Health-related quality of life in glioma patients: the added value of combining clinical trial datasets

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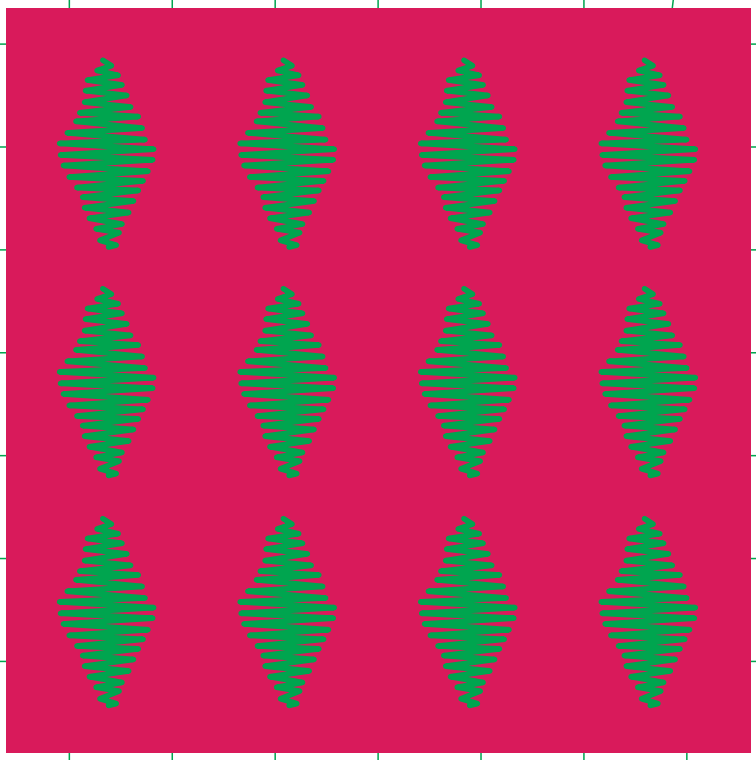

Chapter 5:

Symptom clusters in newly diagnosed glioma patients: which symptom clusters are independently associated with functioning and global health status?

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Abstract

Introduction: Symptom management in glioma patients remains challenging, as patients suffer from various concurrently occurring symptoms. This study aimed to identify symptom clusters and examine the association between these symptom clusters and patients' functioning.

Methods: Data of the CODAGLIO project was used including individual patient data from previously published international randomized controlled trials (RCTs) in glioma patients. Symptom prevalence and level of functioning were assessed with EORTC QLQ-C30 and QLQ-BN20 self-report questionnaires. Associations between symptoms were examined with Spearman correlation coefficients and partial correlation networks. Hierarchical cluster analyses were performed to identify symptom clusters. Multivariable regression analyses were performed to determine independent associations between the symptom clusters and functioning, adjusted for possible confounders.

Results: 4307 newly diagnosed glioma patients from 11 RCTs completed the EORTC questionnaires before randomization and were included in the analysis. Many patients (44%) suffered from 5-10 symptoms simultaneously. Four symptom clusters were identified: a motor cluster, a fatigue cluster, a pain cluster, and a gastrointestinal/seizures/bladder control cluster. Having symptoms in the motor cluster was associated with decreased (≥10 points difference) physical, role, and social functioning (Beta's ranged from -11.3 to -15.9, all $p<0.001$), independent of other factors. Similarly, having symptoms in the fatigue cluster was found to negatively influence role functioning (Beta of -12.3, $p<0.001$), independent of other factors.

Conclusion: Two symptom clusters, the fatigue and motor cluster, were frequently affected in glioma patients and were found to independently have a negative association with certain aspects of patients' functioning as measured with a self-report questionnaire.

Introduction

Patients with a glioma, the most prevalent malignant primary brain tumor[1], suffer from a variety of symptoms during the course of disease, including fatigue, cognitive problems, behavioral problems and motor dysfunction[2]. Many patients experience more than one symptom simultaneously[3], and typically more symptoms are experienced than reported to or detected by clinicians[4,5]. Depending on the definition, two or more symptoms that are related to each other and occur together are referred to as a symptom cluster, and associations between symptoms within a symptom cluster are stronger than associations among different symptom clusters and/or separate symptoms[6,7]. Identification of these symptom clusters may aid symptom management, because the co-occurrence of symptoms may have a larger impact on patients' functioning and overall health-related quality of life (HRQoL) than each symptom alone[8]. If management is aimed at improvement of patients' functioning, targeting these specific symptom clusters may provide an opportunity.

In other cancer populations, several symptom clusters have been identified[9,10], which were found to be associated with patients' functioning. In glioma patients, however, symptom clusters have not been studied sufficiently. The few studies that were conducted have limitations, including limited sample sizes or the lack of inclusion of glioma-specific symptoms[9,11,12]. Patients with a glioma may suffer from generic cancer symptoms such as fatigue and mood disorders, but also from disease-specific symptoms such as seizures, headaches, motor deficits, or cognitive deficits[13,14]. Both these generic and disease-specific symptoms may be associated with a patients' well-being and functioning, including physical, role, emotional, cognitive, and social functioning.

The aim of this study was to identify symptom clusters in a large sample of newly diagnosed glioma patients, and to investigate the associations between the identified symptom clusters and patients' functioning and global health status/ quality of life.

