Journal of Neurology
https://doi.org/10.1007/s00415-020-09731-5

REVIEW

Steroids use and survival in patients with glioblastoma multiforme: a pooled analysis

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Received: 13 December 2019 / Revised: 22 January 2020 / Accepted: 24 January 2020

Abstract

Introduction Steroids are commonly used for managing brain edema in patients with glioblastoma multiforme (GBM), treated with surgery and concomitant temozolomide-based chemoradiotherapy (CTRT). The adverse effects of glucocorticoids include lymphopenia, hyperglycemia, and risk of infection. We report the results of a meta-analysis evaluating the effects of steroids on outcome when associated with the treatment of GBM.

Methods PubMed, the Cochrane Library, and Embase were searched from inception until September 2019 for observational or prospective studies reporting prognosis of adult patients with GBM and treated or not treated with steroids. Overall survival (OS) was the primary endpoint, and progression-free survival (PFS) was the secondary endpoint. The effect size was reported as hazard ratios (HRs) with a 95% confidence interval (CI), and an HR > 1 associated with the worst outcome in steroid users compared to non-users.

Results Twenty-two publications were retrieved from studies selected for a total of 8,752 patients. In the primary analysis ($n = 22$ studies reporting data), OS was reduced in GBM patients taking steroids during treatment (HR = 1.54, 95% CI 1.37–1.75; $p < 0.01$). Similarly, PFS was inferior in steroid users in $n = 9$ studies with data available (HR = 1.28, 95% CI 1.1–1.49; $p < 0.01$).

Conclusions In patients with GBM and treated with RT and/or CT, association with steroids significantly reduces survival and PFS. Use of the lowest dose of glucocorticoids for the shortest period needed to achieve the treatment goals and prevention of steroid-associated complications are essential aims of treatment of this disease.

Keywords Glioblastoma · Steroids · Adverse events · Radiotherapy · Survival · Meta-analysis

Introduction

Glioblastoma multiforme (GBM) is a lethal disease that is treated with radical surgery or biopsy and then with concomitant, temozolomide (TMZ)-based, chemoradiation (CTRT).

In patients with brain tumors and in particular in high-grade gliomas (e.g., GBM) steroids are used for the treatment of brain edema and related symptoms. High-dose glucocorticoids reduce cerebral edema and can improve headaches and neurologic deficits caused by vasogenic edema. In patients with moderate to severe symptoms or risk of herniation, the usual initial dose of dexamethasone is 8 mg once/twice per day. For asymptomatic patients, steroids are not required, however, often a minimal dose is offered particularly when antitumor therapy [radiotherapy (RT)] may worsen edema. Glucocorticoids are associated with several side effects on many organ systems (e.g., serious

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Published online: 30 January 2020

