Gender disparities in lung cancer survival from an enriched Florida population-based cancer registry☆

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A R T I C L E   I N F O

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A B S T R A C T

Background: Previous studies have revealed gender disparities in lung cancer survivorship, but comprehensive inclusion of clinical/individual variables which affect outcomes is underreported. We utilized the Florida Data Cancer System (FCDS) to examine associations between gender and lung cancer survivorship while controlling for prognostic variables on a large population-based scale.

Methods: A retrospective cohort analysis utilizing the FCDS, linked to Florida Agency for Health Care Administra tion and US Census Bureau tracts for patients diagnosed with primary lung cancer (n = 165,465) from 1996 to 2007. Primary outcome measures included median survival time and mortality. Multivariable Cox regression models, independent sample T-tests, and descriptive statistics were utilized with significance defined as p < 0.05.

Results: 165,465 cases were analyzed revealing 44.3% females and 55.7% males. The majority of patients were white/Caucasian, males, middle-high socioeconomic status, lived in urban areas, and geriatric age. Females had longer median survival compared to males (9.6 vs 7.1 months). Multivariable analyses showed that women had better survival after controlling for sociodemographic, clinical, and comorbidity covariates. Males had higher risk of mortality than females (aHR = 1.17, 95%CI 1.14–1.19, p < 0.01).

Conclusions: Individuals of higher socioeconomic status experienced greater survivorship compared to those of lower socioeconomic status. Women experienced significantly better survival for lung cancer at multiple time frames after controlling for covariates compared to men. Interventions aimed at public education and access to high-quality healthcare are needed to ameliorate socioeconomic and gender-based disparities in lung cancer survivorship. Future studies should investigate gender differences in lung cancer while incorporating individual socioeconomic status and treatment received.

1. Introduction

Cancers of the lung are among the most prevalent malignancies in the United States (US) with adenocarcinoma representing the most common type of lung carcinoma [1–3]. The American Cancer Society estimates that 234,030 new cases of lung cancer occurred in the US in 2018 and 228,150 cases in 2019, leading to 154,050 deaths and 142,670 deaths, respectively [1,2,4]. An interesting disparity reported in previous literature regarding lung cancer is the better survivorship of female patients compared to males [5–11]. According to the National Cancer Institute’s Surveillance, Epidemiology, and End Results (NCI-SEER) program, there are 63.5 deaths per 100,000 men compared to 39.2 deaths per 100,000 women of all race/ethnicity groups for cancer of the lung and bronchus, with women diagnosed with small cell lung cancer (SCLC) experiencing a particularly prominent survival advantage [5]. Previous studies utilizing NCI-SEER data from 1975 to 1999 have indicated that although women have a greater incidence of lung cancer compared to men, they also experience higher stage-specific survival

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rates than male counterparts [6–8]. Univariate and multivariable analyses have demonstrated that female gender is associated with improved lung cancer survivorship, with females diagnosed with non-small cell lung cancer (NSCLC) experiencing greater survivorship compared to males in a phase III Eastern Cooperative Oncology Group (ECOG) trial [8–10].

However, there are numerous influences besides gender which may play a role in the increased survivorship of female patients compared to males including age and smoking history, among other variables [11]. In particular, greater exploration of the impact of relevant socioeconomic and individual factors such as patient race/ethnicity and insurance status has the potential to further explain why female lung cancer patients may experience greater survivorship compared to male counterparts. Therefore, this review aims to utilize the 1996–2017 Florida Cancer Data System (FCDS) registry data enhanced with Florida Agency for Health Care Administration (FL-AHCA) information to assess for potential economic inequalities in survivorship for female lung cancer patients by accounting for patient race/ethnicity, comorbidities, smoking status, insurance status, marital status, hospital characteristics, treatment type, and carcinoma grade with the hypothesis that female lung cancer survivorship is associated with a higher overall socioeconomic status.

