Higher Prevalence and Poorer Prognosis of EGFR Mutant Lung Adenocarcinoma in US Hispanics

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ABSTRACT

Introduction: Activating mutations in Epidermal growth factor receptor (EGFR) occur in approximately 15% White, 40-50% of Asian and 15% of Black patients with lung adenocarcinoma. However, its prevalence in the nearly 60 million U.S. Hispanics/Latinos has not been well characterized. Herein we evaluate EGFR mutation frequency in U.S. Hispanic/Latino patients with lung adenocarcinoma at an academic institute serving a large multi-ethnic area.

Methods: We queried our prospective database (2015-2019) for lung adenocarcinoma patients who underwent surgical resection and had routine mutational analysis by a targeted gene panel. We identified 768 patients and were able to stratify 668 patients by self-identified race/ethnicity. We compared demographics (chi-square) and survival (Kaplan-Meier).

Results: From 2015-2019, 668 patients met inclusion criteria and were evaluated for incidence of common targetable EGFR mutations. EGFR mutations were present in 30% of all patients with Hispanics/Latino experiencing an incidence of 35%, significantly more than non-Hispanic White patients, p=0.019. Overall survival at 3 years was not significantly different amongst racial/ethnic groups. However, in patients with EGFR mutations, 3-year overall survival was significantly worse in Hispanic/Latino patients in comparison to non-Hispanic White patients (62% vs 96%, p=0.021). There was no difference in the pathologic stage or surgical procedure amongst racial/ethnic groups.

Discussion: Approximately one-third of U.S. Hispanics with lung adenocarcinoma displayed EGFR mutations which were associated with decreased overall survival compared to White and Asian patients. Increasing mutational analysis and investigation of biological differences of this growing ethnic group is essential for optimal targeted treatment strategies as well as in the design of future clinical trials.

1. Introduction

The Hispanic/Latino population of the United States represents a significant and growing segment of the total population[1]. Projections suggest that this demographic will continue to increase, comprising an estimated 29% of the US population by the year 2060 [2]. Unfortunately, lung cancer is a significant health concern for this group, with Latino men experiencing the highest mortality rate amongst all cancers[3]. Additionally, Hispanic/Latino Americans face disparities in disease prevention, screening and outcomes, including poor survival rates and reduced likelihood of early diagnosis when compared to non-Hispanic White (NHW) patients[4]. These issues have prompted the American Lung Association's 2022 State of Lung Cancer report to call for urgent action to address these disparities and improve outcomes for Hispanic Americans.

In recent years, there has been major shifts in the treatment early-stage resectable lung cancer. One major advancement has been the use to targeted therapies due to the advancements and prevalence of tumor genomic analysis. Epidermal growth factor receptor (EGFR), a transmembrane protein that functions in growth factor signaling is the most well-known example of a targetable mutation non-small cell lung cancer (NSCLC), specifically lung adenocarcinoma with a remarkable response to Tyrosine kinase inhibitors (TKI). First becoming standard of care in advanced EGFR mutant positive disease, *a* randomized trial has now demonstrated remarkable increase in disease free and overall survival and is the gold standard in early-stage patients (Stage IB-IIA) after surgical treatment [5–7]. Importantly, the prevalence of EGFR mutations varies by race and ethnicity, with estimates ranging from 13-18% in non-Hispanic White patients to 60-75% in east Asian females without history of smoking[8–10]. However, the incidence of EGFR mutations in other races/ethnicities is unclear, due to lack of routine genetic testing, with certain ethnic and racial groups more likely to not be tested or included in clinical trials.

In the United States, a paucity of data exists regarding the incidence of EGFR mutations in Hispanic/Latino patients and its impact on survival. A multinational study of 5,738 samples from Latin America estimated the frequency of EGFR mutations in late-stage metastatic NSCLC was higher in NHW patients, with roughly 26% of cases carrying these mutations [11].

Interestingly, the incidence varied widely within each Country, with a suggestion that up to 90% of those with EGFR mutations have indigenous/Mestizo heritage [12]. In this study, we sought to identify the incidence of EGFR mutations in a large, tertiary care center located in a densely populated and multicultural city and to examine the impact of these mutations on survival in the US Hispanic population with early-stage surgically resectable lung adenocarcinoma.

