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Review

Medical futility regarding cardiopulmonary resuscitation in in-hospital cardiac arrests of adult patients: A systematic review and Meta-analysis

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Abstract

Aim: For some patients, survival with good neurologic function after cardiopulmonary resuscitation (CPR) is highly unlikely, thus CPR would be considered medically futile. Yet, in clinical practice, there are no well-established criteria, guidelines or measures to determine futility. We aimed to investigate how medical futility for CPR in adult patients is defined, measured, and associated with do-not-resuscitate (DNR) code status as well as to evaluate the predictive value of clinical risk scores through meta-analysis.

Methods: We searched Embase, PubMed, CINAHL, and PsycINFO from the inception of each database up to January 22, 2021. Data were pooled using a fixed-eects model. Data collection and reporting followed the PRISMA guidelines.

Results: Thirty-one studies were included in the systematic review and 11 in the meta-analysis. Medical futility defined by risk scores was associated with a significantly higher risk of in-hospital mortality (5 studies, 3102 participants with Pre-Arrest Morbidity (PAM) and Prognosis After Resuscitation (PAR) score; overall RR 3.38 [95% CI 1.92–5.97]) and poor neurologic outcome/in-hospital mortality (6 studies, 115,213 participants with Good Outcome Following Attempted Resuscitation (GO-FAR) and Prediction of Outcome for In-Hospital Cardiac Arrest (PIHCA) score; RR 6.93 [95% CI 6.43–7.47]). All showed high specificity (>90%) for identifying patients with poor outcome.

Conclusion: There is no international consensus and a lack of specific definitions of CPR futility in adult patients. Clinical risk scores might aid decision-making when CPR is assumed to be futile. Future studies are needed to assess their clinical value and reliability as a measure of futility regarding CPR.

Keywords: Medical futility, Cardiopulmonary resuscitation, Clinical risk score, Do not resuscitate, In-hospital mortality, Neurological outcome

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Introduction

Background

Patients requiring cardiopulmonary resuscitation (CPR) for an in-hospital cardiac arrest (IHCA) have a high risk of mortality and only about 17% to 22% survive until hospital discharge.[1–4] Additionally, a considerable proportion of CPR survivors suffer from subsequent neurologic disabilities.[2,4,5] Despite advances in critical care and resuscitation measures, survival rates have only slightly increased during the last decades[5–7] and even decreased in some patient groups, such as elderly patients.[3] While CPR was originally intended for patients who experience a sudden and unexpected cardiac arrest with a presumed high chance of functional recovery,[8] the intervention has become a standard procedure performed in almost any cases of cardiac arrests.[9] However, in hospitalized patients with severe illness and/or debilitating comorbidities survival to discharge with a favorable neurologic outcome is highly unlikely. In such patients, CPR may be considered medically futile.[1,10] Yet, in clinical practice, there are no established criteria to determine medical futility regarding resuscitation in case of IHCA.

Importance

The concept of medical futility regarding resuscitation has been discussed for decades with no international consensus being achieved. Common criticisms concern the usefulness and implementation of futility in clinical practice due to a lack of established criteria and ethical considerations.[11,12] Still, futility remains an essential topic for clinical decision-making in daily practice.[1,13] There are national guidelines such as the medical-ethical guidelines on code status decisions published by the Swiss Academy of Medical Sciences.[14] These state that resuscitation is indicated if there is a chance that the patient survives without severe neurologic impairments. However, because definitions of futility are rather vague and lack specific criteria, implementation in clinical practice remains difficult. There have been different attempts to define futility based solely on expected in-hospital mortality rates without considering neurological outcome.[15] However, accurate estimation of survival after CPR is challenging and varies significantly among different physicians.[16] In one study, physicians have overestimated the likelihood of survival of adult patients with IHCA by as much as 300%,[17] while another study found that physicians can predict patient survival after IHCA no better than chance.[18] Further, a significant number of patients with a very low likelihood of survival after IHCA still have no do-not-resuscitate (DNR) orders in place in clinical practice.[19]

Goals of this investigation

The objective of this systematic review and meta-analysis was to understand the concept of medical futility regarding CPR in case of IHCA of adult patients by investigating definitions of medical futility regarding resuscitation, assessment of futility for in-hospital CPR, and the prevalence of DNR orders in hospitalized patients in whom CPR would be deemed futile.

Methods

Types of studies, participants, and outcomes

Data collection and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[20] We included peer-reviewed studies discussing and/or evaluating medical futility regarding CPR in adult hospitalized patients. Studies were eligible if they reported either a definition of futility regarding CPR, clinical measures to assess futility, and/or rates of DNR orders in patients for whom CPR attempt was deemed futile. No restrictions concerning age or gender of adult participants were applied. No publication date restrictions and no language restrictions were used.

Studies were excluded if one of the following criteria was present: 1) medical futility regarding resuscitation not addressed / population does not include patients in whom futility regarding resuscitation is assessed, 2) patients < 18 years, 3) no clinical peer-reviewed study or conference poster/abstract, and 4) no information on any of the predefined outcome parameters.

Due to the exploratory nature of our study, we did not define specific hypotheses. This manuscript is based on the MOOSE Checklist of Meta-analyses and Observational Studies (see eTable 2 in the Supplementary Material).[21]

Search terms for identification of studies

We searched the digital databases Embase, PubMed, CINAHL and PsycINFO, using a comprehensive search strategy consisting of a combination of subject headings and free-text words. The search strategy was developed together with a librarian (H.E.) experienced in systematic reviews. The final search strategy is provided in the Supplementary Material to ensure traceability and reproducibility of our results. To identify additional studies, we screened all references of eligible studies through the cited reference search of Web of Science and PubMed and applied the similar articles search of PubMed. The latest search was performed on January 22, 2021.

Study selection

Three investigators (H.C., A.V. and K.B.) screened the titles and abstracts of articles regarding inclusion and exclusion criteria. Two reviewers (H.C. and A.V.) independently assessed the full texts of all remaining studies and disagreements were resolved through discussion with a third reviewer (K.B.).