2. Material and methods

A retrospective cohort analysis was performed utilizing data from the US Census Bureau, FCDS and FL-AHCA regarding lung cancer incidence and inpatient outpatient procedures to treat lung carcinoma from 1996 to 2007. This report was conducted in line with the STROCSS criteria [12]. The FCDS is a statewide cancer registry funded by the Florida Department of Health (FL-DOH) and the Centers for Disease Control and Prevention’s National Program of Cancer Registries (CDC-NPCR) which receives annual information from 252 hospitals, 127 radiation therapy centers, 453 surgery centers, and 3360 physician offices in the state of Florida [13]. We report data in accordance with research agreements with FCDS and utilized one cohort of patients according to FCDS patient inclusion criteria: adult patients who were at least 18 years of age, diagnosed with primary lung cancer, and resided in the state of Florida when diagnosed [13]. Matches between the FCDS and FL-AHCA data were confirmed with the patient’s date of birth and gender. Patients were not involved in study design of this analysis.

Survival time was defined as the elapsed time from lung cancer diagnosis to death or last follow-up for alive patients. Patient residency and the year 2000 US Census Bureau information was utilized to approximate the patient’s neighborhood socioeconomic status (NSES), defined as the percentage of households living below the federal poverty line: lowest (≥20%), middle-low (≥10% and <20%), middle-high (≥5% and <10%), and highest (<5%). NSES was utilized as previous studies have indicated that this measure yielded similar results to more complex composite scores, with poverty as an ideal indicator because this metric produces similar results to multivariable indices incorporating multiple contributing factors to socioeconomic status such as education and total asset possession [14,15]. Additionally, NSES was utilized over individual socioeconomic status information on the basis that individual SES data was not available in our dataset as well as to account for geographical area-based socioeconomic differences which may have implicit influences on patient health [16].

Multivariable Cox regression models were fitted by including variables of patient race/ethnicity, smoking status, insurance, marital status, hospital characteristics, treatment, cancer stage, cancer grade, and comorbidities in order to examine overall survivorship as the primary clinical outcome. Adjusted hazard ratios (aHRs), corresponding 95% confidence intervals (95% CI), and independent sample T-tests were calculated with significance defined as \( p < 0.05 \). Data management and statistical analyses were performed using SAS v9.4 statistical software for Windows (SAS Institute Inc., Cary, NC, USA). This study was conducted in compliance with ethical principles, was reviewed and approved by the FL-DOH and University of Miami institutional review boards. The Research Registry UIN of this study is: researchregistry6293. [17].

3. Results

3.1. Patient characteristics

Our sample initially included information on 179,630 adults ≥18 years of age in the state of Florida diagnosed with SCLC or NSCLC carcinoma-in-situ or higher staging from 1996 to 2007. Of this total, 14,165 patients were excluded on the basis of missing information regarding gender, race/ethnicity, NSES, SEER stage, or survival time, yielding 165,465 patients included in the final dataset. As seen in Table 1, the dataset was comprised of 73,276 (44.3%) female and 92,189 male (55.7%) patients. The majority of patients were white (n = 152,880; 92.4%), non-Hispanic (n = 155,402; 93.9%), most commonly middle-high NSES (n = 61,840; 37.4%), possessed Medicare insurance (55.6%), and were married (53.2%). Most patients lived in urban areas (93.0%), and were treated at low-volume hospitals (64.4%) and non-teaching hospital hospitals (92.6%). The majority of patients had a current or past history of smoking (73.3%). Females comprised a larger proportion of the never-smoker group (n = 8677; 11.8%) compared to males (n = 5666; 6.1%). Both male and female patient populations were comprised of primarily geriatric individuals (age ≥ 65) [Table 1]. There was no significant difference in mean age at time of cancer diagnosis between males and females (70.1 years vs. 69.5 years, \( p > 0.05 \)). In addition, the median age at diagnosis was similar for both genders at 71.0 years (male interquartile range [IQR] = 15 years, female IQR = 14 years).

3.2. Clinical and pathological characteristics

Lung carcinomas were most commonly graded as poorly differentiated (23.0%), with more males (24.0%) than females (21.7%) being diagnosed with this grade [Table 2]. The predominant histological type of the tumors was adenocarcinoma (27.7%), comprising 25.0% of lung malignancies in males and 31.0% of lung malignancies in females. More male patients (20.6%) were diagnosed with squamous cell cancer (SCC)/combine complex than females (14.2%). The most common treatment received by patients was radiotherapy (39.3%), followed by chemotherapy (31.6%), and surgery (21.6%).

