit of <0.35	1[22]	1 study reported inverse stat. sign. association with survival
Presence of more than 2 acute diseases	1[22]	1 study reported inverse stat. sign. association with survival
Other factors (gender, history of diabetes mellitus, congestive heart failure or COPD, pre-arrest functional cardiopulmonary statues, cause of the arrest)	1[22]	1 study reported not sign. association with survival
BMI 25-29.9 vs. BMI 18.5-24.9	1[8]	OR 1.18 (1.11 to 1.24)
BMI >30 vs. BMI 18.5-24.9	1[8]	OR 1.18 (1.08 to 1.29)
BMI ≤25-30 vs. BMI 18.5-25	1[10]	OR 1.23 (0.98 to 1.56)**
Intra-arrest		
Shockable cardiac rhythm	1[3]	OR 1.65 (1.05 to 2.61)
Low-flow time (until extracorporeal CPR)	1[3]	MD −17.15 min (−20.90 to −13.40)
Total cardiac arrest time	1[3]	MD −11.49 min (−22.78 to −0.19)
Blood lactate level before CPR started	1[3]	MD −4.12 mmol/L (−6.0 to −2.24)
Duration of chest massage ≤ 5 mins vs. >5 mins	1[22]	1 study reported stat. sign. association with survival
VF/VT vs. other rhythms	1[22]	2 studies reported association with survival
Other factors (arrest time, CPR time)	1[22]	1 study reported no sign. association with survival

Post-arrest		
Blood lactate on ICU admission	1[3]	MD −4.13 mmol/L (−6.38 to −1.88)
Creatinine level within 24 hours after ICU admission	1[3]	MD −0.37 mg/dl (−0.54 to −0.19)
SOFA score	1[3]	MD −1.71 (−2.93 to −0.50
PAR >5	1[5]*	OR 0.06 (0.00 to 1.11)**
PAR >7	1[5]*	OR 0.04 (0.00 to 0.71)**
Modified PAM >6	1[5]*	OR 0.10 (0.01 to 0.77)**
PAM >3	1[5]*	OR 0.12 (0.02 to 0.91)**

* Data extracted from Ebell (2011) represent a sub-selection (by authors) of the factors for which survival probability is less than 3.5% and more than 50 patients with variable of interest; more detailed estimates for other factors can be found in the full text of this systematic review (see ref. 5).
** Calculated from reported values.

Table 2b: Prognostic factors assessed for favourable neurological outcome* in adults experiencing in-hospital cardiac arrest (OR=Odds Ratio; BMI=Body Mass Index)

Prognostic factor	Number of reviews	Pooled result
Pre-arrest		
BMI 25-29.9 vs. BMI 18.5-24.9	1[8]	OR 1.16 (1.06 to 1.28)
BMI >30 vs. BMI 18.5-24.9	1[8]	OR 1.09 (0.96 to 1.23)
Intra-arrest		
Shorter low-flow time	1[3]**	OR 1.04 (1.00 to 1.08]
Decreased blood lactate level	1[3]**	OR 1.31 (1.13 to 1.52)

* Definition of favourable neurological outcome: Cerebral Performance Categories (CPC) 1 or 2 (i.e., neurological disability from absent to moderate).
** Calculated from reported values.

