Review Article

Neurocognitive state and quality of life of patients with glioblastoma in Mediterranean countries: a systematic review

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Background: Gliomas are the most common primary tumors of the central nervous system (CNS). The most common subtype of glioma in adults is grade IV astrocytoma, known as glioblastoma (GB) multiforme. Despite advances in treatment, GB remains a lethal tumor with a poor prognosis, and patients face serious quality of life (QoL) issues. Its poor prognosis is a real public health problem. The present study aimed to determine the exact neurocognitive status and QoL in patients with GB in the Mediterranean region and the different predictive factors responsible for their deterioration.

Methods: This systematic review was conducted in accordance with PRISMA guidelines. The protocol was registered in the PROSPERO (Identifier: CRD42020188936). The following databases have been independently searched by 2 authors: PubMed, Science Direct, Scopus and Google Scholar.

Results: Thirteen studies were selected (n=13). Four studies (n=4) focused solely on cognitive assessment, five studies (n=5) focused on quality-of-life assessment, and four (n=4) were simultaneously assessed QoL and neurocognitive status. The majority of studies in this review use (Mini-Mental State Examination, MMSE) for an overall cognitive assessment (n=5), other studies use specific batteries for an in-depth assessment of cognitive functions (n=3). The study revealed several affected functions: short and long-term memory, executive functions (EFs), and visuo-constructive abilities. Scale of European Organization for Research and Treatment of Cancer and the Functional Assessment of Cancer Therapy are among the most widely used instruments for assessing QoL. For factors influencing neurocognitive status and QoL, the present review found that: The Karnofsky Performance Scale (KPS), tumor location, age, sex and type of treatment are the most identified. Other studies have reported other factors, such as tumor progression, development of emotional distress, and coping strategies adopted.

Discussion: We conclude that there were many changes in patients with GB during the course of the disease and that most of them were related to age and disease progression. The use of coping strategies based on social support has a positive impact on the QoL.

Keywords: Quality of life (QoL); cognition; systematic review; glioblastoma (GB); Mediterranean

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Introduction

Gliomas are the most common primary tumors of the central nervous system (CNS). The most common subtype of glioma in adults is grade IV astrocytoma, known as glioblastoma (GB) according to the World Health Organization (WHO) (1). GB accounts for 54% of all glioma (2). The incidence of GB is 1.6 times higher in men than in women and twice as high in Caucasians compared to Africans and African Americans, with a lower incidence in Asians and American Indians (3).

The current standard treatment of GB follows the Stupp protocol, which consists of radiotherapy (RT) with both concurrent and adjuvant temozolomide (TMZ) (4). The Karnofsky Performance Scale (KPS) score is a widely used measure to stratify patient prognosis and determine appropriate management in GB (5).

Despite advances in neurosurgery, RT and chemotherapy, GB remains a lethal tumor with a poor prognosis, with a median overall survival (OS) estimated between 15 to 17 months (6-12), and a 5% survival rate at five years (2). It is therefore a serious disease involving, in the short term, the vital prognosis. Referring to its poor prognosis, GB constitutes a real public health problem, as well as a challenge for health systems around the world (13,14).

In addition, patients with GB face serious quality of life (QoL) decline, including motor deficits, personality changes, cognitive deficits, language disorders (aphasia) or visual field defects (15,16). Indeed, cognitive deterioration is considered to be the main indicator of poor disease progression after treatment (17,18), moreover a comprehensive neuropsychological assessment is time consuming and difficult for patients. This has led to the use of cognitive screening tools such as the Mini-Mental State Examination (MMSE) (19). Therefore, the preservation of QoL and neurocognitive abilities is of great importance, given the short life expectancy of patients (20-26).

Several studies have shown that age is an important prognostic factor in patients with GB (27,28). In this sense, a recent review of the literature revealed several predictors of deterioration in QoL and neurocognitive status in patients with GB including, age, sex, type of treatment and psychological status of the patient (29). Other studies consider that factors affecting neurocognitive function may be related to the patient, the tumor and the treatment (30-33).

To improve QoL, the American Society of Clinical Oncology (ASCO) guidelines recommend palliative care for patients with advanced cancer (34). A recent meta-analysis of studies confirms that palliative care is associated with improved QoL and reduced physical and psychological symptom burden (35).

Several studies have found that Health-related quality of life (HRQOL) may differ in patient populations with glioma, with different geographic, social and cultural backgrounds (16,36-38); in fact, the perception of HRQoL and the way in which health problems are expressed can vary from one country to another, which can clarify this difference (39). In this sense, the Association of Radiation Therapy and Oncology of the Mediterranean mentioned in its report the heterogeneity of the data of GB patients in the Mediterranean countries (namely survival and QoL), and that this may be due to the difference in socioeconomic status between the countries of southern Europe and North Africa or the Middle East (40).

