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Clinical paper

Health-related quality of life after out-of-hospital cardiac arrest – a five-year follow-up study

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Abstract

Background: Health-related quality of life (HRQoL) is affected after out-of-hospital cardiac arrest (OHCA), but data several years after the arrest are lacking. We assessed long-term HRQoL in OHCA survivors and how known outcome predictors impact HRQoL.

Methods: In adult OHCA survivors, HRQoL was assessed five years post arrest using Short-form 36 (SF-36), EQ-5D-3 L (EQ-5D) and Hospital Anxiety and Depression Scale (HADS) among others. Results were compared to the next of kins' estimates and to a Norwegian reference population.

Results: Altogether 96 survivors were included mean 5.3 (range 3.6–7.2) years after OHCA. HRQoL compared well to the reference population, except for lower score for general health with 67.2 (95%CI (62.1; 72.3) vs. 72.9 (71.9; 74.0)), p = 0.03. Younger (≤58 years) vs. older survivors scored lower for general health with mean (SD) of 62.1 (27.5) vs. 73.0 (19.5), p = 0.03, vitality (55.2 (20.5) vs. 64.6 (17.3), p = 0.02, social functioning (75.3 (28.7) vs. 94.1 (13.5), p < 0.001 and mental component summary (49.0 (9.9) vs. 55.8 (6.7), p < 0.001. They scored higher for HADS-anxiety (4.8 (3.6 vs. 2.7 (2.5), p = 0.001, and had lower EQ-5D index (0.72 (0.34) vs. 0.84 (0.19), p = 0.04. Early vs. late awakeners had higher EQ-5D index (0.82 (0.23) vs. 0.71 (0.35), p = 0.04 and lower HADS-depression scores (2.5 (2.9) vs. 3.8 (2.3), p = 0.04. Next of kin estimated HRQoL similar to the survivors' own estimates.

Conclusions: HRQoL five years after OHCA was good and mainly comparable to a matched reference population. Stratified analyses revealed impaired HRQoL among younger survivors and those awakening late, mainly for mental domains.

Keywords: Out-of-hospital cardiac arrest, Quality of life, Long-term follow-up, Outcome

Introduction

Survival after out-of-hospital cardiac arrest (OHCA) has improved over the last 20 years due to an improved local chain of survival.[1–3] Although the majority of discharged patients survive with good neurological outcome (Cerebral Performance Category (CPC) 1–2 or modified Rankin Scale 0–3),[4] global hypoxic injuries affect health-related quality of life (HRQoL) and cognitive function after cardiac arrest (CA, both in-hospital CA and OHCA).[5–7] Typical symptoms are anxiety, depression, fatigue and loss of

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memory.[7,8] The impact on daily life and HRQoL in the years following CA is difficult to predict. Nevertheless, this is of utmost importance to document, because information concerning HRQoL is as important to patients and relatives as information about survival. The International Liaison Committee on Resuscitation (ILCOR) recently recommended a patient-reported outcome (PRO) set for research in CA survivors up to one year after CA.[9] There is little documentation on HRQoL after this first year.[8,10,11]

Factors such as age, gender, time from arrest to return of spontaneous circulation (ROSC), and to awakening affect neurological outcome.[12,13] However, the recently published NORCAST trial, exploring prognostication in hospitalized OHCA survivors with persisting coma, showed that both a longer time from arrest to ROSC and to awakening were insufficient predictors for reliable outcome prognostication.[14] Nevertheless, how these factors affect long-term HRQoL has not yet been investigated.

Thus, the aim of the present study was to investigate cerebral performance and HRQoL among OHCA survivors more than four years after hospital discharge by comparing these findings with age- and gender-specific Norwegian reference population norms. Secondary objectives were to evaluate the impact of age, gender and time to ROSC and awakening on HRQoL and how the next of kin rated the survivors' HRQoL.

Methods

Study design and population

The present prospective observational study is an a priori planned sub study of NORCAST.[14] In total, 259 comatose, resuscitated adult OHCA patients were prospectively enrolled on admission to Oslo University Hospital Ullevål from September 2010 to January 2014. They were treated according to a standard treatment protocol, including targeted temperature management (TTM) at 33 °C for 24 h.[3] After four years, 117 were still alive and included in the present study. All survivors eligible for an ambulatory HRQoL follow-up were enrolled from June 2017 to May 2018. Patients not able to attend due to death or disease or not answering phone calls or mail, were CPC-scored based on information from relatives, general practitioners and available medical records (Fig. 1).

Survivors not able to physically attend the ambulatory follow-up, but willing to respond to questionnaires, received questionnaires by mail. Those not responding, received a reminding letter with a new set of questionnaires after four weeks.

Outcome assessment

CPC was used to categorize cerebral outcome after CA with CPC 1–2 defined as good neurological outcome.[4]

HRQoL was assessed using the Short-Form-36 Health Survey Version 1 (SF-36), EuroQoL-5D-3 L (EQ-5D), Hospital Anxiety and Depression Scale (HADS) and Fatigue Severity Scale (FSS). The next of kin was also asked to estimate the survivor's health by completing EQ-5D (except for EQ-VAS). Both parties completed the questionnaires separately.

