



Clinical paper

Organ support therapy in the intensive care unit and return to work in out-of-hospital cardiac arrest survivors—A nationwide cohort study



Signe Riddersholm^{a,b,*}, Kristian Kragholm^{c,d}, Rikke Nørmark Mortensen^d, Steen Moller Hansen^d, Mads Wissenberg^{e,h}, Freddy K. Lippert^e, Christian Torp-Pedersen^{c,d,f}, Christian F. Christiansen^g, Bodil Steen Rasmussen^{a,b}

^a Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital, Denmark

^b Clinical Institute, Aalborg University, Denmark

^c Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

^d Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark

^e Emergency Medical Services Copenhagen, University of Copenhagen, Copenhagen, Denmark

^f Institute of Health Science and Technology, Aalborg University, Denmark

^g Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

^h Department of Cardiology, Copenhagen University Hospital, Gentofte, Denmark

ARTICLE INFO

Article history:

Received 23 October 2017

Received in revised form

22 December 2017

Accepted 1 January 2018

Keywords:

Out-of-hospital cardiac arrest

Return to work

Organ failure

Organ support

Intensive care unit

ABSTRACT

Aim: With increased survival after out-of-hospital cardiac arrest (OHCA), impact of the post-resuscitation course has become important. Among 30-day OHCA survivors, we investigated associations between organ support therapy in the Intensive Care Unit (ICU) and return to work.

Methods: This Danish nationwide cohort-study included 30-day-OHCA-survivors who were employed prior to arrest. We linked OHCA data to information on in-hospital care and return to work. For patients admitted to an ICU and based on renal replacement therapy (RRT), cardiovascular support and mechanical ventilation, we assessed the prognostic value of organ support therapies in multivariable Cox regression models.

Results: Of 1087 30-day survivors, 212 (19.5%) were treated in an ICU with 0–1 types of organ support, 494 (45.4%) with support of two organs, 26 (2.4%) with support of three organs and 355 (32.7%) were not admitted to an ICU.

Return to work increased with decreasing number of organs supported, from 53.8% (95% CI: 49.5–70.1%) in patients treated with both RRT, cardiovascular support and mechanical ventilation to 88.5% (95% CI: 85.1–91.8%) in non-ICU-patients. In 732 ICU-patients, ICU-patients with support of 3 organs had significantly lower adjusted hazard ratios (HR) of returning to work (0.50 [95% CI: 0.30–0.85]) compared to ICU-patients with support of 0–1 organ. The corresponding HR was 0.48 [95% CI: 0.30–0.78] for RRT alone.

Conclusions: In 30-day survivors of OHCA, number of organ support therapies and in particular need of RRT were associated with reduced rate of return to work, although more than half of these latter patients still returned to work.

© 2018 Elsevier B.V. All rights reserved.

Introduction

Survival of out-of-hospital cardiac arrest (OHCA) has increased during the last decade [1]. Several studies have shown that prehospital interventions and the clinical condition at hospital admission are associated with both short and long-term outcome [1–3]. Fur-

ther, recent studies have shown how pre-hospital interventions (e.g. bystander interventions) are related to functional outcome measures [4,5]. However, knowledge of the prognostic value of the post-resuscitation in-hospital care and related interventions is sparse, and the long-term prognosis of patients with multiple organ failure following OHCA is unknown.

Cardiac arrest causes a degree of general ischemia, which leads to the complex post-cardiac arrest syndrome in patients who gain return of spontaneous circulation [6]. The syndrome resembles the systemic inflammatory response syndrome (SIRS), and severity depends on the cause of cardiac arrest, the degree of reperfusion

* Corresponding author at: Department of Anesthesiology and Intensive Care Medicine, Aalborg University Hospital, Hobrovej 18-22, 9100 Aalborg, Denmark.
E-mail address: s.riddersholm@rn.dk (S. Riddersholm).

injury, the underlying pathology, the extent of myocardial dysfunction and co-morbidity burden [6]. However, it has not been investigated whether the post arrest syndrome reflects only temporary damage or if it is a reflection of underlying permanent injuries leading to long-term disabilities.

Early interventions are hypothesized to decrease the duration of the no- or low-flow period, and hereby decrease the risk of anoxic tissue injury caused by the cardiac arrest. In line with this, bystander interventions have previously been shown to be associated with reduced hospital length of stay and risk of admission to an ICU as a proxy for reduced morbidity following OHCA [7]. Furthermore, in the ICU, number and severity of organ failures are well-known predictors of mortality [8,9]. Still, little is known on how the in-hospital treatment and the need of organ support therapy following OHCA predicts the long-term prognosis and in particular function in survivors.

Return to work indicates a favourable prognosis without major functional deficits [5] and previous studies of 30-day survivors after OHCA have shown rates of return to work of up to 76% [5,10]. Therefore, we investigated associations between need of organ support therapy, as a proxy for multiple organ failure, before day 30 after cardiac arrest and return to work in 30-day survivors.

Methods

Study setting

This cohort study used data from the Danish Cardiac Arrest Registry, to which emergency medical services (EMS) personnel have reported every case of OHCA where a resuscitation attempt was initiated since June 1st, 2001 [1].

In Denmark, basic life support-trained ambulance personnel are dispatched to all OHCA emergencies, and advanced life support-trained mobile emergency care units staffed with paramedics or anesthesiologists are dispatched to rendezvous with the ambulance personnel. Access to pre- and in-hospital health care in Denmark including admission to an ICU is tax financed and thereby available for all patients. However, the indication for admission to and treatment in an ICU is a clinical decision. All admissions to and major treatments at Danish ICUs are reported to the Danish National Registry of Patients and used by the Danish Intensive Care Database [11].