Table 3a: Prognostic factors assessed for survival to discharge in adults experiencing out-of-hospital cardiac arrest (OR=Odds Ratio; MD=Mean Difference; BMI=Body Mass Index; EMS=Emergency Medical Services; VF/VT=Ventricular Fibrillation/Ventricular Tachycardia)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
Race (black vs. white)	1[18]	OR 0.72 (0.60 to 0.86)
Gender (women vs. men)	1[1*]	OR 1.10 (1.03 to 1.20)
	1[7]	2 studies reported no association with survival, especially when taking into account other factors (age, witnessed arrest etc.)
Age	1[21]	8 studies reported stat. sign. reverse association between age and survival
Nursing home residency	1[21]	2 out of 6 studies reported sign. reverse association with survival
BMI 25-29.9 vs. BMI 18.5-24.9	1[8]	OR 1.05 (0.86 to 1.24)**
BMI >30 vs. BMI 18.5-24.9	1[8]	OR 0.86 (0.44 to 1.70)**
BMI 25-29.9 vs. BMI 18.5-24.9	1[10]	OR 1.08 (0.53 to 2.17)***
Intra-arrest		
Cardiac arrest witnessed by bystander	1[15]	OR 0.34 (0.07 to 1.66) to 4.42 (1.81 to 10.80)****
Cardiac arrest witnessed by EMS	1[15]	OR 1.65 (0.63 to 4.34) to 6.04 (4.12 to 8.85)****
Bystander CPR	1[15]	OR 0.98 (0.29 to 3.35) to 5.01 (2.57 to 9.78)****
VF/VT as presenting cardiac rhythm vs. other rhythms	1[15]	OR 2.91 (1.10 to 7.66) to 20.62 (12.61 to 33.72)****
Asystole as presenting cardiac rhythm	1[15]	OR 0.10 (0.03 to 0.31) to 0.33 (0.19 to 0.57)****
Gasping	1[24**]	RR 3.525 (3.03 to 4.10)
Post-arrest		
Return of spontaneous circulation	1[15]	OR 20.96 (7.43 to 59.13) to 99.84 (14.30 to 696.89)****
Conversion to spontaneous shockable rhythm	1[9]	unadjusted OR 1.38 (0.66 to 2.89)
Transport time	1[6]	MD −0.05 minutes (−0.86 to 0.76)

* Bougoin (2015) reports survival at hospital discharge or at 1 month.
** Zhao (2015) included database studies with both adults and children.
*** Calculated from reported data.
**** Stratified by baseline survival rate.

Table 3b: Prognostic factors assessed for favourable neurological outcome* in adults experiencing out-of-hospital cardiac arrest (OR=Odds Ratio; WMD=Weighted Mean Difference; BMI=Body Mass Index)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
Gender (Women vs men)	1[4,7]	OR 1.75 (0.93 to 3.31)
	1[7]	Association with good neurological outcome
Age	1[4]	WMD 0.39 years (-4.47 to 3.69)
BMI 25-29.9 vs. BMI 18.5-24.9	1[8]	OR 0.95 (0.78 to 1.17)
BMI >30 vs. BMI 18.5-24.9	1[8]	OR 0.715 (0.333 to 1.533)
Intra-arrest		
Bystander CPR	1[4]	OR 2.81 (0.95 to 8.32)
Initial shockable cardiac rhythm	1[4]	OR 2.20 (1.30 to 3.72)
Low-flow time (until extracorporeal CPR)	1[4]	WMD -0.11 (-0.21 to -0.01)
Post-arrest		
Conversion to spontaneous shockable rhythm	1[9]	unadjusted OR 3.78 (2.58 to 5.52) adjusted: OR 2.69 (2.00 to 3.62)
Transport time	1[6]	+17 (−10.37 to 44.37)**
Arterial PH on admission	1[4]	WMD 0.12 (0.03 to 0.22)
Lactate concentration	1[4]	WMD -3.52 mmol/L (-5.05 to -1.99)

*Definition of favourable neurological outcome: Debaty (2017): Pittsburgh cerebral performance categories 1–2; Hasan (2014): not defined; Luo (2017): Cerebral performance category scores (CPC) of 1–2; Geri (2017): not defined but seems to be CPC 1-2.
**Unit of time was not specified (we assume it was minutes).