HRQoL scoring tools

Short-Form-36 Health Survey Version 1 (SF-36)

The SF-36 is a general HRQoL questionnaire with 36 questions, comprising eight dimensions: physical and social function (PF/SF), role limitations due

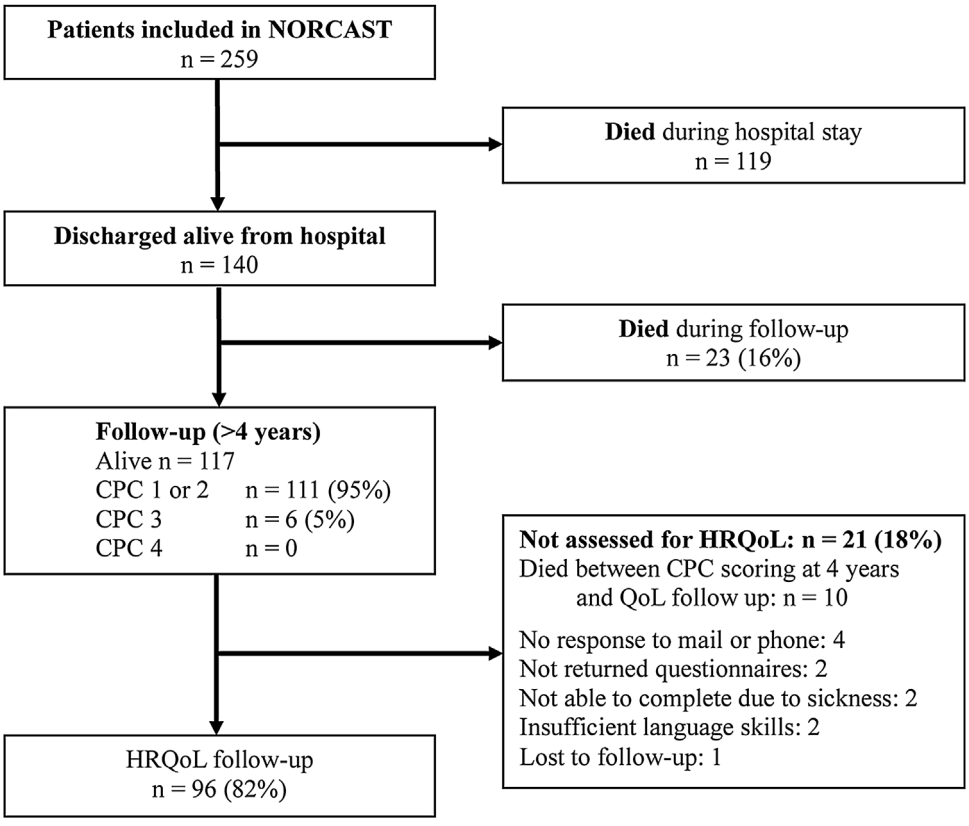

Fig. 1 – Study flowchart.

to physical health (RP) or emotional problems (RE), vitality (VT), bodily pain (BP), emotional well-being (mental health, MH) and general health (GH).[15] Responses to each item were recoded and transformed to a 0−100 scale, with higher scores indicating better HRQoL. Scores were further aggregated into two summary scales, the mental component summary (MCS) and the physical component summary (PCS) which are standardized for comparison with a general population (linear T-score transformation with mean 50 and SD 10).[16]

EuroQoL-5D-3 L (EQ-5D)

The EQ-5D measures health status by providing three possible answers indicating no, some or extreme problems in five different dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A summary score, the EQ-5D index, can be estimated by applying a value set derived from the general population to the individual dimensions. This index scores on a -0.59 to 1.0 scale, with 1.0 representing best possible health and 0 death. Scores less than zero represent health states considered to be worse than being dead.[17] Additionally, the EQ-5D contains a visual analogue scale (EQ-VAS) for estimating own health with a range from 0 to 100 (worst to best imaginable health).[18] General Norwegian population norms for both SF-36 and EQ-5D have recently been published, and were used as reference.[19,20]

Hospital Anxiety and Depression Scale (HADS)

HADS, a 14-item questionnaire for non-psychiatric hospital outpatients, was used to evaluate presence of anxiety and depression. It provides seven questions with a four-level answer from 0 to 3 for each of the two subscales. The score ranges from 0 to 21 on each subscale with higher scores indicating more symptoms of anxiety or depression.[21] For Norway, no validated cut-off values exist,[22] but ≥8 has been shown to give the best balance between sensitivity and specificity and was therefore used.[23] Reference values were derived from the Norwegian HUNT study.[24,25]

Fatigue Severity Scale (FSS)

The FSS is a 9-item tool revealing fatigue, with a range from 1 to 7 for every item. Higher values indicate more fatigue. For the Norwegian population, Lerdal et al. previously suggested "borderline fatigue" with a mean score >4.0 and <5.0, and "severe fatigue" ≥5.0.[26]

Statistical analyses

Survivor characteristics and scores on the questionnaires were described as means and standard deviations (SD) and 95%-confidence intervals as appropriate for symmetrically distributed continuous data. Median, minimum and maximum values were also presented for skewed data. For categorical data, frequencies and percentages were presented. Those attending and not attending the study at follow-up were compared by independent samples t-test for continuous and χ^2-test for categorical variables. For comparison to reference population, age- and gender-specific values were entered for each patient for all SF-36 dimensions and summary scales as well as for all EQ-5D dimensions. Only aggregated mean reference values with corresponding SD and sample size were available for HADS anxiety and depression subscales and FSS. For EQ-5D dimensions, aggregated frequencies from the reference population were available. The independent samples t-test was applied to compare the continuous scores of OHCA survivors to the reference population. In post-hoc analyses, OHCA survivors were stratified by age, dichotomized at median age (to get equal groups), gender, time from arrest to ROSC (tROSC, dichotomized with cut-off 25 min, in accordance with NORCAST[14]) and time to awakening (tAWAK, defined as late, if Glasgow Coma Scale (GCS) <9 72 h after sedation withdrawal). A missing time point for a witnessed OHCA was replaced with the emergency call as a surrogate. Unwitnessed OHCAs were defined as missing values for tROSC analysis. Age and gender groups were compared by independent samples t-test or χ^2-test, as appropriate, and tROSC and tAWAK groups with linear regression analyses adjusting the group differences for age and gender. Distribution of EQ-5D dimension

Table 1 – Baseline characteristics in 96 OHCA survivors.

