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Depression and Inflammation among Epidermal Growth Factor Receptor (EGFR) Mutant Non-Small Cell Lung Cancer Patients

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Abstract

Objectives: Depression is highly prevalent in Non-Small Cell Lung cancer (NSCLC) and is associated with elevated inflammation. However, certain subtypes of driver mutation associated NSCLC such as Epidermal Growth Factor Receptor (EGFR) mutated NSCLC may be associated with less depression given the differences in their underlying biology and disease trajectories. Biological variables such as inflammation, measured by C-reactive protein (CRP), may provide insight into depression variability in EGFR mutant NSCLC.

Methods: Patients with EGFR mutant and wild-type metastatic NSCLC were evaluated for depression using the Hospital Anxiety and Depression Scale (HADS) on a continuous scale and meeting depression screening criteria (HADS ≥ 8). Inflammation was measured using CRP. A mediation model was created to understand how inflammation mediates EGFR wild-type associated depression.

Results: One hundred out of 120 patients with NSCLC were recruited (83.3% response rate). The 20 participants with EGFR mutant NSCLC had less depression (HADS-D 3.0 versus 5.4) ($p < .001$), met depression screening criteria less often ($p = .047$), and exhibited less inflammation [CRP = 0.23 mg/ml versus 2.71 mg/ml] ($p < .001$) in comparison with EGFR wild-type NSCLC. Multivariate linear regression model revealed that only CRP predicted depression ($p = .015$) while controlling for age and sex. Mediation analysis found that lower CRP partially mediated less depression in EGFR mutant NSCLC.

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Conclusion: EGFR mutant NSCLC is associated with less depression but the relationship is partially mediated by lower CRP-related inflammation, which is a stronger predictor of depression than EGFR status. Depression in lung cancer varies by subtype and is significantly related to inflammation.

Keywords

Non-Small Cell Lung Cancer; Depression; Inflammation; C-reactive protein; EGFR Mutant Non-Small Cell Lung Cancer; tumor mutation burden

Background:

Non-small cell lung cancer (NSCLC) has one of the highest rates of co-morbid depression among all cancer types.^{1,2} Depression leads to morbidity, worse quality of life, and shorter overall survival in the general lung cancer setting.^{3,4} The underlying reason for this association is not entirely clear but an association with inflammation has been described in medically healthy populations and in cancer settings that exhibit high rates of depression, such as NSCLC.⁵⁻⁸ Although a causal relationship has not been established, lung cancer has high rates of both depression and inflammation, which raises questions about their relationship.

At the same time, molecularly targetable mutations in NSCLC are increasingly described that help explain clinical behavior of the cancer and may be translated into meaningfully actionable therapeutic targets.⁹ Understanding the influence of tumor biology on the patient experience, and in this case co-morbid depression, would allow clinicians to better anticipate who is going to need additional psychosocial resources and may contribute to a better understanding of the influence of biology on depression in general.

Epidermal Growth Factor Receptor (EGFR) mutated NSCLC is a subset of NSCLC in approximately 15–20 % of North American populations of NSCLC. EGFR ‘driver’ mutations exhibit distinct biological properties. It has a more favorable prognosis in comparison to wild-type EGFR mutated NSCLC given predictable responses to several generations of EGFR inhibitor medications in the majority of patients.¹⁰ Typically, patients respond to an initial EGFR inhibitor for 9–13 months and can have subsequent responses to other oral EGFR inhibitors before needing to be treated with traditional chemotherapy.¹¹ In the current era of NSCLC treatments, patients with EGFR mutant NSCLC may benefit from immunotherapy as well. For these reasons, patients with EGFR mutant NSCLC tend to have an overall improved disease trajectory in comparison to non-driver mutation associated NSCLC.¹²

EGFR mutated NSCLC was shown to be associated with less depression in two small scale observational studies.^{13,14} The findings were limited by incomplete EGFR reporting, small sample sizes, and the lack of a putative causative mechanism. A follow up study found that lower depression in EGFR mutated NSCLC was associated with elevated tumor necrosis factor- α (TNF- α), a pro-inflammatory cytokine.¹⁵ These results stand in contrast to many other studies showing a positive correlation between depression and inflammation in

multiple settings, including lung cancer.^{7,16,17} Therefore, we would expect to see less inflammation in EGFR mutated NSCLC patients who were also less depressed.

