Optimizing the Prediction of Venous Thromboembolism by a Risk Assessment Model in Patients with Glioblastoma

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Abstract

Purpose
To find an optimal model to predict venous thromboembolism specially for glioblastoma by a prospective research.

Methods
Patients with newly histologically confirmed glioblastoma multiform (GBM) were recruited for this study. Status of IDH1, PTEN, P53, BRAF, MGMT and TERT were determined using genetic sequencing through polymerase chain reaction (PCR). Amplification of EGFR was established through fluorescence in situ hybridization (FISH). Competing-risks regression model was performed to calculate the risk of VTE. Clinical and laboratory parameters that were independently predicted risk of VTE were used to develop a risk assessment model (RAM).

Results
145 patients with GBM were included in the present analysis. A total of 48/145 patients (33.1%) developed VTE, all 48 patients were found to be IDH1wt. D-dimer, ECOG score and EGFR status were suggested to be significantly associated with the VTE risk in multivariable analysis. High ECOG score (>2), high D-dimer (>1.6 μg/mL) and EGFR amplification were used as the strongest independent predictors of increased risk of VTE. The cumulative incidence of VTE was 17.2% for patients with score 0 (n = 29), 23.6% for patients with score 1 (n = 55) and 63.8% for patients with score 2 (n = 35) or score 3 (n = 12) by application of a RAM.

Conclusion
GBM patients with IDH1 mutation were at very low risk of VTE. In IDHwt patients, by applying a VTE risk assessment model, we could identify patients with a very high and low risk of VTE.

Introduction
Venous thromboembolism (VTE) is common in cancer patients, and its incidence rates differ widely in different tumor types [1–2]. Compared with cancers in other sites, brain tumor patients are reported to be at relatively higher risk group of developing VTE, especially in malignant glioma patients, with the incidence rates between 10% and 30% [3–4]. Besides cancer type, the incidence of VTE is also closely related with the malignant degree of the tumor. Glioblastoma, the most common and malignant primary brain tumor, is suggested to be at higher risk of VTE than other types of gliomas [5–6]. These suggest that VTE is closely associated with specific tumor type and there may be cancer type-specific pathways of VTE.
Glioblastoma multiform (GBM) is a highly malignant and heterogeneous tumor. According to the 2016 WHO classification of CNS tumors, gliomas can be divided into different groups by oncogenetic mutations and tumor grade [7]. But currently, no consensus has been made regarding the optimal molecular classification for clinical practice of treatment for GBM. By large-scale profiling studies of GBM, Verhaak et al described a molecular classification of GBM into Proneural, Neural, Classical, and Mesenchymal subtypes [8]. Labussière et al have proposed another new molecular classification of GBM based on TERT promoter (TERTp) mutation, EGFR amplification, and IDH1 mutation by analysis of prognosis [9]. However, it has already formed a consensus that molecular classification of glioma is better than histological grading in guiding treatment and judging the prognosis of glioma.

Coagulopathy in cancer is suggested to be affected by oncogenic mutations [10–11]. Many oncogenetic mutations in GBM have been reported to be closely with VTE, like IDH, EGFR, PTEN et al [12–15]. However, only little data exist to predictive of venous thromboembolism by combined oncogenetic mutations and blood biomarkers. In this study, we have combined analysis of clinical markers, oncogenetic mutations and plasma biomarkers in routine clinical practice to try to find an optimal model to predict venous thromboembolism in GBM by a prospective research.

Methods

Patient selection

From May 2017 to August 2019, patients with glioblastoma were recruited for this study based on the following eligibility criteria: 18 years or older, newly histologically confirmed glioblastoma, received total or subtotal tumor resection, information regarding status of IDH, BRAF, TERTp, PTEN, P53 mutations, EGFR amplification and MGMT promoter methylation was available. Patients with a prior history of VTE or continuous anticoagulation therapy were excluded. The pathological grading criteria were based on the latest standards of World Health Organization (WHO) classification system [7] and pathology was determined by a senior neuropathologist in all cases. All patients signed the information consent to review and use their medical records. 18 months follow up were performed for each patient until the occurrence of VTE or death or loss of follow-up.

Molecular data

Mutational status of IDH1, PTEN, P53, BRAF and TERTp were determined using genetic sequencing through polymerase chain reaction (PCR). MGMT promoter methylation was determined by methylation specific PCR. Amplification of EGFR was established through fluorescence in situ hybridization (FISH).