Table 4a: Prognostic factors assessed for survival to discharge in adults experiencing either in or out-of-hospital cardiac arrest (OR=Odds Ratio; SMD=Standardised Mean Difference; BMI=Body Mass Index; NIRS= Near-infrared Spectroscopy ; ETCO2=End-Tidal Carbon Dioxide; PACO2=Arterial Carbon Dioxide Tension)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
BMI <18.5 vs. BMI 18.5-24.9	2[8,10*]	OR 0.74 (0.60 to 0.91)**; OR 0.78 (0.65 to 0.94)
BMI 25-29.9 vs. BMI 18.5-24.9	2[8,10*]	OR 1.14 (0.93 to 1.39)**; OR 1.17 (1.11 to 1.24)
BMI >30 vs. BMI 18.5-24.9	2[8,10*]	OR 1.05 (0.87 to 1.28); OR 1.11 (0.91 to 1.35)**
Intra-arrest		
NIRS values (combined initial & mean)	1[2]	SMD 1.63 (1.34 to 1.92)
Mean NIRS saturation values	1[2]	SMD 1.14 (-0.05 to 2.33)
Initial NIRS saturation values	1[2]	SMD 1.66 (1.36 to 1.96)
Initial ETCO2 ≥ 10 vs. <10	1[13]	OR 11.41 (1.44 to 90.17)
Initial ETCO2 ≥ 20 vs. <20	1[13]	OR 13.82 (3.58 to 53.37)
20-min ETCO2 ≥ 10 vs. <10	1[13]	OR 5.14 (0.53 to 49.50)
20-min ETCO2 ≥ 20 vs. <20	1[13]	OR 20.00 (1.97 to 203.32)
Higher ETCO2	1[20]	5 studies reported sign. association with survival. Unclear whether this was confirmed in all remaining studies.
Post-arrest		
High PACO2 (hypercarbia) vs. normal (normocarbia)	1[12]	3/6 studies reported sign. association between normocarbia and survival
High PACO2 (hypercarbia) vs. normal (normocarbia)	1[12]	Peto OR 1.30 (1.23 to 1.38)
High PACO2 (hypercarbia) vs. low (hypocarbia)	1[12]	1/6 studies reported sign. association between hypocarbia and survival

* Ma (2018) reports survival at discharge or at 6 months.
** Calculated from reported values.

Table 4b: Prognostic factors assessed for favourable neurological outcome* in adults experiencing either in or out-of-hospital cardiac arrest (OR=Odds Ratio; SMD=Standardised Mean Difference; BMI=Body Mass Index; NIRS= Near-infrared Spectroscopy; PACO2=Arterial Carbon Dioxide Tension; NSE=neuron-specific enolase)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
BMI <18.5 vs. BMI 18.5-24.9	2[8,10]	OR 0.76 (0.54 to 1.07); OR 1.06 (0.65 to 1.72)**
BMI 25-29.9 vs. BMI 18.5-24.9	2[8,10]	OR 1.11 (1.02 to 1.21); OR 1.39 (1.18 to 1.64)**
BMI ≥30 vs. BMI 18.5-24.9	2[8,10]	OR 0.94 (0.67 to 1.32); OR 1.16 (0.93 to 1.45)**
Intra-arrest		
NIRS values (combined initial & mean)	1[2]	SMD 2.12 (1.14 to 3.10)
Mean NIRS saturation values	1[2]	SMD 1.34 (-0.10 to 2.79)
Initial NIRS saturation values	1[2]	SMD 2.44 (2.02 to 2.86)
Post-arrest		
Rebound hyperthermia vs. not	1[11]	OR 0.65 (0.47 to 0.88)**
Severe rebound hyperthermia (>38.5°C) vs. not	1[11]	OR 0.52 (0.53 to 0.78)**
Low PACO2 (hypocarbia) vs. normal (normocarbia)	1[12]	2/4 studies reported association of normocarbia with favourable neurological outcome; in 2 studies, there was no significant association. Data were not pooled due to heterogeneity.
High PACO2 (hypercarbia) vs. normal (normocarbia)	1[12]	Peto OR 1.69 (1.13 to 2.51)
High PACO2 (hypercarbia) vs. low (hypocarbia)	1[12]	1/4 studies reported association of hypocarbia with favourable neurological outcome. In 3 studies there was no significant association. Data were not pooled due to heterogeneity.
NSE	1[19]	2 studies reported no sign. association of NSE with favourable neurological outcome on admission; 3 studies reported stat. sig. associations with increased NSE levels at time points between day 1 and day 3.
S-100B	1[19]	1 study reported stat sign. association of decreased S-100B with favourable neurological outcome on admission; 2 studies reported stat. sign. association with decreased S-100B between day 1 and day 3.

