Available online at ScienceDirect

Resuscitation

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

Clinical paper

Mechanical chest compression and extracorporeal life support for out-of-hospital cardiac arrest. A 30-month observational study in the metropolitan area of Milan, Italy

Giovanni Mistraletti[a,b,*], *Armando Lancioni*[c,d], *Gabriele Bassi*[d], *Francesca Nespoli*[c,d], *Michele Umbrello*[e], *Silvia Salini*[f], *Alberto Zangrillo*[g], *Federico Pappalardo*[h], *Anna Mara Scandroglio*[g], *Giuseppe Foti*[c,i], *Leonello Avalli*[i], *Nicolò Patroniti*[j], *Ferdinando Raimondi*[k], *Elena Costantini*[k], *Emanuele Catena*[l], *Davide Ottolina*[l], *Claudia Ruffini*[l], *Maurizio Migliari*[m], *Giovanni Sesana*[n], *Roberto Fumagalli*[c,d,n,1], *Antonio Pesenti*[a,o,1], *the mechCPR-ECLS investigators*[2]

Abstract

Background: Return of spontaneous circulation (ROSC) is achieved in 25% of out-of-hospital cardiac arrest (OHCA) patients. Mechanical chest compression (mechCPR) may maintain better perfusion during transport, allowing hospital treatments like extracorporeal circulation life support (ECLS). We aim to assess the effectiveness of a pre-hospital protocol introduction.

Methods: Observational, retrospective study assessing all OHCA patients aged 12–75, with no-flow time <20 min in a metropolitan area (Milan, Italy, 2013–2016). Primary outcomes: ROSC and Cerebral Performance Category score (CPC) ≤2 at hospital discharge. Logistic regressions with multiple comparison adjustments balanced with propensity scores calculated with inverse probability of treatment weighting were performed.

Results: 1366 OHCA were analysed; 305 received mechCPR, 1061 manual chest compressions (manCPR), and 108 ECLS. ROSC and CPC ≤2 were associated with low-flow minutes (odds ratio [95% confidence interval] 0.90 [0.88–0.91] and 0.90 [0.87–0.93]), shockable rhythm (2.52 [1.71–3.72] and 10.68 [5.63–20.28]), defibrillations number (1.15 [1.07–1.23] and 1.15 [1.04–1.26]), and mechCPR (1.86 [1.17–2.96] and 2.06 [1.11–

Abbreviations: OHCA, Out-of-hospital cardiac arrest, CPR, Cardiopulmonary resuscitation, mechCPR, Mechanical chest compression for CPR, manCPR, Manual chest compression for CPR, ECLS, Extracorporeal life support, ROSC, Sustained recovery of spontaneous circulation, CPC, Cerebral Performance Category, VF/pVT, Ventricular fibrillation/pulseless ventricular tachycardia, PCI, Primary coronary intervention, ALS, Advanced life support (by the emergency, out-of-hospital physician), BLS, Basic life support (by certified volunteers on the ambulance), SOREUM, Sala Operativa Regionale Emergenza Urgenza Metropolitana, AREU, Azienda Regionale Emergenza Urgenza, LUCAS-2 ®, Lund University Cardiac ASsist device 2 ®, ET-CO_2, End-tidal carbon dioxide, DNR, Do Not Resuscitate orders, ER, Emergency Room, DBD, Tissues/organs donation after brain death, PEA, Pulseless electrical activity

* Corresponding author at: Università degli Studi di Milano, Dipartimento di Fisiopatologia medico-chirurgica e dei Trapianti, A.S.S.T. Ovest Milanese, UOC Anestesia e Rianimazione, Via Giovanni Paolo II, C.P. 3, Legnano (MI), Italy.

E-mail addresses: giovanni.mistraletti@unimi.it (G. Mistraletti), armando.lancioni@unimi.it (A. Lancioni), gabriele.bassi@ospedaleniguarda.it (G. Bassi), francesca.nespoli@unimi.it (F. Nespoli), michele.umbrello@asst-santipaolocarlo.it (M. Umbrello), silvia.salini@unimi.it (S. Salini), zangrillo.alberto@hsr.it (A. Zangrillo), fedepappa.71@gmail.com (F. Pappalardo), scandroglio.mara@hsr.it (A.M. Scandroglio), g.foti@asst-monza.it (G. Foti), l.avalli@asst-monza.it (L. Avalli), nicoloantonino.patroniti@unige.it (N. Patroniti), ferdinando.raimondi@humanitas.it (F. Raimondi), elena.costantini@-humanitas.it (E. Costantini), emanuele.catena@asst-fbf-sacco.it (E. Catena), ottolina.davide@asst-fbf-sacco.it (D. Ottolina), claudia.ruffini@asst-fbf-sacco.it (C. Ruffini), m.migliari@asst-monza.it (M. Migliari), giovanni.sesana@ospedaleniguarda.it (G. Sesana), roberto.fumagalli@unimib.it (R. Fumagalli), antonio.pesenti@unimi.it (A. Pesenti).

[1] Co-last authors.

[2] The members of the mechCPR-ECLS investigators are listed in Appendix A at the end of the article.

https://doi.org/10.1016/j.resuscitation.2022.11.025

Received 6 October 2022; Received in Revised form 25 November 2022; Accepted 28 November 2022

3.81]). With resuscitation times >13 min, mechCPR achieved more frequently ROSC compared to manCPR. Among ECLS patients, 70% had time exceeding protocol: 8 (7.5%) had CPC ≤2 (half of them with low-flow times between 45 and 90 min), 2 (1.9%) survived with severe neurological disabilities, and 13 brain-dead (12.0%) became organ donors.

Conclusions: MechCPR patients achieved ROSC more frequently than manual CPR patients; mechCPR was a crucial factor in an ECLS protocol for refractory OHCA. ECLS offered a chance of survival to patients who would otherwise die.

Keywords: Out-of-hospital cardiac arrest, Cardiopulmonary resuscitation, Mechanical chest compressions, Extracorporeal membrane oxygenation, Neurological outcome, Anoxic brain damage

Introduction

Out-of-hospital cardiac arrest (OHCA) is a challenge for public health,[1–2] as only 25% of patients achieve a sustained return of spontaneous circulation (ROSC), and only one-third of them leave the hospital alive.[3–4] Approximately 20% of OHCA patients first present with shockable rhythms,[5] and despite being the minority of cases, >80% of survivors come from this group. Few advanced life support (ALS) therapies improve outcomes after OHCA. Timely interventions,[6] such as prompt first-aid resuscitation efforts and rapid hospital transport, determine the *survival chain* in OHCA and may preserve the patient's full neurologic function.[7]

OHCA patients are usually treated *in the field* until ROSC or death declaration; treatments are frequently interrupted if ROSC is not achieved within 30–45 min.[8] Guidelines suggest avoiding transferring an OHCA patient before ROSC; however, in the case of refractory rhythms, subsequent therapies may only be available in hospitals; thus, prolonging cardiopulmonary resuscitation (CPR) on the scene is not reasonable from this perspective.[9]

Patients undergoing manual CPR (manCPR) cannot be moved safely from the scene because of its low quality in rapidly moving ambulances. Mechanical chest compressions (mechCPR) overcome this barrier, ensuring adequate cerebral perfusion during transport, thus allowing treatments such as percutaneous coronary intervention (PCI) or extracorporeal life support (ECLS).[8,10] Extensive studies on mechCPR have been performed,[11] but they have yet to focus on mechCPR in structured ECLS programs.

