


The role of age in post-cardiac arrest therapy in an elderly patient population

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ABSTRACT

Aim: We investigated the effect of age on post-cardiac arrest treatment outcomes in an elderly population, based on a local database and a systemic review of the literature. *Methods:* Data were collected retrospectively from medical charts and reports. Sixty-one comatose patients, cooled to 32–34 °C for 24 h, were categorized into three groups: younger group (≤ 65 years), older group (66–75 years), and very old group (> 75 years). Circumstances of cardiopulmonary resuscitation (CPR), patients' characteristics, post-resuscitation treatment, hemodynamic monitoring, neurologic outcome and survival were compared across age groups. Kruskal-Wallis test, Chi-square test and binary logistic regression (BLR) were applied. In addition, a literature search of PubMed/Medline database was performed to provide a background. *Results:* Age was significantly associated with having a cardiac arrest on a monitor and a history of hypertension. No association was found between age and survival or neurologic outcome. Age did not affect hemodynamic parameter changes during target temperature management (TTM), except mean arterial pressure (MAP). Need of catecholamine administration was the highest among very old patients. During the literature review, seven papers were identified. Most studies had a retrospective design and investigated interventions and outcome, but lacked unified age categorization. All studies reported worse survival in the elderly, although old survivors showed a favorable neurologic outcome in most of the cases. *Conclusion:* There is no

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evidence to support the limitation of post-cardiac arrest therapy in the aging population. Furthermore, additional prospective studies are needed to investigate the characteristics and outcome of post-cardiac arrest therapy in this patient group.

KEYWORDS

elderly, cardiopulmonary resuscitation, post-resuscitation therapy, target temperature management, hemodynamic monitoring

INTRODUCTION

Populations around the world are aging rapidly as life expectancy increases and fertility decreases. The number of people above 90 is expected to reach 30 million by 2030 [1]. In addition, the probability of cardiac arrest increases with age [2]. These facts implicate a considerable rise in the proportion of old and very old patients suffering from cardiac arrest and treated in the intensive care unit (ICU) after return of spontaneous circulation (ROSC) [3, 4]. Ample evidence points into the direction that older age is associated with worse outcomes after out-of-hospital cardiac arrest (OHCA) [5–13]. Moreover, comorbidities, frailty, and pathophysiological changes related to advanced age may influence the benefits and outcome of post-cardiac arrest therapy.

Post-resuscitation treatment as a link of chain-of-survival plays an important role in the quality of patients' management after cardiac arrest [14]. It focuses on the prevention and therapy of post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, ischemic-reperfusion syndrome, and the precipitating cause of cardiac arrest [15]. Target temperature management (TTM) is one of the key elements in neuroprotection in comatose patients after ROSC and the application of 32–36 °C is recommended in these cases [14]. However, current guidelines do not differentiate between the management of older and younger patients. There are only a few studies describing the quality and outcome of cardiopulmonary resuscitation (CPR) and post-cardiac arrest therapy in the elderly [16–22].

The aim of our study was to investigate the characteristics and outcome of post-cardiac arrest treatment and effect of age on post-cardiac arrest treatment outcomes in an elderly population, based on a local database and a systemic review of the literature.

MATERIALS AND METHODS

We screened 254 patients who underwent a successful CPR after OHCA or in-hospital cardiac arrest (IHCA) and were admitted to the ICU of Semmelweis University Heart and Vascular Center due to a suspected cardiac origin between January 2008 and January 2015. Only comatose patients treated with a thermo-feedback cooling device who were older than 18 years and had no end-stage illness in history were included into our analysis. Patients, whose suspected cause of cardiac arrest was active bleeding, hypovolemia or sepsis were excluded from the investigation. Altogether 25 patients were excluded due to insufficient documentation and lack of data. In total, 61 patients were included into our study. Medical charts were reviewed retrospectively to obtain demographic data, previous medical history, circumstances of CPR,



management in the first 48 h after ROSC, hemodynamic parameters (heart rate, mean arterial pressure (MAP), cardiac index, systemic vascular resistance index and serum lactate level) during the different phases of TTM, length of ICU stay, length of mechanical ventilation, cerebral performance category (CPC) score and survival. Patients were categorized into three groups based on their age: 1. Younger (Y) group (patients aged 65 years or younger), 2. Older (O) group (patients between 66 and 75 years), 3. Very Old (VO) group (patients older than 75 years). As the oldest patient was 84 years old, no older age groups were created.

The Semmelweis University Regional and Institutional Committee of Science and Research Ethics approved our study (approval Nr.: 19/2019). No informed consent was acquired according to our national regulations due to the retrospective nature of the study.