* Definition of favourable neurological outcome: Cournoyer (2016): "good neurologic outcome", no further information; Kakavas: good recovery vs severe disability; Ma (2018): neurological recovery (CPC 1–2); Makker (2017): Poor neurological outcome (CPC) of 3–5; McKenzie (2017): CPC scores of 1 or 2; Shinozaki (2009): "return to independent daily life": CPC 1 or 2, GOS 4 or 5.
** calculated from reported values

Table 5a: Prognostic factors assessed for survival to discharge in children experiencing either in- or out-of-hospital cardiac arrest (OR=Odds Ratio); PICU=Paediatric Intensive Care Unit)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
Age <1 year	1[14]*	OR 0.92 (0.5 to 1.7)
Location	1[14]*	Out of hospital: 5.8% (3.9% to 8.6%) PICU: 30.1% (23.4% to 37.9%) In-patient (incl. ICU): 37.2% (23.7% to 53.0%)
Intra-arrest		
Initially shockable vs. non-shockable rhythm	1[14]*	OR 0.60 (0.35 to 1.00)
Shorter duration of resuscitation vs. longer duration	1[14]*	3 studies reported an association with survival at discharge

*13 of 17 studies included in Phillips et al. (2015) reported survival to discharge; two reported survival at 1 month; one survival at 1 year and in one study the survival endpoint was undefined.

Table 5b: Prognostic factors assessed for favourable neurological outcome* in children experiencing either in- or out-of-hospital cardiac arrest (PICU=Paediatric Intensive Care Unit)

Prognostic factor	Number of reviews	Pooled results
Pre-arrest		
Age > 1 year	1[14]	2 studies reported stat. sign. association with favourable neurological outcome
Location	1[14]	Out of hospital: around 3% (3 studies). PICU: 17% to 71% (4 studies) In-patient: not reported
Intra-arrest		
Initially shockable vs. not shockable rhythm	1[14]	1 study reported stat. sign. association with favourable neurological outcome; in another study there was none.
Any CPR vs. no CPR by bystander		1 study reported stat. sign. association with favourable neurological outcome
Arrest occurring at day vs. at night	1[14]	1 study reported stat. sign. association with favourable neurological outcome
Arrest occurring on working week days vs. weekends/holidays	1[14]	1 study reported stat. sign. association with favourable neurological outcome
Instructions from telephone contract to bystander	1[14]	1 study reported association with favourable neurological outcome

* Definition of favourable neurological outcome: either normal functioning, or mild to moderate disability.

