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ORIGINAL REPORT

RELEVANCE OF COGNITION TO HEALTH-RELATED QUALITY OF LIFE IN GOOD-OUTCOME SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST

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Objective: **For survivors of out-of-hospital cardiac arrest (OHCA) with good outcomes, it is not known whether and how health-related quality of life is affected by the cognitive impairments frequently observed in these patients. This study explores how neuropsychological tests of memory, executive and psychomotor functioning relate to the physical and mental aspects of health-related quality of life in functionally independent and community dwelling OHCA survivors discharged early from hospital.**

Methods: **The study included 42 adult survivors (mean age 62 years, 38 males). Health-related quality of life was measured approximately 3 months post-OHCA with the Medical Outcome Study Short Form 36 (SF-36). Cognition was measured with established neuropsychological tests. Regression analyses were used to examine associations between neuropsychological domains and physical and mental health-related quality of life, respectively, when controlling for age, education and length of coma.**

Results: **The physical, but not the mental, component of the SF-36 was significantly worse than Norwegian population data. Neuropsychological tests showed frequent impairments most often in the memory domain. Worse psychomotor functioning was associated with worse physical health-related quality of life, whereas worse memory performance was associated with worse mental health-related quality of life.**

Conclusion: **The cognitive impairments frequently reported in OHCA survivors with good outcomes may compromise health-related quality of life. Cognitive functioning should be addressed even in survivors with rapid recovery.**

Key words: cardiac arrest; cognitive impairments; health-related quality of life; SF-36; neuropsychology.

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INTRODUCTION

Most survivors of out-of-hospital cardiac arrest (OHCA) have a good outcome, experience no overt neurological impairments, remain functionally independent, and report a health-related quality of life (HRQL) equal to age-matched controls who have not experienced an OHCA (1–4). Cognitive outcomes after successful resuscitation show a rather frequent occurrence of residual cognitive problems (2, 5, 6), typically described as mild to moderate impairments in memory, executive and psychomotor functioning (7). It is not known whether or how cognitive impairments relate to HRQL in OHCA survivors with good outcomes (3, 8). Some authors have concluded that the residual cognitive impairments do not affect HRQL or are too subtle to be functionally important (2, 9). Others describe cognitive impairments as a major challenge in research on HRQL outcomes after an OHCA, and argue that the importance of cognition to HRQL should be further explored with neuropsychological methodology (3, 8, 10, 11).

To our knowledge, Lim et al. (12) conducted the only previous study that directly examined the effect of cognitive performance using traditional neuropsychological tests on HRQL after an OHCA. They found that the overall severity of cognitive performance, particularly memory impairments measured 3 months after an OHCA, were strongly associated with significantly poorer results of HRQL after 3 months and were equally predictive of HRQL 12 months after resuscitation.

The objective of the present study was to further explore whether and how performance on widely used, empirically well-validated and norm-based neuropsychological measures relate to HRQL in a sample of OHCA survivors with a good outcome. We defined a good outcome as living independently after an early hospital discharge and having the ability to perform a neuropsychological assessment 3 months post-arrest. OHCA survivors are in a subgroup that does not systematically receive professional attention for possible residual cognitive impairments after hospital discharge.

To address these research questions, we examined whether neuropsychological tests of memory, executive and psychomo-

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tor functions administered 3 months after an OHCA were associated with HRQL measured by the SF-36. When examining the association between neuropsychological test performance and HRQL, we considered it relevant to control for age and education, as is recommended in the SF-36 research literature for demographically mixed samples (13). We also controlled for time to awakening after resuscitation, which has shown a strong influence of functional outcomes in general and in cognitive tests performance specifically (6, 7, 11, 12, 14). In accordance with the results of Lim et al. (12), we expected that worse performance on neuropsychological tests, particularly in the memory domain, would result in poorer HRQL.

