Neuro-Oncology Advances

8(1), vdag194, 2026 | https://doi.org/10.1093/noajnl/vdag194 | Advance Access publication July 23, 2026

Tumor treating fields plus temozolomide maintenance after radiochemotherapy in Chinese grade 4 gliomas: Efficacy and predictive biomarkers

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Abstract

Objective. The EF-14 trial established the survival benefit of adding Tumor Treating Fields (TTFields) to maintenance temozolomide (TMZ) following standard radiochemotherapy in glioblastoma (GBM). Whether this benefit is reproducible in Chinese grade 4 glioma patients in real-world practice—and what biomarkers predict response—remains unknown. This study evaluates TTFields efficacy in a Chinese cohort and explores predictive biomarkers.

Methods. We conducted a retrospective analysis of Chinese patients with grade 4 gliomas who underwent surgery and postoperative radiochemotherapy, followed by maintenance TMZ with or without TTFields treatment at Tongji Hospital, Huazhong University of Science and Technology, between November 2019 and November 2024. The Kaplan–Meier method was used to plot survival curves for overall survival (OS) and progression-free survival (PFS), and the log-rank test was applied for group comparisons. Univariate Cox proportional hazards regression analysis was performed to identify factors associated with PFS and OS. Subgroup analyses were conducted, and results were visualized using forest plots.

Results. A comprehensive dataset of 64 postoperative grade 4 glioma patient records was compiled in the study. Among them, 22 patients (34.4%) were administered TTFields treatment. The TTFields-treated group demonstrated a significant improvement in OS compared to the non-TTFields-treated group (median OS: 15 months vs. 11 months, $P = .047$). Univariate Cox analysis identified the chromosome 7 gain and chromosome 10 loss as a significant risk factor for shortened PFS (HR = 2.294; 95% CI, 1.268-4.150; $P = .006$) and OS (HR = 2.831; 95% CI, 1.507-5.316; $P = .001$). Subgroup analysis revealed that TTFields treatment resulted in better PFS for O6-methylguanine DNA methyltranferase (MGMT)-unmethylated patients (HR [95% CI] = 2.269 [1.066-4.83], $P = .033$) and isocitrate dehydrogenase (IDH) wild-type patients (HR [95% CI] = 2.101 [1.029-4.291], $P = .042$). In terms of OS, TTFields treatment was associated with improved OS in patients with multiple surgical sites (HR [95% CI] = 4.148 [1.073-16.033], $P = .039$), MGMT-unmethylated patients (HR [95% CI] = 2.421 [1.113-5.263], $P = .026$), IDH wild-type patients (HR [95% CI] = 2.169 [1.039-4.526], $P = .039$), and those with Ki-67 < 20% (HR [95% CI] = 9.398 [1.122-78.75], $P = .039$).

Conclusion. In this retrospective cohort of Chinese patients with grade 4 glioma, adding TTFields to maintenance TMZ therapy following standard postoperative radiochemotherapy was associated with improved OS compared with maintenance TMZ alone, whereas the improvement in PFS did not reach statistical significance. The co-occurrence of chromosome 7 gain and chromosome 10 loss was identified as a significant risk factor for shorter PFS and OS. Exploratory subgroup analyses suggested greater potential benefit in patients with MGMT-unmethylated tumors, IDH wild-type tumors, multiple surgical sites, or Ki-67 < 20%. Given the small sample size, retrospective non-randomized design, and wide confidence intervals in some subgroup estimates, these findings should be interpreted cautiously and validated in larger prospective multicenter studies.

Received December 5, 2025; accepted July 18, 2026.

Key Points

- TTFields plus TMZ maintenance vs TMZ alone improved OS in Chinese grade 4 gliomas.
- MGMT-unmethylated, IDH-wild, multiple sites, Ki-67 < 20% had OS benefit from TTFields.
- Chromosome 7 gain and 10 loss was a negative prognostic factor for both PFS and OS.

Importance of the Study

While the EF-14 trial established TTFields plus temozolomide (TMZ) as a standard for newly diagnosed glioblastoma, its real-world effectiveness in grade 4 gliomas and the biomarkers predicting response remain poorly defined. This retrospective study of 64 Chinese patients with grade 4 gliomas provide real-world evidence that adding TTFields to maintenance TMZ following postoperative radiochemotherapy significantly improves overall survival (OS) (15 vs. 11 months, $P = .047$). Importantly, we identified that O6-methylguanine DNA methyltranferase (MGMT)-unmethylated, isocitrate dehydrogenase (IDH) wild-type, multiple surgical sites, and Ki-67 < 20% subgroups may derive greater benefit. These findings offer clinically accessible biomarkers to guide personalized TTFields therapy. Future multicenter prospective studies are warranted to validate these exploratory observations and refine patient selection.

High-grade gliomas (HGGs), particularly World Health Organization (WHO) grade 4 tumors, including glioblastoma (GBM) and other molecular variants, represent some of the most lethal and challenging cancers in adults, characterized by treatment resistance and frequent recurrence.[1-3] The standard multimodal treatment for newly diagnosed grade 4 gliomas, especially GBM, includes maximal safe resection followed by concurrent radiochemotherapy and maintenance chemotherapy with temozolomide (TMZ).[4] Despite these efforts, the prognosis for patients with these aggressive tumors remains poor, with a median overall survival (OS) of approximately 15 months for GBM[5] and a 5-year survival rate of only 6.9%.[6-8]

Tumor Treating Fields (TTFields) therapy uses low-intensity, intermediate-frequency alternating electric fields (1-3 V/cm, 100-500 kHz) to apply biophysical forces on charged and polarizable molecules, delivered transcutaneously.[9] TTFields inhibit tumor cell growth by disrupting mitotic spindle formation during metaphase,[10-12] disrupting DNA repair,[13,14] and promoting immunogenic effects.[15-17] In 2015, the FDA approved TTFields therapy for newly diagnosed GBM patients, based on the results of the EF-14 clinical trial (NCT00916409).[18,19] The trial demonstrated a median progression-free survival (PFS) of 6.7 months for patients receiving TTFields plus TMZ, compared to 4 months for those on TMZ alone. The median OS was 20.9 months for the TTFields plus TMZ group, versus 16.0 months for the TMZ-alone group.[18,19] This marked the first major breakthrough in treating newly diagnosed GBM since the STUPP protocol (maximal safe resection followed by radiotherapy with concurrent and adjuvant TMZ) was introduced in 2005.[20] Numerous clinical studies have confirmed the safety of TTFields, noting minimal side effects.[9]