Patient management

Standardized post-resuscitation therapy and TTM based on our institutional protocol were initiated as soon as possible after the admission of the patients to the ICU. The goal parameters given by European Resuscitation Council (ERC) guidelines were utilized to guide our post-resuscitation management [14]. Beside the standard monitoring of ICU patients (oxygen saturation, electrocardiogram, invasive arterial blood pressure, diuresis, blood gas and serum lactate level analysis, and echocardiography), advanced hemodynamic monitoring with PiCCO™ (Pulse index Contour Cardiac Output; Pulsion Medical System, Feldkirchen, Germany) was applied, if it was available. Measurements with thermodilution were performed every 12 h during the first 48 h after the initiation of TTM. An acute coronarography was performed with percutaneous coronary intervention (PCI) and/or intra-aortic balloon pump (IABP) insertion, if indicated. Catecholamines were applied in mono- or combination therapy to support the cardiovascular system, if clinically indicated. In the cases of severe cardiac impairment, levosimendan treatment was initiated.

Patients were cooled to 32–34 °C according to ERC guidelines [14]. TTM consisted of three phases: induction, maintenance, and rewarming. Patients received 30 mL/kg crystalloids, and a Blanketrol III™ (Cincinatti SubZero Products, Cincinatti, USA) thermo-feedback device was used during the induction phase. The target temperature was upheld with the same device during the maintenance phase. After 24 h, rewarming was performed passively until normothermia was reached. Patients' core temperature was measured with an esophageal thermometer. Sedation was sustained with intravenous opioids and benzodiazepines, and intravenous muscle relaxant was administered in the case of severe shivering during TTM.

Outcome

Primary outcomes were 30-day and 1-year survival and neurologic outcome. Neurologic outcome was assessed with the CPC score: CPC 1 or 2 scores stand for a good and CPC 3–5 for a bad neurologic outcome.

Secondary outcomes were hemodynamic changes and catecholamine administration during TTM.

Statistical analysis

Demographic data (age, gender), circumstances of CPR (location, basic life support performed, monitor used at the time of cardiac arrest, initial rhythm), past history (hypertension,



hyperlipidemia, myocardial infarction, diabetes, stroke), cause of cardiac arrest (ST elevation myocardial infarction, non-ST elevation myocardial infarction, other), therapeutic steps in the first 48 h after ROSC (acute PCI, levosimendan treatment, ejection fraction at the admission of ICU, IABP insertion, PiCCO application, catecholamine therapy, serum lactate level, MAP, heart rate, cardiac index and systemic vascular resistance index) and length of ICU stay, length of mechanical ventilation, and CPC score were compared between the three groups.

Categorical variables were presented as numbers and percentages. Continuous variables were described with medians and interquartile ranges. No more than 5% of values were missing and were replaced with median. The chi-square test was applied for categorical variables and the Kruskal-Wallis test with Dunn's post hoc analysis for continuous variables.

The Kaplan-Meier curve was drawn and the log-rank test was performed to present and compare 30-day and 1-year survival between the three groups.

Binary logistic regressions (BLRs) and receiver operating characteristic (ROC) curve analyses were conducted. CPC, 30-day survival and 1-year survival represented the dependent variable and age constituted the independent variable. The level of significance was set at $P < 0.05$.

Statistical analysis was performed using SPSS v25.0 (SPSS Inc., Chicago, IL). Figures were created using GraphPad Prism version 8.1.1. (GraphPad Software, La Jolla, CA).

Literature review

A literature research was conducted through the PubMed/Medline database in December 2019 using the keywords (“cardiopulmonary resuscitation” OR “post-resuscitation*” OR “post-cardiac arrest*” OR “therapeutic hypothermia” OR “target temperature management”) AND (elderly OR age*) in order to provide a background. Inclusion criteria were original, full text articles investigating the outcome of old (age >65 years) patients suffering a successful CPR and receiving post-cardiac arrest therapy. Articles older than five years, articles not written in English, case reports, case series, reviews, publications without full text, studies investigating extracorporeal CPR and papers not discussing the aspects of post-cardiac arrest therapy were excluded. Titles and abstracts found during the literature search were screened to select appropriate papers for final evaluation.

RESULTS

Patient characteristics

Table 1 shows basic characteristics of patients, circumstances of CPR, main steps in the first 48 h of post-resuscitation therapy and neurologic outcome. Age was significantly associated with having a cardiac arrest on a monitor and a history of hypertension, with younger patients having a significantly lower probability of these conditions than older or very old patients (subgroup analysis not shown). Older and very old patients spent more days at the ICU, but this difference was only tendentious, not significant ($P = 0.081$). The length of mechanical ventilation was similar in all age groups.

No other differences were found between the age groups in the other assessed variables, including PiCCO administration.



