Archives of Pharmaceutical Sciences Ain Shams University 2024; Vol. 8(2): 328-339

OPEN ACCESS

Clinical Pharmacy

Original Article

Prognostic Factors for Platinum-Chemotherapy Response and Survival Outcomes in Patients with Advanced Stage Non-Small Cell Lung Cancer

Yara S. Abdelwahed[a*], Lamia M. El Wakeel[b], Ahmed A. Nagy[c], May A. Shawki[b]

[a]*Clinical Pharmacy Unit, Ain Shams Specialized Hospital, Cairo, Egypt*
[b]*Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*
[c]*Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt*

ABSTRACT

The majority of patients diagnosed with non-small cell lung cancer (NSCLC) present with the disease in an advanced stage, consequently experiencing a diminished overall survival rate. The influence of patients' characteristics on their response to treatment and survival rates remains ambiguous. The current study evaluated the effect of patients' prognostic variables on clinical outcomes of platinum-based chemotherapy in NSCLC patients. A total of seventy-five patients with stage IIIB–IV NSCLC were enrolled; baseline demographics and clinical data were collected. Patients received gemcitabine/platinum combination therapy. Response to treatment was evaluated using the RECIST Version 1.1. Patients were monitored over 18 months after the initiation of treatment to assess the overall survival outcomes and progression-free survival. The associations between the clinicopathological and treatment parameters and the patient's response and survival were analyzed. The current study found that poor response to treatment was associated with a performance status (PS) of 2 compared to PS 0-1 ($p = 0.005$) and receiving carboplatin rather than cisplatin doublets ($p= 0.004$). Poor survival was associated with being males ($p = 0.027$) and having stage IV of the disease ($p = 0.020$). Age at diagnosis, histopathology, smoking status, family history of cancer, and number of chemotherapy cycles were not associated with treatment outcomes. In conclusion, in terms of radiological response cisplatin was more effective than carboplatin and PS 0-1 was associated with better response among the study cohort. While males and stage IV disease were independently associated with shorter survival in patients with advanced stages of NSCLC receiving platinum.

Keywords: *Non-small cell lung cancer; prognosis; progression-free survival; overall survival; platinum chemotherapy.*

***Correspondence** | Yara S. Abdelwahed; Clinical Pharmacy Unit, Ain Shams Specialized Hospital, Cairo, Egypt. Email: yara.awes@gmail.com

Citation | Abdelwahed YS., El Wakeel LM., Nagy AA, Shawki MA, 2024. Prognostic Factors for Platinum-Chemotherapy Response and Survival Outcomes in Patients with Advanced Stage Non-Small Cell Lung Cancer. Arch Pharm Sci ASU 8(2): 328-339
DOI: 10.21608/aps.2024.308259.1185

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 01 August 2024. **Accepted** 29 August 2024.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

Lung cancer continues to rank among the most frequently encountered neoplastic diseases on a global scale, accounting for nearly 25% of all cancer-related mortalities **[1]**. The 2022 statistics from the Global Cancer Observatory (GLOBOCAN) highlighted that lung cancer accounted for 2.4 million newly diagnosed cases, representing 12.4% of the worldwide cancer incidence. Furthermore, it continued to be the leading cause of cancer-associated mortality, with an estimated 1.8 million deaths attributable to this malignancy **[2]**. Within the spectrum of lung cancer, NSCLC emerges as the most prevalent subtype, characterized by an average 5-year overall survival (OS) rate of approximately 24% **[1]**. Despite the advent of numerous diagnostic techniques aimed at early detection of

NSCLC, a considerable percentage of patients are identified at an advanced state and/or get postponed therapy **[1, 2]**. As a result, more than 50% of these cases are detected during the disease's advanced stages **[3]**.

In advanced-stage NSCLC, the prognosis is particularly poor. Patients diagnosed with stage IIIB or IV NSCLC typically have a median overall survival (OS) of less than 12 months, even with the administration of platinum-based chemotherapy, which remains the cornerstone of treatment. The 5-year survival rate for patients with stage IV NSCLC is estimated to be less than 5%, underscoring the aggressive nature of the disease and the limited effectiveness of current therapeutic options **[4, 5]**.

Platinum-based chemotherapy has been recognized as the primary therapeutic modality for patients diagnosed with advanced-stage NSCLC who demonstrate a satisfactory performance status **[3]**. Despite this, the response rate (RR) to such treatment remains suboptimal, estimated to range from merely 20% to 40%, thereby resulting in the majority of patients maintaining stable disease or experiencing disease progression **[6]**. Furthermore, numerous studies concerning patients with advanced NSCLC have consistently reported unsatisfactory OS outcomes **[7]**.

