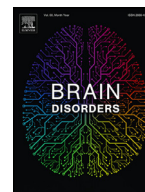




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Impact of COVID-19 pandemic on the management of glioma patients around the world. An evidence-based review

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ABSTRACT

Background: The coronavirus pandemic has affected many health care services worldwide since the emergence of the first case in Wuhan. Surgical neuro-oncology care is a fundamental part of hospital services, making it susceptible to strategic changes amid the COVID-19 pandemic.

Methods: An electronic search on several databases (PubMed/Medline, Scopus, and Google Scholar) from the beginning of the pandemic to the end of 2020, each paper was reviewed independently. The publication inclusion and exclusion criteria were done using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Results: Eight studies were found to be eligible for our meta-analysis. Most of the studies were on a retrospective basis, except one which was retrospective and prospective. An overall of 951 glioma patients' were included for surgical admission from the beginning of the pandemic until 2020. Seventy-four patients' had mortality outcomes, and 250 patients had complications for both surgical admitted and non-surgical admitted purposes.

Conclusions: To our knowledge, we made the first systematic review and meta-analysis regarding the management of glioma patients' during the pandemic of COVID-19. Our main findings are that the number of surgical admissions for glioma patients' did not significantly differ between COVID-19 negative and COVID-19 positive cases; however, surprisingly, we found that both overall complications and mortality outcomes were more significant COVID-19 negative patients' from the reported studies.

1. Introduction

The coronavirus pandemic has affected many health care services worldwide since the emergence of the first case in Wuhan. Surgical neuro-oncology care is a fundamental part of hospital services, making it susceptible to strategic changes amid the COVID-19 pandemic. Surgical neuro-oncology is an intensive care unit (ICU) bed-consuming specialty that creates a dilemma in continuing surgical care delivery amid the pandemic. Facing an exhausting pandemic redirected different ICU facilities such as ventilators, personal protective equipment, and medical staff to COVID-19 cases, which subsequently disrupted offering surgical neuro-oncology services. Instability regarding offering a proper health care service for critical cancer patients was somewhat observed amid the pandemic. Moreover, patients with glioblastoma are fragile to face their health status and COVID-19 infection. A suggested reason for that is the relative immunocompromise of those patients from previous radiation and chemotherapy [1]. The postoperative mortality rate is higher in patients with cancer than those with benign diseases, as supported

by a specific cohort study [2]. Several times, surgery cannot be postponed either due to the tumor's size or the rapid progression of cerebral edema. Considering the long-term effects of that pandemic, prompt policies should be assigned to prevent the deleterious outcome of postponing glioblastoma (GBM) surgeries. The benefit of indulging in urgent surgery to resect GBM should be balanced with the risk of exposing the patient and the staff to COVID-19 infection, which is a problematic issue. It was advised by the American college of surgeons to postpone any elective cancer surgery amid the COVID-19 pandemic. [3]. Neurosurgical associations published their guidelines for the management of malignant brain tumors amid the pandemic [4]. Each center in different countries of the world has reacted to the pandemic governed by the pandemic's effect on each country; therefore, the guidelines applied were modified accordingly. To date, there is no meta-analysis has been published investigating how COVID-19 affected the rate of surgical admissions in glioma patients and the occurrence of complications or associated mortality among different centers that published their experience. In this study, we aim to perform a meta-analysis of the available published data concerning the management of glioma patients in the published literature from the beginning of the pandemic to the end of 2020 con-