METHODS

Subjects

The study was approved by The Regional Committee for Medical Research Ethics in North Norway (institutional protocol number 2009/1395). The data collection was prospective and took place at the University Hospital of North Norway. We aimed to include all survivors of sudden, non-traumatic, normothermic OHCA of cardiac aetiology, between 18 and 85 years, discharged alive from the cardiac ward with good functional outcomes over a 3-year period (2010–2013). We identified survivors as having good functional outcome if they were living independently and receiving no organized care after discharge from the hospital and with ability to perform a valid neuropsychological assessment and the self-report questionnaire SF-36 3 months after resuscitation. Furthermore, hospital discharge had to be early after resuscitation. Specifically, the participants had to be living at home after hospital discharge for the past 4 weeks before follow-up assessment. This was important because the SF-36 questions use the past 4 weeks as a reference point. With this definition of a good outcome, we aimed to target the survivors who are not offered any follow-up assessment or rehabilitation for possible cognitive impairments in standard care. The cohort from which the present sample of 42 good-outcome survivors is drawn has been described in detail previously (14). An additional 3 good outcome survivors were added later, as described below. To summarize, 200 OHCA victims were treated at the cardiac ward in the study period. Patients who died before or during hospital admission were not registered. A total of 132 of these OHCAs were of cardiac cause with survival to discharge. After exclusion criteria were applied ($n=46$), loss to death before 3 months ($n=4$), loss to follow-up ($n=19$), and refusal to participate ($n=15$), 45 survivors were eligible for the follow-up assessment. A further 6 survivors were excluded; 4 due to missing SF-36 surveys and 2 because they were not independent in living at follow-up. A previous article describes the neuropsychological outcomes of 45 survivors from this cohort (14). In the present study, 39 of the participants overlap with the sample described previously. Three of the survivors included in the present study were examined shortly after the analyses for the previous publication was completed.

Exclusion criteria were designed to control for any condition that would increase the likelihood of cognitive dysfunction prior to OHCA or that would interfere with the validity of test recordings. The exclusion criteria were: previous cardiac arrest, heart surgery within the previous year, severe anoxic brain injury due to cardiac arrest with inability to perform the follow-up assessment or non-independence in living, prior brain trauma, neurological disease, prior stroke, severe somatic disease, ongoing depression or alcohol/substance abuse, psychiatric disorder, hearing or sight impairments, non-fluency in the Norwegian language, learning disability or dementia.

Ongoing depression, which may negatively influence performance on neuropsychological measures and the SF-36, was evaluated in all participants with the Hospital Anxiety and Depression Scale (8, 15, 16). None of the survivors included in the present article scored above the cut-off for depression (17).

Medical data were obtained from patients' medical records at the hospital. Information regarding participants' living situation and work status was obtained from patient interviews.

Functional outcome measures

Health-related quality of life. The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (18) consists of 2 summary scales, a physical component scale and a mental component scale, that are divided into 8 subscales: physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), mental health (MH), emotional role (RE), social function (SF) and vitality (VT). The questionnaire asks patients about their perception of how their health status has interfered with their psychological, social and physical functioning for the previous 4 weeks. The SF-36 Norwegian version 1.2 was used (13). The participants' data were compared with age- and gender-corrected normative data from the general Norwegian population (13). The online calculator for norm-based data scoring (http://www.sf36.org/nbscalc/index.shtlml) was applied for each survey, and the results provided in normalized T-scores. When standardizing the scores according to the T-score distribution the means are 50 and the standard deviations are 10 across all summary scales and subscales on the SF-36 in the comparator group (1). Thus, a direct comparison between the participants' T-scores and the age- and gender-corrected normative data in the general Norwegian population can be viewed in a single graph. Fig. 1 shows the standardized SF-36 results from the 42 participants.

Neuropsychological measures. The tests used are shown in Table II. Neuropsychological tests results were arranged in 3 domains: memory, executive and psychomotor functioning. The priority of domains was based on knowledge of which cognitive functions are most frequently observed as impaired in OHCA survivors with good outcomes and in accordance with the recommendation for neuropsychological test selection in the consensus statement for resuscitation science outcome studies by the American Heart Association (6, 7, 19, 20). The tests were drawn from a larger battery (14). All tests are applied widely in clinical practice and research on cognitive functioning for various groups. The tests have established construct validity and published normative data for comparison with sex, age and sometimes education matched populations (21–23). All tests are standardized in Norwegian. A composite Z-score was computed for each cognitive domain.