3.3. Association between survival and gender

Median survival time (MST) increased accordingly by NSES level [Table 3]. A longer MST was observed for female patients than male patients (9.6 months vs. 7.1 months) (\( p < 0.001 \)). Survival rates were also higher in females compared to male patients at 1, 3, and 5 years after diagnosis as demonstrated in Fig. 1 (\( p < 0.001 \)). Multivariable analyses demonstrated that women had better survival than men after controlling for race/ethnicity, NSES, and other sociodemographic/clinical/comorbidity covariates [Table 4 & Fig. 1]. In our fully adjusted model, males had higher risk of mortality than females (aHR = 1.17, 95% CI: 1.14–1.19, \( p < 0.01 \)). No significant interactions between gender, race/ethnicity, and NSES were detected in fully adjusted models.

4. Discussion

It was found that the majority of adult patients who were diagnosed with primary lung carcinoma in the state of Florida from 1996 to 2007 where white/Caucasian, males, middle-high NSES, lived in urban areas, and were of a geriatric age. Poorly differentiated adenocarcinoma was the most common type of lung malignancy diagnosed, with the most frequently received treatments being radiotherapy, followed by
Our study indicates that when controlling for known prognostic factors such as patient medical comorbidities and smoking status, NSES exerted a significant impact on lung cancer survivorship, with both male and female patients of a higher NSES experiencing greater survivorship compared to more socioeconomically disadvantaged counterparts. These findings are supported by previous literature and may be due to the influence of multiple factors including a greater ability of higher NSES patients to access and receive high quality care and ancillary services throughout the duration of their treatment, as well as a greater amount of health literacy and knowledge regarding lung cancer diagnoses and treatment [18-20]. Critical to the discussion of socioeconomic status on the survivorship of lung cancer patients is the type of insurance possessed by patients. Previous studies have shown that higher quality insurance is associated with greater detection and treatment complications, hospital duration of stay, and mortality of lung carcinoma patients, the benefit of possessing comprehensive insurance by higher-NSES individuals may stem from early disease detection and management more…

### Table 1
Demographic characteristics of lung cancer by gender.

| Variable               | All patients N | Female N | Male N | Female % | Male % |
|------------------------|---------------|----------|--------|----------|--------|
| All patients           | 165,465       | 100.0    | 73,276 | 100.0    | 92,189 | 100.0 |
| Race                   |               |          |        |          |        |       |
| White                  | 152,880       | 92.4     | 68,562 | 93.6     | 84,318 | 91.5  |
| Black                  | 11,462        | 6.9      | 4165   | 5.7      | 7297   | 7.9   |
| NA                     | 57            | 0.0      | 16.0   | 0.0      | 41.0   | 4.4   |
| Asian                  | 526           | 0.3      | 275.4  | 0.4      | 251.0  | 0.3   |
| PI                     | 45            | 0.0      | 21.0   | 0.0      | 22.0   | 0.0   |
| AIP                    | 115           | 0.1      | 51.0   | 0.1      | 64.1   | 0.1   |
| Other                  | 380           | 0.2      | 184.3  | 0.3      | 196.2  | 0.2   |
| Hispanic Origin        |               |          |        |          |        |       |
| Non-Hispanic           | 155,402       | 93.9     | 69,770 | 95.2     | 85,632 | 92.9  |
| Hispanic               | 10,063        | 6.1      | 3506   | 4.8      | 6557   | 7.1   |