Following its approval in the U.S., TTFields therapy has gained additional regulatory endorsements and guideline adoptions across Europe and Asia, broadening its acceptance among a larger patient population and treatment centers. Concurrently, advances in preclinical and clinical research have elucidated the biological mechanisms of TTFields, contributing to the optimization of treatment regimens.[15,21-23] However, concerns persist regarding the practical challenges of using the device and critiques about selection bias in the EF-14 study, which may limit the generalizability of its findings. Consequently, there is growing interest in understanding the real-world efficacy of TTFields therapy.

Furthermore, as not all patients with HGGs respond uniformly to TTFields, identifying predictive factors for response is crucial to determine which individuals are most likely to benefit from this treatment, holding significant clinical implications. The objectives of this study were: (1) to investigate whether adding TTFields to maintenance TMZ therapy, initiated after completion of standard postoperative radiochemotherapy (consistent with the EF-14 protocol), improves outcomes in Chinese patients with grade 4 gliomas and (2) to explore potential clinical features or genomic alterations that may predict responsiveness to TTFields. Our results indicate that O6-methylguanine DNA methyltransferase (MGMT)-unmethylated patients and isocitrate dehydrogenase (IDH) wild-type patients are more likely to benefit from TTFields therapy.

Methods

Patients and Eligibility Criteria

We collected clinical data from 64 grade 4 glioma patients in the study. These patients underwent surgery and radiochemotherapy, followed by maintenance TMZ with or without TTFields therapy, at Tongji Hospital, affiliated with Tongji Medical College, Huazhong University of Science and Technology, between November 2019 and November 2024. All histological tissue slides were prepared, and glioma diagnoses were confirmed by 2 senior neuropathologists (names withheld for blinded review) based on the

2021 WHO Classification of Tumors of the Central Nervous System,[24] with inter-observer agreement ≥95%. Patients in the TTFields group met the following criteria: (1) histologically diagnosed grade 4 glioma; (2) received surgery and concurrent radiochemotherapy (STUPP protocol); (3) TTFields therapy duration of no less than 4 weeks and a daily usage rate ≥ 75%, initiated after completion of concurrent radiochemotherapy during the maintenance TMZ phase; (4) availability of tumor samples for genetic testing. Non-TTFields group patients also underwent surgery and radiochemotherapy (STUPP protocol) at Tongji Hospital during the same period and met criteria 1, 2, and 4 but did not receive TTFields during the maintenance TMZ phase. Patients who initiated TTFields but failed to meet the compliance threshold ($n=20$, including 16 patients with compliance <75% and 4 patients with duration <4 weeks) were excluded from both groups to avoid confounding the comparison between adequate TTFields therapy and no TTFields therapy.

During the study period, a total of 187 patients were diagnosed with grade 4 glioma at our institution. Of these, 146 received the Stupp protocol. TTFields therapy was offered to 42 patients based on factors, including financial resources, insurance coverage, patient preference, and available genetic testing data. Among these, 20 patients either declined or discontinued TTFields early (compliance <75% or duration <4 weeks) were excluded from the final analysis. The remaining 22 patients met the inclusion criteria and comprised the TTFields group. Among the 104 patients who received the Stupp protocol but were never offered TTFields, 42 with available genetic testing data were selected as the non-TTFields group (Figure 1).

Baseline characteristics collected included age, sex, surgical site, extent of resection, pathological type, MGMT methylation status, IDH mutations, chromosome 7 gain, and chromosome 10 loss (assessed by fluorescence in situ hybridization [FISH]; both criteria required), Ki-67 expression (categorized as <20%, 20%-50%, and ≥50%),[25-27] TTFields usage, Karnofsky Performance Status (KPS) scores (dichotomized as >70 vs.≤ 70), PFS, and OS.

Figure 1 (patient flowchart) was designed and refined with the assistance of ChatGPT (GPT-5, OpenAI). The initial draft of the flowchart structure was generated by the AI tool based on the study's inclusion and exclusion criteria provided by the authors. All content, data, and the final structure were fully reviewed, verified, and approved by all authors, who take full responsibility for its accuracy and integrity.

Ethics Declaration

Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology (Approval No.: TJ-IRB202406007).

Statistical Analysis

Survival analysis was performed using the Kaplan-Meier method, and group comparisons were made using the log-rank test. Univariate Cox proportional hazards regression models were used to assess the impact of various clinical and genomic factors on PFS and OS. The results are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs). Baseline characteristics between groups were compared using chi-square tests. To explore the treatment effect of TTFields across different patient populations, subgroup analyses were performed, and the results were summarized using forest plots. All statistical tests were two-sided, with a significance level set at $P<.05$. Time-zero for both PFS and OS was defined as the date of surgery (histological diagnosis). Statistical analyses were performed using IBM SPSS Statistics 26 and R software version 4.2.0, while visualizations were created with GraphPad Prism 8.0.2.