Risk of bias evaluation

We evaluated the risk of bias for every relevant outcome of all included studies using The Cochrane Collaboration's tool for assessing risk of bias.[22] Two authors (K.B. and A.V.) independently assessed the risk of bias for all studies and resolved disagreements by discussion until consensus was found. A detailed description of the risk of bias assessment can be found in the Supplementary Material.

Analysis

We express dichotomous data risk ratios (RR) with 95% confidence intervals (CI). Data were pooled using a fixed-effects model. Heterogeneity (inconsistency) was identified through visual inspection of the forest plots. We used the I^2 statistic, which quantifies inconsistency across studies, to assess the consequences of heterogeneity on the meta-analysis. A considerable level of heterogeneity is indicated by an I^2 statistic of 50% or more.[23] Cut-off values for stratification were chosen based on the frequently used cut-offs in the literature.[24–28] Accordingly, a PAM or PAR score > 8, a GO-FAR score $\geq$ 14 and a PIHCA score $\leq$ 3% indicate that CPR would be medically futile. We also calculated the risk scores' specificity separately for each study. We applied narrative synthesis if data were not suitable for direct comparison.

Statistical analyses were performed using the METAN package in Stata (Stata MP, version 15.1; StataCorp LP), and a two-sided $p < .05$ was considered statistically significant.

Results

Identified studies

A total of 1966 records were identified through database searches and other sources. We removed duplicates (n = 86) and discarded 1621 studies after screening titles and abstracts. Of the remaining 259 full-text articles, 31 studies[1,4,24–52] were eligible for inclusion (Fig. 1).

Description of studies

Table 1 lists characteristics of the 11 studies included in the meta-analysis. Detailed information on the remaining 20 studies solely included in the qualitative synthesis are shown in eTable 2. Publication dates ranged from 1989 to 2019, and studies were conducted mostly in the United States,[24,26,27,29,34,35,39,42,45,47,48] and in European countries such as Sweden,[4,28,31,49] and England.[40,41,44] Study sample sizes ranged from 29 to 96,499 per trial. Half of the studies included hospitalized patients receiving CPR after IHCA[1,4,24,33,34,26–28,41–43,46–49] and in three studies the study population consisted of hospitalized patients without IHCA.[25,30,40,52] Yet, some studies included more specific patient populations such as elderly patients,[35,44] oncological patients,[36,38] critically ill patients,[39] severe burn patients,[32] or patients with multiple IHCA.[29] One study only included patients with established DNR orders.[45]

Definitions of futility

Twenty-seven studies included short descriptions or definitions of medical futility for CPR. These varied broadly in content and specificity, and rarely consisted of more than one or two sentences. Six studies defined futility as a very low likelihood of survival after CPR following cardiac arrest[1,10,33,39,45,52] with one of them specifying a "1% chance of surviving 2 months after CPR".[39] Nine studies evaluating clinical risk scores solely presented a cut-off score indicating futility[24,42,44,52] or extremely low chance of survival with favorable neurologic outcome, defined as Cerebral Performance Category 1[10,47,48] or 1 to 2.[28,49] Ten studies provided unspecific definitions, defining futility either based on clinical conditions, e.g., age, metastatic cancer, or "acute or chronic impairments in almost any organ system in elderly patients" or based on an outcome, e.g., "prolonging the patient's suffering and therefore harming the patient".[25,30,31,35,36,38,40,45,50,51] However, none of these definitions included specific thresholds or criteria for futility. Four studies reported specific scenarios in which CPR would be futile, such as patients with a recurrent cardiac arrest or severe burn injuries.[29,32,34,37]

DNR code status in patients for whom CPR was deemed futile

Four studies reported how many patients for whom CPR was deemed futile had a DNR code status.[39,40,44,52] The definitions of futility among these studies and the rates of DNR code status varied considerably. In the study of Aarons et al.[40] junior doctors gave a statement concerning the appropriateness of resuscitation in case of IHCA for each included patient. Of all patients for whom CPR was perceived as futile, 27% (n = 24) had DNR orders. Stewart et al.[44] evaluated medical inpatients with a mean age of 84 years. CPR was judged futile if the patients' Pre-Arrest Morbidity (PAM) index scores were >4 and their Prognosis After Resuscitation (PAR) scores were >5 at the same time. Of these patients where CPR was considered to be futile, 44% (n = 17) had a DNR code status. Becker et al.[52] assessed 2889 patients hospitalized at the Division of Traumatology/Orthopedics or Internal Medicine. Futility regarding CPR was defined as a Good Outcome Following Attempted Resuscitation (GO-FAR) score $\geq$ 14 and/or a Clinical Frailty Scale (CFS) rating of $\geq$7. Of all patients where CPR was determined futile (n = 467), 69.2% had a DNR code status documented in their medical charts. Teno et al.[39] calculated a time-to-event prediction model in a sample of critically ill patients including diagnosis, age, number of hospital days before study entry, cancer diagnosis, neurologic function, and several physiologic measures all assessed on day 3 after study entry. CPR was determined as futile if the chance of 2-month survival was estimated to be 1% or less. The majority of those patients, i.e., 71% (n = 82) had a DNR order.

Meta-analysis of pre-arrest risk scores

The included studies examined different pre-arrest factors and pre-arrest risk scores based on these factors. Several risk scores were found in the systematic search to assess the pre-arrest risk of death during hospitalization after CPR for IHCA in individual patients. Eleven studies were included in the meta-analysis[4,24,41,43,26–28,46–49] that assessed the following four pre-arrest risk scores: the Pre-arrest morbidity (PAM) index, the Prognosis After Resuscitation (PAR) score, the Good Outcome Following Attempted Resuscitation (GO-FAR) score and the Prediction of Outcome for In-Hospital Cardiac Arrest (PIHCA) score. In the supplementary material, we provide a detailed overview of these clinical risk scores (eTable 1).

