Long-Term Disabilities of Survivors of Out-of-Hospital Cardiac Arrest

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Word count: 3265 words

Abstract word count: 277 words

Long-term disabilities of survivors of out-of-hospital cardiac arrest: the Hanox study

Running title: Outcome of awakened survivors of OHCA

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Conflict of interest

AC received fees for travel and lectures from BARD. MD reports having receving fees from Lungpacer Medical Inc. RS received grants from the French Ministry of Health, the French society of intensive care medicine (SRLF) and the European society of intensive care medicine (ESICM), and lecture fees from Baxter. CEL reports having receiving fees from Bayer Healthcare, ThermoFischer Brahms, Biomérieux, Faron, Carmat, Aerogen, Merck Sharp & Dohme, outside the submitted work. Other authors declare that they have no conflicts of interest to declare in relation with the current manuscript.

Funding: Funded by the Direction de la Recherche Clinique et du Développement and the French Ministry of Health; Programme Hospitalier de Recherche Clinique 2011 (grant no. 111012).

Abbreviation list

BADS Behavioural Assessment of Dysexecutive Syndrome

CPC cerebral performance category

CART Classification and Regression Tree

CI confidence interval

EEG electroencephalogram

FAB Frontal Assessment Battery

FOUR Full Outline of UnResponsiveness

GCS Glasgow coma score

GOS-E Glasgow outcome scale–extended score

HR-QOL health-related quality of life

ICU intensive care unit

Q1-Q3 quartile 1-quartile 3

M month

MMSE Mini-Mental State Examination

mRS modified Rankin scale

MDS-UDPRS Movement Disorders Society Unified Parkinson's Disease Rating Scale

NIHSS National Institute of Health Stroke Score

OHCA out-of-hospital cardiac arrest

RBANS Repeatable Battery for the Assessment of Neuropsychological Status

SD standard deviation

Abstract

Background: Long-term outcomes of awakened survivors of out-of-hospital cardiac arrest (OHCA) is poorly known.

Research Question: What are the month (M)-18 outcomes of survivors of out-of-hospital cardiac arrest (OHCA) who awakened during the first 2 weeks post-OHCA and their poor-outcome risk factors?

Study Design and Methods: All OHCA survivors with Glasgow coma score ≥12 during the first 2 weeks post-OHCA were enrolled in six ICUs and followed at M3, M6, M12 and M18. The primary outcome measure was Glasgow outcome scale-extended (GOS-E) at M18. Secondary outcome measures included evaluation of neurological, behavioral and cognitive disabilities, health-related quality of life (HR-QOL), anxiety and depression, and poor-outcome risk factors (GOS-E≤6) at M18.

Results: Among 139 included patients, 98 were assessable for the primary outcome measure. At M18, 64 (65%) had full recovery or minor disabilities (GOS-E>6), 18 (18%) had moderate disabilities but were autonomous for daily-life activities (GOS-E=6), 12 (12%) had poor autonomy (GOS-E<6 but >1) and 4 had died. Percentages of GOS-E>6 patients increased significantly over the 18-month study period. At M18, no patients had major neurological disabilities, 20% had cognitive disabilities, 32% had anxiety symptoms, 25% had depression symptoms, and their HR-QOL was impaired as compared to sex- and age-matched population. Low-flow time, Sequential Organ-Failure Assessment Score at admission, coma duration >3 days after CA or mechanical ventilation on days 3 and 7 were associated with poor functional outcome.

Interpretation: Among patients who awoke (GCS≥12) in the 14 days following OHCA, 35% had moderate-to-severe disabilities or had died at M18. Interestingly, patients improved until

M18 post-OHCA. Risk factors associated with poor functional outcome were low-flow time, clinical severity at ICU admission, prolonged coma duration and mechanical ventilation.

Clinical trial registration: ClinicalTrials.gov (Identifier NCT02292147)

Key words: cardiac arrest, prognosis, disability

Survivors of out-of-hospital cardiac arrest (OHCA), particularly those in persistent coma, may have long-term disabilities [1–3]. Although prediction of comatose patients' neurological outcomes is now relatively well-standardized using a multimodal approach based on difficult cases [3,4], prognoses of patients awakening during the first days after intensive care unit (ICU) admission are not well-known. Results of small observational studies showed they may experience executive, memory and behavioral impairments [5–7]. According to a large observational study [8], 14-day survivors of OHCA had good prognoses at 1 year but some had persistent disabilities; another large study evaluating OHCA survivors' health-related quality of life (HR-QOL) at 1 year found that a majority of survivors had good outcomes and acceptable HR-QOL [9]. However, we lack data regarding the precise long-term outcomes of patients awakening post-OHCA, especially the percentage with persistent disabilities. Moreover, risk factors of poor prognosis for this subset of patients (those awakening during the ICU stay) are not known.

Therefore, the prospective, multicenter, observational Hanox study was designed to evaluate the long-term outcomes and disabilities of awakened OHCA survivors, and to identify their risk factors for poor functional outcome.

Methods

Study design

Six ICUs and four rehabilitation departments in Paris (listed in the Appendix) participated in this observational, prospective study from to March 2013 to February 2016. It was sponsored by the Assistance Publique–Hôpitaux de Paris, with a grant from the French Ministry of Health (PHRC 2011 no. 111012). An independent Ethics Committee (Comité de Protection des Personnes Ile-de-France VI) approved the protocol on May, 11th 2012.

This study is registered at ClinicalTrials.gov (Identifier: NCT02292147).

Study participants

Survivors ≥18 years old, who awoke during the 14 days post-OHCA with a Glasgow coma score (GCS)≥12 were eligible. The patient or his/her legally authorized representative gave written consent before inclusion; for those unable to consent at the time of inclusion, follow-up consent was obtained whenever possible.

Exclusion criteria were: preexisting uncontrolled neurological disease (including multiple sclerosis, Parkinson's disease, debilitating stroke, amyotrophic lateral sclerosis, dementia); preexisting chronic psychiatric disease (including autism, schizophrenia, bipolar disorder or neuroleptic treatment); preexisting blindness or deafness; preexisting evolutive malignancy; preexisting dependency; patients under guardianship, unable to understand or speak French or living outside Paris area.

Study objectives and evaluation measures

The main objective was to evaluate the long-term functional outcomes of awakened OHCA survivors (with GCS≥12 at inclusion). The primary outcome measure, GOS-E score at month (M)18, is a scale that ranges from 1 (death) to 8 (full recovery or minor symptoms that do not affect daily life) [6] (see **Supplemental Table 1**).