Results

Cohort Characteristics

Between November 2019 and November 2024, a total of 187 patients were diagnosed with grade 4 glioma at our institution. Of these, 146 received the Stupp protocol, and 64 met the inclusion criteria for this study (Figure 1). Among the 64 included patients, 22 (34.4%) underwent TTFields therapy and 42 (65.6%) did not. Baseline characteristics were well-balanced between the 2 groups, with no statistically significant differences observed (all $P>.05$, Supplementary Table S1). In the TTFields group, 86.36% were over 40 years old, compared to 73.81% in the non-TTFields group ($P=.249$). Males comprised approximately 45.45% of the TTFields group and 52.38% of the non-TTFields group ($P=.599$). Regarding surgical sites, 50.00% of patients in the TTFields group had a single surgical site, compared with 69.05% in the non-TTFields group, whereas multiple surgical sites were observed in 50.00% and 30.95% of patients, respectively; this difference was not statistically significant ($P=.135$). Additionally, 40.91% of the TTFields group underwent gross total resection versus 54.76% in the non-TTFields group ($P=.292$). Pathological subtypes included GBM and non-GBM HGGs, accounting for 72.73% and 27.27% of the TTFields group, respectively, and 69.05% and 30.95% in the non-TTFields group ($P=.760$). Tumor biomarker alterations in TTFields-treated patients included MGMT-methylated (18.18%, $P=.605$), IDH-mutant (13.64%, $P=.943$), chromosome 7 gain and chromosome 10 loss (68.18%, $P=.299$), and Ki-67 ≥50% (27.27%, $P=.206$), compared to 23.81%, 14.29%, 54.76%, and 30.95%, respectively, in the non-TTFields group. KPS scores were also well balanced between the 2 groups: the proportion of patients with KPS score > 70 was 54.55% in the TTFields group and 64.29% in the non-TTFields group, with no statistically significant difference ($P=.448$) (Supplementary Table 1).

PFS and OS Comparison Between TTFields and Non-TTFields Groups

Patients in the TTFields group showed significantly prolonged OS compared to those without TTFields therapy (median OS: 15 months vs. 11 months, $P=.047$, Figure 2A).

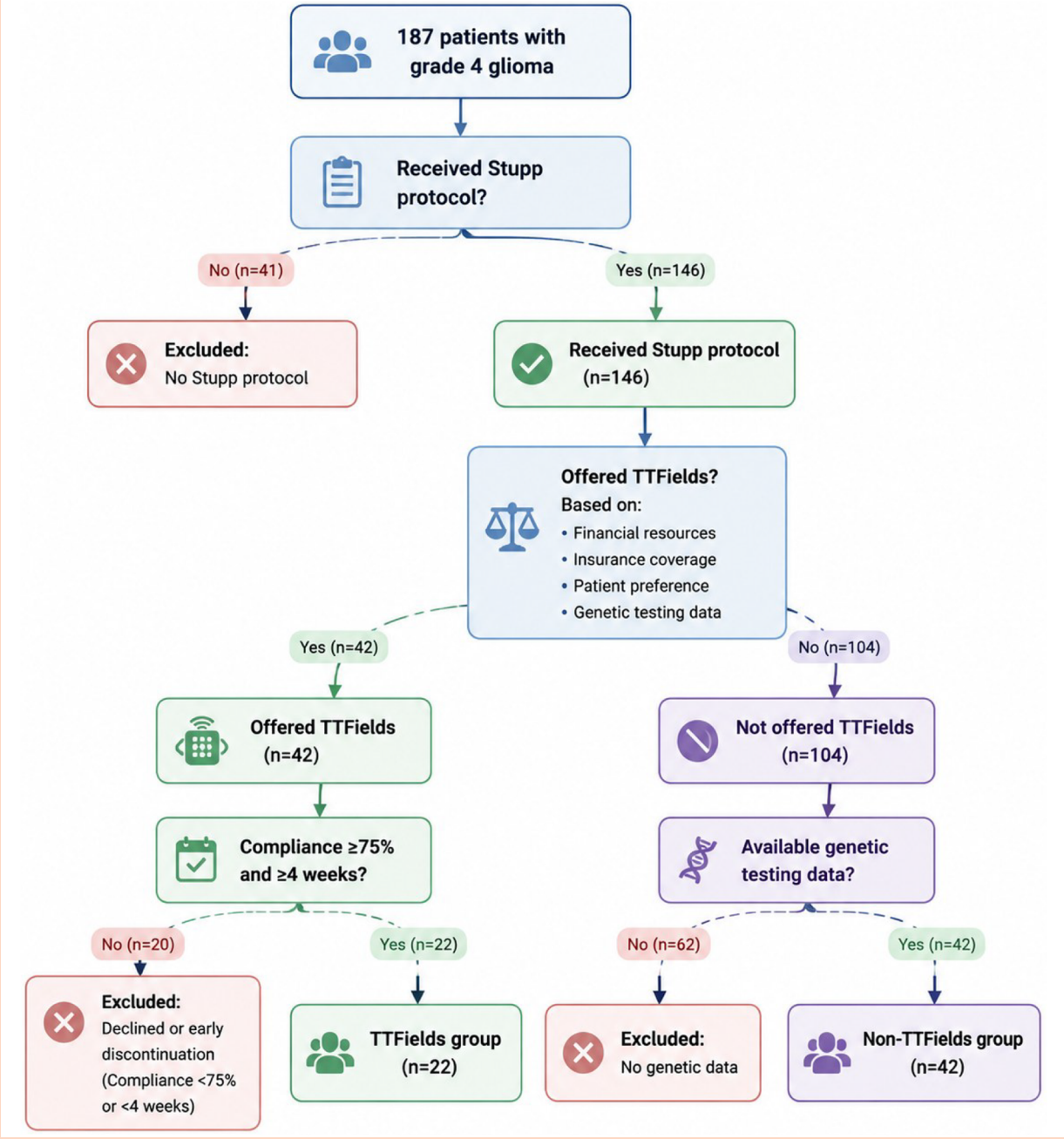

Figure 1. Flowchart of patient selection and study cohort formation.

However, there was no significant difference in PFS between the 2 groups (median PFS: 12 months vs. 7 months, $P=.057$, Figure 2B).