Table 1. Basic characteristics, circumstances of CPR and post-cardiac arrest therapy in the first 48 h after ROSC

	Total N (%) or Median (25%, 75%)	age <65 years N (%) or Median (25%, 75%)	age 65–75 years N (%) or Median (25%, 75%)	age >75 years N (%) or Median (25%, 75%)	P
Total	61 (100%)	31 (100%)	23 (100%)	7 (100%)	
Age (years)	64 (56, 69)	56 (48, 62)	69 (67, 71)	79 (78, 81)	<0.001
Gender (male)	42 (69%)	22 (71%)	16 (70%)	4 (57%)	0.772
<i>Circumstances of CPR</i>					
OHCA	50 (82%)	27 (87%)	19 (83%)	4 (57%)	0.176
BLS performed	49 (80%)	23 (74%)	20 (83%)	7 (100%)	0.282
Patient on monitor at the time of CA	8 (13%)	0 (0%)	5 (22%)	3 (43%)	0.003
Shockable initial rhythm	42 (69%)	23 (74%)	13 (57%)	6 (86%)	0.226
<i>Past history</i>					
Hypertension	43 (70%)	17 (55%)	19 (83%)	7 (100%)	0.017
Hyperlipidemia	29 (48%)	11 (35%)	13 (57%)	5 (71%)	0.125
Diabetes	17 (28%)	6 (19%)	7 (30%)	4 (57%)	0.124
Myocardial infarction	15 (25%)	4 (13%)	8 (35%)	3 (43%)	0.089
Stroke	6 (10%)	2 (6%)	3 (13%)	1 (14%)	0.663
<i>Origin of cardiac arrest</i>					
STEMI	37 (61%)	19 (61%)	16 (70%)	2 (29%)	0.150
NSTEMI	8 (13%)	3 (10%)	3 (13%)	2 (29%)	0.409
Other	16 (26%)	9 (29%)	4 (17%)	3 (42%)	0.358
<i>Therapy in the first 48 h after ROSC</i>					
Acute PCI	49 (80%)	25 (81%)	19 (83%)	5 (71%)	0.807
Levosimendan	6 (10%)	1 (3%)	3 (13%)	2 (29%)	0.102
Ejection fraction at admission to ICU (%)	37.0 (29.0, 48.0)	40.0 (30.0, 50.0)	36.0 (25.0, 44.0)	31.0 (23.0, 37.0)	0.204
IABP	15 (25%)	4 (13%)	9 (39%)	2 (29%)	0.084
Length of IABP use (days)	0 (0, 0)	0 (0, 0)	0 (0, 2.5)	0 (0, 2)	0.089
PiCCO	31 (51%)	15 (48%)	12 (52%)	4 (57%)	0.904
Serum lactate 0 (mmol/L)	4.4 (3.0, 6.1)	4.4 (3.2, 5.7)	4.0 (2.2, 7.5)	5.0 (3.1, 7.8)	0.531
Serum lactate 12 (mmol/L)	2.1 (1.4, 3.2)	2.6 (1.4, 3.2)	2.1 (1.4, 4.5)	2.0 (1.4, 2.7)	0.925
Serum lactate 24 (mmol/L)	1.8 (1.2, 3.2)	1.8 (1.2, 3.2)	1.7 (1.2, 3.2)	2.6 (1.7, 3.3)	0.527
Serum lactate 48 (mmol/L)	1.7 (1.3, 2.5)	1.6 (1.2, 2.2)	2.0 (1.3, 2.5)	3.1 (1.0, 6.2)	0.326
Length of ICU stay (days)	7 (4.0, 8.0)	5.0 (3.3, 7.0)	7.0 (4.0, 10.0)	10 (5.0, 11.0)	0.081
Length of mechanical ventilation (days)	5.0 (3.5, 7.0)	5.0 (3.0, 7.0)	6.0 (4.0, 7.0)	5.0 (5.0, 8.0)	0.220
<i>Temperature changes in the first 48 h after ROSC</i>					
T0 (°C)	36.0 (35.3, 36.4)	35.7 (35.3, 36.5)	36.1 (35.2, 36.3)	36.2 (34.4, 36.4)	0.833
T12 (°C)	32.7 (32.2, 33.1)	32.7 (32.0, 33.0)	32.6 (32.1, 33.1)	33.0 (32.3, 33.5)	0.570

(continued)



Table 1. Continued

	Total N (%) or Median (25%, 75%)	age <65 years N (%) or Median (25%, 75%)	age 65–75 years N (%) or Median (25%, 75%)	age >75 years N (%) or Median (25%, 75%)	<i>P</i>
T24 (°C)	32.7 (32.1, 33.0)	32.7 (32.1, 33.1)	32.4 (32.1, 33.0)	32.9 (32.3, 33.0)	0.778
T48 (°C)	36.6 (36.2, 37.0)	36.6 (36.1, 37.0)	36.6 (36.2, 36.8)	36.7 (36.0, 37.0)	0.775
Time to reach target temperature (hours)	3.8 (2.0, 5.1)	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	3.8 (2.5, 6.0)	0.676
<i>Outcome</i>					
CPC 1, 2 at ICU discharge	18 (30%)	8 (26%)	7 (30%)	3 (43%)	0.666

Legends: Kruskal-Wallis and Chi-square tests were applied, $P < 0.05$ is bolded. CPR: cardiopulmonary resuscitation; OHCA: out-of-hospital cardiac arrest; BLS: basic life support; CA: cardiac arrest; STEMI: ST segment elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; ROSC: return of spontaneous circulation; PCI: percutaneous coronary intervention; ICU: intensive care unit; IABP: intra-aortic balloon pump; PiCCO: Pulse index Contour Cardiac Output; CPC: cerebral performance category; T: temperature.