Secondary objectives were to assess long-term neurological, cognitive and behavioral disabilities, dependence, HR-QOL, anxiety and depression and relatives' caretaking burden. Apart from GOS-E, functional disability was also assessed using the modified Rankin scale (mRS) [10] (**Supplemental Table 2**). Neurological disability was evaluated with the National Institute of Health Stroke Score (NIHSS) [11] and the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UDPRS) [12]; cognitive disability using Mini-Mental State Examination (MMSE) [13], the Repeatable Battery for the Assessment of

Neuropsychological Status (RBANS) [14] and the Frontal Assessment Battery (FAB) [15]; behavioral changes used self-rating and proxy-rating scales of the Behavioural Assessment of Dysexecutive Syndrome (BADS) questionnaire [16]; dependence for daily living activities using the Functional Independence Measure [17,18]. Moreover, HR-QOL was assessed with the short form-36 (SF-36) questionnaire, sex- and age-matched as previously described [19,20]; anxiety and depression using the Hospital Anxiety and Depression Scale [21]. Last, relatives' caretaking burden was evaluated with Zarit's Burden Inventory Scale [22]. In the ICU, consciousness evaluation used the GCS and the Full Outline of UnResponsiveness (FOUR) score [23]. We also explored predictive factors associated with poor functional outcome, defined as a Glasgow outcome scale–extended score (GOS-E)≤6 [24]. We choose this cutoff to define poor functional outcome because the population we included in the study had an *a priori* good prognosis: indeed, patients who awoke in the ICU with a Glasgow coma score ≥12 are supposed to have no or minor disabilities, including capability of returning to work.

Study procedure

After inclusion, patients were prospectively followed during their ICU and hospital stays, and procedure and ICU- and hospital-event parameters were recorded. OHCA parameters were recorded using the Utstein criteria [25]. At ICU discharge, consciousness was evaluated using the GCS and FOUR score.

After hospital discharge, patients were seen during outpatient visits at M1, M6, M12 and M18 post-OHCA in the participating neurology or rehabilitation departments (see **Figure 1** for detailed study procedures). At M1, a neurologist assessed patients for consciousness, neurological and cognitive disabilities, and an electroencephalogram (EEG) was obtained. A modified Synek scale [26] was applied to interpret EEGs (**Supplemental Table 3**). At M3, a psychologist interviewed patients by phone to evaluate vital status, GOS-E and global

functional status.

At M6, M12 and M18 visits, a hospital physical medicine and rehabilitation physician evaluated patients' functional status, dependence, neurological, cognitive and behavioral status using the tools described above. All visits were performed by experienced physicians, following a standardized approach to evaluate primary and secondary outcomes. GOS-E was determined by patient interview. Anxiety and depression as well as HR-QOL were also assessed during these visits. RBANS was evaluated only at the M18 visit.

Statistical analyses

Data are expressed as median [quartile 1- quartile 3]([Q1–Q3]), mean (± standard deviation [SD]) or mean (95% confidence interval (CI)), as appropriate. Between-group comparisons used Student's *t*-test or Mann–Whitney *U*-tests for continuous variables and χ^2 for categorical variables. A univariable logistic-regression model tested the impact of each clinical characteristic and ICU event on poor functional outcome. For this analysis, 123 patients were used: 98 with known M18 outcome; and outcomes at M12 (n=10), M6 (n=13) and M3 (n=2) were used for the remaining 25 patients. All analyses were computed with R software, version 3.5.1 (R Foundation) at a two-sided, 5% alpha risk.

Results

Among the 140 included patients, one with exclusionary evolutive cancer had his ICU-stay parameters recorded at inclusion but not thereafter; hence, 139 patients were analyzed (**Figure 1**). Four patients, classified as GOS-E 1, died on day 18, 24, 458 or 507 post-inclusion.

Patients' ICU-admission, inclusion and OHCA characteristics are reported in **Table 1**. Briefly, patients were young (median age 55 years), 77% men, and only a minority had

comorbidities. OHCA occurred mostly in public places, with short no- and low-flow times. Median [Q1-Q3] OHCA-to-inclusion time was 6 [3–9] days.

In-ICU events are reported in **Table 2**. Eighty-eight (67%) of 132 patients had an EEG during their ICU stays; only half of them were normal.

The M6, M12 and M18 visits were completed, respectively, by 104 (75%), 91 (65%) and 94 (68%) patients, but only 74 patients were evaluated at the 3 visits (characteristics of these 74 patients are reported in Table 1).

No patient was hospitalized in rehabilitation unit during follow-up, but ambulatory care by physiotherapists or other caregivers was not recorded.

Primary outcome

Ninety-eight (71% of those included) patients' GOS-E scores could be determined: 36 (37%) had a GOS-E of 8; 28 (29%) a GOS-E of 7; 18 (18%) a GOS-E of 6; 8 (8%) a GOS-E of 5, 4 (4%) a GOS-E of 4 and 4 (4%) a GOS-E of 1. In other words, 64 (65%) patients had recovered fully or had minor disabilities (GOS-E>6), 18 (18%) had moderate disabilities but were autonomous for daily-life activities (GOS-E=6), 12 (12%) had poor autonomy (GOS-E< 6 but >1) and four had died.

Among the 41 patients for whom primary outcome could not be determined, 26 were lost-to-follow-up, 10 patients decided not to come at the M18 visit, and the investigator canceled the visit for unknown reason in the remaining 5. As compared to the 98 evaluable patients, patients who could not be evaluated at M18 were similar except for their medical history: they had more frequent history of myocardial infarction (29% vs. 10%, p=0.006), diabetes mellitus (16% vs. 2%, p = 007=) and were frequently tobacco users (73% vs. 54%; p = 0.035).

Secondary outcomes

GOS-E kinetics over time

Figure 2 displays the GOS-E evolution over time for the 74 patients who completed the 3 protocol-specified visits (see Supplemental Figure 1 and **Supplemental Table 4** for values). The percentages of those with good functional outcome (i.e. GOS-E>6), increased over the 18-month study period; from 52% at M3 to 65% at M18 months (p<0.01)) (**Supplementary Figures 2 and 3**).

Neurological disabilities

Patients' persistent neurological disabilities at M6, M12 and M18 are reported in **Table 3** for the 74 patients who completed the 3 protocol-specified visits and **Supplemental Table 5** for the whole population. The vast majority of them had no neurological disabilities, with no significant change between M6 and M18 post-OHCA (**Supplemental Figure 4**).

Cognitive disabilities

The M1-evaluation findings for 112 patients are reported in **Supplemental Table 6**: the MMSE was >25 for 86% and <20 for 7%. Most patients had normal EEG tracings but 38% had minor abnormalities. Although a majority of patients had no cognitive disabilities during follow-up, MMSE remained constant at ≤25 for 20% at M12 and M18 (**Table 3** and **Supplemental Fig. 4**). The M18 RBANS evaluations for 71 (76%) patients yielded a median global cognition score of 93 [79–103]. The distributions of values for the different RBANS score components and the global score are shown in **Figure 3**. The global score was <80 for 28% of the patients.