Univariate Cox Regression Analysis for PFS

Univariate Cox analysis identified the chromosome 7 gain and chromosome 10 loss (HR = 2.294; 95% CI, 1.268-4.150; $P=.006$, Table 1) as a significant risk factor for shortened PFS, while factors such as the treatment group (HR = 1.930; 95% CI, 0.980-3.799; $P=.057$, Table 1), gender (HR = 1.389; 95% CI, 0.771-2.503; $P=.273$, Table 1), age (HR = 1.665; 95% CI, 0.772-3.588; $P=.193$, Table 1), surgical site (HR = 0.678; 95% CI, 0.361-1.273; $P=.227$, Table 1), extent of resection (HR = 1.304; 95% CI, 0.723-2.351; $P=.378$, Table 1), pathological type (HR = 1.118; 95% CI, 0.586-2.136; $P=.734$, Table 1), MGMT methylation (HR = 0.656; 95% CI, 0.323-1.333; $P=.244$, Table 1), IDH mutation (HR = 0.592; 95% CI, 0.212-1.658; $P=.318$, Table 1), Ki-67 expression (20%-50%: HR = 0.989; 95% CI, 0.479-2.043; $P=.976$; ≥50: HR = 1.562; 95% CI, 0.717-3.403; $P=.262$, Table 1), and KPS score (HR = 0.781; 95% CI, 0.432-1.412; $P=.413$, Table 1) had no significant influence on PFS.

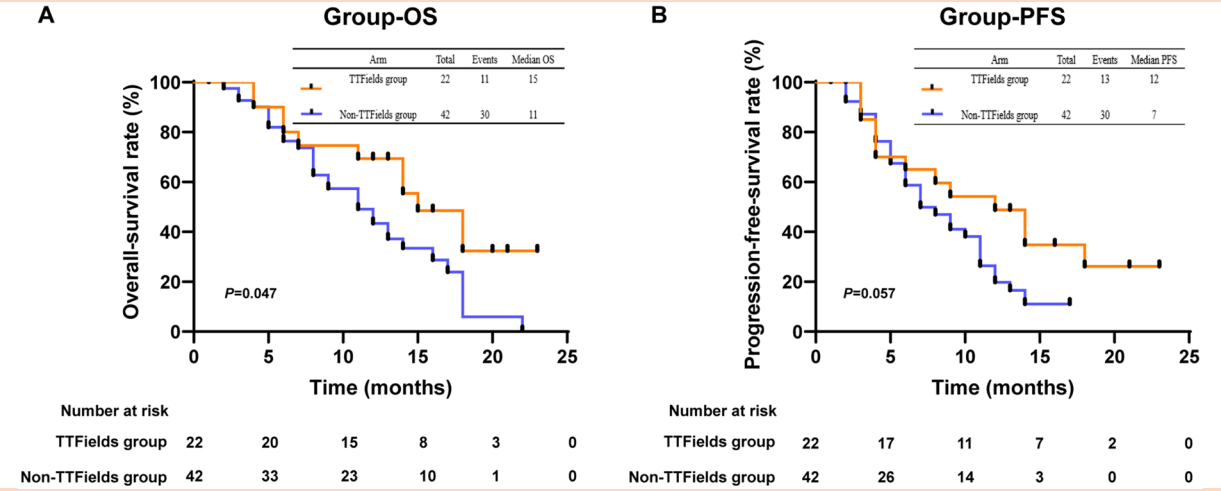

Figure 2. PFS and OS comparison between TTFields and non-TTFields groups.

Univariate Cox Regression Analysis for OS

Univariate Cox regression analysis for OS indicated that the treatment group (HR = 2.033; 95% CI, 1.009-4.096; *P*=.047, Table 2) and the chromosome 7 gain and chromosome 10 loss (HR = 2.831; 95% CI, 1.507-5.316; *P*=.001, Table 2) were statistically significant factors. Specifically, patients in non-TTFields and chromosome 7 gain and chromosome 10 loss groups shortened OS. In contrast, other factors such as gender (HR = 1.698; 95% CI, 0.901-3.199; *P*=.102, Table 2), age (HR = 1.458; 95% CI, 0.644-3.300; *P*=.365, Table 2), surgical site (HR = 0.717; 95% CI, 0.375-1.372; *P*=.315, Table 2), extent of resection (HR = 1.346; 95% CI, 0.729-2.486; *P*=.342, Table 2), pathological type (HR = 1.212; 95% CI, 0.615-2.391; *P*=.579, Table 2), MGMT methylation (HR = 0.587; 95% CI, 0.269-1.281; *P*=.181, Table 2), IDH mutation (HR = 0.707; 95% CI, 0.251-1.993; *P*=.513, Table 2), Ki-67 expression (20%-50%: HR = 0.821; 95% CI, 0.377-1.788; *P*=.620; ≥50: HR = 1.345; 95% CI, 0.606-2.983; *P*=.466, Table 2), and KPS score (HR = 0.723; 95% CI, 0.387-1.351; *P*=.310, Table 2) did not show significant influence on OS.

Predictors of Survival in Grade 4 Glioma Patients Treated with TTFields

To further explore factors affecting response to TTFields, subgroup analysis was conducted on clinical and genomic characteristics. MGMT-unmethylated patients (HR [95% CI] = 2.269 [1.066-4.83], *P*=.033, Figure 3), and IDH wild-type patients (HR [95% CI] = 2.101 [1.029-4.291], *P*=.042, Figure 3) showed improved PFS with TTFields therapy. Regarding OS, TTFields treatment was associated with a better OS in patients with multiple surgical sites (HR [95% CI] = 4.148 [1.073-16.033], *P*=.039, Figure 4), MGMT-unmethylated patients (HR [95% CI] = 2.421 [1.113-5.263], *P*=.026, Figure 4), IDH wild-type patients (HR [95% CI] = 2.169 [1.039-4.526], *P*=.039, Figure 4), and those with Ki-67 < 20% (HR [95% CI] = 9.398 [1.122-78.75], *P*=.039, Figure 4).

Discussion

TTFields, as an emerging therapeutic modality, primarily exert their effects by interfering with the mitotic processes of tumor cells, thereby inhibiting their proliferation.[28] Although clinical applications of TTFields have demonstrated promising safety and efficacy in several studies,[29,30] it remains crucial to delve deeper into their adaptability across different patient populations and to identify potential biomarkers that may predict treatment responses.

