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Predictors of quality of life after resective extratemporal epilepsy surgery in adults in long-term follow-up

Alaa Eldin Elsharkawy [b,*], Theodor May [c], Rupprecht Thorbecke [a], Alois Ebner [a,*]

[a] Department of Presurgical Evaluation, Bethel Epilepsy Centre, Germany
[b] Neurosurgical Department, Bethel Epilepsy Centre, Germany
[c] Society for Epilepsy Research, Bethel Epilepsy Centre, Germany

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ABSTRACT

Purpose: To present long-term outcome and predictors of the health related quality of life (HRQOL) in a large group of patients operated for refractory extratemporal epilepsy.
Methods: A German QOLIE-31 questionnaire and additional questions has been mailed for all adult patients operated for extratemporal epilepsy in the Bethel Epilepsy Centre, between 1992 and 2003, 87 patients were eligible for this study.
Results: Seizure freedom, intake of antiepileptic drugs (AEDs), presence of AEDs side effect medical comorbidities and driving a car were significantly correlated to HRQOL in all subscales of QOLIE-31. Gender, age at epilepsy onset, the presence of a partner, psychiatric disease, the presence of auras and tumour pathology have a correlation to QOL in some subscales.

Stepwise regression for all patients revealed that seizure freedom and medical comorbidities were highly predictive for most of the subscales of QOLIE-31. Intake of anti-epileptic drugs and AED side effects had a modest effect on QOL. The need for psychiatric treatment predicted poor cognitive function scores. Epilepsy onset at an older age predicted a minimal increase in the overall health scores. An aura at the last follow-up predicted poor medication scores.

Regarding the importance of the predictors, seizure freedom and medical comorbidities were the most important predictors of QOL after surgery. AED intake and side effects had an intermediate effect on QOL; however, the gender of the patient and age at epilepsy onset had a minimal effect on QOL.
Conclusions: HRQOL after extratemporal epilepsy surgery has multiple determinants. Medical comorbidities should be considered a negative risk factor for QOL during preoperative and postoperative evaluation process.

1. Introduction

The main goal of epilepsy surgery is to provide long-term seizure freedom and improvement of health related quality of life (HRQOL). Extratemporal epilepsy surgery has become more effective over the years[1] and a seizure-free outcome is now in the range of 47–60% in the long-term follow-up.[2]

In general, studies reporting outcome after extratemporal epilepsy surgery are rare, especially in respect of QOL. There is only one study about extratemporal QOL, presenting short-term outcome in a small group of patients.[3] Prior studies presented the QOL after extratemporal epilepsy surgery in mixed groups with extratemporal and temporal epilepsies.[4] Despite the reports which showed improvement of HRQOL in short-term studies[5,6] and studies concerning long-term outcome beyond 5 years,[7,8] outcome and predictors for QOL after extratemporal resective epilepsy surgery as a subgroup of the operated patients are still relatively unknown in long-term follow-up. Our aim was not to study the effect of surgery on QOL. Our aim was to study the perceived quality of life in adult patients who underwent extratemporal epilepsy surgery and to find the predictors of QOL in long-term follow-up.

2. Patient data collection methods

A German version of the Quality of Life in Epilepsy-31 (QOLIE-31) questionnaire[9,10] was sent to all adult patients (16 years and more) who had undergone extratemporal lobe (ETL) epilepsy surgery for refractory epilepsy between 1992 and 2005 in the

* Corresponding authors at: Klinik Mara, Maraweg 21, 33617 Bielefeld, Germany. Tel.: +49 52177278870; fax: +49 52177278872.
E-mail addresses: alaa.elsharkawy@mara.de (A.E. Elsharkawy), alois.ebner@mara.de (A. Ebner).

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Bethel Epilepsy Centre, Bielefeld, Germany. We excluded patients with mental retardation, patients with Rasmussen encephalitis (progressive disease with special characters) as well as patients who did not answer the questionnaire by themselves.