The clinical and demographic attributes of patients, in conjunction with treatment-related factors, have been proposed as influential determinants of RR and OS in those with advanced-stage NSCLC. Nevertheless, findings from earlier investigations have been inconsistent. For example, certain studies have demonstrated that non-smokers exhibit superior objective RR to chemotherapy compared to smokers **[8]**, whereas other studies have failed to confirm this association **[9, 10]**. Moreover, certain studies have delineated the histopathologic subtype of squamous cell carcinoma as a detrimental prognostic indicator relative to adenocarcinoma **[11, 12]**. Conversely, other research has reported no significant relationship between squamous versus non-squamous histology and survival outcomes in patients diagnosed with advanced-stage NSCLC **[13, 14]**. Besides, both cisplatin and carboplatin were reported to have comparable effectiveness, and there were no differences between both agents in RR and patient survival in advanced NSCLC in some trials **[15, 16]**. On the contrary, other trials reported that cisplatin has superior efficacy than carboplatin and is more beneficial in terms of RR of advanced NSCLC patients **[17, 18]**. Consequently, the degree to which the efficacy of treatment and the likelihood of survival in individuals with advanced lung cancer who are undergoing platinum-based chemotherapy as the standard care regimen is predicted by initial patient demographics and therapeutic factors remains ambiguous. Enhanced understanding in this domain would facilitate more informed clinical decision-making and enable more precise prognostication of treatment outcomes.

Thus, this research endeavor aimed to rigorously examine the variables impacting therapeutic response and survival outcomes in a cohort of Egyptian patients diagnosed with advanced NSCLC and subjected to platinum-based chemotherapy.

2. Materials and Methods

2.1. Study Design and Setting

An observational cohort study was performed in the Department of Clinical Oncology at Ain Shams University Hospitals, Cairo, Egypt, involving Egyptian patients diagnosed with advanced stage III/IV NSCLC who were scheduled to receive platinum-based chemotherapy.

2.2. Study Population

Patients presenting to the Clinical Oncology Department underwent a thorough eligibility assessment to ascertain their suitability for inclusion in the study. The criteria for inclusion encompassed the following: age of more than18 years, confirmed diagnosis of stage IIIB–IV NSCLC (unresectable stages), chemo-naive with planning to receive (cisplatin/carboplatin) and gemcitabine as the first-line treatment according to the current guidelines **[19]**, ECOG PS score ranges from 0 to 2 and normal kidney and liver function. Patients with central nervous system metastases or other primary cancer or patients refusing treatment were excluded from the study.

Informed consent was appropriately procured from every participant engaged in the study, and the Declaration of Helsinki's guiding principles were strictly followed throughout the investigation. Ethical approval was obtained from the Faculty of Pharmacy's ethical committee at Ain Shams University (204/2018).

2.3. Methods

Baseline patients' demographics, tumor characteristics, family history, comorbidities, ECOG PS score, and smoking status were collected at enrolment. The radiological response was assessed every 2 to 3 cycles. Assessment of treatment response was carried out following the RECIST version 1.1 **[20]**. The overall objective RR was determined by aggregating the number of patients achieving partial or complete responses. Patients were monitored for 18 months commencing from the initiation of chemotherapy to evaluate progression-free survival (PFS) and OS.

2.4. Statistical Analysis

The Statistical Package for Social Sciences (IBM SPSS) version 27 (SPSS Inc, Chicago, USA) facilitated the execution of all analytical processes. Proportions were used to delineate categorical variables, while continuous variables were expressed as means with S.D. The normality of continuous data was assessed using the Shapiro-Wilk test and Kolmogorov–Smirnov test, guiding the choice of parametric or non-parametric tests. Chi-square or Fisher's exact tests were used for categorical comparisons, while independent t-tests or Mann-Whitney U tests were applied for continuous data based on normality.

Survival analysis was performed using Kaplan–Meier estimates, and the Log-rank test was applied to assess variations in survival distributions across independent variables. An ordinal logistic regression model was attempted to adjust for confounders in assessing disease response, but it lacked goodness of fit ($p > 0.05$). Hence, the analysis was conducted using univariate methods, including Chi-square and Fisher's exact tests, to evaluate the associations between clinical variables and tumor response. Significance was set at p-values < 0.05, with all statistical values reported as two-sided.

3. Results

3.1. Baseline Characteristics

The median age of patients was 55 years. Males comprised 73.3% of patients and non-smokers represented 34.7%. On presentation, 55 patients had stage IV disease. The predominant histological subtype was lung adenocarcinoma, which constituted 74.7% of the participants. At the start of chemotherapy, thirty-two patients had ECOG PS of 2. Most of the platinum-based chemotherapy (60%) was cisplatin-based and most patients (66.7%) completed 4 or more cycles of chemotherapy.