Recently, the use of mechCPR has increased, even if not openly recommended by guidelines.[12] The first preclinical investigations[13–14] reported good efficacy[10,15–16] and safety.[17] Nevertheless, large prospective trials[18–20] found no outcome differences between manCPR and mechCPR, with some possible harms.[21] However, it is hard to make conclusive analyses about its role in the whole clinical pathway since treatments beyond the early resuscitation process may be confounding.[22]

ECLS supports both cardiac and pulmonary function. Technical improvements and percutaneous cannulation have made it feasible in emergencies, and its use has increased over the past years.[23] Observational studies have reported higher survival rates and favourable neurological outcomes with ECLS[24] after OHCA,[25] also considering prolonged resuscitation times.[26] Encouraging results have been recently published in the first prospective randomised controlled trial (RCT),[27] while results from other RCTs are still pending.[28]

In 2013, a new pre-hospital rescue protocol was applied to the metropolitan area of Milan: physicians were allowed to use mechCPR or manCPR at their discretion, thus offering the opportunity for this retrospective observational study to evaluate the real-life rescue teams' work with a pragmatic approach. We first analysed the impact of pre-hospital mechCPR. Then, since ALS could be followed by in-hospital ECLS,[29–30] we attempted to describe the effect of this latter intervention.

Methods

When the mechCPR-ECLS protocol (Fig. 1S) was introduced in Milan, scientific evidence from the literature concerning the efficacy of ECLS after OHCA was considered sufficiently strong.[10] After a test trial at San Gerardo Hospital, Monza,[31–32] a metropolitan protocol was established (see Electronic Supplementary Material, ESM, for details) with the following shared criteria for eligibility: 1) age between 12 and 75 years; 2) no-flow time from collapse to basic life support team (BLS) arrival equal or less than 6 min; 3) end-tidal CO_2 ($ET\text{-}CO_2$) equal or more than 10 mmHg after 20 min of CPR; 4) low-flow time from collapse to hospital admission equal or less than 45 min. Ineligibility criteria were end-stage cardiomyopathy with no transplant indication, severe aortic valve regurgitation, aortic dissection, peripheral vasculopathy, and terminal malignancy. A mechCPR compression device was not mandatory, although strongly recommended since guidelines[9] suggested its use during transport; given the observational and pragmatic nature of the study, the treatments offered by medical teams were different depending on the physicians' choices.

Study design and authorisation

The primary outcomes of this retrospective, observational, multicentre study were: 1) CPR effectiveness assessed by the number of patients with ROSC; 2) neurological outcome measured as the number of patients discharged from the hospital with a Cerebral Performance Category (CPC) score of 1 or 2. Secondary outcomes included: time to ROSC; emergency room (ER) survival; survival to hospital discharge; multi-organ donation after brain or cardiac death.

The study inclusion criteria were: OHCA patients attended by ALS medical teams and managed by the Milan dispatch centre during the first 30 months after the protocol introduction (from September 1st, 2013, to February 29, 2016). The study exclusion criteria were pregnancy, age <12 or >75 years, no flow time >20 min or not determinable, and Do Not Resuscitate (DNR) orders. It is noticeable, that exclusion and inclusion criteria for the present study are different from the inclusion criteria of the mechCPR-ECLS protocol, to detect treatments that deviated from the protocol, too.

The Monza Ethics Committee authorised the study (Prot. 2462; 15th December 2016). According to local legislation, informed consent was obtained from survivors or their legal representatives if non-competent.[33] Physicians were allowed to use mechCPR or manCPR at their discretion, and an ECLS 4-point network (see

ESM) was established to direct patients for further treatments in case of refractory OHCA.

Data gathering and statistical analyses

Data regarding time and rescue operations were taken from the electronic emergency management system used by the dispatch centre. Clinical data were taken from the physician's medical records on the scene. Outcome data for the whole dataset of patients came from the registers of each hospital where OHCA patients were admitted (i.e. both the four ECLS centres and the other 18 metropolitan hospitals).

Control groups (manCPR and no-ECLS) were compared with *intervention* groups (mechCPR and ECLS). Two logistic regression models were planned, using the propensity score[34] based on the probability of every patient to undergo manCPR or mechCPR and to receive or not receive ECLS, respectively.

Considering the different numbers of OHCA patients in the case and control groups, both propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) have been applied. It is well known that, despite some similarities, sometimes these two techniques behave differently, mainly because matching selects some controls and discards others, while IPTW includes all study units. The study is externally valid when no discrepancies are found between these methods.

All the covariates available before the decision to use mechCPR or manCPR and to use ECLS or not were considered to build the propensity score models.[35] Hence, it was possible to highlight which ones were associated with the medical decision to use mechCPR and ECLS. The covariates were patients' age and sex, event location, witnessed collapse, traumatic OHCA, bystander CPR, no flow time, and low flow time before the ALS team arrived. These data were used for both the propensity models. Time of ALS assistance and use of mechCPR were added variables for propensity scores regarding ECLS.

To identify the variables potentially influencing the outcomes, the statistical analysis was performed using logistic regression models with multiple comparison adjustments, and inverse probability weighted propensity scores[36] to control for confounding.[37] For "time to ROSC", the comparison between manCPR and mechCPR was made first by the Kaplan-Meier method; after that, the probability of obtaining ROSC was modelled with a simple logistic model. Organ donation was only analysed with descriptive statistics. For all comparisons, a $p < 0.05$ was considered statistically significant. All analyses were performed using Stata version 12 (Stata Corp, College Station, TX, USA).

Table 1 – Case-mix of all OHCA patients.

	Total OHCA 1366	manCPR 1061 (77.7)	mechCPR 305 (22.3)	ECLS 108 (7.9)
MechCPR system on board	585 (42.9)	314 (29.6)	271 (89.1)	70 (64.8)
Age (years)	62 [51–69]	63 [52–70]	60 [50–68]	53 [43–63]
Male	1016 (74.5)	768 (72.5)	248 (81.3)	101 (93.5)
OHCA after trauma	155 (11.4)	144 (13.6)	11 (3.6)	2 (1.9)
Public place	443 (32.5)	325 (30.7)	118 (38.7)	63 (58.3)
Witnessed	1304 (96.2)	1015 (96.4)	289 (95.4)	106 (98.1)
Bystander CPR	501 (36.9)	348 (33.0)	153 (50.5)	70 (65.4)
First presentation rhythm				
VF	439 (32.1)	293 (27.6)	146 (47.9)	74 (69.2)
pVT	3 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)
PEA	258 (18.9)	201 (19.0)	57 (18.7)	10 (9.3)
Asystole	666 (48.8)	564 (53.3)	102 (33.4)	23 (21.5)
No-flow time (min)	9 [6–11]	9 [6–11]	9 [6–12]	8 [6–12]
Low-flow during BLS (min)	5 [2–10]	5 [2–10]	5 [2–9]	5 [2–9]
Low flow during ALS (min)	31 [20–42]	29 [18–40]	38 [28–48]	42 [29–50]
Time to ROSC (min)	22 [15–34]	21 [14–30]	30 [18–42]	34 [19–59]r
Death on the scene	498 (36.5)	469 (44.2)	29 (9.5)	0 (0.0)
Sustained ROSC	413 (30.4)	324 (30.6)	89 (29.3)	15 (14.2)
ER survival	487 (36.1)	319 (30.1)	168 (55.1)	108 (100.0)
Survival at 24 h	356 (27.3)	244 (23.0)	112 (36.7)	68 (63.0)
ICU survival	178 (13.7)	132 (12.4)	46 (15.1)	10 (9.3)
Hospital survival	164 (12.7)	119 (11.2)	45 (14.8)	10 (9.3)
CPC score at hospital discharge				
1	87 (6.8)	61 (6.0)	26 (9.2)	6 (5.6)
2	18 (1.4)	11 (1.1)	7 (2.5)	2 (1.9)
3	27 (2.1)	21 (2.1)	6 (2.1)	1 (0.9)
4	28 (2.2)	22 (2.2)	6 (2.1)	1 (0.9)
5	45 (3.5)	23 (2.3)	22 (7.8)	18 (16.7)
Multiple organ donation	33 (2.4)	16 (1.5)	17 (5.6)	13 (12.0)

Out-of-hospital cardiac arrest patients, described according to the Utstein style. Variables are presented as absolute numbers (percentage), or as median [interquartile range]. OHCA: out-of-hospital cardiac arrest; manCPR: manual chest compression for cardio pulmonary resuscitation; mechCPR: mechanical chest compression for cardio pulmonary resuscitation; ECLS: extracorporeal life support; VF: ventricular fibrillation; pVT: pulseless ventricular tachycardia; PEA: pulseless electrical activity; BLS: basic life support (certified rescuers on board); ALS: advanced life support (physician on board); ROSC: sustained return of spontaneous circulation; ER: emergency room; ICU: intensive care unit; CPC: cerebral performance categories.