Outcome measures

The baseline clinical characteristics of the patients regarding age, sex, Eastern Cooperative Oncology Group (ECOG) score, body mass index (BMI), hemiparesis, duration of follow-up and occurrence of VTE was collected. The main outcome measure was the occurrence of VTE within 18 months after inclusion of the study. Either deep venous thrombosis (DVT), pulmonary embolus (PE), or cerebral venous sinus
thrombosis (CVST) confirmed by imaging was considered to be VTE in this study. Venous blood sample was collected on the day of enrollment, D-dimer and platelet count were measured within 2 hours after collection.

**Statistical analysis**

The primary outcome was time to first VTE after study inclusion, with the patient’s death as a competing event. The data were censored after 18 months follow-up or loss to follow-up. Competing-risks regression model according to Fine and Gray [16] was performed to calculate the risk of VTE. Univariate and multivariable competing risk analysis were used to compare differences in time to first VTE between age, sex, ECOG score, BMI, hemiparesis, IDH, PTEN, P53, BRAF, TERTp mutation status, MGMT promoter methylation status and EGFR amplification status. Parameters that were independently predicted risk of VTE were used to develop a risk assessment model (RAM). Statistical significance was set at $p \leq 0.05$. Analyses were performed using Stata 15.

**Results**

**Baseline characteristic of the study population**

In this study, 145 patients with GBM were included in the present analysis. The median follow-up of patients included in the analysis was 15.8 months (range, 1.6 to 18 months). During the 18 months follow-up period, 21 (14.4%) patients died without VTE. The detailed clinical characteristics of the study population, extent of surgical resection are summarized in Table 1, baseline laboratory parameters and molecular information are summarized in Table 2.
Table 1
Clinical Characteristics of the total study patients

| Factors                        | Value                      |
|--------------------------------|----------------------------|
| Age years (IQR)                | 57 (23–76)                 |
| Gender (%)                     |                            |
| Female                         | 57 (39.3%)                 |
| Male                           | 88 (60.7%)                 |
| ECOG score (%)                 |                            |
| <=2                            | 101 (69.7%)                |
| > 2                            | 44 (30.3%)                 |
| BMI (kg/m²) (IQR)              | 22 (18–28)                 |
| Extent of surgical resection (%)|                            |
| Subtotal resection             | 101 (69.7%)                |
| Total resection                | 44 (30.3%)                 |
| Hemiparesis (%)                |                            |
| Present                        | 32 (22.1%)                 |
| Absent                         | 113 (77.9%)                |

IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; BMI: body mass index.
Table 2
Baseline laboratory variables of the total study patients

| Factors                                 | Value                           |
|-----------------------------------------|---------------------------------|
| **Platelet count (x10^9)(IQR)**         | 169 (49–494)                    |
| **D-dimer (µg/mL) (IQR)**               | 0.65 (0.28–3.58)                |
| **MGMT promoter status (%)**            |                                 |
| Methylated                              | 54 (37.2%)                      |
| Unmethylated                            | 91 (62.8%)                      |
| **IDH1 status (%)**                     |                                 |
| Wild type                               | 131 (90.3%)                     |
| Mutant                                  | 14 (9.7%)                       |
| **BRAF status (%)**                     |                                 |
| Wild type                               | 139 (95.9%)                     |
| Mutant                                  | 6 (4.1%)                        |
| **TERT status (%)**                     |                                 |
| Wild type                               | 45 (31%)                        |
| Mutant                                  | 100 (69%)                       |
| **PTEN status (%)**                     |                                 |
| Wild type                               | 103 (71%)                       |
| Mutant                                  | 42 (29%)                        |
| **EGFR status (%)**                     |                                 |
| Wild type                               | 85 (58.6%)                      |
| Mutant                                  | 60 (41.4%)                      |
| **P53 status (%)**                      |                                 |
| Wild type                               | 109 (75.2%)                     |
| Mutant                                  | 36 (24.8%)                      |

IQR: interquartile range.

Thromboembolic events during follow up
During the follow-up time, a total of 48/145 patients (33.1%) developed VTE, detailed clinical information on patients with and without VTE are list in Table 3, baseline laboratory parameters and oncogenetic mutations status on patients with and without VTE are list in Table 4. 27/48 patients with VTE (56.2%) were male and 32/48 patients (66.7%) received subtotal resection. 28/48 patients (58.3%) had isolate DVT, 8/48 patients (58.3%) had isolate PE and 12/48 patients (25%) had both DVT and PE. When comparing based on oncogenetic mutations status, all 48 patients were found to be IDH1wt and 47/48 patients (97.9%) were BRAFwt. Besides, 42/48 patients (87.5%) were TERTmt and P53wt.