Methods

Study population

Patients included in this study participated in previously published phase II and III randomized controlled trials (RCTs) including adult patients with both recurrent and newly diagnosed glioma (Supplementary Table 1). Over 6000 patients are included in the CODAGLIO (i.e. COmbining clinical trial DAtasets in GLIOma) project[15]. For the purpose of the current analysis, focusing on identifying symptoms clusters at the time of diagnosis, only RCTs involving newly diagnosed glioma patients and using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and QLQ-BN20 module were included. All RCTs were approved by the ethical committees of all participating centers and all patients gave their informed consent to participate in the respective RCT. Moreover, all principal investigators of these RCTs gave permission for use of the collected data within the CODAGLIO project.

Measurements

Generic cancer- and brain tumor-specific symptoms, as well as levels of functioning were measured with the EORTC QLQ-C30 and the QLQ-BN20 questionnaire. The EORTC QLQ-C30 version 3.0[16] and the brain-cancer specific QLQ-BN20[17] were administered at baseline, i.e. before the start of the allocated treatment (after surgery and irrespective of supportive treatment), and at prespecified time points during follow-up. The EORTC QLQ-C30 is the core EORTC questionnaire that includes 30 items, comprising five functioning scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life scale, and six single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties). The QLQ-BN20 is specifically designed for brain tumor patients and consists of 20 items, comprising four symptom scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and seven single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). Responses for all items are on a four-point Likert scale (i.e. not at all, a little, quite a bit, and very much), except for the global health status/quality of life scale, which is scored on a seven-point Likert scale ranging from very poor to excellent. For both questionnaires, raw scores were linearly transformed to a scale from 0 to 100 according to the standard EORTC procedures[18]. For the functioning scales and the global health status/quality of life scale, a higher score indicates a better HRQoL. For the symptom scales and items, higher scores indicate more symptoms and worse functioning, respectively.

Other sociodemographic and clinical variables collected including age, sex, type of tumor (WHO grade II or III astrocytoma, oligodendroglioma, and oligoastrocytoma, or WHO grade IV glioblastoma), WHO performance status (PS) (0 versus 1 versus 2), and type of surgery (resection versus biopsy)).

Statistical analysis

Descriptive methods were used to summarize baseline sociodemographic, clinical and HRQoL data, including the prevalence and severity of symptoms. For this study, only fully completed baseline HRQoL forms were considered. To evaluate differences between patients with and without a completed HRQoL baseline form (i.e., possible selection bias), several clinical characteristics were compared using the Chi-square test for categorical data, and an independent Student's t-test for continuous variables. Mean scores on the functioning scales of the included patients were compared to a healthy normgroup to have an indication of the level of functioning of the included patients[19].

Clustering of the symptoms was carried out in three steps, and we chose to define a symptom clusters as having a minimum of two symptoms. First, to explore symptom clustering, Spearman correlational analyses were carried out on all symptom scales and single items of the EORTC QLQ-C30 and QLQ-BN20, except financial difficulties and future uncertainty, which we did not classify as symptoms (i.e. defined as 'a physical or mental feature which is regarded as indicating a condition of disease'). The magnitude of the correlations were interpreted as follows: between 0 and $\pm$0.3 as 'little if any'; between $\pm$0.3 and $\pm$0.5 as 'low'; between $\pm$0.5 and $\pm$0.7 as 'moderate'; and above $\pm$0.7 as 'high'[20]. Next, the associations amongst the symptoms were presented in an unregularized partial correlation network based on Spearman correlations, which was used to examine whether the associations between the symptoms were still present when adjusting for the other symptoms. The network model was estimated using the Gaussian graphical model which estimates a network of partial correlation

coefficients[21,22]. Network models provide an alternative method to visualise associations and consist of nodes (circles, the symptoms) and edges (lines, the relation between the symptoms). Each link in the network represents a partial correlation coefficient between two symptoms after controlling for the other symptoms. We included at least two symptoms in the symptom clusters.

Thereafter, hierarchical cluster analysis (HCA) was performed as a last step to assess how the symptom scales/items cluster[23]. HCA is an exploratory technique that identifies groups of symptoms based on similarity between them: symptoms within the same cluster resemble each other, but differ from those in another symptom cluster[24]. The symptoms were included as continuous variables in the HCA and the similarity between the different clusters was assessed with the average-linkage-between-groups method, using the Euclidean distance. A dendrogram for the symptom clusters was plotted to illustrate the arrangement of the variables produced by clustering. A stronger similarity between the symptoms is reflected by a smaller distance between the branches. In order to determine the optimal number of clusters, a range of clusters from one (all symptoms clustered together) to 18 (all symptoms as separate single symptoms) was produced in the cluster membership analysis. The optimal number of clusters was based on the results of all three steps: the correlation analysis, the partial spearman matrix and the HCA. Subanalyses in predefined subgroups based on sex, age (<55 versus ≥55 years), WHO performance status (WHO=0/1 versus WHO=2), resection (biopsy versus resected) and type of tumor (glioblastoma versus non-glioblastoma) were performed to investigate whether the symptom clusters were invariant across subpopulations. Also, a subanalysis for tumor location was carried for patients with such information available.