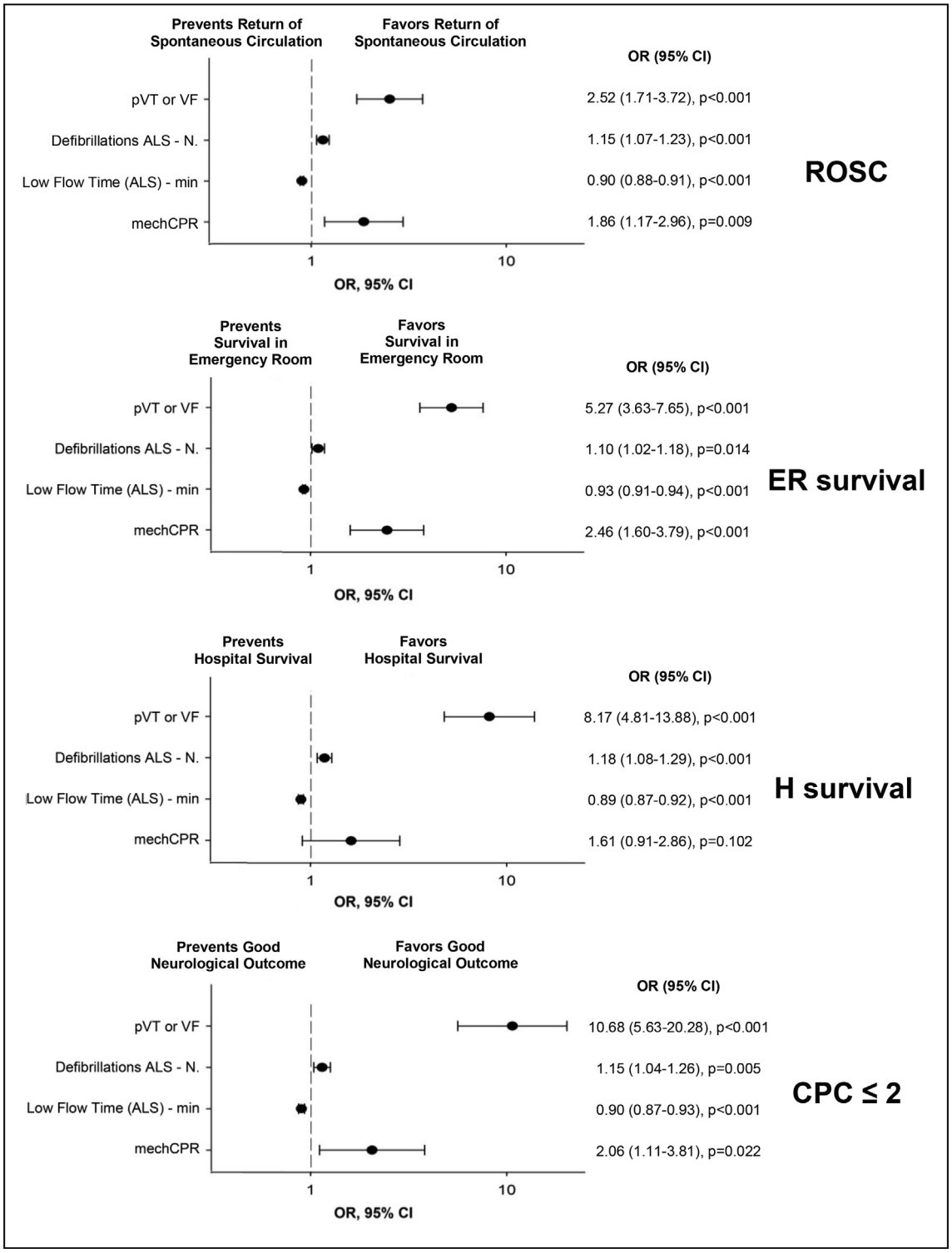

Fig. 1 – Each logistic model weighted on the dataset of 1366 patients describes the relative effect of the four variables significantly associated with outcomes. X axis, logarithmic scale. OR (95% CI): Odds Ratio (95% confidence interval); pVT: pulseless ventricular tachycardia; VF: ventricular fibrillation; ALS: advanced life support; mechCPR: mechanical chest compression for cardiopulmonary resuscitation; ROSC: sustained return of spontaneous circulation; ER survival: survival when transferred from emergency room; H survival: survival to hospital discharge; CPC: cerebral performance category.

Results

Study population and selection criteria

From September 1st, 2013, to February 29, 2016, namely the first 30 months from protocol implementation, 11,783 emergency calls for OHCA were received by the dispatch centre, and 8175 were not treated with further ALS due to probable unfavourable prognosis (i.e., evident signs of death, very old age, explicit DNR orders) or due to organisational issues (immediate unavailability of ALS, extreme proximity to a hospital). Of the remaining 3608 OHCA, 2242 were further excluded: 946 were out of the age range, 455 had a no-flow time longer than 20 min or non-determinable, and 841 had DNR orders (Fig. 2S) 0.1366 OHCA patients were thus included in the present study. Of these, 1061 received manCPR until death or hospital admission, while 305 received mechCPR after a variable period of manCPR (until ALS arrival). The patients' main details are given in Table 1, while Table 1S summarises all the available variables, following the Utstein style, also reporting the balancing adequacy obtained with the matched propensity score approach for CPR: all the p values of the considered variables become lower than 0.10 after matching. On the contrary, the expected propensity score on ECLS could not be generated due to the lack of surviving patients in the no-ECLS group.

In almost half the cases, the physicians in charge could directly decide on either mechCPR or manCPR since their rescue vehicles were equipped with a LUCAS-2 ® device (Tab. 1). However, if the mechCPR-ECLS protocol was activated and the ALS team on the scene lacked a mechCPR device, a second vehicle equipped with a LUCAS-2 ® was immediately activated to join the scene as soon as possible.

Treatments and conditions with positive outcomes

Four variables were significantly associated with our primary and secondary outcomes (survival to ER and to hospital discharge): a shockable rhythm, the total number of defibrillations, every minute of ALS assistance, and the use of mechCPR. Fig. 1 reports the results from the logistic regression models with IPTW; similar results were obtained with PSM approach, as reported in Fig. 3S.

Duration of ALS assistance (defined from ALS team scene arrival to either ROSC or death declaration) was associated with poor outcome: for each added minute, the probability of survival decreased by about 11%. Thus, it is fundamental to consider whether this variable affects other variables.[38] We, therefore, made an exploratory analysis of the relationship between the duration of ALS and the achievement of ROSC. ALS assistance was significantly longer in the mechCPR group than with manCPR, both in case of survival and death (Fig. 2, panel A). The probability of ROSC under mechCPR or manCPR was separately related to the duration of ALS: both fell exponentially over time, but with different slopes: after 13 min of ALS, the odds for ROSC became higher in the mechCPR-group. (Fig. 2, panel B).