2. Methodology

We performed a retrospective analysis of a prospectively maintained thoracic surgery database at our institution, approved by the Weill Cornell Institutional Review Board from 2015 to 2019. All patients included in the database provided written informed consent. Patients included in this analysis were all ages 18 or older, with diagnosis of lung adenocarcinoma and provided self-identification of race/ethnicity. Additionally, those that were included had routine mutational analysis by a targeted gene panel to evaluate for EGFR mutation present on exons 18-21. Included patients were divided by self-identified race/ethnicity into four groups, non-Hispanic White, Asian, Hispanic, and Black.

Basic demographics and clinical characteristics were compiled and compared between racial groups with non-Hispanic White patients as reference. Pathologic stage is presented in concordance with the American Joint Committee on Cancer TNM Staging system, 8th edition. Categorical variables were compared using Chi-Squared or Fisher Exact tests, where appropriate. Continuous variables were compared with Mann Whitney U testing and presented as median with interquartile range. Overall and disease-free survival were evaluated at 3-years utilizing the Kaplan-Meier Method and compared between groups using Log-Rank test. All statistical analysis was performed using IBM SPSS version 25 (SPSS Inc., Chicago, IL), with statistical significance evaluated at the 0.05 alpha level.

3. Results

From 2015 to 2019, 1035 patients were identified at our center that underwent surgical resection of lung cancer. 768 underwent resection for lung adenocarcinoma with 668 patients providing self-identified race/ethnicity and routine mutational analysis on resection specimens. Patients identifying as non-Hispanic White predominated the analysis representing 66% (442/668) of patients, with Hispanic patients accounting for 8% (55/668) (**Table 1**). Hispanic patients in comparison to non-Hispanic White patients had median age of 69 (63 – 75) vs 72 (66 – 78), p=0.054, were predominantly female, 62% (33/55) vs 61% (266/442), p=0.860 and had a history of smoking 59% (31/55) vs 83% (362/442), p<0.001. The pathologic stage distribution and surgical procedure were similar between racial groups (**Table 1**). EGFR mutations were present in 30% (200/668) of all patients with those self-identifying as Asian containing the greatest proportion of EGFR mutations at 66% (82/121) vs Hispanic, 35% (19/55), 20% (10/50) of Black patients and 20% (89/442) of non-Hispanic White patients.

Overall survival was not significantly different at 3 years amongst racial/ethnic groups without stratification for EGFR mutational status. With a median follow up of 24.4 months, Hispanic patients with EGFR mutations had worse 3-year overall survival than non-Hispanic White patients and Asian patients (62% vs 96% vs 90%, p=0.021 & 0.075 respectively) (**Figure 1A**). In patients without EGFR mutations, Hispanic patients had similar 3-year overall survival to non-Hispanic White, and Asian patients (**Figure 1B**).

4. Discussion

In this study, we investigated the incidence of targetable EGFR mutations and their impact on survival in Hispanic/Latino patients with surgically resectable lung adenocarcinoma in a single institution analysis. We found that the frequency of targetable EGFR mutations in Hispanic/Latino patients was 35% of Hispanic patients, which was significantly higher than in NHW patients. While unadjusted 3-year overall survival rates were similar across different racial and ethnic groups, we observed that Hispanic patients with an EGFR mutation exhibited worse 3-year overall survival than NHW counterparts, indicating that the presence of EGFR mutations may lead to poorer prognosis in Hispanic/Latino patients even with similar pathologic staging. [13].

The incidence of EGFR mutations in lung adenocarcinoma varies based on race and ethnicity, with the highest incidence reported in non-smoking Asian females[13]. In contrast, the incidence of EGFR mutations in Hispanic patients in Latin