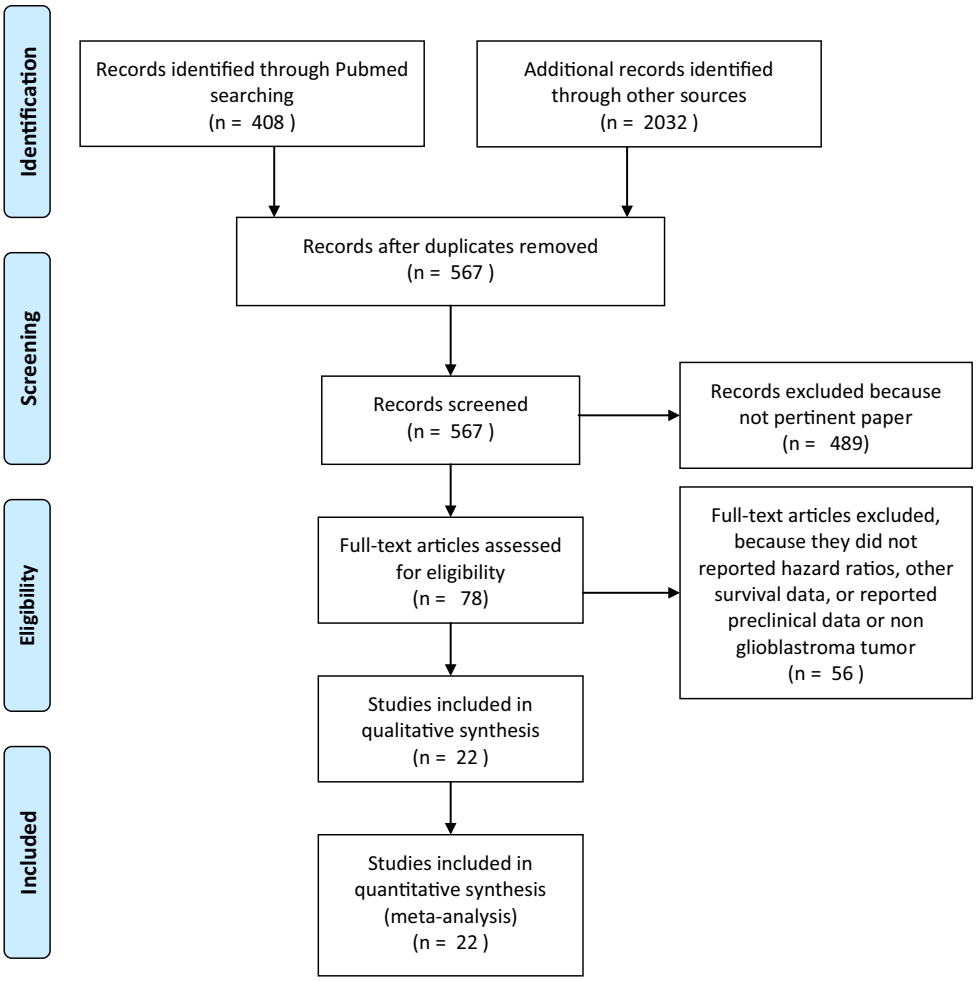

Fig. 1 Flow diagram of included studies

infections, sepsis, and thrombosis). Long-term glucocorticoid is a significant independent predictor of numerous adverse effects and that the risk is both dose- and duration-dependent. One study suggests that even short-term glucocorticoid use may be associated with serious adverse effects. In adult patients, in fact, use of steroids increased the odds of venous thromboembolism and sepsis [1].

We have performed a systematic review and meta-analysis to evaluate if the use of steroids may affect survival in patients with GBM.

Material and methods

Search strategy and inclusion criteria

The present review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations [2]. Electronic searches were performed from inception up to September 2019 using Embase, PubMed, SCOPUS, and The Cochrane Library. The studies were searched using the terms: (glioblastoma OR glioma) AND (steroids or dexamethasone) AND survival. All identified articles were then systematically assessed for inclusion and exclusion criteria independently by two investigators (FT and FP).

The inclusion criteria used to screen articles were (1) confirmed histopathological cases of GBM, (2) evaluation of survival (OS and/or PFS) according to intake of corticosteroids (yes versus no), (3) a hazard ratio (HR) statistic accompanied by 95% confidence interval (CI) from univariate or adjusted Cox multivariate analysis, and (4) cohorts of adult patients. The exclusion criteria were (1) low-grade glioma and (2) cohorts of patients under 18 years of age. When institutions published duplicate studies involving overlapping patients or increased lengths of follow-up, the most updated reports were included for quantitative assessment. Only publications involving human subjects and in English language were considered.

Data extraction

Two investigators (FT and FP) independently extracted data of interest (author and year of publication, number of

