Tumor Mutation Burden and Depression in Lung Cancer: Association With Inflammation

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ABSTRACT

Background: Patients with lung cancer with greater systemic inflammation have higher rates of depression. Tumor mutation burden (TMB) predicts immunotherapy response in patients with lung cancer and is associated with intratumoral inflammation, which may contribute to systemic inflammation and depression. This study evaluated whether higher TMB was associated with increased depression and systemic inflammation in patients with lung cancer. **Patients and Methods:** Patients with metastatic lung cancers were evaluated for depression severity using the Hospital Anxiety and Depression Scale. TMB was measured using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets. Inflammation was evaluated using C-reactive protein (CRP) level and neutrophil-to-lymphocyte ratio (NLR). **Results:** A total of 96 patients with adequate TMB testing were evaluated. The average number of mutations (TMB) was 10.8 (SD, 10.9). A total of 19% of patients endorsed clinically significant depression symptoms. TMB was significantly correlated with depression severity ($r = 0.34$; $P = .001$) and NLR ($r = 0.37$; $P = .002$) but not CRP level ($r = 0.19$; $P = .07$). TMB was also higher in patients receiving chemotherapy (mean, 12.0) and immunotherapy (mean, 14.4) versus targeted therapy (mean, 4.8). A multivariate model found that TMB ($\beta = 0.30$; $P = .01$) and CRP level ($\beta = 0.31$; $P = .01$) were independently associated with depression; there was no significant interaction effect of TMB $\times$ CRP and depression. A similar multivariate model showed no independent effect for NLR and depression ($\beta = 0.16$; $P = .17$) after accounting for TMB. **Conclusions:** These data provide evidence for biologic depression risk in patients with lung cancer who have high levels of TMB. The underlying mechanism of the association is not clearly related to inflammation but warrants further analysis to broadly elucidate the mechanism of biologically derived depression in cancer.

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Background

Depression is most prevalent in patients with lung cancers, among all cancer subtypes, despite new and novel lung cancer treatments.^{1,2} Therefore, depression is one of the most problematic cancer comorbidities for a large number of patients because lung cancer is also the most prevalent cancer worldwide.³ An approach to depression in cancer as a symptom and a disease has not advanced rapidly enough, primarily due to a lack of understanding of the biologic mechanism underlying its co-occurrence with cancer.⁴ One of the most promising areas of research for understanding higher rates of depression in various cancers is the relationship between depression and inflammation.^{5,6} This relationship has become increasingly clear and helps explain the higher prevalence of depression in medically ill populations, such as those with cancer, and why depression in these comorbid populations tends to be harder to treat.^{7–10} Depression treatments, both pharmacologic and psychotherapeutic, have been shown to work, but are affected by the inflammatory environment and can be improved upon by understanding and addressing the underlying mechanism.^{11–15}

At the same time, increased awareness of inflammatory mechanisms has led to a paradigmatic shift in the understanding of cancer biology and treatments. One such discovery is the relationship between tumor mutation burden (TMB) or tumor mutation load and immunotherapy response based on the underlying association between creating neoantigens and adaptive immunity response.^{16–19} TMB may be an even stronger predictor of immunotherapy response than PD-L1 expression, which is the current standard for determining the appropriateness of immunotherapy in the frontline setting.²⁰ A consequence of this relationship is that highly mutated cancers are more likely to respond to immunotherapy but may also engender a higher amount of systemic inflammation and therefore depression.²¹

Although immunotherapy response to high TMB rests on the immune system's ability to respond to cancer-related immunogenicity, there is a large amount

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of evidence supporting the association between immune system activation (ie, inflammation) and depression.²² Dysregulated immune responsiveness has been associated with the development of depression in both healthy and medically ill patients.²³ This link between depression and inflammation has been supported by the frequent occurrence of depression following administration of the proinflammatory cytokine interferon- α .^{24,25} Likewise, animal research has supported this association through the induction of a sickness-like state that mimics depression after the administration of lipopolysaccharide,^{8,24–26} an endotoxin that induces inflammation. In addition, the emergence of cytokine-induced depression may be prevented or treated by administering prophylactic antidepressant and/or anticytokine treatment, further implicating the role of inflammation in the development of depression.^{11,15}

