Correlation of natural language assessment results with health-related quality of life in adult glioma patients

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OBJECTIVE Impairments of speech are common in patients with glioma and negatively impact health-related quality of life (HRQoL). The benchmark for clinical assessments is task-based measures, which are not always feasible to administer and may miss essential components of HRQoL. In this study, the authors tested the hypothesis that variations in natural language (NL) correlate with HRQoL in a pattern distinct from task-based measures of language performance.

METHODS NL use was assessed using audio samples collected unobtrusively from 18 patients with newly diagnosed low- and high-grade glioma. NL measures were calculated using manual segmentation and correlated with Quality of Life in Neurological Disorders (Neuro-QoL) outcomes. Spearman’s rank-order correlation was used to determine relationships between Neuro-QoL scores and NL measures.

RESULTS The distribution of NL measures across the entire patient cohort included a mean ± SD total time speaking of 11.5 ± 2.20 seconds, total number of words of 27.2 ± 4.44, number of function words of 10.9 ± 1.68, number of content words of 16.3 ± 2.91, and speech rate of 2.61 ± 0.20 words/second. Speech rate was negatively correlated with functional domains (rho = −0.62 and p = 0.007 for satisfaction with social roles; rho = −0.74 and p < 0.001 for participation in social roles) but positively correlated with impairment domains (rho = 0.58 and p = 0.009 for fatigue) of Neuro-QoL.

CONCLUSIONS Assessment of NL at the time of diagnosis may be a useful measure in the context of treatment planning and monitoring outcomes for adult patients with glioma.

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KEYWORDS glioma; natural language; aphasia; task-based language testing; oncology

Gliomas are the most common intrinsic brain tumors, with nearly 20,000 new diagnoses annually.1,2 Aphasia, the generalized loss of language function and communication, is frequently observed in patients with glioma occurring within the frontal, parietal, and temporal perisylvian regions of the dominant hemisphere.3–5 This is due to glioma’s ability to disrupt networks that contribute to motor, language, and cognitive processing. The result is that aphasia and impaired communication are two of the most significant contributors to poor health-related quality of life (HRQoL) and reduced survival.5–8 Schemes to assess language processing and to treat patients with aphasia have the potential to improve patient outcomes.5,7–11

HRQoL metrics have become increasingly important measures for understanding disease-specific morbidity, mainly when assessed together with standard patient outcome measures such as progression-free and overall survival. Patient-reported HRQoL measures are negatively impacted by disease progression and the effects of treatment.12,13 Aphasia severity, as assessed with task-based measures, negatively impacts functional domains of HRQoL; however, the correlation between natural language (NL) measures and HRQoL remains unknown.8,14,15

Common task-based measures of language, such as the Western Aphasia Battery (WAB) and Quick Aphasia Battery (QAB), offer precise and multifaceted language assessments. Although such tests are undoubtedly comprehensive, administration of task-based measures can be a burden for clinical populations, particularly when applied longitudinally throughout the disease trajectory. These challenges are due to both patient- and disease-specific

ABBREVIATIONS HRQoL = health-related quality of life; Neuro-QoL = Quality of Life in Neurological Disorders; NL = natural language; QAB = Quick Aphasia Battery; WAB = Western Aphasia Battery.


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factors, such as the prevalence of other nonphasic neurological impairments and chronic fatigue. Williamson et al. conducted a study of stroke patients and showed that WAB scores did not correlate with patients’ quality-of-life outcomes. Therefore, it may be optimal for clinicians to have the ability to establish risk and predict a patient outcome on the basis of parameters outside task performance. Patterns of NL may be of prognostic significance in clinical populations; however, they have not been studied in adult glioma patients.

NL is the instinctual written or spoken language profile that an individual has developed throughout his or her lifetime. Recent psycholinguistic analyses suggest that change in patterns of NL may be an accurate measure for assessing clinical and behavioral conditions. Changes in NL may include shifts in specific function words or alterations in total language output. NL analysis of speech has been shown to determine changes in cognitive status and possibly detect early stages of dementia. In Parkinson’s disease patients, a slower speech rate was correlated with worsening disease progression. Variations in NL structure may offer unique behavioral indicators of short-term health-related outcomes in glioma patients. Analysis of the aforementioned information-rich components of NL processing may be accomplished either manually or via machine learning algorithms. In this study, we tested the hypothesis that baseline NL measures of adult patients with glioma would correlate with preoperative scores on functional and impairment HRQoL domains in patterns distinct from task-based measures of language performance.

