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# Factors associated with first-line bevacizumab use in advanced non-squamous, non-small cell lung cancer

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## Abstract

*Introduction:* Bevacizumab was approved for treatment of advanced non-squamous, non-small cell lung cancer (NSCLC) in the US in late 2006. Information on its uptake and patient and tumor factors associated with its use is lacking. *Materials and methods:* This was a longitudinal, retrospective cohort study of patients with stage IIIB/IV non-squamous NSCLC aged 21 years or greater diagnosed between 2005 and 2010 at four Cancer Research Network sites. Patients were categorized as receiving first-line carboplatin-paclitaxel (CP) or carboplatin-paclitaxel-bevacizumab (CPB) within 120 days of diagnosis. Information on patient and tumor characteristics was obtained from queries of sites' electronic tumor registries and administrative databases. Factors independently associated with CPB use were evaluated using bivariate and multivariate logistic regression analyses. *Results:* A total of 1109 patients with advanced NSCLC were included with 198 (17.9%) and 911 (82.1%) patients receiving CPB and CP, respectively. Bevacizumab use increased modestly during the study period, peaking in 2008 at 18.5%. In bivariate analyses, patients who received CPB were younger with less comorbidity and well to moderately differentiated tumors while patients who received CP were more likely to have had hypertension, peripheral vascular disease, and a prior hospitalization. Factors independently associated with CPB use included younger age, well/moderately differentiated tumor grade, no prior hospitalization, and more recent study year. *Conclusions:* Use of bevacizumab in patients with advanced NSCLC increased rapidly then moderated. Younger patients and those with lower risks for adverse effects were more likely to receive bevacizumab.

***Keywords:*** carcinoma; non-small-cell lung; angiogenesis inhibitors; diffusion of innovation; managed care programs; health services accessibility; population characteristics

## Introduction

Over the past decade, lung cancer has been the second most prevalent cancer diagnosed in males and females and resulted in the most cancer-related deaths in males aged ≥40 years and females aged ≥60 years [1-4]. In 2010, the overall prevalence of lung cancer in the U.S. was approximately 125 cases per 100,000 persons per year [5]. Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of the new lung and bronchus cancer cases in the U.S. and most of these cases represent advanced disease (stage IIIB/IV) [4].

Currently, there is only a small pool of drugs that have been approved for first-line treatment of advanced or metastatic NSCLC [6]. Among these drugs is bevacizumab (Avastin®). Bevacizumab is a recombinant monoclonal antibody that originally was approved by the U.S. Food and Drug Administration (FDA) in 2004 for first-line treatment

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of metastatic carcinoma of the colon and rectum when used in combination with intravenous 5-fluorouracil [7]. Bevacizumab selectively binds to human vascular endothelial growth factor (VEGF), decreasing VEGF activity resulting in a reduction in tumor vascularization and decrease in tumor growth [7, 8]. In October 2006, the FDA approved bevacizumab use as first-line treatment in advanced non-squamous NSCLC when administered in combination with carboplatin and paclitaxel [7].

Although the results of the Eastern Cooperative Oncology Group (ECOG 4599) demonstrated a statistically significant improvement in survival with the addition of bevacizumab [9], it is unclear whether the 2-month survival improvement is viewed as being clinically significant by physicians in the community, particularly relative to its toxicity. Numerous clinical and biological markers can influence a patient's candidacy for bevacizumab use (Table 1). Additionally, the clinical data that support bevacizumab's efficacy in patients with advanced NSCLC suggest diminished efficacy in patients aged ≥65 years, which constitutes the majority of individuals diagnosed with NSCLC [9]. Furthermore, recent Phase I and Phase II trials have identified a promising dose/dense metronomic chemotherapy regime for NSCLC of cisplatin, oral etoposide, and bevacizumab. However while this regime showed significant antitumor activity, the incidence of adverse events (e.g., pneumonia, thromboembolism, depression) appeared to be correlated with increasing bevacizumab dose [10, 11].