Baseline characteristics			Values
Gender, male		n (%)	84 (88)
Age at cardiac arrest [years]		Mean (SD)	57 (12.2)
		Median (min−max)	58 (22−81)
Age at follow-up [years]		Mean (SD)	63 (12.1)
Witnessed cardiac arrest, yes (n = 95)		n (%)	94 (99)
Received bystander CPR		n (%)	89 (93)
VF/VT as initial rhythm (n = 94)		n (%)	81 (86)
Time to ROSC [min] (n = 94)		Mean (SD)	22 (17.2)
		Median (range)	17 (3−105)
Patients with ROSC > 25 min (n = 91)		n (%)	26 (29)
Targeted temperature management (TTM)		n (%)	92 (96)
Number of patients with late awakening (n = 90)		n (%)	21 (23)
CPC 4 years after OHCA	CPC 1	n (%)	90 (94)
	CPC 2	n (%)	5 (5)
	CPC 3	n (%)	1 (1)
	CPC 4	n (%)	0

OHCA: Out-of-hospital cardiac arrest; CPR: cardiopulmonary resuscitation; VF: ventricular fibrillation; VT: ventricular tachycardia; ROSC: Return of spontaneous circulation; TTM: Targeted temperature management; late awakening, defined as Glasgow Coma Scale < 9 three days after sedation withdrawal; CPC: Cerebral performance category.

scores were compared with reference population scores using the χ^2-test for homogeneity. Age and gender adjustments for EQ-5D items could not be performed due to too low frequencies in some categories.

All statistical analyses were performed by SPSS 26 (IBM Corp, Armonk, NY, USA). Two-sided tests were used and results with P-values <0.05 were considered statistically significant.

Ethics

The NORCAST study was approved by the Regional Committee for medical and health research ethics (2010/1116a REC south-east) and written consent was obtained from the next of kin during the first 24 h after OHCA. Consent was confirmed by all survivors eligible for HRQoL assessment and their next of kin at follow-up.

Results

Four years after their OHCA, 111 of 117 (95%) survivors had CPC 1 or 2 and six (5%) had CPC 3. Of note, two of the CPC 3 survivors suffered from psychiatric disorders/dementia prior to their OHCA. Among those alive after four years, 10 had died before HRQoL assessment and 11 (9%) were excluded for different reasons, leaving 96 survivors completing HRQoL at follow-up mean 5.3 (3.6−7.2) years after their OHCA (Fig. 1). Mean age at follow-up was 63 (28−85) years, 84 (88%) were male. Median tROSC was 17 (ranging 3−105) minutes, and median time from arrest to awakening 5.5 (0−36) days. Among 90 survivors with registered tAWAK, 21 (23%) were categorized as having late tAWAK (Table 1). The only attending CPC 3 survivor needed assistance to complete the survey. All other participants completed the questionnaires on their own. There were no differences in age, gender, initial rhythm and cause of arrest between those attending and not attending HRQoL assessment (not tabulated).

HRQoL, fatigue and psychological distress

Overall, HRQoL was good and comparable to the age- and gender-adjusted Norwegian reference population, as shown with similar SF-36 component summary and EQ-5D index scores (Table 2). Among the eight SF-36 dimensions, the OHCA survivors only scored lower than the reference population for general health and trended lower for vitality (Table 2). For the EQ-5D dimensions, they stated a lower mobility and more self-care problems than the reference population (Fig. 2).

Anxiety was present in 5% and depression in 15% of the survivors. Mean HADS scores for depression and anxiety corresponded with those from the reference population, however with a trend towards less anxiety symptoms among the OHCA survivors (Table 2). Borderline was present in 11 (13%), severe fatigue in 19 (22%) of 85 survivors. The OHCA survivors had a lower mean FSS score than the reference population (Table 2).

Outcome predictors and HRQoL

Younger survivors (≤58 years) showed lower SF-36 scores for general health, vitality, social function, mental health, and MCS than older OHCA survivors. (Table 3). In addition, the EQ-5D index was lower in younger survivors and fewer younger than older survivors stated “not being anxious or depressed” on EQ-5D (Table 4). Furthermore, mean HADS-anxiety score was higher in younger survivors (Table 4).

OHCA survivors with early tAWAK had less mobility problems than those with late tAWAK according to the EQ-5D (Table 4). They had also a higher EQ-5D index and a lower mean HADS-depression score than survivors awakening late (Table 4). There were no tROSC- or gender-related differences in HRQoL or fatigue (Tables 3 and 4).

