

# Evaluating the Khorana Score in Advanced EGFR-Mutated NSCLC Patients Receiving First-Line Osimertinib

Melissa Yacur, Najeebah A Bade, Shubha V Srinivas and Amin Benyounes\*

Inova Schar Cancer Institute, USA

\*Corresponding author: Amin Benyounes, Inova Schar Cancer Institute, Fairfax, Virginia, USA

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## ABSTRACT

Venous thromboembolism (VTE) poses a significant risk in patients with non-small cell lung cancer (NSCLC), particularly those with driver mutations, such as in the Epidermal Growth Factor Receptor (EGFR). While the Khorana Score is commonly used to predict VTE risk in general oncology patients, its relevance in genetically defined subgroups, such as EGFR-mutated NSCLC patients, remains unclear. This retrospective study evaluated the correlation between the Khorana Score and VTE incidence in 47 advanced EGFR-mutated NSCLC patients receiving first-line osimertinib at the Inova Schar Cancer Institute. Baseline demographics and Khorana Score components were recorded, including platelet count, white blood cell count, body mass index, hemoglobin, and erythropoietin stimulating agent use, with VTE incidence as the primary outcome. VTE was observed in 19.1% of patients, but the Khorana Score did not significantly correlate with VTE development. Median progression-free survival (PFS) was 13.87 months in the VTE group compared to 9.9 months in those without VTE. Our findings suggest that the Khorana Score may not be a reliable predictor of VTE risk in EGFR-mutated NSCLC patients treated with osimertinib, likely due to its design for a more heterogeneous cancer population. Further research is warranted to develop tailored VTE risk models for this distinct patient subgroup.

**Keywords:** Khorana Score; EGFR Mutation; Non-Small Cell Lung Cancer (NSCLC); Venous Thromboembolism (VTE); Osimertinib; Risk Assessment; Progression-Free Survival (PFS); Thrombosis in Cancer; Targeted Therapy

## Introduction

Venous thromboembolism (VTE) represents a significant cause of morbidity in non-small cell lung cancer (NSCLC), with a pooled incidence of venous thromboembolism and pulmonary embolism of 6 and 3%, respectively [1]. A systemic review of thrombotic events in NSCLC with various driver mutations, including 5767 subjects from 20 studies, showed an incidence of 12% (95% CI: 8–17%) [2]. As non-small cell lung cancer is genetically heterogeneous, studying it within the known molecular subtypes is imperative. EGFR mutations represent 22.2–64.5% (depending on country) of non-squamous NSCLC [3]. The FLAURA study was an international multicenter, double-blind, randomized trial in subjects with newly diagnosed EGFR mutated non-small cell lung cancer to osimertinib vs. early generation tyrosine kinase inhibitors. The incidence of pulmonary embolism was 1.4% in the osimertinib arm. This study served as the basis for osi-

mertinib approval in many countries, including the United States, in the first-line setting [4].

The MARIPOSA study compared the combination of amivantamab and lazertinib, two new EGFR-targeted drugs, to osimertinib. Nine percent of patients receiving frontline osimertinib in this study developed VTE [5]. While the drugs themselves may carry inherent VTE risk, we know that a metastatic cancer diagnosis is a risk factor on its own. Several risk calculator models exist to estimate VTE risk in cancer patients. The most widely used is the Khorana score. The model was developed based on 1365 patients from an observational prospective cohort of outpatient cancer patients. The variables incorporated were the site of the primary tumor, pre-chemotherapy platelet count, hemoglobin level or use of erythropoietin stimulating agent, pre-chemotherapy white blood cell count, and Body Mass Index. The low, intermediate, and high-risk groups carried a VTE risk of

0.3%, 2%, and 6.7%, respectively [6]. Given the heterogeneity of the study group, we applied the Khorana score to our cohort of patients with genetically defined advanced non-small cell lung cancer and activating EGFR mutations who received first-line osimertinib. Our goal was to correlate the Khorana score with the risk of developing VTE retrospectively.

Results

A total of 47 patients were included (Table 1), of which 70.2% were female. Adenocarcinoma was the most common histology. EGFR

exon 19 deletion and L858R point mutations were the most common EGFR mutations, 52.2% and 32.6%, respectively. 54.3% of patients had baseline brain metastases. The breakdown of VTE incidence across different Khorana Score categories is detailed in Table 2. The median Khorana score was 1, and the incidence of VTE was 19.1%. The Khorana score did not correlate with the development of VTE. The median PFS of patients who experienced VTE was 13.87 95% CI (1.34, NR), and 9.9 months 95% CI (7.18, 15.6) for patients who did not experience VTE (Figure 1).