In this regard, and considering the importance of studying QoL for proper management of symptoms, pain, and reduction of complications and treatment costs, and in the absence of extensive studies on the exact QoL status of GB patients in this region. The present study aimed to determine the exact neurocognitive status and QoL in patients with GB in the Mediterranean region and the different predictive factors responsible for their deterioration.

We present our article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1900) (41).

Methods

The protocol was registered and published (PROSPERO: 2020 CRD42020188936) (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188936).

Research strategy

The following databases have been independently researched by two authors (MAB et AK): PubMed, ScienceDirect, Scopus and Google Scholar).

Initially, titles and abstracts were selected for relevant articles by two independent authors (MAB and AK). The decisions were blinded, in case of disagreement, the two authors discussed the disparities and resolved them.

The inclusion Criteria for the selection of studies are as follows: (I) articles published in English and French in the Mediterranean region;(II) published between 2005 and March 2020 (III) with GB patients, aged over 18 years,

Table 1 Keywords used for database searches

Participant	Outcome	Location
"Glioblastoma" OR "high-grade glioma	"Quality-of-life" or "neurocognitive-functions" or "neurocognitive states"	Albania OR Algeria OR Bosnia and Herzegovina OR Croatia OR Cyprus OR Egypt OR France OR Greece OR Israel OR Italy OR Lebanon OR Libya OR Malta OR Monaco OR Montenegro OR Morocco OR Palestine OR Slovenia OR Spain OR Syria OR Tunisia OR Turkey.

histologically confirmed (whole population or reported separately as a sub-population).

Studies published outside the Mediterranean, clinical trials, randomized studies, published case series (n≤10), systematic reviews, scale validation studies, letters to the editor and conference papers were excluded.

The key words used are: "Quality-of-life" or "neurocognitive-functions" or "neurocognitive states" and "glioblastoma" or "high-grade glioma"/"Qualité de vie" ou "Fonction Neurocognitive" et "Glioblastome" ou "Gliome de haut grade" (*Table 1*).

Data extraction and analysis

Data extraction was carried out independently by two authors (MAB and AK). The data extracted from the selected articles were as follows: age, gender, type of treatment, the tool used to assess neurocognitive status and QoL, timing of data collection, neurocognitive status and QoL scores, and predictive factors of neurocognitive status and QoL in GB patients.

Risk of bias in individual studies

The assessment of the risk of bias was conducted independently by two authors using The Joanna Briggs Institute's "Checklist for Analytical Cross Sectional Studies (42).

Both reviewers independently assessed the methodological quality of the studies, and then the agreement between the results of the two reviewers was analyzed by the Kappa statistical coefficient (κ).

Results

Study characteristics

Thirteen studies (n=13) were selected (the flowchart is shown in *Figure 1*). According to the study design (n=13) were cross-sectional observational studies measuring the neurocognitive status and/or QoL in patients with GB (38,43-54).

Four studies (n=4) focused solely on cognitive assessment (45,50,51,54), five studies (n=5) focused on quality-of-life assessment (43,46,47,49,53), and four (n=4) were simultaneously assessed QoL and neurocognitive status (38,44,48,52).

In ten studies (n=10), patients began follow-up testing sessions after surgery and before chemoradiotherapy (38,43,44,46-52), In two other studies (n=2), data collection was before and after surgery (45,54), and only one study (n=1) whose follow-up started from the appearance of a recurrent tumor (53).

The Kappa statistical coefficient was (κ=0.67), the evaluation of the quality of the studies was considered "good" with a mean score of 7.38/8 (the results of the methodological evaluation of the studies are presented in *Table 2*).

According to the age of the target population of the selected studies, nine studies (n=10) targeted all ages (over 18 years of age) (38,43-46,49,51-54) and three studies (n=3) focused only on an older population (≥65 years old) (47,48,50).

The studies in this review found a mean age ranging from 49 to 74 years, however, only one study did not specify the patients mean age (51). As for the sex ratios, eleven studies (n=11) revealed a male predominance with a ratio between 1.03 and 2.25 (43-46,48-54), and a ratio between 0.61 and 0.95 was reported in two other studies (38,47,55) (*Table 3*).

Assessment of neurocognitive functions in patients with GB

In the present review, the choice of cognitive tests used to assess brain tumors depends on the purpose of the assessment, the majority of studies in this review use MMSE for an overall cognitive assessment (n=5) (38,44,48,51,52), other studies use specific batteries for an in-depth assessment of cognitive functions (n=3) (45,50,54) (*Table 4*).