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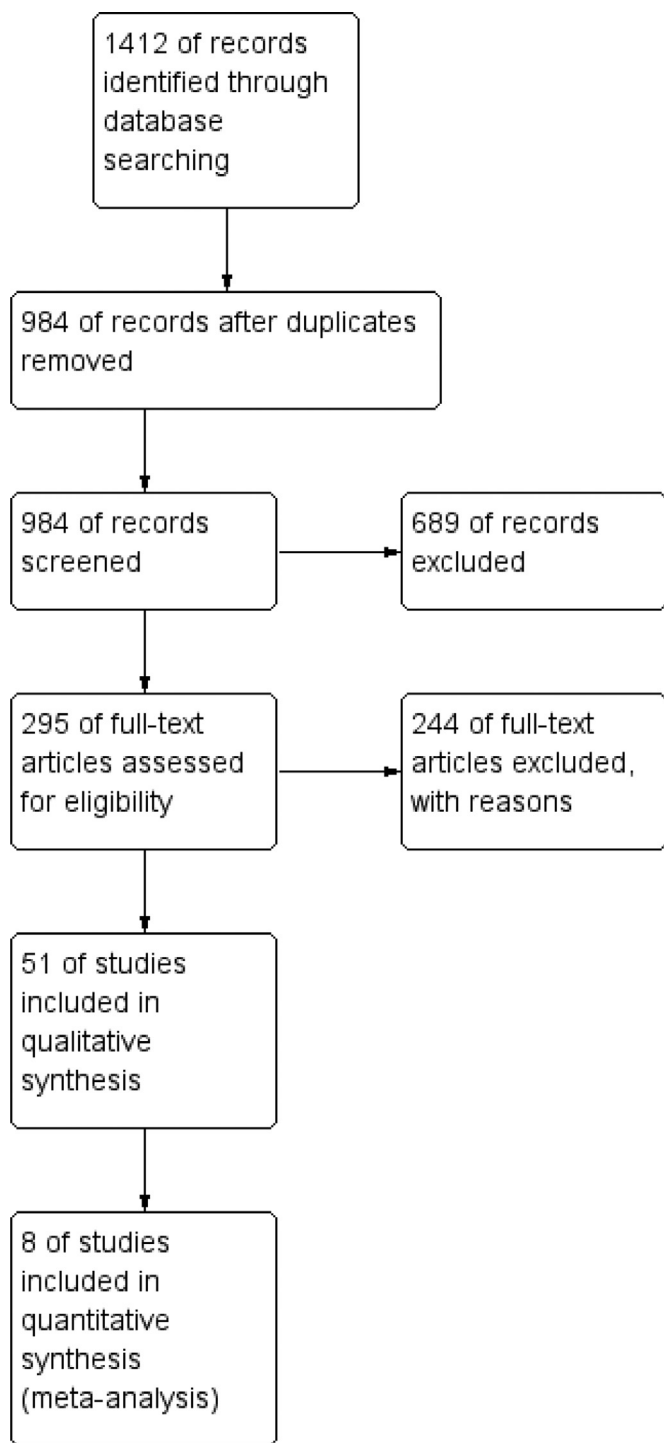


Fig. 1. PRISMA flowchart for inclusion and exclusion of the studies.

cerning the number of operated surgeries, postoperative complications, and mortality outcomes.

2. Materials and methods

An electronic search on several databases (PubMed/Medline, Scopus and Google Scholar) was done by two authors (AYA, MAA) using the keywords (“Glioma AND COVID-19”, “Glioma AND SARS-CoV-2”, “Glioblastoma AND COVID-19”, “Glioblastoma AND SARS-CoV-2”, “Oligodendroglioma AND COVID-19”, “Oligodendroglioma AND SARS-CoV-2”, “Astrocytoma AND COVID-19”, “Astrocytoma AND SARS-CoV-2”,

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Amoo 2020	+		+	+	-	+	+
Bajunaid 2020	+	+	+		+		+
Goyal 2020	-		+	+	-	+	
Lubansu 2020		-		+	+		
Meybodi 2020		+	+	-	-	+	
Patel 2020	+			-	-	+	+
Sahoo 2020		+	-	+	-	+	
Sarpong 2020	+	+		+	+		+

Fig. 2. Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.

“Ependymoma AND COVID-19”, “Neurosurgical practice AND COVID-19”, “Neurosurgical practice AND SARS-CoV-2”, “Neurosurgery AND COVID-19” and “Neurosurgery AND SARS-CoV-2”) from the beginning of the pandemic to the end of 2020 each paper was reviewed on an independent basis. Conflicts between the authors have been solved by the re-screening method. The publication inclusion and exclusion criteria were done using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

A total number of 1412 articles were identified on the databases searching phase and listed on PRISMA chart diagram Fig. 1, 984 articles were eligible for abstract screening to determine whether the article is eligible for the analysis or not. The full-text screening phase included 295 articles by two authors (AYA, MAA) on an independent basis to check the included details about the management of glioma patients’ during the pandemic of COVID-19 during 2020. Data from 51 articles were used for qualitative synthesis (systematic review). Data from 8 articles were extracted into two groups for the quantitative synthesis (meta-analysis), COVID-19 negative and COVID-19 positive glioma

Table 1
Details for the studies included in the meta-analysis.