Table 2 – HRQoL (SF-36, HADS and FSS) five years after out-of-hospital cardiac arrest.

		n	NORCAST sample Mean (95% CI)	Reference population[1] Mean (95% CI)	p-value[2]
SF-36	Physical functioning	96	80.1 (75.5; 84.7)	84.1 (82.6; 85.6)	0.10
	Role − physical	93	69.1 (60.4; 77.8)	73.2 (70.9; 75.5)	0.37
	Bodily pain	96	75.0 (70.0; 80.3)	72.4 (71.5; 73.2)	0.34
	General health	92	67.2 (62.1; 72.3)	72.9 (71.9; 74.0)	0.03
	Vitality	96	59.8 (55.8; 63.7)	63.8 (63.2; 64.4)	0.05
	Social functioning	96	84.5 (79.6; 89.4)	86.7 (86.1; 87.4)	0.37
	Role − emotional	93	81.0 (74.0; 88.0)	84.1 (82.7; 85.6)	0.38
	Mental health	96	80.4 (76.9; 83.8)	82.2 (81.9; 82.4)	0.30
	Physical component summary	88	46.5 (44.3; 48.8)	48.0 (47.4; 48.7)	0.22
	Mental component summary	88	52.1 (50.2; 54.1)	53.5 (53.3; 53.7)	0.16
EQ-5D-3 L	Index		0.78 (0.72; 0.84)	0.83 (0.82; 0.84)	0.10
HADS	Anxiety	96	3.7 (3.1; 4.4)	4.40 (4.36; 4.43)	0.05
	Depression	96	2.8 (2.3; 3.4)	3.30 (3.2; 3.33)	0.10
HADS	Anxiety	96	14 (15)		
Caseness n (%)	Depression	96	5 (5)		
Fatigue Severity Scale		85	3.6 (1.4)	4.0 (1.3)	0.009

HRQoL: Health-related quality of life, SF-36: 36-Item Short Health Survey Version 1, HADS: Hospital Anxiety and Depression Scale, FSS: Fatigue Severity Scale, Mean range for SF-36 dimensions: 0−100, range for EQ-5D index: -0.59 − 1.0, mean range for HADS: 0−21, Cut-off for anxiety and depression - caseness ≥ 8, mean range for FSS 1-7.

[1] SF-36: n = 5396, EQ5D: n = 2108, HADS-A: n = 41131, HADS-D: n = 41440, FSS: n = 1893.

[2] Independent-samples t-test.

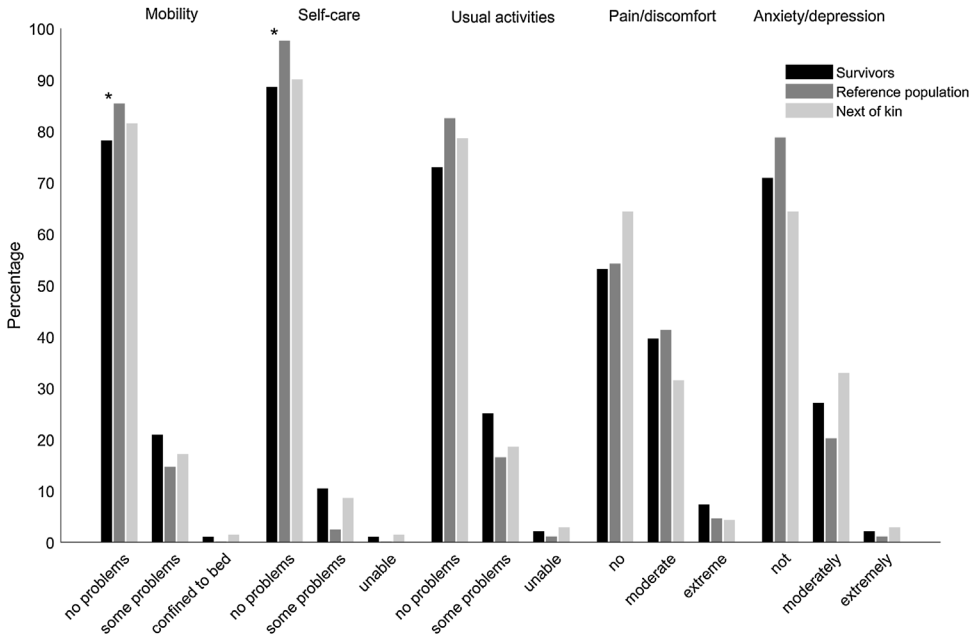

Fig. 2 – EuroQoL 5D-3L health status after OHCA; self-rating by OHCA survivors, estimation by the next of kin and values from the Norwegian reference population.
***mobility; p=0.002 for OHCA survivors vs. reference population, χ^2-test**
***self-care; p<0.001 for OHCA survivors vs. reference population, χ^2-test**

Next of kin

The next of kin estimated the OHCA survivors health status similar to the survivors' own estimates on EQ-5D (Fig. 2).

Discussion

As far as we know, this is the first study in OHCA survivors from the TTM era reporting HRQoL outcome five years after OHCA. We found an overall satisfactory HRQoL, quite comparable with a general reference population after gender- and age-adjustment. Nevertheless, younger OHCA survivors reported mainly lower mental HRQoL, and more symptoms of anxiety and depression than older survivors. Late awakeners also reported lower health status in general and lower mobility than those awakening early. Importantly, the next of kin estimated the survivors' health status similar to the survivors' own estimates.