Studies using specific batteries for an in-depth assessment of cognitive functions have revealed several affected

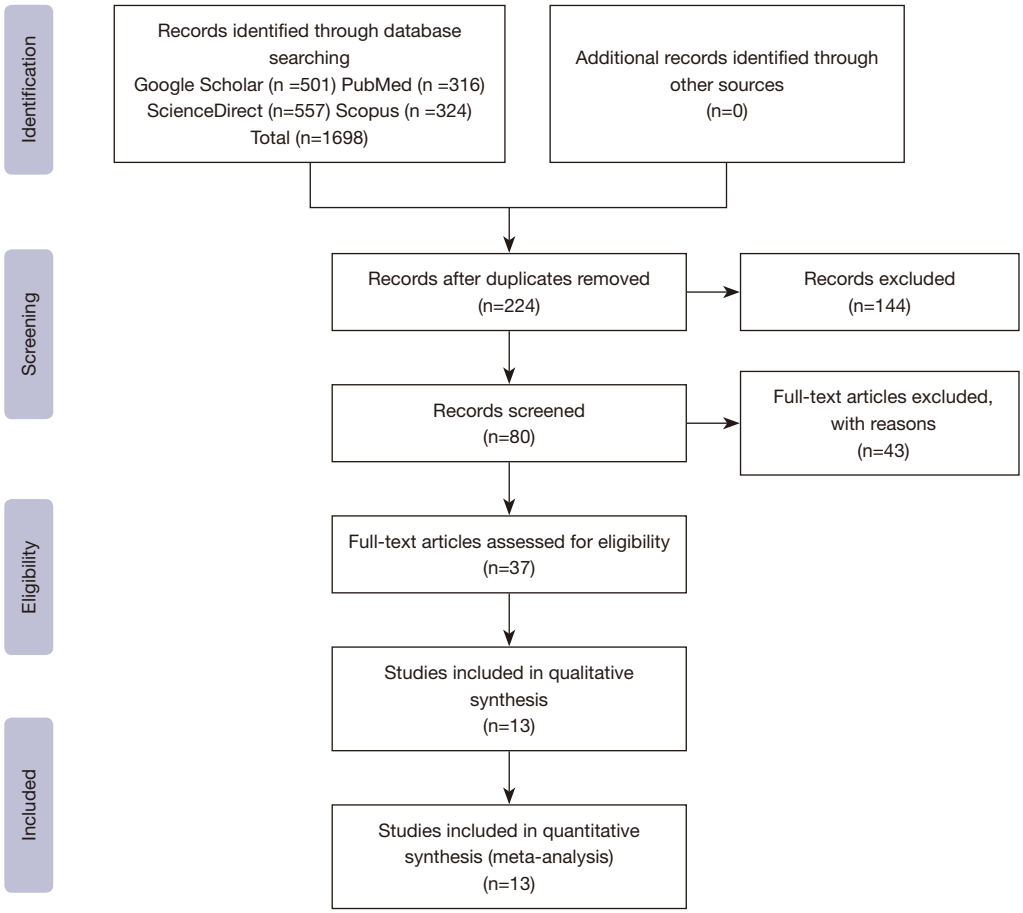

Figure 1 Flow diagram of included studies.

Table 2 Quality assessment tool for cross-sectional studies

Criteria	(43)	(44)	(45)	(52)	(46)	(47)	(48)	(49)	(50)	(38)	(51)	(54)	(53)
Were the criteria for inclusion in the sample clearly defined?	1	1	1	1	1	1	1	1	0	1	1	1	1
Were the study subjects and the setting described in detail?	1	1	1	1	1	1	[1]	1	1	1	1	1	1
Was the exposure measured in a valid and reliable way?	1	1	1	1	1	1	1	1	1	1	1	1	1
Were objective, standard criteria used for measurement of the condition?	1	1	1	1	1	1	1	1	1	1	0	1	1
Were confounding factors identified?	1	1	1	1	1	1	1	1	1	1	0	0	1
Were strategies to deal with confounding factors stated?	1	1	1	1	1	1	0	0	1	0	0	1	1
Were the outcomes measured in a valid and reliable way?	1	1	1	1	1	1	1	1	1	1	1	1	1
Was appropriate statistical analysis used?	1	1	1	1	1	1	1	1	1	1	1	1	1
Score	8	8	8	8	8	8	7	7	7	7	5	7	8