In this study, grade 4 glioma patients receiving TTFields plus TMZ as maintenance therapy following radiochemotherapy exhibited a statistically significant improvement in OS compared with those receiving TMZ maintenance alone through univariate Cox regression analysis. This finding aligns with previous studies, such as the EF-14 trial, which highlighted the effectiveness of TTFields in GBM patients.[18,19,29] The median OS in the non-TTFields group (11 months) was shorter than the 15-16 months typically reported in clinical trials, a pattern also observed in other real-world studies.[31] This discrepancy may reflect real-world factors, including patient heterogeneity, treatment delays, socioeconomic barriers, and the inclusion of patients with poorer performance status, which are common in retrospective cohort studies.[31-33] This highlights the importance of real-world evidence to complement clinical trial data.

An important consideration in interpreting these results is the non-randomized allocation of TTFields therapy. In this real-world cohort, the decision to offer TTFields was influenced by a confluence of factors, including financial resources, insurance coverage, availability of genetic testing data, and patient preference.[34] Patients who received TTFields were more likely to have comprehensive insurance coverage or sufficient financial resources to afford the out-of-pocket costs, as TTFields is not covered by the national basic medical insurance in China.[35] Additionally, patient preference played a significant role: some individuals highly valued the novelty of TTFields and were motivated to comply with the device's daily usage requirements,

Table 1. Univariate Cox Regression Analysis for PFS

						95%CI	
	B	SE	Wald	*P*	HR	Lower	Upper
Group							
TTFields					1.000		
Non-TTFields	0.657	0.346	3.616	0.057	1.930	0.980	3.799
Gender							
Male					1.000		
Female	0.329	0.300	1.199	0.273	1.389	0.771	2.503
Age							
≤40 years old					1.000		
>40 years old	0.510	0.392	1.692	0.193	1.665	0.772	3.588
Surgical site							
Single site					1.000		
Multiple surgical sites	–0.389	0.321	1.462	0.227	0.678	0.361	1.273
Total resection							
No					1.000		
Yes	0.265	0.301	0.778	0.378	1.304	0.723	2.351
Pathological type							
GBM					1.000		
Non-GBM	0.112	0.330	0.115	0.734	1.118	0.586	2.136
MGMT methylation							
Unmethylated					1.000		
Methylated	–0.422	0.362	1.359	0.244	0.656	0.323	1.333
IDH mutation							
Wildtype					1.000		
Mutant	–0.524	0.525	0.995	0.318	0.592	0.212	1.658
KI67 (%)							
<20					1.000		
20–50	–0.011	0.370	0.001	0.976	0.989	0.479	2.043
≥50	0.446	0.397	1.258	0.262	1.562	0.717	3.403
Chromosome 7 gain and chromosome 10 loss							
No					1.000		
Yes	0.83	0.302	7.541	0.006	2.294	1.268	4.150
KPS Score							
≤70					1		
>70	–0.247	0.302	0.669	0.413	0.781	0.432	1.412

while others declined due to concerns about scalp dermatitis, the burden of carrying the device, or the need for a caregiver's assistance.[36,37] Additionally, excluding patients with suboptimal TTFields compliance may have introduced a "healthy adherer" bias.[38] However, baseline KPS scores were balanced between groups (P=.448), indicating that the observed OS benefit was not driven by performance status differences. While our findings align with the EF-14 trial, the magnitude of benefit should not be directly compared, and future prospective studies with rigorous adjustment for socioeconomic and behavioral confounders are needed.

Beyond treatment efficacy, our univariate Cox regression analysis identified chromosome 7 gain and chromosome 10 loss as a significant risk factor for shortened PFS and OS. This finding is consistent with a substantial body of literature establishing chromosome 7 gain and chromosome 10 loss as the most frequent cytogenetic alteration and a defining diagnostic criterion for IDH-wildtype glioblastoma.[39] A recent scoping review confirmed that this alteration is consistently associated with shorter survival.[39] Furthermore, multiple studies have validated its role as an independent prognostic factor, with one multi-institutional study reporting HR of 0.798 for survival in patients with this co-alteration.[40] The chromosome 7 gain and chromosome 10 loss signature is frequently associated with aggressive clinical behavior and is commonly accompanied by other adverse genetic alterations, including epidermal growth factor receptor (EGFR) amplification and telomerase reverse transcriptase (TERT) promoter mutations.[41] While the exact mechanisms by which chromosome 7 gain/chromosome 10 loss drives aggressive tumor biology are still being elucidated, its principal clinical value lies in aiding diagnosis, molecular classification, and risk stratification.[42] Our results support the

Table 2. Univariate Cox Regression Analysis for OS

	B	SE	Wald	*P*	HR	95%CI Lower	95%CI Upper
Group							
TTFields					1.000		
Non-TTFields	0.709	0.357	3.938	0.047	2.033	1.009	4.096
Gender							
Male					1.000		
Female	0.529	0.323	2.679	0.102	1.698	0.901	3.199
Age							
≤40 years old					1.000		
>40 years old	0.377	0.417	0.819	0.365	1.458	0.644	3.300
Surgical site							
Single site					1.000		
Multiple surgical sites	–0.333	0.331	1.009	0.315	0.717	0.375	1.372
Total resection							
No					1.000		
Yes	0.297	0.313	0.902	0.342	1.346	0.729	2.486
Pathological type							
GBM					1.000		
Non-GBM	0.193	0.347	0.309	0.579	1.212	0.615	2.391
MGMT methylation							
Unmethylated					1.000		
Methylated	–0.532	0.398	1.789	0.181	0.587	0.269	1.281
IDH mutation							
Wildtype					1.000		
Mutant	–0.346	0.529	0.429	0.513	0.707	0.251	1.993
KI67(%)							
<20					1		
20-50	–0.197	0.397	0.246	0.620	0.821	0.377	1.788
≥50	0.296	0.407	0.530	0.466	1.345	0.606	2.983
Chromosome 7 gain and chromosome 10 loss							
No					1.000		
Yes	1.041	0.322	10.472	0.001	2.831	1.507	5.316
KPS Score							
≤70							
>70	–0.324	0.319	1.032	0.310	0.723	0.387	1.351

incorporation of cytogenetic testing for chromosome 7 gain and chromosome 10 loss into routine clinical workup to more accurately assess patient prognosis.