Table 3
Comparison of Clinical Characteristics between Patients with and without VTE.

| Factors                          | Patients with VTE (n = 48) | Patients without VTE (n = 97) | P value |
|----------------------------------|---------------------------|-------------------------------|---------|
| Age years (IQR)                  | 54 (28–68)                | 57 (23–76)                    | 0.083   |
| Gender (%)                       |                           |                               | 0.441   |
| Female                           | 21 (43.8)                 | 36 (37.1)                     |         |
| Male                             | 27 (56.2)                 | 61 (62.9)                     |         |
| ECOG score (%)                   |                           |                               | 0.422   |
| <3                               | 31 (64.6)                 | 69 (71.1)                     |         |
| >=3                              | 17 (35.4)                 | 28 (28.9)                     |         |
| BMI (kg/m²) (IQR)                | 23 (20–26)                | 21 (18–28)                    | 0.352   |
| Extent of surgical resection (%) |                           |                               | 0.582   |
| Subtotal resection               | 32 (66.7)                 | 69 (71.1)                     |         |
| Total resection                  | 16 (33.3)                 | 28 (28.9)                     |         |
| Hemiparesis (%)                  |                           |                               | 0.863   |
| Present                          | 11 (22.9)                 | 21 (21.6)                     |         |
| Absent                           | 37 (77.1)                 | 76 (78.4)                     |         |
| Site of thrombotic event (%)     |                           |                               |         |
| Isolated DVT                     | 28 (58.3)                 |                               |         |
| Isolated PE                      | 8 (16.7)                  |                               |         |
| DVT and PE                       | 12 (25)                   |                               |         |

IQR: interquartile range; ECOG:Eastern Cooperative Oncology Group; BMI: body mass index.
Table 4
Comparison of baseline Laboratory Characteristics between Patients with and without VTE

| Factors                  | Patients with VTE (n = 48) | Patients without VTE (n = 97) | P value |
|--------------------------|----------------------------|------------------------------|---------|
| **Platelet count (x10^9)\%** |                            |                              | 0.961   |
| >=196                    | 20 (41.7)                  | 40 (41.2)                    |         |
| < 196                    | 28 (58.3)                  | 57 (58.8)                    |         |
| **D-dimer (µg/mL)**      |                            |                              | 0.016   |
| >=1.6                    | 32 (66.7)                  | 44 (45.4)                    |         |
| < 1.6                    | 16 (33.3)                  | 53 (54.6)                    |         |
| **MGMT promoter status** |                            |                              | 0.494   |
| Methylated               | 16 (33.3)                  | 38 (39.2)                    |         |
| Unmethylated             | 32 (66.7)                  | 59 (60.8)                    |         |
| **IDH1 status**          |                            |                              |         |
| Wild type                | 48 (100)                   | 83 (85.6)                    |         |
| Mutant                   | 0 (0)                      | 14 (14.4)                    |         |
| **BRAF status**          |                            |                              | 0.664   |
| Wild type                | 47 (97.9)                  | 92 (94.8)                    |         |
| Mutant                   | 1 (2.1)                    | 5 (5.2)                      |         |
| **TERT status**          |                            |                              | 0.001   |
| Wild type                | 6 (12.5)                   | 39 (40.2)                    |         |
| Mutant                   | 42 (87.5)                  | 58 (59.8)                    |         |
| **PTEN status**          |                            |                              | < 0.001 |
| Wild type                | 25 (52.1)                  | 78 (80.4)                    |         |
| Mutant                   | 23 (47.9)                  | 19 (19.6)                    |         |
| **EGFR status**          |                            |                              | 0.001   |
| Wild type                | 19 (39.6)                  | 66 (68)                      |         |
| Mutant                   | 29 (60.4)                  | 31 (32)                      |         |
| **P53 status**           |                            |                              | 0.016   |
| Wild type                | 42 (87.5)                  | 67 (69.1)                    |         |
Table 5
Univariate and multivariable logistic and competing risk regression models with all risk factors.