Elevated inflammatory markers, such as tumor necrosis factor α (TNF- α), IL-6, and C-reactive protein (CRP), have been associated with depression severity in patients with lung cancer.^{27,28} Comorbid depression in patients with lung cancer is linked to worsened quality of life and lower overall survival rates.^{1,29} However, survival rates for patients with lung cancer and depression who receive antidepressant treatment may be comparable to those of their nondepressed counterparts, similar to the effect of addressing depression in other cancer groups.^{1,30} A national study found that multiple psychosocial characteristics were associated with worse depression but did not characterize an association between lung cancer biology and depression.³¹ A better understanding of the link between immune functioning, TMB, and depression may help to more effectively target specific patient groups (eg, those with high TMB or inflammation) and inform future treatments for depression in the cancer setting.⁶

Two measures of immune functioning that can be routinely obtained in the clinical setting are CRP and neutrophil-to-lymphocyte ratio (NLR). CRP is an acute phase reactant and biomarker produced by the liver in response to multiple proinflammatory cytokines, especially IL-6, which primarily reflects the innate immune response.^{32,33} CRP, along with the proinflammatory cytokines TNF- α , IL-6, and IL-1 β , is consistently associated with depression in various patient populations.^{34–38} NLR is derived from the absolute neutrophil and lymphocyte counts obtained from a CBC and has been evaluated as a marker of depression and other mood disorders.³⁹ High NLR is associated with worse cancer-related prognosis^{40,41} and has been shown to be associated with a lower chance of benefit from immunotherapy.⁴² These 2 markers provide a general measure of inflammation, reflecting both the innate and adaptive immune systems, and are easily adaptable to clinical care.

Treatment of depression in patients with cancer remains a challenge for the oncology community.⁴³ Identification of the biologic pathways between lung cancer and depressive symptoms will improve understanding of the co-occurrence of depression in cancer. An association between TMB and depression might help facilitate the identification of patients at risk for depression while identifying characteristics of their cancer and possible responsiveness to immunotherapy. We hypothesized that TMB would be associated with depression and that this relationship would be moderated by immune system activation.

Patients and Methods

Surveys and laboratory values were collected from patients from May through November 2017 as part of standard clinical practice. The Memorial Sloan Kettering Cancer Center Institutional Review Board approved this study. Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Patients

The study cohort included men and women with histologically confirmed stage IV lung cancers, including small cell lung cancer and non-small cell lung cancer (NSCLC) such as squamous cell carcinoma and nonsquamous cell carcinoma (eg, adenocarcinoma and other), who were undergoing active treatment, spoke English, and had an ECOG performance status ≤ 2 .⁴⁴ Patients with other cancers or those not undergoing treatment of their metastatic lung cancer were excluded. Patients had to be on active treatment for at least 1 month and had to be >1 month from receiving their lung cancer diagnosis to be included.

Of 170 potential participants, 140 returned survey information (82.4% response rate); 96 of the 140 respondents (68.6%) had adequate tissue samples for tumor mutational analysis.

Procedure

Patients completed the questionnaire packet during a routine clinic visit at any point along the treatment trajectory. In other words, data were collected on patients undergoing anticancer treatments at any point. CRP and NLR laboratory values were obtained the same day the questionnaires were completed. A list of available mental health resources was provided in the survey packet. A board-certified psychiatrist oversaw the study and was available for consultation.

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), time since diagnosis, type of treatment (eg, chemotherapy, immunotherapy, targeted therapy), line of therapy (ie, first, second, third, or beyond), and whether they were taking an antidepressant medication. Of note, all data were collected before initiation of standard-of-care first-line chemoimmunotherapy for lung cancer. Therefore, there was no overlap in treatment categories and no patients surveyed had received first-line immunotherapy followed by chemotherapy.

Biologic Characteristics

The following biomarkers were collected as part of routine clinical monitoring.

1. TMB was measured using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) platform.⁴⁵ TMB is defined as the total number of nonsynonymous single nucleotide or insertion/deletion mutations divided by the coding region captured in each panel (341 genes, 0.98 Mb; 410 genes, 1.06 Mb; 468 genes, 1.22 Mb). Targeted next-generation sequencing with the MSK-IMPACT platform allows derivation of an accurate estimate of TMB compared with whole-exome sequencing performed for the same DNA library ($R^2 = 0.76$).^{46,47}
2. CRP values were obtained from turbidimetric immunoassay in a CLIA-certified laboratory.⁴⁸ Inter- and intra-assay coefficient of variation is reliably <5%. CRP values were log-transformed before data analysis, because CRP data are not normally distributed; however, untransformed values are also reported for ease of interpretation.
3. NLR was obtained from the CBC. The ratio was calculated by dividing the neutrophil count by the lymphocyte count.