3.2. Response Analysis

Association analysis between patients' response to treatment and their clinicopathological and treatment characteristics, revealed that patients who had better ECOG

performance status (PS: 0-1) had better response than those with PS: 2 (p= 0.005). In addition, patients who received a cisplatin-based chemotherapy regimen were associated with better responses rather than those who received carboplatin (p= 0.004). These data are represented in **Table 1**.

Table 1. Clinical factors affecting patients' response to platinum chemotherapy (n = 75)

Variable	PR n (%)	SD n (%)	PD n (%)	p-value
Gender				
Male	11 (20)	27 (49.1)	17 (30.9)	0.591[a]
Female	3 (15)	9 (45)	8 (40)	
Age				
<55	10 (25.6)	18 (46.2)	11 (28.2)	0.291[b]
≥55	4 (11.1)	18 (50)	14 (38.9)	
Smoking status				
Non-smoker	7 (26.9)	10 (38.5)	9 (34.6)	0.456
Ever smoker	7 (14.3)	26 (53.1)	16 (32.7)	
Family history				
No	8 (13.1)	30 (49.2)	23 (37.7)	0.074[a]
Yes	6 (42.9)	6 (42.9)	2 (14.2)	
Histological subtype				
Adenocarcinoma	9 (16.1)	30 (53.6)	17 (30.4)	
Squamous cell carcinoma	4 (30.8)	5 (38.5)	4 (30.7)	0.299[b]
Other	1 (16.7)	1 (16.7)	4 (66.6)	
ECOG PS				
0-1	11 (25.6)	24 (55.8)	8 (18.6)	0.005[b]
2	3 (9.4)	12 (37.5)	17 (53.1)	
Stage				
III	1 (5)	14 (70)	5 (25)	0.102[b]
IV	13 (23.6)	22 (40)	20 (36.4)	
Type of platinum				
Cisplatin	12 (26.7)	24 (53.3)	9 (20)	0.004[b]
Carboplatin	2 (6.7)	12 (40)	16 (53.3)	
Number of cycles				
<4	6 (20)	14 (46.7)	5 (33.3)	0.751[b]
≥4	8 (16)	22 (44)	20 (40)	

ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressed disease; SD, stable disease; PR, partial response; statistical tests; a. Chi-square test; b. Fisher's exact test. P-value < 0.05 is considered significant.

3.3. Survival Analysis

At the end of the study, disease progression occurred in 61 patients. No statistically significant difference in PFS time was observed across patients concerning any of their clinicopathological or treatment variables, as detailed in **Table 2.**

Analysis of OS revealed statistically significant differences in male and female patients, with the male gender being linked to shorter OS (p= 0.027). Staging of the disease was also correlated with OS, patients who had stage 4 of NSCLC showed shorter OS than patients having stage 3 of the disease (p= 0.020) as demonstrated in **Table 3**, **Fig.1,** and **Fig. 2**.

4. Discussion

In the management of lung cancer, prognosis is critically important for guiding patient care and informing clinical decision-making **[21]**. The treatment approach to advanced-stage lung cancer is based mainly on the precise staging of the disease, tumor histologic subtype, molecular testing for driver mutations, and patient's performance status alongside the availably and expected outcomes of treatments **[22]**.

Table 2. The effect of potential prognostic factors on progression-free survival (PFS) rates among study participants (n=75)

Factor	Total number n (%)	No. of events n (%) [a]	Median for survival time [b]	95% confidence interval	p-value [c]
Gender					
Male	55 (73.3)	49 (89.1)	5.82	(5.29-6.71)	0.667
Female	20 (26.7)	12 (60)	6.00	(5.23-7.38)	
Age					
<55	39 (52)	32 (82.1)	6.00	(5.22-6.77)	0.675
≥55	36 (48)	29 (80.6)	5.00	(4.01-5.98)	
Smoking status					
Non-smoker	26 (34.7)	21 (80.8)	6.69	(5.22-8.13)	0.376
Ever smoker	49 (65.3)	40 (81.6)	5.90	(4.87-6.94)	
Family history					
No	61 (81.3)	48 (78.7)	6.04	(5.09-6.98)	0.785
Yes	14 (18.7)	13 (92.9)	6.64	(4.74-8.55)	
Histological subtype					
Adenocarcinoma	56 (74.7)	48 (85.7)	6.20	(5.29-7.11)	0.906
Squamous cell carcinoma	13 (17.3)	8 (61.5)	6.56	(3.69-9.41)	
Other	6 (8)	5 (83.3)	5.20	(2.07-8.32)	
ECOG PS					
0-1	43 (57.3)	39 (90.7)	6.11	(5.43-6.87)	0.190
2	32 (42.7)	22 (68.8)	6.48	(4.57-8.38)	
Stage III	20 (26.7)	16 (80)	6.01	(5.09-6.91)	
IV	55 (73.3)	45 (81.8)	5.00	(4.25-5.75)	0.893
Type of platinum					
Cisplatin	45 (60)	39 (86.7)	6.01	(5.26-6.74)	0.942
Carboplatin	30 (40)	22 (73.3)	5.02	(3.41-6.61)	