After the identification of the clusters, patients were classified as having 'symptoms' or 'no symptoms' for both the symptom clusters and the single symptoms. Patients were classified as having symptoms when they reported mild to severe symptoms on at least one item in a symptom cluster, or on the single symptoms. Thereafter, univariable linear regression analyses were performed to determine the association between each symptom cluster and the five functioning scales (physical, cognitive, emotional, role and social functioning) and the global health status/quality of life scale. Subsequently, six multivariable linear regression analyses were performed for each functioning scale and the global health status/quality of life scale including the symptom cluster, single symptoms as well as relevant clinical/sociodemographic variables (sex, age, WHO PS, type of tumor and type of surgery), to determine the independent association between the symptom clusters and the functioning scales and the global health status/quality of life scale. All variables were included simultaneously, allowing adjustment for confounders for the associations between the symptom clusters and functioning. In each multivariable regression model, a two-tailed P-value <0.05 was considered statistically significant. In terms of clinical relevance, beta coefficients ≥10 were considered clinically relevant and beta coefficients ≥20 were considered a large effect, corresponding with a 10 and respectively 20 point change in HRQoL scores[25]. Analyses were performed using IBM SPSS, version 23.0[26], and R[27] with the qgraph package[22].

Results

Patient population
A total of 11 RCTs (Supplementary Table 1)[28-38] were analyzed, comprising 5287 patients with newly diagnosed glioma, of whom 4307 patients (81%) completed a full HRQoL baseline form. When comparing patients who completed a HRQoL form with patients who did not, a selection bias towards a healthier population was observed. Patients with a HRQoL form were younger (mean of 54 versus 57 years, p<.001), had a better WHO PS (percentage of patients with WHO score 0-1 was 88% versus 81%, p=.001), more often had a resection rather than biopsy (82% versus 79%, p=.025) and were less often diagnosed with glioblastoma (69% versus 73%, p=.007).

Level of functioning and symptom prevalence and severity
As a group, the included patients scored lower on all functioning scales and the global health status/quality of life scale compared to the general European population[19] (≥10 points difference between the groups), representing an impairment in functioning. On the individual patient level, impaired functioning was observed ranging from 38% of patients for physical functioning to 69% of patients for cognitive functioning (Table 2).

On the individual patient level, 4183 of 4307 included patients (97%) self-reported at least one symptom. Most patients tallied between one and four (40%) or between five and ten concurrent symptoms (44%), while 562 patients (13%) reported more than ten concurrent symptoms (Table 1). Among the 18 reported symptoms, fatigue was the most prevalent, experienced by 86% of patients, followed by drowsiness (60%) and motor dysfunction (55%)(Table 2). In terms of severity of the symptoms, the majority of symptoms were experienced as mild, and less often as moderate or severe (Figure 1).

Symptom clusters
The strength of the correlations between symptoms was low to moderate, ranging between .01 and .59, with the strongest correlations found for fatigue with drowsiness (.59) and motor dysfunction (.52), for pain and headache (.57) and for motor dysfunction with weakness of the legs (.52) (Supplementary Table 2). A graphical representation of the Spearman correlations between symptoms is presented in Figure 2, based on the partial correlation matrix. Fatigue and motor dysfunction were the symptoms that showed the largest centrality in terms of closeness, betweenness and strength, i.e. measures indicating the importance of the symptoms in the network, of the correlation with the other symptoms (Supplementary Figure 1).

Thereafter, HCA was performed to identify clusters based on the similarities between them, illustrated by the dendrogram (Figure 3). Based on the correlation analyses, the partial correlation matrix and the cluster membership analysis/dendrogram, the clustering step consisting of four symptom clusters and eight single symptoms was found most suitable based on both clinical considerations and the spearman correlation matrix. The four symptom clusters were as follows: 'pain cluster' (consisting of pain and headache), 'motor cluster' (consisting of motor dysfunction and weakness of the legs), 'fatigue cluster' (consisting of fatigue and drowsiness), and 'gastrointestinal/seizures/bladder control cluster' (consisting of nausea and vomiting, diarrhea, seizures and bladder control). The pain cluster, the motor cluster and the fatigue cluster were consistently

found across the subgroups: age, sex, WHO PS, tumor type and surgery, while the gastrointestinal/seizures/bladder control cluster was not observed in patients with a low WHO performance status and non-glioblastoma patients (data not shown). Data on tumor location were available for 2283 of 4307 of patients (53%). The motor cluster and fatigue cluster were consistently found in patients with different tumor locations, whereas the pain cluster and the gastrointestinal/seizures/bladder control cluster were not found across all tumor locations (data not shown).

Table 1. Baseline sociodemographic and clinical characteristics of all patients participating in the randomized controlled trials, and separately for those who have a valid baseline health-related quality of life (HRQoL) form.