Anxiety and Depression

Severity of anxiety and depressive symptoms was measured using the Hospital Anxiety and Depression Scale (HADS), which has been well validated and widely used in the lung cancer setting.^{49–51} The HADS is a 14-item symptom rating scale that was developed to identify clinically significant anxiety and depressive symptoms among medically ill patients.⁴⁹ It is divided into a 7-item anxiety (HADS-A) and depression (HADS-D) subscales. Responses are rated on a scale from 0 to 3 points, such that total scores on each subscale may range from 0 to 21 points. A cutoff of 8 on the HADS-D subscale is used most commonly to identify clinically significant depression, with an average sensitivity and specificity of 0.80 when contrasted with a diagnosis of depression.^{49,51}

Statistical Analysis

Correlational analyses were used to evaluate associations with depression (HADS-D subscale score) as a continuous dependent variable, using Pearson correlation coefficients for quasi-normally distributed independent variables and Spearman correlation coefficients for skewed independent variables (eg, CRP). Independent samples *t*-tests and ANOVA were used to test for group differences between categorical independent variables. A multivariate linear regression model was created using variables that were statistically significant in univariate analyses and included covariates that were identified a priori. Statistical analyses were performed using SPSS Statistics, version 24 (IBM Corp), and all statistical tests were 2-tailed with a significance level of 0.05.

Results

Patient characteristics are presented in Table 1. Patients had, on average, 10.8 tumor mutations (SD, 10.9), with a range of 0 to 53. Clinical and demographic variable associations with TMB are listed in Table 2. TMB was significantly correlated with depression ($r = 0.34$; $P = .001$), but not anxiety ($r = 0.06$; $P = .56$), and was significantly associated with NLR ($r = 0.37$; $P = .002$) and absolute neutrophil count ($r = 0.30$; $P = .006$). TMB was not significantly correlated with CRP level, although this association approached significance ($r = 0.19$; $P = .07$). TMB was also associated with treatment type; patients receiving immunotherapy had higher TMB (mean, 14.4 mutations) than patients receiving targeted therapy (4.8 mutations) ($F = 5.14$; $P = .008$).

As reported previously, depression was significantly associated with CRP level and treatment type.^{52,53} Depression scores were significantly higher in patients receiving chemotherapy and immunotherapy compared with those receiving targeted therapy (see Table 2). In addition, depression was significantly correlated with NLR ($r = 0.21$; $P = .017$) and absolute neutrophil count ($r = 0.24$; $P = .008$).

Multivariate models were used to assess the association between TMB, inflammatory markers (CRP and NLR), and depression while controlling for age, sex, and treatment types (chemotherapy, immunotherapy, targeted therapy) (Table 3). Inflammatory markers CRP and NLR were assessed separately given their moderate collinearity ($r = 0.41$; $P < .001$). In the first step of the model, only treatment type significantly predicted depressive symptom severity. When TMB was added to this model, this variable contributed significantly to the prediction of depression, but none of the covariates remained significant. In the model containing CRP (using the log-transformed variable), both TMB ($\beta = 0.30$; $P = .01$) and CRP ($\beta = 0.31$; $P = .01$) were independently associated with depression severity. This model accounted for 18.7% of the variance in depression (adjusted R^2).