Behavioral disabilities

BADS score evaluation of behavioral disabilities was comparable for patients and relatives (no significant difference between patients and relatives scores at each evaluation visit) with significant improvement in BADS scores from M6 to M18 in both patients and relatives ($P<0.001$ for trend over time). Moreover, there were positive correlations at M6 ($r=0.66$, $p<0.01$), M12 ($r=0.52$, $p<0.01$) and M18 ($r=0.63$, $p<0.01$) between patients and relatives scores (**Table 3**).

Dependence to daily living activities

Only one patient had a Functional Independence Measure score <63 at M18 (vs. 0 for other times) and, thus, was deemed dependent for daily living activities (**Supplemental Table 5**).

Anxiety, depression and quality of life

The percentages of patients with anxiety and depression symptoms were stable throughout follow-up (P = NS for trend over time). HR-QOL was assessed at M6, M12 and M18, respectively for 98, 84 and 74 patients, but in 52 patients at the 3 time points: except for bodily pain, social functioning and mental health, these 52 patients reported decreased HR-QOL in all evaluated domains, compared to an age- and sex-matched French population [27] (**Figure 4**). Mental and physical aggregate components of the SF-36 score increased over time (**Table 3**, $p<0.001$ for trends over time).

Relatives' caretaking burdens

Less than half of the relatives could be evaluated with Zarit's scale during follow-up (**Table 3**), without baseline differences in patients whose relative caretaking burdens could be evaluated as compared to patients whose relative caretaking burdens could not be evaluated. At M18, relatives estimated their caretaking burdens to be moderate for 6% of them, light for

24% and absent or minor for 71%; none considered it heavy (**Table 3**). The percentages of relatives with light, moderate or absent burdens were similar at M6 and M12.

Factors associated with poor functional outcome

According to univariable analyses, low-flow time (OR 1.03 per minute increase, 95% CI 1.0–1.06), SOFA score at ICU admission (OR 1.23, 95% CI 1.07–1.42), duration of coma >3 days (OR 2.66, 95% CI 1.19–5.56), mechanical ventilation on day 3 (OR 15.17, 95% CI 1.96–117.4) and day 7 (OR 2.32, 95% CI 1.07–5.05) were associated with poor functional outcome (GOS-E≤6 at M18) (see **Supplemental Table 7**).

Discussion

In this prospective study, we found that, at M18 post-OHCA, 65% of the survivors who awakened during their ICU stays with a GCS≥12 had recovered fully or had only minor disabilities. Notably, the percentage of patients with good outcomes (i.e., those with a GOS-E>6) increased significantly from M3 to M18 post-OHCA ($p<0.01$). Of note, improvement in outcome was predominant and significant from M3 to M6, and less important thereafter. Moreover, although most patients had no major neurological disabilities, 20% had cognitive disabilities, 32% had anxiety symptoms and 25% had depression symptoms, and 28% had a global RBANS score <80, i.e., worse than for patients with moderate traumatic brain injury. Furthermore, their HR-QOL was impaired, compared to a sex- and age-matched French population. Also, risk factors traditionally associated with poor outcome (low-flow time, SOFA-score–assessed disease severity at ICU admission, duration of mechanical ventilation and ICU stay) were also associated with GOS-E≤6 at M18. Future larger studies to confirm our data or find specific risk factors may be encouraged.

Most studies that evaluated OHCA patients' outcomes defined good outcome as a cerebral performance category (CPC) of 1 or 2 [3]. However, patients with CPC 2, and even with CPC 1, may have long-term disabilities, e.g., memory or executive disorders [5,28]. Like Smith et al. [9], we chose to assess outcome with GOS-E, which is more detailed than the CPC, because of our specific study population (patients awakened post-OHCA with GCS≥12): the GOS-E is probably more accurate and precise to detect minor disabilities than CPC. Moreover, we investigated not only functional outcomes but also neurological and cognitive disabilities, anxiety, depression and HR-QOL, and relatives' caretaking burdens. Notably, our results indicated that recovery continued for up to 18 months post-OHCA. It had previously been found that functional outcomes could improve 1 year post-OHCA [6–8] but our study is the first to evaluate long-term outcomes beyond M12.

Moulaert et al. evaluated 141 OHCA survivors at 1-year and found that 15% had depression and anxiety, 28% had post-traumatic stress disorders, 13% had cognition disorders and 52% suffered from fatigue [8]. Importantly, the authors observed change over time, with attenuation of cognitive disabilities, post-traumatic stress disorders and HR-QOL, but not anxiety, depression and fatigue during the first year post-OHCA [8]. Our results are similar but with a higher percentage of patients with cognitive disabilities. The discrepancies between our findings and theirs might be explained by several factors: first, the same disability-evaluating scores were not used in the two studies; second, case-mix and inclusion criteria differed. We included patients who awakened (with GCS≥12) during the 14 days post-OHCA, whereas Moulaert et al. investigated patients who survived 2 weeks after OHCA, without providing any information about their consciousness levels at inclusion, but excluded 97 patients because they were included in the experimental group of a randomized–controlled trial. Another difference with Moulaert's study is the highest proportion of patients with anxiety and depression; 32 and 25% of anxiety and depression for our patients vs. 15% for Moulaert's

patients. However, the rates observed in our patients were not higher than those previously reported, a meta-analysis reporting rates of depression between 14 and 45%, and rates of anxiety between 13 and 61% after CA [29]. Lastly, our follow-up lasted until M18 (vs. M12 in Moulaert's study), and disabilities may continue to evolve from M12 to M18 [6–8].

In a randomized–controlled trial, those same authors found that a semi-structured nursing intervention, intended to detect cognitive and emotional problems early, provide appropriate information and emotional and practical support, promote self-management techniques, with referral to specialized services, if necessary, starting a median [range] of 24 [9–70] days after OHCA, improved survivors' outcomes [30]. The results demonstrated that, compared with standard care, use of that intervention was associated, at 1 year with, better HR-QOL and less anxiety and better emotional state. However, the intervention did not impact caregivers' outcomes [30]. Those observations may have a direct impact on OHCA survivors. Because our risk-scale model enabled us to identify, with good specificity, patients at risk of a poor outcome at M18 with three simple variables, these patients may be good candidates for specific and intensive rehabilitation program(s), or at least be identified as such and oriented accordingly for specialized follow-up. Indeed, because we observed improvement of patients' functional outcomes over time, it could be presumed that specific programs targeting patients at risk of poor functional outcomes might improve their prognoses. However, that hypothesis remains to be determined in future interventional studies.