Table 1 Characteristics of included studies

Author/year	Type of study	No of patients	Treatment	Median age	Steroid dose/%	Median follow-up (months)	Type of analysis	Covariates of MVA for OS	Quality (NOS score)
Adeberg/2016	Retrospective	262	Biopsy/S → RT (60 Gy) + TMZ (63%) or RT alone (60 Gy) (36.6%)	NR	NR	NR	MVA (OS) UVA (PFS)	Simultaneous temozolomide therapy, biopsy, persistent hyperglycemia	6
Bhavsar/2016	Retrospective	841	S → RT (60 Gy) + TMZ	56.07	NR/73	NR	MVA (OS) UVA (PFS)	Age, gender, BMI, ASA score	6
Carson/2007	Pooled analysis of 10 phase 1–2 studies	333	Systemic ($n=6$ studies) or locoregional therapy ($n=4$ studies) after progression of disease	49.8	NR/70.5				6
Colavolpe /2012	Retrospective	25	S → RT + TMZ → Bev (recurrent GBL)	60.3	44.6 mg (MP)/68	NR	MVA	SUV max	5
Coleman/2018	Retrospective	100	Prior CT TMZ 76% or prior RT (92%)	47.5	NR/63	NR	MVA	Steroid use, poor PS, NRL	6
Darlix/2013	Retrospective	58	Biopsy/S → RT (60 Gy) + TMZ → TMZ	54	9.6/31	NR	MVA (OS) UVA (PFS)	NR	5
Gorlia/2008	Retrospective	573	Biopsy/S → RT + TMZ	NR	NR/71	NR	MVA	Combined treatment with TMZ, more extensive tumor resection, age, mini-mental state examination score, corticosteroid treatment	7
Gorlia/2012	Retrospective	300	Biopsy/S → RT (60 Gy) + TMZ → TMZ (46%) or RT alone or RT + another CT (53%) or no RTT (1%)	53.5	NR/65.3	NR	MVA (OS) UVA (PFS)	WHO PS, baseline steroids, number of target lesions, frontal location, tumor size	7
Grossman/2011	Retrospective	96	S → RT + TMZ	57.4	NR/82	NR	UVA	NR	5
Huang/2013	Retrospective	91	RT + TMZ → Bev (recurrent GBL)	56.3	4 mg/56	NR	MVA	Number of recurrences, change in steroid dose	
Le Rhun/2018	Prospective and retrospective	1273	RT + TMZ → TMZ	57	NR/40.9	NR	MVA	Age, extent of resection, WHO PS, steroid use, MGMT status	7
Michaelsen/2013	Retrospective	225	Biopsy/S → RT (60 Gy) + TMZ → TMZ	59.2	NR/73	NR	MVA	Age, corticosteroid therapy, PS	6

Table 1 (continued)

Author/year	Type of study	No of patients	Treatment	Median age	Steroid dose/%	Median follow-up (months)	Type of analysis	Covariates of MVA for OS	Quality (NOS score)
Munck af Rosenschold/2019	Retrospective	521	Biopsy/S → RT (60 Gy) + TMZ → TMZ	60	> 15 mg day/56	NR	MVA (OS), UVA (PFS)	MGMT status, age, PS, GTV, BTV PET, mean brain dose, mean brainstem dose	6
Pitter/2016	Retrospective	2027	Biopsy/S → RT + TMZ → TMZ or RT alone*	NR	NR/64	NR	MVA (OS) UVA (PFS)°	MSKCC: RPA class, TMZ; EORTC: age, PS, extent of surgery; GGN: treatment, extent of surgery, age, PS	7
Quillien/2019	Prospective cohort	117	Bev ± CT or CT	58.6	NR/59	NR	MVA	Neutrophil count	–
Shields/2015	Retrospective	73	RT + TMZ ± Bev → TMZ ± Bev	61	NR/49	15.6	MVA	Bev, extent of resection, age, gender, RT dosage, smoking status, and BMI	7
Tabouret/2013	Retrospective	100	Bev + CPT11	57.9	NR/83	NR	MVA	Age, gender, PS, n° of prior line of therapy, delay since diagnosis	5
Urup/2016	Retrospective	216	Bev + CPT11	56	37.5 mg/71	7.4	MVA	PS, multifocal diseas, neurocognitive deficit	6
Van Linde/2017	Retrospective	299	CT (34.7%), resurgery (18.7%), reirradiation (7%) or BSC (40%)	59	NR/55.7	NR	MVA	Treatment, age, tumor extent, extent of initial resection, RFS, PS	5
Welch/2013	Retrospective	988	S → CT (66%) + RT (87%)	66	NR/85	NR	MVA	Age, PS, metformin, PPAR-gamma, sulfonylurea, biopsy, CT, RT, CTRT	6
Wirsching/2018	Phase 2	75	RT + Bev (67%) vs RT (33%)	70	NR/44	NR	MVA	Treatment arm, age, PS, MGMT status	-

Table 1 (continued)