Survival and neurologic outcome

30-day and 1-year survival (Fig. 1), as well as neurologic outcome (Table 1) were not different across the age groups. Age was a poor predictor of 30-day survival, 1-year survival and neurologic outcome after successful CPR in our study population (Figs. 2–4).

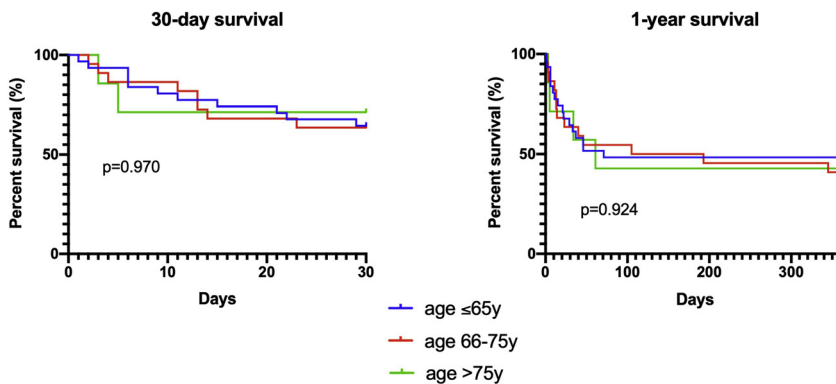


Fig. 1. Comparison of 30-day and 1-year survival between age groups. Kaplan-Meier curves and log-rank test were performed



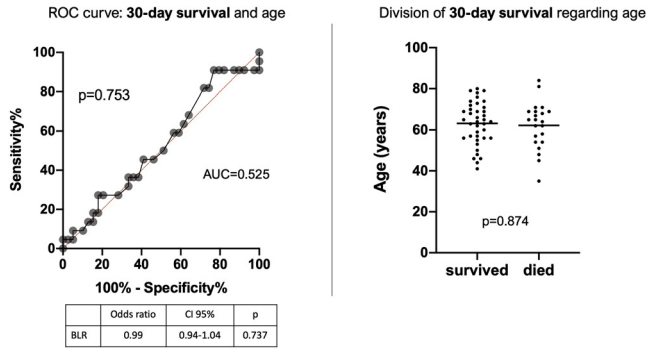


Fig. 2. ROC (receiver operating characteristic) curve describing the relationship between age and 30-day survival. AUC: area under curve. Binary logistic regression (BLR) was performed. Scatter plot with median is shown on the right with the results of Chi-square test

Hemodynamic management

Fig. 5 shows the comparison of heart rate, MAP and the rate of catecholamine administration during the different phases of TTM between the groups. Very old patients had significantly lower MAP during low temperature and after rewarming than younger patients. Additionally, older patients had a lower MAP 24 h after the initiation of TTM than younger patients. Furthermore, older and very old patients were more likely than younger patients to receive catecholamines at the initiation of cooling and during low temperature.

Of those 31 patients who received PiCCO™, cardiac index and systemic vascular resistance index measured during the different phases of cooling were similar in all age categories (Fig. 6).

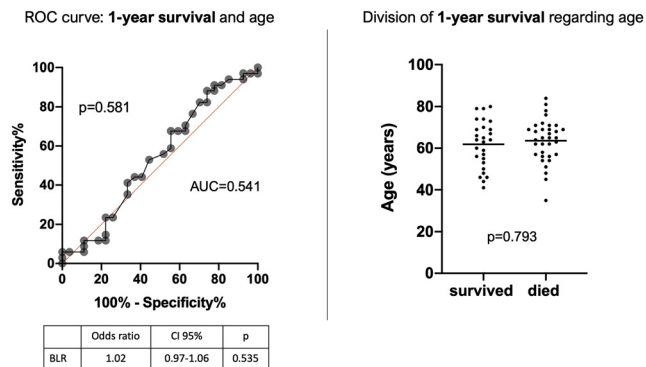


Fig. 3. ROC (receiver operating characteristic) curve describing the relationship between age and 1-year survival. AUC: area under curve. Binary logistic regression (BLR) was performed. Scatter plot with median is shown on the right with the results of Chi-square test



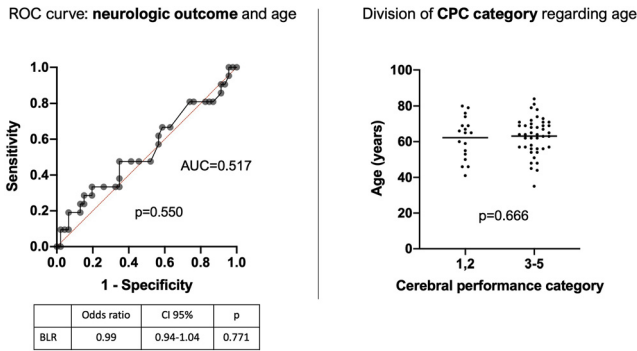


Fig. 4. ROC (receiver operating characteristic) curve describing the relationship between age and neurologic outcome. AUC: area under curve. CPC: cerebral performance category. Binary logistic regression (BLR) was performed. Scatter plot with median is shown on the right with the results of Chi-square test