Although the summary scores for SF-36 and EQ-5D overall indicated a good HRQoL, our OHCA survivors scored lower on general health, mobility and self-care and trended lower for vitality than the reference population. A previous five-year follow-up study by Graf et al. found lower HRQoL in SF-36 compared to a reference population.[27] Noteworthy, this study is from the pre-TTM era, which might impact neurological outcome.[28] Moulaert et al. described normal HRQoL with normal summary scores for SF-36 3.6 years after CA (27% received TTM).[29] In a TTM trial substudy, HRQoL six months post-arrest was comparable to a reference population using SF-36 summary scores.[30] However, Geri et al. recently reported normal SF-36 summary scores in an observational study, but five of eight dimensions showed significantly lower values.[10] Importantly, PCS and MCS do not necessarily reflect all individual dimensions of SF-36,[31] indicating that conclusions relying on summary scores should be drawn with caution.[5]

The presence of anxiety and depression was low among our patients. Mean HADS scores were comparable to the reference population, but with a trend towards a lower score for anxiety. The TTM trial group described a slightly higher prevalence of anxiety (24%) and depression (13%) six months post-arrest among OHCA survivors.[32] It is unclear if these differences can be explained by different follow-up time points, or by other underlying pre- or inhospital factors. In a retrospective study from 2009, however, Wachelder et al.[11] reported that 13% of CA survivors suffered from anxiety three years after CA, comparable to our findings, whereas the rate of depression was slightly higher. The recently published HANOX study assessed both HRQoL (SF-36) and anxiety and depression (HADS) in OHCA survivors at different time points up to 18 months post arrest. They found impaired HRQoL compared to the reference population, with stable values during follow-up. The prevalence of anxiety and depression also remained unchanged over time.[33] Whether HRQoL, anxiety and depression can improve many years after CA is unclear and has not been studied in detail and more studies analysing changes over time are needed.

In our cohort, mean FSS score was lower than in the reference population while fatigue occurred in the same proportion.[26] This is in contrast to two Dutch studies from Moulaert et al.[6] and Wachelder et al.,[11] reporting a higher prevalence of fatigue with 55% and 56% one and approximately three years after CA. This could partly be due to a higher proportion of patients receiving TTM in our study, partly due to different follow-up time points.[6,11] However, a more plausible explanation is that we used a higher FSS-score (≥5) as threshold for fatigue, based on findings by Lerdal et al.,[26] which corresponds better with the prevalence of fatigue in the Norwegian population.[34] By using a lower threshold, we would have ended up with 36% suffering from severe fatigue, which still seems to be lower than described in the Dutch studies.[6,11] Noteworthy, we had 13% missing FSS-data, which could have affected the present results. We do not have a clear explanation for this, but FSS was the last questionnaire to complete.

Table 3 – HRQoL five years after OHCA; stratified post-hoc analyses of Short-Form-36 Health Survey Version 1 (SF-36).

	Gender			Age			Time to ROSC			Awakening		
	Female	Male	p-value [1]	≤58 yrs	>58 yrs	p-value[1]	≤25 min	>25 min	p-value[2]	Early	Late	p-value[2]
Physical functioning, n	12	84		49	47		64	26		69	21	
Mean (SD)	75.0 (22.7)	80.8 (22.6)	0.4	81.5 (24.7)	78.6 (20.2)	0.54	80.3 (22.8)	82.7 (16.3)	0.78	83.3 (18.6)	73.5 (28.0)	0.07
Role physical, n	12	81		48	45		61	26		67	20	
Mean (SD)	50.0 (48.9)	71.9 (40.6)	0.09	65.1 (44.0)	73.3 (40.0)	0.35	72.1 (40.6)	63.5 (46.0)	0.38	73.9 (40.2)	57.5 (44.5)	0.11
Bodily pain, n	12	84		49	47		64	26		69	21	
Mean (SD)	63.7 (27.9)	76.6 (25.7)	0.11	73.9 (28.1)	76.0 (24.2)	0.7	75.4 (28.0)	73.6 (22.7)	0.7	77.1 (24.8)	72.8 (26.9)	0.50
General health, n	12	80		49	43		62	24		67	21	
Mean (SD)	60.9 (27.6)	68.1 (24.1)	0.35	62.1 (27.5)	73.0 (19.5)	0.03	70.2 (23.3)	60.9 (27.7)	0.22	68.6 (25.0)	63.9 (21.2)	0.29
Vitality, n	12	84		49	47		64	26		69	21	
Mean (SD)	52.1 (19.4)	60.9 (19.4)	0.14	55.2 (20.5)	64.6 (17.3)	0.02	61.2 (18.1)	56.5 (23.2)	0.48	61.1 (18.9)	57.4 (20.7)	0.28
Social functioning, n	12	84		49	47		64	26		69	21	
Mean (SD)	76.0 (26.4)	85.7 (24.0)	0.2	75.3 (28.7)	94.1 (13.5)	<0.001	87.5 (22.6)	77.4 (25.5)	0.12	87.1 (21.9)	78.6 (26.9)	0.05
Role emotional, n	12	81		48	45		61	26		67	21	
Mean (SD)	63.9 (36.1)	83.5 (33.0)	0.06	77.8 (36.6)	84.4 (30.6)	0.35	81.4 (34.2)	82.1 (31.6)	0.96	82.6 (32.5)	82.5 (32.7)	0.91
Mental health, n	12	84		49	47		64	26		69	21	
Mean (SD)	75.9 (16.2)	81.0 (17.0)	0.33	74.5 (17.8)	86.5 (13.5)	<0.001	81.9 (16.6)	77.2 (16.4)	0.44	80.3 (15.8)	79.8 (19.7)	0.56
PCS, n	12	76		48	40		58	24		65	20	
Mean (SD)	42.8 (11.7)	47.1 (10.7)	0.2	46.5 (11.4)	46.7 (10.2)	0.93	47.0 (11.0)	46.1 (10.2)	0.72	48.1 (10.1)	43.2 (10.6)	0.07
MCS, n	12	76		48	40		58	24		65	20	
Mean (SD)	48.8 (8.9)	52.6 (9.2)	0.18	49.0 (9.9)	55.8 (6.7)	<0.001	53.0 (8.8)	50.0 (9.8)	0.18	52.4 (8.8)	52.2 (9.8)	0.94

HRQoL Health-related quality of life; OHCA: Out-of-hospital cardiac arrest; Awakening: early: Glasgow Coma Scale ≥ 9 72 h after sedation withdrawal; ROSC: Return of spontaneous circulation; PCS: Physical component summary; MCS: Mental component summary.