In the studies included in the meta-analysis, the mean age varied between 60 years[48] and 72 years.[49] Further, male gender ranged between 58 %[27,47] and 65%.[24,48] All studies included inpatients receiving CPR after IHCA. Overall, the meta-analysis comprised 118,315 patients.

Five studies with 1621 patients reported PAM scores and in-hospital mortality with a low risk of bias.[24,26,41,43,46] The overall analysis showed that the PAM index was associated with a significantly higher risk of in-hospital death at a cut-off score of PAM > 8 (RR 4.10 [95 %CI 1.39–12.11]). Heterogeneity among trials was low (I^2 = 0.0%, p = .638). Specificity in the individual studies ranged from 98% to 100% (eTable 3).

Four studies with 1481 patients reported PAR scores and mortality with a low risk of bias.[26,41,43,46] The PAR score was associated with a significantly higher risk of death until discharge at a cut-off score of PAR > 8 (RR 3.11 [95 %CI 1.59–6.05]). Heterogeneity among trials did not have a significant impact (I^2 = 54.5%, p = .086). Results of the PAM and PAR scores are shown in Fig. 2. Specificity in the individual studies ranged from 83% to 100% (eTable 3).

Five studies with 114,585 patients reported GO-FAR scores and poor neurologic outcome or in-hospital death with a low risk of bias.[4,27,28,47,48] The GO-FAR score was associated with a significantly higher risk of poor neurologic outcome (CPC $\leq$ 1) and in-hospital death at a cut-off score of GO-FAR $\geq$ 14 (RR 6.92 [95 %

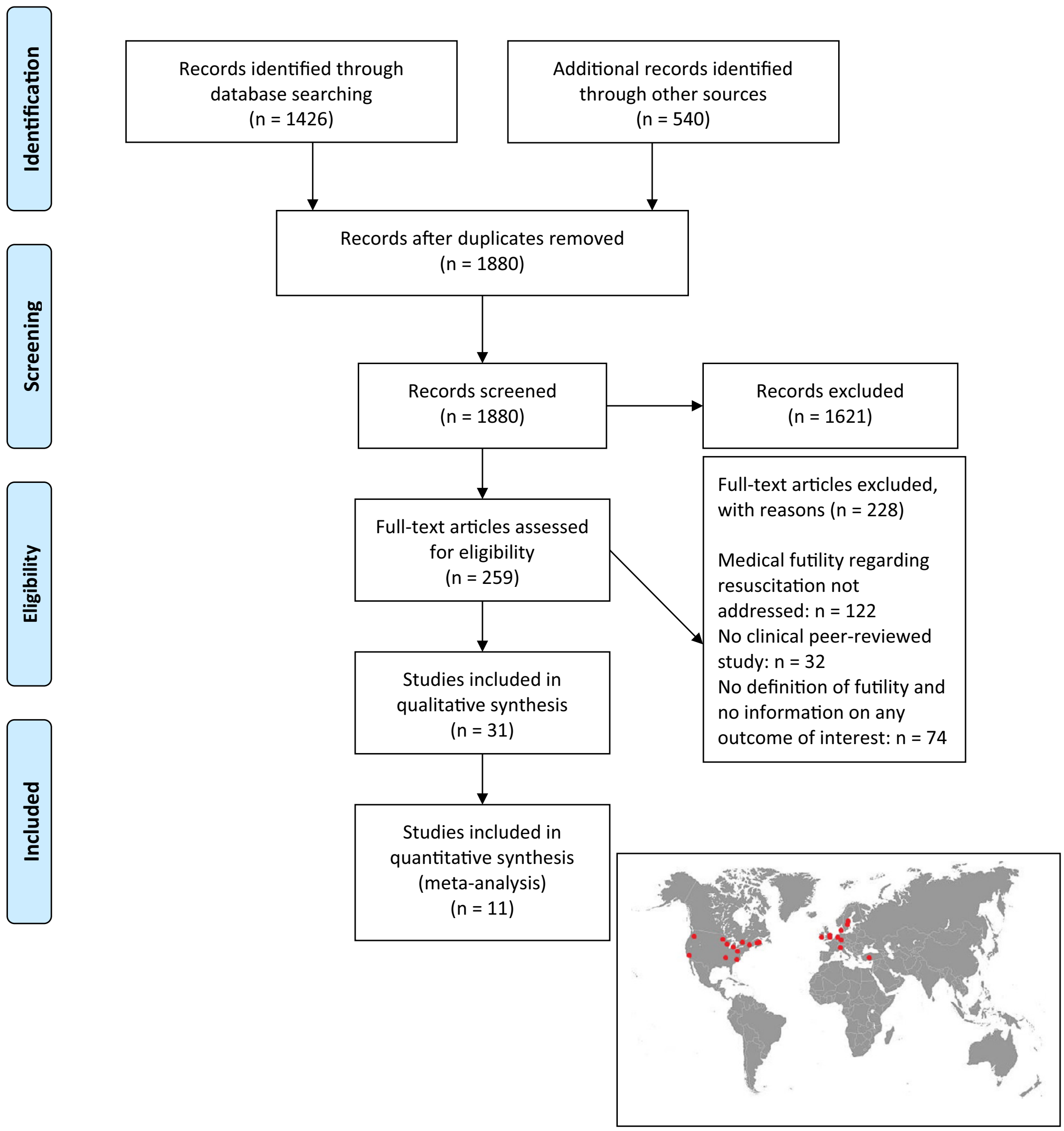

Fig. 1 – PRISMA flow diagram of the study selection process.

CI 6.42–7.46]). There was high heterogeneity among trials (I^2 = 81.1%, p < .001). Specificity in the individual studies ranged from 89% to 97% (eTable 3).

One study with 628 patients evaluated the PIHCA score[49] and poor neurologic outcome or in-hospital death with a low risk of bias. A very low or low (≤3% chance of favorable neurological survival) PIHCA score was associated with a significantly higher risk of poor neurologic outcome (CPC ≤ 2) and death until discharge (RR 11.46 [95% CI 1.65–79.61]). The specificity was 99% (eTable 3). Due to inclusion of only one study, heterogeneity could not be calculated. Results of the GO-FAR and PIHCA score are shown in Fig. 3.