ECOG PS; Eastern Cooperative Oncology Group performance status. [A] Raw percentage from the total number of patients in each factor.[b] Estimation was limited to the largest survival time if it was censored.[c] *p* value was computed by Log-Rank test, $p < 0.05$ is statistically significant.

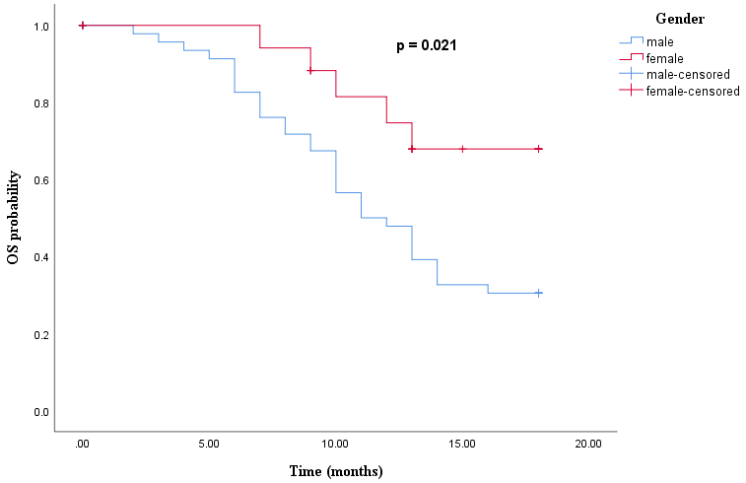

Fig. 1. Kaplan Meier curve showing the effect of patient's gender on overall Survival.

Table 3. The effect of potential prognostic factors on overall survival (OS) rates among study participants (n=75)

Factor	Total number n (%)	No. of events n (%) [a]	Median for survival time [b]	95% confidence interval	p-value [c]
Gender					
Male	55 (73.3)	32 (58.2)	11.00	(8.51-13.49)	0.021
Female	20 (26.7)	5 (25)	15.53	(13.67-17.39)	
Age <55	39 (52)	19(48.7)	13.58	(12.12-15.03)	0.998
≥55	36 (48)	18(50)	12.77	(11.16-14.71)	
Smoking status					
Non-smoker	26(34.7)	15(57.7)	12.00	(10.54-13.46)	0.249
Ever smoker	49(65.3)	22(44.9)	14.00	(9.35-17.11)	
Family history					
No	61(81.3)	29(47.5)	13.31	(11.32-14.67)	0.902
Yes	14 (18.7)	8(57.1)	13.07	(10.54-15.61)	
Histological subtype					
Adenocarcinoma	56 (74.7)	28(50)	13.17	(11.83-14.52)	0.237
Squamous cell carcinoma	13 (17.3)	4(30.8)	13.89	(10.43-17.35)	
Other	6 (8)	5(83.3)	11.60	(9.89-13.31)	
ECOG PS					
0-1	43 (57.3)	22(51.2)	13.50	(12.11-14.89)	0.718
2	32 (42.7)	15(46.9)	12.41	(10.32-14.51)	
Stage III	20 (26.7)	6 (30)	15.14	(13.26-17.02)	0.045
IV	55 (73.3)	31 (56.4)	11.05	(9.47-12.63)	
Type of platinum					
Cisplatin	45 (60)	25(55.6)	12.00	(9.79-14.21)	0.142
Carboplatin	30 (40)	12(40)	16.00	(12.48-16.10)	

ECOG PS; Eastern Cooperative Oncology Group performance status. [a] Raw percentage from number of patients in each factor. [b] Estimation was limited to the largest survival time if it was censored.[c] *p* value was computed by Log-Rank test, $p < 0.05$ is statistically significant.