[1] Independent samples t-test.

[2] Linear regression model adjusting the differences for gender and age.

Table 4 – HRQoL five years after OHCA; stratified post-hoc analyses of EQ-5D-3 L (EQ-5D), HADS and Fatigue Severity Scale.

			Gender[1]		Age		Time to ROSC[1]		Awakening[1]	
			Female	Male	≤ 58 yrs	>58 yrs	≤25 min	>25 min	Early	Late
EQ-5D	EQ-5D index[2]	n	12	84	49	47	64	26	69	21
	(-0.4 – 1.0)	Mean (SD)	0.74 (0.25)	0.79 (0.28)	0.72 (0.34)[a]	0.84 (0.19)	0.79 (0.26)	0.79 (0.28)	0.82 (0.23)	0.71 (0.35)[a]
	Mobility[3]	No problems	9 (75.0)	66 (78.6)	38 (77.6)	37 (78.7)	50 (78.1)	21 (80.8)	59 (85.5)	13 (61.9)[b]
	(n, %)	Some problems	3 (25.0)	17 (20.2)	10 (20.4)	10 (21.3)	14 (21.9)	5 (19.2)	10 (14.5)	7 (33.3)
		Unable	0	1 (1.2)	1 (2.0)	0	0	0	0	1 (4.8)
	Self-care[3]	No problems	12 (100)	73 (86.9)	41 (83.7)	44 (93.6)	57 (89.1)	24 (92.3)	63 (91.3)	18 (85.7)
	(n, %)	Some problems	0	10 (11.0)	7 (14.3)	3 (6.4)	7 (10.9)	2 (7.7)	6 (8.7)	2 (9.5)
		Unable	0	1 (1.2)	1 (2.0)	0	0	0	0	1 (4.8)
	Usual activities[3]	No problems	7 (58.3)	63 (75.0)	31 (63.3)	39 (83.0)	49 (76.6)	17 (65.4)	53 (76.8)	14 (66.7)
	(n, %)	Some problems	5 (41.7)	19 (22.6)	16 (32.7)	8 (17.0)	14 (21.9)	9 (34.6)	15 (21.7)	6 (28.6)
		Unable	0	2 (2.4)	2 (4.1)	0	1 (1.6)	0	1 (1.4)	1 (4.8)
	Pain/discomfort[3]	No	3 (25.0)	48 (57.1)	23 (46.9)	28 (59.6)	33 (51.6)	15 (57.7)	40 (58.0)	8 (38.1)
	(n, %)	Moderate	8 (66.7)	30 (35.7)	21 (42.9)	17 (36.2)	26 (40.6)	9 (34.6)	26 (37.7)	11 (52.4)
		Extreme	1 (8.3)	6 (7.1)	5 (10.2)	2 (4.3)	5 (7.8)	2 (7.7)	3 (4.3)	2 (9.5)
	Anxiety/depression[3]	Not	7 (58.3)	61 (72.6)	29 (59.2)	39 (83.0)[c]	47 (73.4)	16 (61.5)	47 (68.1)	16 (76.2)
	(n, %)	Moderately	5 (41.7)	21 (25.0)	18 (36.7)	8 (17.0)	17 (26.6)	9 (34.6)	21 (30.4)	4 (19.0)
		Extremely	0	2 (2.4)	2 (4.1)	0	0	1 (3.8)	1 (1.4)	1 (4.8)
HADS-Depression[2] (0–21)		n	12	84	49	47	64	26	69	21
		Mean (SD)	3.7(2.8)	2.7 (2.8)	3.4 (3.1)	2.3 (2.3)	2.4 (2.9)	3.5 (2.5)	2.5 (2.9)	3.8 (2.3)[a]
HADS-Anxiety[2] (0–21)		n	12	84	49	47	64	26	69	21
		Mean (SD)	4.4 (2.2)	3.6 (3.3)	4.8 (3.5)	2.7 (2.5)[d]	3.4 (3.0)	4.7 (3.8)	3.8 (3.4)	3.9 (2.8)
FSS[2] (1–7)		n	10	75	42	43	59	21	66	14
		Mean	4.4 (1.4)	3.5 (1.4)	3.8 (1.5)	3.4 (1.3)	3.4 (1.5)	4.0 (1.3)	3.6 (1.5)	3.5 (1.1)

HRQoL Health related quality of life; OHCA: Out-of-hospital cardiac arrest; HADS: Hospital Anxiety and Depression Scale; FSS: Fatigue Severity Scale; Awakening: early: Glasgow Coma Scale ≥ 9 72 h after sedation withdrawal; ROSC: Return of spontaneous circulation.

[1] All analyses for time to ROSC and Awakening: Linear regression model, adjusted for gender and age.

[2] Independent-samples t-test, [3] χ^2-test.

[a] p = 0.04.

[b] p = 0.02.

