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Clinical paper

Detailed analysis of health-related quality of life after out-of-hospital cardiac arrest



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Abstract

Aim: To describe the detailed health-related quality of life (HRQoL) in survivors from the TTM-trial and to investigate potential differences related to sex and age.

Methods: This is a cross-sectional study originating from a large prospective international, multicentre trial, including 442 respondents who answered the Short Form-36 item Questionnaire Health Survey version 2[®] (SF-36v2[®]) at a structured follow-up 6 months after out-of-hospital cardiac arrest (OHCA). Statistical analysis between independent groups were performed with Mann-Whitney U or Chi-square. Age was analysed primarily as a dichotomised variable.

Results: Although overall physical and mental health were within the normal range, a substantial proportion of respondents had impaired function at domain-specific levels, particularly in Role-Physical (50%) and Role-Emotional (35%). Females scored significantly lower than males in; Physical Functioning (41.7 vs. 47.9, $p < 0.001$), Role-Physical (40.4 vs. 44.3, $p = 0.02$), General Health (47.0 vs. 50.5, $p = 0.02$), Vitality (47.2 vs. 52.7, $p < 0.001$), and Role-Emotional (41.5 vs. 46.2, $p = 0.009$). Those ≤ 65 years scored significantly better in Physical Functioning (47.9 vs. 44.1 $p < 0.001$), while those > 65 years scored significantly better in Vitality (50.8 vs. 53.7, $p = 0.006$) and Mental Health (50.3 vs. 52.6, $p = 0.04$).

Conclusions: Many OHCA survivors demonstrated impaired function in HRQoL at a domain level, despite most patients reporting an acceptable general HRQoL. Females reported worse HRQoL than males. Older age was associated with a worse Physical Functioning but better Vitality and Mental Health. Role-Physical and Role-Emotional aspects of health were especially affected, even when effects of age and sex were accounted for.

Keywords: Cardiac arrest, Quality of life, SF-36v2, Outcome, Cross-sectional studies

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<https://doi.org/10.1016/j.resuscitation.2018.10.028>

Received 31 May 2018; Received in revised form 18 October 2018; Accepted 28 October 2018

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Introduction

Outcome following out-of-hospital cardiac arrest (OHCA) has primarily been reported in terms of mortality or with the Cerebral Performance Categories (CPC) scale¹. Historically, there has been limited focus on patient-reported outcomes (PRO) in resuscitation research. Recently, the relevance of health-related quality of life (HRQoL) has received attention as a meaningful PRO².

Although symptom-specific outcome assessments report that cognitive, emotional and physical problems are common in OHCA-survivors, studies show that most survivors are functionally independent and have a good to acceptable HRQoL^{3,4}. The reason for this may be that although some symptoms are common in OHCA survivors, they have little effect on general HRQoL. An alternative explanation is that generic measures of HRQoL may lack the granularity of assessment important to capture a more detailed appreciation of the impact of ill-health or disease. In the general population age and sex have important influence on HRQoL⁵, but less is known about how they affect HRQoL amongst OHCA survivors.

Previous studies of HRQoL after OHCA were mostly based on small samples⁴, often with high levels of missing data, with few studies reporting detailed information on different health domains. A recent review concluded that there is limited evidence to support any specific instrument to report HRQoL after OHCA, but the Short Form-36 item Questionnaire Health Survey version 2[®] (SF-36v2[®]) was one of the most promising^{6,7}.

There were no differences in the Physical and Mental Component Summary measures (PCS and MCS) of the SF-36v2[®] between the intervention groups from the Target Temperature Management (TTM) trial⁸; therefore the groups were combined in the present study. Detailed information on different health domains, with investigation of possible associations with important variables such as sex and age, were not reported⁸. As component summary measures may reduce the granularity of assessment, it is important to interpret the results in combination with domain scores in order to fully understand details of HRQoL⁹.

To better understand OHCA-survivors' needs after hospital discharge it is important to investigate HRQoL in a large, robust, prospective cohort. The aim of this study was therefore to describe the detailed HRQoL of survivors from the TTM-trial and to investigate possible differences related to sex and age.

Methods

Study design, setting and population

This is a post-hoc study of the TTM-trial¹⁰, an international multicentre (36 ICU-sites) study conducted from November 2010 to January 2013. Inclusion criteria were adult patients (≥ 18 years) resuscitated from OHCA of presumed cardiac cause, who remained unconscious (Glasgow Coma Scale < 8) after sustained ROSC > 20 min. The TTM-trial received ethical approval in each country¹⁰. Before follow-up, written informed consent was obtained from the respondents.