**Table 1** Clinical and biological markers potentially contraindicated for bevacizumab use in lung cancer patients*

| *Marker* |
|---|
| Small cell lung cancer |
| Performance status >1 |
| Predominantly squamous cell carcinoma |
| Tumor invasion into major blood vessels |
| Radiation therapy within previous 21 days |
| Major surgery or trauma in previous 28 days |
| Major surgery planned in following 28 to 42 days |
| Uncontrolled hypertension |
| Major cardiovascular or cerebrovascular disease |
| Coagulopathy |
| Proteinuria or renal dysfunction |
| Hepatic dysfunction |
| Unhealed wound, ulcer/gastrointestinal perforation, varices, or fracture |
| Pregnancy, lactation, or childbearing intentions |
| Metastases within the central nervous system |
| Recent hemoptysis |
| Thromboembolism |
| Therapeutic anticoagulation |
| Non-steroidal anti-inflammatory agent use/Antiplatelet use (including aspirin) |

*Adapted from bevacizumab package insert [7] and Sanders et al. [9]

Studies have examined the patient and tumor characteristics associated with bevacizumab use in colorectal cancer [12], but none have explored the characteristics of NSCLC patients who have received bevacizumab. The purpose of this study is to assess the associations of NSCLC patient and tumor characteristics and first-line bevacizumab use in community oncology. Identifying factors that may play a role when oncologists consider using bevacizumab as a treatment option for NSCLC can provide a better understanding of bevacizumab's use in community settings and a baseline for efforts to understand evidence-based lung cancer care.

## Materials and methods

*Study design and setting*

This is a longitudinal, multi-site, retrospective cohort study. Data were obtained from four non-profit managed care organizations that are members of the Cancer Research Network (CRN) [13], including three Kaiser Permanente regions (Colorado, Northern California, and Northwest) and Group Health Cooperative (Washington). The CRN promotes collaborative cancer research in the integrated health care settings of its member institutions. The four health systems participating in this study have a combined membership of approximately six million members. The majority of cancer care was delivered by salaried physicians in plan-owned facilities at these organizations. Combined therapy of carboplatin-paclitaxel-bevacizumab (CPB) for patients with non-squamous NSCLC was first identified at the study sites in 2005. Thus, the comparison groups include patients diagnosed with non-squamous NSCLC between 2005 and 2010 who received either first-line carboplatin-paclitaxel (CP) or CPB. Data from each study site were extracted and transferred to Kaiser Permanente Colorado for analysis. This study was approved by the Institutional Review Boards of the four participating study sites.

*Patient population*

The study sample included patients identified from each study site's tumor registry. Patients were ≥21 years of age, diagnosed with stage IIIB/IV non-squamous NSCLC between January 1, 2005 and December 31, 2010, and followed through December 31, 2011. Patients with health plan enrollment at the time of pathologically-confirmed cancer diagnosis, NSCLC as their primary cancer diagnosis, who did not receive concurrent definitive radiation and chemotherapy (i.e., administration dates of the individual modalities were within 14 days of each other), and survived at least one month after cancer diagnosis were included. Patients were followed from cancer diagnosis until death, health plan termination, or the end of the study, whichever came first.

*Data collection*

The CRN uses a federated database, the Virtual Data Warehouse (VDW), where data are stored in common data structures across study sites [13]. This model allows

a programmer at one site to develop analytic algorithms that can be run independently at each site to extract the necessary data elements for the study. Data are derived from each health systems' electronic medical records (EMRs) and claims databases. The VDW contains patients' diagnoses captured with International Classification of Diseases (ICD)-9 codes, health services procedure data as captured with Healthcare Common Procedure Coding System (HCPCS) [including Current Procedural Terminology (CPT) codes] and Diagnosis-Related Group (DRG) codes, and pharmacy data that are captured with National Drug Codes (NDC).

Each CRN site maintains a list of all specific NDCs ever approved for dispensing by its pharmacies. The VDW includes tumor registry data with information on each patient's diagnosis by ICD-O code, sequence, diagnosis date, AJCC stage, tumor grade and morphology, and dates of initial cancer-related surgery, radiation therapy, and chemotherapy treatment [14]. In addition, the VDW includes information on patient demographics, hospitalizations, outpatient visits, and insurance types. Furthermore, the VDW includes a Census database. Measures of socioeconomic status (e.g., median family income) and patients' residential addresses, which were mapped to Census block data using geocoding software, are included in the database. Death data were derived from the VDW tumor registries and membership databases, state-level death datasets, and data from the Social Security Administration.