[c] p = 0.03.

[d] p = 0.001.

Among the previously known predictors for HRQoL outcome, age was the most prominent factor. In line with the one-year data from Smith et al.,[35] younger OHCA survivors in our cohort also stated lower HRQoL, especially for the SF-36 dimensions general and mental health and social functioning on SF-36. This sounds reasonable because the consequences of a reduced HRQoL might be more threatening for younger people due to their essential role for their families and work. Not being able to fulfill this role as prior to their OHCA may be assumed to generate existential worries. Geri et al. on the other hand, reported that younger age predicted better physical HRQoL.[10] However, a high drop-out rate may explain some of these differences. Importantly, the fact that younger OHCA survivors seem to suffer from mental health and anxiety five years after their arrest underlines that more structured cognitive and psychological rehabilitation should be provided.[36]

Both male gender, longer tROSC and longer time to awakening are associated with worse neurological outcome after OHCA,[12,37] but only tAWAK showed some associations related to HRQoL in the present study. Rey et al. showed among 402 comatose CA patients, that late awakening was associated with more delirium and unfavourable neurological outcome.[38] In a study from the pre-TTM era, long tROSC was related to impaired HRQoL,[39] which could not be confirmed by the present study. It is important to emphasize that tROSC is a pure quantitative parameter affected by many different factors. Noteworthy, in the NORCAST trial, with approximately 50% good outcome among 259 comatose OHCA patients, median tROSC was 27 min.[14]

HRQoL estimated by the next of kin corresponded well with the OHCA survivors' own estimates. This strengthens the validity of the survivors' self-reports. Smith et al. found similar results by comparing survivors and proxies as groups, though not in a one-by-one comparison.[35]

Limitations

Our study has several limitations. First, it is a single centre observational study which limits generalisation of our results. Second, due to practical reasons the HRQoL follow-up was performed over a shorter time period (eight months) than the NORCAST time period (four years), leading to the relatively wide follow-up time spread from 3.6 to 7.2 years after OHCA. Third, 11 patients were lost to follow-up. Although there were no differences in baseline characteristics between those attending and not attending, we cannot exclude that missing data of these survivors could have influenced the results. Fourth, five patients and their next of kin completed the questionnaires at home, and it is unclear if this was done separately. Due the low number, this has not influenced the overall results. Fifth, we used well established general HRQoL-instruments, as recommended for HRQoL assessment after CA,[9] but none of these are especially validated for this patient group. Sixth, for the questionnaires used, no minimal clinical

important difference is defined, even if attempts are made for the EQ-5D index. To what extend the statistical significance can be transferred to a clinically important difference remains uncertain. Seventh, the EQ-5D-3 L is criticized for being inaccurate due to its ceiling effect.[40] However, a Tobit-regression model, less vulnerable for ceiling effects, confirmed the present t-test results. Finally, we only have aggregated mean reference values for HADS and FSS, and the absence of age and gender adjustments might limit comparison with our OHCA survivors.

Conclusions

In this prospective observational study of 96 OHCA survivors, health-related quality of life five years post-arrest was generally good and comparable to a Norwegian general reference population in most test dimensions. Stratified analyses revealed, however, impaired health-related quality of life among younger patients and those with longer time to awakening, mainly for mental domains. Survivors' quality of life estimated by the next of kin corresponded well with the survivors' own estimates.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the content.

CRediT authorship contribution statement

Henning Wimmer: Project administration, Methodology, Investigation, Formal analysis, Writing - original draft. Christofer Lundqvist: Conceptualization, Methodology, Investigation, Writing - review & editing. Jūratė Šaltytė Benth: Formal analysis, Writing - original draft, Writing - review & editing. Knut Stavem: Formal analysis, Data curation, Writing - review & editing. Geir Ø. Andersen: Investigation, Conceptualization, Writing - review & editing. Julia Henriksen: Investigation, Writing - review & editing. Tomas Drægni: Software, Data curation. Kjetil Sunde: Conceptualization, Methodology, Supervision, Writing - review & editing. Espen R. Nakstad: Conceptualization, Methodology, Supervision, Writing - review & editing.

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REFERENCES

[1]. Lund-Kordahl I, Olasveengen TM, Lorem T, Samdal M, Wik L, Sunde K. Improving outcome after out-of-hospital cardiac arrest by strengthening weak links of the local Chain of Survival; quality of advanced life support and post-resuscitation care. Resuscitation 2010;81:422–6.

[2]. Yan S, Gan Y, Jiang N, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care 2020;24:61.

[3]. Tomte O, Andersen GO, Jacobsen D, Draegni T, Auestad B, Sunde K. Strong and weak aspects of an established post-resuscitation treatment protocol-A five-year observational study. Resuscitation 2011;82:1186–93.

[4]. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2015;96:328–40.

[5]. Bohm M, Lilja G, Finnbogadottir H, et al. Detailed analysis of health-related quality of life after out-of-hospital cardiac arrest. Resuscitation 2019;135:197–204.

[6]. Moulaert VRM, van Heugten CM, Gorgels TPM, Wade DT, Verbunt JA. Long-term Outcome After Survival of a Cardiac Arrest: A Prospective Longitudinal Cohort Study. Neurorehabil Neural Repair 2017;31:530–9.

[7]. Caro-Codon J, Rey JR, Lopez-de-Sa E, et al. Long-term neurological outcomes in out-of-hospital cardiac arrest patients treated with targeted-temperature management. Resuscitation 2018;133:33–9.