Table 1	*White (n=442)*	*Hispanic (n=55)*	*Asian (n=121)*	*Black (n=50)*
Characteristic				
Median age, IQR	72 (66 – 78)	69, (63 – 75) **p=0.054**	68, (62 – 74) **p<0.001**	67, (62 – 73) **p=0.001**
Gender, Female	266 (61%)	33 (62%) p=0.860	55 (45%) **p=0.001**	34 (68%) p=0.335
Smoking, Yes	362 (83%)	31 (59%) **p<0.001**	54 (45%) **p<0.001**	42 (84%) p=0.862
EGFR Mutation Frequency	89 (20%)	19 (35%) **p=0.019**	82 (66%) **p<0.001**	10 (20%) p=0.994
Procedures				
Sub-lobar resection	166 (38%)	18 (30%)	33 (27%)	16 (32%)
Lobectomy	266 (60%)	36 (68%)	86 (71%)	34 (68%)
Pneumonectomy	7 (2%)	1 (2%) p=0.589	2 (2%) p=0.132	0 (0%) P=0.470
Pathology stage				
Path stage 0/IA/IB	334 (76%)	42 (80%)	84 (72%)	39 (78%)
Path stage IIA/IIB	42 (9%)	5 (9%)	18 (15%)	4 (8%)
Path stage IIIA/IIIB	54 (12%)	5 (9%)	12 (10%)	5 (10%)
Path stage IV	8(2%)	1 (2%) p=0.937	4 (3%) P=0.275	2 (4%) p = 0.628

America ranges from 8 and 35%, reflecting the genetic and cultural diversity of the region[13]. Recent research has shed new light on the influence of germline genetics on EGFR mutation frequency among those with Native

American/Indigenous ancestry[14]. This study found that the correlation between ancestry and increased mutation frequency in the EGFR gene was stronger at the local genome level than the global genome level, indicating that germline genetics may play a role in the risk of EGFR-mutant lung cancer among those with Native American/Indigenous ancestry[14].

In the United States, the Hispanic population in New York City is highly diverse, with the majority identifying with Dominican/Caribbean heritage and approximately 16% identifying with Mexican heritage [15]. Data on the incidence of EGFR mutations in patients from the Dominican Republic/Caribbean are scarce, but a study of 1,417 Mexican patients reported a similar incidence of 36.7%, mirroring the findings within this study [11].

This finding is surprising given the phenomenon known as the "Hispanic paradox," in which Hispanic/Latino patients have shown statistically significant better overall survival in most cancers, including lung cancer, stage for stage than non-Hispanic White and Black patients in previous literature[16]. However, the worse prognosis observed in Hispanic patients with EGFR mutations in this cohort is unclear. Nonetheless, limited representation of the Hispanic population in lung cancer clinical trials due to limited access and research centers is a critical issue, as differences in survival and quality of life may exist between patients treated in the community oncology center versus those treated in clinical trials[17,18]. Factors such as lack of health insurance, healthcare providers unfamiliar with societal recommendations on genetic testing, and patients misconceptions about biomarker testing may contribute to the disparities in outcomes [19]. Previous studies have shown that Hispanic/Latino patients have similar response rates to TKI therapy as non-Hispanic White patients, with response rates of 60% compared to 75% [19,20] . Therefore, treatment is appropriate and should be available to all EGFR mutant NSCLC patients. To ensure equitable care for Hispanic/Latino patients, access to mutational analysis and subsequent TKI therapy must remain a priority for all stages of NSCLC. Further enrollment in clinical trials and community engagement is critical to overcome the aforementioned obstacles and ensure equitable care for Hispanic/Latino patients.

Limitations

The study presented here recognizes certain limitations that must be considered when interpreting its results. Firstly, although our institution is located in a highly diverse metropolitan area, the number of Hispanic patients included in our cohort is relatively small. Secondly, the surgical database used in this study is potentially subject to selection bias, as it only includes NSCLC patients deemed suitable for surgical resection, and therefore may not represent the entire population of patients with EGFR mutations. Additionally, the adjuvant treatments received by patients, such as TKI inhibitors and

chemotherapy, are not known in our cohort. Lastly, although the use of a three-year follow up endpoint which provides valuable information not previously available, it still represents a limited endpoint.

Tables and Figures

Baseline Demographics and Clinical Characteristics

Figure 1. Overall Survival by EGFR mutational status.