Study population

We identified 30-day survivors between 18 and 65 years, employed prior to the OHCA incident. Before 2005, ICU admission was not completely registered [11], and therefore we only included patients during 2005–2014. Patients not receiving any social benefits, as well as patients on maternity leave, leave-of-absence or public state education grants in a five-week span before cardiac arrest were defined as working at baseline [5]. As we assessed renal replacement therapy (RRT) as part of the need of organ support, we excluded patients treated with dialysis in the year before OHCA.

Study design

From the Danish Cardiac Arrest Registry, we included information on date and location of arrest, whether a bystander initiated CPR and/or defibrillated the patient, witness status, time interval between recognition of arrest/emergency dispatch center call and ambulance arrival and whether the patient was awake at hospital arrival. Status at arrival (comatose or awake) was recorded by ambulance personnel and did hereby not include whether the patient woke up in the emergency department. The unique civil personal registration number given to all Danish residents at birth

or upon immigration was used to gather data from other Danish nationwide registries. We retrieved data on age, sex and civil status from the Danish Civil Personal Registration registry and presumed cause of arrest (cardiac vs. non-cardiac) was determined using data from the Danish National Patient Registry and the Danish Cause of Death Registry [1,5]. Data on date of death was retrieved from the Danish Cause of Death Registry. Data on comorbidities were obtained from the Danish National Patient registry as well as the Danish National Prescription Registry (eTable 1) [12,13]. We retrieved data on organ support and 'simplified Acute Physiology Score' (SAPS II) from the Danish National Patient Registry [11,13], however SAPS II was only sufficiently registered from 2011 and onwards. Employment status was obtained from a registry administered by the Danish Labor Market Authority (DREAM registry) and was available on a weekly basis until July 2016. We obtained information on educational level from Statistics Denmark [14,15].

Exposures

Main exposure was number of severe organ failures within 30 days after OHCA among patients admitted to an ICU. We defined organ failure according to organ-support therapy in the ICU, identifying three types of organ support: 1. Mechanical ventilation defined by invasive ventilator support; 2. Cardiovascular support, defined by need of inotropic agents or vasopressors; and 3. RRT defined by renal support in the ICU. Based on the accumulated number of organ support therapies, and whether the patient was admitted to an ICU before day 30, we divided the patients into four groups: 1. Non-ICU-patients, 2. ICU-patients with support of 0-1 organ, 3. ICU-patients with support of two organs and, 4. ICU-patients with support of three organs.

In secondary analyses, we assessed the impact of the individual types of organ support and frequent combinations of organ support on return to work.

Outcomes

Outcome was return to work. We defined return to work as the first 2-week-span from day 30, during which no social benefits except from maternity leave, leave-of-absence and state education fund codes occurred. 30-day-survivors were followed from day 30 after OHCA for return to work, death, emigration or end of study (June 30, 2016).

Statistics

We presented categorical variables using percentages and frequencies, and continuous variables using medians and 25th and 75th percentiles. For return to work with mortality as competing risk, we depicted cumulative incidences using the Aalen-Johansen estimator. We calculated time to death and return to work for 30-day-survivors counting from day 30. Among patients admitted to an ICU we performed Cox regression models to assess the association between individual and number of organ support therapies and outcomes. We created a directed acyclic graph (DAG) [16] to identify covariates for our multivariable models. Covariates included patient age, sex, comorbid conditions, and calendar year of arrest, as well as status of living alone and patient educational level (eFigure 2). To ensure that the need of organ support is not driven or confounded by prehospital variables (bystander CPR, bystander defibrillation and witness status) or only reflected cognitive status at arrival, we added these in twofinal separate multivariable models. Missing data were imputed using multiple imputation methods (using the Substantive Model Compatible Fully Conditional Specification package in R). Data was missing at random (MAR). Assumption of proportional hazards was checked

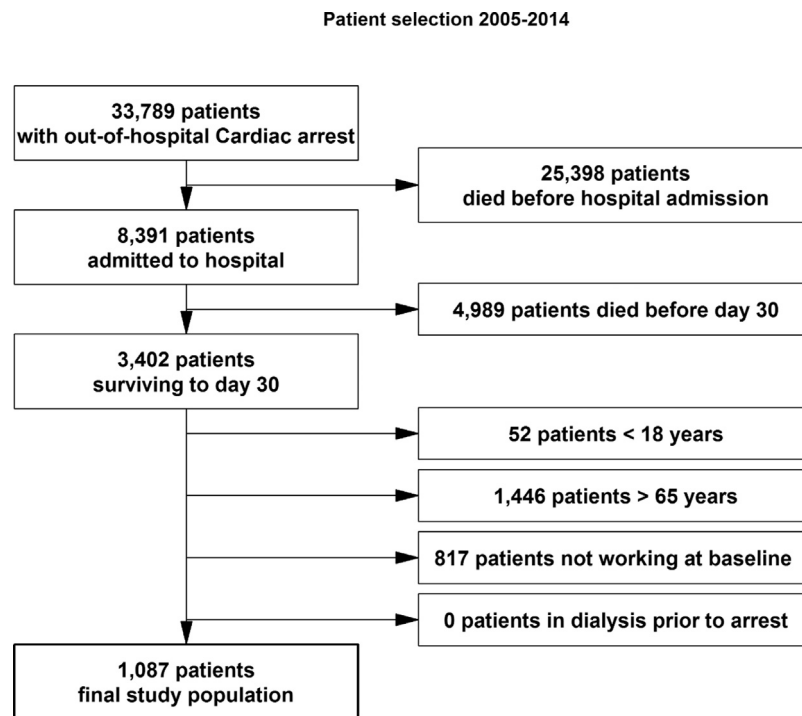


Fig 1. Patient selection from the Danish cardiac arrest registry.

by log–log plots and Martingale residuals and were in all cases adequately met. We tested for interaction between organ support calendar year – before and after 2010 and presumed cause of arrest. No interactions were seen. Data management and analyses were performed using SAS version 9.4 and R statistical software package version 3.3.3, respectively [17].