Data collection

At 180-days after OHCA, survivors were invited to participate in a face-to-face follow-up with a test battery, taking a total time of 60 min⁸. If the respondents were not able to answer the questionnaire by themselves, it was considered acceptable with proxy-reports.

Outcome measure

For generic patient-reported HRQoL, the standard form of the SF-36v2[®] was used, which has well defined psychometric properties⁶. The SF-36v2[®] is a 36-item questionnaire, summarised into eight health domains: Physical Functioning (10 items), Role-Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role-Emotional (3 items), and Mental Health (5 items). These eight health domains aggregate into two component summary measures that provide a summary of the respondent's HRQoL from a broad physical and mental health perspective, the PCS and MCS⁵. One item, the Self-Evaluated Transition (SET), evaluates the respondents' view of change in general health over the last year, but is not included in the domain categorization or scoring⁵.

Scores of the eight SF-36v2[®] domains and the two composite scores are presented as T-scores derived from the 2009 U.S. general population. A score of 50 is regarded as the norm-mean with one standard deviation (SD) equalling 10 points. When analysing SF-36v2[®] group-level results, scores three points below or above 50 should be considered outside the average norm. For individual results, T-scores < 45 indicate impaired functioning in that domain. For all health domains, higher scores indicate better HRQoL⁵.

Socio-demographical data

Information on socio-demographical, pre-hospital data and other clinical variables were collected both at the time of inclusion to the study and at the follow-up meeting.

Statistical analysis

Descriptive statistics are presented with categorical data as frequencies and percentages. Continuous data for the main outcome measure, SF-36v2[®], is presented with mean values and 95% confidence intervals (CI), other continuous data with mean and SD or median and interquartile range (IQR). Age was used both as a continuous and a dichotomised variable with a cut-off of 65 years, which is the retirement age in most of the participating countries¹¹. Sex was used as a binary variable; male vs. female. For hypothesis testing between two independent groups with variables on ordinal scale and for continuous variables on interval scale, the non-parametric Mann-Whitney *U* test was used. For hypothesis testing of frequency differences of categorical and binary variables between two independent groups, Chi-square χ^2 test was used. The clinical relevance of mean difference in SF-36v2[®] scores was assessed using Cohen's *d*, a standardised measure of effect size (ES), and was computed as the difference between two group means, divided by the SD. To classify the importance of the difference, ES was interpreted as: 0.20–0.49 small, 0.50–0.79 moderate, and values ≥ 0.80 considered large¹². The Cronbach's coefficient α was used to evaluate internal consistency and estimate of reliability and was considered acceptable if values were > 0.70 ¹³. Floor and ceiling effects were defined if the proportion of respondents with the lowest or the highest possible score on each SF-36v2[®] domain were $> 15\%$ respectively¹³.

Quality Metric Health OutcomesTM Scoring Software 4.5 was used to compute SF-36v2[®] NBS results. IBM SPSS Statistics for Macintosh version 22 (Armonk, NY: IBM Corp.) was used to carry out all statistical analyses and *p*-values < 0.05 was considered to be statistically significant. All tests are two-tailed.

Results

At follow-up 180-days post-OHCA, 442 (90%) of the 491 survivors in the TTM-trial responded to the SF-36v2[®] (Fig. 1), where 440 were complete responses and 7% (n = 31) answered the questionnaire by proxy. Clinical characteristics are presented in Table 1. The 49 non-respondents had similar age and sex distribution, but a significantly poorer CPC ($p < 0.001$).

Regarding internal consistency, Cronbach's α was greater than 0.70 for all domains of the SF-36v2[®]. A ceiling effect was present for the domains Physical Functioning (15%), Role-Physical (21%), Bodily Pain (44%), Social Functioning (47%) and Role-Emotional (41%) (Supplementary Table I).

HRQoL

The composite scores of the SF-36v2[®] (PCS 48.1/MCS 49.9) indicated overall HRQoL within the normal range (Fig. 2). The majority of the respondents (53%, n = 232), scored within or above average on both PCS and MCS.

