

Association Between Brain Metastases and Immunosuppression in Lung Cancer - A Retrospective Cohort Study

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Abstract

Background/Objectives:

Lung cancer is a leading cause of cancer-related morbidity and mortality. Brain metastases (BMets) are common, yet the influence of immunosuppression and co-morbidities on their incidence and outcomes remains unclear.

Methods:

Using the 2022 National Inpatient Sample, we identified hospitalized lung cancer patients across the United States. Multivariable logistic regression assessed associations between BMets, immunosuppression and other co-morbidities, and inpatient mortality.

Results:

Patients with BMets were younger than those without (66.5 vs 70.6 years, $p < 0.001$) and more often treated in large size (56% vs 51%, $p < 0.001$) and teaching hospitals (81% vs 76%, $p < 0.001$). Hypogammaglobulinemia (OR 1.11, CI 0.51–2.38), chronic steroid use (OR 1.10, CI 0.98–1.23), immunosuppressant use (OR 1.22, CI 0.29–5.23), and human immunodeficiency virus infection (OR 1.19, CI 0.64–2.21) were associated with higher but non-significant odds of BMets. End stage renal disease (ESRD) (OR 0.67, CI 0.49–0.92), liver disease (OR 0.75, CI 0.65–0.87), and heart failure (OR 0.70, CI 0.64–0.77) were linked with lower odds of BMets. Predictors of higher inpatient mortality included neutropenia (OR 1.20, CI 1.01–1.42), protein-energy malnutrition (OR 1.21, CI 1.14–1.30), ESRD (OR 1.37, CI 1.10–1.71), and heart failure (OR 1.36, CI 1.26–1.47).

Conclusions:

Immunosuppression and co morbidities influence BMets patterns and inpatient mortality in lung cancer. While traditional immunosuppressive states were not significantly associated with BMets, comorbidities such as neutropenia, malnutrition, ESRD, and heart failure increased mortality risk. These findings highlight the need for prospective studies to better define these associations.

1. Introduction

Lung cancer remains a leading cause of cancer death worldwide and a major driver of the global cancer burden [1, 2]. Around 40–50% of brain metastases arise from lung primaries and these events carry substantial neurologic morbidity and excess mortality [3]. Studies have revealed that younger age, female gender, adenocarcinoma, advanced stage of cancer, mutations in epidermal growth factor receptor (EGFR), anaplastic lymphocyte kinase (ALK), and rearranged during transfection (RET) genes have a positive correlation while prophylactic brain irradiation and squamous cell carcinoma had a negative correlation with brain metastasis (BMets) in lung cancer [4, 5]. Transcriptomic studies suggest suppressed adaptive and innate immune response to tumor cells in the brain, however the exact

mechanism of occurrence of BMets in lung cancer patients remains unknown [6]. Incidence at diagnosis can be as high as 26.8% in non-small cell lung cancer (NSCLC), underscoring the role of tumor biology in central nervous system (CNS) tropism [5]. Immunotherapy has transformed outcomes for subsets of advanced NSCLC, but it has also exposed uncertainties about intracranial dissemination and treatment response, and immune microenvironment within the brain [3, 7].

A converging body of work implicates immune dysregulation in BMets development and progression. Resected NSCLC BMets exhibit a suppressed immune microenvironment, and restricted T-cell repertoires compared with extracranial disease, consistent with local immune escape in the brain [8, 9]. In parallel, mechanistic and translational data suggest systemic (peripheral) tumor-induced immunosuppression blunts antitumor surveillance and facilitates metastatic seeding to the brain [10]. These lines of evidence have sparked debate about the relative contributions of peripheral versus local (intratumoral) immune dysfunction, and about how iatrogenic or comorbidity-related immunosuppression intersects with tumor-intrinsic pathways to shape CNS risk [3, 4, 7–9]. Motivated by these gaps, we evaluated how systemic immunosuppression relates to the occurrence of BMets in NSCLC using a contemporary national cohort and presented our findings at Society of Neuro-Oncology/American Society of Clinical Oncology (SNO/ASCO) CNS metastases conference, 2025 [11].

2. Materials and Methods

This is a retrospective cohort study conducted using the 2022 National Inpatient Sample (NIS). NIS is an administrative database developed by the Agency for Healthcare Research and Quality for the Healthcare Cost and Utilization Project (HCUP). The NIS represents approximately 35 million hospitalizations annually and contains patient- and hospital-level data, including diagnoses and procedures, demographics (age, sex, race), primary payer, ZIP code, median household income, discharge timing, total charges, length of stay, and other hospitalization elements. Direct identifiers are not included. Because the dataset is publicly available and de-identified, this study was exempt from Institutional Review Board review.