	All patients (n=5287), n (%)	Patients who completed a HRQoL form (n=4307), n (%)	Patients who did not complete a HRQoL baseline form (n=980), n (%)	P-value
Male	3191 (60)	2659 (62)	532 (54)	<.001
Female	2096 (40)	1648 (38)	448 (46)	
Age (mean, SD)	54 (14)	54 (14)	57 (13)	<.001
Gr II/III, A/O/OA	1594 (30)	1331 (31)	263 (27)	.007
Gr IV glioblastoma	3693 (70)	2976 (69)	717 (73)	
WHO PS 0-1	4597 (87)	3805 (88)	792 (81)	
WHO PS 2	659 (13)	487 (11)	172 (18)	.001
Missing	31 (1)	15 (0)	16 (2)	
Biopsy	985 (19)	780 (18)	205 (21)	
Resection	4287 (81)	3514 (82)	773 (79)	.025
Missing	15 (0)	13 (0)	2 (0)	
0 symptoms	-	124 (3)	-	-
1-4 Concurrent symptoms	-	1725 (40)	-	
5-10 concurrent symptoms	-	1896 (44)	-	
>10 concurrent symptoms	-	562 (13)	-	

Gr, grade of the tumor; A, Astrocytoma; O, Oligondendroglioma; AO, Oligoastrocytoma; WHO, World Health Organisation; Performance Status; SD, standard deviation

Table 2. Number of patients with impaired functioning and with symptoms

Functioning scales	mean (SD)	Patients with impaired functioning [a] n (%)
Global health status	63.9 (22.6)	1828 (42)
Physical functioning	81.5 (22.1)	1648 (38)
Role functioning	65.2 (33.3)	2351 (55)
Emotional functioning	71.7 (23.8)	1824 (42)
Cognitive functioning	72.5 (27.3)	2961 (69)
Social functioning	69.3 (30.3)	2865 (67)
Symptoms	**mean (SD)**	**Patients with symptoms [b] n (%)**
Fatigue (scale)	34.9 (25.3)	3706 (86)
Nausea and vomiting (scale)	4.6 (12.1)	759 (18)
Pain (scale)	14.7 (21.7)	1882 (44)
Dyspnea (item)	10.9 (21.3)	1063 (25)
Insomnia (item)	24.9 (29.9)	2135 (50)
Appetite loss (item)	10.8 (22.1)	1008 (23)
Constipation (item)	12.7 (24.2)	1135 (26)
Diarrhea (item)	5.6 (15.5)	588 (14)
Visual disorder (scale)	13.2 (20.3)	1924 (45)
Motor dysfunction (scale)	17.4 (22.8)	2363 (55)
Communication deficit (scale)	19.1 (25.6)	2304 (54)
Headache (item)	19.9 (26.3)	1894 (44)
Seizures (item)	6.1 (18.6)	519 (12)
Drowsiness (item)	27.5 (27.4)	2593 (60)
Hair loss (item)	9.8 (22.8)	833 (19)
Itchy skin (item)	9.8 (20.8)	949 (22)
Weakness of legs (item)	14.8 (26.0)	1288 (30)
Bladder control (item)	8.1 (20.3)	726 (17)

[a] patients who reported a ≥10 points lower score compared to the normgroup[18]; [b] patients who reported any symptoms (mild to severe)

Figure 1. Severity of symptoms for the selected symptoms scales/items measured with the EORTC QLQ-C30 and QLQ-BN20 questionnaires. A darker color indicates more severe symptoms. The single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, headache, seizures, drowsiness, hair loss, itchy skin, weakness of the legs, and bladder control) were rated as: no, mild, moderate, and severe. For the symptom scales (fatigue, visual disorder, motor dysfunction, communication deficit, nausea and vomiting, and pain), the symptoms consisted of multiple items. The figure represents the severity on a 0–100 scale, where 0 (white) indicates no symptoms and 100 (black) indicates severe symptoms.

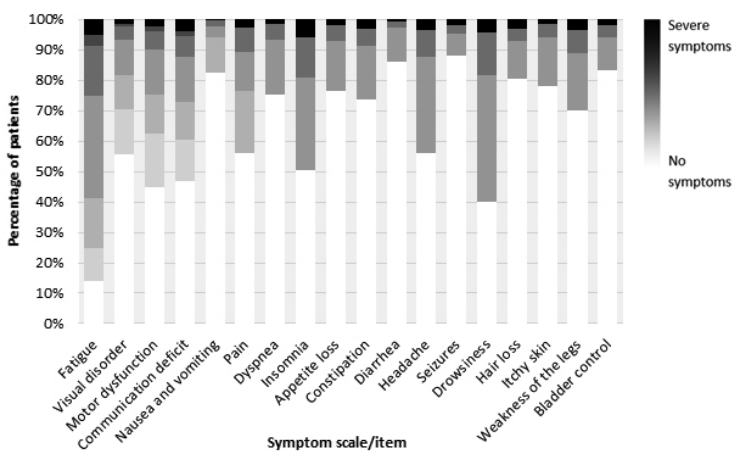


Figure 2. Spearman correlation matrix of selected symptoms measured with the EORTC QLQ-C30 and QLQ-BN20 questionnaires. Thicker and darker lines represent stronger partial correlations. Continued lines represent positive partial correlations, dotted lines represent negative partial correlations. The position of the variables represent the closeness, node strength, and betweenness of the variables. Central variables with more connections and thicker lines are most strongly correlated with other variables. AP, appetite loss; BC, bladder control; CD, communication deficit; CO, constipation; DI, diarrhea; DY, dyspnea; DR; drowsiness; FA, fatigue; HA, headache; HL, hair loss; SL, insomnia; IS, itchy skin; MD, motor dysfunction; NV, nausea and vomiting; PA, pain; SE, seizures; VD, visual disorder; WL, weakness of the legs.