C-reactive protein (CRP) is an acute phase reactant and biomarker produced by the liver in response to multiple pro-inflammatory cytokines, especially IL-6.^{18,19} It has been associated with depression and other measures of psychological distress in both medically healthy and chronically ill populations.^{16,20} CRP is a biomarker that has been more consistently associated with depression, along with the pro-inflammatory cytokines, TNF- α , interleukin-6 (IL-6), and IL-1 β as compared with other depression biomarkers.^{16,17,21} CRP elevation is also associated with depression severity²². There are no studies to date that have evaluated an association between EGFR mutated NSCLC and CRP.

Therefore, this study evaluated the difference in depression prevalence in EGFR mutant versus wild-type NSCLC and their corresponding associations with inflammation as measured by CRP. We hypothesize that a lower prevalence of depression in patients with EGFR mutant NSCLC will be mediated by less inflammation. Understanding variations in depression prevalence based on underlying molecular differences in cancer biology is important for ultimately understanding the relationship between cancer and depression and even the biological underpinning of depression in general.

Methods:

The Memorial Sloan Kettering Cancer Center Institutional Review Board (IRB) approved this study MED18–165, “Survey of Routine Markers of Inflammation and Psychological Variables in Patients with Metastatic Lung Cancer” on August 15th, 2018. Surveys and lab values were collected from participants from May 2017 to November 2017 as part of standard of care practice. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Men and women with histologically confirmed stage IV NSCLC who were undergoing active treatment, spoke English, and had a performance status of ECOG 2 or greater were included. Participants were being treated for lung cancer at a single institution site. Participants with other cancers or not undergoing treatment for their metastatic lung cancer were excluded. Participants had to be on active treatment for at least one month and had to be more than one month post lung cancer diagnosis to be included.

Procedure

Participants were asked to participate in a one-time survey by a treating staff member (e.g., nurse practitioner, medical oncologist) in a consecutive manner. Participants filled out the questionnaire containing standardized survey questions, and CRP laboratory values were obtained the same day that the questionnaires were completed. Referrals to available psychological services were provided in the survey, and patients were asked to raise any concerns with clinic staff and, in particular, to notify a staff member if they felt significantly depressed or had suicidal thoughts.

Measures

Patient demographic and medical characteristics.—Participant demographic information was obtained from the medical record and included age, race/ethnicity, sex, marital status, body mass index (BMI), length of time since diagnosis, type of treatment (e.g., chemotherapy, immunotherapy, targeted therapy), line of treatment (i.e., 1st, 2nd, 3rd or beyond), and whether they were taking an antidepressant medication.

Biological Characteristics.—EGFR mutant status was determined by multiplex PCR. CRP values were obtained by turbidimetric immunoassay in a Clinical Laboratory Improvement Amendments (CLIA) certified lab.²³ Inter- and intra-assay coefficient of variation is reliably less than 5%.

Depression.—Depression severity was measured by the Hospital Anxiety and Depression scale (HADS), which has been validated in the lung cancer setting.^{24,25} The HADS is a 14-item symptom rating scale that was developed to identify clinically significant cases of anxiety and depressive disorders among medically ill patients.²⁴ It is divided into 7-item anxiety (HADS-A) and depression (HADS-D) subscales. Responses are rated 0 to 3 points such that total scores range from 0 to 21 points with higher scores indicating worse anxiety or depression. A cut-off of 8 on the HADS-D subscale is most commonly used to identify clinically significant depression, with an average sensitivity and specificity of 0.80.^{24,26} Because research on inflammation has focused primarily on depression, not anxiety, only HADS-D data were analyzed in this study.