*Study outcomes*

The primary outcome was an analysis of the factors independently related to first-line CPB use. Eligible patients receiving first-line CP with or without bevacizumab were identified using VDW pharmacy, procedure, and infusion databases using methods described previously [15-17]. The date of the first chemotherapy treatment administration was considered the chemotherapy start date. First-line therapy was defined as all chemotherapy agents administered within eight days of the chemotherapy start date. Secondary outcomes included an assessment and comparison of patient clinical, demographic, and sociodemographic characteristics between patients who received first-line CPB vs. CP.

*Data analysis*

Patient age at the time of NSCLC diagnosis was calculated. The presence of specific comorbidities was determined using the Quan adaptation of the Charlson comorbidity index, modified to exclude cancer diagnoses [18]. The algorithm was applied to diagnoses associated with inpatient and outpatient events that occurred prior to cancer diagnosis. Patient comorbidities were identified from ICD-9 coded outpatient diagnoses prior to date of NSCLC diagnosis. Invasive surgery during the 28 days prior to the start of chemotherapy was identified from the inpatient encounter, tumor registry, and ambulatory surgery registry datasets with DRG and procedure codes. Hospitalizations within six months of the NSCLC diagnosis date were identified from inpatient encounter datasets. Surrogate patient-level measures of median annual family income were obtained from VDW Census database.

All analyses were performed comparing the CPB group to the CP group. Patient characteristics were reported as means, medians, and standard deviations for interval-level variables and percentages for categorical variables. Wilcoxon rank-sum tests and chi-square tests of association or Fisher's Exact tests (where applicable) were used to assess differences between groups for interval-level and categorical variables, respectively. To identify factors associated with receiving CPB, all factors with a $p<0.2$ in the bivariate analyses (plus patient sex) were entered into a logistic regression model with adjustment for the clustering of practices by health plan [19]. Factors were assessed for multicolinearity. No substantial multicolinearity (i.e., rho$>$0.3) was detected. Two-way factor interactions were constructed and tested for statistical significance. No interactions were statistically significant and, thus, none were included in the final model. All analyses were performed using SAS v9.1.3 (SAS Software Inc., Cary, NC).

## Results

There were 1109 patients diagnosed with NSCLC in the participating CRN sites during the study period who were included in the analysis. A total of 198 (17.9%) and 911 (82.1%) patients received CPB and CP, respectively (Table 2). Patients were more likely to have received CPB in years 2007 - 2008 ($p<0.001$) and 2009 - 2010 ($p=0.001$) compared to 2005 - 2006. Patients in the CPB group were more likely to be younger ($p<0.001$) and have a lower comorbidity index score ($p=0.034$) than patients in the CP group. Patients in the CPB group were also more likely to have had a well or moderately differentiated tumor ($p<0.001$). Conversely, patients in the CP group were more likely to have had diagnoses of hypertension ($p=0.014$) and peripheral vascular disease ($p=0.047$), and a hospitalization in the six months prior to NSCLC diagnosis date ($p<0.001$).

In the multivariate modeling with adjustment for the clustering of practices by health plan, patients aged 66 to 70 years (odds ratio (OR)=0.51, 95% confidence interval (CI)=0.30-0.86) and aged $>$ 70 years (OR=0.44, 95% CI=0.27-0.71) were associated with decreasing likelihood of receiving CPB compared to patients aged $<$ 60 years (Figure 1). In addition, patients with one or two (OR=0.35, 95% CI=0.17-0.754) and three or more (OR=0.53, 95% CI=0.3-0.83) hospitalized days in the six months prior to NSCLC diagnosis were associated with a decreased likelihood of receiving CPB compared to patients with zero hospitalized days. Converesely, patients with well or moderately differentiated tumors were associated with an increased likelihood of receiving CPB compared to patients with an unknown tumor grade (OR=2.1, 95% CI=1.39-3.29). In addition, patients diagnosed in years