| Factors       | Univariate Analysis | Multivariable Analysis |
|---------------|---------------------|------------------------|
|               | HR                  | 95% CI                 | P  | HR                  | 95% CI                 | P  |
| Age           | 0.993               | 0.973–1.013            | 0.514 | 0.990               | 0.967–1.013            | 0.413 |
| Sex           | 1.227               | 0.696–2.164            | 0.478 | 1.111               | 0.623–1.979            | 0.721 |
| ECOG score    | 2.187               | 1.195–4.002            | 0.011 | 2.976               | 1.443–6.136            | 0.003 |
| BMI           | 1.095               | 0.622–1.928            | 0.753 | 0.896               | 0.487–1.649            | 0.726 |
| Hemiparesis   | 1.277               | 0.630–2.588            | 0.497 | 1.000               | 0.441–2.265            | 0.999 |
| Surgical resection | 0.737     | 0.428–1.265            | 0.269 | 0.682               | 0.392–1.185            | 0.175 |
| Platelet count | 1.000               | 0.997–1.003            | 0.830 | 0.999               | 0.995–1.003            | 0.788 |
| D-dimer       | 2.318               | 1.281–4.197            | 0.005 | 2.829               | 1.355–5.906            | 0.006 |
| IDH1          | 1                   |                        |      |                      |                        |     |
| BRAF          | 0.407               | 0.064–2.596            | 0.342 | 0.564               | 0.136–2.345            | 0.432 |
| TERT          | 1.584               | 0.803–3.123            | 0.184 | 1.445               | 0.685–3.047            | 0.332 |
| MGMT          | 0.720               | 0.400–1.294            | 0.273 | 0.633               | 0.326–1.229            | 0.177 |
| PTEN          | 2.208               | 1.264–3.857            | 0.005 | 1.809               | 0.911–3.593            | 0.090 |
| EGFRa         | 2.622               | 1.464–4.696            | 0.001 | 2.191               | 1.146–4.190            | 0.018 |
| P53           | 0.517               | 0.219–1.219            | 0.132 | 0.490               | 0.206–1.164            | 0.106 |

ECOG: Eastern Cooperative Oncology Group; BMI: body mass index.

Competing-risk regression

The competing-risk regression was used to analyze the hazard ratios (HRs) of developing VTE for each parameter in univariate and multivariable proportional subdistribution models. The detailed information are listed in Table 5. ECOG score, D-dimer, PTEN status and EGFR status were suggested to be significantly associated with the VTE risk in univariate analysis. In multivariable analysis, all the variables in the univariate analysis were included. ECOG score, D-dimer and EGFR status remained significantly associated with the VTE risk.

Factors | Patients with VTE (n = 48) | Patients without VTE (n = 97) | P value |
|---------|---------------------------|-------------------------------|---------|
| Mutant  | 6 (12.5)                  | 30 (30.9)                     |         |

VTE: venous thromboembolism.
We used a statistical stepwise forward-selection process to design a VTE risk assessment model in 131 IDHwt patients. High ECOG score (> 2), high D-dimer (> 1.6 µg/mL), and EGFR amplification were used as the strongest independent predictors of increased risk of VTE. One point was assigned, respectively. The cumulative incidence of VTE was 17.2% for patients with score 0 (n = 29), 23.6% for patients with score 1 (n = 55) and 63.8% for patients with score 2 (n = 35) or score 3 (n = 12) by application of a RAM ; (P < 0.001; Fig. 1).

Discussion

In this study, we have designed a prospective research to investigate the relationship between tumor-specific biomarkers and VTE in GBM patients. We have examined 7 routinely tested molecular factors in IDHwt patients, shows that the status of EGFR and PTEN are significantly correlated with VTE by univariate analysis. Other prognostic factors such as TERTp, P53, BRAF and MGMT has no influence in the risk of VTE. PTEN is no longer significantly correlated with VTE events by multivariable analysis. We finally found 1 clinical marker, 1 molecular and 1 plasma biomarker predicting substantially increased risk of VTE in IDHwt GBM patients: namely, ECOG score, EGFR status and D-dimer. We tested the biomarkers by a VTE risk assessment model and found that patients with low ECOG score (≤ 2), low D-dimer (< 1.6µg/mL) and no EGFR amplification have the lowest risk of developing VTE (17.2%, score = 0), the risk of VTE was 63.8% for patients assigned to the high-risk group (score = 2 or 3).