Statistical Analysis

The primary outcome of this study was to compare depression in EGFR mutant and wild-type NSCLC and to evaluate its associations with inflammation while controlling for demographic and clinical variables. CRP values were log transformed prior to data analysis since CRP data are not normally distributed; however, untransformed values are also reported for ease of interpretation. Demographic and clinical characteristics among EGFR mutant and EGFR wild-type NSCLC were compared using independent t-tests for continuous predictor variables or chi square testing for categorical predictor variables. In addition, univariate analysis was performed to evaluate associations with depression (HADS) as a continuous dependent variable using Pearson correlations for continuous predictor variables and Spearman for skewed predictor variables (CRP), independent t test for categorical predictor variables, and ANOVA for ordinal predictor variables. A multivariate linear regression model was created using statistically significant covariates and a-priori control variables.

The mediation hypothesis was tested by regression analysis according to the Baron and Kenny causal steps method.²⁷ Three subsequent regression models were calculated to test the conditions necessary to establish a mediator effect. Step 1 tested EGFR as a predictor of depression while controlling for age and sex. Step 2 tested EGFR as a predictor of inflammation (CRP) while controlling for age, sex, and BMI. Step 3 tested EGFR as a predictor of depression while controlling for age, sex, and the mediating variable, CRP (inflammation). Statistical procedures were performed using the SPSS version 24 software

(SPSS, Chicago, IL 2013), and all statistical tests were two-tailed with a 5% significance level.

Results:

Sample Characterization

Out of 120 potential participants, 100 returned survey information (83.3% response rate). Twenty participants had EGFR mutant NSCLC (20%). Sample characteristics of the entire cohort, along with comparisons between EGFR mutant and wild-type NSCLC are presented in Table 1. Patients with EGFR mutant NSCLC had less depression ($p<.001$) and were less likely to meet depression screening criteria ($p=.047$) while also exhibiting less inflammation [CRP =0.23 mg/ml versus 2.71 mg/ml] ($p<.001$) in comparison to EGFR wild-type NSCLC. Patients with EGFR mutant NSCLC were more likely to have adenocarcinoma NSCLC ($p=.033$) and be receiving a targeted treatment ($p<.001$), while there was also a trend towards being female ($p=.056$). Time with disease, line of treatment, BMI, marriage status, race, and antidepressant use were not significantly different between cohorts. The average age was 66.1 (SD6.9) and amount of time with disease was 15 months with 55.3% of patients still on their first line of treatment.

Primary Analyses

Univariate linear regression analysis found that depression was associated with elevated CRP ($p<.001$), and EGFR wild-type status ($p=.002$) (Table 2). A multivariate linear regression model was created to evaluate the association of clinically significant predictor variables with depression while controlling for predictor variables (age and sex). Treatment type was excluded from the model due to co-linearity with EGFR status ($r=.788$) since all the patients with EGFR mutant NSCLC were receiving targeted therapies. The model found that only CRP (log transformed) predicted depression ($p=.009$) (Table 3).

Test of mediation hypothesis

In order to understand the relationship between EGFR mutant NSCLC and depression further, a mediation analysis using inflammation (CRP) as a mediator was created. Table 4 shows the results of three separate regression analyses testing the hypothesis that inflammation (CRP) mediates the relationship between EGFR status and depression. Step 1 found that EGFR predicted depression ($\beta=-.22$, $p=.032$) while controlling for age and sex. Step 2 found that EGFR predicted less inflammation (CRP) ($\beta=-.29$, $p=.007$) while controlling for age, sex, and BMI. In step 3, after including the mediator variable inflammation (CRP) as a predictor into the regression model, the effect of EGFR status on depression decreased ($\beta=-.16$, $p=.118$). The difference between b_c and $b_{c'}$ was not statistically significant (Sobel test: $z_s=.14$, $p=.88$). CRP was thus a partial mediator of the association between EGFR mutation status and depression. The original regression coefficient of the effect of EGFR mutation status on depression decreased by 24% when CRP was included as a predictor; hence 24% of the effect of EGFR mutation status on depression was mediated by CRP inflammation. Figure 1 illustrates the mediator effect. This mediation analysis shows that the association between EGFR mutation status and depression is partially mediated by inflammation (CRP).