Table 1. Patient Clinical and Demographic Characteristics

	Total M (SD)
Tumor mutational analysis	10.8 (10.9)
Age, y	66.1 (9.2)
BMI	26.2 (5.4)
Time since diagnosis, mo	14.1 (14.3)
NLR, mg/mL	6.4 (10.1)
Neutrophil count, mg/mL	5.3 (4.1)
Lymphocyte count, mg/mL	1.3 (0.8)
CRP level, mg/L	2.1 (3.6)
Anxiety score (HADS-A)	5.4 (3.9)
Depression score (HADS-D)	4.8 (3.5)
Meets Screening Criteria	n (%)
Anxiety (HADS-A ≥ 8)	19 (20.0%)
Depression (HADS-D ≥ 8)	18 (18.9%)
Sex	
Female	58 (61.1%)
Male	37 (38.9%)
Disease type	
Adenocarcinoma	76 (79.2%)
Squamous cell carcinoma	6 (6.3%)
Small cell lung cancer	9 (9.4%)
Not otherwise specified	4 (4.2%)
Treatment type	
Chemotherapy	41 (46.1%)
Immunotherapy	28 (31.5%)
Targeted therapy	20 (20.8%)
Missing	16 (11.4%)
Line of therapy	
First	55 (57.3%)
Second	26 (27.1%)
Third or beyond	11 (11.5%)
Missing	4 (4.2%)
Race/Ethnicity	
Nonwhite ^a	14 (14.6%)
White	81 (84.4%)
Married	
Yes	69 (72.6%)
No	26 (27.4%)
Antidepressant	
Yes	22 (22.9%)
No	73 (77.1%)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; M, mean; NLR, neutrophil-to-lymphocyte ratio.
^aIncludes Asian, black, and Hispanic.

The addition of the TMB $\times$ CRP interaction did not contribute significantly to this model ($\beta = -0.00$; $P = .97$).

A similar model was generated testing the contribution of NLR instead of CRP. This model indicated that only TMB ($\beta = 0.30$; $P = .02$) was associated with depression severity, whereas NLR was not significantly associated with depression ($\beta = -0.07$; $P = .58$). There was no significant TMB $\times$ NLR interaction in this model ($\beta = 0.14$; $P = .22$).

A final set of multiple regression models was estimated that included interaction effects between treatment types (chemotherapy, immunotherapy, and targeted therapy) and TMB or CRP in explaining depression severity. These models did not generate any significant interaction effects (data available upon request).

Discussion

Lung cancer with high TMB was associated with depression independently of lung cancer subtype, treatment type, or other markers of inflammation. Inflammation, as measured by CRP level, also provided an independent contribution to depressive symptoms even after considering the impact of TMB. TMB seems to identify a subtype of lung cancer with higher depression severity. Given the implications of TMB and local immune functioning (in the tumor microenvironment),⁵⁴ an association between TMB and depression was hypothesized to be driven by a greater amount of systemic inflammation created in high TMB lung cancer that then leads to an inflammation-induced depression. However, the mechanism of the association does not seem to be straightforward. The interaction effect between TMB and CRP was not significant, suggesting no synergistic effects in predicting depression. However, the association between TMB and CRP approached significance ($P = .07$), suggesting that such an association may be present but only detected with larger sample sizes. Although NLR was associated with depression, this relation dissipated when TMB was placed in the model and there was no interaction effect between TMB and NLR in predicting depression either.

Nevertheless, the presence of high TMB seems to identify a subtype of lung cancer with a higher prevalence of depression that is independent of other aspects of immune functioning. Of note, both the average TMB and the rate of clinically significant depression among patients in this sample were consistent with other large epidemiologic studies of patients with lung cancer, supporting the generalizability of these findings.^{47,55} As seen in other studies, driver mutation-associated forms of NSCLC (eg, *EGFR*-mutated) treated with targeted therapy were associated with much lower TMB.⁵⁶ Studies have found that *EGFR*-mutated NSCLC, with presumably lower TMB, also carry lower rates of depression.^{57,58} However, Jacobs et al⁵⁷ found that nondepressed patients with *EGFR*-mutant lung cancer also had elevated TNF- α levels, but other markers of general inflammation were not collected. Conversely,