Discussion

In this systematic review and meta-analysis, we investigated the concept, measures and application of medical futility regarding CPR after IHCA in clinical routine. We included 30 studies in the qualitative review and 11 in the meta-analysis. Aside from theoretical articles from the field of medical ethics, we found only few clinical definitions of futility regarding CPR and no international consensus including specific definitions or criteria that allow for concrete implementation in clinical practice. Still, several studies proposed different pre-arrest objective risk scores for the definition of futility[44,52] or to assess extremely low chance of survival (with favorable neurologic outcome, i.e. CPC 1 or CPC 1 to 2).[4,24,28,42,47–49] In meta-analyses, these four risk scores, i.e. PAM index, PAR score, GO-FAR score and PIHCA score, were associated with in-hospital mortality and – in the case of the GO-FAR and PIHCA score - in-hospital mortality and poor neurologic outcome defined as CPC 1 and CPC 1 to 2, respectively. Several findings of this review need further discussion.

First, we found a wide variation in definitions of futility, which were mostly either unspecific or limited to certain clinical conditions. In line with a systematic review on medical futility without focus regarding resuscitation[53] and current opinion of leading experts on the topic,[54] none of the studies in our review reported a definition including specific and well-defined criteria that would allow identification of patients

Table 1 – Summary of the studies included in the meta-analysis.

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
George et al. 1989[24]	To evaluate pre-arrest factors potentially predictive for survival after CPR for IHCA and devising a multifactorial scoring system, the Pre-Arrest Morbidity (PAM) Index, to evaluate pre-arrest morbidity in individual patients.	USA (Tennessee)	n = 140, patients receiving CPR after IHCA (65% men, age 18–92). Cardiac arrest is defined as acute circulatory failure for which both chest compression and artificial ventilation were initiated.	Prospective cohort study	Consecutive hospitalized patients undergoing CPR between July 1 through December 31, 1985 were prospectively identified. Data were collected through review of medical records and telephone interviews with survivors after 3 months. For comparison, data of hospitalized patients who died within the same six-month follow-up period but who did not receive CPR were also recorded.	Patients with a PAM score > 8 would not be expected to survive.	**Outcome:** Immediate success of CPR (restoration of pulse and maintenance of a systolic blood pressure for at least one hour without chest compression), survival to discharge and long-term survival at 3-month follow-up. **Measures:** Review of medical records concerning clinical characteristics before, during and after the resuscitation; telephone interviews with survivors 3 months after the arrest.	**Pre-arrest factors** associated with in-hospital mortality after CPR: hypotension, azotemia, age $\geq$ 65 years. The following cut-off values of the PAM score were defined for identifying extremely low likelihood of long-term survival: PAM score $\geq$ 7: less than 15% survived to discharge/were still alive 3 months later; PAM score > 8 (n = 24): none of these patients survived to discharge. When PAM score and other pre-arrest factors (azotemia, hypotension, and congestive heart failure) were assessed in a multivariate analysis, only PAM was significantly associated.
Ebell et al. 1997[26]	To evaluate the three clinical risk scores PAM index, PAR score, and the APACHE III score regarding their ability to predict survival to discharge after in-hospital CPR.	USA (Michigan and Illinois)	n = 656, inpatients of three hospitals with CPR after IHCA. Exclusion: observed IHCA, no documentation of CPR measures.	Retrospective cohort study	Medical records available during the first 24 hours after hospital admission of all inpatients who had received CPR after an IHCA were reviewed and APACHE III, PAR, and PAM scores were calculated.	none	**Outcome:** Survival to discharge after CPR for IHCA. **Measures:** APACHE III, PAM and PAR score rated based on medical records, demographic, clinical, and laboratory variables from medical records.	5.3% (n = 35) of patients survived to discharge (37.8% initially). None of the three clinical risk scores could effectively discriminate between survivors and non-survivors (neither immediate survival nor survival to discharge). This might be due to low statistical power caused by the small number of survivors. APACHE III did not discriminate. PAM: Only 11 of 656 patients had scores > 8, none of whom survived to discharge. PAR: 131 patients with scores > 8, 6 survived to discharge. Patients identified by the PAR score as non-survivors to discharge had a survival rate of 4.6%, not significantly different from the overall survival rate of the study population of 5.3%.
O'Keefe & Ebell 1994[43]	To compare the PAR score and PAM index regarding their ability to predict non-survival after CPR for IHCA.	Ireland	n = 274, inpatients of all wards who had received CPR after IHCA over a 2-year period, average age 70.1 years.	Retrospective cohort study	Medical records of inpatients who had received CPR after IHCA were reviewed. PAR and PAM were calculated based on the most recent data prior to cardiac arrest. Both a priori (based on the original publications) and post hoc (based on data of the current study, specificity set at 100%) cut-off values were applied.	none.	**Outcome:** Survival to discharge after in-hospital CPR for IHCA. **Measures:** Retrospective review of medical records regarding demographic, clinical and laboratory data, main diagnoses, daily medications, and survival to discharge.	Twenty-five (9.1%) survived to discharge. A priori cut-off values (>8 for both PAR and PAM) identified only few of the non-survivors: PAR identified 24 and PAM detected only 5 with a sensitivity of 9.6% (PAR) and 2% (PAM). Post hoc cut-off values set at 100% specificity detected 59 (PAR) and 23 (PAM) patients with a sensitivity of 23.7% (PAR) and 9.2% (PAM).