Author/year	Type of study	No of patients	Treatment	Median age	Steroid dose/%	Median follow-up (months)	Type of analysis	Covariates of MVA for OS	Quality (NOS score)
Woo/2018	Retrospective	159	S (75%) → RT (33.5%) or CTRT (45.4%) or TMZ (7.8%)	56	NR/NR	NR	MVA	Tumor location, extent of resection	5

S surgery, *RT* radiotherapy, *CT* chemotherapy, *MVA* multivariate analysis, *UVA* univariate analysis, *OS* overall survival, *PFS* progression-free survival, *RFS* relapse-free survival, *TMZ* temozolomide, *Bev* bevacizumab, *CPT11* irinotecan, *MP* methylprednisolone, *BSC* best supportive care, *BMI* body mass index, *PS* performance score, *GBL* glioblastoma, *NRL* neutrophil-to-lymphocyte ratio, *GTV* gross tumor volume, *BTV* biological target volume, *PPAR-gamma* peroxisome proliferator-activated receptor gamma, *NR* not reported

*Analysis of three retrospective cohorts MSKCC, EORTC NCIC CE.3 study and GGN

°Only EORTC and GGN cohorts

^Retrospective analysis of three randomized studies (CENTRIC, CORE AND AVAGLIO)

patients, type of study, treatment received, dose and duration of steroids, median follow-up, and type of analysis). The quality of included studies was assessed by Newcastle–Ottawa Scale (NOS) [3].

Statistical analysis

The outcome of interest was the prognostic effect of steroids intake reported as HR and its respective 95% CI. Overall survival was the primary endpoint and PFS was the secondary endpoint. The HRs of each selected study were pooled together to provide the overall estimate. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity [4]. A random-effects model was tested, and in the case of $I^2 < 50\%$, a fixed-effects model was also considered. Publication bias was assessed through the generation of funnel plots for OS and assessed for asymmetry by Begg's and Egger's test. All p values were two-sided with significance set at $p < 0.05$. Statistical analyses were conducted with the Review Manager computer program, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Among 2,440 publications retrieved using electronic search, 22 studies were eligible for meta-analysis (Fig. 1), for a total of 8752 patients [5-26]. Baseline characteristics of included studies and treatments received are presented in Table 1. Nineteen were retrospective series, two were prospective studies, and one was a retrospective series with a prospective validation cohort. The median age was 60.6 years. Steroids were assumed by 55% of patients.

Overall in the primary analysis, use of steroids was associated with a reduced survival (HR = 1.54, 95% CI 1.37–1.75; $p < 0.01$; Fig. 2). The analysis regarded 22 studies, and for the high heterogeneity ($I^2 = 75\%$), a random-effects model was adopted.

Progression-free survival was also decreased in steroid versus nonsteroid users (HR = 1.28, 95% CI 1.1–1.49; $p < 0.01$; Fig. 3). The analysis regarded nine studies, and for the high heterogeneity ($I^2 = 82\%$), a random-effects model was adopted.

Risk of bias through Begg's funnel plot was not significant. Egger's test showed conversely evidence of bias ($p < 0.01$). In sensitivity analyses, the influence of individual studies on the overall risk was carried out. Hazard ratios ranged from 1.5 to 1.58 by sequentially omitting one study at each turn. Meta-regression showed that effect size was not driven or larger in trial with greater numerosity ($P = 0.22$).