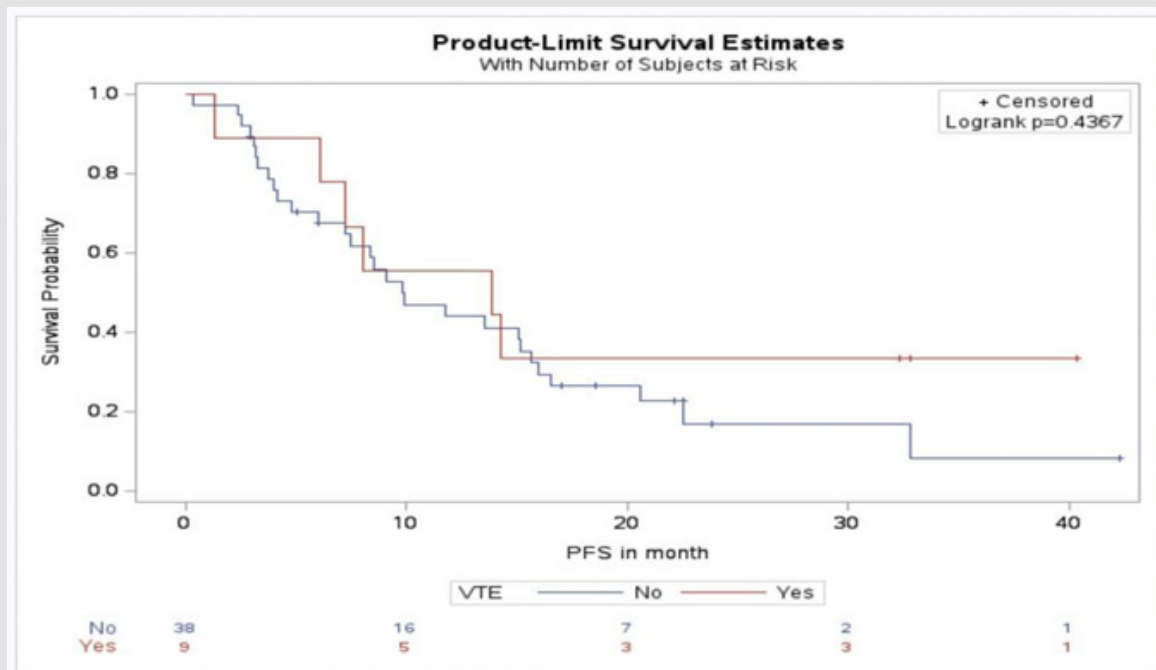
Table 1: Baseline Demographics and Clinical Characteristics of Patients with Advanced EGFR-Mutated NSCLC.

| Total Patients          | N=47         |
|-------------------------|--------------|
| Age at Diagnosis        |              |
| Mean (SD)               | 62.9 (11.27) |
| Median                  | 63           |
| Range                   | 42.0-83.0    |
| Gender, N (%)           |              |
| Female                  | 33 (70.2%)   |
| Male                    | 14 (29.8%)   |
| EGFR Type, N (%)        |              |
| Exon 19 deletion        | 24 (52.2%)   |
| L858R point mutation    | 15 (32.6%)   |
| Other                   | 8 (15.2%)    |
| Histology, N (%)        |              |
| Adenocarcinoma          | 43 (93.5%)   |
| Squamous cell carcinoma | 2 (4.3%)     |
| Other                   | 2 (4.3%)     |
| Brain metastases, N (%) |              |
| Absent                  | 21 (45.7%)   |
| Present                 | 25 (54.3%)   |
| VTE, N (%)              |              |
| Absent                  | 38 (80.9%)   |
| Present                 | 9 (19.1%)    |

Table 2: Incidence of VTE in Patients by Khorana Score Categories.