Methods

The study received institutional review board approval from the University of California, San Francisco Committee for Human Research. All patients provided written informed consent to participate after the study’s nature and design were fully described and related questions had been answered.

Consecutive adult patients aged 18–85 years at diagnosis with glioma completed initial language assessments. All tumors were within the frontal, parietal, or temporal lobes and diagnosed between August 2017 and September 2018. Only patients with dominant-hemisphere gliomas were included in this study, with the hemisphere of language dominance determined on the basis of cortical activation during picture-naming and text-reading language tasks that were administered with magnetoencephalography. The control group included patients with benign intracranial lesion (e.g., meningioma, colloid cyst). Patients were excluded from this study if they 1) had a prior cranial operation or traumatic brain injury, 2) were not primary English speakers, 3) had clinical or radiographic evidence of ongoing seizure activity, and/or 4) had baseline impaired cognition that rendered them unable to complete QAB language assessments. Language tasks included 1) picture naming, 2) text reading, 3) auditory naming, 4) syntax, and 5) 4-syllable word repetition.

For each patient, NL measures were analyzed from an average of 10 separate 30- to 60-second audio samples (10 minutes of audio samples per participant) obtained with a 60-minute cognitive assessment battery conducted by an independent study coordinator on a single day. The audio recordings were manually transcribed by one of the authors (S.G.A.), and NL coding was done using these transcriptions. NL output measures included total time speaking, total number of words, number of function words, number of content words, and speech rate, which is the ratio of total number of words to total time speaking.

Function words were defined as words that provided structural or grammatical relationships with other words. Content words were interpreted as words that name objects of reality and their qualities. Audio files were coded manually by coauthors blinded to clinical outcome. QAB was administered and scored by a speech pathologist or trained research assistant according to an established protocol. A score of 4 on QAB was a correct answer; a score of 3 was a correct answer that was delayed > 3 seconds or self-corrected; a score of 2 was an answer where at least half the phonemes were correct; a score of 1 was an answer that was incorrect but somewhat related to the target; and a score of 0 was an unrelated response within 6 seconds or no answer.

HRQoL was assessed using adult version 1.1 of the Quality of Life in Neurological Disorders (Neuro-QoL) assessment tool. Neuro-QoL is a set of questionnaires that addresses common issues in neurological diseases. Each domain is stratified into two categories: function (cognition, participation and satisfaction with social roles and activities, upper- and lower-extremity function, and positive affect) and impairment (stigma, sleep disturbance, fatigue, emotional dyscontrol, depression, and anxiety). Specifically, for this tool, anxiety was defined as unpleasant thoughts or feelings related to fear, helplessness, worry, and hyperarousal. Depression was defined as self-reported feelings of loss, hopelessness, negative mood, decreased positive affect, or negative views of self. Fatigue was described as self-reported sensations ranging from tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that decreases one’s capacity for physical, functional, social, and mental activities. Upper-extremity function involved one’s ability to carry out various activities involving digital, manual, and reach-related functions (including fine motor and self-care functions). Lower-extremity function included one’s ability to carry out various activities involving the trunk region, body movement, ambulation, balance, or endurance. The cognitive functional domain was used to assess perceived difficulties in cognitive abilities or the application of such abilities to everyday tasks. Emotional dyscontrol consisted of a set of disease and treatment-related manifestations, including disinhibition, emotional lability, irritability, impatience, and impulsiveness. Positive affect and well-being included aspects of a person’s life related to a sense of well-being, satisfaction, or overall sense of purpose and meaning. Sleep disturbance included perceptions of sleep quality, sleep depth, and restoration associated with sleep. The ability to participate in social roles and activities was the degree of involvement in one’s usual social roles, activities, and responsibilities, including those related to work, family, and friends. At the same time, satisfaction with social roles and responsibilities was defined as satisfaction with involvement in one’s usual social roles,
activities, and responsibilities. Stigma involved perceptions of self and publicly enacted negativity, prejudice, and discrimination due to disease.\textsuperscript{8} Neuro-QoL was administered and scored by a trained independent research assistant according to an established protocol.\textsuperscript{8} Each assessment was scored with normalized mean t-scores for each domain and standardized to a score of 50. Scores higher than 60 on the functional domains and lower than 50 on the impairment domains were considered desirable. Impairment was assessed in the study population, and patients with scores $>1$ SD beyond the normative mean were deemed to have impaired function.