When investigating the sub-domains in more detail, respondents scored lower than the normative average in the following three domains: Physical Functioning, Role-Physical, and Role-Emotional (Fig. 2). The domain where most OHCA-survivors reported problems at an individual level was Role-Physical, with 50% of the cohort reporting scores indicating impaired function in work or other activities because of physical problems (Supplementary Table II). One of four OHCA-survivors reported that they had to either cut down time or had difficulties in performing work or other activities *all or most of the time* (Role-Physical). Detailed information for the Role-Physical and Role-Emotional domains are presented in Figs. 3 and 4. The percentage that reported problems at an individual level were 35% for both Physical Functioning and Role-Emotional. The domains where the least number

of respondents reported problems were Bodily Pain (21%), Vitality (25%) and Mental Health (25%) (Supplementary Table II).

When effects by age were included, the result of the Role-Physical and Role-Emotional were consistent, with a large fraction of OHCA-survivors reporting poor HRQoL in Role-Physical and Role-Emotional, irrespective of age. Physical Functioning was significantly worse among the older age-group compared to the younger (48.5 vs 44.1, $p < 0.001$, ES 0.4) (Table 2), and 46% vs. 29% had a T-score < 45 (Supplementary Table II). For Vitality and Mental Health there were also significant differences between the age-groups, with the poorer scores reported by the younger age-group (Vitality 50.8 vs 53.7, young vs old, $p = 0.006$, ES -0.3 ; Mental Health 50.3 vs 52.6, young vs old, $p = 0.04$, ES -0.2) (Table 2).

Females had significantly lower scores in both PCS and MCS compared to males (PCS 44.6 vs 48.8, $p = 0.007$; MCS 47.4 vs 50.4, $p = 0.03$). Females also scored significantly lower in the health domains of Physical Functioning, Role-Physical, General Health, Vitality, and Role-Emotional (Table 2). The greatest difference in scores between males and females was in Physical Functioning (ES 0.6) (Table 2) with 54% of the females reporting an impaired Physical Functioning, compared with 32% of the males (Supplementary table II).

When stratified by sex, only Role-Physical and Role-Emotional was affected among the males. For these two domains, male OHCA-survivors had a T-score difference corresponding to an ES of 0.6 (Role-Physical) and 0.5 (Role-Emotional), when compared with their counterparts from the 2009 U.S. general population. The magnitude of difference was larger for female OHCA-survivors compared to sex-adjusted norm values: Role-Physical (ES 0.9), Role-Emotional (ES 0.8), and Physical Functioning (ES 0.7) (Supplementary Table III).

Self-evaluated transition

For the SET-item, 43% scored their health somewhat or much worse than one year previously, while 21% of the respondents scored that the change in their health in general was somewhat or much better. There were no significant differences between males and females, nor the age-groups at the SET-item (Supplementary Table IV).

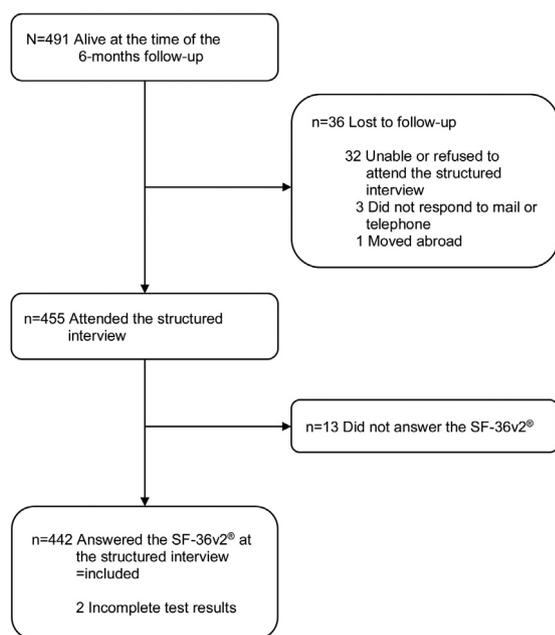


Fig. 1 – Flowchart for inclusion of respondents. All steps are part of the original TTM-study. Abbreviations: SF-36v2[®], The Short Form-36 item Questionnaire Health Survey version 2[®].

Discussion

This study showed that although overall HRQoL was reported to be good at 6 months after OHCA, detailed analysis revealed that substantial proportions of the respondents reported poor health, particularly related to role-functioning. In addition, many of the survivors reported that their general health 6 months after the OHCA was worse than 1 year ago. Females reported a poorer HRQoL than males, and older OHCA-survivors reported more problems with physical aspects of health, but better mental HRQoL, than the younger OHCA-survivors.