Figure 1A: Overall Survival for EGFR (mutation)

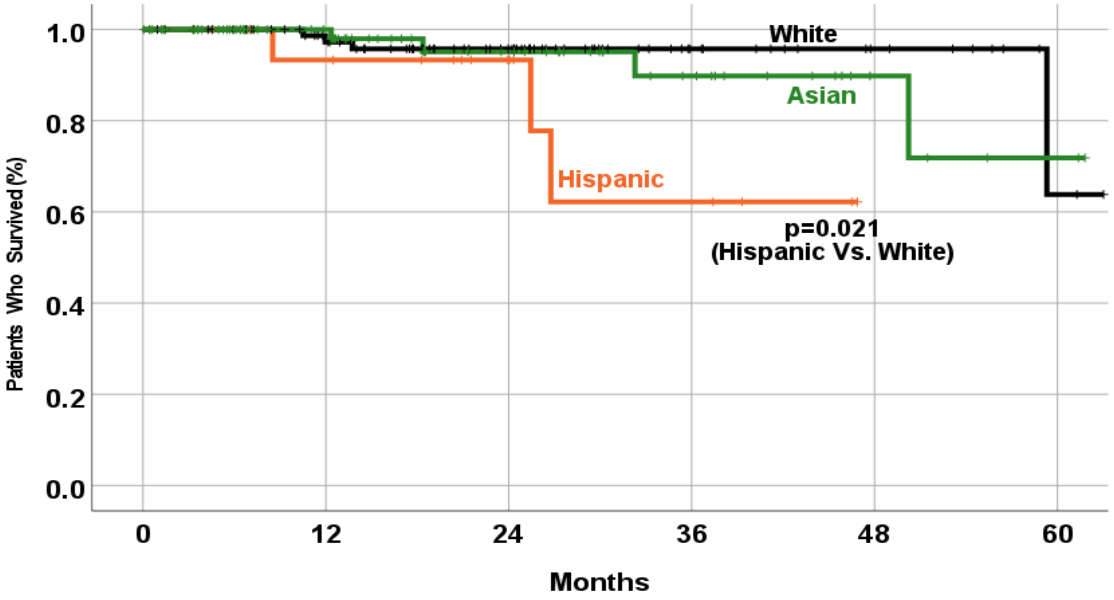
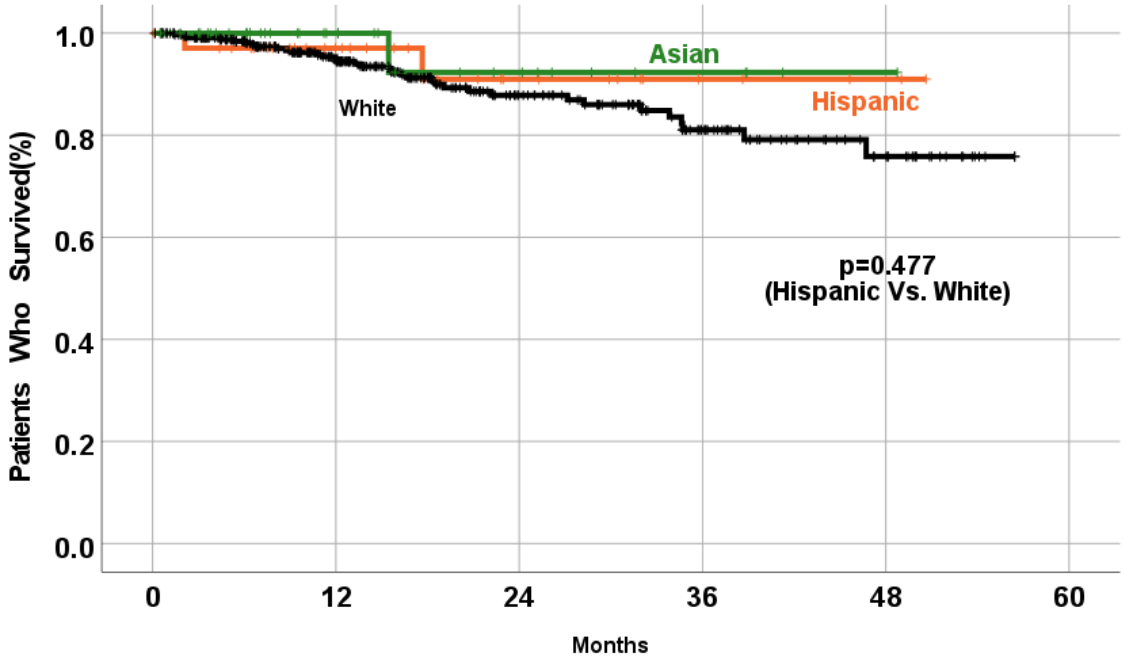


Figure 1B: Overall Survival for EGFR (wild type)



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