**Table 2** Baseline characteristics by reception of first-line bevacizumab status

| *Characteristic* | *Overall cohort (n=1109)* | *CP + bevacizumab (n=198)* | *Only CP (n=911)* | *P-value*[a] |
|---|---|---|---|---|
| Mean Age[b] (SD) | 63.5 (10.1) | 60.3 (10.2) | 64.2 (9.9) | <0.001 |
| Age[b] Categories (n, %) | | | | <0.001 |
| < 60 years | 370 (33.4) | 89 (45.0) | 281 (30.9) | |
| 60 to 65 years | 249 (22.5) | 52 (26.3) | 197 (21.6) | |
| 66 to 70 years | 190 (17.1) | 24 (12.1) | 166 (18.2) | |
| > 70 years | 300 (27.1) | 33 (16.7) | 267 (29.3) | |
| Female (n, %) | 565, 51.0% | 102, 51.5% | 463, 50.8% | 0.860 |
| Mean charlson comorbidity index[b] (SD) | 1.1 (1.7) | 0.9 (1.5) | 1.1 (1.8) | 0.034 |
| Stage 4 at diagnosis (n, %) | 890, 80.3% | 168, 84.9% | 722, 79.3% | 0.073 |
| Race (n, %) | | | | |
| White | 885, 79.8% | 159, 80.3% | 726, 79.7% | 0.846 |
| Asian | 116, 10.5% | 22, 11.1% | 94, 10.3% | 0.741 |
| Black/African American | 80, 7.2% | 11, 5.6% | 69, 7.6% | 0.320 |
| Other/Undeclared | 28, 2.5% | 6, 3.0% | 22, 2.4% | 0.617 |
| Hispanic ethnicity (n, %) | 42, 3.8% | 4, 2.0% | 38, 4.2% | 0.215 |
| Tumor grade (n, %) | | | | |
| Well/moderately differentiated | 154, 13.9% | 44, 22.2% | 110, 12.1% | <0.001 |
| Poor/Undifferentiated | 233, 21.0% | 32, 16.2% | 201, 22.1% | 0.065 |
| Unknown | 722, 65.1% | 122, 61.6% | 600, 65.9% | 0.256 |
| Comorbidity diagnosis[b] (n, %) | | | | |
| Bleeding | 0, 0.0% | 0, 0.0% | 0, 0.0% | 1.000 |
| Congestive heart failure | 36, 3.3% | 6, 3.0% | 30, 3.3% | 0.850 |
| Chronic pulmonary disease | 269, 24.3% | 53, 26.8% | 216, 23.7% | 0.363 |
| Cerebrovascular disease | 50, 4.5% | 7, 3.5% | 43, 4.7% | 0.467 |
| Diabetes | 116, 10.5% | 14, 7.1% | 102, 11.2% | 0.086 |
| Diabetes w/ Complications | 55, 5.0% | 6, 3.0% | 49, 5.4% | 0.168 |
| Hypertension | 558, 50.3% | 84, 42.4% | 474, 52.0% | 0.014 |
| Myocardial infarction | 45, 4.1% | 7, 3.5% | 38, 4.2% | 0.681 |
| Mild Liver disease | 24, 2.2% | 5, 2.5% | 19, 2.1% | 0.700 |
| Peripheral vascular disease | 82, 7.4% | 8, 4.0% | 74, 8.1% | 0.047 |
| Renal disease | 66, 6.0% | 7, 3.5% | 59, 6.5% | 0.113 |
| Rheumatologic disease | 33, 3.0% | 8, 4.0% | 25, 2.7% | 0.331 |
| Median total comorbidity count[c] (mean, SD) | 0 (0.7, 1.1) | 0 (0.6, 1.1) | 0 (0.7, 1.1) | 0.111 |
| Total comorbidity count > 0 (n, %) | 483, 43.6% | 77, 38.9% | 406, 44.6% | 0.144 |