That physical health decline with advancing age has previously been reported in OHCA-survivors¹⁴. This is understandably related to the normal ageing process and pre-arrest comorbidity¹⁵. When results in this study were stratified for age and sex, the difference related to problems with Physical Functioning was more prominent, while poor health in Role-Physical and Role-Emotional was reported by a substantial number of OHCA-survivors irrespective of age or sex.

The fact that the Role-Physical and Role-Emotional were most affected confirm findings from previous studies^{16–18}, implying that OHCA-survivors experience problems in accomplishing work or other daily activities as a result of physical and/or emotional issues. Role functioning is an important outcome in survivors, and the results reported here is in line with results of societal participation and return-

Table 1 – Characteristics of the OHCA survivors from the TTM-trial who responded to SF-36v2[®], 180 days post cardiac arrest (N = 442).

	Total (N = 442)	Male (n = 374)	Female (n = 68)	p-value	Age ≤65 years (n = 283)	Age >65 years (n = 159)	p-value
Age, years md (IQR)	60 (12)	62 (15)	59 (21)	0.33 ^a	56 (13)	72 (6)	–
Age-groups							
18-65 years, n (%)	283 (64)	237 (63)	46 (68)	0.50 ^b	283 (100)	–	–
Male sex, n (%)	374 (85)	374 (100)	–	–	237 (84)	137 (86)	0.50 ^b
Bystander CPR, yes n (%)	348 (79)	297 (79)	51 (75)	0.41 ^b	220 (78)	128 (81)	0.50 ^b
ROSC, min, md (IQR)	20 (15.3)	20 (15)	20 (13)	0.22 ^a	20 (16)	20 (15)	0.41 ^a
LOS ICU, days, md (IQR)	5 (5)	5 (5)	5 (5)	0.50 ^a	5 (6)	6 (4)	0.27 ^a
LOS Hospital, days, md (IQR)	15 (15)	15 (15)	17 (14)	0.24 ^a	13 (15)	17 (14)	0.03 ^a
CPC				0.45 ^a			0.09 ^a
1, n (%)	359 (81)	306 (82)	53 (78)		236 (83)	123 (77)	
2, n (%)	60 (14)	49 (13)	11 (16)		37 (13)	23 (15)	
3, n (%)	21 (5)	18 (5)	3 (4)		8 (3)	13 (8)	
4, n (%)	2 (<1)	1 (<1)	1 (2)		2 (1)	0 (0)	

Abbreviations: CPC, Cerebral Performance Category; CPR, Cardiopulmonary Resuscitation; ICU, Intensive Care Unit; IQR, Interquartile range; LOS, Length of stay; Md, median; OHCA, Out-of-Hospital Cardiac Arrest; ROSC, Return of Spontaneous Circulation.

^a Mann-Whitney U test.

^b Chi-Square test.