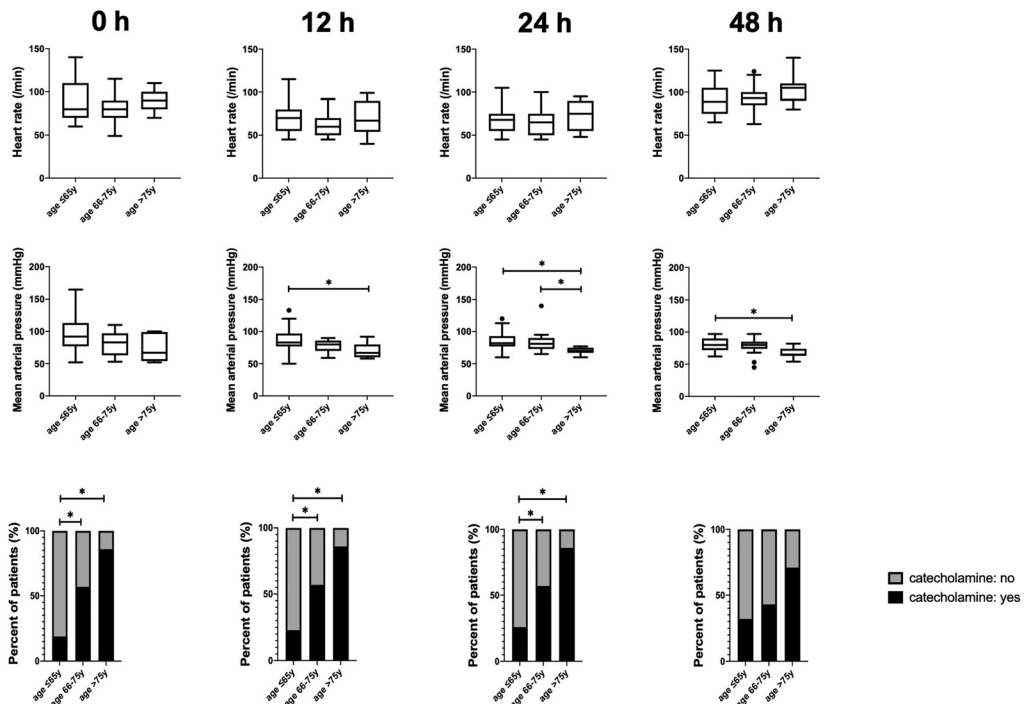


Fig. 5. Comparison of heart rate, mean arterial pressure and catecholamine administration during the first 48 h after ROSC between the groups. 0 h: initiation of target temperature management; 12 and 24 h: target temperature management (32-34 °C); 48 h: measurement after rewarming. Kruskal-Wallis and Dunn's post hoc test were performed for continuous, and Chi-square test for categorical variables. Star: $P < 0.05$. Box-and-whiskers plot are interpreted with Tukey method



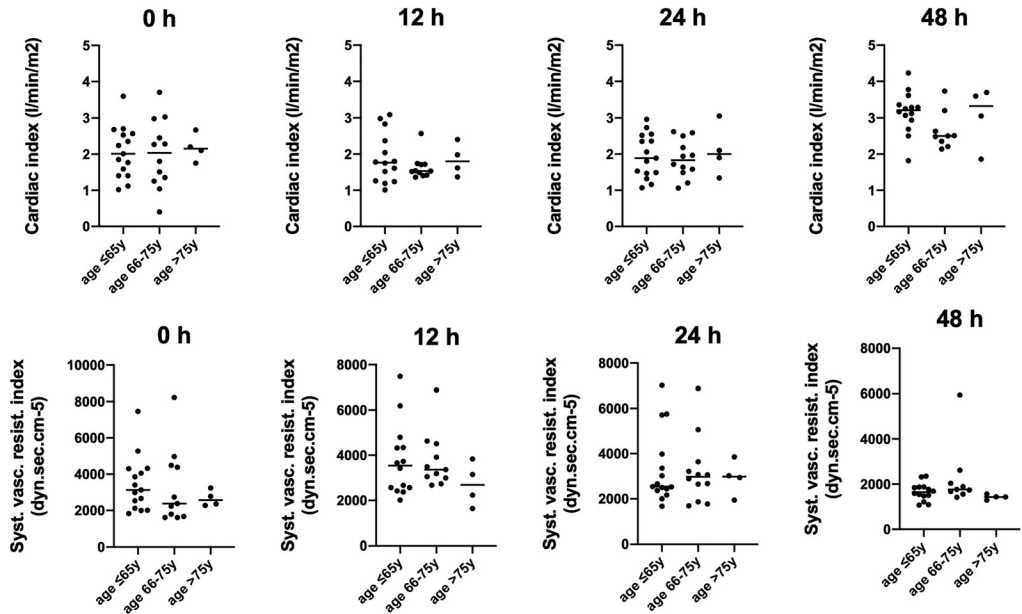


Fig. 6. Comparison of cardiac index and systemic vascular resistance index during the first 48 h after ROSC between the age groups (among the subgroup treated with PiCCO™). 0 h: initiation of target temperature management; 12 and 24 h: target temperature management (32–34 °C); 48 h: measurement after rewarming. Kruskal-Wallis and Dunn’s post hoc test were performed