### Table 2
Pathological and clinical characteristics.

| Variable               | All patients N | Female N | Male N | Female % | Male % |
|------------------------|---------------|----------|--------|----------|--------|
| All                     | 165,465       | 100.0    | 73,276 | 100.0    | 92,189 | 100.0 |
| Co-morbidity            |               |          |        |          |        |       |
| None                   | 13,699        | 8.3      | 5337   | 7.3      | 8362   | 9.1   |
| 1–2                    | 5910          | 3.6      | 2662   | 3.6      | 3248   | 3.5   |
| 3–4                    | 12,702        | 7.7      | 6015   | 8.2      | 6687   | 7.3   |
| ≥5                     | 133,154       | 80.5     | 59,262 | 80.9     | 73,892 | 80.2  |
| SEER Stage              |               |          |        |          |        |       |
| Localized              | 27,347        | 16.5     | 13,621 | 18.6     | 13,726 | 14.9  |
| Regional, direct       | 19,960        | 12.1     | 8699   | 11.9     | 11,261 | 12.2  |
| extension + lymph      |               |          |        |          |        |       |
| nodes                  | 14,142        | 8.5      | 6365   | 8.7      | 7777   | 8.4   |
| Regional, lymph only   | 66,028        | 39.9     | 28,354 | 38.7     | 37,674 | 40.9  |
| Unknown/Unstaged       | 37,988        | 23.0     | 16,237 | 22.2     | 21,751 | 23.6  |
| Types of lung cancer   |               |          |        |          |        |       |
| NSCLC                  | 20,593        | 12.4     | 9874   | 13.5     | 10,719 | 11.6  |
| SCLC                   | 98,541        | 59.6     | 43,338 | 59.1     | 55,203 | 59.5  |
| Other                  | 46,331        | 28.0     | 20,074 | 27.4     | 26,257 | 28.5  |
| Grade                  |               |          |        |          |        |       |
| Undifferentiated       | 12,125        | 7.3      | 5457   | 7.4      | 6668   | 7.2   |
| Poorly-differentiated  | 38,048        | 23.0     | 15,884 | 21.7     | 22,164 | 24.0  |
| Moderately-            | 18,916        | 11.4     | 8570   | 11.7     | 10,346 | 11.2  |
| differentiated         | 90,882        | 54.7     | 40,315 | 55.2     | 50,567 | 55.6  |
| Well-differentiated    | 14,142        | 8.5      | 6365   | 8.7      | 7777   | 8.4   |
| Unknown/not stated     | 37,988        | 23.0     | 16,237 | 22.2     | 21,751 | 23.6  |
| Regional Nodes         |               |          |        |          |        |       |
| Positive               | 20,141        | 12.2     | 9810   | 13.4     | 10,331 | 11.2  |
| No                     | 11,890        | 7.2      | 5367   | 7.3      | 6523   | 7.1   |
| Unknown                | 133,434       | 80.6     | 58,099 | 79.3     | 75,335 | 81.7  |
| Histologic Type        |               |          |        |          |        |       |
| Adenocarcinoma         | 45,808        | 27.7     | 22,750 | 31.0     | 23,058 | 25.0  |
| Squamous/combine       | 29,336        | 17.7     | 10,382 | 14.2     | 18,954 | 20.6  |
| complex                |               |          |        |          |        |       |
| Neuroendocrine         | 2580          | 1.6      | 1523   | 2.1      | 1057   | 1.1   |
| Large cell             | 7936          | 4.8      | 3284   | 4.5      | 4652   | 5.0   |
| Other                  | 15,424        | 9.3      | 6690   | 9.1      | 8734   | 9.5   |
| Unknown                | 64,381        | 38.9     | 28,647 | 39.1     | 35,734 | 38.8  |
| Chemotherapy           |               |          |        |          |        |       |
| No                     | 95,994        | 58.0     | 43,368 | 59.2     | 52,626 | 57.1  |
| Yes                    | 52,305        | 31.6     | 22,954 | 31.3     | 29,351 | 31.8  |
| Unknown                | 17,166        | 10.4     | 6954   | 9.5      | 10,212 | 11.1  |
| Radiation Therapy      |               |          |        |          |        |       |
| No                     | 87,238        | 52.7     | 40,605 | 55.4     | 46,633 | 50.6  |
| Yes                    | 65,028        | 39.3     | 27,424 | 37.4     | 37,604 | 40.9  |
| Unknown                | 13,199        | 8.0      | 5247   | 7.2      | 7952   | 8.6   |
| Surgery                |               |          |        |          |        |       |
| No                     | 117,283       | 70.9     | 51,254 | 69.9     | 66,029 | 71.6  |
| Yes                    | 35,725        | 21.6     | 17,087 | 23.3     | 18,638 | 20.2  |
| Unknown                | 12,457        | 7.5      | 4935   | 6.7      | 7522   | 8.2   |