Statistical analysis

All analyses were performed using SPSS version 22 (IBM SPSS, USA). Descriptive statistics were used to present the demographic, medical and resuscitation characteristics of the study population. In 2 patients, the Grooved Pegboard Test was not conducted due to reduced sensory perception in their fingers caused by a peripheral injury prior to their OHCA. Trail Making Test scores were missing for 1 patient, Rey Complex Figure Test scores for 4 patients, California Verbal Learning Test-2 scores for 1 patient, and the Stroop Color-Word test scores for 5 patients. The missing data in the neuropsychological tests were replaced by a series mean, which is the group mean of the specific variable in the sample.

One participant had 2 missing answers and 2 participants had one missing answer on the SF-36. The scoring program replaced the missing data points with the individual's mean value on the specific subscale to which the missing value belonged. Due to a procedural error, 2 patients had only the main summary scores on the SF-36. The subscale scores were replaced with the sample's means.

To test whether the participants' SF-36 standardized T-scores were significantly different from the normative population's standardized T-scores, we used 1-sample t-tests that were Bonferroni corrected to adjust for multiple comparisons.

Group comparisons were performed by 1-way analysis of variance (ANOVA).

A correlation analysis was used to examine the relationship between the SF-36's main components and the possible predictor variables. Variables were not significantly deviant from the normal distribution, as shown by skewedness values, Kolmogorov-Smirnov tests and a visual examination of the box-plots of the variables.

The influence of the predefined predictors was assessed with separate multiple regression analyses for the physical and the mental components of the SF-36, respectively (both with backward selection). The same predictors were used for both analyses: age and education (in years), length of coma (in h) and the 3 neuropsychological domains (psychomotor, executive and memory functioning presented in Z scores). All variables were continuous.

The models were examined for outliers, residuals independence, normality and multicollinearity. The assumptions for linear modelling were met. No outliers above 2 standard deviations (SD) were detected in the regression models. Variance inflation factors were below 1.16.

A p-value ≤ 0.05 was considered statistically significant for the regression analyses and for the correlational analysis.

Table I. *Overview of sample characteristics (*n = *42)*

	n (%)	Mean (SD)	Median (Min–Max)
Demographics			
Male	38 (90.5)		
Age at arrest		62.4 (11)	62 (43–83)
Years of education		11.5 (4.1)	11.5 (5–22)
Marital status: married	39 (93)		
Days since arrest		105 (7.3)	104.5 (80–131)
Days since discharge from the hospital		85 (6.9)	84.5 (67–112)
Employed before arrest	21 (50)		
Retired before arrest	21 (50)		
Employed 3 months after arrest	3 (7)		
Cardiac arrest and resuscitation			
Witnessed arrest	41 (97.5)		
Received bystander CPR	42 (100)		
Initial cardiac rhythm			
Ventricular fibrillation	40 (95)		
Atrial fibrillation	1 (2.5)		
Asystole	1 (2.5)		
Minutes from collapse to ROSC		16	15 (2–42)
Coma duration (h)		31.6 (42.7)	19 (0.2–172)
PCI			
Yes	34 (81)		
No	8 (19)		
CABG			
Yes	1 (2.5)		
No	41 (97.5)		
ICD			
Yes	29 (69)		
No	13 (31)		
Therapeutic hypothermia			
Yes	18 (43)		
No	24 (57)		
Previously diagnosed cardiac condition			
Myocardial infarction	8 (19)		
Ischaemia	2 (5)		
Hypertension	9 (21)		
Diabetes	5 (12)		

CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; ICD: implantable cardioverter defibrillator.

RESULTS

Sample characteristics

Forty-two adult survivors of a first-time, normothermic OHCA of cardiac cause with good outcomes were included in the present study. The demographic and medical characteristics of the sample are shown in Table I. It is worth mentioning that the survivors in general had resuscitation characteristics associated with preferable outcomes in terms of survival and morbidity (24). In addition, all patients received bystander resuscitation. Bystander resuscitation is associated with better HRQL scores (25).