Ethics

This study was approved by the Danish Data Protection Agency (2007-58-0015, internal reference GEH-2014-017/I-Suite no. 02735). In Denmark, it is not required to obtain ethical approval for register-based studies.

Results

Patients, characteristics, and distribution of organ support therapy

From January 1 2005 to December 2014, 3402 (10.1%) of 33,789 OHCA patients survived to day 30. Of these 1087 (32.0%) were between 18 and 65 years of age and employed prior to OHCA (Fig. 1). 212 patients (19.5%) were treated in the ICU with 0–1 organ support treatments and 494 (45.4%) were treated in the ICU with 2 organs supported and 26 (2.4%) with three organs supported, 355 patients (32.7%) were not treated in the ICU.

Table 1 shows baseline characteristics according to number of organ support therapies. Patients with the largest number of organ support were less likely to have had an arrest in a public location, less likely to have received bystander interventions and less likely to be awake at hospital arrival.

In 212 patients with 0–1 registered types of organ support, 142 (67.0%) received mechanical ventilation, 34 (16.0%) were treated with cardiovascular support and none with renal replacement therapy. Among 494 patients treated with 2 types of organ support, 492 (99.6%) were treated with respiratory support and 489 (99.0%) were treated with circulatory support and only 7 (1.4%) received renal support. 26 patients had all three types of organ support. The

Simplified Acute Physiology Score (SAPS) increased with increasing number of organs supported (Table 2).

Characteristics for non-30-day survivors are shown in eTables 3–5.

Return to work

In a two-year follow-up period, 80.5% [95% CI: 78.1–82.9%] of 30-day survivors had returned to work and mortality was 3.1% [95% CI: 2.1–4.2%]. Patients not treated in the ICU had the highest return to work rate of 88.5% [95% CI: 85.1–91.8], followed by 82.4% [95% CI: 77.1–87.6%] for patients with 0–1 organs supported, 77.3% [95% CI: 73.4–81.2%] for patients with 2 organs supported and lastly, 59.8% [95% CI 49.5–70.1] for patients with support of 3 organs (Fig. 2A).

Factors associated with return to work

In multivariable Cox regressions for 732 patients admitted to an ICU, we explored the associations between organ support and return to work.

Degree of organ failure

In multivariable Cox regression analysis adjusted for both baseline and prehospital variables patients treated in the ICU with support of 3 organs had a significantly lower chance of return to work compared to patients treated with support of 0–1 organs (HR 0.50 [95% CI: 0.30; 0.85]) (Fig. 31.C). Ratios were similar to hazard ratios found in unadjusted analysis (Fig. 31A) and analysis without adjustment for prehospital variables (Fig. 31B). Additionally, in sensitivity analysis excluding EMS-witnessed cases, or only including comatose patients, in analysis adjusted for status at arrival (comatose or awake), and in complete case analyses, results were similar (eFigures 6–12). No interaction was found between organ support and calendar year-group or presumed cause of arrest.

Table 1
Demographic and prehospital variables by number of organ support.

Demographic variables	Non ICU (n = 355)	ICU support of 0-1 organs (n = 212)	ICU support of 2 organs (n = 494)	ICU support of 3 organs (n = 26)	P-value
Age, median [25%–75%]	52.0 [46.0,58.0]	51.0 [45.0, 59.0]	53.0 [46.0, 59.0]	52.5 [40.2, 59.0]	0.74
Male	277 (78.0)	174 (82.1)	410 (83.0)	22 (84.6)	0.29
Prehospital variables					
CPR by bystander	148 (88.6)	151 (84.4)	349 (78.1)	13 (56.5)	<0.001
Missing	188	33	47	3	
Defibrillation by bystander	34 (23.3)	26 (16.1)	31 (7.7)	NA**	<0.001
Missing	209	51	91	3	
Public location of arrest	211 (68.7)	126 (66.3)	236 (51.0)	11 (44.0)	<0.001
Missing	48	22	31	NA**	
Unwitnessed arrest	16 (4.7)	22 (10.8)	73 (15.4)	NA**	
Arrest witnessed by bystander	150 (44.5)	156 (76.5)	370 (78.1)	22 (84.6)	
Arrest witnessed by EMS	171 (50.7)	26 (12.7)	31 (6.5)	3 (11.5)	<0.001
Missing	18	8	20	0	
Time interval*, median [25%–75%]	10.0 [6.0, 13.0]	9.0 [6.0, 13.0]	9.0 [6.0, 13.0]	6.0 [4.0, 10.0]	0.23
Missing	229	62	109	5	
Initial shockable rhythm	119 (37.4)	47 (23.4)	82 (17.3)	6 (26.1)	<0.001
Missing	37	11	21	3	
Defibrillated by EMS	254 (81.4)	153 (80.5)	391 (89.9)	19 (76.0)	0.001
Missing	43	22	59	NA**	
COPD	NA**	4 (1.9)	5 (1.0)	0 (0.0)	0.46
Ischemic heart disease	43 (12.1)	18 (8.5)	68 (13.8)	NA**	0.23
Kidney disease	3 (0.8)	NA**	2 (0.4)	NA**	0.18
Diabetes	18 (5.1)	11 (5.2)	28 (5.7)	NA**	0.93
Outcomes					
Awake at hospital arrival	176 (66.4)	33 (18.6)	10 (2.2)	0 (0.0)	<0.001
Missing	90	35	32	NA**	
Length of hospital stay, median [25%–75%]	6.0 [4.0, 10.0]	14.0 [9.0, 21.0]	16.0 [11.0, 30.0]	38.0 [27.0, 60.5]	<0.001
1-year survival	NA**	209 (98.6)	479 (97.0)	23 (88.5)	<0.001

Data show Data show characteristics according to organ support among 30-day survivors. Abbreviations: EMS, emergency medical service; CPR, cardiopulmonary resuscitation. *Time between recognition of arrest/emergency call and EMS arrival. ** NA, not available, due to legislation in accordance with the policy of Statistics Denmark that does not allow report of personal identifiable data, i.e. a very low number or a similarly low difference between a number and the total number of observations.