Study	Country	Type of study	COVID-19 negative (surgical)	COVID-19 positive (surgical)	Mortality outcome	Complications (Surgical and non-surgical)	Quality assessment score
Meybodi 2020 et al. [10]	Iran	Retrospective	41	38	N/A	N/A	2 (fair)
Sarpong 2020 et al. [11]	USA	Retrospective	104	3	43	130	4 (well)
Lubansu 2020 et al. [12]	Belgium	Retrospective	48	4	16	N/A	3 (good)
Goyal 2020 et al. [13]	India	Retrospective + Prospective	30	12	N/A	N/A	2 (fair)
Amoo 2020 et al. [14]	Ireland	Retrospective	39	50	N/A	N/A	2 (fair)
Patel 2020 et al. [15]	USA	Retrospective	49	35	N/A	N/A	2 (fair)
Bajunaid 2020 et al. [16]	Saudi Arabia	Retrospective	144	88	15	120	4 (well)
Sahoo 2020 et al. [17]	India	Retrospective	158	108	N/A	N/A	2 (fair)

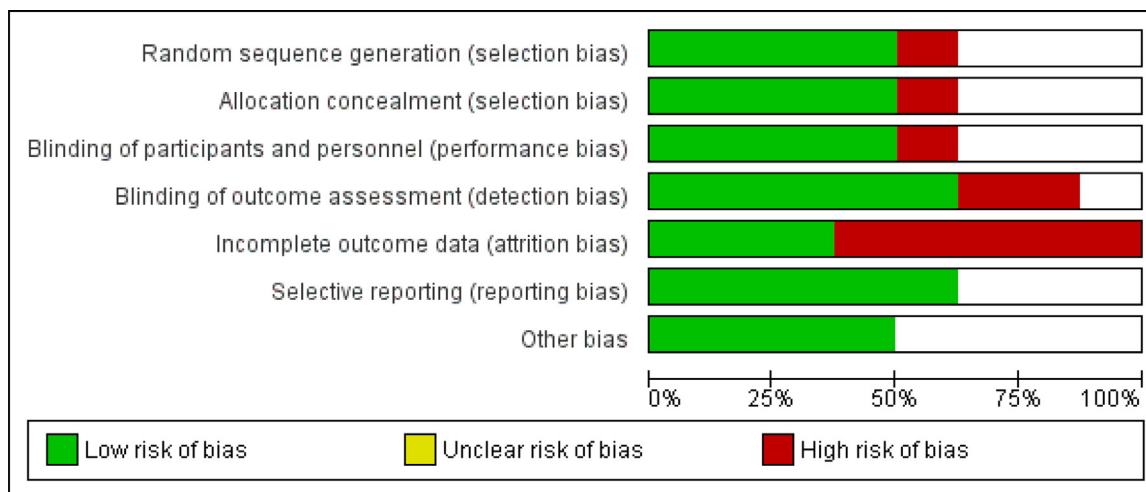


Fig. 3. Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies.

cases. The analysis was done dichotomously according to the number of surgical admissions, complications, and mortality outcomes between the two groups.

2.1. Statistical analysis

Quantitative synthesis (meta-analysis) was made using Review Manager V5.4.1 by (AYA) and revised by (MAA). The analysis results were pooled among the studies, and the results were weighted at the 95% CI data sensitivity can vary. The inconsistency I^2 test was also measured. The sampling error within a sample is a part of the variance (or error) due to differences between studies rather than solely due to sampling error. It is common for heterogeneity to be high when I^2 is greater than 75% and when I^2 is less than 25%. If we had no significant statistical variance, we would get a fixed-effect model.

2.2. Publication bias and quality assessment

We made a modified assessment methodology concerning the studies involved in the quantitative synthesis to ensure the quality and availability of each study’s data separately, and the assessment methodology maximum score is 4 (1= poor, 2= fair, 3= good, 4= well) Table 1. Cochrane risk of bias assessment tool was used to estimate each study’s bias on an independent basis. The results were primarily moderate quality studies included in the analysis, according to the risk of bias assessment tool Fig. 2, Fig. 3. We also used the funnel plot for publications bias estimation on 95% CI. The result was an asymmetrical shape; however, the number of the included studies is less than ten Fig. 4. For the same reason, we were not able to do Egger’s test for publication bias.