The variability in treatment responses among specific patient populations warrants attention. In this study, MGMT-unmethylated patients and IDH wild-type patients were found to be more likely to benefit from TTFields treatment. This observation corroborates earlier research indicating that MGMT methylation status could serve as a crucial predictive biomarker for TTFields efficacy.[23] The methylation status of the MGMT gene is intricately linked to the sensitivity of tumors to chemotherapeutic agents, with MGMT-unmethylated patients typically exhibiting poorer responses to chemotherapy.[43] In this context, TTFields may offer a valuable alternative therapeutic option.

IDH mutations are prevalent in human malignancies and are associated with favorable disease prognosis.[44] Studies have shown that the median survival for GBM patients with IDH wild-type is approximately 15 months, while those with IDH mutations can expect a median survival of around 31 months.[44] Similar trends are observed in anaplastic astrocytomas, where IDH wild-type patients have a median survival of 20 months compared to 65 months for IDH-mutant patients.[44,45] A case report suggested that TTFields can extend PFS in IDH-mutant anaplastic astrocytomas and delay pathological progression to GBM.[46] In a study focusing on IDH-mutant WHO grade 4 astrocytomas, patients treated with TTFields often experienced longer median PFS than those who did not receive TTFields (24.4 months vs. 18.5 months).[47] Our data demonstrated that IDH wild-type grade 4 glioma patients receiving TTFields treatment showed significantly better outcomes than those who did not. This finding aligns with the exploratory subgroup analyses of the multicenter retrospective study by Zhou et al., which

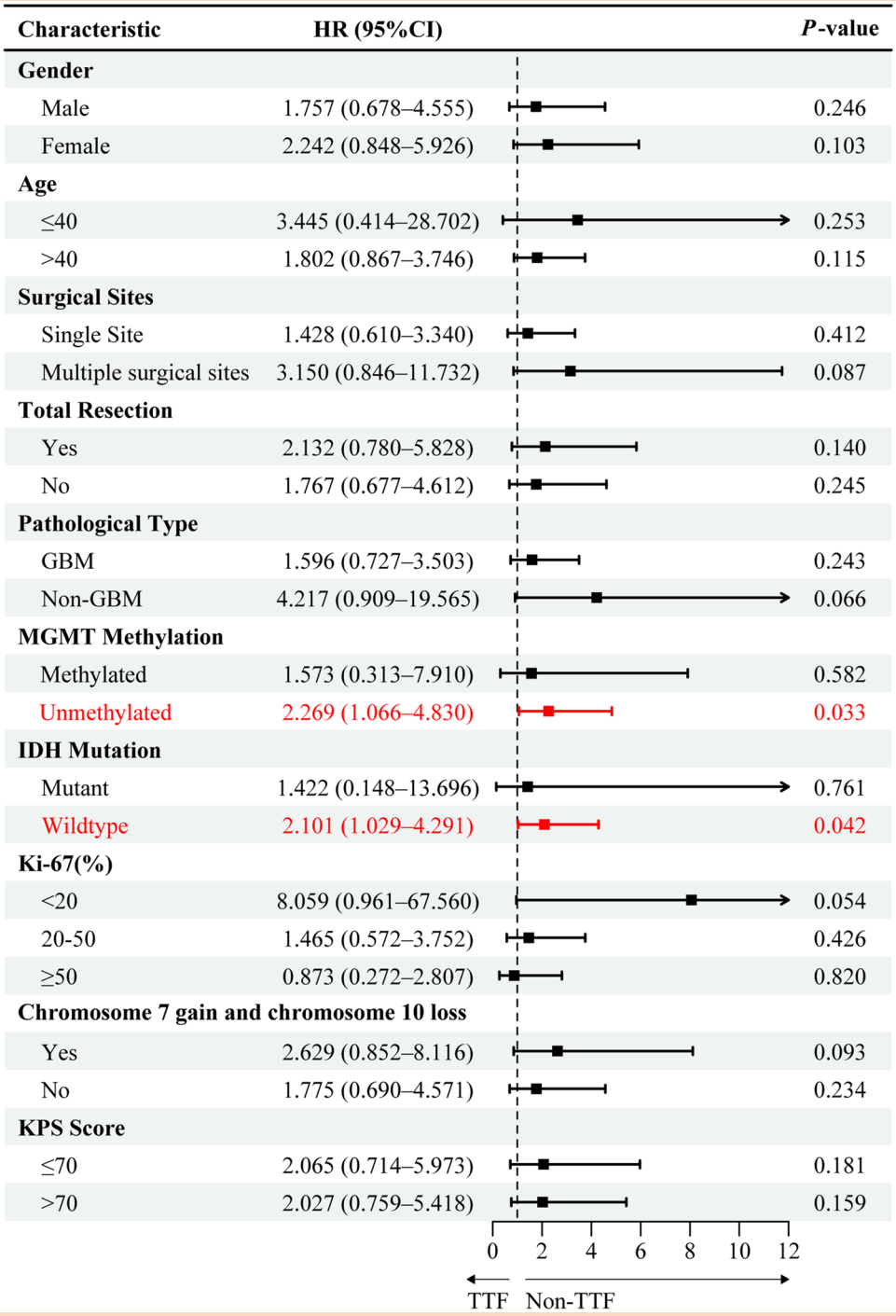

Figure 3. Forest plot of PFS.

indicated that wild-type IDH status might predict a greater benefit from TTFields,[48] collectively providing a strong reference for treatment selection in this patient population.