Health-related quality of life and work status

Fig. 1 displays the results from the SF-36. On the SF-36, 80% of the sample reported a mental HRQL and 60% reported a physical HRQL within the average or better than the average of the comparison population. The overall physical HRQL component was significantly below the normative mean. The subscales with impaired scores were the *general health* subscale and the *physical role functioning* subscale. In addition, the *emotional role function* subscale was significantly impaired. Lower scores on the *general health* subscale indicate that a significant number of survivors answered that their perceived health was poor and believed it was likely to worsen. Both role functioning subscales ask whether emotional problems and physical health have interfered with performing work and daily activities as usual. Thus, the impaired role functioning subscales may, in part, directly mirror the low rate of return to work in the sample, where half of the survivors were employed full-time before their OHCA, but only 7% had returned to work at 3 months.

Neuropsychological tests

Table II shows the neuropsychological test results of the sample. The percentage of scores that fall below 1 and 1.5 SD are

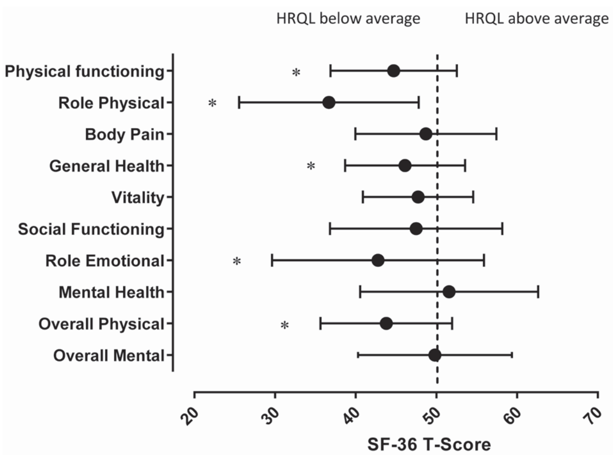

Fig. 1. *indicate significantly different from the normative mean ($p < 0.01$), Bonferroni corrected. Short Form 36 (SF-36) results from the 42 survivors presented in standardized T-scores in comparison with general age- and gender-corrected Norwegian population normative data (mean = 50, standard deviation = 10 for all summary scales and subscales). Circles represent means and bars represent standard deviations.

Table II. *Description of neuropsychological test results*

	Mean Z (SD)	Min–Max	% Below –1 SD	% Below –1.5 SD
Psychomotor				
Grooved Pegboard dominant hand	–0.34 (0.99)	–2.8–1.8	19	7
Grooved pegboard non-dominant hand	–0.58 (0.85)	–3–1.2	21	10
DK Trail Making Test 5	0.51 (0.54)	–1–1.7	5	0
Memory				
CVLT recall short delay	–0.30 (1.04)	–3.0–1.5	24	10
CVLT recall long delay	–0.42 (1.14)	–3.5–1.5	33	33
Rey CF recall short delay	0.18 (1.47)	–3–2.9	26	17
Rey CF recall long delay	0.25 (1.5)	–3–3	21	17
Executive				
DK Trail Making Test 2	0.01 (0.85)	–3–1.33	10	5
DK Trail Making Test 4	0.19 (0.86)	–3–1.33	8	8
DK Color–Word 3 (Stroop task)	–0.15 (1.08)	–3.0–1.33	10	10

All scores are presented as Z-scores (mean = 0, SD = 1). Higher scores indicate better performance. SD: standard deviation; DK: Delis–Kaplan Executive Function System; CVLT: California Verbal Learning Test–2: Rey CF: Rey Complex Figure Test.

displayed in the table for descriptive purposes. Scores below 1 SD from the mean may indicate impairment in individuals with high education levels or above-average premorbid functioning. Scores below 1.5 SD from the mean are more generally accepted as clinically significant (26). The test results varied from above average to more severely impaired across tests and patients. As expected, most frequently impaired tests were found in the memory domain (6, 7, 12, 19).

Univariate analyses of the SF-36 with the demographic and medical variables

High homogeneity in sample characteristics with regard to marital status, sex, initial cardiac arrest and resuscitation characteristics made these variables uninteresting for sub-group analyses. A 1-way ANOVA displayed no significant differences in the SF-36's mental or physical components on the following dichotomous variables: therapeutic hypothermia, ICD, pre-existing cardiac condition, percutaneous coronary intervention (PCI), or work status; all Fs < 3.7, all p-values < 0.10.