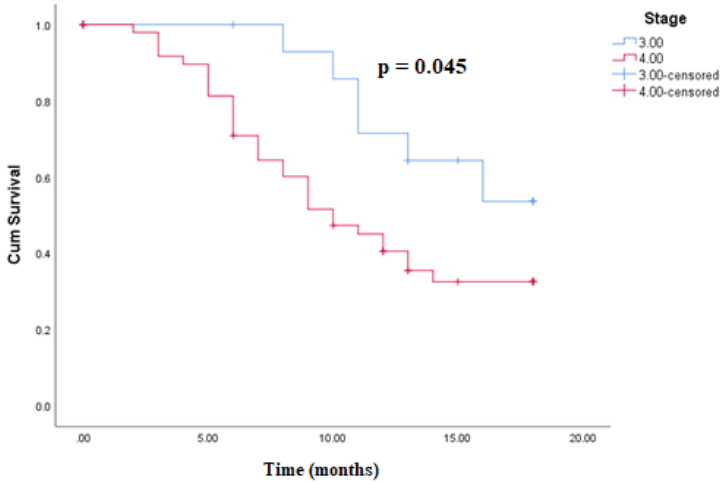

Fig. 2. Kaplan Meier curve showing the effect of cancer stage on patient's overall survival.

Hence, the scrutiny of prognostic factors, which involves the intricate linkage of baseline clinical and treatment covariables to resultant outcomes, serves as a pivotal endeavor that substantially enriches the framework of clinical research. However, most of the previously conducted studies were retrospective and focused mainly on investigating factors affecting survival more than factors affecting response to treatment.

In this hospital-based cohort study, eight potential prognostic factors were analyzed and evaluated for correlations to response and survival of stage III-IV NSCLC patients receiving first-line platinum-based protocols. Diverging from other research that investigated patients with advanced-stage NSCLC who received platinum-based chemotherapy, the current study reported a lower objective RR to chemotherapy. Specifically, the ORR observed in this study was 19%, whereas a British study reported a rate of 36%, and a Japanese study noted an ORR of 27% **[23, 24]**, despite comparable distributions of sex, age, and tumor histopathology. Additionally, at least 50% of the study population remained alive 12 months post-chemotherapy initiation, aligning with findings from previous research in the Middle East and Africa (MEA) **[25]**, but falling short of rates observed in global cohorts **[26]**. This variation may be ascribed to the restricted access to innovative pharmaceuticals and targeted therapies within Egypt and other developing nations. As a result, it becomes imperative for the Egyptian healthcare system to emphasize the analysis of clinical and pathological prognostic factors to improve patient management and efficiently allocate resources.

It is well-established that lung cancer prevalence exhibits a strong age-related dependency, with the risk of the disease escalating with advancing age, predominantly affecting individuals in the 65–74-year age bracket **[27]**. However, the link between treatment outcomes and age at diagnosis remains controversial. In the current investigation, no substantial association was discerned between age and treatment outcomes in NSCLC patients as defined by OS, RR, and PFS. This was following the results of a randomized phase III multicentre study conducted by the European Society for Medical Oncology in patients with metastatic/advanced NSCLC, in which subgroup analysis between elderly and non-elderly patients showed similar efficacy of first-line gemcitabine + carboplatin in terms of OS, RR, and time to progression **[28]**. Similarly, in the more recent Indian study, patients' age at diagnosis was reported not to be associated with response or survival outcomes of advanced NSCLC patients receiving platinum therapy **[8]**. Nevertheless, an analysis utilizing the Surveillance, Epidemiology, and End Results database, which encompassed NSCLC patients diagnosed between 2004 and 2013, identified age at diagnosis as a significant prognostic factor. This study revealed that both overall and cancer-specific survival rates were more favorable in younger patients compared to their older counterparts **[29]**. Moreover, a Japanese investigation evaluating the clinicopathological features and survival outcomes between younger and older patients with NSCLC demonstrated that the survival rate in the younger cohort was superior to that observed in the older population **[30]**. This discrepancy in the results of the present study might be attributed to the fact that those studies included various stages of the disease not only late advanced stages as in the present study.

Analysis of the smoking status of the patients, first-degree family history of cancer, and the histologic subtype of the NSCLC among the present study population also revealed no correlations with the platinum chemotherapy outcomes nor patients' survival which are following results of previous reports **[8, 10, 13,**

14, 31].

In the current study, there was a statistically significant gender difference in OS, but not RR, among patients with NSCLC where males had shorter OS and a higher tendency to event occurrence (death) than females. These results align with previous extensive population-based research, which has consistently demonstrated that male gender is linked to reduced survival and poorer prognosis in patients with NSCLC, irrespective of the disease stage **[32, 33]**. The observed disparities in prognosis and mortality between sexes are likely attributable to a complex interplay of factors. These encompass a variety of environmental factors, such as pollutant exposure, dietary practices, and smoking status, in addition to inherent biological disparities, including the influence of sex hormones and distinct immune system responses between females and males **[34]**.