Literature review

3,419 articles were identified and screened during the literature search and finally seven were included into the review (Fig. 7). Tables 2 and 3 summarize the characteristics and results of the incorporated articles. Six papers applied a retrospective analysis and only one article used

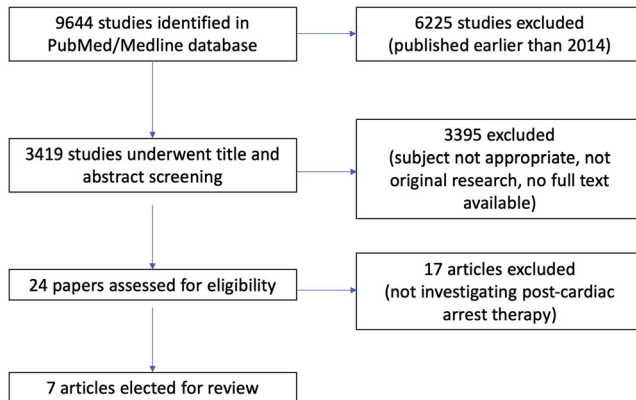


Fig. 7. Process of literature search in PubMed/Medline database





Table 2. Characteristics of the included studies

Author	Study period	Study design	Location of CA	N	Age classification	Outcome	Survival	Good neurologic outcome among survivors
Winther-Jensen et al.	2010–2013	multicenter, post-hoc analysis of TTM-trial	OHCA	950	<65, 66–70, 71–75, 76–80, >80y	survival and neurologic outcome (CPC category and Rankin scale)	* <65y: 70%, 66–70y: 55%, 71–75y: 55%, 76–80y: 38%, >80y: 28%	& <65y: 62%, 66–70y: 39%, 71–75y: 42%, 76–80y: 30%, >80y: 18%
Winther-Jensen et al.	2007–2011	multicenter, prospective	OHCA	2,509	<80 and >80y	successful CPR, 30-day survival, neurologic outcome (CPC category)	* <80y: 45%; >80y: 20%	# <80y: 84%; >80y: 79%
Aissaoui et al.	2011–2015	retrospective	OHCA	1,502	<65, 65–75, >75y	neurologic outcome and survival at hospital discharge	\$ <65y: 44%, 65–75y: 42%, >75y: 28%	☆ <65y: 42% 65–75y: 38%, >75y: 24%
Roedl et al.	2008–2016	retrospective	OHCA, IHCA	48	>90y	evaluation of patient characteristics, ICU- and neurologic outcome survival	6-month: 29%; 1-year: 23%	6-month: 92%; 1-year: 55%
Hiemstra et al.	2001–2010	retrospective	OHCA	810	<75 and >75y		\$ <75y: 57% >75y: 33%	# <75y: 97%, >75y: 92%
Wallmüller et al.	1992–2015	retrospective	OHCA	1885	<50, 50–64, 65–74, >75y	comparison of patients with TTM and without (neurologic outcome)	□ <50y: 59%, 50–64y: 52%, 65–74y: 35%, >75y: 27%	× <50y: 51%, 50–64y: 48%, 65–74y: 34%, >75y: 30%

(continued)

Table 2. Continued

Author	Study period	Study design	Location of CA	N	Age classification	Outcome	Survival	Good neurologic outcome among survivors
Pätz et al.	2001–2012	multicenter, retrospective	OHCA	902	<65, 65–74,75–84, >85y	28-day and 180-day survival, favorable neurologic outcome (CPC 1, 2)	1-month: <65y: 70% 65–74y: 49%, 75–84y: 34%, >85y: 35% 6-month: <65y: 63% 65–74y: 39%, 75–84y: 24%, >85y: 27%	1-month: <65y: 80% 65–74y: 80%, 75–84y: 68%, >85y: 70% 6-month: <65y: 85% 65–74y: 90%, 75–84y: 75%, >85y: 63%

Legends: CA: cardiac arrest; N: number of patients included into the study; TTM: target temperature management; OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; y: year; * 30-day survival; \$ survival at hospital discharge; □ 6-month survival; & CPC1, 2 at 180 days; # CPC 1, 2 at hospital discharge; ☆ CPC 1, 2 at ICU discharge; × CPC 1, 2 after 6 months. The different age groups are highlighted bold in the table.