Herein, survivors estimated that their HR-QOL had declined, with no clear improvement over time. Bohm et al. found the same results: they evaluated HR-QOL of Temperature-Targeted–Management trial survivors [31], and found that, despite general HR-QOL reported acceptable by many survivors, it was impaired for many others [32]. Our results agree with those findings, and reinforce them: unlike previous studies, we explored HR-QOL at different times, and found that HR-QOL remained stable throughout the study period. Whether or not

HR-QOL could improve in those patients beyond M18 remains to be determined. Using the SF-36 to assess 255 OHCA survivors after a median [Q1-Q3] 38 [12–78] months between OHCA and interview, Geri et al. found that their HR-QOL did not differ from that of an age- and sex-matched population. Although theirs was a retrospective study with inherent bias due to that design, we cannot exclude that OHCA survivors' HR-QOL might improve over time [33].

Our work has several limitations. First, we included patients who awoke in the first 2 weeks after CA, and we cannot exclude that including patients who awoke later would have led to same results. Second, only 74 patients were evaluated at the three pre-specified visits at M6, M12- and M18. Other patients consulted at only one or two of them, and reason for unavailability was not recorded. However, when taking into account only those 74 patients who were evaluated all three times, results were similar. Third, we followed patients until 18 months post-OHCA and showed that they improved over time, even after 1 year. However, whether or not they continued to improve beyond M18 is unknown. Thus, it would be interesting to pursue these patients' follow-up, to assess the evolution of their improvement. Fourth, although we excluded patients with known neurologic and psychiatric disease, we cannot exclude that some of them may have preexisting neurological or psychological impairment that could have altered the results. Fifth, we know from previous studies that ICU survivors' HR-QOL may be diminished, with cognitive function decline [20,34]. Pandharipande et al. found that 24% of survivors 1 year after ICU discharge had the same cognitive impairment as patients with mild Alzheimer's disease [34]. Moreover, Lijla et al. found, in a study comparing survivors from the TTM trial to ST-elevation myocardial infarction without cardiac arrest patients, that these latter had also cognitive impairments, suggesting that not only brain injury during CA may occur [35]. Therefore, without a control group, it is difficult to know whether or not our patients' disabilities were only attributable to OHCA or partly due to

the consequences of an ICU stay or underlying cardiac disease. However, although ICU stay may have a role in cognitive dysfunction, it seems likely that the disabilities observed after critical illness would be more related to the causative disease than to the ICU stay itself. Moreover, one strength of our study is the detailed and repeated long-term follow-up. Last, although no patient was hospitalized in a rehabilitation unit during follow-up, it is not known whether or not patients received ambulatory care by physiotherapists or other caregivers. Whether or not such interventions, if performed, would have an impact on our results is not known.

Interpretation

In summary, survivors awakening during the 14 days following OHCA have good long-term prognoses; however, some may experience neurological, cognitive, behavioral and psychological disabilities. Importantly, the prognosis may improve, and disabilities regress until M18 post-OHCA and perhaps beyond. Whether or not specific rehabilitation programs for these patients or those at risk of poor functional outcomes could improve those outcomes remains to be determined.

Acknowledgments

Authors contributions: A.P. and C.E.L. take full responsibility for the integrity of the work. A.P. and C.E.L designed the study and wrote the protocol. A.C., N.D., E.G., M.D., R.S. and C.E.L. included the patients in the intensive care units. A.P., V.N., H.R., P.A. and E.B. performed the follow-up of patients. D.H. and A.L. conducted the statistical analysis. A.P., D.H., A.L. and C.E.L. analyzed and interpreted the data. A.P. and C.E.L. wrote the manuscript. All authors critically reviewed and approved the final version of the manuscript.

The authors would like to thank Delphine Baumann, Aurélie Zindjirdjian, Gaëlle Kpalma and Karine Martin for their help organizing the study, and Janet Jacobson for her help during the preparation and correction of the manuscript.

Role of the funding source

The funding source was not involved in the analysis, interpretation and writing of the manuscript.

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Figure Legends

Fig. 1 Flow chart of the study with study visits and procedures at each time point. ICU, intensive care unit. EEG, electroencephalogram. GOS-E, Glsagow outcome scale-extended. PMR, physical medicine and rehabilitation. RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Fig.2 Kinetics of Glasgow outcome scale-extended in the 74 patients with complete follow-up, displayed as alluvial plot. GOS-E, Glasgow outcome scale-extended. Data are missing at 3 months for 16 patients (NA, not available).

Fig. 3 Cognition score in survivors of out-of-hospital cardiac arrest at month 18. The box plots show the components and the global scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The internal horizontal bar is the median, the internal + is mean; the upper and lower limits of the boxes are the quartile1 and quartile 3, respectively; and the bars are 1.5 times the interquartile range. The black circles are outliers. The pink line and pink band indicate the normal value and standard deviation.

Fig. 4 Health-related quality of life of survivors of out-of-hospital cardiac arrest. Comparison of the SF-36 scores of 52 cardiac arrest survivors (pink bars) vs. the normative values of an age- and sex-matched French general population (blue bars) at 6 (M6), 12 (M12) and 18 (M18) months The SF-36 score combines 36 items exploring 8 domains (physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional and mental health). Individual component scores range from 0 (poor) to 100 (excellent). The box plots report: the internal horizontal line is the median; the lower and upper box limits are the quartile1 and quartile 3, respectively; bars represent the 95%

confidence intervals. The black circles are outliers. P values are given for comparisons between survivors and normative values. *SF-36* 36-Item Short-Form Health Survey. There was a significant improvement over time (P<0.001).

Table 1 Characteristics before the event and at ICU admission of the 139 OHCA survivors and of the 74 who completed the 3 pre-specified visits

Characteristics	Overall population N =139	Patients who completed follow-up N = 74
General pre-OHCA		
Age (years)	55 (46–65)	56 (47–66)
Male sex	107 (77)	58 (78)
Body mass index (kg/m^2)	25.7 (23.6–27.8)	25.4 (23.3–27.1)
Residence characteristics		
Live at home	136/137 (99)	74 (100)
Live alone	25/136 (18)	10 (14)
Needs help for daily living	3 (2)	1 (1)
McCabe & Jackson score >2	8 (6)	2 (3)
Comorbidities before cardiac arrest		
Myocardial infarction	22 (16)	9 (12)
Heart failure	14 (10)	8 (11)
Diabetes mellitus	9 (6)	1 (1)
Current smokers	84 (60)	42 (57)
Chronic obstructive pulmonary disease	6 (4)	2 (3)
Cirrhosis	0	0
Cancer	8 (6)	3 (4)
OHCA characteristics		
Where it occurred		
Home	41/134 (31)	18/71 (25)
Public place	56/134 (42)	30/71 (42)
Other	37/134 (28)	23/71 (32)
Witnessed OHCA	131/138 (95)	69/73 (95)
Witnessed basic life support	111/130 (85)	59/68 (87)
No-flow time, min	2 (0–5)	1 (0–5)
Low-flow time, min	15 (10–20)	15 (10–22)
Shockable rhythm	113/138 (82)	64/73 (88)
Attempted defibrillation	125 (90)	68 (92)