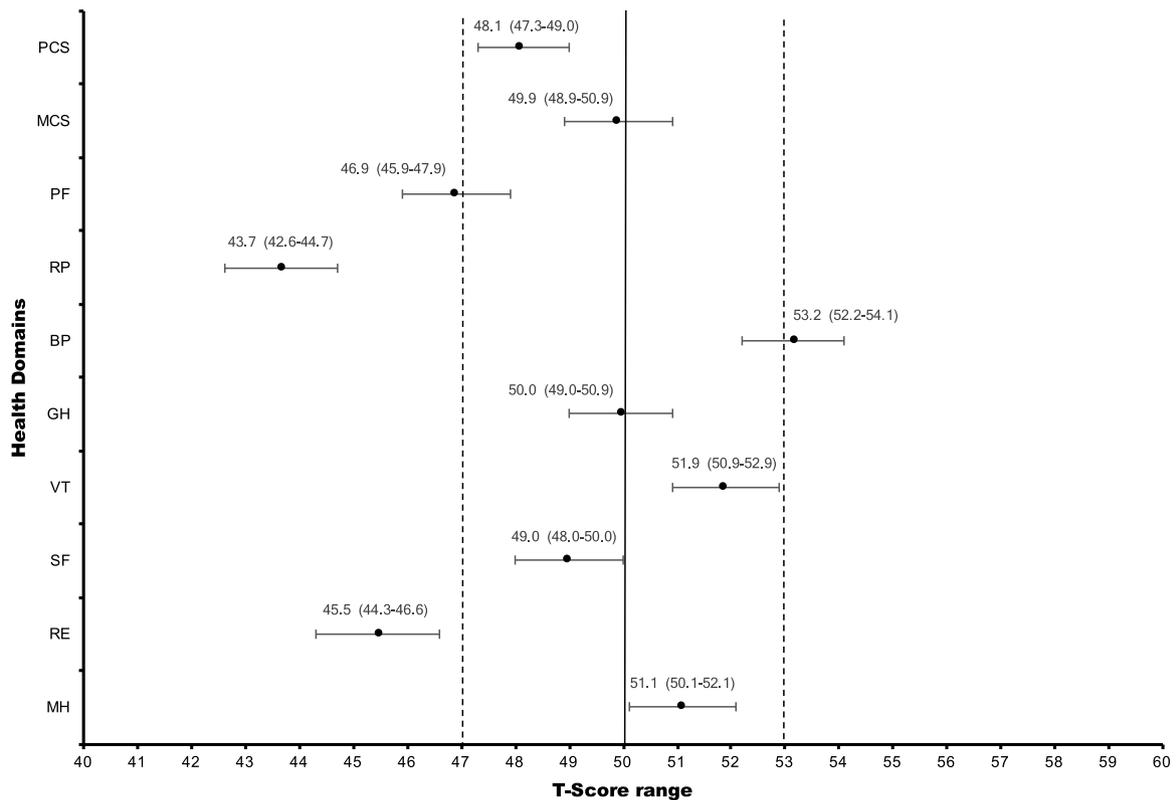


Fig. 2 – Group results for Health Domains and Component Summary Measures (n = 440). The markers represent mean T-score and the error bars a 95% Confidence Interval (CI). Vertical solid line represents the 2009 U.S. General population norm of T-score 50. The dotted lines at 47 and 53 represent the cut-off for group results considered within average. Physical Functioning (PF) reflect the presence and degree of limitations between the extremes of physical activities; Role-Physical (RP) assess role limitations with work or other daily activities because of physical problems; Bodily Pain (BP) measures the intensity of pain and the degree of its interference with normal activities; General Health (GH) evaluates the respondent’s perception and expectations of his or her health; Vitality (VT) measures energy levels and fatigue; Social Functioning (SF) assesses the impact of either physical or emotional problems on quantity and quality of normal social activities; Role-Emotional (RE) represent role limitations with work or other daily activities as a result of emotional problems; Mental Health (MH) comprises items from major mental health dimensions (anxiety, depression, loss of emotional control, and psychological well-being).