In the current work, the RR was not significantly different between stage IIIB and stage IV cases. However, patients with stage IV disease had statistically significantly lower OS than patients with stage IIIB, which was similar to a Turkish study that reported lower median OS time but similar RR in stage IV compared to stage IIIB NSCLC patients treated with cisplatin with vinorelbine or gemcitabine **[35]**. This finding indicates the rapid and poor prognosis among metastatic stages of NSCLC patients and reflects the effect of the spread of the cancer to distant sites of the body.

Regarding the prognostic value of the patient's PS; the current study showed that the PS of patients was positively correlated to the objective response to platinum therapy where patients who had better ECOG PS (score= 0-1) had a statistically significantly better response than those with lower PS (score= 2). Similarly, Jeon and his colleagues previously reported that low patients' PS is an independent risk factor for worse response to platinum therapy and low OS in Korean NSCLC patients **[36]**. The present study could not find an association between the PS of the patients and their survival outcomes. This finding contradicts the results of previous studies which reported that patients with advanced-stage NSCLC who have had poor pre-treatment PS had poor OS compared to patients who had a better PS **[37, 38]**. The variance observed in these findings is most likely attributable to the limited sample size in the present study.

In the same manner, the present study reported that cisplatin resulted in a better response than carboplatin among patients with the group of patients who received cisplatin showing higher PR and lower tumor resistance to therapy. Nonetheless, no statistically significant variance in survival outcomes was discerned between the two pharmacological agents. These findings are in agreement with the meta-analysis conducted by Griesinger et al., which encompassed 12 randomized controlled trials. Their comparative analysis of carboplatin versus cisplatin-based chemotherapy regimens in advanced NSCLC patients revealed that there is no considerable divergence in the overall survival outcomes between the two therapeutic approaches. Nonetheless, cisplatin-based therapy demonstrated a slight, yet notable, improvement in the overall response rate **[39]**.

The current study was limited by being a small sample size single-centered study. Additionally, genetic testing to identify driver mutations was not conducted, which could have provided insights into patient response to targeted therapies. Furthermore, the study included only one platinum doublet regimen, limiting the ability to compare the efficacy of different chemotherapy combinations.

Conclusion

The current study suggests that an ECOG PS of 0-1, female gender, and administration of cisplatin/gemcitabine as first-line therapy in stage IIIB/IV NSCLC are predictive of more favorable treatment outcomes. Conversely, factors such as histological subtype of NSCLC, age at diagnosis, and smoking status did not significantly influence the outcomes in this study cohort.

Recommendations

Multicentre studies with a large number of patients including driver mutation assessment and diverse platinum-based doublet regimens are necessary to gain a more comprehensive understanding of the prognosis in patients presenting with advanced-stage NSCLC.

List of Abbreviations

CR, Complete response; ECOG, Eastern Cooperative Oncology Group; GLOBOCAN, Global Cancer Observatory; NSCLC, Non-small cell lung cancer; OS, Overall survival; PD, Progressive disease; PFS, Progression-free survivalPR, Partial response; PS, Performance status; RECIST, Response Evaluation Criteria in Solid Tumours; RR, Response rate; SD, statable disease; S.D, Standard deviation.

Declarations

Consent to publish:

All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

This observational study was approved by the Faculty of Pharmacy, Ain Shams University, Cairo, Egypt research ethics committee for experimental and clinical studies under number 204/2018. The study was conducted following the declaration of Helsinki as revised in 2013. Informed consent was obtained from all individual participants included in the study.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Conflict of interest

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

Funding statement

No funding source was received.

Authors contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Yara S. Abdelwahed, Ahmed A. Nagy, and May Ahmed Shawki. The first draft of the manuscript was written by Yara S. Abdelwahed and was revised by all authors. All authors read and approved the final manuscript.

5. References

1. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS, Lung cancer. Lancet, 2021. 398(10299): 535-554. https://doi.org/10.1016/s0140-6736(21)00312-3
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2024. 74(3): 229-263. https://doi.org/10.3322/caac.21834
3. Casal-Mouriño A, Ruano-Ravina A, Lorenzo-González M, Rodríguez-Martínez Á, Giraldo-Osorio A, Varela-Lema L, et al., Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. Transl Lung Cancer Res, 2021. 10(1): 506-518. https://doi.org/10.21037/tlcr.2020.03.40
4. Deboever N, Mitchell KG, Feldman HA, Cascone T, Sepesi B Current Surgical Indications for Non-Small-Cell Lung Cancer.

