Clinical paper

Changes in health status and health related quality of life from six months to five years in out-of-hospital cardiac arrest survivors – A NORCAST sub study

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Abstract

Background: Brain injury in out-of-hospital cardiac arrest (OHCA) survivors affects health status and health-related quality of life (HRQoL). It is unknown how HRQoL evolves over time, and assessments at different time points may lead to different results.

Methods: In a NORCAST sub study, OHCA survivors eligible for health status (EQ-5D-3L) and HRQoL (SF-36) assessments were examined six months and five years after OHCA. At five-year follow-up, survivors also retrospectively assessed their health status for each consecutive year following OHCA. The next of kin independently assessed health status and HRQoL of their respective OHCA survivors.

Results: Among 138 survivors alive after six months and 117 after five years, 80 (88% male) completed both follow-ups. Health status and HRQoL remained stable over time, except for increasing SF-36 mental summary score and decreasing physical functioning and physical component score. Anxiety and depression levels were generally low, although younger survivors stated more anxiety than older survivors. Retrospective assessment showed reduced health status for the first two years, which increased only from the third year. Explorative analyses revealed that younger age, longer time to return of spontaneous circulation (tROSC) and late awakening affected health status, particularly in the first two years post-arrest.

Conclusions: OHCA survivors showed stable health status and HRQoL with only minor differences between six months and five years. Younger survivors with long tROSC, late awakening, and more anxiety and depression symptoms at six months, had reduced health status the first two years with significant improvements towards the fourth year.

Keywords: Out-of-hospital cardiac arrest, Health-related quality of life, Health status, changes, Outcome, Brain injury

Introduction

Hypoxic-ischemic brain injury (HIBI) is a severe complication of cardiac arrest (CA) considered to be the main cause of neurological disability and death\textsuperscript{1,2}. The severity of HIBI has impact on cognitive function\textsuperscript{3}, affecting health status and health-related quality of life (HRQoL)\textsuperscript{4,5}. Cognitive function seems to hardly improve in CA survivors after the first year\textsuperscript{6}, and a current position paper therefore recommends a follow-up period of one year\textsuperscript{7}. The same time perspective is proposed for HRQoL assessments\textsuperscript{7}. However, if and how HRQoL changes over longer time periods is more uncertain. While two studies showed impaired HRQoL six and 18 months after out-of-hospital cardiac arrest (OHCA)\textsuperscript{8,9}, we recently showed that HRQoL was comparable to an age- and gender-matched population five years after OHCA\textsuperscript{10}. These differences could be explained by different treatment strategies, evaluation methods, outcome parameters or, primarily, different cohorts. Given the increasing life expectancy for CA survivors, information about long-term prognosis regarding health status and HRQoL is of crucial importance for patients, their relatives, and health care workers.

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Thus, the aim of the present study was to compare health status, HRQoL, anxiety and depression six months and five years after OHCA in one cohort, also including how the next of kin evaluated the survivors’ HRQoL. Secondary, we intended to retrospectively assess how health status changed consecutively, year by year, in the first five years following OHCA, assessed both by survivors and their next of kin. Finally, we wanted to investigate how factors previously shown to affect outcome like age, tROSC and time to awakening (tAWAK), influenced HRQoL over time.

**Methods**

**Study design and population**

This study was a pre-specified follow-up study of the NORCAST trial. From September 2010 through January 2014, 259 survivors with both witnessed and unwitnessed OHCA, >18 years of age and still comatose on admission to Oslo University Hospital Ullevål were prospectively enrolled in NORCAST. Post-resuscitation care followed our standard treatment protocol with targeted temperature management at 33 °C (TTM33) for 24 h.

All survivors and their next of kin were invited to an ambulatory follow-up approximately six months and more than four years after their OHCA to assess health status, HRQoL, anxiety and depression. Whereas the six-month follow-up was carried out consecutively between 2010 and 2014, long-term follow-up extended from June 2017 through May 2018, resulting in assessments after median 5.4 (3.7–7.3) years. Patients not able to attend clinical follow-up received questionnaires by mail. A reminder with the same set of questionnaires was sent after four weeks with a new phone call after two more weeks to those not responding. Survivors who could not be reached were only assessed according to the Cerebral Performance Category (CPC) based on information from their next of kin, primary care physicians, and available medical records. Only data from survivors attending both follow-ups were included in prospective analyses. For the retrospective year-by-year health status assessment, data from all survivors attending the five-year follow-up were included.