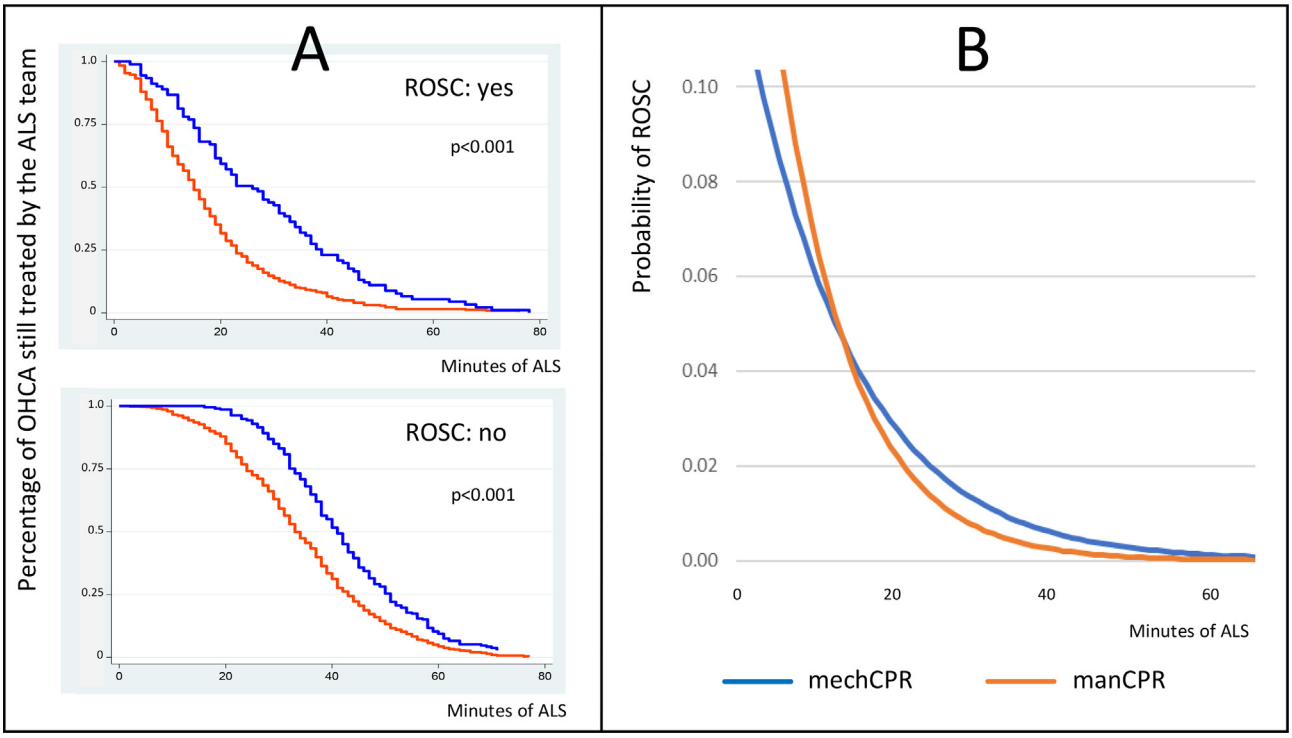

Fig. 2 – Panel A: OHCA cases were divided between ROSC or not; in both conditions, mechCPR was continued for longer before stopping because of ROSC or death declaration. Panel B: all the OHCA cases were pooled to build a logistic model (that considers the continuous variable ALS time in minutes, the dummy variable mechCPR/manCPR, and their interaction) to describe the probability of ROSC. Since with mechCPR, this probability falls less steeply, after 13 min of ALS - when there are still more than 80% of assisted patients - the likelihood of ROSC begins to be higher than with manCPR. ROSC: sustained return of spontaneous circulation; OHCA: out-of-hospital cardiac arrest; ALS: advanced life support; mechCPR: mechanical chest compression for cardiopulmonary resuscitation; manCPR: manual chest compression for cardiopulmonary resuscitation.

Adherence to the shared protocol and neurological outcomes

Among the 1366 OHCA patients, 108 received ECLS treatment (Fig. 4S). In more than 70% of cases, the cut-offs for protocol inclusion (<6 min of no-flow time and <45 min of low-flow time) were not respected. Fig. 3 and Table 2S illustrate the neurological outcomes according to adherence to the protocol. Half of the patients who achieved a good neurological outcome had a low-flow time longer than 45 min, even up to 90 min.

Table 3S lists the features of these patients according to their neurological outcomes. In patients treated with ECLS, regardless of protocol inclusion criteria, 7.4% had a good neurological outcome; significant neurological disability occurred in 1.9%. In those with unfavourable neurological outcomes, organ donation was possible in 12.0% of patients.

Discussion

Approaching OHCA calls for a complex interaction among subsequent players: BLS by first responders, ALS by dispatched emergency physicians, followed by advanced care in the hospital. It is hard to distinguish the specific importance of *each item of the survival chain* because of their unavoidable interdependence.[39] The present observational, retrospective study describes the results of the first 30 months after introducing a shared mechCPR-ECLS protocol for OHCA in the Milan metropolitan area (Italy). The protocol involved more than 200 professional ALS workers and more than 3000 certified volunteers on ambulances (BLS). The large number of cases analysed and the availability of a mechCPR device only in about half of the ALS teams allowed us to adequately stratify the propensity for receiving mechCPR, using this probability for weighting its effect in a multivariate assessment. Patients receiving mechCPR thus had higher odds of a good outcome than those treated with manCPR only. Of the enrolled patients without ROSC, 9.3% survived if treated with ECLS, 80% with a good neurological outcome, but none otherwise; this is in line with other study results.[40]

Likely, our control group (manCPR) performed poorly compared to what has been described in the international literature.[18–19] These pragmatical observations showing better outcomes by using a mechCPR approach are probably due to a difference between the actual effectiveness of the LUCAS-2 ® device, i.e. how it worked in practice, instead of its theoretical efficacy, i.e. how well it measured in controlled trials.

We consistently found that the most critical factors in terms of chances of ROSC and good neurological outcome were quick ALS assistance and a shockable rhythm. Firstly, for every minute of CPR, the probability of survival decreases by 11%; secondly, when the rhythm is shockable, there is a twofold probability of ROSC and a tenfold probability of a good neurological recovery. Unfortunately, neither the rhythm nor the duration of CPR can be controlled. At the same time, the type of chest compression delivered can: for each minute of mechCPR, the probability of good recovery decreases less than with manCPR. With ALS times longer than 13 min, in this peculiar real-world setting, mechCPR achieved more frequently ROSC compared to manCPR, thus making our results inconsistent with previous studies,[41–42] possibly because of better chest compressions and shorter hands-off time during the hospital transfer.