Discussion:

This study reveals depression heterogeneity among patients with NSCLC and specifically that those patients with EGFR mutations have less depression. These findings are consistent with other small studies but also demonstrate that this relationship is at least partially mediated by the presence of less inflammation.^{13–15} CRP, as an acute phase reactant, serves as a good marker of overall innate inflammation, which is the product of several pro-inflammatory cytokines. CRP, along with other pro-inflammatory cytokines, is a validated biomarker for depression.²² CRP has also been studied as a predictive biomarker of antidepressant treatment response making it an ideal biomarker to study in determining levels of inflammation and depression.^{28,29} While CRP elevation has demonstrated associations with depression in multiple settings, the lack of inflammation in this setting partially mediates the protection of EGFR mutant NSCLC patients from depression.

Is the relationship between EGFR mutation status and depression mediated by other mechanisms besides less inflammation that protect patients with EGFR mutant NSCLC from depression? Are there other mechanisms that protect this subgroup of patients from depression? This type of NSCLC is also generally associated with a more indolent disease course since over 85% EGFR mutant NSCLC respond to tyrosine kinase inhibitors, albeit for a prescribed and limited length of time.³⁰

The primary question that this study raises is that of the protective mechanism against depression in this subgroup while the larger group of NSCLC experiences a higher prevalence of depression. Although clinical indices such as age, performance status, lines of treatment, or time with disease did not differ significantly between EGFR mutant and wildtype groups, there still may be other unaccounted for clinical factors suggesting that those with EGFR mutant NSCLC perhaps experience a more indolent course. Aside from a greater number of patients with adenocarcinoma, the other primary difference between the two groups was that all patients with EGFR mutant NSCLC were on oral targeted therapy. For this reason, it is not possible to ascertain whether treatment type plays a role in depression prevalence and is a major limitation of this study. Mechanistically, this is a crucial question that deserves to be answered, perhaps with large epidemiologic data that would take into account those patients with EGFR mutant NSCLC not on targeted therapies and/or receiving additional types of therapy. However, our findings are still clinically relevant as the clinician should be aware that regardless of treatment type, EGFR wild-type patients may be more likely to experience depression, which may influence psychosocial evaluations of patient with lung cancer and how limited psychosocial resources are allocated.

Future directions for these findings may include testing other forms of ‘driver mutation’ NSCLC to see if there is some protective effect on depression. Some types of mutations do not have particular types of targeted therapies associated with them and may serve to elucidate the relationship between disease biology and targeted treatment effect. Understanding the relationships between tumor biology and psychological effects is important not only for its clinical ramifications, but also because it may help us understand the biology of depression and its association with cancers in general.³¹ There are many

forms of depression and certain symptoms are much more common in medically ill patients, which perhaps represent depression subtypes or other forms of symptom clusters.³² Understanding the relationships between tumor biology and the somatic milieu of inflammation and other factors may, at some point, lead to understanding how to better treat these forms of depression in medically ill patients with particular symptom clusters.

The biological underpinning of NSCLC is becoming increasingly understood.³³ While variable numbers of key ‘driver’ and ‘passenger’ mutations alter the biology of NSCLC, they may also influence their associated NSCLC-related depression profiles through inflammation or other mechanisms.³¹ The influence that cancer-related mutations (somatic and inherited) have on the trajectory of cancer and response to anticancer treatments should extend to their psychological ramifications as well.³⁴ Since the type of somatic tumor mutations appear to be related to inflammation, at least in the case of EGFR mutations, other driver mutations and perhaps the number of somatic tumor mutations or tumor mutation burden (i.e., TMB) may also have psychological ramifications in relation to depression, in particular. Inflammation may be the mechanism by which the number of and kind of mutations influences depression.^{35,36} But this needs to be explored further.