Table 2
in-hospital characteristics by degree of organ support for 30-day survivors admitted to an ICU before day 30.

Organ support	ICU support of 0-1 organs (n = 212)	ICU support of 2 organs (n = 494)	ICU support of 3 organs (n = 26)	P-value
Renal replacement therapy	0 (0.0)	7 (1.4)	26 (100.0)	<0.001
Cardiovascular support	24 (11.3)	489 (99.0)	26 (100.0)	<0.001
Mech. ventilation started within the first 24 h after OHCA	108 (50.9)	453 (91.7)	22 (84.6)	<0.001
Mech. ventilation started after 24 h after OHCA	34 (16.0)	39 (7.9)	4 (15.4)	<0.001
Duration of intensive care				
<0.25 days	0 (0.0)	0 (0.0)		
0.25–13 days	14 (8.0)	9 (1.9)	0 (0.0)	
14–30 days	162 (92.0)	457 (95.4)	23 (92.0)	
>30 days	0 (0.0)	13 (2.7)	NA**	
missing	36	15	<3	<0.001
Duration of mechanical ventilation				
No mechanical ventilation	NA**			
0.25–7 days	117 (55.2)	400 (81.0)	16 (61.5)	
>7 days	NA**	38 (7.7)	NA**	<0.001
SAPS(2011-14)	(n = 99)	(n = 263)	(n = 16)	
SAPS II*, mean (sd)	31.8 (10.3)	50.4 (16.8)	50.6 (18.7)	<0.001
SAPS, registered as irrelevant	26(66.7)	17 (84.4)	NA**	
Missing	60	159	9	

Data show in-hospital variables by number of organs supported. OHCA: Out-of-hospital Cardiac arrest, SAPS: Simplified Acute Physiology Score.*Only registered sufficient after 2010. ** NA, not available, due to legislation in accordance with the policy of Statistics Denmark that does not allow report of personal identifiable data, i.e. a very low number or a similarly low difference between a number and the total number of observations.

Return to work in distributions and combinations of organ support

The study population encompassed six combinations of organ support of a considerable size. For these combinations, we depicted the cumulative incidence of return to work with death as a competing risk in Fig. 1B, where number of patients in each group is given in the legend. Within 2 years 86.7% [95% CI: 76.7–96.6] of ICU-

patients with no organ support returned to work, in patients treated with only circulatory support 83.3% [95% CI: 68.4–98.2] returned to work, followed by 80.4% [95% CI: 73.9–98.2] in patients with only mechanical ventilation. In patients treated with mechanical ventilation and cardiovascular support 76.2% [95% CI: 72.4–80.0] returned to work. Adjusted hazard ratios of return to work by com-