**Scoring tools**

We used the Short-Form-36 Health Survey version 1 (SF 36) to assess HRQoL, EuroQol-5D-3L (EQ-5D) to analyse health status, and Hospital Anxiety and Depression Scale (HADS) to reveal anxiety and depression symptoms. At five-year follow-up, the survivors were also asked to assess their health status retrospectively for each consecutive year after OHCA, using a 0–100 visual analogue scale.

Survivors and their next of kin completed the questionnaires separately. The next of kin assessed the survivors’ health status by completing the EuroQol-5D-3L (except for the EQ visual analogue scale (EQ VAS)) at both time points and the retrospective health status assessment at five-year follow-up.

**Short-Form-36 health survey version 1 (SF-36)**

SF-36 contains 36 questions yielding four domains which reflect physical health (physical functioning, role-physical, bodily pain, and general health) and four domains reflecting mental health (vitality, social functioning, role-emotional, and mental health). The ordinal answers were transformed to a 0–100 scale for each domain. Higher values indicate higher HRQoL. Additionally, a single summary score for physical health (physical component summary score, PCS) and mental health (mental component summary score, MCS) was derived from the four physical and mental domains, respectively.

**EuroQol-5D-3L (EQ-5D)**

The EQ-5D estimates health status by covering five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with three possible answers each (no, some or extreme problems). EQ-5D index reflects health status as a summary score by weighting the five dimensions on a basis of normal population values, with 0 = death and 1 = best health. In addition, the participants rate their health status on EQ VAS from 0 (worst) to 100 (best health) at the same day.

**Hospital Anxiety and Depression Scale (HADS)**

HADS aims to reveal anxiety (HADS-A) and depression (HADS-D) symptoms by means of seven questions on a four-level category (0–3), resulting in a score from 0 to 21 for depression and anxiety, respectively, with higher values indicating more symptoms. Since no Norwegian cut-off values exist, the internationally recommended cut-off value of ≥8 was used.

**Retrospective health status assessment**

To obtain information about the survivors’ health status between the six-month and five-year follow-up, survivors and their next of kin retrospectively estimated the survivors’ health status for each year after OHCA on a 0–100 scale analogous to the EQ VAS at five-year follow-up.

The original five-level rating scale (poor to excellent) was replaced by the final VAS scale after the first four survivors had completed the original scheme. Hence, the first four registrations were excluded from further analyses. Importantly, these are retrospective data and are subject to recall bias and have to be interpreted with caution.

**Ethics**

The NORCAST study was approved by the Regional Committee for medical and health research ethics (2010/1116a). Written consent was obtained from all survivors and their next of kin.

**Statistical analyses**

Statistical analyses were performed in SPSS v27, SAS v9.4 and STATA v17. All tests were two-sided and results with p-values <0.05 were considered statistically significant. Continuous data were described as means and standard deviations (SD) if symmetrically distributed, and otherwise as medians and minimum and maximum values. Categorical data were presented as frequencies and percentages. Characteristics of those attending and not attending at follow-up were compared by independent samples t-test for continuous and χ²-test for categorical variables. Changes between six-month and five-year follow-up in continuous outcome variables were assessed by a linear mixed model, while a generalized linear mixed model was performed to assess changes in categorical variables. The models included random effects for survivors and fixed effects (non-linear whenever necessary) for time. Agreement between survivors’ and next of kin’s reporting of the retrospective health status was assessed by Bland-Altman analysis.

As an exploratory approach, a growth mixture model (GMM) was estimated for the retrospective health status assessment data. The method attempts to identify groups of survivors following distinct trajectories throughout the follow-up period by exploiting a set of sta-
stistical criteria. The criteria used were Bayes Information Criterion, where a smaller value means a better model, within-group probability of at least 0.8, reasonably large groups and non-overlapping 95% confidence intervals (CIs) of the identified trajectories. The identified groups were compared by independent samples $t$-test or $\chi^2$-test, as appropriate, with respect to age, HADS-A and HADS-D at six months, iROSC, and tAWAK.