Two striking differences stand out when analysing the percentages of patients treated with manCPR vs mechCPR. Firstly, if the physician in charge decided to begin mechCPR, the patient was usually transferred to the hospital, even outside the mechCPR-ECLS protocol. Less than 15% of patients without ROSC undergoing mechCPR were declared dead at the scene, as opposed to more than 60% of those treated with manCPR (Fig. 4). Secondly, considering both the different sizes groups (78% manCPR and 22% mechCPR) and ALS duration (29 [18–49] min for manCPR vs 38 [28–48] min for mechCPR, p <0.001) suggests the occurrence of a case of Simpson's paradox (see the ESM for further discussion).[43]

We could not build a propensity score on ECLS because of the lack of "control cases"[44]: no patient in the non-ECLS group survived. Despite the still high mortality, 7.4% had a good neurological outcome; these results are likely not obtainable with any other currently available treatment. More than 70% of all patients who received ECLS and 50% of patients with good neurological outcomes exceeded no-flow (6 min) and low-flow times (45 min) designated by the protocol, challenging its rules. The introduction of ECLS strategies after OHCA offers previously inconceivable possibilities.[8,27] Moreover, since the present study covers only the first 30 months after the introduction of the mechCPR-ECLS protocol, we cannot exclude that better results might have been reached subsequently.[45]

Study limitations

The present study has several limitations. First, it is observational and retrospective. Even after statistical correction for all the available observed covariates, it is very likely that some unobserved covariates might have influenced our findings. Second, these observations were obtained in a unique context: the first 30 months after introducing a new, shared protocol in a metropolitan area. These features make the results difficult to replicate. Moreover, the hospitals available for ECLS were chosen because of their vast experience with extracorporeal circulation after cardiac surgery and because they covered the whole metropolitan area being theoretically reachable within 20 min by ambulance. Third, the quality of both manCPR and mechCPR was not controlled: we can speculate there might have been less hands-off time and more effective mechCPR during hospital transport, but no data were gathered to measure this key point. Fourth, emergency physicians were free to decide whether to use mechCPR in any specific scenario, according to the dispatch centre indications, in default of a local protocol specific for the mechCPR use. Fifth, protocol inclusion criteria were not respected in more than 70% of cases; we decided to describe our results, given that half of the patients who achieved a good neurological outcome were outside the inclusion criteria. Sixth, ET-CO_2 measurement was frequently lacking in medical charts; this makes it hard to verify the importance of restoring perfusion, especially concerning the choice of no-flow time limits. Seventh, 69.4% of OHCA patients assisted by rescue teams without an out-of-hospital physician were excluded; in this case, it is impossible to state whether these choices introduced confounding or excluded patients who might have been eligible for ECLS. All these points weaken the conclusions but simultaneously are closer to real everyday medical assistance, warranting a revision of inclusion and exclusion criteria for mechCPR-ECLS protocols.

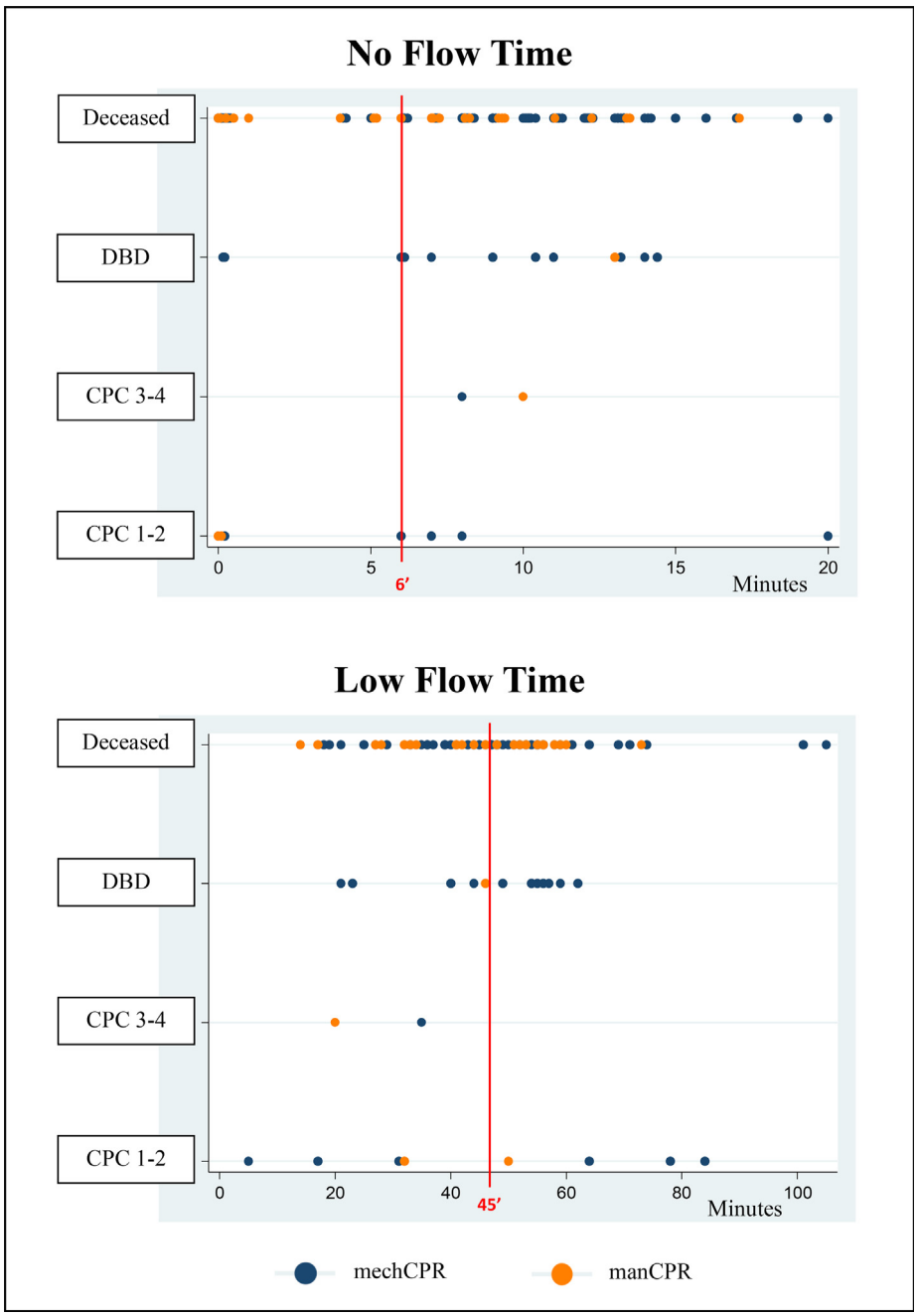

Fig. 3 – The 108 patients given ECLS, according to their hospital neurologic outcomes. In more than half the cases, the assistance times from witnessed OHCA were longer than specified in the locally shared protocol, having the thresholds of 6 min for the no flow time, and of 45 min for the hospital admission. ECLS: extracorporeal life support; DBD: organ donation after brain death; CPC: cerebral performance category; OHCA: out-of-hospital cardiac arrest.

Is there space for prospective randomised trials?

In the past few years, our group tried to design a prospective, randomised trial on ECLS after OHCA. This option was then excluded for two main reasons. First, the outcome improvement offered by ECLS and the substantial absence of any other comparable treatment made a hypothetical control group unethical.[46] Second, the impossibility of identifying a single point when to interrupt a complex chain of assistance meant that OHCA patients could not be transported to the hospital without the prospect of ECLS. The complete absence of recovery among non-ECLS treated patients[27] led us to speculate that, in the absence of ECLS, OHCA patients presenting refractory rhythms may inevitably be destined to die and instead, once they have achieved ROSC, they lose the indication for ECLS.[47] Even if full neurological recovery can be expected to be low in the "treatment arm", it would be zero in a hypothetical adequately selected "control arm" without ECLS. This simple but unexpected observation[48] poses burdensome ethical questions about designing and conducting future prospective RCTs with ECLS after OHCA.