The study included adult hospitalizations with lung cancer using the International Classification of Diseases, Revision Tenth (ICD-10) diagnosis codes. Hospitalizations were then stratified by the presence or absence of brain metastases. To ensure that intracranial disease reflected metastasis from lung cancer, we excluded encounters with codes for primary brain tumors and for brain metastases attributable to other primaries like breast, melanoma, and renal cell carcinoma. Baseline covariates included patient demographics like age, gender, race, primary payer, ZIP code, and level income quartile and hospital characteristics like bed size, region, and teaching status. Co-morbidities of interest were type 2 diabetes mellitus, coronary artery disease, hypertension, congestive heart failure (CHF), current smoking, alcohol use, chronic liver disease, chronic kidney disease (CKD) and end-stage renal disease (ESRD), chronic obstructive pulmonary disease (COPD), protein-energy malnutrition (PEM), prior bone marrow transplant (BMT), human immunodeficiency virus (HIV) infection, and chronic hepatitis. We also captured indicators of immunosuppression and related complications during the hospitalization

including neutropenia, hypogammaglobulinemia, and current use of systemic corticosteroids or other immunosuppressants. Outcomes were in-hospital mortality, length of stay (LOS), and total hospitalization charges.

All analyses incorporated HCUP discharge weights to generate national estimates and accounted for the complex survey design. Analyses were performed in Stata/BE 18 (Stata Corp, College Station, TX) following HCUP-recommended methods (Taylor series linearization). We compared baseline characteristics between lung cancer hospitalizations with versus without brain metastases. Categorical variables were compared using survey-adjusted Rao–Scott χ^2 tests; continuous variables were compared using survey-weighted means with adjusted Wald tests. To identify factors associated with the presence of brain metastases, we fit a multivariable survey-weighted logistic regression including demographics, hospital characteristics, and comorbidities selected a priority based on clinical relevance and data availability. Results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs) and two-sided p-values. In secondary analyses, we used a similar multivariable framework to evaluate predictors of in-hospital mortality among lung cancer hospitalizations. Statistical significance was defined as $p < 0.05$.

3. Results

This study included 371,945 hospitalizations of lung cancer patients out of whom 69,050 (19%) had BMets and 302,895 (81%) did not. Table 1 shows that patients with BMets were younger than those without BMets (66.5 vs 70.6 years, $p < 0.001$) and as a result, insurance coverage for Medicaid was higher in the BMets group while Medicare coverage was higher in the non-BMets group. BMets patients were treated more frequently in large (56% vs 51%, $p < 0.001$), teaching (81% vs 76%, $p < 0.001$) hospitals reflecting the complexity of care required for these patients. Tables 2 and 3 show lower odds of BMets in patients with coronary artery disease, CHF, liver disease, PEM, and ESRD. Conversely, hypertension was associated with a an increased risk of BMets. Table 4 shows that inpatient mortality among lung cancer patients with brain metastases was significantly correlated with CHF, ESRD, PEM, and neutropenia. Notably, PEM showed strong associations with both lower risk of brain metastases and higher mortality, suggesting it may reflect more advanced systemic illness.

Table 1
Demographic characteristics of patients with lung cancer with and without brain metastases

Variable		No BMets (N = 302,895)	BMets (N = 69,050)
Age (years)		70.63	66.47
Female (%)		48%	49%
Race (%)	White	77%	72%
	Black	12%	15%
	Hispanic	5%	6%
	Asian	3%	5%
	Others	2%	2%
Income quartile (%)	(lowest)	30%	29%
	(highest)	19%	21%
Primary payer (%)	Medicare	69%	57%
	Medicaid	9%	14%
	Others	22%	29%
Hospital region (%)			
	Northeast	20%	21%
	Midwest	24%	26%
	South	41%	39%
	West	15%	15%
Hospital bed size (%)	Small	20%	17%
	Medium	28%	27%
	Large	51%	56%
Key 1 : BMets = brain metastases			

Table 2
Clinical characteristics of patients with lung cancer with and without brain metastases