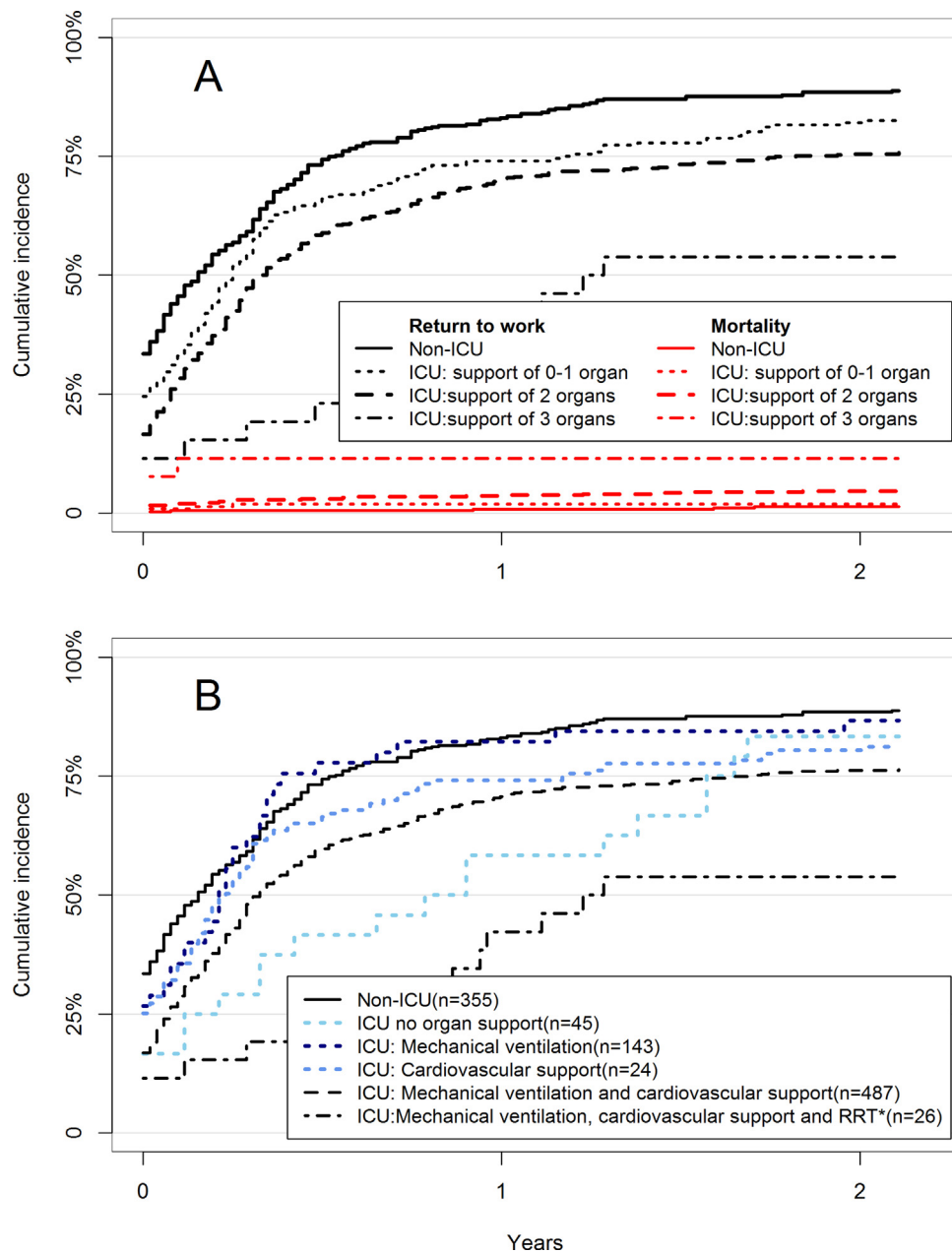


Fig. 2. Cumulative incidence of A: Return to work and mortality by degree of organ support, B: Return to work in common distributions and combinations of organ support.

binations of organ support therapies with ICU-patients with no organ support as reference are shown in Fig. 4.

Individual types of organ support

In three separate multivariable Cox regression analyses of the association between each individual type of organ support and return to work, patients with cardiovascular support had reduced chance of return to work, when compared to ICU-patients without cardiovascular support (HR 0.0.81 [95% CI: 0.66–0.98]). Similarly, patients with RRT had reduced chance of return (HR 0.48 [95% CI: 0.30–0.78]), when compared to patients without RRT. This was not the case for mechanical ventilation (HR 1.03 [95% CI: 0.77–1.39]) (Fig. 32A–C).

Discussion

This study of return to work among 1087 30-day OHCA survivors found that a substantial proportion of patients, even in need

of extensive organ support therapy, returned to work. The majority of 30-day-survivors who returned did so within the first year after day 30 indicating OHCA patients who do return, do so rather fast and that chances of return are small if patients have not returned within one year following OHCA. Patients admitted to an ICU after OHCA had reduced rate of return to work compared to patients not admitted to an ICU. This rate decreased with increasing number of organs supported, so that patients with the combination of mechanical ventilation, circulatory support as well as RRT had the least chance of return to work. Still, more than half of these patients returned to work.

Severity of the post-cardiac arrest syndrome depends on several factors including the cause of the arrest, bystander interventions, early prehospital intervention, comorbidities and the duration of the no- and low-flow time [6]. The extent of organ support treatment after OHCA may therefore reflect a combination of several factors.

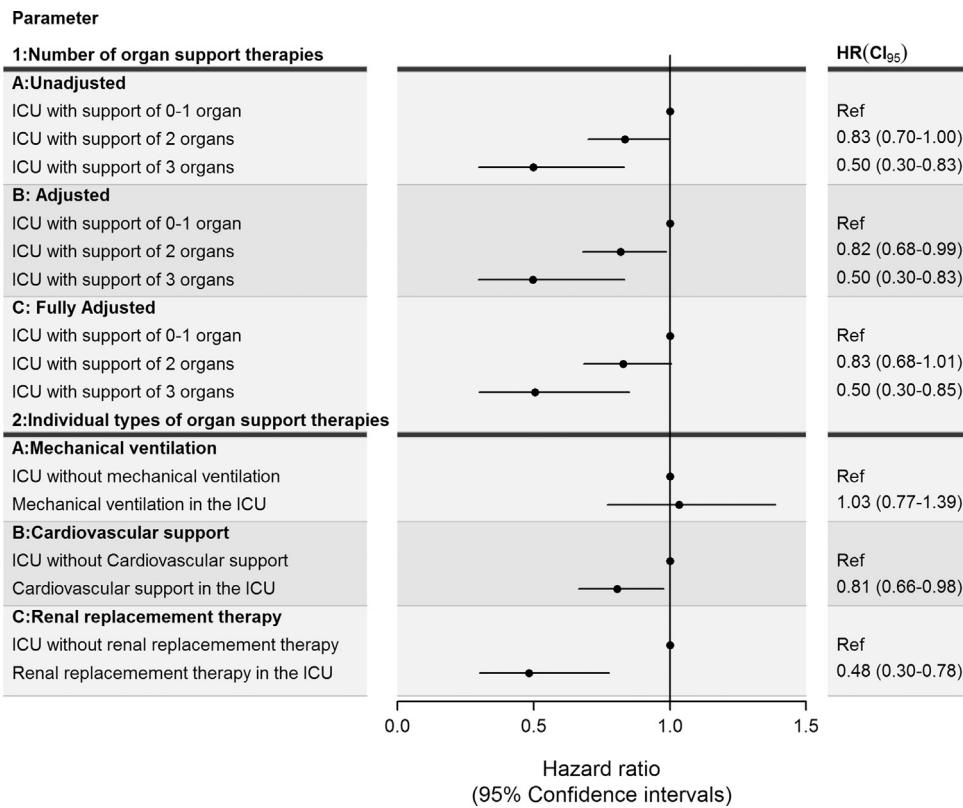


Fig. 3. Multivariable Cox regressions of return to work by: 1 Number of organ support therapies. 1A: Unadjusted, 1B: Adjusted for age, sex, educational level, status of living alone, calendar year, chronic obstructive pulmonary disease, kidney disease, diabetes and ischemic heart disease. 1C: Adjusted for age, sex, bystander cardiopulmonary resuscitation and witness status, educational level, status of living alone, calendar year, chronic obstructive pulmonary disease, kidney disease, diabetes and ischemic heart. 2: Individual types of organ support therapies: 2A: Mechanical ventilation in the ICU adjusted for renal replacement therapy and cardiovascular support, 2B: Cardiovascular support in the ICU adjusted for renal replacement therapy, mechanical ventilation 2C: Renal replacement therapy in the ICU adjusted for cardiovascular support and mechanical ventilation. All three model are adjusted for age, sex, educational level, status of living alone, calendar year, chronic obstructive pulmonary disease, kidney disease, diabetes and ischemic heart disease. Data show return to work for 30-day survivors. The hazard ratio denotes the relative hazard rate of return to work for the parameter compared to its reference after adjustment for confounders.