| | | | | |
|---|---|---|---|---|
| Year of NSCLC diagnosis (n, %) | | | | |
| 2005 - 2006 | 367, 33.1% | 41, 20.7% | 326, 35.8% | <0.001 |
| 2007 - 2008 | 382, 34.5% | 88, 44.4% | 294, 32.3% | 0.001 |
| 2009 - 2010 | 360, 32.5% | 69, 34.9% | 291, 31.9% | 0.429 |
| Surgery[d] (n, %) | 17, 1.5% | 3, 1.5% | 14, 1.5% | 0.982 |
| At least one hospitalization[c] (n, %) | 348, 31.4% | 38, 19.2% | 310, 34.0% | <0.001 |
| Count of days hospitalized[c] (n, %) | | | | |
| 0 | 761, 68.6% | 160, 80.8% | 601, 66.0% | <0.001 |
| 1 - 2 | 94, 8.5% | 9, 4.6% | 85, 9.3% | 0.029 |
| >2 | 254, 22.9% | 29, 14.7% | 225, 24.7% | 0.002 |
| Insurance type[b] (n, %) | | | | 0.278 |
| Commercial | 794, 71.6% | 148, 74.8% | 646, 70.9% | |
| Other | 315, 28.4% | 50, 25.3% | 265, 29.1% | |
| Median family income[b] (n, %) | | | | |
| <$45130 | 219, 19.8 | 36, 18.2% | 183, 20.1% | 0.542 |
| $45130 - $57286 | 228, 20.6% | 44, 22.2% | 184, 20.2% | 0.523 |
| $57287 - $66019 | 221, 19.9% | 47, 23.7% | 174, 19.1% | 0.139 |
| $66020 - $82651 | 224, 20.2% | 38, 19.2% | 186, 20.4% | 0.697 |
| >$82651 | 217, 19.6% | 33, 16.7% | 184, 20.2% | 0.256 |
| Mean family income[b] (SD) | $65338 ($25195) | $64685 ($23476) | $65479 ($25562) | 0.790 |
| Mean time to initiation of chemotherapy after diagnosis (days, SD) | 46.5 (24.7) | 46.7 (27.2) | 46.4 (24.1) | 0.640 |

CP = Carboplatin + paclitaxel
[a] P-value from bivariate analysis
[b] As of NSCLC diagnosis date
[c] In the six months prior to NSCLC diagnosis date
[d] In the 28 days prior to NSCLC diagnosis date

2007 - 2008 (OR=2.42, 95% CI=1.58-3.72) and 2009 - 2010 (OR=1.86, 95% CI=1.18-2.93) were associated with an increased likelihood of receiving CPB compared to patients diagnosed in years 2005 - 2006.