At ICU admission		
SAPS II	58 (49–67)	59 (49–68)
SOFA score	10 (8–12)	10 (8–12)
Glasgow coma score	3 (3–3)	3 (3–3)
Four score	4 (0–5)	4 (0–5)
Shock	36 (26)	21 (28)
During the first 24 h post-ICU admission		
Worst clinical parameter		
Temperature	32.8 (32.3–34.1)	32.9 (32.3–34)
Mean arterial pressure	62 (58–68)	63 (58–66)
Heart rate	56 (45–69)	54 (45–67)
Worst biological parameters		
pH	7.28 (7.19–7.33)	7.28 (7.21–7.34)
Serum lactate, mmol/L	2.9 (1.7–5.1)	2.9 (1.6–4.8)
PaO_2	88 (68–120)	90 (69–120)
Blood S100B protein, µg/L [a]	0.33 (0.2–0.72)	0.33 (0.19–0.58)
Procedures		
Hypothermia	103 (74)	56 (76)
Time with temperature <34°C during the first 24 h, h [b]	14 (7–24)	13 (7–24)
Coronary angiogram	122 (88)	67 (91)
Angioplasty	61/122 (50)	34/67 (51)
Time from OHCA to study inclusion, days	6 (3–9)	6 (4–10)
FOUR score at inclusion	16 (16–16)	16 (16–16)
Mini-Mental Status at inclusion [c]	14 (8–17)	14 (10–17)
Glasgow coma score at inclusion	15 (14–15)	15 (14–15)

Results are expressed as n (%) or median (Q1-Q3). When data were missing, the number of assessable patients is reported

OHCA out-of-hospital cardiac arrest, *CA* cardiac arrest, *ICU* intensive care unit, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ-Failure Assessment

[a] data available for 102/139 of the whole population and 54/74 of those who completed the 3 follow-up visits

[b] data available for 99/139 of the whole population and 55/74 of those who completed the 3 follow-up visits

[c] data available for 137/139 of the whole population and 74/74 of those who completed the 3 follow-up visits

Table 2 Events occurring during the ICU stays of the 139 OHCA patients and of the 74 who completed the 3 pre-specified visits

Parameter	Overall population	Patients who completed follow-up
	N =139	N = 74
Days from admission to opening eyes	2 (1–3)	2 (1–3)
Seizures	4 (3)	3 (4)
Status myoclonus	7 (5)	3 (4)
Need for circulatory support	13 (9)	7 (10)
Need for renal replacement therapy	27 (19)	16/70 (22)
Shock		
Cardiogenic	12 (9)	5 (7)
Hypovolemic	4 (3)	3 (4)
Septic	5 (4)	3 (4)
Cardiac arrest recurrence	4 (3)	2 (3)
Ventricular fibrillation/ventricular tachycardia	6 (4)	3 (4)
Atrial fibrillation	1 (1)	1 (1)
Electroencephalogram score		
2	1/84 (1)	1/42 (2)
3	1/84 (1)	1/42 (2)
4	3/84 (4)	0
5	8/84 (10)	5/42 (12)
6	22/84 (26)	10/42 (24)
7	6/84 (7)	4/42 (10)
8	43/84 (51)	21/42 (50)
MV on day 3	115 (83)	63 (85)
MV on day 7	44 (32)	26 (35)
Duration of MV	4 (2–8)	4 (2–8)
Duration of ICU stay, days	6 (4–11)	15 (14–15)
Blood S100B protein, µg/L		
Day 1 (ICU admission)	0.33 (0.2–0.72)	0.33 (0.19–0.58)
	N = 99	N = 54
Day 2	0.13 (0.07–0.22)	0.12 (0.07–0.22)
	N = 96	N = 53
Day 3	0.1 (0.06–0.15)	0.1 (0.07–0.14)
	N = 85	N = 46
Glasgow coma score at ICU discharge	15 (14–15)	15 (14–15)

Results are expressed as median (Q1-Q3) or *n* (%), as appropriate. When data were missing, the denominator is the number of assessable patients

ICU intensive care unit, *OHCA* out-of-hospital cardiac arrest, *MV* mechanical ventilation

Table 3 Disabilities at month (M) 6, 12 and 18 in the 74 patients with complete follow-up

Score	At M6	At M12	At M18
Functional disabilities			
Modified Rankin score [a]			
1	56 (74)	58 (76)	58/77 (75)
2	10 (13)	10 (13)	11/77 (14)
3	8 (11)	4 (5)	2/77 (3)
4	0	2 (3)	2/77 (3)
5	0	0	0
6	2 (3)	2 (3)	4/77 (5)
Neurological disabilities			
NIHSS score			
<5	64/70 (91)	63/66 (95)	60/63 (95)
5–12	6/70 (9)	3/66 (5)	3/63 (5)
>12	0	0	0
Cognitive disabilities			
MMSE			
<20	1/70 (1)	2/66 (3)	0
20–25	10/70 (14)	11/66 (17)	13/62 (21)
>25	59/70 (84)	53/66 (80)	49/62 (79)
FAB			
<15	13/70 (19)	10/66 (15)	8/62 (13)
Behavioral disabilities			
BADS patient	*n*=68	*n*=68	*n*=58
	13 (4–24)	17 (8–25)	19 (7–25)
BADS relative	*n*=34	*n*=35	*n*=34
	13 (4–24)	14 (7–27)	17 (9–33)
Dependence to daily living			
Functional Independence Measure [b] <63	0	0	0
Anxiety and depression [c]			
Anxiety ≥8	26/70 (37)	23/68 (34)	16/60 (27)
Depression ≥8	13/70 (19)	17/68 (25)	13/60 (22)
Health-related quality of life [d]			

SF-36 mental score	64 (44–79)	65 (48–81)	66 (51–83)
SF-36 physical score	61 (42–78)	69 (46–82)	67 (48–82)
Relatives' caretaking burden			
Zarit's scale [e]			
<21	27/34 (79)	21/35 (74)	24/34 (71)
21–40	5/34 (15)	7/35 (20)	8/34 (24)
40–60	2/34 (6)	2/35 (6)	2/34 (6)
>60	0	0	0

Results are expressed as median (Q1-Q3) or *n* (%). When data were missing, the number of assessable patients is reported

[a] Values for 76 patients at M6 and M12 (includes the 2 patients who died before M6) and 77 patients at M18 (includes the 4 patients who died before M18. One value is missing).

NIHSS National Institute of Health Stroke Score: score to quantify impairment caused by a stroke. Minimum score is 0, maximum 42. A score above 5 indicates moderate impairment.