Of the 200 questionnaires that were sent out, 50 addresses (25%) were not correct but, among the others, 100 patients (66.7%) replied. We excluded 13 replies (13%) because other family members filled in the questionnaire. This left 87 patients (58%) who were included in this analysis. All questionnaires were self-administered, completed at home, and returned by post. Furthermore, data were extracted from patient files regarding details of the preoperative seizure types and frequency, presurgical investigations, surgical procedures, and postoperative outcome at short- and long-term follow-up. Additional study-specific questions regarding seizures and auras during the previous year, AEDs used and their side effects, employment, driving a car, the presence of a partner and psychiatric treatment were sent with the QOLIE-31. Demographic data, clinical characteristics and additional data are in Table 1.

2.1. Non-responder patients

As mentioned above, there were 113 patients who did not receive the questionnaire, did not reply or whose reply was excluded because it was not independently given. The data of all patients (responders, non-responders, non-independent responders) were analyzed to investigate any bias in the respondent group. The data were similar in all three groups. Data were not statistically different in responder and non-responder ($p > 0.05$), Mann–Whitney tests and chi-square tests.

2.2. Questionnaire

2.2.1. Quality of Life in Epilepsy-31

The Quality of Life in Epilepsy-31 (QOLIE-31) is a self-administered questionnaire. QOLIE-31 is the short form of the QOLIE-89 and consists of 31 items.[11]

The QOLIE-31 is an internationally used epilepsy-specific questionnaire to self-assess quality of life. Its psychometric properties have been investigated in various studies.[12] The QOLIE-31 is made up of 7 subscales: overall quality of life, seizure worry, emotional well-being, energy/fatigue, cognitive function, medication effects, and social function. The responses can yield seven individual scores (one per subtest) and a total (composite) score.

2.3. Statistical analysis

ANOVAs and correlation analyses were performed to investigate the effect of various factors (e.g. seizure freedom and side effects of AED therapy) on QOLIE-31 subscales. Correlation coefficients (r, Pearson correlation coefficient) or 'Eta' (η) were used to describe the extent of these factors; the Eta-squared statistics describe the proportion of variance attributable to a factor (e.g. seizure freedom) in relation to the total variance. Eta is a generalization of the point-biserial correlation coefficient and of the Pearson correlation coefficient for the case of curvilinear relationship. Eta is closely related to the effect size 'f' of the Analysis of Variance (ANOVA) proposed by Cohen (1977). A small ($f = 0.1$), medium (0.25) or large (0.5) effect size corresponds to Eta values of 0.1, 0.24, 0.37, respectively. According to Nunnally and Bernstein (1994), Eta values >0.3 can be regarded as 'important'.

The relationship between the following variables and QOL was investigated:

'Sociodemographic' data: age, gender, marital status (y/n), partner* (y/n), employment*, driver's license (y/n)*, driving a car (y/n)*.

Epilepsy related: time since last seizure, age at onset of epilepsy, side of operation/focus (left/right), pathology.

The relationship between QoL and time since last seizure was analyzed using the following variables/model assumptions:

- Dichotomic model: Seizure-free since surgery (y/n)
- 'Linear model': time since last seizure (months).

Table 1
Summary of clinical characteristics and risk factors in 87 adult patients.

Variable	Male (56)	Female (31)	Total (87)
Demographic and epilepsy related data (years)			
Mean age at seizure onset (mean ± S.D.) (years)	14.1 ± 12	13.5 ± 12.3	13.9 ± 12
Mean epilepsy duration	15.6 ± 10.2	16.8 ± 11.6	16 ± 10.6
Mean age at surgery	29.9 ± 11.7	30.3 ± 12.2	30.1 ± 11.8
Mean duration since surgery which QOL was measured	7.1 ± 3.6	7.3 ± 3.4	7.2 ± 3.5
Mean age at reply	37.4 ± 11.4	37.2 ± 13.2	37.3 ± 12
Site of the epileptic focus			
Frontal	30 (53.6%)	12 (38.7%)	42 (48.3%)
Posterior cortical	24 (42.9%)	15 (48.4%)	39 (44.8%)
Multilobar	2 (3.6%)	4 (12.9%)	6 (6.9%)
Additional data			
Comorbidities (total 86)			
No	36 (65.5%)	14 (45.2%)	50 (58.1%)
Yes	19 (34.5%)	17 (54.8%)	36 (41.9%)
Job situation (total 87)			
No	21 (37.5%)	13 (41.9%)	34 (39.1%)
Yes	35 (62.5%)	18 (58.1%)	53 (60.9%)
Psychiatric treatment (total 85)			
No psychiatric treatment	46 (83.6%)	23 (76.7%)	69 (81.2%)
Psychiatric treatment	9 (16.4%)	7 (23.3%)	16 (18.8%)
Diving car (total 86)			
Driving	25 (45.5%)	12 (38.7%)	37 (43%)
No driving	30 (54.5%)	19 (61.3%)	49 (57%)
Having a partner (total 87)			
No	28 (50%)	13 (41.9%)	41 (47.1%)
Yes	28 (50%)	18 (58.1%)	46 (52.9%)