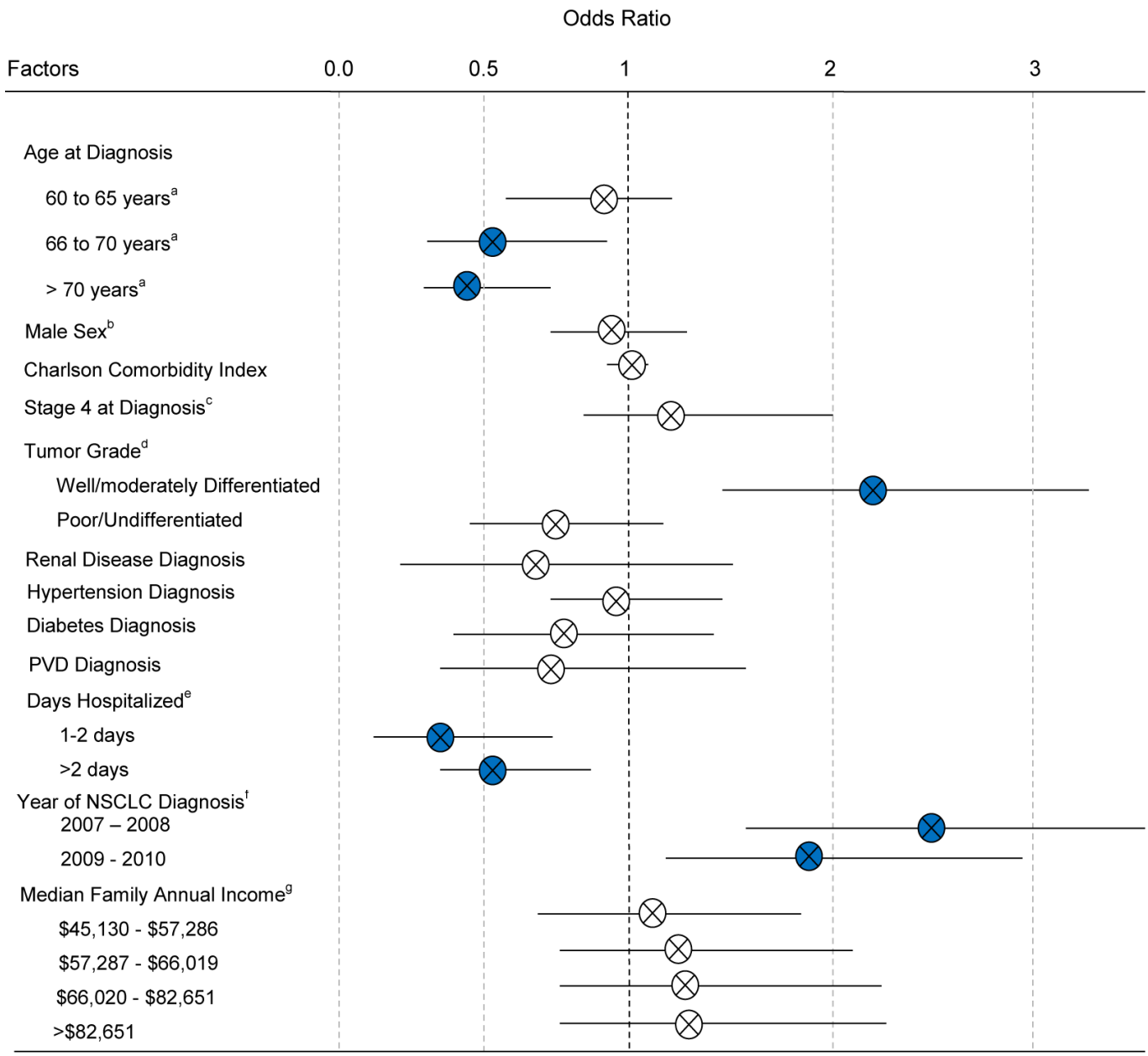
## Discussion

We utilized a large cohort of patients with non-squamous NSCLC from four distinct geographic areas. Our analysis illustrates that patients who received CPB were younger, diagnosed with NSCLC in the later years of the study, and tended to have a well or moderately differentiated tumor. Conversely, patients who received CP alone appeared to be higher risk patients as they were older and more likely to have had a recent hospitalization. To our knowledge, this is the first study to examine patient and tumor characteristics associated with carboplatin-paxlitaxol-bevacizumab treatment of advanced, non-squamous NSCLC.

That older pateints were less likely to receive CPB is not surprising as CPB is not associated with better survival in senior patients with advanced NSCLC [20, 21]. Similarly, that higher risk patients were less likely to receive CPB may be related to their performance status (PS) as Sandler and colleagues in their seminal trial of bevacizumab in NSCLC excluded patients with an ECOG PS>1 or the oncologist's perception of likelihood of side effects and complications [9]. While PS is generally not recorded outside the clinical trial setting nor as part of routine cancer care, recent hospitalization and older age have been noted as predictors of poor PS [22].

Our identification of tumor characteristics associated with CPB use in NSCLC is novel. Validated information on biomarkers that are predictive of bevacizumab's effectiveness has been lacking until recently [23]. Patients with tumors that invaded or were in close proximity to major blood vessels were excluded from Phase II and

**Figure 1** Factors independently associated with receiving bevacizumab.




Factors highlighted with blue circles are statistically significantly associated with receiving bevacizumab
[a] Compared to < 60 years
[b] Compared to females
[c] Compared to Stage 3b at diagnosis
[d] Compared to non-small cell carcinoma morphology
[e] Compared to zero days hospitalized
[f] Compared to 2005 - 2006
[g] Compared to <$45130
PVD - peripheral vascular disease; NSCLC – non-small cell lung cancer; c-statistic=0.724

III trials (so as to decrease the risk of hemorrhage) of bevacizumab use in NSCLC [24]. Patients with poor/undifferentiated and unknown tumor grades in our cohort were less likely to receive CPB suggesting that oncologists may have deemed these patients at too high risk for hemorrhage or other toxicities and, thus, did not prescribe CPB for these patients.

Bevacizumab was one of the first clinically-mature antiangiogenesis agents to be manufactured. In our analysis, we found that CPB uptake started modestly with 16% of study patients receiving it in 2005 (prior to FDA approval for advanced NSCLC). The rate of CPB use in our cohort peaked in 2008 (at 18%) and then moderated. Though the exact reason for this moderation

is uncertain, it may be due to a combination of reasons, including bevacizumab's high cost for only a small two-month life extension, continuing discoveries regarding bevacizumab's safety, patient preference, or increasing clinician-level experience with bevacizumab toxicity.