Table 3 Patient demographics and study designs in included studies

Author [year]	Country	Type of study	Assessment objective		Sample size GB/ All high Glioma	Age, Mean age [Min, Max]	Sex ratio	Side			Treatment		
			QoL	NCF				Left, n [%]	Right, n [%]	Bilateral, n [%]	Surgery		CCR RT/RT + TMZ (%)
											Partial, %	Total, %	
Tanzilli [2020] (50)	Italy	A cross-sectional		*	79	74 [65–85]	2.16	38 [48]	33 [42]	8 [10]	39	24	62
Yavas [2012] (38)	Turkish	A cross-sectional	*	*	65/118	52 [19–70]	0.61	56 [47.5]	59 [50]	3 [2.5]	67.8	17.8	95.8
Lombardi [2018] (52)	Italy	A cross-sectional	*	*	111	60 [25–79]	1.64	51 [46]	58 [52.2]	2 [1.8]	54.1	37.8	100
Dallabona [2017] (45)	Italy	A cross-sectional		*	26/30	59.3 [32–83]	1.72	18 [60]	12 [40]	–	N/A	N/A	N/A
Minniti [2009] (47)	Italy	A cross-sectional	*		43	73 [70–79]	0.95	–	–	–	44.18	16.30	100
Minniti [2013] (48)	Italy	A cross-sectional	*	*	65	73 [70–81]	1.03	–	–	–	72.30	15.38	100
Younis [2009] (51)	Egypt	A cross-sectional		*	17/52	[22–67]	1.36	–	–	–	23.04	4.69	N/A
Zigiotto [2020] (54)	Italy	A cross-sectional		*	23/33	56 [75–32]	1.87	13 [56.5]	10 [43.5]	–	–	100	N/A
Lucchiari [2015] (46)	Italy	A cross-sectional	*		49/73	48.9 [26–65]	1.92	–	–	–	N/A	N/A	100
Giovagnoli [2005] (53)	Italy	A cross-sectional	*		43/94	44.5	1.76	38 [40.4]	56 [59.6]	–	69.14	N/A	100
Scartoni [2020] (49)	Italy	A cross-sectional	*		26	53.4 [30–69]	2.25	13 [50]	13 [50]	–	N/A	N/A	100
Baumstarck [2016] (44)	France	A cross-sectional	*	*	37/42	58.3 [18–79]	1.47	–	–	–	N/A	N/A	93/N/A
Baumstarck [2018] (43)	France	A cross-sectional	*		33/38	64 [49–71]	1.71	–	–	–	N/A	N/A	89.5/N/A

*, available; N/A, not available; QoL, quality of life; NCF, neurocognitive functions; GB, glioblastoma; CCR, concomitant chemoradiotherapy; RT, radiotherapy; TMZ, temozolomide.

functions. For the first study, short and long term memory (LTM), executive functions (EFs), and visuo-constructive abilities (CA) were the functions most affected at follow-up (50). For the second study, the highest percentages of patients with impairments were found for long-term memory tasks (both visuospatial and verbal), constructive skills, and the visual attention task (45). Moreover, in the third study, memory and constructive praxis were the most affected (54).

For neurocognitive status after surgery and before radio-chemotherapy, the first study reported that 58.2% of patients had multi-domain cognitive impairment, 30.3% had single-domain cognitive impairment and only 9% had no cognitive impairment (50). In the second study the MMSE score was <27 in 76% of patients, however in a third study, the mean cognitive level of the MMSE scale was between 26.7 and 27.2 (44) (*Table 4*).

The included studies revealed several factors influencing neurocognitive status and QoL including Karnofsky's level (KPS), tumor location, age, gender and type of treatment. In addition to these factors, other studies have reported other factors, such as tumor progression, development of

Table 4 Neurocognitive assessment of patients with glioblastoma

Study	Tests	Neurocognitive assessment	
		Baseline	Follow-up
(50)	MMSE/Digit and Corsi Span Test/ RAVLT/ROCF/CPM/FAB/TMT	25% of patients did not present cognitive impairment/75% showed at least one cognitive deficit	Cognitive deficits worsened in 29.5% of patients/And improved in 47% of patients
(38)	MMSE	N/A	Scores of orientations (P=0.017), attention and calculation (P=0.005), and language (P=0.003) significantly decreased at the 18th month when compared to T0
(52)	MMSE	The average cognitive level of the MMSE scale, ranging between 26.7 and 27.2	A statistically significant lower score for patients older than 65 years of age at 9 months after RT (P=0.0031)
(45)	RepW/RepNW/RepS/ReaW/ReaNW/ ReaS /LCNT/NN/NV/ACW/ACS/ VCW/VCS/NRep/NRea/VPF/VSF/DS/ CS/15RWL-IR/ROCF-DC/LCA/LCS/ AM/TMTA/TMTB/TMTB-A	The percentage of patients showing impairment: [VCS: 33.3%]/[VPF: 36.6%]/ (ROCF-DC: 53.3%)/(15RWL-DR: 46.7%)/ (LCA: 23.3%)	Improvement in 7 tasks (VCS: P=0.028)/(NV: P=0.036)/(LCNT: P=0.007)/(CS: P=0.01)/ (15RWL-Rec: P=0.049)/(ROCF-DC: P=0.049)
(48)	MMSE	Mean score MMSE: 26.1	MEAN SCORE MMSE :1st follow-up 4 week: 26.3/12 week: 26.9/24 week: 27.5/48 week: 27.5
(51)	MMSE	MMSE: Normal 4/Mild 5/Moderate 8/ Severe 0	MMSE: Normal 2/Mild 7/Moderate 7/Severe 1
(54)	(DO)/(PHO)/(SEM)/(DIGIT)/CS/OST/ (LINE)/(ATT)/(TMT)	Patients of AWg have a better performance in selective attention (76.8% of targets detected) before surgery compared to patients of ASg (60.7%) (P<0.01)	Cognitive state is not changed after treatment P=0.083/no differences have been found between patients (ASg) and (AWg)
(44)	MMSE	76% MMSE <27/24% MMSE ≥27	N/A