MMSE Mini-Mental State Examination: 30-point questionnaire to measure cognitive impairment. A score above 25 indicates normal cognition, a score between 20 and 25 indicates mild cognitive impairment and a score <20 indicates moderate cognitive impairment.

FAB: Frontal Assessment Battery: battery of 6 subtests to assess executive function. A value <15 indicates executive dysfunction.

BADS Behavioural Assessment of Dysexecutive Syndrome. Score to evaluate behavioral disabilities by comparing scores from patients and scores from relatives. Differences between patients and relatives scores were not different at the 3 time points.

[b] Functional independence measure: 18-item measurement tool that explores individual's physical, psychological and social function. A score <63 means possibility of home discharge [18].

[c] Measured by the Hospital And Depression (HAD) scale[21] : a score ≥8 for each category indicates symptoms of anxiety or depression.

[d] Health-related quality of life evaluated with the SF-36 score, which combines 36 items exploring 8 domains (physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional and mental health). The aggregate physical and mental component summary measures range from 0 (poor) to 100 (excellent).

[e] Zarit's scale: evaluate relatives' caretaking burden. A score <21 indicates absent or minor burden, a score between 21 and 40 indicates light burden, a score between 40 and 60 indicates

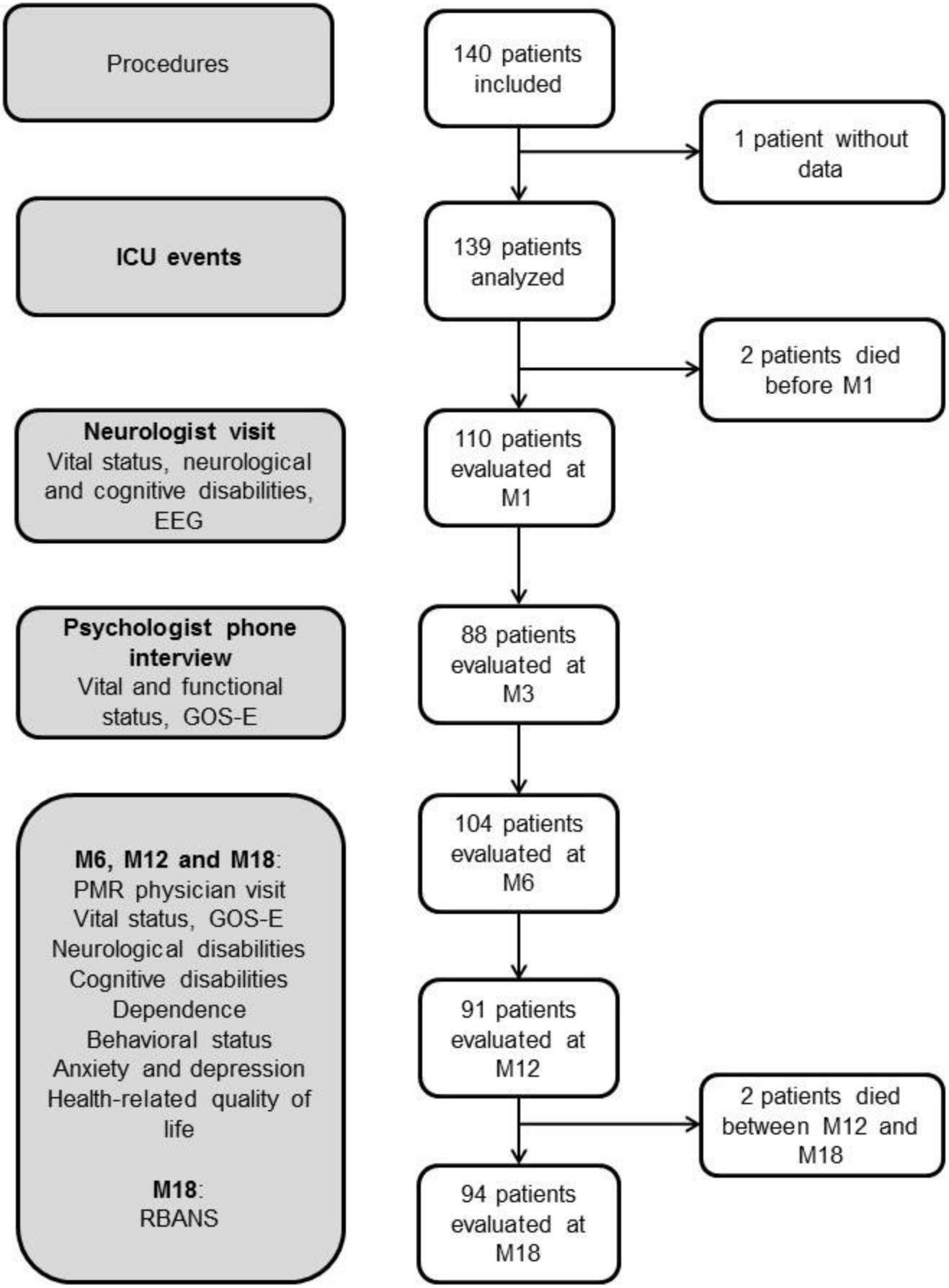
moderate burden and a score >60 indicates heavy burden.