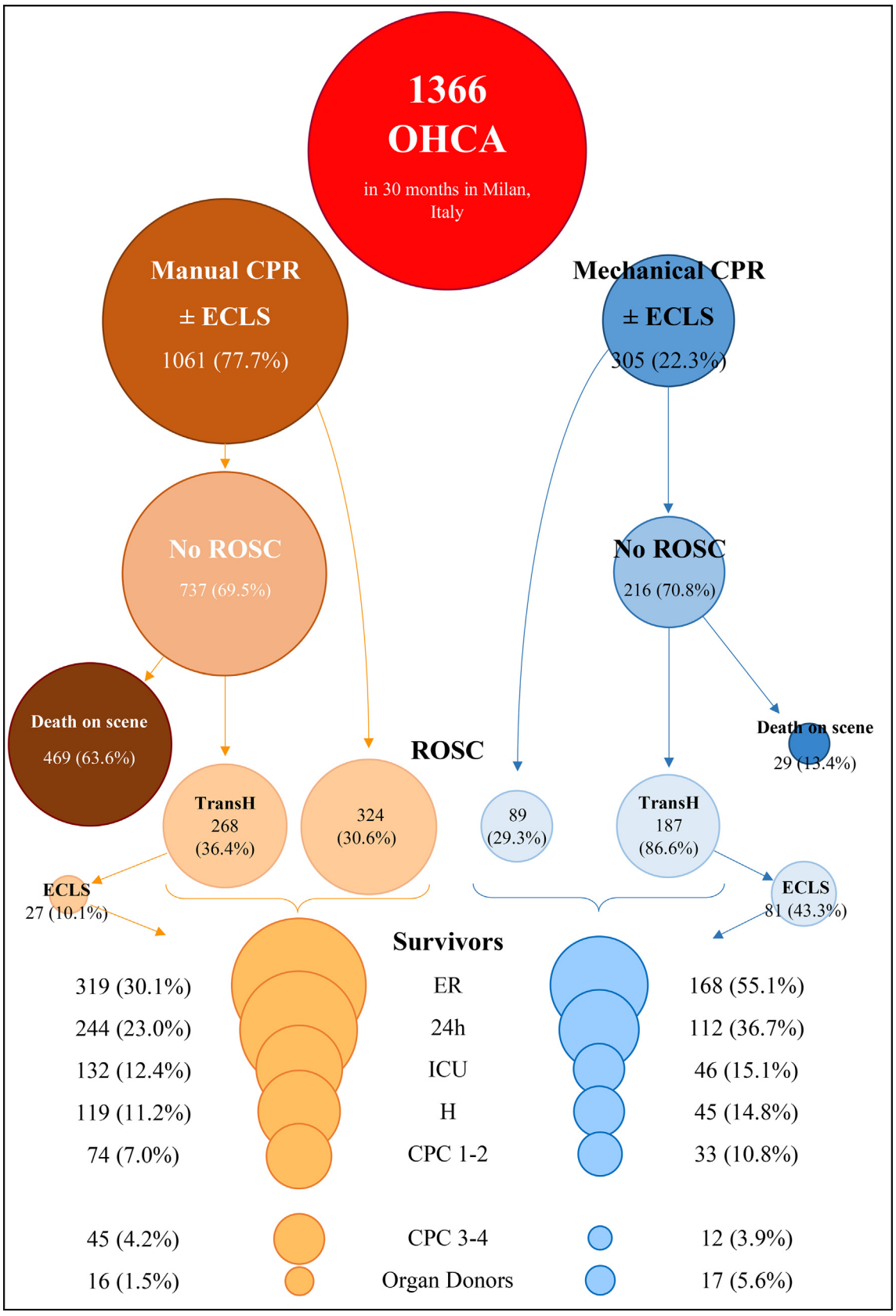

Fig. 4 – Graphical representation of OHCA absolute numbers described in the present study. OHCA: out-of-hospital cardiac arrest; CPR: cardiopulmonary resuscitation; ECLS: extracorporeal life support; ROSC: sustained return of spontaneous circulation; TransH: patients transferred to hospital without ROSC; ER: emergency room; 24 h: survivors the day after the OHCA; ICU: intensive care unit; H: hospital; CPC: Cerebral Performance Category.

Conclusions

In this observational retrospective study regarding a real-world metropolitan setting, the use of mechCPR improved all investigated outcomes, from early ROSC to a good neurological outcome at hospital discharge. The relative effectiveness of mechCPR increased with the duration of rescue medical assistance, becoming significant after 13 min. ECLS allowed some patients with refractory OHCA to survive and increased the number of potential organ donors, even shortly after its introduction in a pre-hospital shared protocol. This therapeutic strategy is worth considering for selected OHCA patients as a new and promising indication, especially in those with refractory shockable rhythms.

Ethics approval and consent to participate

This observational trial was approved by the Ethics Committee of Monza, referring to all studies cooperating with the Milan metropolitan area dispatch centre: Prot. 2462 of 15th December 2016.

Written informed consent was taken from all surviving and able patients or their legal guardians. According to ethics committee indications, a written declaration of information received was collected from relatives when it could not be given. Patients or their next of kin can withdraw from the study at anytime.

Social Media & Promotion

In 1366 retrospectively analysed out-of-hospital cardiac arrest victims, mechanical chest compression seemed to raise the odds of a good neurological outcome, especially for those needing prolonged resuscitation manoeuvres. Extracorporeal life support offered a chance of recovery for patients who would otherwise have died.

Study Question: Do mechanical chest compressions perform better than manual ones in out-of-hospital cardiac arrest? Is extracorporeal life support for refractory cardiac rhythms of value?

Results: In 1366 retrospectively analysed out-of-hospital cardiac arrest victims, the characteristics associated with better outcomes were low-flow time, shockable rhythms, number of defibrillations, and mechanical chest compressions. Among the 108 patients treated with extracorporeal circulation, 7.5% had a good neurological outcome.

Interpretation: Mechanical chest compressions and extracorporeal resuscitation are associated with better neurological recovery after out-of-hospital cardiac arrest.

Consent for publication

Besides informed consent to participate, specific permission to use anonymised data for scientific purposes was collected from or for all survived patients.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Funding

This study did not receive any grant and was done with departmental funding only. The corresponding author, Giovanni Mistraletti, MD, had full access to all the data in the study and had final responsibility for the decision to submit. He takes responsibility for the data's integrity and the data analysis's accuracy.

Authors' contributions

GM is the principal investigator of the present study. GM and GB are responsible for the conception, protocol design, and data collection organisation. MU and SS provided statistical guidance and were responsible for the final statistical analysis. AL, GB, FN, and GS were responsible for data handling and relations with the dispatch centre. AZ, FP, AMS, GF, LA, NP, FR, EC, EC, DO, CR, and MM were responsible for the enrolment of patients and data gathering at each ECLS hospital. GM and AP obtained permission from the ethics committee for this project. GM and AL wrote the first manuscript draft; GB, MU, GS, RF, and AP, revised the draft for important intellectual content. All authors have read and approved the final version and submitted the present manuscript to Resuscitation.