- Non-linear model: non-linear transformation of time since last seizure assuming that the impact of the last seizure on quality of life decreases exponentially with time [exp(−time since last seizure)].

Antiepileptic drugs (AED): AEDs (y/n), side effects of AEDs (none, mild, moderate, severe).

Co-morbidity: other diseases (y/n)*, handicapped ID (y/n)*, psychiatric complications (psychiatric treatment/psychotherapy during the last 12 months) (y/n)*.

Stepwise regression (forward) analyses were performed using only those variables as predictors, which were significantly related with QOL and self-rated cognitive impairment. For statistical analysis SPSS for Windows (Version 16.0, SPSS Inc., Chicago, IL) was used.

3. Results

3.1. Seizure outcome

At the last follow-up, 45 patients (51.7%) were seizure free for at least 1 year. From these, 27 patients (31%) had been seizure free since surgery (best group), 42 patients (48.3%) had seizures after surgery but achieved remission at some point during the follow-up period, 59 patients (67.8%) were aura free and 28 patients (32.2%) had various types of aura at the last follow-up. There was a significant difference between women and men ($p = 0.016$), with women reporting the presence of an aura more often than men. In the group of the 45 seizure-free patients, 6 of these (13.3%) still experienced various types of aura.

3.2. Medication and side effects

Successful discontinuation of AEDs without a relapse of seizures for a minimum of 1 year prior to this study was possible for 16 patients (18.4%). Of those patients who continued taking medication, 24 patients (27.6%) were on monotherapy, 29 patients (33.3%) were on 2 drugs and 17 patients (19.5%) were on polytherapy. Various forms of side effects were reported by 38 patients (43.7%). They were mild in 17 patients (19.5%) and moderate to severe in 21 patients (24.1%). In 25 patients (28.7%) there had been a change in medication prior to follow-up. This change most often consisted of AEDs being discontinued.

3.3. Comorbidities

Medical comorbidities affected 36 patients (41.9%) and required regular treatment. Most frequent was bronchial asthma (14%) followed by gastroenterological diseases (11%), skin diseases (11%), as well as elevated blood pressure and orthopaedic diseases (6%). Psychiatric and psychotherapy treatment was administered to 18 patients (20.7%), either in hospital or in outpatient facilities.

3.4. Quality of life outcome

Univariate analysis showed that seizure freedom, intake of antiepileptic drugs, presence of AED side effects, medical comorbidities and driving a car were significantly correlated to HRQOL in all subscales of QOLIE-31. Furthermore, the presence of an aura at the last follow-up correlated with all QOL subscales except for cognitive function, overall quality of life and the QOLIE-31 total score. Gender, age at epilepsy onset, the presence of a partner, tumour pathology and psychiatric treatment had a correlation to QOL in some subscales (Table 2).

3.5. Duration of seizure freedom

Relationships between the duration of seizure freedom and QOL subscales were mainly non-linear. The results indicate that QOL increase during the first 2 years and subscales remained stable or even decrease, however some subscales like cognitive function energy/fatigue and well-being scores showed a greater decrease over time than the other subscales. The total QOLIE-31 score for cases of seizure remission less than 6 months was 57.6 ± 16. For seizure remission between 6 months and 2 years it was 70.7 ± 15.3, whereas for remission between 2 years and 5 years

Table 2
Factors related with quality of life—Eta or Pearson correlation coefficients.