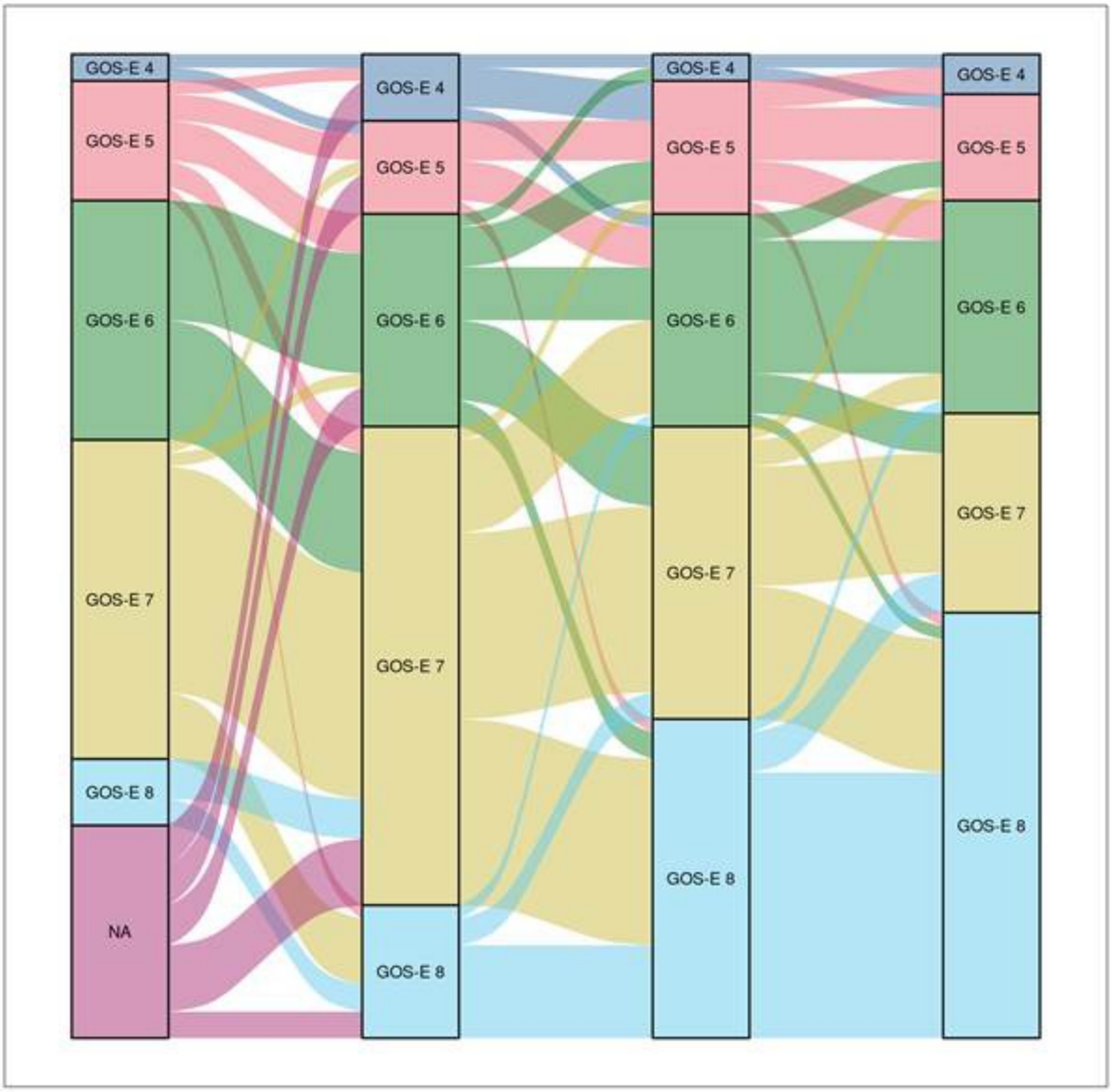
APPENDIX

Study sites and investigators

Members of the Hanox Study Group according to hospital: **Hôpitaux Universitaires Pitié-Salpêtrière–Charles-Foix, APHP, Paris:** Médecine Intensive Réanimation: Guillaume Hékimian, Nicolas Bréchot, Mathieu Schmidt, Alain Combes, Charles-Edouard Luyt; Pneumologie et Médecine Intensive Réanimation: Alexandre Demoule, Martin Dres, Julien Mayaux; Médecine Physique et Réadapatation: Anne Peskine, Hélène Robert, Pascale Pradat-Diehl, Eléonore Bayen; Neurophysiologie: Vincent Navarro; Neuroradiologie: Damien Galanaud. **Hôpital Cochin, APHP, Paris:** Médecine Intensive Réanimation: Nathalie Marin, Julien Charpentier, Alain Cariou, Jean-Paul Mira; Radiologie: Olivier Vignaud. **Hôpital Européen Georges-Pompidou, APHP, Paris:** Médecine Intensive Réanimation: Emmanuel Guérot, Jean-Luc Diehl, Jean-Yves Fagon. **Hôpital Lariboisière, APHP, Paris:** Médecine Intensive Réanimation: Nicolas Deye, Bruno Mégarbane; Neuroradiologie: Jean-Pierre Guichard; Physiologie Clinique: Nathalie Kubis; Médecine Physique et Réadapation: Alain Yelnik. **Hôpital Bichat–Claude-Bernard, APHP, Paris:** Médecine Intensive Réanimation: Romain Sonneville, Lila Bouadma, Jean-François Timsit; Radiologie: Isabelle Klein. **Hôpital Raymond-Poincaré, APHP, Garches:** Médecine Intensive Réanimation: Tarek Sharshar; Médecine Physique et Réadaptation: Philippe Azouvi; Radiologie: Robert Carlier. **Hôpital Sainte-Anne, Paris:** Médecine Physique et Réadaptation: Florence Colle.

Current address for Dr Sharshar is Service de Réanimation Neurochirurgicale, Hôpital Sainte-Anne, Paris


Procedures
ICU events
Neurologist visit
Vital status, neurological and cognitive disabilities, EEG
Psychologist phone interview
Vital and functional status, GOS-E
M6, M12 and M18:
PMR physician visit
Vital status, GOS-E
Neurological disabilities
Cognitive disabilities
Dependence
Behavioral status
Anxiety and depression
Health-related quality of life
M18:
RBANS
140 patients included
1 patient without data
139 patients analyzed
2 patients died before M1
110 patients evaluated at M1
88 patients evaluated at M3
104 patients evaluated at M6
91 patients evaluated at M12
2 patients died between M12 and M18
94 patients evaluated at M18