Elicottero Niguarda (Eco1)	Giovanni Sesana
MSA Niguarda (Alfa1)	Vincenzo Grifone, Siro Ravasi
MSA Garbagnate (Alfa2)	Enrico Boselli
MSA Fatebenefratelli (Alfa5)	Elena Galassini
MSA San Paolo (Alfa6)	Elena Assi
MSA San Carlo (Alfa7)	Giancarlo Fontana
MSA Sacco (Alfa8)	Claudia Ruffini
MSA Cernusco (Alfa10)	Catello Pontecorvo
MSA San Gerardo (Alfa11)	Maurizio Migliari
Ospedale Niguarda	Roberto Fumagalli
Ospedale San Gerardo – Monza	Giuseppe Foti
Ospedale San Raffaele	Alberto Zangrillo
Ospedale Sacco	Emanuele Catena, Antonio Castelli
Ospedale Humanitas	Fernando Raimondi
Ospedale San Paolo	Davide Chiumello
Ospedale San Carlo	Fabiola Carrieri
Ospedale Legnano	Federico Valdambrini, Matteo Lucchelli, Sabrina Baltieri
Ospedale Fatebenefratelli	Marco Cigada
Ospedale di Cinisello Balsamo	Daniela Anelati
Ospedale Saronno	Benedetta Franchi
Ospedale Magenta	Gianni Negri
Ospedale Cernusco	Paolo Calzavacca
Ospedale Policlinico di Milano	Antonio Pesenti
Ospedale Rho	Carla Maria Pessina
Ospedale Carate	Maria Pia Ferrario
Ospedale San Donato	Francesco Bedogni
Ospedale Melzo	Catello Pontecorvo

Ospedale Multimedica	Massimo Vota
Ospedale S. Ambrogio	Andrea Schiraldi
Ospedale S. Giuseppe	Marco Bordonali
Ospedale S. Luca	Giovanni Battista Perego
Ospedale Città Studi	Sara Bonizzato
SOREUM 118 - Area metropolitana	Filippo Bernasconi, Maurizio Migliari, Alessandra Sforza
Università degli Studi di Milano	Giulia Casotto, Katerina Negri
Università degli Studi Milano-Bicocca	Gabriele Fior, Beatrice Barbic, Andrea Danieli, Andrea Pisa, Serena Vaghi, Hedwige Gay

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.

Acknowledgements

First, the authors thank Alberto Zoli and all the AREU members (https://www.areu.lombardia.it) for their close collaboration during the clinical protocol development and the study. The authors also thank Luigi Mariani, PhD, for his essential help in statistical analysis and Maurizio Migliori, MD, for his continuous support and cooperation with the SOREUM dispatch centre. The authors are very grateful to the medical students who helped collect data from the hospitals in the Milan metropolitan area. The authors also thank all the SOREUM and "Articolazione Aziendale Territoriale 118 Milano" employees and the staff of the participating ICUs for their essential cooperation. The corresponding author would like to dedicate the present study to all the physicians, nurses, residents, students, paramedics, and certified volunteers who every day do their best to care for OHCA people with passion, hope, and competence. We are grateful to J.D. Baggott for language editing.

A. AppendixComplete list of mechCPR-ECLS investigators.

Elicottero Niguarda (Eco1)	Giovanni Sesana
MSA Niguarda (Alfa1)	Vincenzo Grifone, Siro Ravasi
MSA Garbagnate (Alfa2)	Enrico Boselli
MSA Fatebenefratelli (Alfa5)	Elena Galassini
MSA San Paolo (Alfa6)	Elena Assi
MSA San Carlo (Alfa7)	Giancarlo Fontana
MSA Sacco (Alfa8)	Claudia Ruffini
MSA Cernusco (Alfa10)	Catello Pontecorvo
MSA San Gerardo (Alfa11)	Maurizio Migliari
Ospedale Niguarda	Roberto Fumagalli
Ospedale San Gerardo – Monza	Giuseppe Foti
Ospedale San Raffaele	Alberto Zangrillo
Ospedale Sacco	Emanuele Catena, Antonio Castelli
Ospedale Humanitas	Fernando Raimondi
Ospedale San Paolo	Davide Chiumello
Ospedale San Carlo	Fabiola Carrieri
Ospedale Legnano	Federico Valdambrini, Matteo Lucchelli, Sabrina Baltieri
Ospedale Fatebenefratelli	Marco Cigada
Ospedale di Cinisello Balsamo	Daniela Anelati
Ospedale Saronno	Benedetta Franchi
Ospedale Magenta	Gianni Negri
Ospedale Cernusco	Paolo Calzavacca
Ospedale Policlinico di Milano	Antonio Pesenti
Ospedale Rho	Carla Maria Pessina
Ospedale Carate	Maria Pia Ferrario
Ospedale San Donato	Francesco Bedogni
Ospedale Melzo	Catello Pontecorvo
Ospedale Multimedica	Massimo Vota
Ospedale S. Ambrogio	Andrea Schiraldi
Ospedale S. Giuseppe	Marco Bordonali
Ospedale S. Luca	Giovanni Battista Perego
Ospedale Città Studi	Sara Bonizzato
SOREUM 118 - Area metropolitana	Filippo Bernasconi, Maurizio Migliari, Alessandra Sforza
Università degli Studi di Milano	Giulia Casotto, Katerina Negri
Università degli Studi Milano-Bicocca	Gabriele Fior, Beatrice Barbic, Andrea Danieli, Andrea Pisa, Serena Vaghi, Hedwige Gay

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.11.025.

Author details

the mechCPR-ECLS investigators[2] [a]*Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Italy* [b]*UOC Anestesia e Rianimazione, Ospedale Nuovo di Legnano, ASST Ovest Milanese, Milano, Italy* [c]*Dipartimento di Medicina e Chirurgia, Università degli Studi di Milano-Bicocca, Milano, Italy* [d]*Servizio di Anestesia e Rianimazione 1, Dipartimento di Anestesia e Rianimazione, Grande Ospedale Metropolitano Niguarda, Milano, Italy* [e]*S.C. Anestesia e Rianimazione II, Ospedale San Carlo Borromeo, ASST dei Santi Paolo e Carlo, Milano, Italy* [f]*Dipartimento di Economia, Management e Metodi Quantitativi, Data Science Research Center, Università degli Studi di Milano, Italy* [g]*Dipartimento Cardio-Toraco-Vascolare, IRCCS Ospedale San Raffaele, Milano, Italy* [h]*Dipartimento di Anestesia e Rianimazione Cardio-Toraco-Vascolare, AO SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy* [i]*UOC Anestesia e Rianimazione, Ospedale San Gerardo, ASST Monza, Italy* [j]*Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate, Università degli Studi di Genova, Italy* [k]*Dipartimento di Anestesia e Rianimazione, Humanitas Clinical*