SCLC = small cell lung cancer, NSCLC = non-small cell lung cancer.
than the modality or duration of treatment received [21,22]. The implications of these findings are that socioeconomically disadvantaged cancer patients may benefit from greater implementation of interventions aimed at improving their access to high quality healthcare, as well as additional efforts aimed at improving education regarding the importance of screening and early symptoms to ameliorate any disparity conferred by unfavorable insurance coverage [23,24].

However, our findings also indicate that after controlling for relevant covariates, women of higher NSES have a significantly higher lung cancer survival rate compared to male counterparts at multiple time frames post-diagnosis and further substantiates previous literature which have implicated a gender disparity in lung cancer survivorship between women and men [25,26]. The evaluation of both intrinsic and extrinsic confounders is necessary in order to further delineate these gender disparities. Our findings that women comprised the majority of patients who have never used tobacco products and developed adenocarcinoma is supported by previous literature and highlights a possible predilection for this gender to develop adenocarcinoma in comparison to males, possibly due to the greater influence of endogenous and exogenous estrogens and progestins, as well as a greater frequency of mutations in the tumor suppressor gene p53 and proto-oncogene K-RAS [27–29]. This greater risk for women to develop lung carcinoma is compounded when the influence of tobacco is introduced [29]. However, the higher survivorship observed for female patients of higher-NSES in our study may indicate that although the incidence of lung cancer is higher among women, an increased willingness to seek medical attention and utilize necessary services aimed at improving morbidity and mortality may be a considerable influence in these individuals experiencing greater survivorship [30].

Table 3
Median and survival rates, n = 165,465.

|                | Median survival (months) | Survival rates (%) at time (years) after diagnosis |
|----------------|--------------------------|-----------------------------------------------|
|                |                          | 1 year | 3 years | 5 years |
| Overall        | 8.1                      | 39.9   | 18.2    | 12.0    |
| Gender         |                          |        |         |         |
| Female         | 9.6                      | 44.4a  | 21.9a   | 15.0a   |
| Male           | 7.1                      | 36.4a  | 15.3a   | 9.7a    |
| Raceb          |                          |        |         |         |
| White          | 8.1                      | 40.2   | 18.5    | 12.3    |
| Black          | 7.0                      | 36.2   | 14.4    | 8.8     |
| NA             | 4.8                      | 36.5   | 9.8     | 4.9     |
| Asian          | 10.8                     | 45.8   | 20.9    | 12.3    |
| PI             | 12.9                     | 51.3   | 21.6    | 10.3    |
| AIP            | 11.0                     | 48.0   | 21.5    | 12.4    |
| Other          | 8.9                      | 44.6   | 18.4    | 13.0    |
| Hispanic Origin|                          |        |         |         |
| No             | 8.0                      | 39.9   | 18.2    | 12.0    |
| Yes            | 8.4                      | 40.5   | 17.9    | 12.0    |
| NSES           |                          |        |         |         |
| Lowest         | 6.5                      | 34.8   | 13.7    | 8.6     |
| Middle-low     | 7.6                      | 38.4   | 16.8    | 11.0    |
| Middle-high    | 8.5                      | 41.2   | 19.4    | 12.8    |
| Highest        | 9.6                      | 44.0   | 21.7    | 15.0    |

* Females possessed significantly higher survival rates than males at the 1, 3, and 5 year time points after diagnosis (p < 0.001).

b Race abbreviations are as follows: NA=Native American, PI=Pacific Islander, AIP=Asian Indian or Pakistani; NSES: Neighborhood Socioeconomic Status; Lowest (≥20%); Middle-Low (≥10% and <20%); Middle-High (≥5% and <10%); Highest (<5%).

Fig. 1. Survival Plots (a) Gender (b) Race (c) Hispanic or non-Hispanic (d) NSES: L = Lowest (≥20%), ML = Middle-Low (≥10% and <20%), MH = Middle-High (≥5% and <10%), and H = highest (<5%) NSES.
None of the models included interaction terms. There are no significant interactions between gender and race, ethnicity, and NSES respectively in model 5.  