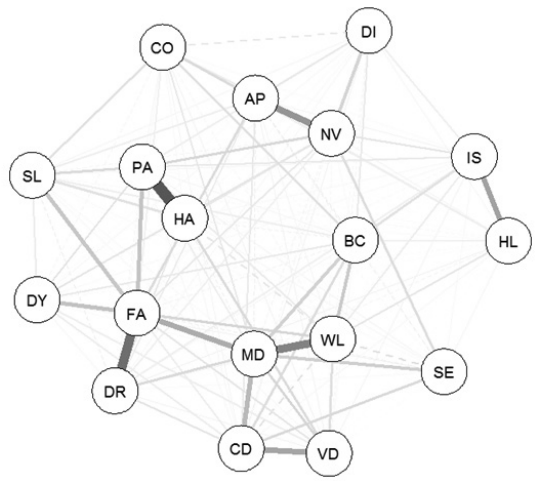
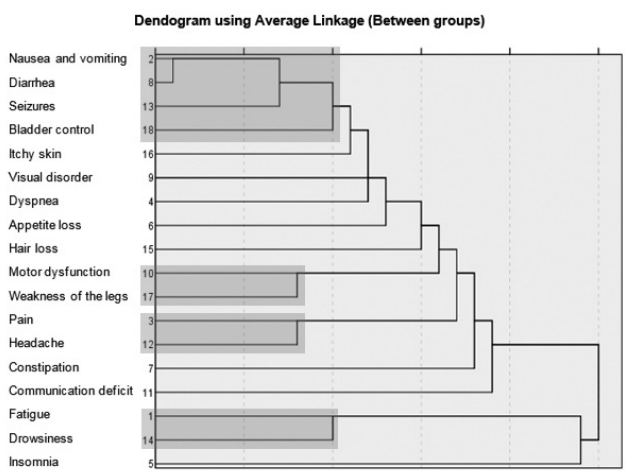


Figure 3. Dendrogram illustrating the results of the hierarchical cluster analysis (HCA). The distance at which the branches join indicates the similarity between the symptoms (shorter branches represent greater similarity). Symptoms with greater similarity were clustered first, presented on the left side of the figure. This cluster analysis shows that nausea and vomiting were clustered as a first step, followed by seizures (step 2). Next, pain and headache (step 3) and motor dysfunction and weakness of the legs were clustered (step 4), and so on. The optimal number of clusters was determined at step 6, resulting in the 4 clusters indicated in this figure (indicated in gray).



Prevalence of the symptom clusters
Most patients (88%) experienced symptoms in the fatigue cluster, followed by the motor cluster (59%), the pain cluster (56%) and the gastrointestinal/seizures/bladder control cluster (43%). The majority of patients experienced symptoms in several symptom clusters: 79% of the patients experienced symptoms in at least two clusters, 51% of the patients experienced symptoms in at least three clusters and 22% of the patients experienced symptoms in all four clusters. The symptom clusters that occurred most frequently together were the fatigue and the motor cluster, which was experienced by 56% of the patients, and the fatigue and pain cluster, experienced by 53% of the patients.

Association between symptom clusters and functioning and global health status/quality of life
Results of the univariable regression analyses showed that the four symptom clusters negatively influenced all functioning scales and the global health status/quality of life scale, except for the association between the pain cluster and physical functioning (beta's ranged from -9.25 to -30.94, all p<.001). Results of the multivariable regression analyses indicated that only the motor cluster and the fatigue cluster negatively influenced functioning in the presence of other factors (Table 3). The motor cluster had a clinically relevant negative impact on patients' physical, role, and social functioning (Beta's ranged from -11.3 to -15.9, all p<.001), whereas the fatigue cluster had a clinically relevant negative impact on the patient's role functioning (Beta -12.3, p<.001). With respect to the single symptoms, visual disorder and communication deficit negatively influenced cognitive functioning in the presence of other factors (Table 3).

In addition, results of sub-analyses showed that the impact of functioning was larger, and entailed more functioning scales in patients with symptoms in ≥3 symptom clusters compared to patients with symptoms in only one or two clusters (data not shown). For example, when selecting only those patients with symptoms in one symptom cluster (13% of the patients), there was no clinical impact on patients' functioning scales. When selecting patients who experienced symptoms in ≥3 clusters (51% of the patients), the motor cluster had a clinically relevant negative impact on the same functioning scales, but with a larger impact (Beta's ranged from -13.4 to -16.6), and the fatigue cluster had a clinically relevant negative impact on global health, physical functioning, and social functioning, in addition to role functioning. Also, the impact was larger (betas ranged from -13.3 for the global health status to -27.8 for role functioning). Consequently, patients who experience symptoms in more symptom clusters are likely to experience a larger impact on functioning.

Table 3. Multivariable linear regression analysis showing the association between the four symptom clusters and the functional scales and the global health status/quality of life scale, adjusted for important confounding variables.