Cancers (Basel), 2022. 14(5): https://doi.org/10.3390/cancers14051263

5. Guo H, Li H, Zhu L, Feng J, Huang X, Baak JPA, "How Long Have I Got?" in Stage IV NSCLC Patients With at Least 3 Months Up to 10 Years Survival, Accuracy of Long-, Intermediate-, and Short-Term Survival Prediction Is Not Good Enough to Answer This Question. Front Oncol, 2021. 11: 761042. https://doi.org/10.3389/fonc.2021.761042
6. Sirohi B, Ashley S, Norton A, Popat S, Hughes S, Papadopoulos P, et al., Early response to platinum-based first-line chemotherapy in non-small cell lung cancer may predict survival. J Thorac Oncol, 2007. 2(8): 735-740. https://doi.org/10.1097/JTO.0b013e31811f3a7d
7. Spini A, Gini R, Rosellini P, Singier A, Bellan C, Pascucci A, et al., First-Line Pharmacotherapies and Survival among Patients Diagnosed with Non-Resectable NSCLC: A Real-Life Setting Study with Gender Prospective. Cancers (Basel), 2021. 13(23): 6129 https://doi.org/10.3390/cancers13236129
8. Garg A, Iyer H, Jindal V, Vashistha V, Ali A, Jain D, et al., Prognostic factors for treatment response and survival outcomes after first-line management of Stage 4 non-small cell lung cancer: A real-world Indian perspective. Lung India, 2022. 39(2): 102-109. https://doi.org/10.4103/lungindia.lungindia_408_21
9. Abbasi S, Badheeb A, Prognostic Factors in Advanced Non-Small-Cell Lung Cancer Patients: Patient Characteristics and Type of Chemotherapy. Lung Cancer Int, 2011. 2011: 152125. https://doi.org/10.4061/2011/152125
10. Ye W, Yang Y, Wang J, Kadziola Z, Rajan N, Qin S Prognostic factors for patients with advanced non-small cell lung cancer treated with gemcitabine-platinum as first-line therapy in an observational setting in China. Thorac Cancer, 2014. 5(4): 319-324. https://doi.org/10.1111/1759-7714.12095
11. Hirsch FR, Spreafico A, Novello S, Wood MD, Simms L, Papotti M, The prognostic and predictive role of histology in advanced non-small cell lung cancer: a literature review. J Thorac Oncol, 2008. 3(12): 1468-1481. https://doi.org/10.1097/JTO.0b013e318189f551
12. Galli G, Rossi G. Lung cancer histology-driven strategic therapeutic approaches. Shanghai Chest. 2020. 10:4.
13. Mahdy EH, Kamel TH, AbelAal DA, Kamal El-Din KR, Prognostic Factors of Non-Small Cell Lung Cancer and Their Relation to the Clinical Outcomes. The Egyptian Journal of Hospital Medicine, 2018. 72(4): 4355-4361. https://doi.org/10.21608/ejhm.2018.9288
14. Kelly K, Chansky K, Mack PC, Lara PN, Jr., Hirsch FR, Franklin WA, et al., Chemotherapy outcomes by histologic subtypes of non-small-cell lung cancer: analysis of the southwest oncology group database for antimicrotubule-platinum therapy. Clin Lung Cancer, 2013. 14(6): 627-635. https://doi.org/10.1016/j.cllc.2013.06.010
15. Zatloukal P, Petruželka L, Zemanová M, Kolek Vt, Skřičková J, Pešek M, et al., Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer, 2003. 41(3): 321-331. https://doi.org/https://doi.org/10.1016/S0169-5002(03)00233-2
16. Vasconcellos VF, Marta GN, da Silva EM, Gois AF, de Castria TB, Riera R, Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. Cochrane Database Syst Rev, 2020. 1(1): Cd009256. https://doi.org/10.1002/14651858.CD009256.pub3
17. Rajeswaran A, Trojan A, Burnand B, Giannelli M, Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first-line treatment of metastatic non-small cell lung

carcinoma: a systematic review of randomized controlled trials. Lung Cancer, 2008. 59(1): 1-11. https://doi.org/10.1016/j.lungcan.2007.07.012