Variable	Overall quality of life	Energy/ fatigue	Well-being	Cognitive function	Social function	Seizure worry	Medication effects	Overall score health	Total score QOLIE-31
Sex	.09	.18	.23*	.02	.06	.06	.10	.12	.10
Partner (y/n)	.19	.15	.25*	.6	.8	.11	.11	.13	.12
Driving a car (y/n)	.41***	.31**	.43***	.29**	.53***	.52***	.33**	.52***	.53***
Having a job (y/n)	.20	.21	.15	.16	.13	.15	.11	.08	.15
Age at onset	.17	.20	.12	−.03	−.04	.06	−.01	.25*	.06
Age at surgery	.03	.13	.09	−.18	−.06	.12	−.10	.18	.00
Age at reply	−.02	.09	.04	−.21	−.09	.13	−.13	.13	−.04
Epilepsy duration	−.17	−.10	−.05	−.17	−.04	.06	−.10	−.10	−.08
Duration of seizure freedom (linear)	.26*	.17	.16	−.01	.31**	.47**	.25*	.40**	.29*
Duration of seizure freedom (non-linear)	.51**	.28**	.35**	.28**	.51**	.64**	.42**	.59**	.50**
Seizure free since surgery	.36**	.27*	.33**	.25*	.40**	.45**	.36**	.49**	.40**
Presence of Aura (with or without seizures)	.16	.26*	.22*	.10	.24*	.26*	.39***	.27*	.21
AED (y/n)	.39***	.23*	.26*	.31**	.38**	.36***	.46***	.42***	.35**
Type of side effects of AED	.44***	.32*	.38**	.37**	.30*	.45***	.46***	.25	.42**
Side effect (y/n)	.43***	.31**	.38***	.35**	.29**	.41***	.46***	.25*	.41***
Comorbidity	.46***	.41***	.48***	.38***	.39**	.37**	.34**	.41***	.44***
Psychiatric treatment	.14	.13	.10	.27*	.08	.14	.13	.07	.10
Handicapped pass (y/n)	.31**	.21	.33**	.29**	.26*	.13	.15	.33**	.28*
Tumours	.11	.09	.09	.12	.25*	.09	.06	.02	.16
Side of surgery	.12	.17	.11	.04	.09	.12	.21	.10	.15
FCD	.12	.10	.02	.03	.22	.12	.06	.15	.12
Resection area	.06	.15	.08	.11	.06	.17	.15	.15	.11

Level of significance [***$p < 0.001$, **$p < 0.01$, *$p < 0.05$].

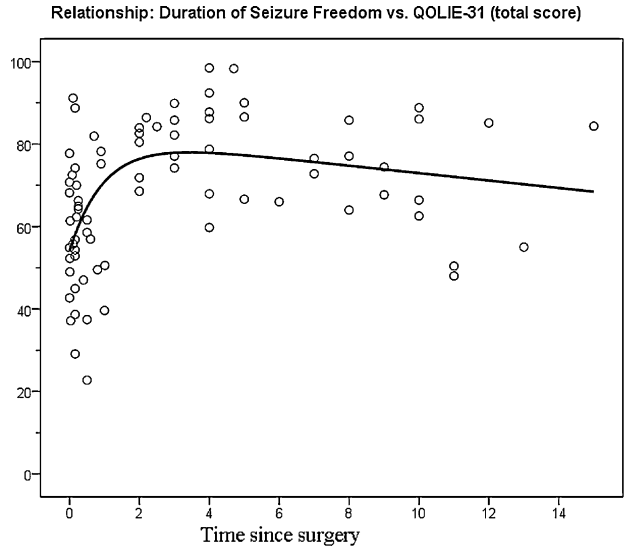

Fig. 1. QOL scores related to seizure remission duration.

it was 82.6 ± 11.2 and 71.2 ± 12.8 for seizure remission for more than 5 years (Fig. 1).

3.6. AEDs and AED side effects

AED intake, the occurrence of side effects due to AEDs and the intensity of the side effects (mild, moderate or severe) were associated with a lower QOL scores. The total score was 60.4 ± 15.7 in patients with side effects, and 74.6 ± 15.5 in patients who had no side effects, but it reached 81.1 ± 12.7 in patients who had stopped taking AEDs.