[8]. Buanes EA, Gramstad A, Sovig KK, et al. Cognitive function and health-related quality of life four years after cardiac arrest. Resuscitation 2015;89:13–8.

[9]. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation 2018;127:147–63.

[10]. Geri G, Dumas F, Bonnetain F, et al. Predictors of long-term functional outcome and health-related quality of life after out-of-hospital cardiac arrest. Resuscitation 2017;113:77–82.

[11]. Wachelder EM, Moulaert VR, van Heugten C, Verbunt JA, Bekkers SC, Wade DT. Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. Resuscitation 2009;80:517–22.

[12]. Martinell L, Nielsen N, Herlitz J, et al. Early predictors of poor outcome after out-of-hospital cardiac arrest. Crit Care 2017;21:96.

[13]. Lybeck A, Cronberg T, Aneman A, et al. Time to awakening after cardiac arrest and the association with target temperature management. Resuscitation 2018;126:166–71.

[14]. Nakstad ER, Staer-Jensen H, Wimmer H, et al. Late awakening, prognostic factors and long-term outcome in out-of-hospital cardiac arrest - results of the prospective Norwegian Cardio-Respiratory Arrest Study (NORCAST). Resuscitation 2020;149:170–9.

[15]. Ware JE, Kosinski M, Gandek B. SF-36 health survey : manual & interpretation guide. 2. ed] Lincoln, RI: QualityMetric Inc; 2000.

[16]. Ware JEJ, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. 5th edn. Bosten, MA: Health Assessment Lab, New England Medical Center; 1994.

[17]. Parkin D, Devlin N, Feng Y. What Determines the Shape of an EQ-5D Index Distribution? Med Decis Making 2016;36:941–51.

[18]. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337–43.

[19]. Stavem K, Augestad LA, Kristiansen IS, Rand K. General population norms for the EQ-5D-3 L in Norway: comparison of postal and web surveys. Health and quality of life outcomes 2018;16:204.

[20]. Garratt AM, Stavem K. Measurement properties and normative data for the Norwegian SF-36: results from a general population survey. Health and quality of life outcomes 2017;15:51.

[21]. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

[22]. Leiknes KA, Dalsbø TK, Siqveland J. Måleegenskaper ved den norske versjonen av Hospital Anxiety and Depression Scale (HADS). [Psychometric assessment of the Norwegian version of the Hospital Anxiety and Depression Scale (HADS)]. Folkehelseinstituttet. 2016.

[23]. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69–77.

[24]. NTNU Hunt Research Centre. HUNT Databank: HUNT4 Questionnaire 2 (NT4BLQ2): HADS: Anxiety. https://hunt-db.medisin.ntnu.no/hunt-db/#/variable/20300.

[25]. NTNU Hunt Research Centre. HUNT Databank: HUNT4 Questionnaire 2 (NT4BLQ2): HADS Depression. https://hunt-db.medisin.ntnu.no/hunt-db/#/variable/20299.

[26]. Lerdal A, Wahl A, Rustoen T, Hanestad BR, Moum T. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. Scand J Public Health 2005;33:123−30.

[27]. Graf J, Muhlhoff C, Doig GS, et al. Health care costs, long-term survival, and quality of life following intensive care unit admission after cardiac arrest. Crit Care 2008;12:R92.

[28]. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication: A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350−79.

[29]. Moulaert VR, Wachelder EM, Verbunt JA, Wade DT, van Heugten CM. Determinants of quality of life in survivors of cardiac arrest. J Rehabil Med 2010;42:553−8.

[30]. Cronberg T, Lilja G, Horn J, et al. Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33 degrees C vs 36 degrees C After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA Neurol 2015;72:634−41.

[31]. Taft C, Karlsson J, Sullivan M. Do SF-36 summary component scores accurately summarize subscale scores? Qual Life Res 2001;10:395−404.

[32]. Lilja G, Nilsson G, Nielsen N, et al. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation 2015;97:68−75.

[33]. Peskine A, Cariou A, Hajage D, et al. Long-term disabilities of survivors of out-of-hospital cardiac arrest: the Hanox study. Chest 2020, doi:http://dx.doi.org/10.1016/j.chest.2020.07.022.

[34]. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res 1998;45:53−65.

[35]. Smith K, Andrew E, Lijovic M, Nehme Z, Bernard S. Quality of life and functional outcomes 12 months after out-of-hospital cardiac arrest. Circulation 2015;131:174−81.

[36]. Moulaert VR, van Heugten CM, Winkens B, et al. Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: A randomised controlled trial. Int J Cardiol 2015;193:8−16.

[37]. Feng D, Li C, Yang X, Wang L. Gender differences and survival after an out-of-hospital cardiac arrest: a systematic review and meta-analysis. Intern Emerg Med 2020, doi:http://dx.doi.org/10.1007/s11739-020-02552-4.

[38]. Rey A, Rossetti AO, Miroz JP, Eckert P, Oddo M. Late Awakening in Survivors of Postanoxic Coma: Early Neurophysiologic Predictors and Association With ICU and Long-Term Neurologic Recovery. Crit Care Med 2019;47:85−92.

[39]. van Alem AP, Waalewijn RA, Koster RW, de Vos R. Assessment of quality of life and cognitive function after out-of-hospital cardiac arrest with successful resuscitation. Am J Cardiol 2004;93:131−5.

[40]. Andrew E, Nehme Z, Bernard S, Smith K. Comparison of health-related quality of life and functional recovery measurement tools in out-of-hospital cardiac arrest survivors. Resuscitation 2016;107:57−64.