Correlations between the predictor variables and the SF-36's mental and physical components are shown in Table III.

Predictors of health-related quality of life

The memory composite score alone was most strongly associated with the mental component score on the SF-36. The physical component on the SF-36 was most strongly associated with the psychomotor composite score alone. Although the associations were significant, the percentage of explained variation in both SF-36 components was rather low. Age, education, coma length and the executive function composite score did not contribute significantly in the model. Table IV shows the complete statistics of the regression models.

DISCUSSION

In the existing OHCA literature, it is argued that if cognitive functioning is a determinant of HRQL, cognitive impairments should be systematically addressed after an OHCA (8).

The present results support the claim that cognitive functioning is important for HRQL after an OHCA even in good outcome survivors (3, 8, 12). We found a significant relationship between neuropsychological test performance and the SF-36 3 months after successful resuscitation. Worse performances in specific neuropsychological domains were significantly related to worse reports of physical and mental HRQL in separate ways. The memory domain was significantly associated with mental HRQL. As memory function worsens, so does mental HRQL. The memory domain reflects the ability to encode, store and retrieve both visual and verbal declarative knowledge. The ability to adequately remember and retrieve information is essential for social interaction and work-related activities, among others (8, 11, 27). Worse physical HRQL could be predicted from poorer performance on tests of fine-motor functioning and psychomotor speed, functions that are essential in the performance of several instrumental daily activities (8).

Our study is one of few to explore whether the cognitive impairments frequently found in survivors with good outcomes, when measured with well-validated neuropsychological tests, are associated with impairments in HRQL. Most previous studies that explore the effect of cognition on HRQL after an OHCA have used self-reports of cognitive complaints or cognitive screening tools to assess cognition, and conflicting conclusions are reported (2, 8–11, 28, 29). We managed to find only 1 prior study with traditional neuropsychological methodology that directly assesses the effect of neuropsychological test performance on HRQL after an OHCA (12) and none that applied the widely used HRQL questionnaire SF-36 for this

Table III. *Pearson correlations between SF-36 and predictors*

	SF-36 Mental	Age	Education	Coma duration	Psychomotor	Memory	Executive
SF-36 Physical	0.47**	0.10	0.05	0.08	0.38**	0.18	0.01
SF-36 Mental		0.22	–0.03	0.14	0.21	0.32**	0.03
Age at arrest			–0.40**	–0.12	0.12	0.21	0.03
Education				–0.21	–0.12	0.13	0.22
Coma duration					–0.20	–0.37*	–0.33*
Psychomotor						0.31*	0.14
Memory							0.36*

*p<0.05, **p<0.01. Education is shown in years, and coma duration is measured in h.

Table IV. *Regression models*

	B	t	β	*p*
Regression 1: Overall Physical component of SF–36. (R^2=0.15, F=(1, 41)=6.92, *p*=0.012), *n*=42				
Included variable				
Psychomotor composite score	5.03	2.63	0.38	0.012
Excluded variables	B	t	Partial correlation	*p*
Years of education	0.10	0.64	0.10	0.53
Age at arrest	0.06	0.38	0.06	0.70
Memory composite score	0.07	0.43	0.07	0.67
Executive composite score	–0.48	–0.32	–0.05	0.75
Coma duration	0.16	1.06	0.17	0.30
Regression 2: Overall Mental component of SF–36. (R^2=0.18, F=(2, 41)=4.22, *p*=0.02), *n*=42.				
Included variables				
Memory composite score	3.8	2.74	0.43	0.009
Coma duration	–0.06	–1.91	–0.30	0.063
Excluded variables	B	t	Partial correlation	*p*
Years of education	–0.02	–0.15	–0.02	0.88
Age at arrest	0.17	1.16	0.18	0.25
Executive composite score	–0.32	–0.2	–0.03	0.82
Psychomotor composite score	0.16	1.04	0.17	0.84

purpose. Lim et al. (12) found a strong relationship between neuropsychological performance, the Sickness Impact Profile and the Frenchay Activities Index. Different from Lim et al. (12), we did not exclude survivors based on length of coma. Although coma duration is the most informative single predictor of cognitive and functional outcomes in group studies, it cannot foresee the long-term outcome of possible mild to moderate cognitive disability on a case-by-case basis in clinical practice (8, 12, 27).