While clinical trials showed that the addition of bevacizumab provided an approximately two-month increase in the median progression-free survival in patients with NSCLC versus standard chemotherapy [9, 20], its price, which can reach $100,000 per patient [25], may have limited its use. In June 2008, the United Kingdom's National Institute for Clinical Health and Excellence (NICE) stated its inability to recommend the use of bevacizumab in conjunction with platinum-based chemotherapy for advanced NSCLC due to having not received appropriate evidence from the manufacturer or sponsor [26]. Thomas Reuters reported that Roche, the co-manufacturer of bevacizumab, chose not to provide clinical and cost-effectiveness data to NICE as they suspected that their data would not meet NICE's cost-effectiveness threshold [27]. Laboratory and clinical studies further identified bevacizumab's risk for adverse effects, such as thrombotic glomerular injury in the kidneys [28, 29]. Furthermore, recent information from Correale and colleagues has identified that treatment adverse events appear to be linked to increasing bevacizumab dose [10, 11]. As information on bevacizumab's limited effectiveness, high cost, and adverse effects became better established, oncologists and patients with NSCLC may have become more reserved in their consideration of bevacizumab therapy.

We identified no studies that examined the uptake and use of bevacizumab in lung cancer. However, studies that have examined factors associated with the use of bevacizumab in colon cancer [12, 30] have noted that female sex and younger age were independently associated with receiving CPB [12]. Conversely, we did not identify an association with sex and CPB use as females were evenly distributed between those patients who did and did not recieive CPB. Interestingly, recent comparative effectiveness results from Zhu and colleagues suggest a survival benefit with CPB treatment in males with NSCLC [20]. However, Neugut and colleagues reported that no factors were independently associated with receiving CPB in colon cancer [30].

Patients with a diagnosis of hypertension, peripheral vascular disease, and renal disease were less likely to receive CPB in our bivariate analyses. However, these factors were not found to be associated with CPB use after accounting for other factors in multivariate analyses. Hypertension is a commonly noted adverse effect of bevacizumab [7]. Nevertheless, other factors (e.g., age, tumor characteristics) may have played a more prominent role in treatment choice, particularly in light of the numerous anti-hypertensive medications that are available for hypertension management. Similarly, comorbidity burden was not found to be asscociated independently with CPB use even though it has been reported to be a strong predictor of PS [21]. Despite the high cost of CPB, we did not find that greater family income or insurance type were associated independently with CPB use. While this is encouraging, it may be related to our cohort being made up solely of insured patients.

The strengths of this study include a large multi-site cohort of patients with NSCLC, validated information on chemotherapy treatment, manually-chart abstracted tumor registry data to characterize patients' tumors, and clinical medical record-derived information. Nevertheless, our study had limitations. We were unable to identify PS at the time chemotherapy was initiated. We did examine factors that are predictors of PS; however, they are not perfect proxies for PS [22]. We did not collect information on other factors that may be related to CPB use (e.g., number of primary sites involved, metastatic site involvement, over-the-counter non-steroidal anti-inflammatory agents use, anticoagulant use, smoking status at diagnosis, history of hemoptysis) since we did not perform chart reviews or conduct patient interviews. While recent evidence suggests that systemic inflammatory status is useful to predict bevacizumab benefit in NSCLC [23], we did not have access to myeloid-derived inflammatory cells' laboratory values to assess their role in CPB use in our population. On the other hand, we assessed a substantial number of factors that are available in electronic medical records for their relationship to CPB use. In addition, our study was limited to patients receiving oncology care in the U.S. Health systems outside the U.S. may have different experiences with CPB uptake. Nevertheless, our data provide important information on the uptake and use of CPB in the oncology community at-large.

## Conclusions

Identifying factors that may play a role when oncologists consider using bevacizumab as a treatment option for NSCLC provide an understanding of bevacizumab's use in community settings. We found strong uptake of bevacizumab in a cohort of patients with advanced NSCLC, even prior to its FDA approval for this condition. While bevacizumab use increased in the first years of our study, it then moderated. We found that increasing age and prior hospitalization (i.e., patients at higher risk of adverse effects) were associated independently with lower likelihood of bevacizumab while specific tumor characteristics (i.e., well/moderately differentitated tumor grade) were associated independently with higher likelihood of bevacizumab use. These findings suggest that bevacizumab use in the community is guided by clinical trial results. By providing baseline knowledge of NSCLC care, these findings can guide future studies of evidence-based non-squamous NSCLC care in the community.

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### Conflict of interest

None of the authors report any potential or actual conflicts of interest.

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