ROCF, Rey-Osterrieth Complex Figure; RAVLT, Rey Auditory Verbal Learning Test-Recall; CPM, Raven's Colored Progressive Matrices 38; FAB, frontal assessment battery; TMT, trail making test A and B; DCT, drawings Copy test.; RepW, repetition of words; RepNW, repetition of non-words; RepS, Repetition of sentences; ReaW, reading of words; ReaNW, reading of non-words; ReaS, reading of sentences; LCNT, naming of nouns (Laiacona-Capitani); NN, naming of nouns; NV, naming of verbs; ACW, auditory comprehension of words; ACS, auditory comprehension of sentences; VCW, visual comprehension of words; VCS, visual comprehension of sentences; NRep, repetition of numbers; NRea, reading of numbers; VPF, verbal fluency on phonemic cue; VSF, verbal fluency on semantic cue; DS, digit-span; CS, Corsi-span; 15RWL-IR, 15 Rey's word list: immediate recall; LCA, Lines cancellation task, visual attention: accuracy; LCS, Lines cancellation task, visual attention: speed; AM, attentional matrices, visual selective attention; TMTB-A, trail making test, executive function; DO, object denomination; PHO, phonemic fluency; SEM, semantic fluency; DIGIT Digit span; OST, Rey's complex figure: delayed recall; LINE, line cancellation; ATT, attentional matrix; AWg, Awake surgery Group.

emotional distress, and coping strategies adopted.

In this review, three studies (n=3) addressed the effect of age on neurocognitive status in older patients >65 years, compared to younger patients (38,45,52). For the first study, the results yielded a statistically significant lower score for patients over 65 years of age at 9 months after RT (P=0.0031) (52). The second study, only the recall score (P=0.048) was found to be statistically significant between the different age groups (38), Similarly, the results of the third study revealed better cognitive performance scores in patients under 65 years of age (45). In addition, another study showed that the best MMSE scores in the elderly population were observed in patients with a KPS ≥70 (P=0.01) (48).

For tumor-related factors, a one study showed that preoperative performance in attention, language and

verbal memory tasks depended on several factors including the joint effect of tumor volume and the volume of surrounding edema. The same study revealed major deficits in patients with left lateralized tumor, particularly insular and temporal (45). On the other hand, two other studies did not reveal a significant difference in the MMSE score and the location of the tumor (48,50).

Regarding the type of surgery used, one study compared neurocognitive function between patients using awake surgery (AWg) and asleep surgery (ASg), at post-surgical assessment and 4-month follow-up assessment, no significant differences were found (54).

The study by Younis and Fayed which aims to assess the effect of RT on cognitive functions after treatment, did not show a significant difference in patients with GB (P=0.083) (51). However, the study by Minniti *et al.* showed a slight improvement in the mean MMSE score from 26.1 in baseline to 27.3 at the fourth follow-up at 48 weeks after radiation therapy (48).

In another study, differences in cognitive function, assessed at each time point, revealed a statistically significant lower score at 9 months after standard Radiation therapy (60 Gy) (P=0.0031) (52).

Another study using MMSE at month 18, compared to the baseline for patients treated with TMZ and RT (external beam administered at a daily dose of 2 Gy with a total dose of 60 Gy), the results showed a significant decrease in orientation, attention, calculus, and language scores (P-values were 0.017, 0.005, and 0.003, respectively) (38).