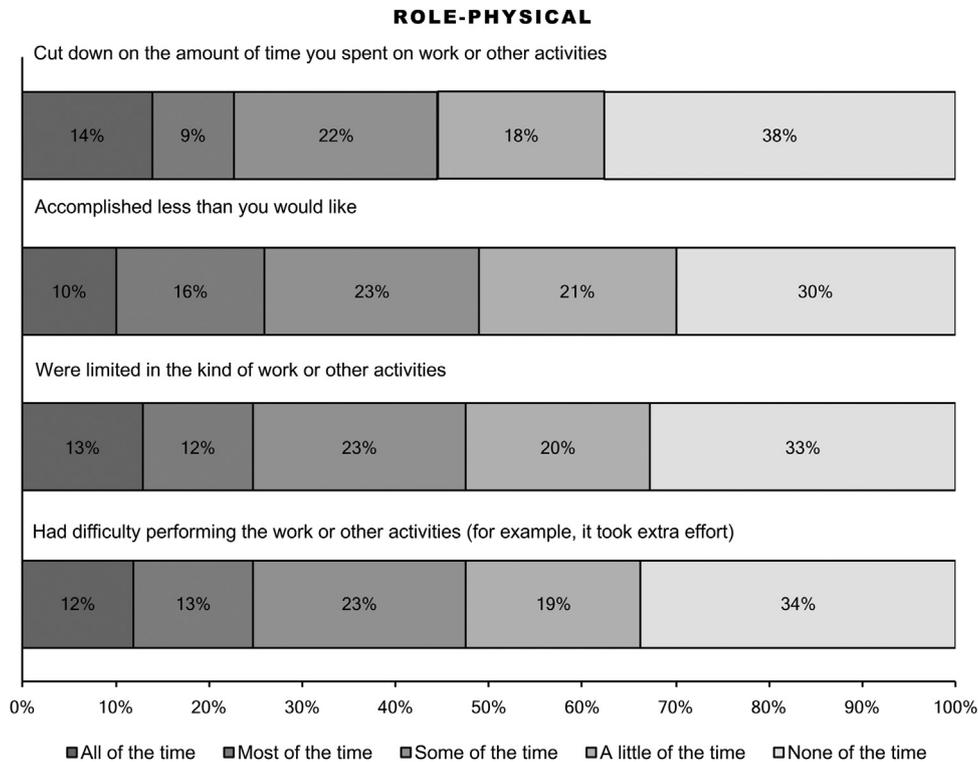


Fig. 3 – Percentage of respondents' individual results of the Short Form-36 item Questionnaire Health Survey version 2[®] subscale Role-Physical (n = 440). “During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?”.

to-work from a sub-sample of the same OHCA-survivors¹⁹. The reasons for role limitations needs further investigation, as they may be caused by other factors such as cardiac morbidity or neurological impairment²⁰. A follow-up intervention (including screening for cognitive/emotional problems, support and information, with referral to specialised care when needed), was found effective for improved HRQoL in specific domains: General Health, Mental Health, and Role-Emotional one year after cardiac arrest²⁰.

In contrast, regarding our results concerning emotional problems (Role-Emotional), the domain of Mental Health was less affected. The 25% of OHCA-survivors in the present study that reported problems with Mental Health is in agreement with reported levels of emotional problems in the same OHCA-survivor cohort²¹. This indicates that problems with Role-Emotional are not solely caused by problems in mental health, such as depressive symptoms. Instead, it seems likely that there are other unknown factors related to Role-Emotional functioning among these patients. For example, fatigue and cognitive problems have been commonly reported in this patient group^{22,23} and may be related to Role-Emotional function.

Strong correlations between Vitality and a fatigue-specific questionnaire among OHCA-survivors have previously been reported²⁴. Interestingly, few patients in the present study reported problems with Vitality. This is in contrast to previous findings where OHCA-survivors experienced greater problems with Vitality^{17,25}. One explanation for this may be that different reference groups were used, which affects the norm based scoring. Furthermore, the fact that older respondents rated Vitality better than the younger age-group differs from earlier results¹⁴. One explanation may be that the younger age-group are more affected by limitations after an OHCA, since the

differences from their pre arrest status may be larger and the demands in their daily life, e.g. related to work. However, this may only in part explain the results, since the younger age-group also had Vitality scores within the average range. Since fatigue is an important predictor for a lower societal participation after OHCA and commonly reported^{19,26,27}, the association between the Vitality and Role-Emotional domains and different types of fatigue needs to be further evaluated in OHCA-survivors.

It was evident that females in the present study scored significantly lower HRQoL compared to males. This finding is in contrast to a study where HRQoL was found to be similar among males and females²⁸. However, when compared with sex-adjusted norm values, the negative impact of OHCA on female's health seems to be amplified, hence the lower HRQoL in females may in fact be a valid observation. Similar sex differences have been reported in a cohort of In-Hospital Cardiac Arrest survivors, where females reported worse health status and more psychological distress compared to males²⁹. In the present study, there were no differences between males and females in the examined independent variables, which could explain this observed difference. Thus, it seems likely that existing differences in health between females and males may be aggravated by the acute illness³⁰. It has been proposed that reduced HRQoL may have more to do with gender roles, than with biological sex³¹.

Even though a majority of survivors experienced acceptable HRQoL, it is not necessarily equal to the HRQoL before the OHCA³. Importantly, nearly half of the respondents in the present study rated their health worse compared to one year ago. Conversely, one of five respondents rated health improved in general. These findings may be an effect of a response shift, demonstrating a change in the value of life