First, patients admitted to an ICU with higher numbers of organ failures were more likely to suffer an unwitnessed arrest, less likely to receive bystander interventions, and less likely to be awake at hospital arrival. As such, the prognostic value of need of organ support therapy on return to work is likely to reflect the degree of anoxic tissue injury caused by the arrest. This is supported by previous studies showing lower ICU admission rates and increased return to work rates in patients with witnessed arrest and/or bystander cardiopulmonary resuscitation [5,7,10]. Thus, our study supports ongoing and future interventions that enhance the early links in the chain of survival including early CPR and defibrillation. However, when adjusting for prehospital variables and arrival-status (comatose or awake), our findings remained unchanged, indicating that need of organ support itself is a predictor of a worse long-term outcome.

The number of organs support therapies reflect a combination of severity of illness in combination with reluctance to initiate treatment if futile. Futility may be affected by the prognosis, age and comorbidities of the patient. However, clinicians may be prone to offer organ support therapies, despite an unfavorable prognosis in younger OHCA patients working prior to arrest. Therefore number of organ support therapies may to a large extent serve as a proxy for organ failures and hereby severity of illness. Several ICU-score-systems have previously been shown to be of low prognostic value after OHCA [18–21]. Contrarily, both the Sepsis-related Organ Failure Assessment (SOFA) score and the Pittsburg Cardiac Arrest Category, based on SOFA in combination with neurological symptoms is able to predict mortality and morbidity [9,22–24].

Therefore, it is plausible that an increasing degree of organ support, and in particular RRT, reflects a severely injured OHCA-patient, explaining the distinct prognostic impact of RRT found in this study. Last, our study findings may reflect that the in-hospital course in itself affects the ability to return to work. We found that non-ICU-patients more often returned to work than patients admitted to the ICU and this difference expanded with an increasing number of organ support therapies. This difference could to some extent be explained by the post-intensive care syndrome [25]. This syndrome consists of physical, cognitive and mental impairments following intensive care treatment, all with a potential effect on quality of life, ability to return to work or otherwise function in society as before ICU-admission. In this context, return to work is only a proxy for a favourable outcome, as we do not know whether patients returned to the same work as before arrest. Further we do not know reasons for not returning as well as reasons for withdrawal, which may be both physical, cognitive or emotional. It would be of great interest to explore these outcomes in future studies. Our finding is in line with previous studies, indicating that cardiac arrest in itself, as well as respiratory failure and use of RRT all are risk factors for development of post-intensive care syndrome [26–28].

Overall, our findings indicate that the severity of illness, measured by number of organ failures, is an independent and important predictor of long-term prognosis in OHCA, and that the impact and role of the in-hospital course on other long-term outcome measures may be further explored in future studies. The dose-response relationship between organ support therapies and return to work warrants a need to explore how organ dysfunction after OHCA is

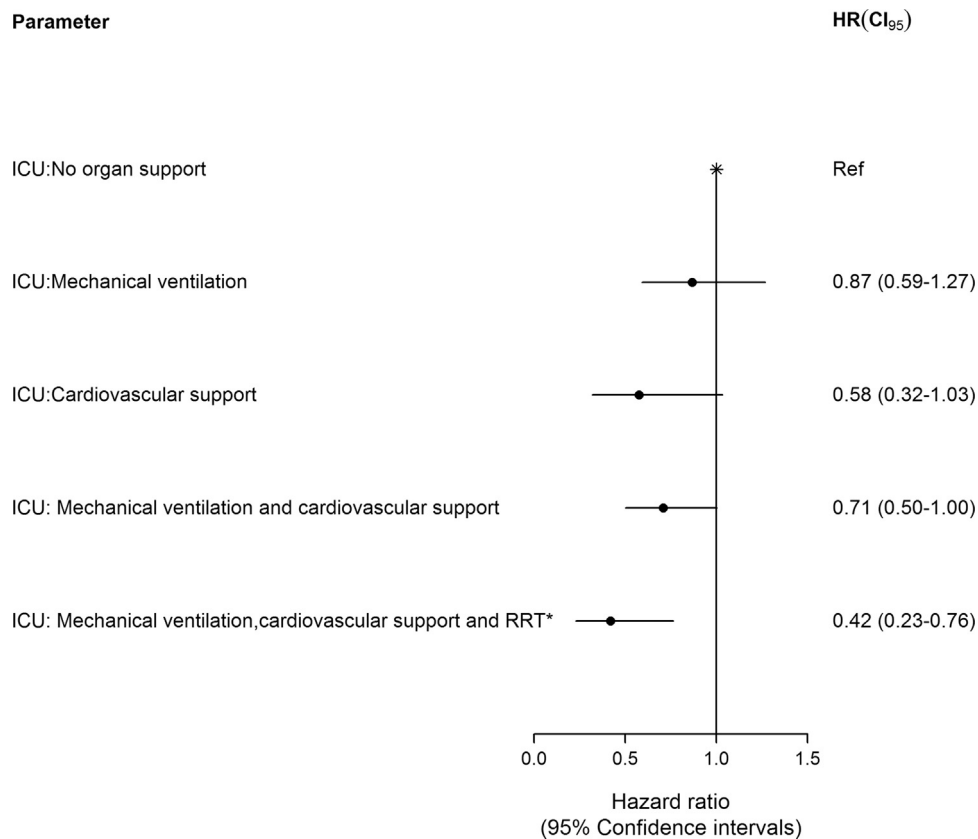


Fig. 4. Multivariable cox regression of return to work by distributions and combinations of organ support. Adjusted for age, sex, educational level, status of living alone, calendar year, chronic obstructive pulmonary disease, kidney disease, diabetes and ischemic heart disease, organ support.

related to physical and mental impairments leading to disability to be able to use organ failure as a guide to inform relatives and rehabilitation.