Table 4
Cox Regression Models for Overall Survival Clustered Hospital, n = 165,465.

| Prognostic factors | Category | Model 1 | Model 2 |
|-------------------|----------|---------|---------|
|                   |          | HR (95% CI) | P value | aHR (95% CI) | P value |
| Gender            | Female   | 1.00 |         | 1.00 |         |
|                   | Male     | 1.23 | <0.001  | 1.17 | <0.001  |
|                   |          | (1.22,1.25) | (1.14,1.19) |         |         |
| Race              | White    | 1.00 |         | 1.00 |         |
|                   | Black    | 1.12 | <0.001  | 0.98 | 0.314   |
|                   |          | (1.10,1.15) | (0.95,1.02) |         |         |
|                   | NA       | 1.39 | 0.024   | 1.17 | 0.196   |
|                   |          | (1.04,1.85) | (0.92,1.50) |         |         |
|                   | Asian    | 0.88 | 0.012   | 0.97 | 0.010   |
|                   |          | (0.80,0.97) | (0.79,0.97) |         |         |
|                   | PI       | 0.83 | 0.268   | 1.07 | 0.342   |
|                   |          | (0.59,1.16) | (0.50,1.12) |         |         |
|                   | AIP      | 0.86 | 0.168   | 0.97 | 0.727   |
|                   |          | (0.70,1.06) | (0.80,1.17) |         |         |
|                   | Other    | 0.95 | 0.386   | 0.94 | 0.342   |
|                   |          | (0.84,1.07) | (0.83,1.07) |         |         |
| Hispanic          | No       | 1.00 |         | 1.00 |         |
|                   | Yes      | 0.99 | 0.205   | 0.94 | 0.015   |
|                   |          | (0.96,1.01) | (0.89,0.99) |         |         |
| NSES              | Lowest   | 1.00 |         | 1.00 |         |
|                   | Middle-Low | 0.90 | <0.001  | 0.96 | 0.001   |
|                   |          | (0.89,0.92) | (0.93,0.98) |         |         |
|                   | Middle-High | 0.84 | <0.001  | 0.92 | <0.001  |
|                   |          | (0.82,0.85) | (0.89,0.94) |         |         |
|                   | Highest  | 0.77 | <0.001  | 0.98 | <0.001  |
|                   |          | (0.76,0.79) | (0.84,0.91) |         |         |

Model 1: Univariate.
Model 2: Multivariate - gender + Race/Ethnicity/SES + demographics + clinical + comorbidities (use individual variables).

Our study design offers several advantages compared to prior studies. While several previous investigations have described gender-related differences in lung cancer survivorship, our analysis considers the impact of individual, institutional, and systematic factors on lung cancer survivorship. The findings suggest that higher NSES is associated with improved survival outcomes, which is consistent with previous literature. However, given the multifactorial nature of individual, institutional, and systematic influences on lung cancer survivorship, we recommend future studies to conduct additional research in this area.

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5. Conclusion
Individuals of higher NSES diagnosed with primary lung cancer in the state of Florida from 1996 to 2007 had a significantly higher survivorship at multiple time points compared to socioeconomically disadvantaged populations, highlighting socioeconomic disparities in survivorship. Additionally, women diagnosed with primary lung cancer experienced significantly higher survivorship compared to men, highlighting a potential gender disparity. This data accentuates the importance of focusing future preventative efforts on public education and the access to prompt healthcare in hopes of narrowing survival disparities in lung cancer.

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Ethical approval

This study was conducted in compliance with ethical principles, was reviewed and approved by the FL-Department of Health and University of Miami institutional review boards.

Trial registry number

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Author contribution

Study design and conception: MB, AE, TS.
Data acquisition, collection, analysis and interpretation: TS, MB, WZ, MS, AE.
Manuscript preparation: AE, MB, WZ, MS, MM, YG, DD, LB, TS.
Critical revision of manuscript: AE, MB, WZ, MS, MM, YG, DD, LB, TS.