Table 2. Variable Associations With TMB and Depression

Variable	TMB		Depression (HADS-D)			
	r	P Value	r	P Value		
TMB	—	—	0.34	.001**		
Age, y	−0.12	.27	0.05	.59		
BMI	−0.03	.80	0.08	.35		
Time since diagnosis, mo	−0.07	.49	−0.03	.78		
NLR	0.37	.002**	0.21	.017*		
Absolute neutrophil count, /mm ³	0.30	.006**	0.24	.008**		
Absolute lymphocyte count, /mm ³	−0.08	.48	−0.08	.28		
CRP level, mg/mL	0.19	.07	0.39	<.001***		
Anxiety (HADS-A)	0.06	.56	0.48	<.001***		
Depression (HADS-D)	0.34	.001**	—	—		
	M (SD)	t	P Value	M (SD)	t	P Value
Sex						
Female	9.8 (10.3)	1.05	.30	4.9 (3.9)	0.86	.38
Male	12.2 (11.6)			5.4 (3.5)		
Disease type						
Adenocarcinoma	10.7 (11.3)	0.03	.97	4.9 (3.9)	1.14	.26
Nonadenocarcinoma	10.7 (9.2)			5.7 (3.3)		
Line of therapy						
First	9.2 (8.1)	2.65	.08	4.8 (3.4)	1.58	.21
Second	14.7 (13.7)			4.9 (4.0)		
Third or beyond	9.0 (6.6)			6.6 (4.5)		
Race/Ethnicity						
Nonwhite ^a	12.6 (11.3)	0.70	.49	6.1 (4.2)	1.27	.21
White	10.4 (10.8)			4.9 (3.6)		
Married						
Yes	11.4 (11.4)	0.95	.35	4.9 (3.5)	0.96	.34
No	9.0 (9.1)			5.6 (4.3)		
Antidepressant						
Yes	15.2 (16.5)	1.60	.12	5.8 (4.2)	1.04	.22
No	9.4 (8.2)			4.9 (3.6)		
	M (SD)	F	P Value	M (SD)	F	P Value
Treatment type						
Chemotherapy	12.0 (11.6)	5.14	.008**	6.1 (4.0)	4.60	.012*
Immunotherapy	14.4 (12.1)			5.0 (3.5)		
Targeted therapy	4.8 (3.6)			3.4 (3.3)		

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; M, mean number of mutations; NLR, neutrophil-to-lymphocyte ratio; TMB, tumor mutation burden.

^aIncludes Asian, black, and Hispanic.

* $P < .05$; ** $P < .01$; *** $P < .001$.

higher TMB lung cancers are generally not associated with driver mutations. Interestingly, patients receiving immunotherapy had higher TMB, as would be expected because they were responding to immunotherapy, but did not

have elevated rates of depression (ie, depression was not impacted by immunotherapy). Therefore, the association between TMB and depression was independent of treatment type.

Table 3. Hierarchical Linear Regression Models of TMB and Inflammation to Explain Depression

Variable: Covariates	Depression (HADS-D)			CI	
	Regression Coefficient	t	P Value	Lower	Upper
Sex	0.02 (0.81)	0.215	.83	−3.829	7.302
Age	0.16 (0.04)	1.471	.15	−1.454	1.804
Treatment (ref: chemotherapy)					
Immunotherapy	−0.13 (0.91)	−1.132	.261	−2.841	0.782
Targeted therapy	−0.29 (1.01)	−2.407	.02*	−4.423	−0.418
F = 2.825; adjusted R ² = 0.049; F change = 2.032, significant F change = 0.098					
Additional Variable: TMB	Depression (HADS-D)			CI	
	Regression Coefficient	t	P Value	Lower	Upper
Sex	−0.01 (0.79)	−0.049	.96	−1.620	1.542
Age	0.21 (0.04)	1.947	.06	−0.002	0.162
Treatment (ref: chemotherapy)					
Immunotherapy	−0.19 (0.89)	−1.602	.11	−3.205	0.348
Targeted therapy	−0.17 (1.05)	−1.342	.18	−3.493	0.682
TMB	0.32 (0.46)	2.567	.01**	0.264	2.089
F = 3.064; adjusted R ² = 0.114; F change = 6.592, significant F change = 0.012					
Additional Variables: TMB & CRP	Depression (HADS-D)			CI	
	Regression Coefficient	t	P Value	Lower	Upper
Sex	−0.06 (0.78)	−0.553	.58	−1.968	1.113
Age	0.18 (0.04)	1.765	.08	−0.009	0.149
Treatment (ref: chemotherapy)					
Immunotherapy	−0.11 (0.88)	−0.959	.34	−2.595	0.909
Targeted therapy	−0.04 (1.07)	−0.340	.74	−2.498	1.770
TMB	0.30 (0.44)	2.563	.01**	0.250	2.001
CRP	0.31 (0.39)	2.784	.01**	0.305	1.843
F = 4.075; adjusted R ² = 0.187; F change = 7.752, significant F change = 0.007					
Variable: TMB × CRP Interaction	Depression (HADS-D)			CI	
	Regression Coefficient	t	P Value	Lower	Upper
Sex	−0.06 (0.78)	−0.550	.58	−1.979	1.123
Age	0.18 (0.04)	1.743	.09	−0.010	0.149
Treatment (ref: chemotherapy)					
Immunotherapy	−0.11 (0.89)	−0.951	.35	−2.620	0.927
Targeted therapy	0.04 (1.09)	−0.332	.74	−2.523	1.803
TMB	0.30 (0.44)	2.539	.01**	0.242	2.007
CRP	0.31 (0.40)	2.716	.01**	0.287	1.867
TMB × CRP interaction	−0.00 (0.41)	−0.033	.97	−0.820	0.793
F = 3.446; adjusted R ² = 0.176; F change = 0.001, significant F change = 0.97					