Limitations

Due to the observational character of the study, our findings do not prove causality, however the purpose of this study was not to address causality but rather to identify in-hospital predictors of return to work.

Administration of organ support and treatment in the ICU may be subject to selection, as physicians carefully select patients for ICU-admission. However, distribution of organ support in patients not surviving to day 30 was comparable to the distribution in our study population and our findings remain after adjustment for age and comorbidities. Due to the register-based design of the study with limited in-hospital data available, we may have underestimated the number of organ failures, as we were only able to identify three types of organ support. For instance, liver-failure is not registered and in addition, we were not able to distinguish between mechanical ventilation due to neurological or respiratory failure. Further, given the small size of the group receiving RRT and the group with support of three organs they may represent a biased sample. However the proportion of patients receiving RRT is similar to another study of OHCA patients [29]. This underestimation of organ failure may explain the finding of the pronounced impact of dialysis on return to work, as need of dialysis may be a marker for other unmeasured organ failures as noted above. Several codes used to define available organ support data have previously been validated: Mechanical ventilation with a positive predictive value (PPV) of 100% (95% CI: 95.1–100) and renal RRT with a PPV of 98.0% (95% CI: 91.0–99.8) [30]. Both under-registration of the three

organ support types and reluctance to initiate treatment in patients with worse prognosis would bias our findings toward no difference between groups. Employment data could also be subject to misclassification. However, identifying a patient as working, using the DREAM registry has been validated, and the positive predictive value is as high as 98% [31]. Finally, some of the prehospital variables had missing data which could introduce a bias. However, analysis with missing data on prehospital variables did not differ from results based on pooled analysis of imputed datasets. Unmeasured confounding, for instance, from unmeasured comorbidity and social factors cannot be excluded. The same goes for residual confounding due to insufficient level of adjustment for confounders already included in our analyses (e.g. quality of CPR). Importantly our findings were robust and persisted in all analyses and across strata of various variables indicating that the relationship between organ-support and return to work after OHCA is real.

Conclusion

Admission to an ICU and increasing number of organ support therapies during hospitalisation are strong independent predictors of reduced chance of return to work, when compared to non-ICU-patients. However, substantial proportions of 30-day survivors were capable of returning to work across all strata of organ support therapies, even among those with all three organs supported.

Funding sources

The Danish Cardiac Arrest Registry is supported by the Danish Foundation TrygFonden.

Conflict of interest

The corresponding author has no conflicts of interests to disclose. Dr. Kragholm has received research grants from The Danish Heart Foundation, The Laerdal Foundation and the Fund of Herta Christensen, Denmark, and has received speaker's honoraria from Novartis. Dr. Steen Hansen reports receiving support from the Danish Foundation Trygfonden, The Danish Heart Foundation, and the Laerdal Foundation. Dr. Steen Hansen has received travelling support to a conference by AstraZeneca. Dr. Torp-Pedersen has received grants from Bayer and Biotronic and has received speaker honorarium from Bayer. Dr. Rasmussen has received research grants from Innovation Fund Denmark and is primary investigator in a study initiated by Ferring. Dr. Lippert has received unrestricted research grants from the Danish Foundation TrygFonden and from Laerdal Foundation. None of these institutions or companies had no influence on the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript for submission. All other authors have no conflicts of interests to disclose.

Acknowledgments

We extend our sincere thanks to the personnel from the Danish Emergency Medical Services for completing case report forms for the Danish Cardiac Arrest Register.

We will also thank the Danish ICUs for reporting data on ICU admission, organ support treatments, and SAPS II scores to the Danish National Registry of Patients according to the definitions made by the Danish Intensive Care Database.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.resuscitation.2018.01.001>.