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Table 1 (continued)

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
Bowker et al. 1999[41]	To evaluate the usefulness of the morbidity scores PAM, modified PAM index and PAR score in predicting unsuccessful/futile CPR.	England	n = 264, consecutive adult patients who had received CPR after IHCA (59% men). Exclusion: OHCA, previous cardiac arrest, no CPR.	Prospective cohort study	Rating of PAM, modified PAM index and PAR score based on information in medical records.	none	**Outcome:** Survival after CPR. **Measures:** Pre-arrest morbidity score (PAM), prognosis after resuscitation score (PAR), modified PAM index (MPI).	Cut-off values indicating zero chance of survival and proportion of patients with respective cut-off value: PAM > 6 (17.8%), PAR > 7 (25.8%), MPI > 6 (20.1%). Sensitivity of scores: PAM 20%, PAR 29%, MPI 22%; combination of all three 42%. Each score identified a different subgroup of patients for whom CPR was unsuccessful with little overlap between the scores. While 100 of these patients were detected by one or more scores only 21 were identified by all three scores.
Ohlsson et al. 2014[46]	To evaluate the predictive performance of the PAM and PAR score regarding survival to discharge of patients receiving CPR after IHCA and to identify new clinically useful parameters.	Sweden	n = 278 (61.3% male, mean age 70.1); inclusion: inpatients who had received CPR after IHCA, 18 years or older; exclusion: OHCA.	Retrospective cohort study	Medical records were screened including all cases of IHCA who were part of a cardiac arrest registry at Skåne University Hospital in Sweden between 2007–2010.	none	**Outcome:** survival to discharge. **Measures:** Variables included in the PAM and PAR score, as well as additional clinical variables such as acute and chronic clinical diagnoses.	A PAR score > 5 was associated with a more than 8-fold increase in the risk of non-survival to discharge. The specificity of both scores increased with elevated scores, PAM- and PAR-scores > 5 and above had a specificity > 90%, which can be helpful to identify patients with the highest risk of failure to survive IHCA. Patients with ST-elevated myocardial infarction (STEMI), with cardiac monitoring and shockable rhythm had a higher likelihood of survival to discharge. Patients with malignancies and dependent functional status were less likely to survive. Many other severe comorbidities, such as chronic heart failure, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney disease, chronic cerebrovascular disease and diabetes mellitus, were not significantly related to reduced survival. Acute conditions such as acute renal failure, acute stroke, acute heart failure and sepsis were also not significantly associated.
Ohlsson et al. 2016[4]	To validate the "Good Outcome Following Attempted Resuscitation" (GO-FAR) score in patients in a Swedish hospital who received CPR after IHCA.	Sweden	n = 278 (61.3% male, mean age 70.1); inclusion: inpatients who had received CPR after IHCA, 18 years or older; exclusion: OHCA	Retrospective cohort study	Medical records were screened including all cases of IHCA who were part of a cardiac arrest registry at Skåne University Hospital in Sweden between 2007–2010.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcome**: Survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FAR score: Neurologically intact at admission, major trauma, acute stroke, metastatic/hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled	Overall survival to discharge independent of neurological function was 20.2%; 78% of the survivors had CPC = 1 and survival to discharge with CPC = 1 was 15.7%. The AUC for the GO-FAR score was 0.85. Patients in the group with low or very low probability of survival

Table 1 (continued)

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
							nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age.	had a likelihood of 2.8%, whereas the groups with average and above average probabilities had likelihoods of 8.2% and 46% for good neurological outcome.
Thai & Ebell 2019[47]	Prospective validation of the Good Outcome Following Attempted Resuscitation (GO-FAR) score for IHCA prognosis.	USA (all states)	n = 62,131 inpatients in 386 hospitals (58.3% male, mean age 65.3 years); inclusion: initial IHCA, 18 years or older, assessment of CPC at discharge, all 13 GO-FAR predictor variables documented.	Retrospective cohort study	Medical data of patients hospitalized experiencing IHCA between 2010 and 2016 were extracted.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcome**: survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FAR score: Neurologically intact at admission, major trauma, acute stroke, metastatic/hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age; hospital size, having residents or interns, ownership type.	The GO-FAR score had similar discrimination, calibration, and classification accuracy as in the original study. Survival rates were somewhat higher due to a secular increase in survival of IHCA. The score performed similarly in hospitals of different sizes, with and without residency training programs, and with different ownership structures. The GO-FAR score accurately classifies patients into risk groups based on their likelihood of survival to discharge with a good neurologic outcome following the occurrence of IHCA.
Rubins et al. 2019[48]	To validate the utility of the GO-FAR score by retrospectively predicting prognosis after IHCA arrest in a US trauma center.	USA (Minnesota)	n = 403 (65.5% male, mean age 60.3 years); inclusion: pulseless IHCA, 18 years or older, initial cardiac arrest; exclusion: OHCA, DNR orders and stopped, subsequent cardiac arrest.	Retrospective observational study	Two authors independently calculated the GO-FAR score for each included case from the electronic health record between 2009 and 2018. The lead author reconciled any differences.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcomes**: survival to discharge, survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FARscore: Neurologically intact at admission, major trauma, acute stroke, metastatic/hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age; timing of IHCA.	Overall survival to discharge was 33.0%; survival to discharge with good neurologic outcome was 17.4%. In the below average survival group calculated by the GO-FAR score (n = 150), only 5.3% survived to discharge with CPC = 1, significantly fewer than in the average (22.5%) or above average (34.1%) groups. GO-FAR score calculated at the time of admission correlated with survival to discharge with good neurologic outcome (AUC 0.68), therefore, the GO-FAR score can estimate the probability that a patient will survive to discharge with good neurologic outcome after an IHCA at time of admission.
Piscator et al. 2018[28]	External validation of the GO-FAR score predicting neurologically intact survival after IHCA in a population-based setting.	Sweden	n = 717 patients (mean age 72 years) / complete cases n = 523 (62% male, mean age 71 years); inclusion: IHCA (=patient who is unresponsive with apnea), 18 years or older.	Retrospective cohort study	Patients were identified through review of electronic patient records of the Swedish Cardiopulmonary Resuscitation Registry between 2013 and 2014.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcome**: survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FAR score: Neurologically intact at admission (GCS = 15), major trauma, acute stroke, metastatic / hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age; gender, race, CA characteristics, hospital location.	22% of the cohort survived with good neurologic outcome. In below average survival groups, 4% survived with good neurologic outcome, compared to average and above average survival groups (32%). In complete case analysis (523 cases) AUC was 0.82 indicating good discrimination. The GO-FAR score has satisfactory discrimination, but assessment of the calibration shows that neurologically intact survival is