Descriptive statistics were used to summarize group characteristics, NL performance, and Neuro-QoL scores. Comparison of NL parameters between the control and glioma patients was performed using the nonpaired t-test. Spearman correlation coefficients were assessed for each NL and QAB measures assessed, we applied Bonferroni correction to control for multiple comparisons. Thus, to adjust for the 5 NL measures and 5 QAB tasks, Spearman correlation coefficients were considered statistically significant at $p < 0.01$. Data were reported as mean and standard error. The alpha level for significance was set at 0.05. Statistical analysis was performed using MATLAB version R2019a (The MathWorks, Inc.).

### Results

This study included 23 adult patients: 18 with newly diagnosed grade II, III, and IV glioma based on the 2016 WHO diagnostic criteria, and 5 in the control group (4 with meningioma and 1 with colloid cyst). The data set included 230 audio samples, totaling 13,040 seconds of unstructured speech, that were manually coded for 5 NL measures. Demographic and tumor characteristics are listed in Table 1.

We first set out to understand and compare the distributions of NL measures across the glioma and control cohorts. This included a mean $\pm$ SD total time speaking of $11.5 \pm 2.20$ seconds for the glioma cohort versus $8.94 \pm 1.3$ seconds for the control cohort ($p = 0.56$), total number of words of $27.2 \pm 4.44$ words versus $28.92 \pm 1.95$ words ($p = 0.84$), number of function words of $10.9 \pm 1.68$ words versus $13.28 \pm 1.01$ words ($p = 0.48$), number of content words of $16.3 \pm 2.91$ words versus $15.64 \pm 2.67$ words ($p = 0.91$), and speech rate of $2.61 \pm 0.20$ words/second versus $3.47 \pm 0.30$ words/second ($p = 0.049$). The distributions of the NL measures between the two groups are shown in Fig. 1.

HRQoL was then measured using Neuro-QoL. Functional domain assessments included a mean t-score for cognition of $41.7 \pm 1.43$, satisfaction with social roles of $44.3 \pm 1.06$, upper-extremity function of $41.7 \pm 2.64$, positive affect of $53.3 \pm 1.68$, lower-extremity function of $48.4 \pm 2.41$, and participation in social roles of $43.6 \pm 1.23$. Across the Neuro-QoL impairment domain, patients had a mean t-score for stigma of $50.3 \pm 1.80$, sleep disturbance of $53.3 \pm 1.74$, fatigue of $47.4 \pm 2.29$, emotional dyscontrol of $49.8 \pm 2.75$, depression of $49.9 \pm 1.93$, and anxiety of $55.98 \pm 2.09$. Figure 2 shows the distributions of Neuro-QoL scores across patients.

Decreased HRQoL was defined as $>1$ SD from established normative values according to an established protocol.\textsuperscript{8} Prevalence of decreased HRQoL was highest for cognition (50% of patients), upper-extremity function (50%), anxiety (33.3%), lower-extremity function (27.8%), participation in social roles (27.8%), satisfaction with social roles (22.2%), sleep disturbance (22.2%), and emotional dyscontrol (22.2%; Table 2).