and Research Center – IRCCS, Rozzano (MI), Italy[j]UOC Anestesia e Rianimazione, Ospedale Luigi Sacco, Milano, Italy [m]AAT Monza Brianza, AREU, Monza, Italy[n]SOREUM Sala Operativa Emergenza Urgenza Metropolitana, AREU, Milano, Italy[o]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018;137:e67–e492.
2. Grasner JT, Herlitz J, Tjelmeland IBM, Wnent J, Masterson S, Lilja G, et al. European Resuscitation Council Guidelines 2021: Epidemiology of cardiac arrest in Europe. Resuscitation 2021;161:61–79.
3. Hawkes C, Booth S, Ji C, Brace-McDonnell SJ, Whittington A, Mapstone J, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation 2017;110:133–40.
4. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res 2015;116:1887–906.
5. Grasner JT, Wnent J, Herlitz J, Perkins GD, Lefering R, Tjelmeland I, et al. Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. Resuscitation 2020;148:218–26.
6. Perkins GD, Graesner JT, Semeraro F, Olasveengen T, Soar J, Lott C, et al. European Resuscitation Council Guidelines 2021: Executive summary. Resuscitation 2021;161:1–60.
7. Stub D, Nehme Z, Bernard S, Lijovic M, Kaye DM, Smith K. Exploring which patients without return of spontaneous circulation following ventricular fibrillation out-of-hospital cardiac arrest should be transported to the hospital? Resuscitation 2014;85:326–31.
8. Yannopoulos D, Bartos JA, Martin C, Raveendran G, Missov E, Conterato M, et al. Minnesota Resuscitation Consortium's Advanced Perfusion and Reperfusion Cardiac Life Support Strategy for Out-of-Hospital Refractory Ventricular Fibrillation. J Am Heart Assoc 2016:5.
9. Soar J, Callaway CW, Aibiki M, Bottiger BW, Brooks SC, Deakin CD, et al. Part 4: Advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2015;95:e71–e.
10. Stub D, Bernard S, Pellegrino V, Smith K, Walker T, Sheldrake J, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). Resuscitation 2015;86:88–94.
11. Wang PL, Brooks SC. Mechanical versus manual chest compressions for cardiac arrest The Cochrane database of systematic reviews 2018;8:CD007260.
12. Poole K, Couper K, Smyth MA, Yeung J, Perkins GD. Mechanical CPR: Who? When? How? Crit Care 2018;22:140.
13. Olasveengen TM, Wik L, Steen PA. Quality of cardiopulmonary resuscitation before and during transport in out-of-hospital cardiac arrest. Resuscitation 2008;76:185–90.
14. Rubertsson S, Karlsten R. Increased cortical cerebral blood flow with LUCAS; a new device for mechanical chest compressions compared to standard external compressions during experimental cardiopulmonary resuscitation. Resuscitation 2005;65:357–63.
15. Ong ME, Ornato JP, Edwards DP, Dhindsa HS, Best AM, Ines CS, et al. Use of an automated, load-distributing band chest compression device for out-of-hospital cardiac arrest resuscitation. JAMA 2006;295:2629–37.
16. Zimmermann S, Rohde D, Marwan M, Ludwig J, Achenbach S. Complete recovery after out-of-hospital cardiac arrest with prolonged (59 min) mechanical cardiopulmonary resuscitation, mild therapeutic hypothermia and complex percutaneous coronary intervention for ST-elevation myocardial infarction. Heart Lung 2014;43:62–5.
17. Smekal D, Lindgren E, Sandler H, Johansson J, Rubertsson S. CPR-related injuries after manual or mechanical chest compressions with the LUCAS device: a multicentre study of victims after unsuccessful resuscitation. Resuscitation 2014;85:1708–12.
18. Perkins GD, Lall R, Quinn T, Deakin CD, Cooke MW, Horton J, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. Lancet 2015;385:947–55.
19. Rubertsson S, Lindgren E, Smekal D, Ostlund O, Silfverstolpe J, Lichtveld RA, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. JAMA 2014;311:53–61.
20. Wik L, Olsen JA, Persse D, Sterz F, Lozano Jr M, Brouwer MA, et al. Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. Resuscitation 2014;85:741–8.
21. Schmidbauer S, Herlitz J, Karlsson T, Axelsson C, Friberg H. Use of automated chest compression devices after out-of-hospital cardiac arrest in Sweden. Resuscitation 2017;120:95–102.
22. Esibov A, Banville I, Chapman FW, Boomars R, Box M, Rubertsson S. Mechanical chest compressions improved aspects of CPR in the LINC trial. Resuscitation 2015;91:116–21.
23. Karagiannidis C, Brodie D, Strassmann S, Stoelben E, Philipp A, Bein T, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. Intensive Care Med 2016;42:889–96.
24. Lunz D, Calabro L, Belliato M, Contri E, Broman LM, Scandroglio AM, et al. Extracorporeal membrane oxygenation for refractory cardiac arrest: a retrospective multicenter study. Intensive Care Med 2020;46:973–82.
25. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engstrom AE, Lagrand WK, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. Intensive Care Med 2016;42:1922–34.
26. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit Care 2014;18:535.
27. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet 2020;396:1807–16.
28. Dennis M, Lal S, Forrest P, Nichol A, Lamhaut L, Totaro RJ, et al. In-Depth Extracorporeal Cardiopulmonary Resuscitation in Adult Out-of-Hospital Cardiac Arrest. J Am Heart Assoc 2020;9:e016521.
29. Kagawa E, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. Resuscitation 2010;81:968–73.
30. Le Guen M, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. Crit Care 2011;15:R29.
31. Avalli L, Maggioni E, Formica F, Redaelli G, Migliari M, Scanziani M, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. Resuscitation 2012;83:579–83.
32. Cesana F, Avalli L, Garatti L, Coppo A, Righetti S, Calchera I, et al. Effects of extracorporeal cardiopulmonary resuscitation on neurological and cardiac outcome after ischaemic refractory cardiac arrest. Eur Heart J Acute Cardiovasc Care 2018;7:432–41.
33. Zamperetti N, Piccinni M, Bellomo R, Citerio G, Mistraletti G, Gristina G, et al. How to protect incompetent clinical research subjects

involved in critical care or emergency settings. Minerva Anestesiol 2016;82:479–85.
34. Leisman DE. Ten Pearls and Pitfalls of Propensity Scores in Critical Care Research: A Guide for Clinicians and Researchers. Crit Care Med 2019;47:176–85.
35. Andersen LW, Kurth T. Propensity scores - A brief introduction for resuscitation researchers. Resuscitation 2018;125:66–9.
36. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivar Behav Res 2011;46:399–424.
37. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107.
38. Perkins GD, Kenna C, Ji C, Deakin CD, Nolan JP, Quinn T, et al. The influence of time to adrenaline administration in the Paramedic 2 randomised controlled trial. Intensive Care Med 2020;46:426–36.
39. Andersen LW, Grossestreuer AV, Donnino MW. "Resuscitation time bias"-A unique challenge for observational cardiac arrest research. Resuscitation 2018;125:79–82.
40. Nee J, Koerner R, Zickler D, Schroeder T, Enghard P, Nibbe L, et al. Establishment of an extracorporeal cardio-pulmonary resuscitation program in Berlin - outcomes of 254 patients with refractory circulatory arrest. Scand J Trauma Resusc Emerg Med 2020;28:96.
41. Hayashida K, Tagami T, Fukuda T, Suzuki M, Yonemoto N, Kondo Y, et al. Mechanical Cardiopulmonary Resuscitation and Hospital Survival Among Adult Patients With Nontraumatic Out-of-Hospital Cardiac Arrest Attending the Emergency Department: A Prospective, Multicenter, Observational Study in Japan (SOS-KANTO [Survey of Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area] 2012 Study). J Am Heart Assoc 2017;6.
42. Youngquist ST, Ockerse P, Hartsell S, Stratford C, Taillac P. Mechanical chest compression devices are associated with poor neurological survival in a statewide registry: A propensity score analysis. Resuscitation 2016;106:102–7.
43. Simpson EH. The interpretation of interaction in contingency tables. J R Stat Soc 1951;13:238–41.
44. Hsu CH, Meurer WJ, Domeier R, Fowler J, Whitmore SP, Bassin BS, et al. Extracorporeal Cardiopulmonary Resuscitation for Refractory Out-of-Hospital Cardiac Arrest (EROCA): Results of a Randomized Feasibility Trial of Expedited Out-of-Hospital Transport. Ann Emerg Med 2021.
45. Chonde M, Escajeda J, Elmer J, Callaway CW, Guyette FX, Boujoukos A, et al. Challenges in the development and implementation of a healthcare system based extracorporeal cardiopulmonary resuscitation (ECPR) program for the treatment of out of hospital cardiac arrest. Resuscitation 2020;148:259–65.
46. Mentzelopoulos SD, Couper K, Voorde PV, Druwe P, Blom M, Perkins GD, et al. European Resuscitation Council Guidelines 2021: Ethics of resuscitation and end of life decisions. Resuscitation 2021;161:408–32.
47. Patricio D, Peluso L, Brasseur A, Lheureux O, Belliato M, Vincent JL, et al. Comparison of extracorporeal and conventional cardiopulmonary resuscitation: a retrospective propensity score matched study. Crit Care 2019;23:27.
48. Choi DS, Kim T, Ro YS, Ahn KO, Lee EJ, Hwang SS, et al. Extracorporeal life support and survival after out-of-hospital cardiac arrest in a nationwide registry: A propensity score-matched analysis. Resuscitation 2016;99:26–32.