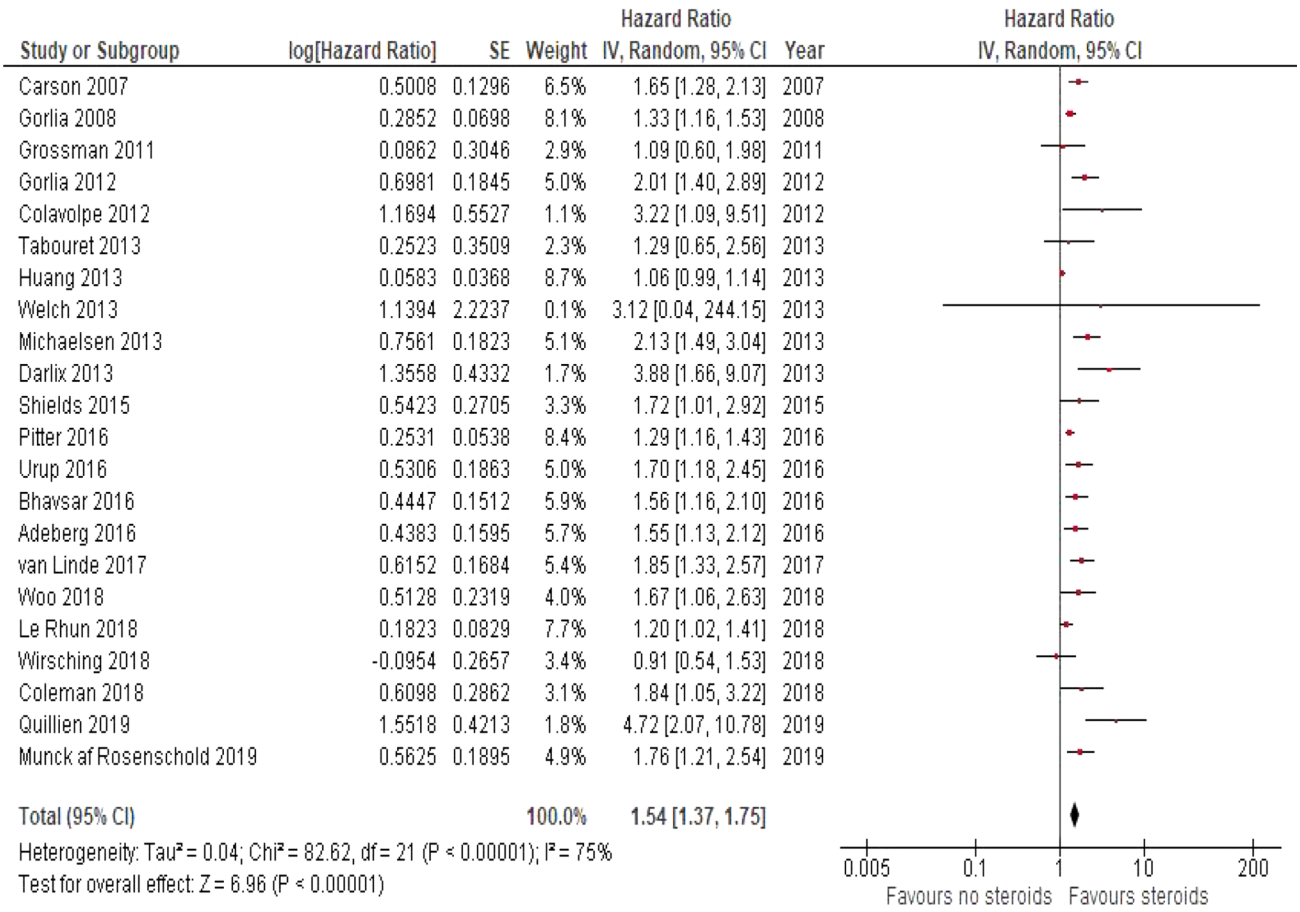

Fig. 2 Forest plot for overall survival in steroid-treated patients

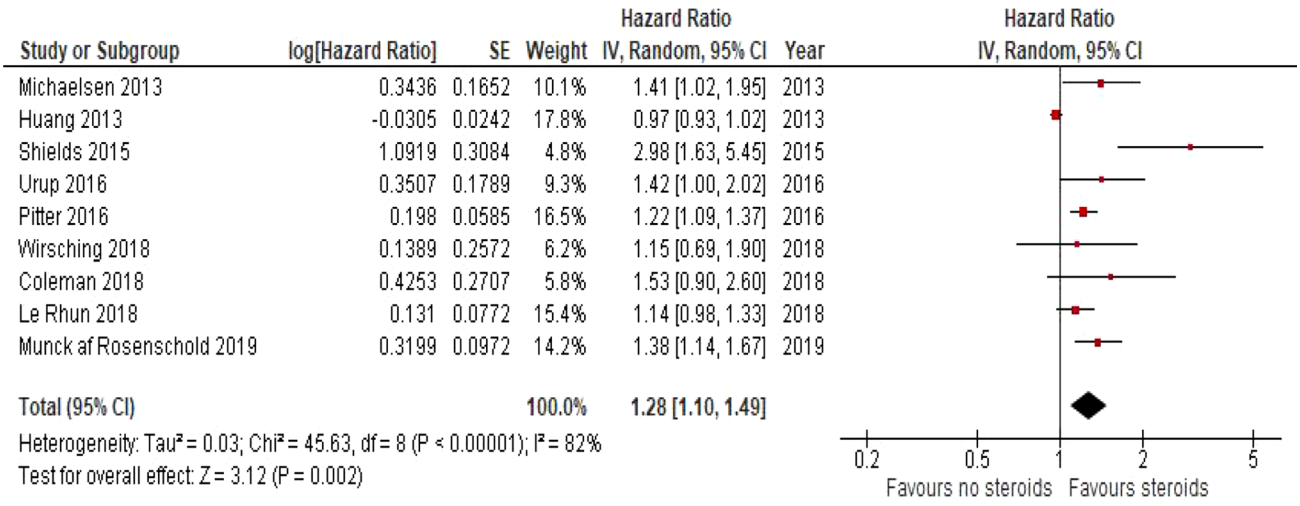

Fig. 3 Forest plot for progression-free survival in steroid-treated patients

Discussion

Despite the lack of prospective trials, corticosteroid given for relief of intracranial edema in brain tumors should be given on the basis of an individualized regimen and tapered slowly [27]. In this systematic review and meta-analysis, use of steroids was found to reduce OS and PFS in patients with GBM treated with CTRT or combination CT for primary or relapsed disease.

The results of this meta-analysis are not surprising due to the potentially detrimental effect of steroid use on the immune system (lymphopenia) and metabolism (hyperglycemia) that can explain the direct role on outcome. Clinically, hyperglycemia remains a relevant concern in GBM treated with corticosteroids for the management of clinical neurological symptoms and cerebral edema following surgical intervention and RT. In a meta-analysis evaluating the prognostic effect of hyperglycemia in patients with gliomas, it was found to confer a statistically significant poorer OS outcome (HR 1.671; $p < 0.01$) [28]. Furthermore, steroids affect the immune system by reducing the number of immune cells in the blood of GBM patients [29]. Dexamethasone appears to promote the development of a glioma stem cell-like phenotype and conferred resistance to physiological stress and CT [30, 31]. Other authors found that dexamethasone-induced leukocytosis decreased OS (HR = 2.25, 95% CI 1.15–4.38; $p < 0.01$) and PFS (HR = 2.23, 95% CI 1.09–4.59; $p < 0.01$). Furthermore, patients with dexamethasone-induced leukocytosis had significantly reduced CD15 + granulocytic- ($p < 0.05$) and CD3 + lymphocytic tumor infiltration ($p < 0.05$) [32]. In a murine PDGFB-driven