Cluster	HRQoL Functioning scales Beta, p-value					
	Global Health status/quality of life scale	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Symptom clusters[a]						
Pain	-5.7 <.001	-2.9 <.001	-4.9 <.001	-5.4 <.001	-3.5 <.001	-3.8 <.001
Motor	-8.8 <.001	-11.6* <.001	-15.9* <.001	-4.5 <.001	-7.3 <.001	-11.3* <.001
Fatigue	-5.7 <.001	-3.8 <.001	-12.3* <.001	-4.9 <.001	-3.7 <.001	-8.3 <.001
Gastrointestinal/seizures/bladder control	-3.7 <.001	-3.6 <.001	-3.4 <.001	-3.6 <.001	-1.3 .067	-2.8 .001
Single symptoms[a]						
Dyspnea	-5.1 <.001	-6.8 <.001	-9.4 <.001	-5.5 <.001	-3.1 <.001	-6.6 <.001
Insomnia	-1.3 .032	-1.3 .020	-2.9 .001	-7.3 <.001	-.46 .498	-5.8 <.001
Appetite loss	-3.8 <.001	-3.6 <.001	-3.4 .001	-5.3 <.001	-5.2 <.001	-4.5 <.001
Constipation	-2.0 .003	-.07 .905	-2.0 .039	-2.5 .001	-3.3 <.001	-1.8 .063
Visual disorder	-4.9 <.001	-2.9 <.001	-6.9 <.001	-4.5 <.001	-14.6* <.001	-5.7 <.001
Communication deficit	-2.6 <.001	-.36 .535	-3.3 <.001	-4.0 <.001	-16.4* <.001	-4.3 .87
Hair loss	-1.0 .172	-.82 .247	1.7 .130	-2.8 .001	.11 .894	-2.5 .018
Itchy skin	.33 .655	-.42 .535	.30 .778	-.48 .555	.63 .448	-2.5 .013
Clinical/sociodemographical variables						
Age	-.12 <.001	-.13 <.001	-.05 .139	-.01 .861	-.05 .064	.06 .076
Female sex (ref: male)	-.24 .689	-4.62 <.001	-.00 .998	-2.1 .001	-.96 .157	-.36 .668
Surgery (ref: biopsy only)	2.26 .003	1.34 .06	-.27 .809	1.78 .034	1.79 .037	.50 .64
Gr IV glioblastoma (ref: Gr II/III, A/O/OA)	-.15 .831	3.2 <.001	-.84 .425	-1.64 .037	-.28 .731	.51 .61
WHO PS 2 (ref: WHO PS 0-1)	-3.3 <.001	-7.8 <.001	-9.7 <.001	-1.27 .015	-3.18 <.001	-5.4 <.001

Gr, grade of the tumor; A, Astrocytoma; O, Oligondendroglioma; AO, Oligoastrocytoma; WHO, World Health Organisation; PS, Performance Status; a severity of symptoms ranging from mild to severe; *clinically relevant difference (≥10 points)

Discussion

The results of this study show that glioma patients experience multiple symptoms simultaneously shortly after surgery, but before initiation of further anti-tumor treatment. This suggests the need for comprehensive symptom assessment at baseline, in order to address symptoms in a timely manner. Consistent with the literature, overall quality of life and functioning was impaired at randomization, i.e. before the start of the allocated treatment, reflecting the impact of the disease and possible surgical and supportive treatment side-effects such as fatigue, insomnia and nausea and vomiting. The most frequently reported symptoms, occurring in more than 40% of the patients were fatigue, drowsiness, motor dysfunction, communication deficits, insomnia, visual disorders, headache and pain, corresponding with the core symptoms in glioma patients[8,39-42]. Results of the correlation analyses (revealing low to moderate correlations), partial correlation matrix and HCA together identified four symptom clusters: a pain cluster, a motor cluster, a fatigue cluster, and a gastrointestinal/seizures/bladder cluster.

The fatigue cluster, comprising both fatigue and drowsiness, was most often prevalent (88%). This result indicates fatigue already is an important symptom in early stages of disease, as patients included in this study were newly diagnosed patients, assessed after surgery but before further anti-tumor treatment. In a previous study in primary brain tumor patients, fatigue clustered with pain, insomnia, motor problems and depression[8]. Although these results were not replicated in the current study, fatigue was more strongly associated with pain, insomnia and motor problems compared to the other symptoms in terms of correlations and position in the network matrix (Figure 2). Mood disorders/complaints were not assessed in the current study as a single symptom. Nevertheless, the emotional functioning scale, that entails questions on mood, was not found to be independently associated with the fatigue cluster in our study.

The second most prevalent cluster was the motor cluster, experienced by 59% of patients. Motor dysfunction and muscle weakness can both be caused by the presence of a tumor in the motor brain region, or even when the tumor is located outside the motor cortex, due to diminished functional connectivity[43]. Also, it can be a side effect of corticosteroids. Indeed, patients who used corticosteroids reported more problems in the motor cluster (67% versus 52%). We found that pain and headache clustered together and one reason may be that pain has many dimensions and patients may have interpreted the item 'Have you had pain' as both bodily pain or headache. Indeed, headache is a known presenting symptom in brain tumor patients[44]. Similar to what has been reported in previous studies, headache and pain were present in almost half of the patients (both 44%)[45,46]. Most patients who experienced pain also experienced headache (74%), and vice versa (73%). However, although the correlation between pain and headache was the second highest found in our study (.57), it can still be interpreted as moderate, indicating that they do not measure the same concept. This is also true for fatigue and drowsiness, with a correlation of .59.

One unexpected finding is the clustering of nausea and vomiting, diarrhea, seizures and bladder control. Clustering of gastrointestinal symptoms was found in earlier studies, however, in our study the symptoms appetite loss and constipation did not cluster with nausea and vomiting and diarrhea. An explanation for the clustering of these symptoms may be statistical, as each of these symptoms showed floor effects[41]. These symptoms are the four least reported, all experienced by less than 25% of

the patients (Table 2), and clustering of these symptoms in the HCA may be the result of numerical similarities rather than clinical similarities.