ROLE-EMOTIONAL

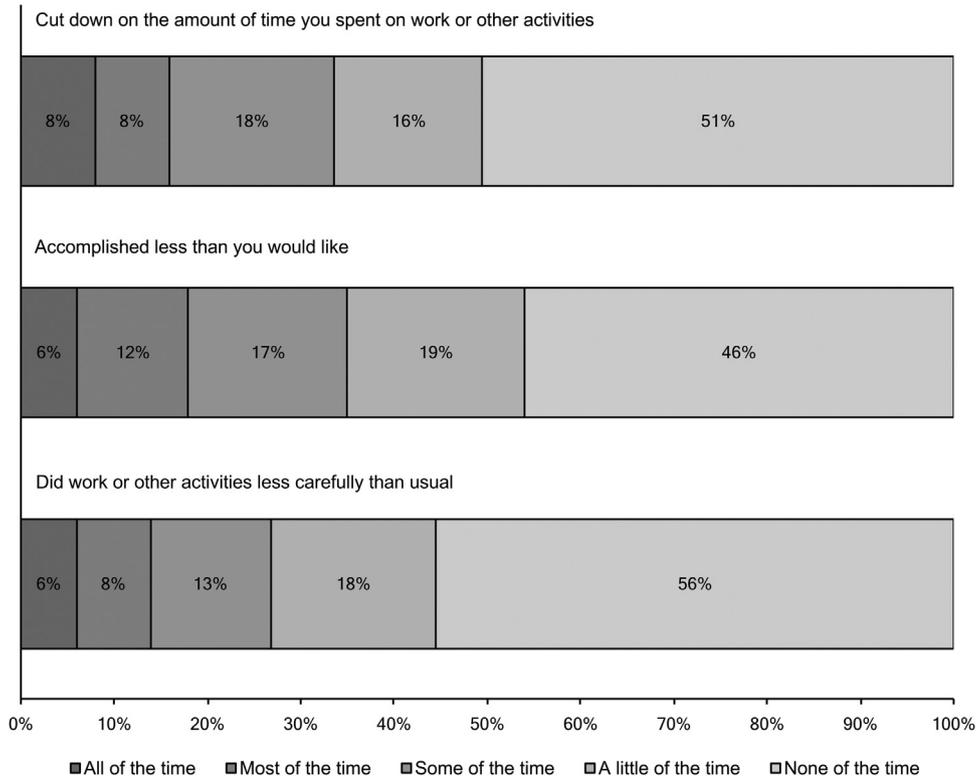


Fig. 4 – Percentage of respondents' individual results of the Short Form-36 item Questionnaire Health Survey version 2[®] subscale Role-Emotional (n = 440). “During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?”.

Table 2 – Comparison of T-Score between dichotomised age-groups and between males and females (n = 440).

Health Domains	Age ≤65 years	Age >65 years	p-value	Effect size ^a	Male	Female	p-value	Effect size ^a
	(n = 282)	(n = 158)			(n = 372)	(n = 68)		
	Mean (95% CI)	Mean (95% CI)			Mean (95% CI)	Mean (95% CI)		
Physical Component Summary	49.1 (48.0–50.2)	46.4 (44.8–48.0)	0.008	0.3	48.8 (47.9–49.7)	44.6 (41.8–47.4)	0.007	0.4
Mental Component Summary	48.8 (47.5–50.1)	51.9 (50.3–53.5)	0.006	–0.3	50.4 (49.3–51.5)	47.4 (44.6–50.2)	0.03	0.3
Physical Functioning	48.5 (47.3–49.6)	44.1 (42.3–46.0)	<0.001	0.4	47.9 (46.8–48.9)	41.7 (38.8–44.6)	<0.001	0.6
Role-Physical	43.9 (42.6–45.2)	43.2 (41.4–45.0)	0.55	0.1	44.3 (43.1–45.4)	40.4 (37.4–43.5)	0.02	0.4
Bodily Pain	53.3 (52.2–54.4)	52.8 (51.3–54.4)	0.72	0.1	53.5 (52.6–54.4)	51.3 (48.5–54.1)	0.29	0.2
General Health	50.1 (48.9–51.3)	49.7 (48.1–51.4)	0.68	0.0	50.5 (49.5–51.6)	47.0 (44.3–49.6)	0.02	0.4
Vitality	50.8 (49.6–52.1)	53.7 (52.1–55.4)	0.006	–0.3	52.7 (51.7–53.8)	47.2 (44.3–50.1)	<0.001	0.6
Social Functioning	48.7 (47.5–49.9)	49.5 (47.8–51.2)	0.35	–0.1	49.3 (48.3–50.4)	47.2 (44.4–50.0)	0.17	0.2
Role-Emotional	45.5 (44.0–47.0)	45.4 (43.4–47.4)	0.89	0.0	46.2 (45.0–47.4)	41.5 (38.0–45.0)	0.009	0.5
Mental Health	50.3 (49.0–51.5)	52.6 (51.1–54.1)	0.04	–0.2	51.5 (50.4–52.5)	49.0 (46.4–51.6)	0.06	0.3

^a Cohen's *d*. Statistical analysis performed with Mann-Whitney *U* test. Pre specified level for statistical significance is <0.05.

that can happen when conditions change³². A weakness of this study was that HRQoL only was measured at a single time point, and therefore cannot demonstrate any changes in HRQoL over time. It has been reported that HRQoL among OHCA-survivors can both improve³³ and decrease³⁴ over time. Presently, little is known concerning HRQoL over longer periods of time nor the time frame for a possible response shift in OHCA-survivors.