Variable	No BMets (N = 302,895)	BMets (N = 69,050)
Diabetes	27%	22%
Coronary artery disease	27%	17%
Hypertension	40%	44%
Congestive heart failure	22%	12%
Smoking	65%	62%
Alcohol use	4%	4%
Liver disease	4%	4%
Chronic kidney disease	4%	3%
End-stage renal disease	1%	1%
COPD	7%	5%
Protein-energy malnutrition	20%	25%
Bone marrow transplant	0%	0%
Neutropenia	3%	3%
Lymphopenia	1%	1.1%
Hypogammaglobulinemia	0%	0%
Steroid use	9%	8%
Immunosuppressant use	0%	0%
HIV infection	0%	0%
Chronic hepatitis	1%	1%
Key 2: BMets = Brain metastases, COPD = Chronic obstructive pulmonary disease, HIV = Human immunodeficiency virus		

Table 3

Association between clinical patient characteristics and brain metastases in patients with lung cancer

Variable	Odds Ratio	95% Confidence Interval	p-value
Diabetes	0.925	0.861–0.994	0.033
Coronary artery disease	0.865	0.802–0.914	< 0.001
Hypertension	1.078	1.010–1.151	0.023
Congestive heart failure	0.704	0.640–0.775	< 0.001
Smoking	0.969	0.907–1.036	0.353
Alcohol use	1.031	0.881–1.205	0.706
Liver disease	0.754	0.652–0.872	< 0.001
Chronic kidney disease	1.061	0.894–1.258	0.501
End-stage renal disease	0.675	0.494–0.922	0.013
COPD	0.922	0.803–1.058	0.247
Protein-energy malnutrition	0.835	0.778–0.897	< 0.001
Bone marrow transplant	1.068	0.256–4.465	0.928
Neutropenia	0.879	0.751–1.029	0.109
Lymphopenia	0.965	0.735–1.266	0.795
Hypogammaglobulinemia	1.106	0.514–2.380	0.797
Steroid use	1.099	0.982–1.229	0.100
Immunosuppressant use	1.224	0.285–5.231	0.785
HIV infection	1.190	0.641–2.211	0.581
Chronic hepatitis	0.972	0.704–1.342	0.862
Key 3: BMets = Brain metastases, COPD = Chronic obstructive pulmonary disease, HIV = Human immunodeficiency virus			

Table 4
Clinical risk factors for inpatient mortality in lung cancer patients with brain metastases

Variable	Odds Ratio	95% Confidence Interval	p-value
Diabetes	0.919	0.860–0.982	0.013
Coronary artery disease	0.921	0.857–0.989	0.024
Hypertension	0.846	0.793–0.903	< 0.001
Congestive heart failure	1.365	1.264–1.474	< 0.001
Smoking	0.578	0.544–0.612	< 0.001
Alcohol use	0.962	0.819–1.129	0.634
Liver disease	1.095	0.954–1.256	0.196
Chronic kidney disease	1.109	0.966–1.274	0.143
End-stage renal disease	1.373	1.102–1.711	0.005
COPD	0.760	0.669–0.864	< 0.001
Protein-energy malnutrition	1.214	1.135–1.299	< 0.001
Bone marrow transplant	1.139	0.525–2.473	0.742
Neutropenia	1.201	1.015–1.421	0.033
Lymphopenia	0.775	0.549–1.095	0.149
Hypogammaglobulinemia	1.318	0.638–2.723	0.455
Steroid use	0.686	0.612–0.769	< 0.001
Immunosuppressant use	1.123	0.363–3.472	0.840
HIV infection	1.088	0.688–1.722	0.718
Chronic hepatitis	0.862	0.622–1.195	0.373
Key 4: BMets = Brain metastases, COPD = Chronic obstructive pulmonary disease, HIV = Human immunodeficiency virus			

4. Discussion

Lung cancer is one of the most common malignancies and causes of cancer-related deaths in the United States, with approximately 226,650 new cases and 124,730 deaths projected for 2025 [12]. Globally, the burden is even greater, with about 2.48 million new diagnoses in 2022 [13]. Brain metastases (BMets) represent a clinically consequential pattern of spread, driving neurological morbidity and worse survival across lung cancer populations [14].

Correlation of demographic information with brain metastasis in lung cancer

In our cohort, patients with BMets were younger, more often female, and less likely to be White than those without BMets. These age patterns are consistent with small-cell lung cancer (SCLC) data showing higher BMets risk in younger patients and poorer survival in older patients once synchronous BMets is present [15, 16]. Additional population-based SCLC analyses support the link between clinical presentation, for example extensive disease, and BMets risk, helping contextualize demographic effects [17]. For non-small cell lung cancer (NSCLC), large cohort data indicate comparable BMets rates in males and females at presentation, with a higher prevalence among Black patients. Also, tumor size and grade were key correlates of BMets in those analyses, however we could not directly measure the variables in our dataset [18].