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Table 1 (continued)

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
								systematically underestimated.
Ebell et al. 2013[27]	To develop and validate an economical pre-arrest point score that can identify patients unlikely to survive CPR after IHCA neurologically intact or with minimal deficits.	USA (all states)	n = 51,240, 58.3% men, mean age 65 years. Inpatients of 366 hospitals with CPR after IHCA. (Patients with previous DNR orders not included).	Get With the Guidelines–Resuscitation registry data set of 51,240 inpatients of 366 hospitals.	Data was divided into training (44.4%), test (22.2%), and validation (33.4%) data sets, multivariate methods to select the best independent predictors of good neurologic outcome based on: several candidate decision models, use of test data set to select the model that best classified patients as having a very low (<1%), low (1%-3%), average (>3%-15%), or higher than average (>15%) likelihood of survival after in-hospital CPR for IHCA with good neurologic status. The final model was evaluated using the validation data set.	CPR is unlikely to lead to long-term, neurologically intact survival. GO-FAR score $\geq$ 14 (low 1–3%, very low < 1%).	**Outcome:** Survival to discharge after in-hospital CPR for IHCA with good neurologic status based on a Cerebral Performance Category (CPC) score of 1. **Measures:** variables of the GO-FAR score.	Overall rate of survival to discharge with a CPC score of 1: 10.4%. Determination of four categories estimating a patient's chance of survival with good neurological outcome as above average (>15%), average (>3% $-$ 15%), low (1–3%) or very low (<1%). **Proportion of futile patients:** The GO-FAR score identified 9.4% of patients as having a very low likelihood of good outcome after CPR (<1%) and another 18.9% as having a low likelihood (1–3%). The GO-FAR score identified 28.3% of patients as having a low or very low likelihood of survival to discharge with good neurological outcome.
Piscator et al. 2019[49]	Development of the PIHCA score, a new pre-arrest prediction model of favorable neurological survival following IHCA.	Sweden	n = 717 patients (mean age 72 years) / complete cases n = 523 (62% male, mean age 71 years); inclusion: IHCA (=patient who is unresponsive with apnea), 18 years or older.	Retrospective cohort study	Data was based on a previous validation of the GO-FAR score (Piscator et al, 2018), redefining and reducing predictor variables resulting in a model of 9 predictors. The likelihood of favorable neurological survival was categorized into very low (<1%), low (1–3%) and above low (>3%).	Very low likelihood (<1%) or low likelihood (1–3%) of favorable neurological survival	**Outcome**: favorable neurological survival at discharge (CPC 1–2) **Measures**: Chronic comorbidity (Charlson Comorbidity Index), neurologically intact at admission, septicemia, medical noncardiac diagnosis, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age.	The PIHCA score had an AUROC of 0.81 and satisfactory calibration. Forty-two percent of patients with above low chance of survival (>3%) and 3% with very low/low chance of survival ($\leq$3%) in the PIHCA score showed favorable neurological outcome. With a cut-off of 3% likelihood of favorable neurological survival, sensitivity was 99.4% and specificity 8.4%; predictive value for classification into $\leq$ 3% likelihood of favorable neurological survival was high (97.4%) and false classification into $\leq$ 3% likelihood of favorable neurological survival was low (0.6%).

The Abbreviations: CPR, cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PAM, Pre-Arrest Morbidity index; PAR, Prognosis After Resuscitation score; APACHE, Acute Physiology and Chronic Health Evaluation score; GO-FAR, Good Outcome Following Attempted Resuscitation score; PIHCA, Prediction of Outcome for In-Hospital Cardiac Arrest score; CPC, Cerebral Performance Category; DNR, do not resuscitate; AUROC, area under the receiver operating characteristic curve.

in whom the chance of futile CPR would be high in clinical practice. However, two studies used clinical risk scores and chose a specific cut-off to determine futility.[44,52] While multiple theoretical articles from the field of medical ethics describe specific concepts of medical futility, researchers closer aligned to clinical practice often emphasize the difficulty of determining and implementing such concepts.[15,54–57] In public and academic discussions about futility, multiple fundamental issues have been raised that hinder an international consensus definition. These include ethical questions and concerns, societal values, cultural beliefs, legal challenges, and clinicians' responsibilities.[9,15,54,58]

So far, the most promising approach to evaluate quantitative futility was based on objective risk scores, i.e., the GO-FAR and PIHCA score regarding expected in-hospital mortality and neurological outcome. Such an approach to define futility *quantitatively* requires the definition of a specific threshold below which CPR would be assumed futile and a clear and clinically meaningful definition of "good outcome".[11] Yet, determining such a cut-off value for use in clinical practice has ethical and clinical challenges and may depend on societal and patient factors and perspectives as well as preferences of patients and families.[55] There may be differences in the perception what the best cut-off should be to define futility. When asked about their estimations of survival of patients in whom they perceived CPR to be futile, several physicians reported probabilities of over 5% and over 10%.[15,45] Further, the two existing clinical risk scores additionally considering neurological outcome differ in their definition of good neurologic function, i.e. CPC 1 in the GO-FAR score vs. CPC 1 to 2 in the PIHCA score.[10,28] Additionally, other meaningful clinical outcomes such as quality of life, self-reliance and severe health impairments, e.g., organ failures, need to be considered and incorporated into the concept of futility regarding CPR.