Table 3. Results of the included studies

Author	TTM	Acute PCI	Catecholamine therapy	Active therapy terminated	Independent predictors of mortality	Independent predictors of favorable neurologic outcome
Winther-Jensen et al.	* all patients received TTM	<65y: 49%,66–70y: 38%,71–75y: 40%,76–79y: 36%, >80y: 15%	NA	<65y:12%, 66–70y: 20%, 71–75y: 14%, 76–79y: 23%, >80y:13%	NA	NA
Winther-Jensen et al.	◦ <80y: 52%,>80y: 32%	<80y: 27%,>80y: 10%	NA	<80y: 10%, >80y: 19%	age >80, CCI>2, non-shockable rhythm, lack of bystander CPR, non-public arrest, longer time to ROSC, lack of TTM arrest at home, no-flow period >3 min, low-flow period >20 min, lack of CAG	NA
Aissaoui et al.	◦ <65y: 64%,65–75y: 66%,>75y: 62%	<65y: 56%,65–75y: 46%, >75y: 50%	NA	NA	arrest at home, no-flow period >3 min, low-flow period >20 min, lack of CAG	CAG, TTM, bystander CPR, arrest at public region, no-flow period shorter than 3 min, low-flow period shorter than 20 min
Roedl et al.	◦ >90y: 13%	NA	>90y: 92%	>90y: 25%	NA	NA
Hiemstra et al.	● <75y: 38%, >75y: 32%	<75y: 43%,>75y: 25%	NA	NA	older age, GCS at admission (at older patients)	NA
Wallmüller et al.	● <50y: 47%,50–64y: 47%,65–74y: 53%, >75y: 50%	NA	NA	NA	increasing age	younger age

(continued)

Table 3. Continued

Author	TTM	Acute PCI	Catecholamine therapy	Active therapy terminated	Independent predictors of mortality	Independent predictors of favorable neurologic outcome
Pätz et al.	● all patients received TTM	No difference by age categories ($P = 0.201$; Fisher's exact test)	NA	NA	increasing age, time to ROSC, lack of bystander CPR, non-cardiac origin of CA	bystander CPR, time of hypoxia, defibrillation performed by EMS

Legends: TTM: target temperature management; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; GCS: Glasgow Coma Scale; CCI: Charleson's Comorbidity Index; CAG: coronary angiography; EMS: emergency medical system; y: year; NA: non-applicable (not analyzed in the referred study); * 33 or 36 °C; ● 32–34 °C; ° level of TTM not define. The different age groups are highlighted bold in the table.



prospectively collected data to investigate the characteristics and outcomes of elderly patients receiving CPR and post-cardiac arrest therapy [16–22]. Most of the studies were multicenter or nationwide evaluations. The outcome of IHCA patients was investigated only in one paper [19]. Neither age grouping, nor the investigated outcome were unified in the studies. Additionally, the rate of TTM was also variable among the papers. The effect of TTM on mortality of the elderly was investigated only in one study, which could not show an association between the application of TTM and survival [16]. Furthermore, the effect of TTM on neurologic outcome was determined in two papers: Winther-Jensen et al. reported an increase in poor neurologic outcome with advanced age, but it was not modified by the level (33 vs. 36 °C) of TTM [22]. Walmüller et al. showed an association between TTM and good neurologic outcome only in patients younger than 65 years [20]. None of the studies examined the hemodynamic effects of TTM in the older patient group. The rate of acute PCI was analyzed in five studies: three of them showed a decline in the number of PCIs performed with increasing age [17, 21, 22]. In addition, Aissaoui et al. described a benefit of PCI on outcome in patients up to 75 years [16]. One article reported the rate of administration of catecholamines: 92% of nonagenarians received catecholamine during post-resuscitation therapy [19]. Three studies described the rate of acute therapy termination, which was higher among older patients [19, 21, 22]. Five papers assessed the independent predictors of mortality [16–18, 20, 21], and three articles described the independent predictors of favorable neurologic outcome [16, 18, 20] (Table 3).

All studies reported worse survival rates in older compared to younger patients. Neurologic outcome among survivors also deteriorated with increasing age, but this decay was more moderate and old patients survived with a favorable neurologic outcome in most of the studies. Moreover, all the studies point out that older age should not be taken into consideration to determine the withdrawal of intensive post-cardiac arrest therapy, since age has no significant predictive value on mortality (Tables 2 and 3).

DISCUSSION

We aimed to give an overview of the management and outcome of elderly patients after successful CPR and post-resuscitation therapy in our retrospective cohort study and systemic literature review.

There are several questions, challenges and ethical dilemmas in the post-cardiac arrest treatment of the aging population. Data from previously published studies demonstrate the association between age and outcome in this patient group [5–13]. However, this relationship is influenced by various factors and therefore expose many questions regarding the nature of this finding.

We could not show any association between age, 30-day or 1-year survival and neurologic outcome at discharge among patients treated after ROSC at our ICU. This finding fully contradicts formerly published data. All papers included in our literature review found a decrease in survival with increasing age, and four of them reported advanced age as one of the independent predictors of mortality [16–22]. On the other hand, the association between age and neurologic outcome was not so obvious, as four studies noticed favorable neurologic outcome among old survivors [17, 19–21]. The rate of good neurologic outcome was the highest among very old patients in our investigation, but this difference was not statistically significant. We would like to



highlight that design, age categorization and measured outcomes were heterogenous in the studies, as were the interventions during post-resuscitation therapy.