The partial mediation of inflammation on depression in EGFR mutated NSCLC may be understood in the context of inflammation and number of tumor associated mutations. Since EGFR is a ‘driver’ mutation, it is expected that this form of NSCLC has less tumor mutation burden (TMB) than other forms of NSCLC that may be more likely caused by environmental carcinogens such as smoking. TMB may be associated with depression by causing a greater amount of inflammation since it creates ‘neoantigens’ and appears more foreign to the immune system.³⁷ In other words, lung cancer with a larger amount of TMB (i.e., non-driver mutation NSCLC) may be associated with more depression because a higher amount of TMB causes more inflammation. In fact, patients with EGFR mutant NSCLC with a higher TMB have been shown to have a worse prognosis and overall survival.^{38,39} It would be of interest to know if those patients with higher TMB also had a higher amount of inflammation and depression. This should be explored in future studies and may also explain why patients with EGFR mutant NSCLC who have less TMB also have less depression.

Study Limitations

This study is limited by its cross-sectional nature and the relatively low number of patients observed. In addition, it would have been helpful to have evaluated other inflammatory markers individually and study a more diverse group of EGFR mutant NSCLC patients who were also on other therapies besides oral tyrosine kinase inhibitors. In addition, patients were aware of their EGFR status, which may have psychological implications given the greater treatment options and prognosis for many patients with EGFR mutated NSCLC. Other studies evaluating depression in EGFR mutated NSCLC evaluated the depression status prior to obtaining the mutation status or starting treatment.^{13,14} The primary limitation of the study is the lack of understanding if the lower depression effect is due to the underlying biology of EGFR mutant NSCLC or the treatment. Depression could be measured in both groups prior to starting any treatment in order to eliminate the effects of

treatment on inflammation. Either way, however, the effect is mediated by inflammation, which partially explains the relationship.

Clinical Implications

While lung cancer carries the highest prevalence of depression among cancer subtypes, there appear to be variations in prevalence in depression based on molecular subtype. Patients with EGFR mutant NSCLC have additional oral treatment options that offer greater survival, and are associated with less inflammation and subsequent depression. This information may be helpful in understanding depression risk and also in understanding the biological basis of depression given the concomitant association with less inflammation in EGFR mutant NSCLC. Interestingly, these findings may begin to provide a biological basis for individual depression risk in cancer subtypes.

In summary, patients with EGFR mutant NSCLC have lower depression scores that are mediated in part by lower inflammation. Future studies to elucidate this relationship are warranted and may help to further explain the relationship between the biology of cancer and psychological ramifications such as depression, in particular.

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Figure 1. Mediation Model linking EGFR mutant Non-Small Cell Lung Cancer (NSCLC), inflammation (C-Reactive Protein), and depression (Hospital Anxiety and Depression Scale)
 $*p < .05$, $**p < .01$

Table 1.

Clinical and Demographic Characteristics of the Sample

	Total (n=100)	EGFR Mutant (n=20)	EGFR Wildtype (n=80)		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>t</i>	<i>p</i>
Age (years)	66.1 (9.6)	65.2 (9.5)	66.3 (9.8)	.446	.657
Body Mass Index	26.0 (5.1)	25.0 (5.3)	26.2 (5.0)	.950	.344
Time with Disease (months)	15.3 (18.0)	15.0 (16.2)	15.3 (18.5)	.070	.944
C Reactive Protein (mg/ml)	2.23 (3.5)	.28 (0.2)	2.71 (3.9)	5.482	<.001 ***
Depression Score (HADS-D) (0–21)	4.9 (4.0)	3.0 (2.4)	5.4 (4.1)	3.318	.002 *
	N (%)				
Meets Depression Criteria Screen				χ^2	<i>p</i>
HADS-D ≥ 8: Yes	21 (21.0%)	1	20	3.858	.05 *
No	79 (79.0%)	19	60		
Gender					
• Female	64 (64.0%)	17	47	3.640	.056
• Male	36 (36.0%)	3	33		
Disease Type					
• Adenocarcinoma	85 (85.0%)	20	65	4.564	.033 *
• Non-adenocarcinoma	15 (15.0%)	0	15		
Treatment Type					
Chemotherapy	41 (41.0%)	0	41	72.561	<.001 ***
Immunotherapy	30 (30.0%)	0	30		
Targeted Therapy	25 (25.0%)	20	5		
Missing	4 (4.0%)	0	4		
Line of Treatment					
• 1 st	55 (55.0%)	14	41	1.800	.406
• 2 nd	31 (31.0%)	4	27		
• 3 rd or beyond	12 (12.0%)	2	10		
• Missing	2 (2.0%)	0	2		
Race/Ethnicity					
• Non-White	17 (17.0%)	2	15	.962	.327
• White	83 (83.0%)	18	65		
Married					
• Yes	73 (73.0%)	13	60	.179	.672
• No	27 (27.0%)	7	20		
Antidepressant					
• Yes	23 (23.0%)	5	18	.102	.749
• No	77 (77.0%)	15	62		