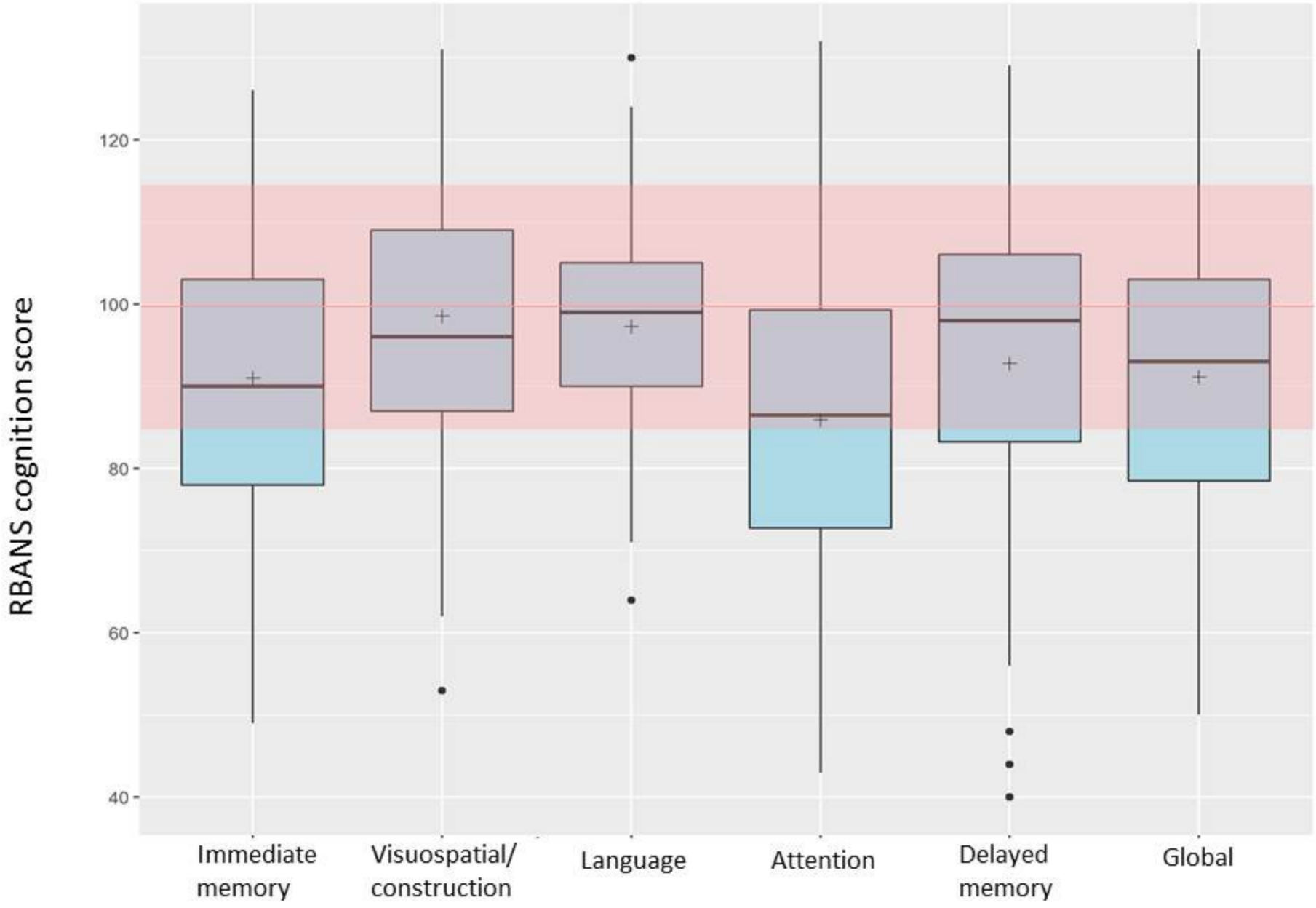


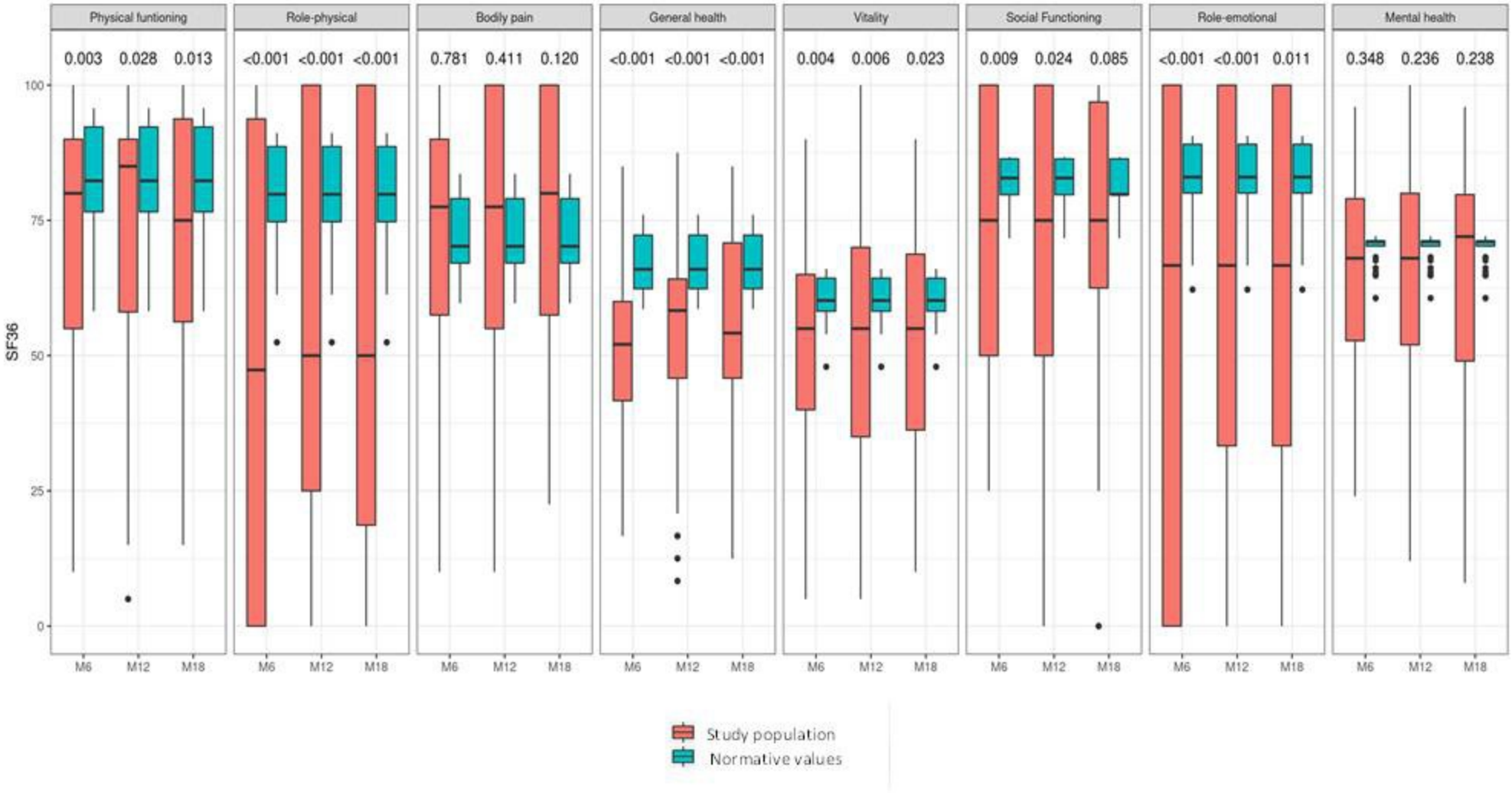
3 months
N = 58

6 months
N = 74

12 months
N = 74

18 months
N = 74


RBANS cognition score
120
100
80
60
40
Immediate memory
Visuospatial/ construction
Language
Attention
Delayed memory
Global


Physical funtioning
Role-physical
Bodily pain
General health
Vitality
Social Functioning
Role-emotional
Mental health
0.003 0.028 0.013
<0.001 <0.001 <0.001
0.781 0.411 0.120
<0.001 <0.001 <0.001
0.004 0.006 0.023
0.009 0.024 0.085
<0.001 <0.001 0.011
0.348 0.236 0.238
SF36
100
75
50
25
0
M6
M12
M18
Study population
Normative values