Moreover, our literature review showed that the rate of therapy termination during post-cardiac arrest therapy was higher in the older population, nonetheless the exact conditions and criteria of this step in the treatment were not specified. Additionally, it was previously described that the rate of CPR initiated by the emergency medical system was lower and CPR duration was shorter among old patients [12].

The population is aging rapidly, and life expectancy is becoming higher. In parallel, there is an increasing number of ICU admissions of patients older than 75 years and of cardiac arrests [23]. Furthermore, elderly people's health conditions are better than before, as is the quality of post-resuscitation therapy [24]. Individual patient factors, premorbid status and the circumstances of CPR and post-cardiac arrest therapy play an important role in the management of elderly patients after ROSC and in the decision of therapeutic strategies.

We also evaluated the differences in post-cardiac arrest treatment between the age groups, and found only a few dissimilarities in our retrospective analysis. The rate of acute PCI was similar among the investigated groups. However, our literature review revealed contradicting information, as some studies showed the same result but others found the opposite [16–18, 21, 22]. TTM was applied in all cases in our retrospective cohort. Additionally, there was no difference in TTM use among younger and older patients in the studies included into our literature review except for two, where older patients were less likely to receive TTM [16–20, 22]. Furthermore, the question of TTM efficacy and its influence on neurologic outcome in the elderly was raised only in two investigations with a contrary result. The post-hoc analysis of TTM-trial showed that age had no impact on the effectiveness of TTM [22]. On the other hand, a retrospective cohort study found a marked effect of mild therapeutic hypothermia on neurologic outcome only among patients below 65 years [20].

The management of hemodynamic changes during post-cardiac arrest therapy and TTM also play an important role in the post-resuscitation period. Nonetheless we found no evidence in the literature published in the last five years assessing the hemodynamic management of the elderly after a successful CPR. The changes in heart rate, MAP, cardiac index and systemic vascular resistance index during TTM were described in our study. We found a significantly lower MAP in old patients during low temperature and after rewarming, but the systemic vascular resistance index and the cardiac index did not differ between the age groups. The decreased MAP in the older patients may be explained by the lower vasoconstrictive response to hypothermia in the elderly, as well as by the increased usage of antihypertensive agents due to hypertension in this patient group. In addition, we showed an increase in catecholamine consumption with increasing age. The need of catecholamines was interpreted only in one paper in our literature review. Roedel at al. found that catecholamines were applied in 92% of patients older than 90 years to maintain sufficient MAP during post-resuscitation therapy [19]. These findings highlight the relevance of hemodynamic management in older patients and the requirement of further studies focusing on this aspect.

There are several pathophysiological changes explaining the differences in hemodynamic parameters and catecholamine consumption between the age groups. It was previously shown that the condition of the cardiovascular system changes with age. Both experimental and clinical studies showed that aging promotes generalized endothelial dysfunction leading to functional alterations in the peripheral vasculature [25]. Moreover, macrovascular endothelial function



impairment and increased endothelial stiffness were found among patients older than 65 years [26]; however, endothelial dysfunction may be regulated with weight-loss in this patient group [27]. NrF2 (nuclear factor-erythroid-2-related factor 2) dysfunction is one of the key elements in promoting cell senescence leading to age-related vascular diseases [28, 29], as its impaired function results in a lower antioxidant response [30]. Furthermore, chronically increased sympathetic nervous system activity also plays an important role in several cardiovascular changes in advanced age resulting hypertension, diastolic dysfunction, and increase in ventricular and aortic wall thickness [31].

The long-standing shear stress during aging with or without hypertension continuously affects vascular endothelial cell integrity and, therefore, vasodilative responsiveness. Both the NO pathway that is responsible for vasodilation, and the alfa-adrenergic receptor-mediated vasopressor regulation are aggravated. Nevertheless, the latter may be the reason for higher noradrenaline need for maintaining an optimal MAP. Our results concerning the lower blood pressure characteristics in older patients refer to the lower vasoreactivity of the elderly under hypothermic conditions, where a physiological systemic vascular resistance increase is expected. Hypertension may also affect cerebral synapses through increased microvascular oxidative stress and inflammation, promoting a more rapid cerebral aging [32].

There is a need for comparable, randomized controlled trials to clarify the issues raised in the management of the elderly after CPR. Neither the data found in the literature, nor the results of our retrospective analysis support the withholding of CPR and post-resuscitation therapy based on age only.

Limitations

Our retrospective analysis has several restrictions, the majority of which are related to its retrospective manner and the small size of the investigated population.

The limitations of our literature review are associated with the design and methodology of data collection of the original papers included. Most of them performed a retrospective analysis based on a nation-wide registry. There were no unified age classifications, investigated treatment options and outcomes. We only included articles published in the last five years, but not earlier. The reason for doing so was the improvement of and the dynamic changes in the assessment of post-cardiac arrest patients during the past decade.

Despite these limitations our study gives a broad overview of all currently available data regarding the management of elderly post-cardiac arrest patients.

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