Socioeconomic context also appeared to shape presentation in our study. Patients with BMets more often came from higher-income ZIP codes and were treated at larger tertiary centers. Prior population-based work in NSCLC with BMets at diagnosis found that lower area-level income is associated with worse survival, consistent with differences in access, timeliness, and intensity of evaluation and treatment [19]. Taken together, these findings suggest that age, sex, race/ethnicity, and socioeconomic factors intersect with tumor biology and disease extent to influence who develops BMets and how patients fare once BMets are present [12–19].

Correlation of immunodeficiency and other co-morbidities with brain metastasis in lung cancer

Studies reveal a significant association between neutrophilia and increased neutrophil-to-lymphocyte ratio and brain metastasis in lung cancer [20]. This highlights the role of inflammation in tumor progression through a reduction in tumor-infiltrating lymphocytes (TILs) and an increase in cytokines related to angiogenesis and neoplastic cell proliferation [21]. Our study showed a negative, but nonsignificant, correlation between neutropenia and BMets which might be related to the role of neutrophils in cancer-related inflammation and tumor progression. Also, neutropenia in hospitalized patients is usually iatrogenic from chemotherapy which might have contributed to the negative correlation with BMets. In our study, lymphopenia was uncommon and was not independently associated with brain metastases after multivariable adjustment. This likely reflects incomplete capture in administrative data, as lymphopenia is coded as lymphocytopenia under ICD-10 and is not consistently billed and may be incorporated under broader immunosuppressive conditions. Conditions like steroid and immunosuppressant use and HIV infection that are known to cause lymphopenia showed a positive, albeit nonsignificant, correlation with BMets. Cytotoxic lymphocytes play a role in immune surveillance against cancer cells. Hence, upregulation of regulatory T (Treg) and concomitant lymphopenia are related to tumor proliferation and spread [10]. In our study, hypogammaglobulinemia had a positive correlation with BMets that was statistically insignificant. Through impairment in B lymphocyte differentiation, studies reveal an association between common variable immunodeficiency (CVID) and lymphoma [22].

Chronic conditions like PEM, ESRD, liver disease, CHF, and COPD are associated with acquired immunodeficient states. PEM is the most common cause of acquired immunodeficiency globally due to weakened cellular and innate immunity. [23] ESRD, on the other hand, affect humoral immunity on top of innate immune system while liver disease reduces complement protein production, hence leading to dysfunction in phagocyte and lymphocyte function. [24, 25] CHF, especially heart failure with reduce ejection fraction, and COPD induce a maladaptive immune response through systemic chronic inflammation and lymphocyte dysfunction. [26, 27] In our study, these co-morbidities had a significant negative correlation with BMets in lung cancer patients. This pattern likely reflects a younger, generally healthier subgroup that survives long enough and is eligible for more intensive staging, thereby increasing the likelihood that intracranial disease is detected. According to earlier research, co-morbid disorders significantly reduce survival regardless of cancer stage [28, 29]. Further evidence of under-diagnosis due to differences in imaging application was provided by a recent study, which found that more than 25% of metastatic NSCLC cases did not undergo brain imaging, especially among older and socioeconomically disadvantaged populations [30]. According to National Comprehensive Cancer Network (NCCN) report, studies show a higher frequency of BMets than those found in clinical settings [31]. Therefore, rather than a decreased inherent hazard of CNS dissemination, our findings most likely reflect early mortality and under-imaging in high-comorbidity groups.

Although hypertension was more prevalent in our BMets group, prior retrospective study by Sahmoun et al. did not identify hypertension as a causal or independent predictor of brain metastases in SCLC [32]. Taken together, our findings support viewing common co-morbidities, especially hypertension, as contextual markers of patient fitness and care pathways rather than direct determinants of CNS spread, whereas PEM likely reflects systemic frailty that adversely affects outcomes once BMets is present.

Correlation of clinical co-morbidities with inpatient mortality in lung cancer with brain metastases

Our study found a significant positive correlation between neutropenia and inpatient mortality in the setting of lung cancer and brain metastases. Neutropenia in hospitalized patients might be related to inpatient chemotherapy that is known to increase infections, mortality, and readmissions [33, 34]. Among conditions causing lymphopenia and hypogammaglobulinemia, our study did not find a significant association with inpatient mortality except for steroid use that had a significant negative correlation with hospital deaths. Contrary to our findings, scientific literature reports higher inpatient deaths with steroid use, especially when they are used for cancer-related symptoms and palliation and not for therapy-related side effects [35].