* $p < .05$

**
 $p < .01$

 $p < .001$

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Table 2.

Association of Epidermal Growth Factor Receptor (EGFR) mutant Non-Small Cell Lung Cancer (NSCLC), demographic and clinical variables, inflammation and depression measured by the Hospital Anxiety and Depression Scale (HADS-D).

Depression (HADS-D)		
	Univariate Analysis	
Variable	<i>r</i>	<i>p</i>
Age	.10	.35
BMI	.12	.25
Time with Disease	-.15	.15
CRP	.354	<.001 ***
	<i>F</i>	<i>P</i>
Line of Treatment	.466	.707
1 st		
2 nd		
3 rd and beyond		
Race	0.447	.720
	<i>t</i>	<i>P</i>
EGFR	3.318	.002 **
Mutant		
Wild-type		
Disease Type	1.250	.296
Adenocarcinoma		
Non-adenocarcinoma		
Sex		
Male	-1.290	.201
Female		
Married		
Yes	0.93	.34
No		
Antidepressant		
Yes	-1.943	.055
No		

*
 $p < .05$

**
 $p < .01$

 $p < .001$

Table 3.

Multivariate analysis of Epidermal Growth Factor Receptor (EGFR) mutant Non-Small Cell Lung Cancer (NSCLC) and inflammation as measured by C-reactive protein (CRP) as predictors of depression.

Variable	Depression (HADS-D)		
	Regression Coefficient	<i>t</i>	<i>p</i>
Control			
• Age	-.05 (.05)	-.482	.631
• Sex	.10 (.90)	.896	.373
CRP (log transformed)	.37 (.70)	3.161	.002 **
EGFR Mutant NSCLC	-.05 (1.2)	-.413	.680
F 3.899 Adjusted R2 .125			

Note:

*
 $p < .05$

**
 $p < .01$

HADS-D, Hospital Anxiety and Depression Scale-Depression

Table 4.

Regression analysis testing the mediation hypothesis in three subsequent steps

Path C (step 1) Depression (HADS-D)					Path A (Step 2) Inflammation (CRP)			
	<i>b</i>	SE	<i>β</i>	<i>p</i>	<i>b</i>	SE	<i>β</i>	<i>p</i>
Control								
• Age	.02	.04	.04	.706	−.01	.04	−.03	.798
• Sex	.60	.85	.07	.482	−.54	.78	−.07	.493
• BMI	-	-	-	-	−.00	.07	−.00	.97
Independent Var								
• EGFR Mutant	−2.11	.97	−.22	.032 *	−2.56	.92	−.29	.007 **
	F 2.102, adjusted R ² =.032				F 1.970 adjusted R ² =.039			
P ath C' and B (step 3) D epression (HADSD)								
Control								
• Age	.01	.04	.03	.401				
• Sex	.71	.84	.08	.730				
Independent Var								
• EGFR Mutant	−1.61	1.02	−.16	.118				
Mediating Var								
• CRP	.31	.11	.28	.008 **				
	F 3.694 adjusted R ² = .102							

*
 $p < .05$ **
 $p < .01$ ***
 $p < .001$