6 Reference List

1. W. Bougouin*, et al.*, "Gender and survival after sudden cardiac arrest: A systematic review and meta-analysis," Resuscitation **94**, 55 (2015).
2. A. Cournoyer*, et al.*, "Near-infrared Spectroscopy Monitoring During Cardiac Arrest: A Systematic Review and Meta-analysis," Acad. Emerg. Med **23**(8), 851 (2016).
3. S. D'Arrigo*, et al.*, "Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: A systematic review and meta-analysis," Resuscitation **121**, 62 (2017).
4. G. Debaty*, et al.*, "Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis," Resuscitation **112**, 1 (2017).
5. M. H. Ebell and A. M. Afonso, "Pre-arrest predictors of failure to survive after in-hospital cardiopulmonary resuscitation: a meta-analysis," Fam Pract. **28**(5), 505 (2011).
6. G. Geri*, et al.*, "Does transport time of out-of-hospital cardiac arrest patients matter? A systematic review and meta-analysis," Resuscitation **115**, 96 (2017).
7. O. F. Hasan*, et al.*, "The influence of female gender on cardiac arrest outcomes: a systematic review of the literature," Curr Med Res Opin. **30**(11), 2169 (2014).
8. S. Kakavas*, et al.*, "The impact of body mass index on post resuscitation survival after cardiac arrest: A meta-analysis," Clin Nutr. ESPEN. **24**, 47 (2018).
9. S. Luo*, et al.*, "Prognostic significance of spontaneous shockable rhythm conversion in adult out-of-hospital cardiac arrest patients with initial non-shockable heart rhythms: A systematic review and meta-analysis," Resuscitation **121**, 1 (2017).
10. Y. Ma*, et al.*, "Association between body mass index and clinical outcomes of patients after cardiac arrest and resuscitation: A meta-analysis," Am J Emerg. Med (2018).
11. P. Makker, Y. Kanei, and D. Misra, "Clinical Effect of Rebound Hyperthermia After Cooling Postcardiac Arrest: A Meta-Analysis," Ther Hypothermia. Temp. Manag. **7**(4), 206 (2017).
12. N. McKenzie*, et al.*, "A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest," Resuscitation **111**, 116 (2017).
13. E. F. Paiva, J. H. Paxton, and B. J. O'Neil, "The use of end-tidal carbon dioxide (ETCO2) measurement to guide management of cardiac arrest: A systematic review," Resuscitation **123**, 1 (2018).
14. R. S. Phillips*, et al.*, "Systematic review and meta-analysis of outcomes after cardiopulmonary arrest in childhood," PLoS One **10**(6), e0130327 (2015).
15. C. Sasson*, et al.*, "Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis," Circ. Cardiovasc. Qual. Outcomes. **3**(1), 63 (2010).
16. Schweizerische Akademie der Medizinischen Wissenschaften (SAMW), 2018. "Reanimationsentscheidungen". Retrieved in August 2018 from: https://www.samw.ch/de/Publikationen/Richtlinien.html
17. Schweizerische Herzstiftung 2018. Retrieved from www.swissheart.ch in August 2018.
18. K. S. Shah, A. S. Shah, and R. Bhopal, "Systematic review and meta-analysis of out-of-hospital cardiac arrest and race or ethnicity: black US populations fare worse," Eur. J Prev. Cardiol **21**(5), 619 (2014).

19. K. Shinozaki*, et al.*, "S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review" Crit Care **13**(4), R121 (2009).
20. O. Touma and M. Davies, "The prognostic value of end tidal carbon dioxide during cardiac arrest: a systematic review," Resuscitation **84**(11), 1470 (2013).
21. E. M. van de Glind*, et al.*, "Pre-arrest predictors of survival after resuscitation from out-of-hospital cardiac arrest in the elderly a systematic review," BMC Geriatr. **13**, 68 (2013).
22. M. S. van Gijn*, et al.*, "The chance of survival and the functional outcome after in-hospital cardiopulmonary resuscitation in older people: a systematic review," Age Ageing **43**(4), 456 (2014).
23. Penny Whiting*, et al.*, "ROBIS: A new tool to assess risk of bias in systematic reviews was developed," Journal of Clinical Epidemiology **69**, 225 (2016).
24. L. Zhao*, et al.*, "The association of gasping and outcome, in out of hospital cardiac arrest: A systematic review and meta-analysis," Resuscitation **97**, 7 (2015).