Regression n=96.

Abbreviations: CRP, C-reactive protein; HADS-D, Hospital Anxiety and Depression Scale-Depression; TMB, tumor mutation burden; TT, targeted therapy.

*P<.05; **P<.01.

There are several possible explanations for how TMB might lead to the development of depression via the adaptive immune system.^{54,59} However, selected T-cell population evaluations would be needed to understand this association, because T cells compose only part of the lymphocyte count, along with B cells, natural killer cells, and others. A dysregulated adaptive immune system (eg, altered cytotoxic T lymphocytes and T-regulatory cells)^{60,61} and abnormal natural killer and T-cell numbers have been reported in patients with major depression.^{62–64} Additionally, T-cell changes seem to predict antidepressant response.^{65–67} However, our study only measured the entire lymphocyte count, which is too general to capture selective T-cell changes. It is also possible that the association between TMB and depression is mediated by other immune markers, such as TNF- α , IL-6, or IL-1 β , rather than CRP, or by factors independent of inflammatory proteins entirely. In short, there may be other mediators of the general adaptation syndrome of stress that are responsible for TMB's association with depression, because unmitigated stress can eventually lead to depression.⁶⁸ Inflammation and/or immunity may still be the mechanism through which TMB is associated with depression, but our study was not powered or sensitive enough to detect this putative relation.

Regardless of the mechanism behind the association between TMB and depression, this is the first study to highlight such an association in any cancer sample. The association between TMB and depression was as strong as the association between inflammation (CRP level) and depression, which is a well-established relationship in many cancer and noncancer settings. TMB accounted for approximately 11% of depression variability and did not have a significant interaction with either inflammatory marker (although the association with CRP approached significance).

This study is limited by its cross-sectional design. It was conducted at a single institution with a relatively small number of participants (particularly for identifying possible interaction effects). Although the HADS-D is a well-accepted measure of depressive symptoms and has established cutoff scores with adequate sensitivity and specificity for identifying a diagnosis of depression, it does not replace a structured clinical interview with an experienced mental health professional. Additionally, the MSK-IMPACT panel is a surrogate for whole-exome sequencing, because only a selected cohort of 410 genes is

analyzed. Prospective testing has found a high correlation between TMB via MSK-IMPACT and whole-exome sequencing ($R^2 = 0.76$).⁴⁷ The slightly reduced accuracy of MSK-IMPACT may have introduced some degree of error, which would have decreased the amount of observed observations in this study. The measurement of immune functioning was also limited to clinically available laboratory values for CRP and NLR. Furthermore, this study did not obtain information on smoking, socioeconomic status, or treatment response, which would have been helpful in understanding the association between inflammation and depression.

Despite these limitations, the findings are novel and enhance understanding of the biologic basis for depression in lung cancer. They also aid in the identification of patients with lung cancer who have depression. Important confounders, such as treatment effects and sources of inflammation (ie, age and BMI), were controlled for, and this sample of patients with metastatic lung cancer eliminated many other cancer-related effects on the biology of associated depression.

Conclusions

This study provides evidence that the frequently reported associations between cancer and depression may be related to underlying cancer biology to a greater extent than previously recognized. TMB represents a cancer-related somatic biologic parameter that may influence depressive symptoms through inflammation induction or another mechanism. These findings warrant future investigation to understand cancer-specific depression and ways to identify and provide depression-specific treatments to patients who are most in need and stand to benefit from reducing depression as a cancer comorbidity.

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