Exploratory analyses stratifying by median age (58 years) at OHCA; gender, tAWAK, defined as late with Glasgow Coma Scale (GCS) < 9 72 h or more after sedation withdrawal, and iROSC, dichotomized using a cut-off of 25 min. Unwitnessed OHCAs were excluded from tROSC analysis due to the unknown OHCA time point.

These analyses were performed for SF-36 PCS and MCS, EQ VAS, EQ-5D index (both survivors and next of kin), HADS-A and HADS-D by including additional fixed effects for stratification variables and the interaction between stratification variables and time into the models described above. Post-hoc analyses estimated the mean values and compared the stratification groups at each time point.

**Results**

Among 138 survivors alive six months after OHCA, 103 (75%) completed HRQoL questionnaires (Fig. 1). At five-year follow-up, 117 (85%) were still alive, with 96 (82%) completing HRQoL questionnaires. In total, 80 patients (76 with CPC 1 and four with CPC 2) attended both six-month (mean 6.7 (4.7–9.4) months) and five-year follow-up (mean 5.3 (3.7–7.3) years) (Fig. 1, Table 1). Among survivors not completing both follow-ups, sixteen attended only long-term follow-up and ten died during the five-year follow-up period. The remaining eleven survivors did not attend for different reasons (Fig. 1).

Patient characteristics are described in Table 1. Among survivors alive at five years, 89% with OHCA of cardiac aetiology attended follow-up vs 75% with non-cardiac aetiology ($p = 0.005$). Otherwise, no differences were found between those attending and not attending HRQoL follow-up, regarding age, gender, tROSC, tAWAK, witnessed arrest, and initial rhythm.

OHCA survivors reported to be in good health at both time points with only minor changes in HRQoL from six months to five years (Table S1, Fig. 2a). Mental health domains (from SF-36), tended to improve over time, resulting in higher MCS after five years (mean difference 2.8 (0.8; 4.8)). Contrary, physical health declined over time with decreasing physical function (mean difference −5.5 (−8.8; −2.2)) and PCS (mean difference −2.2 (−4.3; −0.1)). EQ-5D did not reveal changes in health status from six months to five years (Table S1, Fig. 2a). Mean levels of anxiety and depression symptoms were generally low and stable over time (Table S1).

In the retrospective year-by-year assessment, survivors stated a decreasing health for the first two years after OHCA, followed by significant improvements towards the fourth year (Fig. 3a). Next of kin scorings showed a similar time course supporting this pattern (Fig. 3a). Bland-Altman analysis demonstrated low bias and acceptable limits of agreement between survivors’ and next of kin’s estimations (Fig. S1). The prospective EQ VAS scorings at six months and five years cohered well with the retrospective health status scorings for the first and fifth year (Fig. 3a).

The growth mixture model identified two homogeneous groups of survivors following distinct trajectories: one with an overall lower health status and a u-shaped course reporting low values especially
### Table 1 – Baseline characteristics for OHCA survivors attending Health-Related Quality of Life assessment at both six months and five years (n = 80).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>n (%) or median (min – max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>70 (88)</td>
</tr>
<tr>
<td>Age at cardiac arrest [years]</td>
<td>60 (26–81)</td>
</tr>
<tr>
<td>Witnessed cardiac arrest, yes</td>
<td>78 (97)</td>
</tr>
<tr>
<td>Received bystander CPR</td>
<td>68 (86)</td>
</tr>
<tr>
<td>Primary cardiac OHCA aetiology</td>
<td>78 (97)</td>
</tr>
<tr>
<td>VF/VT as initial rhythm (n = 79)</td>
<td>70 (89)</td>
</tr>
<tr>
<td>Time to ROSC [min] (n = 76)</td>
<td>17 (3–102)</td>
</tr>
<tr>
<td>Survivors with time to ROSC &gt; 25 min (n = 76)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Targeted temperature management (TTM)</td>
<td>78 (98)</td>
</tr>
<tr>
<td>Days from OHCA to GCS ≥ 9 (n = 79)</td>
<td>6 (0–23)</td>
</tr>
<tr>
<td>Number of patients with late awakening (n = 77)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>CPC 1 Best CPC until n = 62 CPC at 6-month follow-up n = 74 CPC at 5-year follow-up n = 76</td>
<td></td>
</tr>
<tr>
<td>CPC 2 discharge n = 13</td>
<td>n = 5</td>
</tr>
<tr>
<td>CPC 3 n = 13</td>
<td>n = 4</td>
</tr>
</tbody>
</table>