In our adjusted analysis, the presence of BMets was not independently associated with worse in-hospital mortality. These outcomes appeared to be driven predominantly by comorbidity burden and systemic illness rather than intracranial involvement alone. Contemporary real-world cohorts echo this nuance. A claims-based database study by Parker et al. spanning the last decade highlights the variability in survival in NSCLC with BMets depending on access to treatment and management of other co-morbidities [36]. Likewise, data from a resource-limited setting showed that limited availability in novel

therapeutic options was related to poor patient survival and outcomes were better in younger cohorts and those with early brain metastasis identification [37]. A large SEER-based analysis involving more than 45,000 cases demonstrated site-specific heterogeneity in risk, with the highest hazards for multiorgan involvement (HR 1.65), followed by liver (HR 1.48), brain (HR 1.32), and bone (HR 1.28) metastases [38]. In line with prior literature [28, 29], our study also showed a significant positive correlation between CHF, ESRD, and PEM and inpatient mortality. Patients with poor Eastern Cooperative Oncology Group (ECOG) performance status and multiple co-morbidities often receive supportive or palliative care instead than more invasive, curative treatment. However, liver disease had no significant correlation and COPD had a significant positive negative correlation with mortality.

In people with DM, optimal glycemic control is significantly associated with better overall survival in lung cancer patients [39]. Our study showed a significant negative correlation between DM and mortality that might be possible in case of well-controlled DM in this cohort. However, National Health and Nutrition Examination Survey (NHANES) database analysis by Fang et al. showed worsening glycemic control in people with DM over the past decade [40].

Timing of BMets detection also carries prognostic weight. In the study by Parker et al., patients whose BMets were identified at initial NSCLC diagnosis experienced more favorable outcomes than those who developed BMets later during the disease course, a pattern consistent with earlier staging, earlier CNS-active therapy, and better overall fitness at the start of treatment [36]. Concordantly, in the REFLECT study on EGFR-mutated NSCLC, median overall survival was 21.8 months when BMets were present at initiation of first-line tyrosine kinase inhibitor (TKI), versus 6.4 months when BMets emerged on treatment [41]. These observations support early BMets detection and start of CNS-active therapy, while simultaneously prioritizing optimization of systemic comorbidities that strongly influence short-term mortality to improve survival in lung cancer patients with BMets.

Limitations and future directions

With a high sample size, this study has external validity, however internal validity may be compromised due to the risk of coding errors and misclassification biases. Tumor-specific details such as histology, stage, molecular alterations, and treatment regimens were not available, which may confound associations. Due to the study design, temporal association between immunosuppression and brain metastases cannot be determined and will need prospective studies for the same. At present, NCCN guidelines recommend screening MRI brain for all SCLC patients and high-risk NSCLC patients, i.e. stages II and higher, tumor size more than 5 cm, and central location of tumor. Inclusion of systemic factors like neutrophilia and lymphopenia into risk-stratification to assess eligibility for surveillance brain MRI may be worth exploring. Future studies comparing outcomes between symptomatic and asymptomatic BMets as well as stage 4 lung cancer with and without brain metastases will give a more comprehensive understanding on prognostication of these cases.

Conclusion

Demographic and socioeconomic factors like younger age, female gender, non-White race, higher socioeconomic status, and hospitalization in larger, tertiary centers are associated with increased detection of brain metastases (BMets) in lung cancer. Immunodeficient states like lymphopenia and hypogammaglobulinemia and inflammatory states with neutrophilia might be related with BMets, however most of these associations were not significant. Co-morbidities like protein-energy malnutrition, end stage renal disease, and heart failure that are related to altered immune function are related with higher mortality in lung cancer patients with BMets while detection of BMets is low in this cohort. These findings underscore the importance of early CNS imaging in high-risk patients and suggest a potential role for systemic immune markers in risk stratification. Prospective studies are needed to further clarify causal relationships and optimize surveillance strategies.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Purva Shah, Samhitha Gundakaram, Raj shah and Basant Elhater. The first draft of the manuscript was written by Purva Shah, Samhitha Gundakaram and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study utilized the National Inpatient Sample (NIS), a publicly available de-identified database from the Healthcare Cost and Utilization Project (HCUP). Because the database contains no patient identifiers, this study was considered exempt from Institutional Review Board (IRB) approval and informed consent was not required.

Human Ethics and Consent to Participate Declarations

Not applicable.

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