3.7. Driving and medical comorbidities

Driving a car was correlated to all subscales of the QOL. Car-driving patients had clearly higher QOL scores. The total score was 60.3 ± 17 in patients who did not drive, but rose to 78.3 ± 10.8 in patients who did. The presence of medical comorbidities requiring medical treatment (either as an in- or out-patient) had strong negative effects on all QOLIE-31 subscales. Total scores here were 75.8 ± 17 in patients who had no medical comorbidities and 58.8 ± 21.1 in patients with one or more medical comorbidity. However driving a car was highly correlated with duration of seizure freedom (2 years), therefore we do not included this variable in the multivariate analysis.

3.8. Univariate analysis: factors correlated with some subscales of QOLIE-31

Male patients had better well-being scores than females and an older age at epilepsy onset had a positive impact on the overall health score. Having a partner had positive effects on the well-being subscale. Psychiatric disease requiring treatment had a negative impact on the cognitive outcome scale of QOLIE-31. Patients with tumour pathology had a higher social function score than other patients.

3.9. Multivariate analysis

Predictors for the whole sample: stepwise regression for all patients revealed that seizure freedom and medical comorbidities were highly predictive for most of the subscales of QOLIE-31 (Table 3). The relation between the duration of seizure freedom and QOL was mainly non-linear. Intake of AEDs and AED side effects had a modest effect on QOL except medication effect. The need for psychiatric treatment predicted poor cognitive function scores. Epilepsy onset at an older age predicted a minimal increase in the overall health scores. An aura at the last follow-up predicted poor medication scores (Table 3). Regarding the degree of importance of the predictors, seizure freedom had the strongest effect on most of subscales predicted by seizure freedom. However, medical comorbidities had the strongest negative effect on energy/fatigue and well-being. Driving a car was a strong predictor for social function. The variance inflation factor (VIF) showed no co-linearity between the predictors (VIF <15).

4. Discussion

The assessment of QOL after epilepsy surgery is increasingly recognized as an important component of clinical care and operative outcome. The analysis shows that QOL in long-term follow-up depends on multiple factors and predictors of QOL varying in the degree of effect dependent mainly on the seizure outcome and general health state.

In the whole sample, seizure freedom was the most important predictor of the QOL even years after surgery. On the other hand, in the best group, duration of seizure freedom had no or only a slight prediction power. These results appear logical as the seizure outcome determines other aspects of life after surgery. Seizure-free patients have to undergo an adjustment process during the transition from chronic disability to normality.[13] After the seizure outcome becomes stabilized, additional factors become decisive for QOL. In contrast, patients who still have seizures after surgery experience a significant disappointment and a sense of failure.[14] In this group, seizure freedom was still the most important predictor of QOL even years after surgery.

The second most powerful factor in our study was the presence of medical comorbidities requiring medical treatment. Medical comorbidities have a negative effect on all subscales of QOLIE-31. Other authors have found that medical comorbid conditions were shown to independently have a significant contribution in predicting overall QOL scores and the number of comorbid conditions was the strongest correlate of QOL.[15,16] Recent studies have documented high rates of comorbidities among people with epilepsy compared with healthy controls.[17] The prevalence ratio of most disorders is two- to five-fold higher in adults with epilepsy.[18] The negative effect on QOL for medical comorbidities may be due to the fact that comorbid disorders impose a significant burden on patients and their families through increased efforts and expense for pharmaceuticals, doctor's appointments, and in-patient hospitalization.[17] Our findings confirm the negative impact of medical comorbidities on QOL. Medical comorbidities should, therefore, be considered during preoperative evaluation and prognosis of surgery.

AEDs came in third with regard to the prediction ability for QOL. In general, AEDs are an important issue in the life of the epilepsy patient. One of the patient's reasons to undergo surgery is to take fewer AEDs. Like other authors we found that AED intake and the presence of self-reported side effects had an effect on QOL. Several authors have also found that AEDs are one of the factors influencing QOL.[19] The negative effect of AEDs on QOL could be due to the possible cognitive side effects of the AEDs[20] or to the negative effects on mood due to the global changes in the excitation levels in the central nervous system.[20]

The presence of AED side effects usually means more medications to treat these side effects or at least highlights the need to change or modify the AEDs. This may lead to a state of uncertainty as to seizure recurrence and constant worry about the future.

Of interest is the fact that the total scores for cognitive function reported by patients were high in the first 2 years after surgery and started to decrease steadily over time. We may explain this continual decrease in cognitive function by the fact that relapses

Table 3
Multivariate analysis (whole sample).