![EQ-5D-3L health status domains](image)

**Fig. 2** – EQ-5D-3L health status domains in out-of-hospital cardiac arrest survivors at six months and five years – assessed by the survivors (2A) and their next of kin (2B). Answer categories “same problems” and “many problems” are merged together due to consistently very few responses for “many problems”. No significant differences were identified for any of the assessments.
in the first two years (G1), and the other with an almost linear course and good health status over time (G2) (Fig. 4). Survivors in G1 were younger, had longer tROSC and presented more anxiety and depression symptoms at six months than G2 survivors (Table 2).

The stratified analyses showed a similar course among younger survivors (<58 years) as the growth mixture model (Fig. 3b). Additionally, younger survivors stated lower mental health compared to those >58 years in both the prospective and the retrospective assessment. Younger and older survivors improved comparably over time (Fig. S3a). However, anxiety symptoms were more common in younger than older survivors with stable values over time (Fig. 3b). Depression symptoms did not differ related to age or time point of assessment.

For survivors with long tROSC (>25 min), the stratified analysis confirmed the results from the growth mixture model showing a significantly lower health status in the first three years after OHCA than those with short tROSC (Fig. 3c). Similar findings for survivors were described by their next of kin (Fig. 3c). Survivors with long tROSC

**Fig. 3** – Retrospective health status assessment using a visual analogue scale (VAS) with 0 = worst and 100 = best possible health status, rated at 5-year follow-up retrospectively for each year after out-of-hospital cardiac arrest (OHCA). CA (cardiac arrest) correspond to pre-arrest health status. EQ VAS mark the prospective measurements (A). Survivor’s health rated by themselves and their next of kin stratified by age (dichotomized at 58 years) (B), and by time to return of spontaneous circulation (ROSC) (C).

**Fig. 4** – Results of growth mixture model for self-assessed health status in 79 OHCA survivors over time.
We found an overall stable health status in the prospective assessment of OHCA survivors from six months to five years after their arrest with only minor changes in HRQoL. Nevertheless, according to SF-36 sum scores, mental health improved and physical health worsened from six months to five years. Retrospectively, survivors assessed their health status to be decreased in the first two years after OHCA, with significant improvements towards the fourth year.

Throughout the follow-up period, two different courses were revealed; one with good and stable health status over time and another with a u-shaped form and a generally lower health status. Survivors following the latter course reported decreasing health status particularly for the first two years, were generally younger, had longer tROSC, and more anxiety and depressions symptoms at six months. Indeed, these are retrospective data with limitations that retrospectively, survivors assessed their health status to be decreased in the first two years after OHCA, with significant improvements towards the fourth year.

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The present findings of a stable long term HRQoL and health status parameters, no differences between groups or changes over time were found.

### Discussion

We found an overall stable health status in the prospective assessment of OHCA survivors from six months to five years after their arrest with only minor changes in HRQoL. Nevertheless, according to SF-36 sum scores, mental health improved and physical health worsened from six months to five years. Retrospectively, survivors assessed their health status to be decreased in the first two years after OHCA, with significant improvements towards the fourth year.

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The present findings of a stable long term HRQoL and health status are comparable to results from a Dutch study, showing primarily early neurological improvements during the first three months after CA with almost normal HRQoL after one year. \(^{24}\) In contrast, the Hanox study showed that six out of eight SF-36 domains did not improve from six to 18 months after CA. \(^{9}\) Noteworthy, the Dutch study included both in-hospital and OHCA survivors and had a higher drop-out of sicker patients, potentially resulting in an overestimation of HRQoL, \(^{24}\) whereas the Hanox and the present study included only comatose OHCA survivors with longer tROSC and longer tAWAK presumably suggesting more severe brain injury. \(^{9}\) However, in both these studies, mental health sum scores improved over time suggesting that some survivors with moderate to severe HiBI may still improve after the first year. In the present study, some physical HRQoL components (PF, PCS) decreased from six months to five years. This could rather be attributed to survivors’ natural ageing process \(^{25}\) than to their OHCA, since we have previously shown that physical health domains compared well to an age-matched reference population five years after OHCA. \(^{10}\)

Both EQ-5D index and EQ VAS showed comparable values at six months and five years. Usually, health status measurements by EQ VAS decline with higher age. \(^{26}\) Therefore, one might expect lower values at five years, rather than a subtle increase. Interestingly, the prospective health status values did not change over time. When only comparing pre-arrest to five-year values in the retrospective assessment, health status did not change over time either. However, the year-by-year evaluation revealed a considerably decreasing health status in the first two years before increasing to the fourth year.