Assessment of QoL in patients with GB

In the present review and for an assessment of QoL, one study (n=1) used only the EORTC C30 questionnaire (47), two studies used EORTC-C30 and PGI (43,44), four studies (n=4) simultaneously used EORTC C30 and EORTCBN20 (38,48,49,52), a single study (n=1) simultaneously used FACT.G, FACT.Br and SEIQoL-DW (46) and only (n=1) used the FLIC questionnaire (53) (*Table 5*).

Regarding the baseline assessment, the studies in this review revealed that fatigue, headache, drowsiness, insomnia, and motor dysfunction were the most affected QoL scale at baseline (38,48,52) (*Table 5*).

During patient follow-up, a first study showed that the hair loss scale showed a statistically significant deterioration in score between the initial assessment and 1 month of concomitant treatment and 3 months after RT (P=0.0125) (52). For two other studies, fatigue worsened significantly (P<0.02) during follow-up in two other studies (47,48). A fourth study reported a slight improvement of headaches during non-significant follow-up (P=0.6149) (52). Studies evaluating the QoL after RT treatment, revealed that a short course of RT (6 fractions of 5 Gy each for a total of 30 Gy over 2 weeks) in combination with TMZ (12 cycles of adjuvant TMZ) in patients >65 years of age with GB has been associated with a survival benefit with no negative effect on HRQOL until the time of disease progression (47,48).

For Chemotherapy-related symptom outcomes, one study found that constipation, nausea, vomiting and loss of appetite worsened during treatment, however only the constipation score deteriorated significantly during adjuvant chemotherapy, with a mean score that differed by 7.6 points between baseline and the third follow-up visit (P=0.03) (48).

Changes in QoL scales after treatment were significantly associated with disease progression in two studies (38,52), however in another study HRQOL was not measured after disease progression (48).

Assessing the impact of age on QoL of patients with GB has been investigated in two studies in this review (38,52). The study by Lombardi *et al.* found that patients 65 years of age and older had greater impairment than younger patients (52), however in the second study baseline overall scores did not differ between different age groups (38). For gender, two studies found that the overall QoL score was higher in men than in women (38,52). Female patients reported greater discomfort than men especially on the hair loss scale.

Regarding the QoL in patients with recurrent GB, the results revealed that re-irradiation with proton therapy (PT) is a safe and effective treatment for these patients. Indeed, PT has no negative effect on HRQOL, but rather seems to preserve HRQOL. Moreover patients who received PT and concomitant TMZ had clinically better QLQC30_Physical values compared to patients who received PT alone (82.4 *vs.* 65.16 points, respectively) (49).

Three studies (n=3) (44,46,53) addressed the relationship between QoL and psychological distress in patients with GB in the Mediterranean region. In the study by Lucchiari *et al.* Data showed that anxiety (beta =–260, P=0.006), and depression (beta =–389, P<0.001) were all significantly associated to QoL as measured by FACT-Br, patients with low levels of depression and anxiety reported better QoL (46). The second study found a negative correlation between the emotional functioning scale of the QLQ-C30 and the scale of anxiety and mood disorder (R=–0.55,

Table 5 Quality of life assessment of patients with glioblastoma

Study	Tests	QOL measure	
		Baseline	Follow-up
(38)	EORTC C30/ EORTC BN20	Fatigue (32.21)/Insomnia (28.02)/ Communication deficit (19.32)/Headache (21.74)/Drowsiness (30.43)	Mean global and functional domains scores of EORTC QLQ-C30 decreased, while symptom domain scores increased/BN-20 scores increased accordingly
(52)	EORTC C30/ EORTC BN20	Role functioning 59.6/Emotional functioning 77.8/Itchy skin 3.6/Future uncertainty 25.1/Drowsiness 25.8/ Weakness of legs 23.4/Hair loss 6.6	Alteration of the Hair Loss and Skin Itch Scale at follow-up with clinically significant improvement in role functioning
(47)	EORTC C30	Fatigue 42/Insomnia 15.1/Constipation 14.6	Scores of functioning scales and the global health status did not change significantly. Fatigue (P=0.02) and constipation (P=0.01) scales slightly worsened over time
(48)	EORTC C30/ EORTC BN20	Insomnia 21.6/Fatigue 43.7/Drowsiness 39.8/Future uncertainty 40.8	No significant changes for insomnia (P=0.2)/Improvement for emotional functioning (P=0.1) and physical functioning (P=0.09)/Fatigue worsened over time
(46)	FACT G/FACT Br/SEIQoL-DW	The mean FACT-Br score was 122.37/The median SEIQoL-DWscore was 72.9 out of a maximum value of 100	N/A
(53)	FLIC	All the patients were cognitively impaired and more anxious	N/A
(46)	FACT G/FACT Br/SEIQoL-DW	All the patients were cognitively impaired and more anxious	
(49)	EORTC C30/ EORTC BN20	(T0–T1): Cognitive and emotional functioning scales were associated with a not significant negative change (<5 points)	None of the domains showed a minimum clinically meaningful change (>10 points)
(44)	PGI/EORTC QLQ-30	The correlation between the emotional functioning scale of the QLQ-C30 and anxiety was R=−0.55, P<0.01	When patients used strategies such as problem solving and positive thinking, they reported significantly higher QoL scores
(43)	PGI/EORTC QLQ-30	The use of avoidance at baseline was linked to a higher 3-month QoL for the patients	The patient's quality of life was lower when the patient used the social support strategy at baseline (effect of using an adaptation strategy on his own quality of life; negative actor effect; β=−0.322; P=0.033)