3. Results

3.1. Studies characteristics

Eight studies were found to be eligible for our meta-analysis. Most of the studies were on a retrospective basis, except one which was retrospective and prospective. An overall of 951 glioma patients’ was included for surgical admission from the beginning of the pandemic until 2020. Seventy-four patients’ had mortality outcomes, and 250 patients had complications for both surgical admitted, and non-surgical (overall) admitted purposes Table 1.

3.2. The number of surgical admissions

Based on the published data from different countries, an overall number of 5469 neurosurgical admitted cases were reported in the literature in the period of our analysis eligibility; however, not all of them were glioma cases. We made a separate analysis to discriminate and assess the glioma cases separately. By analysis, we did not notice a significant difference between the number of COVID-19 positive and COVID-19 negative glioma patients admitted for surgical purposes during the pandemic (OR= 1.04, 95% CI= [0.88, 1.21]) Fig. 5. The number of admitted COVID-19 negative patients was supposed to be decreasing amid the pandemic due to limited occupancy of ICU beds, limited availability of ICU staff persons, and fear of risking the patients for infection. However, the analysis we did on the available studies in the literature did not significantly differ in the number of admissions done for both COVID-19 positive and negative glioma patients.

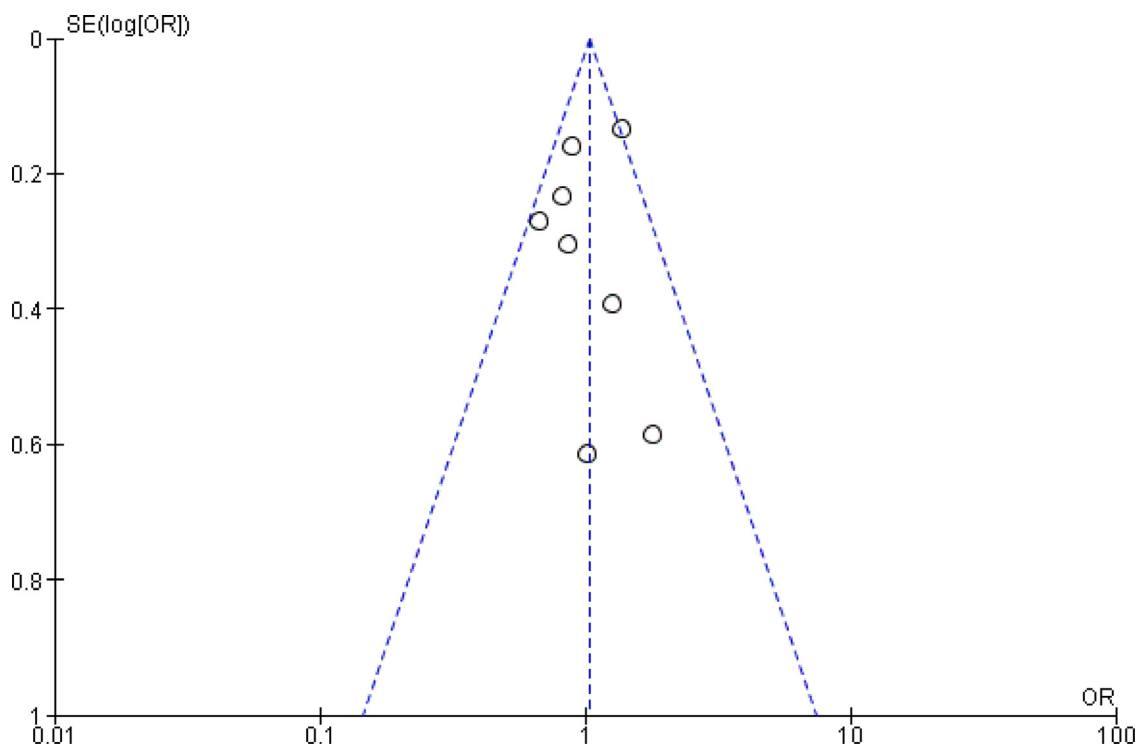


Fig. 4. Funnel plot assessing the publication bias among eight studies to compare events and total. Each circle represents a study that has been included in the meta-analysis. Y-axis (Standard Error), X-axis (Log Odds Ratio).