Our findings that combined analysis of ECOG score, EGFR and D-dimer to built a GBM specific VTE risk assessment model is completely novel. Most of previous studies have tested different biomarkers in pooled patient populations with different types of cancer, however, the numbers of samples for specific cancer are small [17–19]. A multinational cohort study evaluated four clinical prediction scores for VTE in patients with advanced cancer and found that the prediction scores were poor at predicting VTE in cancer patients [20]. The sensitivity and specificity of current prediction models for VTE in clinical practice is not satisfied in cancer patients, explore new models based on biomarkers and pathways of cancer-associated thrombosis in individual cancers are thought to be the best way to solve this problem [21].

With the publication of the 2016 WHO Classification of Tumors of the Central Nervous system, the official diagnostic and grading system of glioma has changed from solely on morphologic features to both on molecular and morphologic features.

Some molecular biomarkers like IDH, TERTp, EGFR, P53, PTEN, BRAF, MGMT are reported to be closely related with prognosis in GBM and recommened to test in clinical practice to assist diagnosis and treatment. Some preclinical and clinical research revealed that these biomarkers are also closely related with the risk of VTE. A study by Unruh et al. reported that mutant IDH1 has potent antithrombotic activity by the production of D-2-hydroxyglutarate (D-2-HG) in glioma patients [22]. NAZARI et al analyzed the different risk of VTE in brain tumor patients and found that the status of IDH1 was closely linked to the risk of VTE, patients with IDH1 mutation were at very low risk of VTE [23]. In line with the present study,
we also found that IDH1 mutation was highly linked with low risk of VTE, none of 14 IDH1 mutant patients in this study developed VTE during follow-up. Rong et al have evaluated the relationship between the expression of EGFR and PTEN and tissue factor expression in glioblastoma and found that they are also highly correlated [24]. Recently, a retrospective study showing no difference in VTE risk according to EGFR amplification status in Grade II-IV Glioma patients. However, only 73 GBM patients had information on EGFR expression and they were not analyzed separately [25]. In contrast with this study, our data shows that the status of EGFR amplification significantly related with VTE risk in IDHwt GBM patients. Our large number of available EGFR information patients and separate analysis may partially explain this discrepancy.

On the other hand, we also evaluated the predictive value of clinical and plasma markers. Previous study have shown that glioma patients with age > 44 years linked with high risk of VTE [26]. However, our result shows no difference between patients with different ages. The median age of diagnosis of GBM is reported to be 64 years old and more than 80% is over 50 years old [27]. In our study, the median age of diagnosis is 57 years old and less than 10% with age < 50 years old. The difference in age distribution may explain this discrepancy. Besides, by univariate and multivariable competing risk analysis, we found that ECOG score is the strongest independent predictors of increased risk of VTE among age, gender, ECOG score, BMI and hemiparesis. Platelet count and D-dimer have been used widely as useful indicators of intravascular thrombosis, consist with previous study [4], our result shows that patients with VTE have significant higher D-dimer than patients without VTE, D-dimer is an independent predictors of VTE. However, no significant difference in Platelet count has been noted between two groups.

Some limitations of our study need to be addressed. This study is a single-center study, the number of IDHmt patients and VTE events is relatively low. Moreover, based on the results of previous studies and routine clinical practice, although we have analyzed 7 oncogenetic mutations and 2 plasma biomarkers and developed a RAM in IDHwt GBM patients, some information of other oncogenetic mutations is not available; for example, CDKN2A and NFKB1A deletion mut

In conclusion, we have combined analysis of clinical and laboratory markers in routine clinical practice of GBM and found that patients with IDH1 mutation were at very low risk of VTE. In IDHwt GBM patients, 1clinical marker, 1 molecular mutation and 1 plasma biomarkers predict substantially increased risk of VTE : namely, ECOG score, EGFR status and D-dimer. by applying a VTE risk assessment model, we could identify patients with a very high and low risk of VTE in clinical practice.

**Declarations**

**Founding:**

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**Authorship statement:**
Analysis and interpretation: YH, HD, ML, SL, YZ. Data analysis: YH, ZL, CX, YZ. Experimental design: YH, HD, ML, YZ.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Conflict of interest:

All authors declare no potential conflicts of interest.

Ethical approval/consent to participate

The study methodologies conformed to the standards set by the Declaration of Helsinki. Approval of the study was obtained from the institutional review board of the Zhongnan Hospital, Wuhan University. All patients who were included in the database were required to sign the study informed consent.

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**Figures**

Cumulative incidence of venous thromboembolism, accounting for competing risk (death from any cause other than fatal VTE) according to our experimental risk assessment model (including ECOG score, D-dimer and EGFR status) in GBM IDHwt patients with scores 0, 1, 2/3.