Predictor	Overall quality of life	Energy/fatigue	Well-being	Cognitive function	Social function	Seizure worry	Medication effects	Overall score health	Total score QOLIE-31
Duration of seizure freedom (non-linear)	19.1*** [.40] (1)				26.8*** [.42] (1)	39.2*** [.64] (1)		24.0*** [.47] (1)	17.0*** [.40] (1)
AED side effects (y/n)			−10.3** [−.31] (2)	−9.9* [−.24] (2)			−19.0*** [−.38] (1)		
Age at epilepsy onset (years)								0.4* [−.18] (3)	
Presence of aura (y/n)							−13.9* [−.26] (2)		
Psychiatric treatment (y/n)				−11.7* [−.23] (3)					
Co-morbidity (y/n)	−12.2** [−.32] (2)	−15.4*** [−.41] (1)	−11.3** [−.34] (1)	−11.2** [−.27] (1)	−13.0* [−.25] (2)			−10.2** [−.25] (2)	−10.5 [−.30] (2)
Sex (f/m)			−7.1* [−.21] (3)						
Constant	78.4	61.7	77.2	77.2	89.9	94.5	85.8	78.0	78.9
VIF	2.8	2.2	3.4	2.7	2.7	2.3	2.6	4.0	2.7
n	85	83	83	81	81	82	79	81	74
R	.59	.41	.57	.48	.56	.64	.53	.65	.58
R^2 (corrected)	.35	.17	.33	.23	.31	.41	.28	.43	.33
Seizure free since surgery (the beast group)									
Duration of seizure freedom (Linear)					−1.46* [.37] (1)				−1.5* [−.43] (1)
Sex			−18.5* [−.53] (1)						
Psychiatric complication				−.69.4* [−.45] (1)					
Constant			78.5	77.1.	102.86				88.9
VIF			1.8	4.8	4.8				2.9
n			26	26	26				22
R			.49	.66	.50				.56
R^2			.21	.40	.22				.24

For each stepwise regression the unstandardized [without brackets,] and standardized regression coefficients [in parenthesis square brackets], level of significance [$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$], order of inclusion (). VIF = variance inflation factor; *n* = number of patients, *R* = multiple regression; R^2 (corrected) = explained variance.

among patients is known to increase over time.[21] It has been reported that cognitive abilities are the most critical feature associated with seizure control.[22,23] Extratemporal surgery includes functional areas in the frontal lobe which have a role in memory and language abilities.[24] Our study presents subjective data; it is a cognitive complaint and so cognitive function may not really be affected. We recommend an objective study for long-term outcome of cognitive functions after extratemporal epilepsy surgery.

In our study, male gender was a predictor for better well-being scores in the whole sample and in the best group. Generally, differential effects of epilepsy surgery on men compared to women have been studied too inconclusively. However, women experience unique epilepsy-related issues including infertility and menstrual irregularities, complicated AED–hormone interactions, pregnancy complications, and, in many cases, child-care responsibilities.[24] It has been reported that the expectations of surgery may differ between men and women. Gender differences may also have an impact on the surgical outcomes and QOL after surgery.

Our study confirms that QOL is determined by multiple factors and that quality of life after epilepsy surgery cannot be computed with the basic formula "fewer seizures = better QOL."

4.1. Limitation of the study

Admittedly our study has limitations. The QOL data presented are retrospective and without preoperative assessment. This study presents patients' subjective data and, in particular, regarding the cognitive function, needs to be followed by objective testing. Nevertheless, the results in our study offer new and valuable insights.

5. Conclusion

QOL after extratemporal epilepsy surgery improved in the first 2 years after surgery and remained relatively stable with a tendency to decrease over time. This decrease was more prominent in the cognitive function subscales. The presence of a partner, driving a car, gender, age at epilepsy onset, psychiatric disease and the presence of auras were correlated and associated with QOL. However, only seizure freedom, medical comorbidities, AED intake, the presence of side effects and the age at epilepsy onset were found to be predictors of QOL in the multivariate analysis. This study highlights two points. First, there is the need for more objective studies on cognitive function after extratemporal epilepsy surgery in long-term follow-up. The second point is that medical comorbidities are important factors in determining the outcome after surgery and should be considered during preoperative and postoperative evaluation.

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