References

- Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA* 2013;310:1377–84. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24084923> [cited 2016 Mar 31].
- Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *N Engl J Med* 2015;372:2307–15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26061835>; <http://www.nejm.org/doi/abs/10.1056/NEJMoa1405796>.
- Malta Hansen C, Kragholm K, Pearson DA, Tyson C, Monk L, Myers B, et al. Association of bystander and first-Responder intervention with survival after out-of-hospital cardiac arrest in north carolina, 2010–2013. *JAMA* 2015;314:255–64. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26197186> [cited 2016 Jun 28].
- Kragholm K, Wissenberg M, Mortensen RN, Hansen SM, Malta Hansen C, Thorsteinsson K, et al. Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest. *N Engl J Med* 2017;376:1737–47. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28467879> [cited 2017 May 16].
- Kragholm K, Wissenberg M, Mortensen RN, Fonager K, Jensen SE, Rajan S, et al. Return to work in out-of-hospital cardiac arrest survivors: a nationwide register-based follow-up study. *Circulation* 2015;131:1682–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25941005> [cited 2016 Mar 29].
- Binks A, Nolan JP. Post-cardiac arrest syndrome. *Minerva Anestesiol* 2010;76:362–8.
- Riddersholm S, Kragholm K, Mortensen RN, Pape M, Hansen CM, Lippert FK, et al. Association of bystander interventions and hospital length of stay and admission to intensive care unit in out-of-hospital cardiac arrest survivors. *Resuscitation* 2017. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28716539> [cited 2017 Aug 1].
- Chang C-H, Chen S-W, Fan P-C, Lee C-C, Yang H-Y, Chang S-W, et al. Sequential organ failure assessment score predicts mortality after coronary artery bypass grafting. *BMC Surg* 2017;17:22. Available from: <http://bmc Surg.biomedcentral.com/articles/10.1186/s12893-017-0219-9> [cited 2017 Jul 10].
- Argyriou G, Vrettou CS, Filippatos G, Sainis G, Nanas S, Routsis C. Comparative evaluation of acute physiology and chronic health evaluation II and sequential organ failure assessment scoring systems in patients admitted to the cardiac intensive care unit. *J Crit Care* 2015;30:752–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25981445> [cited 2017 Jul 10].
- Kragholm K, Skovmoeller M, Christensen AL, Fonager K, Tilsted H-H, Kirkegaard H, et al. Employment status 1 year after out-of-hospital cardiac arrest in comatose patients treated with therapeutic hypothermia. *Acta Anaesthesiol Scand* 2013;57:936–43. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23750664> [cited 2016 Mar 29].
- Christiansen CF, Møller MH, Nielsen H, Christensen S. The danish intensive care database. *Clin. Epidemiol* 2016;8:525–30. Available from: <https://www.dovepress.com/the-danish-intensive-care-database-peer-reviewed-article-CLEP> [cited 2016 Dec 19].
- Kildemoes HW, Sørensen HT, Hallas J. The danish national prescription registry. *Scand J Public Health* 2011;39:38–41. Available from: <http://s.jp.sagepub.com/cgi/doi/10.1177/1403494810394717> [cited 2017 Jun 16].
- Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin. Epidemiol* 2015;7:449–90. Available from: <https://www.dovepress.com/the-danish-national-patient-registry-a-review-of-content-data-quality-peer-reviewed-article-CLEP> [cited 2016 Dec 19].
- Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011;39:103–5. Available from: <http://s.jp.sagepub.com/cgi/doi/10.1177/1403494811405098> [cited 2015 Oct 15].
- Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;39:91–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21775362> [cited 2017 Jun 24].
- Shrier I, Platt RW, Rothman K, Greenland S, Hernan M, Greenland S, et al. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;8:70. Available from: <http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-8-70> [cited 2016 Sep 16].
- R: The R. Project for Statistical Computing. R Dev. Core Team R A Lang. *Environ. Stat. Comput. R Found. Stat. Comput.*; 2008. Available from: <https://www.r-project.org>.
- Winther-Jensen M, Kjaergaard J, Nielsen N, Kuiper M, Friberg H, Søholm H, et al. Comorbidity burden is not associated with higher mortality after out-of-hospital cardiac arrest. *Scand Cardiovasc J* 2016;50:305–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27385408> [cited 2017 Apr 26].
- Winther-Jensen M, Kjaergaard J, Wanscher M, Nielsen N, Wetterslev J, Cronberg T, et al. No difference in mortality between men and women after out-of-hospital cardiac arrest. *Resuscitation* 2015;96:78–84. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26215480> [cited 2017 Apr 26].
- Skrifvars MB, Varghese B, Parr MJ. Survival and outcome prediction using the Apache III and the out-of-hospital cardiac arrest (OHCA) score in patients treated in the intensive care unit (ICU) following out-of-hospital, in-hospital or ICU cardiac arrest. *Resuscitation* 2012;83:728–33.
- Bisbal M, Jouve E, Papazian L, de Bourmont S, Perrin G, Eon B, et al. Effectiveness of SAPS III to predict hospital mortality for post-cardiac arrest patients. *Resuscitation* 2014;85:939–44. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0300957214004468> [cited 2017 Jul 3].
- Cour M, Bresson D, Hernu R, Argaud L. SOFA score to assess the severity of the post-cardiac arrest syndrome. *Resuscitation* 2016;102:110–5. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S030095721600109X> [cited 2017 Nov 23].
- Rittenberger JC, Tisherman SA, Holm MB, Guyette FX, Callaway CW. An early, novel illness severity score to predict outcome after cardiac arrest. *Resuscitation* 2011;82:1399–404. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21756969> [cited 2017 Nov 23].
- Coppler PJ, Elmer J, Calderon L, Sabedra A, Doshi AA, Callaway CW, et al. Validation of the Pittsburgh cardiac arrest category illness severity score. *Resuscitation* 2015;89:86–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25636896> [cited 2017 Nov 23].
- Turnbull AE, Rabiee A, Davis WE, Nasser MF, Venna VR, Lolitha R, et al. Outcome measurement in ICU survivorship research from 1970–2013: a scoping review of 425 publications. *Crit Care Med* 2016;44:1267–77. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26992067> [cited 2016 Aug 6].
- Guerra C, Linde-Zwirble WT, Wunsch H. Risk factors for dementia after critical illness in elderly Medicare beneficiaries. *Crit Care* 2012;16:R233. Available from: <http://ccforum.biomedcentral.com/articles/10.1186/cc11901> [cited 2017 Apr 26].
- Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med* 2010;153:167–75. Available from: <http://annals.org/article.aspx?doi=10.7326/0003-4819-153-3-201008030-00007> [cited 2017 Apr 26].
- Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012;185:1307–15. Available from: <http://www.atsjournals.org/doi/abs/10.1164/rccm.201111-2025OC> [cited 2017 Apr 26].
- Yanta J, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC. Renal dysfunction is common following resuscitation from out-of-hospital cardiac arrest. *Resuscitation* 2013;84:1371–4. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0300957213002219> [cited 2017 Nov 23].

- [30] Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Nørgaard M. Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report. *Clin. Epidemiol* 2013;5:9–12. Available from: <http://www.dovepress.com/validity-of-the-coding-for-intensive-care-admission-mechanical-ventila-peer-reviewed-article-CLEP> [cited 2017 Jun 27].
- [31] Hjøllund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health* 2007;35:497–502. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17852980> [cited 2016 Apr 8].