Qol, quality of life; EORTC, European Organization for Research and Treatment of Cancer; EORTC QLQ-C30, quality of life instrument for cancer patients; BN20, Brain Cancer Module; FACT Br, Functional Assessment of Cancer Therapy – Brain; FACT-G, Functional Assessment of Cancer Therapy – General; SEIQoL-DW, The Schedule for the Evaluation of the Individual Quality of Life-Direct Weighting; FLIC, Functional Living Index – Cancer; PGI, patient generated index.

P<0.01 and R=−0.62, P<0.01 respectively) (44). The third study showed that higher FLIC total scores were linked to psychological well-being, improved good mood as well as better cognitive status (53) (*Table 6*). The effect of coping strategies on the QoL of GB patients was treated in two studies (43,44). Patients using coping strategies such as problem solving and positive thinking have significantly higher QoL scores in two dimensions (general health and cognitive functioning) (44). The second study found that social support was significantly related to lower QoL scores (role functioning and social functioning scores from the EORTC QLQ-C30; β=−0.432 and −0.485, respectively), while the same study found that avoidance was related to a higher QoL score β=0.419 (43) (*Table 6*).

Discussion

This article is the first systematic review to assess neurocognitive status and QoL in patients with GB in the Mediterranean region. Median survival even after treatment

Table 6 Predictive factors of neurocognitive state and quality of life in patients with glioblastoma

Study	NCF					QoL				
	Factors predictive	R^2/R	Beta	CI	P value	Predictive factors	R^2/R	Beta	CI	P value
Yavas [2012] (38)	Age >60	–		–	0.048	Inoperable tumors	–		–	0.027
						Disease progression			–	<0.001
Lombardi [2018] (52)	Age >60	–		–	0.0031	Age >65[ǂ]	–		2.33–16.56	0.0097
	Location of tumor	–		–	0.0044	Location of tumor[ǂ]	–		–14.08 to 1.78	0.010
						Gender	–		–	<0.01
Dallabona [2017] (45)	Age >65	–		–	<0.05	–	–		–	–
	Overall mass effect	–		–	<0.05	–	–		–	–
	Tumor location	–		–	<0.01	–	–		–	–
Minniti [2013] (48)	KPS ≥70	–		–	0.01	–	–		–	–
Zigiotto [2020] (54)	AWg	–		–	>0.063	–	–		–	–
Lucchiari [2015] (46)	–	–		–		KPS	–	0.372	–	<0.001
						Depression	–	–0.389	–	<0.001
						Anxiety	–	–0.260	–	0.006
Giovagnoli [2005] (53)	–	–		–						
						Cognition	R^2=0.59		–	<0.01
						Mood	R^2=0.40		–	<0.01
						Physical performance	R^2=0.52		–	<0.01
Baumstarck [2016] (44)	–	–		–	–	Anxiety	R=–0.55		–	<0.01
						Mood disorders	R=–0.62		–	<0.01
						Problem solvings	R=0.530			<0.05
						Positive thinking	R=0.376			<0.01
Baumstarck [2018] (43)	–	–		–	–	Avoidance	–	β=0.419		<0.05
	–	–		–	–	Social support		β=–0.432		<0.05

ǂ, only the bladder control scale; [ǂ], the Global health status score. AWg, Awake surgery Group; NCF, Neurocognitive Functions; Qol, Quality of life; CI, Confidence Interval.

for GB is relatively short (2,4,26,56,57), and preservation of neurological function and QoL is an important parameter. Indeed, it is well known that in neuro-oncological patients, cognitive impairment and QoL may be related both to the tumor itself and to the side effects of treatment, including surgery, RT, chemotherapy, corticosteroids and antiepileptics (58).