| VTE <sup>1</sup> , N (%) | Khorana Score |           |            |            |              | P-value             |
|--------------------------|---------------|-----------|------------|------------|--------------|---------------------|
|                          | 1 (N=26)      | 2 (N=9)   | 3 (N=11)   | 4 (N=1)    | Total (N=47) |                     |
| No                       | 20 (76.9%)    | 7 (77.8%) | 10 (90.9%) | 1 (100.0%) | 38 (80.9%)   | 0.7491 <sup>2</sup> |
| Yes                      | 6 (23.1%)     | 2 (22.2%) | 1 (9.1%)   | 0 (0.0%)   | 9 (19.1%)    |                     |

Note:  
<sup>1</sup>Venous thromboembolism  
<sup>2</sup>Fisher Exact P-value



**Figure 1:** Kaplan-Meier Curve for Progression-Free Survival (PFS) Based on Venous Thromboembolism (VTE) Status in Patients with EGFR-Mutated NSCLC. Kaplan-Meier survival analysis depicting PFS in patients with EGFR-mutated non-small cell lung cancer (NSCLC) receiving first-line Osimertinib, stratified by VTE occurrence. The median PFS (mPFS) for patients who developed VTE was 13.87 months (95% CI: 1.34, not reached), while the mPFS for those without VTE was 9.9 months (95% CI: 7.18, 15.6). The log-rank test indicated no significant difference in PFS between the two groups ( $p = 0.4367$ ).

## Discussion

In the original Khorana study, patients with intermediate Khorana scores (1–2) had an approximate VTE rate of 2%. Our study shows that most EGFR-mutated patients at our institution fall into the intermediate risk category but have a much higher incidence of VTE than what would have been predicted by the Khorana model (>20% in our population). This suggests that the Khorana score does not correlate with the development of VTE in patients with advanced EGFR mutated NSCLC receiving frontline osimertinib. One explanation for this may be inherent hypercoagulability induced by EGFR-targeted therapy. EGFR inhibition has been shown to induce platelet activation, which leads to the formation of platelet plugs and triggering of the coagulation cascade [7]. Even in the absence of treatment, an activating EGFR mutation may lead to upregulation of procoagulants, such as tissue factor, compared to what is seen in non-EGFR mutated cancers, leading to hypercoagulability [7,8]. While inhibiting EGFR has been proposed to potentially lower tissue factor expression and decrease VTE risk, these patients remain at an overall increased risk of VTE, highlighting the complex balance of pro- and anti-coagulation factors in this group. One limitation of our study is that it is retrospective with a relatively small sample size, although VTE did occur in 19.1% of patients. A larger prospective study could help validate these results. Importantly, in addition to osimertinib, newer-genera-

tion EGFR-targeted drugs, such as the combination of amivantamab and lazertinib, appear to have an even higher risk of VTE (37%) [5]. It is clear that VTE will remain a major issue to address in the evolving treatment field of EGFR mutated NSCLC, and better predictive models are needed to determine who may benefit from prophylactic anticoagulation to limit morbidity related to VTE.

## Materials and Methods

We identified consecutive patients diagnosed with stage IV EGFR-mutated NSCLC at the Inova Schar Cancer Institute between January 2021 and May 2023. The chart provided Baseline Khorana score elements (platelet count, white blood cell count, body mass index, hemoglobin, and use of an erythropoietin-stimulating agent) at the time of diagnosis. The primary endpoint was correlating the Khorana score at diagnosis to the development of VTE. The secondary endpoints were the incidence of VTE and its impact on progression-free survival (PFS) and overall survival (OS).

## Statistical Methods

Patients' baseline demographics were summarized using descriptive statistics. The VTE rate was estimated with its 95% exact confidence interval. The association between VTE and Khorana score was assessed using the Fisher's Exact test. Kaplan-Meier methodology

was used to analyze OS and PFS. The log-rank test was used to compare the survival rate of the VTE-yes and VTE-no groups. SAS software Version 9.4 (SAS Ins., Cary, NC) was used for data analysis.

### Author Contributions

MY and AB: Conceptualization, writing—original draft preparation, writing—review and editing. NAB: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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### Institutional Review Board Statement

The Institutional Review Board Statement approved this study: U23-01-4953.

### Informed Consent Statement

Patient consent was waived due to retrospective anonymous data review.

### Data Availability Statement

We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section “MDPI Research Data Policies” at <https://www.mdpi.com/ethics>.

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### Conflicts of Interest

The authors declare no conflicts of interest.

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Amin Benyounes. Biomed J Sci & Tech Res



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