18. Kesireddy M, Ganti AK, Cisplatin or carboplatin for advanced non-small cell lung cancer: does it matter? Transl Lung Cancer Res, 2021. 10(9): 3705-3708. https://doi.org/10.21037/tlcr-21-718
19. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al., Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, 2017. 15(4): 504-535. https://doi.org/10.6004/jnccn.2017.0050
20. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al., RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer, 2016. 62: 132-137. https://doi.org/10.1016/j.ejca.2016.03.081
21. Käsmann L, Bolm L, Janssen S, Rades D, Prognostic Factors and Treatment of Early-stage Small-cell Lung Cancer. Anticancer Res, 2017. 37(3): 1535-1537. https://doi.org/10.21873/anticanres.11482
22. Alexander M, Kim SY, Cheng H, Update 2020: management of non-small cell lung cancer. Lung, 2020. 198(6): 897-907.
23. Goring S, Varol N, Waser N, Popoff E, Lozano-Ortega G, Lee A, et al., Correlations between objective response rate and survival-based endpoints in first-line advanced non-small cell lung Cancer: A systematic review and meta-analysis. Lung Cancer, 2022. 170: 122-132. https://doi.org/10.1016/j.lungcan.2022.06.009
24. Kubota K, Sakai H, Katakami N, Nishio M, Inoue A, Okamoto H, et al., A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial. Ann Oncol, 2015. 26(7): 1401-1408. https://doi.org/10.1093/annonc/mdv190
25. Jaloudi M, Rasul K, Khalifa F, Non-small cell lung cancer clinical management patterns in the Middle East and North Africa region. J Cancer Prev Curr Res, 2018. 9(4): 172-176.
26. Divan HA, Bittoni MA, Krishna A, Carbone DP Real-world treatment patterns and outcomes of patients with metastatic nonsquamous non-small cell lung cancer after progression on standard-of-care therapy in the United States. Lung Cancer, 2023. 179: 107177. https://doi.org/10.1016/j.lungcan.2023.107177
27. Adjei AA, Lung Cancer Worldwide. J Thorac Oncol, 2019. 14(6): 956. https://doi.org/10.1016/j.jtho.2019.04.001
28. Treat JA, Gonin R, Socinski MA, Edelman MJ, Catalano RB, Marinucci DM, et al., A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. Ann Oncol, 2010. 21(3): 540-547. https://doi.org/10.1093/annonc/mdp352
29. Subramanian J, Morgenstern D, Goodgame B, Baggstrom MQ, Gao F, Piccirillo J, et al., Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: surveillance, epidemiology, and results (SEER) analysis. J Thorac Oncol, 2010. 5(1): 23-28. https://doi.org/10.1097/JTO.0b013e3181c41e8d
30. Yoneyama R, Saji H, Kato Y, Kudo Y, Shimada Y, Kimura M, et al., Clinicopathological characteristics and treatment strategies for young lung cancer patients. Ann Transl Med, 2019. 7(5): 100. https://doi.org/10.21037/atm.2019.01.69
31. Zhang YH, Lu Y, Lu H, Zhou YM, Development of a Survival Prognostic Model for Non-small Cell Lung Cancer. Front Oncol, 2020. 10: 362. https://doi.org/10.3389/fonc.2020.00362
32. Baiu I, Titan AL, Martin LW, Wolf A, Backhus L, The role of gender in non-small cell lung cancer: a narrative review. J Thorac Dis, 2021. 13(6): 3816-3826. https://doi.org/10.21037/jtd-20-3128
33. Radkiewicz C, Dickman PW, Johansson ALV,

Wagenius G, Edgren G, Lambe M, Sex and survival in non-small cell lung cancer: A nationwide cohort study. PLoS One, 2019. 14(6): e0219206. https://doi.org/10.1371/journal.pone.0219206

34. May L, Shows K, Nana-Sinkam P, Li H, Landry JW, Sex Differences in Lung Cancer. Cancers (Basel), 2023. 15(12): https://doi.org/10.3390/cancers15123111

35. Ozkaya S, Findik S, Dirican A, Atici AG, Long-term survival rates of patients with stage IIIB and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. Exp Ther Med, 2012. 4(6): 1035-1038. https://doi.org/10.3892/etm.2012.714

36. Jeon DS, Kim HC, Kim SH, Kim TJ, Kim HK, Moon MH, et al., Five-Year Overall Survival and Prognostic Factors in Patients with Lung Cancer: Results from the Korean Association of Lung Cancer Registry (KALC-R) 2015. Cancer Res Treat, 2023. 55(1): 103-111. https://doi.org/10.4143/crt.2022.264

37. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, et al., Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. J Thorac Oncol, 2010. 5(5): 620-630. https://doi.org/10.1097/JTO.0b013e3181d2dcd9

38. Käsmann L, Taugner J, Eze C, Roengvoraphoj O, Dantes M, Gennen K et al., Performance Status and Its Changes Predict Outcome for Patients With Inoperable Stage III NSCLC Undergoing Multimodal Treatment. Anticancer Res, 2019. 39(9): 5077-5081. https://doi.org/10.21873/anticanres.13701

39. Griesinger F, Korol EE, Kayaniyil S, Varol N, Ebner T, Goring SM, Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: A meta-analysis. Lung Cancer, 2019. 135: 196-204. https://doi.org/10.1016/j.lungcan.2019.07.010