Furthermore, our analysis revealed a significant association between the proliferation marker Ki-67 and survival outcomes following TTFields treatment. Specifically, patients with a lower Ki-67 index (<20%) demonstrated a markedly better OS benefit from TTFields. This finding aligns with the exploratory conclusion from the multicenter retrospective study by Zhou et al., which suggested that a low Ki-67 index, alongside wild-type IDH1/2 status, may identify a patient population that derives greater benefit from TTFields therapy.[48] On the surface, one might hypothesize that tumors with a high Ki-67 index, indicative of greater proliferative activity, would be more susceptible to TTFields, which primarily target dividing cells. However, our results suggest the opposite. While high Ki-67 suggests greater proliferative activity, such tumors often possess an overwhelmingly aggressive

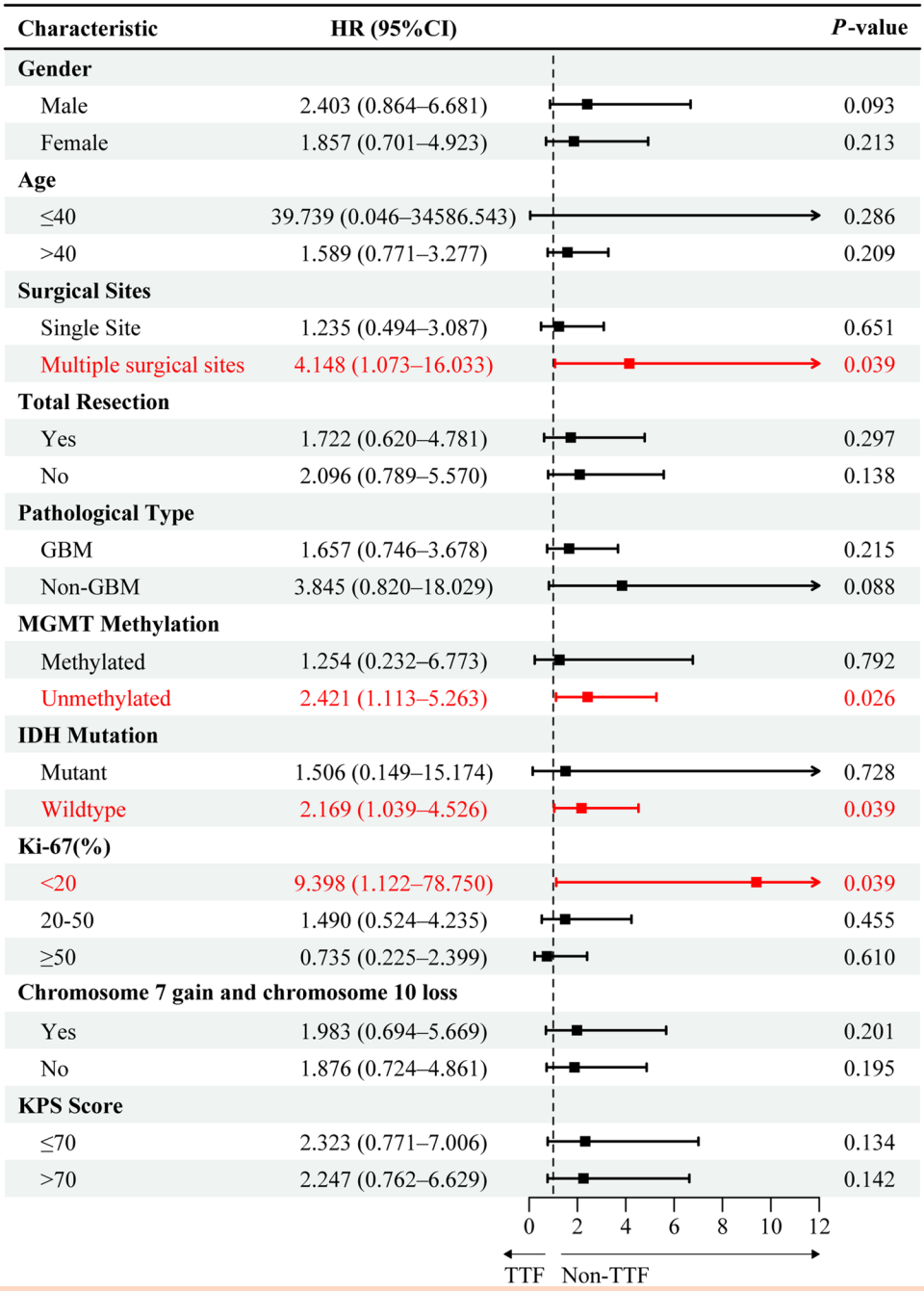

Figure 4. Forest plot of OS.

biology.[49] Their rapid growth may outpace the cytostatic effect of TTFields and be accompanied by other molecular alterations conferring treatment resistance, ultimately obscuring a measurable survival advantage.[50] Conversely, tumors with a relatively low proliferation rate (Ki-67 < 20%) may represent a biological context where TTFields' mechanism is optimally leveraged. These tumors might be less responsive to standard radiochemotherapy, which primarily targets rapidly cycling cells, creating a therapeutic gap.[51] TTFields, by continuously applying tumor-wide mitotic disruption, could provide a crucial complementary effect.[10,52,53] Its ability to induce mitotic catastrophe and immunogenic cell death might be particularly effective against this cell population, leading to more potent and sustained growth inhibition that translates into a clear survival benefit.

Our subgroup analysis also identified that patients with multiple surgical sites appeared to derive an OS benefit from TTFields. Mechanistically, multiple surgical sites in grade 4 gliomas often reflect recurrent disease requiring re-resection, multifocal/multicentric tumor involvement, or a more aggressive phenotype with a propensity for cerebrospinal fluid dissemination.[54] These features are typically associated with a larger spatial distribution of tumor clones, which poses a challenge to focal therapies like radiation but may be

uniquely targetable by TTFields, as the electric field is applied to the whole brain and is not limited to a single surgical cavity.[55] Moreover, each surgical intervention disrupts the blood-brain barrier and induces local inflammation, potentially enhancing the penetration or immunogenic effects of TTFields in previously operated regions.[56] However, the wide confidence interval, driven by the small number of patients with multiple surgeries, demands caution. This finding is hypothesis-generating rather than definitive. It remains unclear whether the benefit is truly driven by TTFields or by unmeasured factors such as more aggressive surgical resections, better post-operative care, or patient selection (eg, those fit enough to undergo repeat surgery). Future studies should prospectively collect the number, timing, and indications of surgical events to disentangle these possibilities.