Although almost all symptom clusters showed a statistically significant association with the level of functioning and the global health status/quality of life, only the motor and fatigue clusters were independently associated, i.e. adjusted for important clinical characteristics, with role functioning (both clusters), physical functioning and social functioning (the motor cluster) at a level that can be considered clinically relevant. Post hoc analyses showed that patients who experience symptoms in more symptom clusters, experience impaired functioning to a larger extent and on more functioning scales. Although not surprising, this study is the first to observe an association between symptom clusters and functioning in glioma patients. Similar results were found in other cancer populations: a pain/fatigue and cognitive cluster impacted physical, role and social functioning in advanced cancer patients[10], and an emotional cluster was found to negatively influence role and social functioning in patients with lung, breast, colorectal and stomach cancer undergoing palliative chemotherapy[47]. The results of our study suggest that a clinically relevant improvement in functioning could be achieved by relieving motor and fatigue symptoms in glioma patients. As the fatigue and motor clusters were also the most frequently affected clusters, and since most patients experienced symptoms in both, reducing the burden of these symptoms may benefit the majority of glioma patients in terms of improved functioning. Also, fatigue and motor problems were found to be most central to other symptoms (Figure 2, Supplementary Figure 1), suggesting that alleviating these symptoms most likely will positively influence the other symptoms as well. Fatigue and motor problems are, however, not easily treated. There is little evidence for pharmacological and non-pharmacological interventions for fatigue in glioma patients[48,49]. The literature on interventions targeting motor problems is scarce, although mobility was improved in patients undergoing multidisciplinary treatment including physical exercise[50,51].

One important limitation of this study is the selection bias towards a healthier population, as the patients included in our analyses were those deemed fit enough to participate in an RCT and who also completed HRQoL questionnaires. This could potentially limit the generalizability of the results. Another limitation is that only baseline data were used in the analyses, and we do not know if the clusters identified pre-treatment are stable during follow-up. Moreover, only symptoms were included that were measured with the QLQ-C30 and the QLQ-BN20 questionnaires. Some relevant symptoms, such as mood disorders or cognitive complaints, were not covered, and therefore the use of instruments that specifically and extensively measure symptoms may be more useful. Furthermore, we included glioma patients with different tumor types in the analyses, and besides the subgroups glioblastoma/non-glioblastoma, could not look further into different molecular subtypes. One implication could be that the results of our study may not be generalizable to all glioma subtypes, as we saw for the gastrointestinal/seizures/bladder control cluster, which was not found in non-glioblastoma patients. Another limitation is that, in the regression analyses, the severity of the symptoms was not taken into account, as patients were classified as having 'no symptoms' or 'symptoms'. One could hypothesize that patients with more severe symptoms in the symptom clusters experience more impaired functioning than patients with mild symptoms only. Another limitation concerns the choices made regarding the definition of 'symptom clusters' and the method used to identify them. First, different definitions of a symptom cluster exist, and there is no consensus on the minimum number of

symptoms required to form a symptom cluster. We chose to define a symptom cluster consisting of at least two symptoms. Of course, this choice impacted our results, as for example the fatigue cluster only consists of two symptoms. Further, the identified symptom clusters, for which we have combined three frequently used methods, i.e. correlation analysis, partial correlation analysis and HCA, might have been different when other methods were used, for example factor analyses. Which is the best method remains a matter of debate[52].

Even though the mentioned selection bias may hamper generalizability of the study results is limited because of the overrepresentation of patients with a better health status, these results may have potential clinical implications. As most patients experience between five and ten symptoms simultaneously, many symptoms may remain unnoticed as only the most severe symptoms are likely to be discussed during a consultation, and subsequently treated. Awareness that patients experience multiple concurrent symptoms, and being aware of the existence of symptom clusters and their association with functioning as measured with a self-report questionnaire, might help clinicians to identify and treat patients with these symptoms in a more timely manner. Also, the awareness of the presence of these co-occurring symptoms could help clinicians to develop interventions with the intention to treat or prevent problems that appear together. Multimodal rehabilitation programs, for example, can be effective in treating multiple symptoms[53], and may subsequently improve functioning. Furthermore, the identified symptom clusters may provide insight into the underlying mechanisms that caused these symptoms. It should be kept in mind, however, that the current study identified symptom clusters before the initiation of anti-tumor treatment including radiotherapy and/or chemotherapy. Further research should aim at investigating symptom clusters over time, to determine whether the identified symptom clusters are stable during the treatment and follow-up phase. Ideally, a prospective study investigating symptom clusters at baseline and during follow-up phases would allow to examine the impact of a specific treatment regimen and the stability of symptom clusters over time. Moreover, future studies could also examine the (added) predictive value of symptom clusters for survival. This would be helpful in initiating interventions at the time patients benefit most from these treatment strategies.