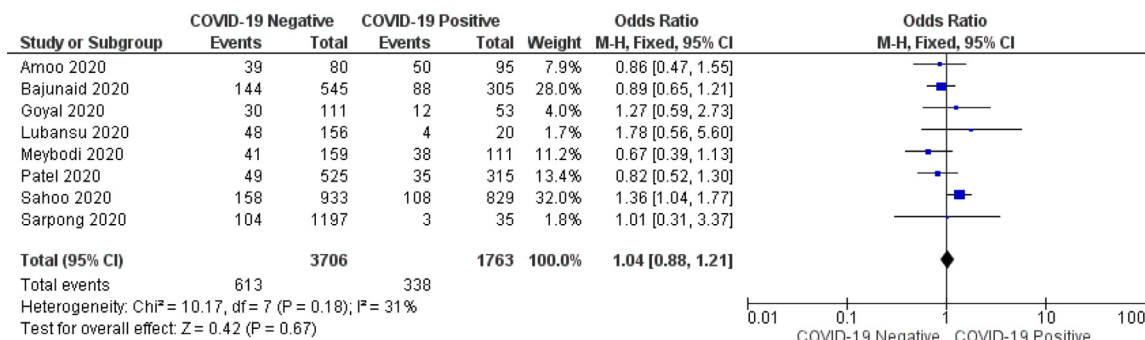


Fig. 5. Forest plot analyzing surgical admissions data for COVID-19 negative and COVID-19 positive glioma cases.

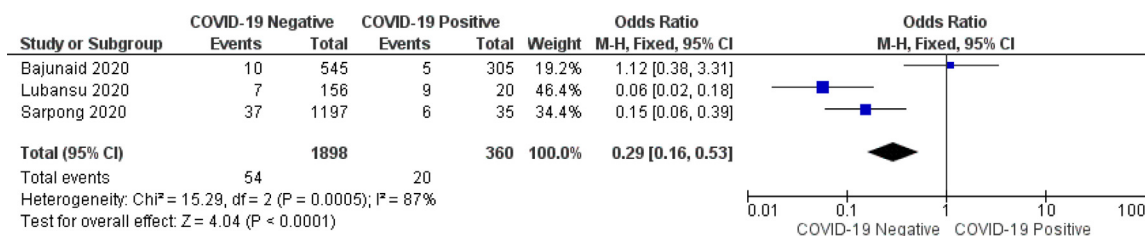


Fig. 6. Forest plot for the mortality of COVID-19 negative and COVID-19 positive glioma cases.

3.3. Mortality outcomes

We also tried to compare the mortality outcome between COVID-19 positive and COVID-19 negative glioma patients through different centers. Interestingly, we noticed that COVID-19 negative glioma patients had more mortality than infected patients (OR= 0.29, 95 CI%= [0.16, 0.53]) Fig. 6. The data was heterogeneous (P = 0.0005, I²=87%), we did sensitivity test analysis, we noticed that the heterogeneity was resolved (P = 0.19, I²= 41%) after excluding Bajunaid 2020 et al.

however, we hypothesize that cause of heterogeneity in this analysis was because of different population and sample size factors.

3.4. Complications

We also found that the complications were more noticed in COVID-19 negative patients than infected patients (OR= 0.70, 95% CI= [0.50, 0.99]) Fig. 7. The data was heterogeneous (P < 0.00001, I²=98%). We declare that the main cause of the heterogeneity in the overall complications analysis is the limited number of studies that reported this out-

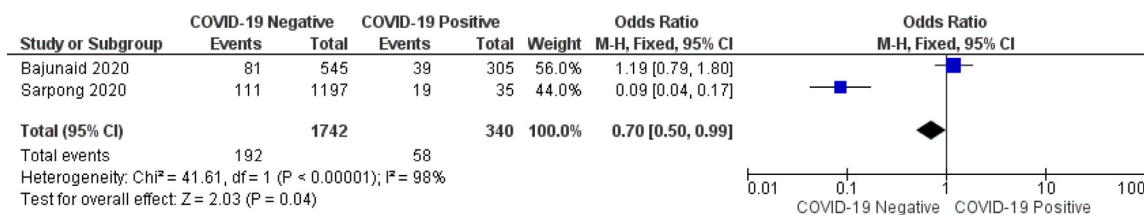


Fig. 7. Forest plot for the overall complications of COVID-19 negative and COVID-19 positive glioma cases.

come, for that the best current statistical solution is ignoring the heterogeneity value, exceptionally. However, the current studies did not detail about causes and types of complications, but several acquired complications with glioma patients' may be related to surgery, COVID-19 infection, or ICU medical complications. Complications related to surgery include wound infection, tumor bed hemorrhage, and neurological morbidities. Sometimes medical complications happen which require proper ICU management. COVID-19 related complications mostly involve the respiratory system with respiratory distress syndrome as the most catastrophic one.