The studies in our review used different neurocognitive assessment tests, our finding of test heterogeneity is supported by a recent systematic review of cognitive assessment methods in glioma research (59), in addition the majority of the studies in our review used short batteries for neurocognitive state assessment instead of the specific in-depth batteries that require a longer time to collect data, which is already recommended in a clinical trial which states that the repeated application of long questionnaires for cancer patients can be a major burden and inconvenience (60). In this sense, other studies stated that for neurocognitive and QoL assessment tests to be useful, they must be short, repeatable and sensitive to changes and

different brain functions (32,61). This helps to avoid bias in results due to a high rate of missing values and to facilitate a synthesis of data on QoL and neurocognitive status.

A correlation between the lesion side and cognitive deficits has been reported in previous studies (55,62). They observed that patients with lesions affecting the left hemisphere had a significantly higher percentage of neuropsychological deficits compared to patients with lesions on the right side. In our review, the results were heterogeneous, in fact two studies were consistent with the results of the literature (38,52). However, two other studies, did not find a correlation between the lesion side and the cognitive deficits, which can be explained by a suffering from bilateral lesions or a poor prognosis of the patients.

The effect of age on neurocognitive status and QoL has been demonstrated in the results of this review (45,50,52), on the other hand, other previous studies showed that age was considered the most important predictor for patients with GB (63-65), adding that for these elderly patients, the alterations of gray and white matter may have been added to the effects of neoplasms and treatments.

Concerning gender, the results report a difference in QoL score between women and men which is in agreement with other studies that found women appeared to be more likely to experience life quality deterioration (61,63), maybe explained by severe depression and anxiety observed in women with brain tumor (66,67).

The purpose of the treatment should not only be to improve survival but also to maintain QoL (19). Combined radio-chemotherapy and other newer treatments can increase survival time, however, these therapies can have side effects. The results of the present study revealed that drowsiness, fatigue and motor dysfunction were the most reported symptoms before treatment (47,48,52). Moreover, after concomitant RCC radio-chemotherapy treatment, fatigue, hair loss and digestive disorders are the most reported symptoms (38,47,48,52). Extrapolation of data from our review may not provide a holistic representation of the effect of treatment on neurocognitive status and QoL in patients with GB.

However, nowadays surgery is the standard treatment, it seeks to preserve motor, cognitive and complex associative functions, with the aim of maintaining a good QoL for these patients. The results of quality-of-life measurements by Tanzilli *et al.* were significant between patients with total surgery and patients with biopsy (50). Likewise, Dallabona *et al.* states that despite a deterioration in neuropsychological performance at early follow-up, surgery may be effective in improving cognitive performance and QoL in patients with GB over time (45), this is in line with the results of a study carried out in Canada showing that radical resections avoid the degradation of QoL and thus prolong optimized survival (68).

For elderly patients with GB, a short course of RT in combination with TMZ has been associated with a survival benefit with no negative effect on HRQOL until the time of disease progression (47,48), the same results were reported in a recent randomized study showing no negative effect of hypofractionated RT on the QoL of elderly patients with GB (69). Other studies suggest that hypofractionated radiation therapy does not produce increased toxicity in the elderly, perhaps because most patients do not live long enough to develop long-term complications (70).

Patients with low levels of depression and anxiety reported better QoL in our review (44,46). Same results were reported by a previous study showing that the presence of depressive symptoms was the most important independent predictor of QoL in patients with malignant brain tumor (71).

To address this high symptom burden, several randomized controlled trials (RCTs) in various groups of advanced cancers other than GBM have shown a positive effect of early integration of palliative care (EIPC) regarding QoL improvement (72-77), however, a recent systematic review revealed paucity of literature regarding the use of palliative care in patients with GB (78), although a new protocol has been published for a randomized phase III trial that aims to evaluate the effect of early PC for GB patients (79).

The results of our review found that coping strategies based on problem solving or positive thinking are associated with better QoL scores, while coping strategies based on social support appear to be a psychological risk factor for a lower QoL (43,44), similar results were reported in a recent study in cancer patients (80).

In the end, the results reported in this study did not show specificity of neurocognitive state and QoL compared with other previous studies reported in regions outside the Mediterranean (16,17,81). The present review had several limitations, namely, the studies in question cover only four countries in total, moreover we do not have any data on the QoL in the Maghreb region, therefore, it is difficult to determine extrapolate conclusions to the general population. Furthermore, the absence of a regression analysis in some observational studies, does not allow to have reliable results on the predictive factors of the neurocognitive state and QoL in patients with GB in the Mediterranean region.

Conclusions

We conclude that there were many changes in patients with GB during the course of the disease and that most of them were related to the Age and progression of the disease. In this sense, and according to the results of this review, health systems should address other modifiable factors in order to improve the QoL of patients with GB in the Mediterranean region, especially through the use and implementation of more effective coping strategies based mainly on social support at the time of diagnosis.

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