glioblastoma model, pretreatment with single doses of dexamethasone for 3 consecutive days profoundly decreased the survival advantage provided by a single 10 Gy dose of irradiation or by a fractionated irradiation schedule. Dexamethasone may also compromise cell proliferation in vivo and this may lead to radioresistance of glioma cells [18].

There are several limitations to this study. Most of these data represent a subset analysis of randomized clinical trials or retrospective studies, and thus, the findings must be interpreted with caution because these were not designed to evaluate outcome according to steroid use. The studies varied in the use of systemic therapies, comorbidities, extent of surgery, and size of tumors. Also, median follow-up was underreported in many trials and relatively short observations length could have captured only early deaths, probably those related with advanced age and/or poor performance status patients only. Finally, many patients, due to the extent of tumor and surgery, with related brain edema need steroids as an asymptomatic measure. The burden of disease may dictate the receipt of steroids and so the prognosis.

Despite these limitations, we report for the first time a prognostic significance associated with steroid use, and it was mostly independent by age, performance status, the extent of resection, and size or location of GBM.

In conclusion, given that randomized controlled clinical trials to address the utility of steroid in GBM are unlikely to be ever performed, this meta-analysis provides the best evidence that steroid may compromise OS and PFS in patients treated for GBM. Studies exploring other steroid-sparing drugs for treating edema and its complications in brain tumors are awaited.

Compliance with ethical standards

Conflicts of interest None to declare.

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