<table>
<thead>
<tr>
<th>TABLE 1. Demographic and clinical characteristics of the glioma cohort</th>
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<td>Patient No.</td>
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We then set out to determine whether NL measures were correlated with results on the functional or impairment domains of Neuro-QoL and whether these correlations differed from those of task-based language assessments. The Bonferroni correction was applied because NL measures included comparisons of multiple variables within the same family. Several Neuro-QoL domains were significantly correlated with speech rate, including satis-

![Image](https://via.placeholder.com/150)

**FIG. 1.** Comparisons of the distributions of 5 NL parameters between the control and glioma cohorts. A: Total number of words. B: Total number of function words. C: Total number of content words. D: Total time speaking. E: Speech rate. Middle lines indicate median, boxes indicate interquartile range, whiskers indicate range, and the asterisk indicates statistical significance (p < 0.05).

![Image](https://via.placeholder.com/150)

**FIG. 2.** Distributions of normalized mean t-scores for each Neuro-QoL domain in the glioma cohort. **Left:** For the functional domains, a score greater than 50 indicates less distress, which is shown as the shaded area. **Right:** For the impairment domains, a score less than 50 indicates less distress, which is shown as the shaded area. Middle lines indicate median, boxes indicate interquartile range, and whiskers indicate range.
TABLE 2. Decreased HRQoL in the glioma cohort (n = 18)

<table>
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<tr>
<th>Domain</th>
<th>No. (%) w/ Decreased HRQoL*</th>
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<tr>
<td>Functional</td>
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<tr>
<td>Cognition</td>
<td>9 (60.0)</td>
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<tr>
<td>Satisfaction w/ social roles</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Upper-extremity function</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Positive affect</td>
<td>1 (5.6)</td>
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<tr>
<td>Lower-extremity function</td>
<td>5 (27.8)</td>
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<tr>
<td>Participation in social roles</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
</tr>
<tr>
<td>Stigma</td>
<td>2 (11.1)</td>
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<tr>
<td>Sleep disturbance</td>
<td>4 (22.2)</td>
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<tr>
<td>Fatigue</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Emotional dyscontrol</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (5.6)</td>
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<tr>
<td>Anxiety</td>
<td>6 (33.3)</td>
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</tbody>
</table>

* Defined as a score of 50 or less for functional domains, or a score of 50 or greater for impairment domains.

Discussion

This study identified a relationship between NL speech rate and distinct HRQoL measures. Functional and cognitive measures, such as assessments focused on language processing, are increasingly recognized for their importance.27 Task-based measures represent the vast majority of functional assessments. However, they are not always feasible to administer and may not fully describe all components of speech.

NL is the written and spoken language profile that an individual develops throughout life.18–22 Generally speaking, NL has seven components: pragmatics, phonology, phonetics, morphology, lexicon, syntax, and semantics.20,28 Function words, including pronouns and adverbs, are generated automatically as opposed to consciously created meaning words.29 Function words by themselves have no semantic purpose, but together they provide a syntactic structure. Patterns of NL shift in response to disease; therefore, they may be useful measures of patient outcomes.8,20 This is the first study of NL in the adult neurooncology setting.

Patient-reported HRQoL outcomes are essential tools used to understand disease in clinical practice. Patients with low- and high-grade glioma experience a wide range of neurological symptoms because the disease has both oncological and neurological ramifications, both of which impact quality of life. Therefore, when considering functional measures such as NL processing, their relationships with HRQoL measures are central. In this study, our glioma cohort had a significantly lower speech rate than our control cohort. In our glioma cohort, there was a negative relationship between speech rate and both patient satisfaction with social roles (rho = −0.62, p = 0.007), participation in social roles (rho = −0.74, p < 0.001), and fatigue (rho = 0.58, p = 0.009; Fig. 3). However, there were no significant correlations between the results of QAB language tasks and Neuro-QoL HRQoL endpoints (Fig. 3).

Conclusions

This research identified a relationship between NL speech rate and distinct HRQoL measures. This is the first study to assess NL measures as a functional endpoint in the adult neurooncology setting.
Acknowledgments

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References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Ammanuel, Hervey-Jumper. Acquisition of data: Ammanuel, Almeida, Kakazida, Hervey-Jumper. Analysis and interpretation of data: Ammanuel, Hervey-Jumper. Drafting the article: all authors. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors. Ammanuel. Statistical analysis: Ammanuel. Administrative/technical/material support: Ammanuel. Study supervision: Hervey-Jumper.

Supplemental Information
Previous Presentations
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