7 Appendices

7.1 Search Strategy Medline

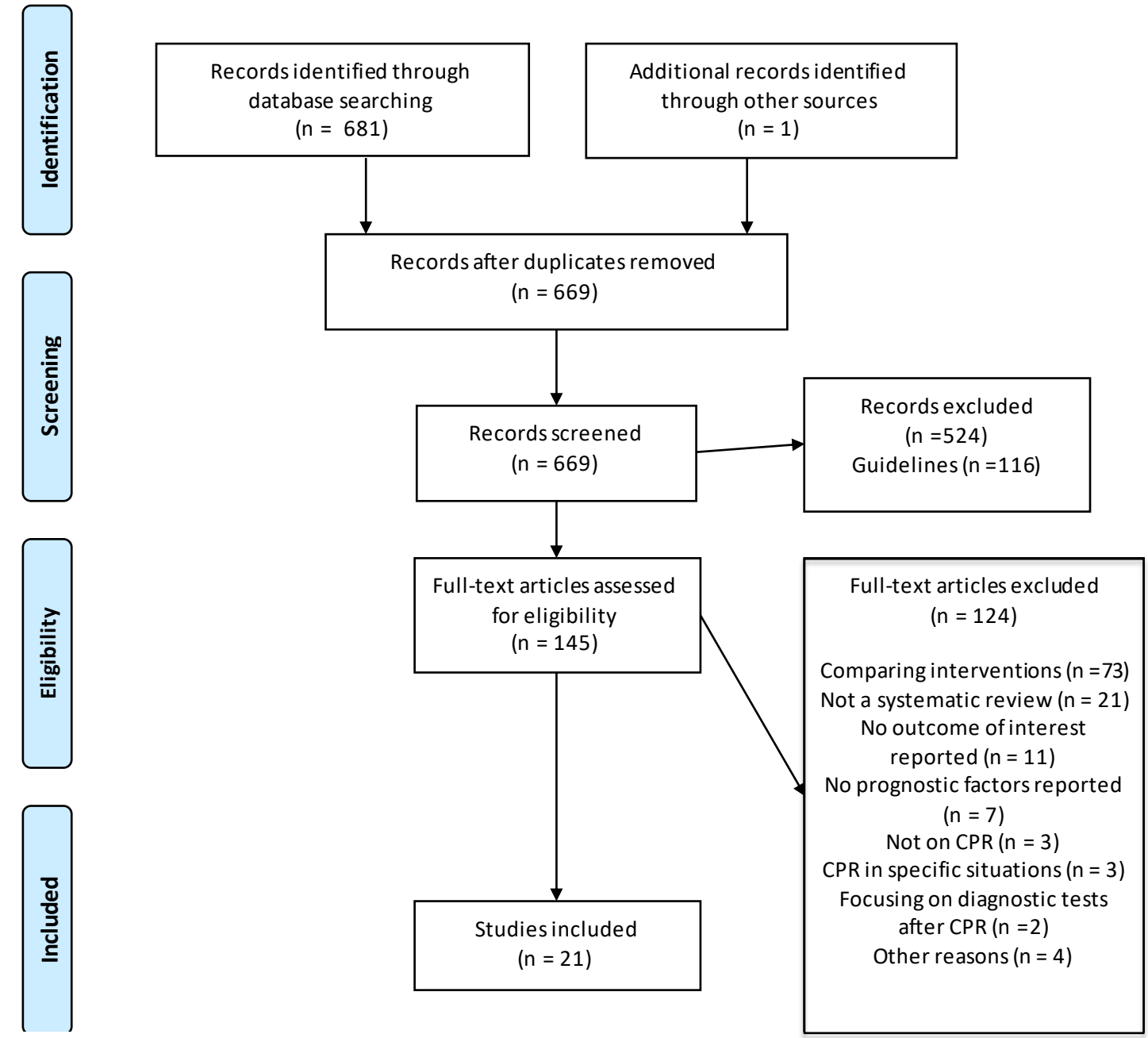
#39, "Search (#37 AND #38)"
#38,"Search (""2008/01/01""[Date - Publication] : ""2018/06/04""[Date - Publication])"
#37, "Search (#35 AND #36)"
#36, "Search (((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt]))))"
#35, "Search (#19 AND #34)"
#34, "Search (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)"
#33,"Search ""sudden death""[Text Word]"
#32,"Search ""cardiorespiratory arrest""[Text Word]"""
#31,"Search ""cardiopulmonary arrest""[Text Word]"
#30,"Search ""heart arrest""[Text Word]"
#29,"Search ""cardiac arrest""[Text Word]"
#28,"Search ""sudden death""[Title/Abstract]"
#27,"Search ""cardio pulmonary arrest*""[Title/Abstract]"
#26,"Search ""cardiopulmonary arrest*""[Title/Abstract]"
#25,"Search ""cardio respiratory arrest*""[Title/Abstract]"
#24,"Search ""cardiorespiratory arrest*""[Title/Abstract]"