The biological mechanisms underlying TTFields provide a theoretical foundation for their clinical application. By applying low-intensity alternating electric fields, TTFields disrupt the mitotic spindle formation during cell division, leading to cell cycle arrest and subsequent inhibition of tumor cell proliferation.[10,52,53] This mechanism allows TTFields to potentially synergize with other treatment modalities, such as radiochemotherapy, enhancing overall therapeutic efficacy.[57] Future investigations should further explore the biomarkers associated with TTFields to better identify which patients are most likely to benefit from this treatment. Through large-scale prospective studies and multicenter clinical trials, the effectiveness of TTFields across diverse patient populations can be validated, thereby providing a more solid evidence base for its clinical application.

Several important limitations of this study must be acknowledged. First, the subgroup analyses, while hypothesis-generating, were based on relatively small patient numbers in certain strata. This is reflected in the notably wide confidence intervals for some HR estimates—such as for patients with multiple surgical sites (HR = 4.148; 95% CI, 1.073-16.033) and those with Ki-67 < 20% (HR = 9.398; 95% CI, 1.122-78.75). Although these results reached nominal statistical significance, the broad CIs indicate considerable uncertainty in the point estimates and imply that the true effect size could vary substantially. Therefore, these particular findings should be interpreted with caution and are considered exploratory in nature. Second, the retrospective, non-randomized design introduces potential selection bias, as treatment decisions were influenced by patient preferences, financial considerations, insurance coverage, and available genetic testing data. Third, we were unable to perform multivariable analysis due to the limited sample size, which may have led to unmeasured confounding. Fourth, we excluded patients with inadequate TTFields use (compliance <75% or duration <4 weeks) to ensure a clean comparison. While this avoids confounding, it precludes analysis of suboptimal adherence—a population with distinct prognostic profiles. Deguchi et al. demonstrated that a 2-group stratification (adequate vs. inadequate TTFields use) yields valuable insights: patients with ≥75% compliance during the first 3 months had significantly longer median PFS than those with lower compliance (12.6 vs. 9.0 months, $P = .04$).[58] Additionally, the single-center nature of this study may limit generalizability to other populations with different healthcare systems and access to TTFields.

The external validity of these findings should be interpreted with caution. This study was conducted at a single Chinese center where TTFields therapy is largely self-funded and influenced by patients' financial resources and insurance coverage, which may have resulted in a selected TTFields-treated cohort.[59] Additionally, inter-regional variations in standard of care—including differences in surgical practice, completion of the Stupp protocol, and access to salvage therapies—may affect both baseline survival and the magnitude of TTFields benefit observed in different settings.[60,61] Therefore, the generalizability of our findings requires validation in larger, multi-regional cohorts. In this regard, a multicenter registry is currently being established in China, which will enable pooled analyses from multiple neuro-oncology centers and provide greater statistical power for subgroup validation and multivariable analyses. Collaboration with the TTFields manufacturer may also help obtain aggregate prescription and treatment-utilization data, such as the total number of patients treated nationally or regionally. Future multicenter studies should integrate clinical characteristics, molecular biomarkers, socioeconomic factors (eg, insurance coverage, financial resources, caregiver support), treatment compliance, and utilization data to better define which patients are most likely to benefit from TTFields.

Conclusions

In this retrospective cohort of Chinese patients with grade 4 glioma, the addition of TTFields to maintenance TMZ following standard postoperative radiochemotherapy was associated with improved OS versus maintenance TMZ alone, whereas the improvement in PFS did not reach statistical significance in the overall cohort. The co-occurrence of chromosome 7 gain and chromosome 10 loss was identified as a significant risk factor for shorter PFS and OS. Exploratory subgroup analyses suggested that patients with MGMT-unmethylated tumors, IDH wild-type tumors, multiple surgical sites, or Ki-67 < 20% may derive greater benefit from TTFields. However, given the small sample size, retrospective non-randomized design, potential selection bias, and wide confidence intervals in some subgroup estimates, these findings should be interpreted with caution. Further validation in larger, prospective, multicenter studies is warranted to confirm these observations and refine patient selection for TTFields therapy.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

glioma | radiochemotherapy | retrospective cohort | tumor treating fields

Authors' Contributions

Qianxia Li, and Jie Rao conceived of and revised the study. Wenjun Zhu searched the literature, produced the figures, and

wrote the manuscript. Xiaoxiao Luo collected data, produced the figures and tables. Guangyuan Hu, and Runkun Wang revised the study. All authors have read and approved the manuscript.

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

Funding

The study was funded by the National Natural Sciences Foundation of China (82503237), China Postdoctoral Science Foundation (2025M781990), Beijing Science and Technology Innovation Fund (KC2021-JX-0186-52) and DCMST.NHC Clinical Research Project (WKZX2023CX030002).

Acknowledgements

Thanks to the Department of Pathology, Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology for providing technical support.

Ethics Approval Statement

Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology (Approval No.: TJ-IRB202406007).

Data Availability

All data generated and analyzed in this study are included in this article. The de-identified individual participant data (including demographic, clinical, biomarker [MGMT, IDH, Chromosome 7 gain and chromosome 10 loss, Ki-67], treatment, and survival [PFS/OS] data) that support the findings of this retrospective study are available from the corresponding author upon reasonable request. *Data Access Conditions*: Request Purpose: Data requests must come from qualified researchers with a methodologically sound proposal for independent scientific inquiry. Approval Process: All requests are subject to review and approval by the Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology. A formal data sharing agreement will be required to ensure data use complies with ethical regulations and for intended purposes only. Timeframe: Supporting data will be made available beginning 6 months after the primary publication of this article and will be accessible for up to 24 months.

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https://doi.org/10.1093/noajnl/vdag194
Clinical Investigations