Table 2
Management of centers around the world for glioma cases during the pandemic.

Study	Country of authors	Population of work	Intervention and outcomes	Future directions
Hameed 2021 et al. [1]	China	Chinese hospitals with surgical neuro-oncology services	Most emergency surgical glioma cases were COVID-19 negative cases, and there were suspensions in some adjuvant therapies and all research activities.	Most participated hospitals will gradually resume their activities with no specific new plans.
Amoo 2020 et al. [14]	Ireland	An Irish tertiary referral center	Acute admissions were higher than usual, while elective admissions were lower than usual. There was a slight delay in admission, while faster discharge than usual.	A proposed plan for pandemics will be implemented
Bernhardt 2020 et al. [18]	Group of countries	Hospitals with surgical neuro-oncology services within authors' countries	Non-elderly patients with glioma were suggested to maintain the standard treatment without significant modifications. Generally, it was recommended to modify the treatment on a "case-to-case" basis and focus on modifying chemotherapy and minimizing immunosuppressive therapies.	We provide the practitioners with alternatives for managing neuro-oncology cases, exceptionally high-grade glioma during the pandemic COVID-19.
Simonelli 2020 et al. [19]	Italy	Italian hospitals with surgical neuro-oncology services	Surgical interventions for glioma patients were discussed carefully by the board of tumors. Medical adjuvant therapeutics were prescribed carefully, especially for immunosuppressive drugs. Maximum safety precautions between the staff were made.	Developing COVID-19 safe pathways for more accessible admissions and working on effective vaccinations and antiviral therapeutics solutions as soon as possible
Mohile 2020 et al. [8]	the Netherlands, Switzerland, and USA	Hospitals with surgical neuro-oncology services within authors' countries	Re-evaluate the services among the pandemic for both surgical and medical neuro-oncology therapy management during the adjusted settings in the healthcare system of the COVID-19 pandemic. The primary priority was given to the adult glioma cases because they have shown a higher risk of morbidity and mortality outcomes.	Proposing a better guiding for neuro-oncology practitioners to provide a better service for the patients, especially for the higher-risk population of glioma
Jean 2020 et al. [20]	USA	Worldwide	Most elective surgical interventions for glioma were canceled, except in "for-profit" cases in low and middle-income countries. Emergent cases were operated on with higher acuity.	Developing guidelines for a better quality service for elective surgical cases amid the pandemic
Pessina 2020 et al. [21]	Italy	Italian hospitals with surgical neuro-oncology services	The board of tumors planned surgical interventions with strict measurements have been undertaken, visits of relatives of the patients' were not allowed, all communications were done using telecommunication methods. Adjuvant therapies were prescribed in a more careful manner.	Proposed plan for pandemics with careful selections and precautions to provide the most optimal therapeutic management
Weller 2020 et al. [22]	Switzerland and Austria	Hospitals with surgical neuro-oncology services within authors' countries	General considerations for clinical practice are focused on challenging the urgency and keeping safety measurements as maximum as possible during the pandemic, and adjusting steroids prescription according to need for glioma patients. Specific considerations for glioma patients are various depending on the emergency of the case.	Future consideration will be made upon the availability of evidence-based guidelines concerning neuro-oncology cases amid the COVID-19 pandemic.

3.5. Global management

We have taken a comprehensive view back at different experiences involved in managing glioma patients' during the pandemic in a time interval from the beginning of the pandemic to the end of 2020; all centers shared the same concept operating on emergent glioma cases. Strict safety precaution measures were adopted in all centers that were reviewed in this review. We took a simple look at the different strategies implemented at those centers regarding admission, inpatient, and discharge policies Table 2.

Table 3
Guidelines for glioma cases amid COVID-19 pandemic.