The concept of *qualitative futility* centers the patient's quality of life instead of quantitative parameters. This approach was only mentioned by two studies in our review.[45,51] If applied consequently, this approach requires an evaluation of patients' subjective quality of life as well as their idea of a meaningful and fulfilling life, considering the potential adverse neurological consequences of CPR. Moreover, the latter seems to become even more prominent with advanced and invasive life-prolonging interventions, such as extracorporeal membrane oxygenation (ECMO), as these can be associated with neurological complications.[59] Still, the potential influence of physicians' value judgments, beliefs and assumptions about the patient's quality of life and the limited number of studies regarding the impact of invasive life-prolonging measures in intensive care on short- and long-term outcome make decisions on qualitative futility challenging in routine care.[15,54–55,57,59]

Only four studies[39,40,44,52] assessed the code status in patients in whom resuscitation was determined futile. The rates of DNR orders in these studies varied due to the high heterogeneity of patient samples, definitions and assessments of futility, making interpretation difficult. While Teno et al.[39] explicitly stated that surrogates and patients participated in decision-making, it is unclear if DNR orders in the other three studies[40,44,52] were unilaterally implemented by physicians or discussed with patients and/or surrogates.

In our meta-analyses, we included 11 studies that applied clinical risk scores to estimate outcome of CPR and reported rates of survival to discharge (with good neurologic outcome) for each individual score.[4,24,41,43,26–28,46–49] The PAM index and a modified version

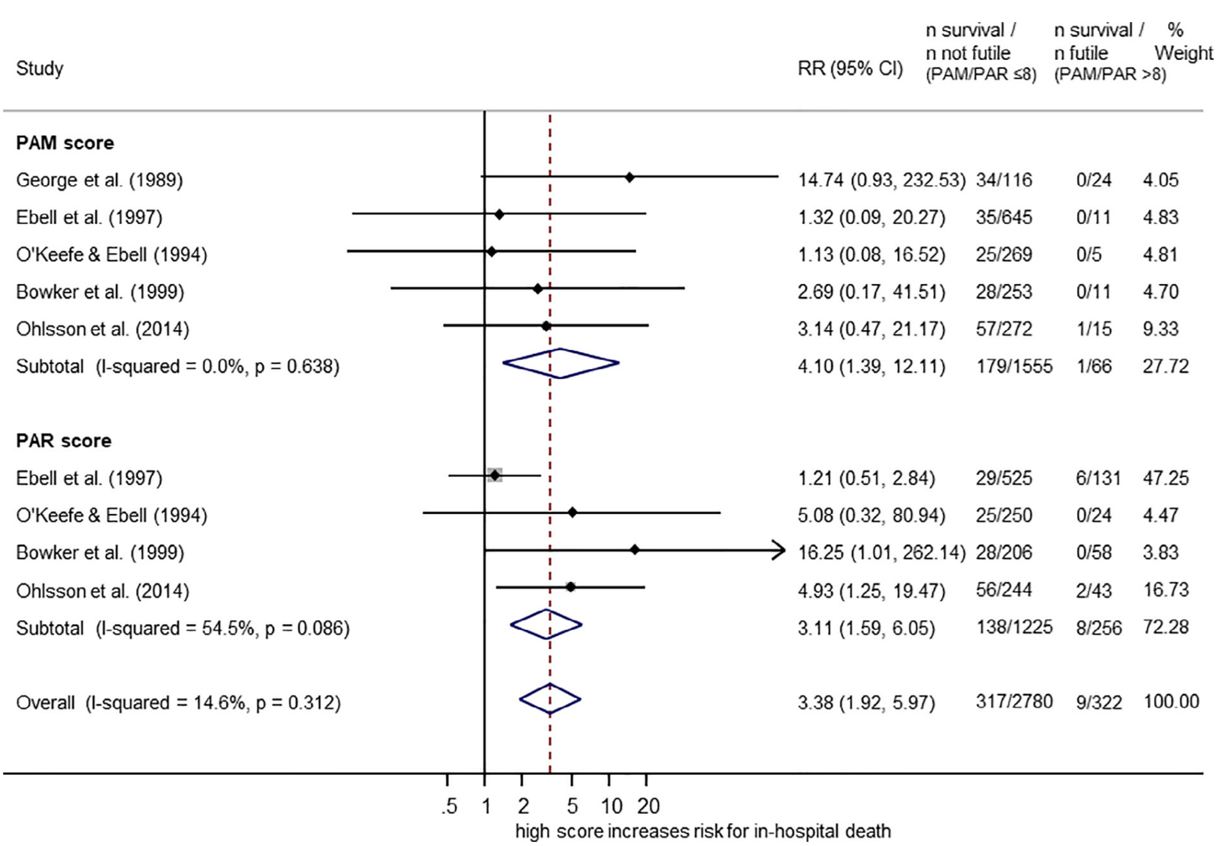

Fig. 2 – Forest plot showing the association of the PAM and PAR score and risk of in-hospital death.