#23,"Search ""heart arrest*""[Title/Abstract]"
#22,"Search ""cardiac arrest*""[Title/Abstract]"
#21,"Search """"death, sudden""""[MeSH Terms]"
#20,"Search heart arrest[MeSH Terms]"
#19,"Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)"
#18, "Search resuscitation [Title/Abstract]"
#17, "Search ""resuscitation""[MeSH Terms]"
#16, "Search resuscitation[Text Word]"
#15,"Search cpr[Text Word]"
#14,"Search cpr[Title/Abstract]"
#13,"Search ""chest compression""[Text Word]"
#12,"Search ""chest compression""[Title/Abstract]"
#11,"Search ""life support""[Title/Abstract]"
#10,"Search ""life support""[Text Word]"
#9, "Search ""heart massage""[Text Word]"
#8, "Search ""heart massage""[Title/Abstract]"
#7, "Search ""heart massage""[MeSH Major Topic]"""
#6, "Search ""cardio pulmonary resuscitation""[Title/Abstract]"
#5, "Search ""cardio pulmonary resuscitation""[Text Word]"
#4, "Search ""cardiopulmonary resuscitation""[Text Word]"
#3, "Search ""cardiopulmonary resuscitation""[Title/Abstract]"
#2, "Search resuscitation[Title/Abstract]"
#1, "Search cardiopulmonary resuscitation[MeSH Terms]"

7.2 Search Strategy Cochrane Database of Systematic Reviews

#1: (resuscitation OR "cardiopulmonary resuscitation" OR "heart massage" OR "life support" OR "chest compression"):ti,ab,kw AND ("heart arrest" OR "cardiac arrest" OR "sudden death" OR "cardiorespiratory arrest" OR "cardiopulmonary arrest"):ti,ab,kw
#2: MeSH descriptor: [Resuscitation] explode all trees
#3: MeSH descriptor: [Cardiopulmonary Resuscitation] explode all trees
#4: MeSH descriptor: [Heart Massage] explode all trees
#5: #1 OR #2 OR #3 OR #4
#6: MeSH descriptor: [Heart Arrest] explode all trees
#7: MeSH descriptor: [Death, Sudden] explode all trees
#8: "heart arrest" OR "cardiac arrest" OR "sudden death" OR "cardiorespiratory arrest" OR "cardiopulmonary arrest"
#9: #6 OR #7 OR #8
#10: #5 AND #9

7.3 PRISMA Flow Diagram



[i]

[i] *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 (www.prisma-statement.org)

7.4 Table S1: Quality assessment of included systematic reviews (using the ROBIS tool)

Review	ROBIS domain 1 (study eligibility)	ROBIS domain 2 (identification and selection of studies)	ROBIS domain 3 (data collection and appraisal of studies)	ROBIS domain 4 (synthesis and findings)	Overall assessment of risk of bias
Bougouin 2015[1]	Low	Low	Low	Low	Low
Cournoyer 2016[2]	Low	Low	Low	High	Low
D'Arrigo 2017[3]	Unclear	High	High	High	High
Debaty 2017[4]	Unclear	High	High	Unclear	High
Ebell 2011[5]	Low	High	High	High	High
Geri 2017[6]	High	High	High	Low	High
Hasan 2014[7]	Low	High	High	High	High
Kakavas 2018[8]	Low	High	High	High	High
Luo 2017[9]	High	High	Low	High	High
Ma 2018[10]	Low	High	Low	Low	High
Makker 2017[11]	High	High	High	High	High
McKenzie 2017[12]	Low	Unclear	High	Low	High
Paiva 2018[13]	Low	Unclear	High	High	High
Phillips 2015[14]	Low	Low	High	High	High
Sasson 2010[15]	High	High	High	Low	High
Shah 2012[18]	Unclear	Low	Low	Unclear	Unclear
Shinozaki 2009[19]	High	High	High	High	High
Touma 2013[20]	High	High	High	High	High
van de Glind 2013[21]	High	High	Unclear	High	High
van Gijn 2014[22]	High	High	Unclear	Low	High
Zhao 2015[24]	High	High	Unclear	Low	High