Most survivors in our sample had good reports of HRQL and no cognitive impairments; however, there were frequent exceptions. The neuropsychological tests also revealed individual survivors with more profound cognitive impairments despite our definition of a good outcome. Thus, this study exemplifies how cognitive impairments may go unrecognized in clinical practice if not actively investigated (6, 8). In clinical practice, it remains a challenge to systematically target individual OHCA survivors who are able to live independently but still experience cognitive disability, which puts them at risk for diminished HRQL long after their hospital discharge.

Our results show that the neuropsychological tests of verbal and visual declarative memory and psychomotor functioning can be useful in a core neuropsychological battery for the assessment of cognitive functioning in OHCA survivors with good outcomes (20). These cognitive tests have shown an association with relevant disease factors, such as coma length, in previous neuropsychological studies of OHCA survivors (6, 14). We now show that some of the same tests have relevance to HRQL even when important control variables, such as age, education level and coma length, are taken into account.

We did not find a consensus or research-based recommendations for cognitive screening instruments in the OHCA literature. Cognitive screening instruments have been validated against neuropsychological tests for good-outcome stroke survivors with promising results for a more efficient identification of survivors with cognitive disability in need of a comprehensive neuropsychological assessment (30, 31).

Three months post-arrest may seem early to assess HRQL (3, 20). Some researchers have suggested that HRQL may improve throughout the first year after an OHCA and that in general, it takes time to recover (32). When including neuropsychological measures of cognition, Lim et al. (12) found that cognitive impairments present at 3 months were equally debilitating after 1 year, indicating little spontaneous recovery of cognitive functioning beyond 3 months. Thus, an early assessment of cognitive functioning after an OHCA may serve as an important surrogate marker for the individual's prospective HRQL and as an important platform for allocating the most appropriate rehabilitation interventions (8, 26, 33).

There are several limitations in the present study that should be mentioned. The sample size was small, which limited the number of predictors that could be examined. Far from all possible predictors that may influence the multidimensional concept of HRQL were taken into account (26, 33, 34). Memory and psychomotor functioning are obviously only some of the cognitive variables that may interfere with HRQL after an OHCA, and the selected neuropsychological tests in this study explained a limited proportion of the variance in the SF-36. Because nearly all comorbidity was excluded, it is tempting to causally relate the impairments in HRQL to cognitive impairments with a common underlying cause for both. However, the study is observational, and a causal interference cannot be drawn from our results. Still, the homogeneity of the sample makes it more probable that the OHCA and related factors were the main cause of the cognitive impairments measured. The present design does not inform about how comorbid disorders and premorbid disability influence cognition and add to the total disease burden after OHCA. Nor does the study inform about OHCA survivors with less fortunate functional outcomes requiring prolonged hospitalization. Use of multiple

HRQL tools rather than a single tool could have improved the external validity of the present findings (4). Different HRQL tools can produce different results.

There are reasons to believe that the importance of cognitive functioning following an OHCA cannot be judged merely on the basis of the presence or absence of an association with a generic HRQL tool. HRQL and neuropsychological tests measure very different constructs (35). Whereas HRQL by definition must be operationalized as a subjective perception of how health influences functioning, cognitive impairment may alter the perception of HRQL and thereby compromise the validity of HRQL scores (36). In addition, considering the high frequency of mild to moderate cognitive impairments reported after an OHCA, it seems important to consider additional outcome instruments of HRQL beyond the generic SF-36, that may be more closely related to the consequences of mild to moderate cognitive impairments (35, 37, 38). However, subjective cognitive complaints tend to correlate poorly with actual cognitive performance on neuropsychological tests (39).

In conclusion, the evaluation of neurocognitive functions is relevant in good outcome survivors of OHCA for targeting the survivors in need of further rehabilitation resources and for allocating the most appropriate resources. The assessment of cognitive functioning is an important supplement to generic HRQL questionnaires, which may lack sensitivity to the functional consequences of mild to moderate cognitive impairment and therefore may not capture the full complexity of HRQL after an OHCA (19, 26, 27, 33).

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