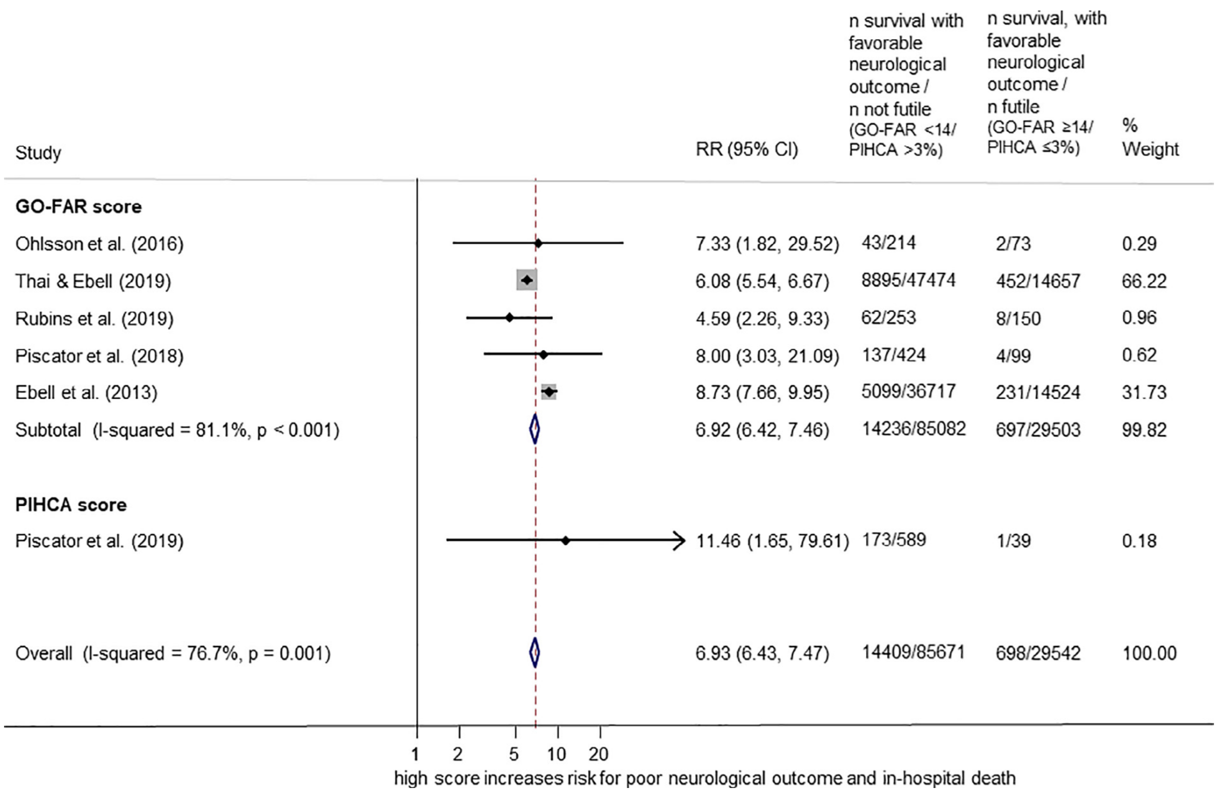

Fig. 3 – Forest plot showing the association of the GO-FAR and PIHCA score and risk of survival with impaired neurological outcome or in-hospital death.

named the PAR score were developed four decades ago, about three decades after the invention of CPR.[60] Surprisingly, we only identified five studies evaluating these scores in relation to survival rates[24,26,41,43,46] and two further studies in relation to rates of DNR orders.[25,44] Further, the studies used different cut-off scores for determining high risk of in-hospital death after CPR. In our meta-analysis, both the PAM and PAR score were associated with in-hospital mortality, albeit with a lower predictive value than the newer GO-FAR score and its derivative, the PIHCA score. Most predictors of the PAM index are variables that were independently associated with mortality following CPR in a previous primary study[61] plus factors deemed relevant by the authors[24] and the PAR score is based on a meta-analysis of 14 studies.[62] The GO-FAR score was developed based on multivariable analyses of a dataset of about 50,000 inpatients with IHCA.[1,27] Further, the GO-FAR and PIHCA score predict survival with good neurologic outcome, which is defined as Cerebral Performance Category (CPC) 1, indicating good cerebral performance, in the GO-FAR score and as CPC 1 to 2 with 2 indicating moderate cerebral disability, in the PIHCA score. These aspects might have contributed to their better performance in our analysis.

Due to the PAM and PAR scores' above-mentioned limitations, we suggest focusing on the GO-FAR and PIHCA score in future research. Further studies are needed to validate the GO-FAR and/or PIHCA score regarding their prognostic accuracy. As a next step, implementation of these scores in clinical practice is needed. Potential benefits and short-comings of using clinical risk scores for decision-making regarding code status need to be assessed, e.g., does decision-making change due to risk scores or is it coherent with clinical impression. Although clinical scores are never perfectly accurate in their prediction of outcome, they may reduce the influence of subjective factors that should not contribute to determining futility such as physicians' individual values and attitudes. Risk scores may help guide physicians in the difficult task of futility assessment to make this evaluation more objective, transparent, and hopefully reliable especially when physicians are still unexperienced. According to the online registration platform ClinicalTrials, there is currently one large randomized trial comparing code status discussions based on a checklist and risk assessment of futility using the GO-FAR score and the Clinical Frailty Scale with usual care (https://clinicaltrials.gov/ct2/show/NCT03872154).

Conclusions

In summary, although in-hospital cardiac arrest occurs in about 2–3% of hospitalized patients and code status discussions and decisions are an integral part of clinical practice, there is only little research on consensus definitions of medical futility. While most clinicians would agree that there is a relevant proportion of patients in whom CPR is likely to be futile, our review found no established definitions of futility for use in clinical practice. International consensus regarding the definition of futility is lacking and tools for its assessment could improve objective code status discussions with patients. Communication about medical futility holds the potential of empowering patients to make informed decisions that are in alignment with their goals of care, avoiding unwanted physical and emotional suffering for them and their relatives, which may come along with unwanted life-sustaining measures and treatments in situations without realistic prospects for a desirable recovery in the individual case. A definition, criteria and measures suitable for the implementation of scoring systems to determine the likelihood of futility in specific clinical scenarios need to fulfill several requirements regarding acceptance, feasibility, and prognostic value, among others. Two recently developed clinical risk scores, the GO-FAR and PIHCA score, showed promising predictive values. However, further studies are needed to evaluate the implementation of such concepts and their assessments in clinical practice.

CRediT authorship contribution statement

Katharina Beck: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing - original draft Writing - review & editing. **Alessia Vincent:** Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft. **Hasret Cam:** Investigation, Methodology. **Christoph Becker:** Conceptualization, Funding acquisition, Writing - review & editing. **Sebastian Gross:** Writing - review & editing. **Nina Loretz:** Writing - review & editing. **Jonas Müller:** Writing - review & editing. **Simon A. Amacher:** Writing - review & editing. **Chantal Bohren: Writing – review & editing**. **Raoul Sutter:** Writing - review & editing. **Stefano Bassetti:** Writing - review & editing. **Sabina Hunziker:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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These had no involvement in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.11.041.

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