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Supplementary data

Supplementary table 1. Included RCTs

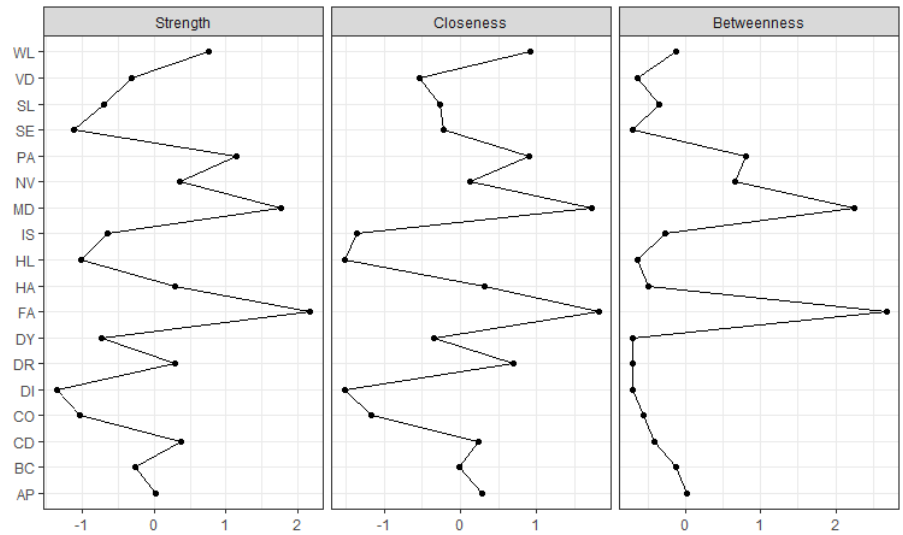
Included RCTs	Patient population	Study sample size	reference
ANOCEF	Elderly glioblastoma	81	1
AVAGLIO	glioblastoma	921	2
GLARIUS	MGMT-non methylated glioblastoma	170	3
EF-14	glioblastoma	700	4
EORTC 26951	Anaplastic oligodendroglioma	292	5
EORTC 22981-26981	glioblastoma	573	6
EORTC 26071 (CENTRIC)	GBM MGMT methylated	504	7
EORTC 22033-26033	Low-grade glioma	700	8
EORTC 26053-22054 (CATNON)	non-1p/19q-co-deleted anaplastic glioma	745	9
NOA-08	Grade III and IV astrocytoma in elderly	373	10
NORDIC	Elderly glioblastoma	342	11

Supplementary table 2. Spearman correlations between the symptom scales/items *Significant

Symptom	FA	NV	PA	DY	SL	AP	CO	DI	VD	MD	CD	HA	SE	DR	HL	IS	WL	BC
Fatigue	-																	
Nausea and vomiting	.27*	-																
Pain	.42*	.29*	-															
Dyspnea	.36*	.19*	.25*	-														
Insomnia	.32*	.14*	.29*	.19*	-													
Appetite loss	.29*	.37*	.22*	.15*	.16*	-												
Constipation	.20*	.14*	.15*	.09*	.16*	.18*	-											
Diarrhea	.13*	.18*	.14*	.09*	.09*	.14*	.02*	-										
Visual disorder	.32*	.13*	.23*	.20*	.17*	.16*	.14*	.06*	-									
Motor dysfunction	.52*	.17*	.30*	.26*	.22*	.17*	.19*	.09*	.35*	-								
Communication deficit	.29*	.13*	.22*	.19*	.18*	.17*	.13*	.09*	.37*	.38*	-							
Headache	.30*	.23*	.57*	.16*	.23*	.17*	.12*	.10*	.22*	.19*	.18*	-						
Seizures	.11*	.13*	.13*	.10*	.07*	.05*	.05*	.04*	.10*	.19*	.17*	.10*	-					
Drowsiness	.59*	.22*	.29*	.26*	.19*	.24*	.16*	.11*	.27*	.41*	.27*	.24*	.11*	-				
Hair loss	.13*	.12*	.10*	.07*	.06*	.12*	.09*	.07*	.08*	.11*	.09*	.08*	.06*	.13*	-			
Itchy skin	.16	.17*	.17*	.11*	.11*	.13*	.08*	.10*	.12*	.14*	.10*	.13*	.07*	.16*	.29*	-		
Weakness of the legs	.41*	.14*	.25*	.25*	.17*	.16*	.13*	.07*	.27*	.52*	.21*	.14*	.07*	.32*	.14*	.16*	-	
Bladder control	.22*	.11*	.17*	.17*	.14*	.08*	.15*	.10*	.17*	.31*	.22*	.10*	.08*	.20*	.11*	.15*	.29*	-

*Significant correlation at the .01 level

Supplementary figure 1. Centrality plot showing the centrality indices: strength, closeness and betweenness between the symptoms. Node strength sums all edges of a symptom with all other symptoms, estimating how strongly a node is directly connected with the network. Closeness provides a measure of how strongly a node is connected indirectly with the network by taking the inverse of all shortest path lengths between a symptom and all other symptoms. Betweenness which indicates how often a symptom is in the shortest paths between other symptoms[12]. Together these measures indicate the importance of the symptoms in the network, with higher values indicating more importance. In this figure, motor dysfunction and fatigue are the most important symptoms.



AP, appetite loss; BC, bladder control; CD, communication deficit; CO, constipation; DI, diarrhea; DY, dyspnea; DR; drowsiness; FA, fatigue; HA, headache; HL, hair loss; SL, insomnia; IS, itchy skin; MD, motor dysfunction; NV, nausea and vomiting; PA, pain; SE, seizures; VD, visual disorder; WL, weakness of the legs.

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