Country	Pre-pandemic Phase	Pandemic Phase	The decline of Pandemic Phase	Early Vaccination Phase	References
Italy	Regular practice routine with more precautions, including increased awareness about the virus highly spread rate, more safety precautions were taken such as; increased hygiene for staff workers.	The admissions were made based on the cases' urgency; priority was for COVID-19 positive glioma cases. Surgical admissions for non-urgent cases were postponed; Outpatient visits numbers were decreased in social distancing precautions.	Similar to the pandemic phase	N/A	[23-28]
Australia	N/A	Australia demonstrated a decrease in elective and emergent admissions; government mandates' implementation led to a significant decrease in cases of the degenerative spine, benign tumors, and vascular interventions. Moreover, trends such as fewer traumatic admissions were associated with the decrease in intra-cerebral hemorrhage patients'.	N/A	N/A	[29]
Belgium	Regular practice routine with more precautions, including increased awareness about the virus highly spread rate, more safety precautions were taken such as; increased hygiene for staff workers.	The admissions were made based on the cases' urgency; priority was for COVID-19 positive glioma cases. Surgical admissions for non-urgent cases were postponed; Outpatient visits numbers were decreased in social distancing precautions.	Similar to the pandemic phase	N/A	[12, 30, 31]
China	Regular practice routine, all emergent surgical cases were performed commonly without screening for COVID-19 positive and COVID-19 negative cases; no special precautions were made. Non-urgent cases were partially postponed depending on the status of each patient individually.	Extensive precautions were taking, and admissions were only for urgent and emergent cases. Inward admissions were relatively decreased, there was re-planning for the surgical staff during operations time.	Precautions were the same as in the pandemic phase, but most of the glioma cases were admitted. COVID-19 positive cases were operated in special hubs; intensive care unit admissions were managed according to each patient's status.	The practice of surgical neuro-oncology is getting back to its' normal routine as before COVID-19, with keeping in mind safety precautions and social distancing regulations. Vaccinations plans are undergoing with priority to elderly patients'.	[24, 32-34]
France	Regular practice routine with more safety precautions such as screening for COVID-19 and increased social distancing.	Screening for COVID-19 before any admissions was necessary; COVID-19 positive cases had a separate admission ward with more safety and precautions. Non-urgent glioma cases were medically managed with postponing for surgical admission.	Like the pandemic phase, it also increases the capacity of admission for urgent and emergent glioma cases. More surgical admissions were taken to develop a strategic safety plan using social distancing, more intensive usage of personal protective equipment, and careful intensive care unit admission.	Similar to the decline of the pandemic phase and developing a strategy in contrast with vaccination.	[30, 35-37]
India	Regular practice without any additional changes	Patients should be evaluated as healthy patients and managed up to seven days (requiring treatment within a month). Precautions were taking a significant risk of aerosol during intubation and endoscopy. Appropriate protective gear is mandatory; surgical admissions were managed according to the urgency.	Like the pandemic phase without much changes, the number of admissions is relatively elevated than most other countries globally; due to India's increased population.	The vaccination plan has not been revealed yet officially.	[13, 17, 38-44]
Saudi Arabia	Regular practice routine without screening for COVID-19	The number of surgical admissions was decreased to about 66% of the number before the pandemic. Priority was according to the urgency of the patients	No changes, similar to the pandemic phase.	Vaccination has been started according to the plan of the ministry of health in Saudi Arabia. There is an increase in several admissions. The priority of admissions is urgency, but most cases are being admitted.	[16, 45-52]

(continued on next page)

Table 3 (continued)

Country	Pre-pandemic Phase	Pandemic Phase	The decline of Pandemic Phase	Early Vaccination Phase	References
USA	Some hospitals have taken early precautions to avoid the spread of COVID-19, which was done by regulating the admissions; some of the hospitals discriminated between admissions for COVID-19 positive and COVID-19 negative glioma cases.	Admissions were mostly including urgent fatal glioma cases. Most of the in-hospital stay durations were decreased, with an exception for intensive care unit cases.	The decline of Pandemic Phase Increasing the admissions capacity is being undertaken; this includes the priority of admissions by the urgency of the case and length of in-hospital stay.	Early Vaccination Phase This is similar to the decline of the pandemic phase and planning a vaccination strategy by giving priority to elderly patients.	[53-65]

4. Discussion

Since December 2019, the coronavirus started in Wuhan and evolved into a catastrophic pandemic disrupting various life aspects internationally. The most common presenting symptoms are fever (87.9%), dry cough (67.7%), and fatigue (38.1%) [5]. COVID-19 clinically progresses the same as SARS-CoV and has an incubation period ranging from 1 to 14 days, which increases the rate of spread of infection [6]. GBM is the most common primary brain tumor, with an individual prevalence of 14.9% of all primary brain tumors [5]. It is considered the most virulent primary brain tumor despite different treatment combinations [6]. The optimal treatment for high-grade glioma is maximal resection plus radiotherapy and chemotherapy [7]. Patients with GBM are at risk of different complications, either surgical or medical. The vulnerability of such a cohort of patients is due to some reasons related to either the tumor or the complications of chemotherapy and radiotherapy. Furthermore, postponing surgical excision may have a bad outcome regarding survival and prognosis.