Longer tROSC is a well-described marker for severe HiBI and was previously associated with unfavourable outcome after OHCA. \(^{27}\) We found a lower health status over the first years and a trend towards reduced mental HRQoL median six months and five years after arrest in survivors with long tROSC, indicating that the effects of brain injury are still noticeable years later. In contrast to long tROSC, younger age usually predicts better outcome. \(^{12,28}\) Nevertheless, younger survivors with predominantly CPC 1 scores had reduced mental HRQoL, more anxiety symptoms and a lower health status than older survivors in the first years post-arrest. Obviously, if relying only on CPC for neurofunctional outcome prediction one might easily overlook CPC 1 survivors whose physical and mental health status is still reduced. Beside these factors, we acknowledge that severe intensive care treatment also impacts on HRQoL, regardless of its triggering cause, known as the post-intensive care syndrome (PICS). \(^{29}\) Thus, it remains unclear to what degree HiBI, PICS, or a combination of these contribute to reduced HRQoL.

Early neurologically-focused rehabilitation seems to improve HRQoL in CA survivors and is recommended in the recent guide-
lines. Based on the present results, we argue that a later HRQoL assessment than the recommended one year, together with rehabilitation screening, should be considered in survivors of younger age and/or with long iROSC as these patients may improve several years after their arrest. Nevertheless, it remains unclear whether these patients would benefit from early intensive rehabilitation, and more studies are indeed warranted.

The present study has several limitations. With only 80 (68%) survivors completing both follow-ups, the small sample size, drop-outs and the single-centre-design reduce the generalizability of our results. Furthermore, we cannot rule out that the number of groups and shapes of trajectories in the GMM might have been different with more patients included. We do not have HRQoL-data from hospital discharge, which could have provided a more complete picture. Although the HRQoL questionnaires used are recommended for OHCA patients, they are not specifically validated for this group. Using VAS for a retrospective year-by-year health status assessment in OHCA survivors is not validated for this purpose, implicating several limitations. Reliability of these retrospective data may be limited due to recall bias although they compare well to some of the prospective assessments and our clinical observations. Similar scorings by the survivors’ next of kin may support reliability of the data, provided that the recall bias did not affect survivors’ and relatives’ scorings in the same way. Indeed, prospective annually follow-ups, preferably at discharge and for some years thereafter, are warranted. Proportionally more survivors with cardiac aetiology participated at follow-up than survivors with non-cardiac aetiology. The latter is known for worse outcome which could lead to selection bias. Noteworthy, there were no differences regarding CPC scores between these groups. Ceiling effect is a known weakness of EQ-5D-3L and EQ-5D-5L is now recommended. Since the 3L-version was used at the six-month follow-up, it was kept at the five-year follow-up for comparison reasons.

As none of the CPC 3 survivors completed both follow-ups their HRQoL is unknown and potentially reduced. However, the low number of CPC 3 survivors would not have considerably affected the overall results. Anxiety was both a symptom in OHCA survivors and associated with reduced health status. It is still controversial whether anxiety impacts on HRQoL or not and remains unclear whether OHCA directly affects mental HRQoL and health status or rather through underlying anxiety symptoms.

Conclusion

OHCA survivors showed an overall stable health status and HRQoL with only minor differences between six months and five years. Their health status worsened in the first two years after OHCA, followed by significant improvements towards the fourth year. This mainly affected younger survivors with a longer time to ROSC and late awakening, and with more anxiety and depression symptoms at six months. These findings are consistent with the independent next of kin assessments.

CRediT authorship contribution statement

Henning Wimmer: Project administration, Methodology, Investigation, Formal analysis.
Jurate Šaltytė Benth: Formal analysis, Writing – review & editing.
Christofer Lundqvist: Conceptualization, Methodology, Investigation, Writing – review & editing. Geir Øystein Andersen: Investigation, Conceptualization, Writing – review & editing. Julia Henriksen: Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.08.019.

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