This study has some limitations. The cohort was dominated by males and the smaller percentage of females may have affected the

result. This unequal sex distribution is however reflective of the target population and hence representative^{15,16,35}. Furthermore, some responses (7%) were conducted by proxy-report, and the validity of those answers may therefore be questioned³⁶. However, there is a value to include responses from proxies as it allows the possibility to include those patients with more severe disabilities, decreasing selection bias^{6,7,37}. Furthermore, respondents pre-arrest status was not measured, and therefore potential pre-existing limitations may have been overlooked. That the 2009 U.S. general population norms

were used as norm reference is also a limitation. However, ten different countries were represented, and not all have norm data for SF-36v2. Thus, the use of this normative data was valid as it was based on a large sample of a general population⁵.

The foremost strength of this study is the well-defined cohort from an international, multicentre setting with information also on non-responders. Missing patients were more likely to have a poor outcome, reflected in the slight differences between the MCS and PCS in present study when compared to the previous report from the same cohort, but where multiple imputation where used in analyses to keep the initial randomized design⁸. Overall, the small number of non-respondents (10%) can be assumed to only have a minimal effect on the result. The present study had a high completion rate to SF-36v2[®] and the results seems to reveal important and detailed information at a domain level on the outcome in OHCA-survivors. Further, we used a well-validated assessment³⁸, although the evidence of SF-36v2[®] as a valid PRO assessment after OHCA is more limited⁶. When the psychometric properties of SF-36v2[®] were evaluated, all domains exceeded the recommended threshold value of 0.70 for Cronbach's coefficients α , indicating good reliability¹³. Although floor effects were negligible for all domains, substantial ceiling effects were found for 5 of the 8 health domains. This indicate lower sensitivity of the SF-36v2[®] to discriminate health in the higher end among OHCA-survivors¹³. Importantly, the ceiling effects reported here was less than in the general population, except for the Bodily Pain⁵. This suggest the SF-36v2[®] to be a promising generic HRQoL assessment for OHCA survivors, although this needs to be tested further. As a generic measure, the SF-36v2[®] may not cover specific aspects of health that matter to OHCA-survivors, and therefore it is recommended that it should be combined with more specific measures⁶, but today there is no OHCA-specific PRO measure available and further work in this area is strongly encouraged.

Conclusions

This study adds important information about the outcome of OHCA survivors. A majority of survivors reported acceptable HRQoL six months post-OHCA. However, there was also a substantial percentage of the cohort with impaired function and limitations especially related to the Role-Physical and Role-Emotional aspects of health. In addition, females reported a substantially worse HRQoL than males and this effect was amplified when compared to sex-adjusted norm values. Older survivors had worse Physical Functioning than the younger, but reported better Vitality and Mental Health. For clinical implication, these results support the importance of identifying those OHCA survivors at risk of poor HRQoL who may benefit from follow-up and specific rehabilitation efforts.

Conflicts of interest

Wise report receiving a single fee from Bard Medical for a lecture. Other authors report no conflicts of interest.

Acknowledgements

This work was supported by The European Union Interreg IVA programme, The Swedish Heart and Lung Association, the Skåne

University Hospital Foundations, the Gyllenstierna-Krappert Foundation, Academy of Caring Sciences at Skåne University Hospital, the Swedish National Health System (ALF), the County Council of Skåne, the Swedish Society of Medicine, the Koch Foundation, the Swedish Heart-Lung Foundation, AFA Insurance Foundation, the Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for medical research, the Segerfalk Foundation and the Tryg Foundation. The study sponsors have no involvement in the study design; in the collection, analysis, and interpretation of the data; in the writing of the manuscript, or in the decision to submit the manuscript for publication.

MB would like to thank the TTM steering group for the opportunity to carry out this study. Also a special thanks to Elisabeth Persson, for valuable support and feedback.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.resuscitation.2018.10.028>.

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