Different associations worldwide set up specific regulations to manage patients with brain tumors during the coronavirus pandemic [8]. To avoid the potential for under-treatment of glioma patients, meanwhile, protecting the working staff and patients against COVID-19 represent a challenge facing oncological centers worldwide. Utilizing ICU beds, personal protective equipment, medical staff availability, and limited outpatients' visits due to social distancing added to the possibility of missing glioma patients. After meticulous reviewing of the literature, we analyzed how different centers dealt with glioma cases amid COVID-19 through their published work. To the best of our knowledge, we performed the first meta-analysis of different studies involving the effect of COVID-19 on the management of glioma in different centers worldwide. Lessons are clear from that health crisis for all health care workers, especially neurosurgeons and neuro-oncologists. Offering uninterrupted oncological surgical service during these difficult times requires prompt and strict regulations to benefit the patients and avoid risking the staff with infection, whether human or hospital-related facilities, reallocation of resources is of paramount value serving the patient without compromise.

4.1. Impact of results on the neurosurgical community

The global neurosurgical community can benefit from this meta-analysis results by considering the management's experience, which has been done in published literature Table 2. The global view that has been summarized is an important step to be reviewed by neurosurgical practitioners worldwide and compare with the management in their institution; however, the decision to change each healthcare center's local guideline is up to the board of COVID-19. Our quantitative synthesis might help to make a better future decision. We experienced post-admission or surgical complications and mortality outcomes more significant in COVID-19 negative cases; this can be hypothesized through different possibilities. First, the COVID-19 negative glioma cases were more liable to complications than glioma COVID-19 positive cases because of the previous history of the most common global morbid complications such as cardiac diseases, hypertension, diabetes, and immunological disorders [9]. Second, the hospitals which administered both COVID-19 positive and COVID-19 negative cases have discriminated their efforts to give better care for the COVID-19 positive cases, as they might hypothesize that there are more liable to morality outcomes. So, there was slight neglect for providing a possible higher quality of healthcare to COVID-19 negative cases. The number of surgical admissions did not differ between both groups. That can be explained the admission of all glioma cases were without discrimination in priority of admission; what we can learn from this that we should care all admitted glioma cases without giving more beneficial services to a specific group than others, including prevention of discrimination for care between COVID-19 positive and COVID-19 negative cases.

4.2. The global neurosurgical guidelines for glioma patients' during COVID-19

We reviewed the current guidelines for glioma patients' from the published literature and summarized them in Table 3. The guidelines were classified according to four phases; the first phase (pre-pandemic phase), from December 2019 to March 2020. The second phase (pandemic phase) is from April 2020 to September 2020. The third phase (decline of pandemic phase) is from October 2020 to December 2020, and finally, the last phase (early vaccination phase) is from January 2021 until now. Each phase has been reviewed critically from the published literature according to the common planned strategies in each country for glioma cases.

5. Conclusion

To our knowledge, we made the first systematic review and meta-analysis regarding the management of glioma patients' during the pandemic of COVID-19. Our main findings are that the number of surgical admissions for glioma patients did not significantly differ between COVID-19 negative and COVID-19 positive cases; however, we found that both overall complications and mortality outcomes were more significant among COVID-19 negative patients' from the reported studies. Our limitations were mainly because of the current limited published studies regarding this topic. We suggest and encourage neurosurgeons and neuro-oncologists worldwide to investigate and ensure more studies about handling neuro-oncology services during COVID-19, especially for glioma cases. The most important messages to be delivered from this systematic review and meta-analysis are, at first, we should not discriminate in either medical or surgical admissions for glioma patients according to their COVID-19 test status, rather than considering the full health status. Second, healthcare workers worldwide should keep up-to-date regarding surgical management guidelines amid the COVID-19 pandemic to offer the best care for the patients before and after surgery.

Declaration of Competing Interest

The authors certify that there is no conflict of interest with any financial organization about the material described in the manuscript.

The author declares no conflict of interest.

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