Heliyon 9 (2023) e21177

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Diagnosis of lung cancer following emergency admission: Examining care pathways, clinical outcomes, and advanced NSCLC treatment in an Italian cancer Center

Giacomo Vallome [a], Iacopo Cafaro [b], Annarita Bottini [c], Chiara Dellepiane [d], Giovanni Rossi [d], Elisa Bennicelli [d], Francesca Parisi [d], Lodovica Zullo [d], Marco Tagliamento [c], Alberto Ballestrero [b,c], Emanuela Barisione [e], Ines Maria Grazia Piroddi [e], Fabrizio Montecucco [f,g], Federico Carbone [f,g], Paolo Pronzato [d], Matteo Lambertini [c,h], Francesco Spagnolo [d,i], Giulia Barletta [d], Lucrezia Barcellini [d], Michele Ferrante [d], Simone Nardin [d], Simona Coco [j], Silvia Marconi [j], Linda Zinoli [c,h], Paolo Moscatelli [k], Eleonora Arboscello [l], Lucia Del Mastro [c,h], Andrea Bellodi [b], Carlo Genova [c,h,*]

[a] U.O. Oncologia Medica, Ospedale Padre Antero Micone, ASL3, Genoa, Italy
[b] U.O. Clinica di Medicina Interna a Indirizzo Oncologico, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[c] Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genoa, Genoa, Italy
[d] U.O. Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[e] U.O. Pneumologia a Indirizzo Interventistico, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[f] First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, Genoa, Italy
[g] IRCCS Ospedale Policlinico San Martino, Genoa, Italian Cardiovascular Network, Genoa, Italy
[h] U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[i] Department of Surgical Sciences and Integrated Diagnostics (DISC), Plastic Surgery Division, University of Genoa, Genoa, Italy
[j] UO Tumori Polmonari, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[k] UO Medicina Interna, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[l] Dipartimento di Emergenza Urgenza e Accettazione (DEA), IRCCS Ospedale Policlinico San Martino, Genoa, Italy

ARTICLE INFO

Keywords:
Lung cancer
Cancer diagnosis
Performance status
Molecular characterization
Emergency department

ABSTRACT

Background: Lung cancer patients diagnosed following emergency admission often present with advanced disease and poor performance status, leading to suboptimal treatment options and outcomes. This study aimed to investigate the clinical and molecular characteristics, treatment initiation, and survival outcomes of these patients.
Methods: We retrospectively analyzed data from 124 patients diagnosed with lung cancer following emergency admission at a single institution. Clinical characteristics, results of molecular analyses for therapeutic purpose, systemic treatment initiation, and survival outcomes were assessed. Correlations between patients' characteristics and treatment initiation were analyzed.
Results: Median age at admission was 73 years, and 79.0 % had at least one comorbidity. Most patients (87.1 %) were admitted due to cancer-related symptoms. Molecular analyses were performed in 89.5 % of advanced non-small cell lung cancer (NSCLC) cases. In this subgroup, two-thirds (66.2 %) received first-line therapy. Median overall survival (OS) was 3.9 months for the

* Corresponding author. Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genoa, Genoa, Italy.
E-mail address: carlo.genova@hsanmartino.it (C. Genova).

https://doi.org/10.1016/j.heliyon.2023.e21177
Received 13 June 2023; Received in revised form 12 October 2023; Accepted 17 October 2023
Available online 19 October 2023

entire cohort, and 2.9 months for patients with metastatic lung cancer. Among patients with advanced NSCLC, OS was significantly longer for those with actionable oncogenic drivers and those who received first-line therapy. Improvement of performance status during hospitalization resulted in increased probability of receiving first-line systemic therapy.
Discussion: Patients diagnosed with lung cancer following emergency admission demonstrated poor survival outcomes. Treatment initiation, particularly for patients with actionable oncogenic drivers, was associated with longer OS. These findings highlight the need for proactive medical approaches, including improving access to molecular diagnostics and targeted treatments, to optimize outcomes in this patient population.

1. Introduction

Lung cancer is the third most common cancer worldwide [1]. In Italy, it ranks second in incidence among men (14.1 %) and third among women (7.3 %), while being the leading cause of oncological death among men (23.9 %) and the second for women (12.5 %) [2]. Non-small cell lung cancer (NSCLC) constitutes 80–90 % of lung cancer cases [3], with adenocarcinoma accounting for over half of NSCLC diagnoses [4,5].

In the past decade, lung cancer outcomes including for patients with advanced stage have significantly improved, mostly due to the availability of effective targeted agents and immune checkpoint inhibitors [6–8]. However, many patients still face poor outcomes. Particularly, patients who receive abrupt diagnosis of lung cancer during admission to Emergency Departments due to cancer-related symptoms often have a dismal prognosis and short survival [9].

In this context, proper staging and diagnostic pathway are crucial; some patients are immediately referred to palliative care due to poor performance status, while others undergo biopsy, but do not receive antineoplastic treatments. In particular, many patients who undergo diagnostic biopsy are initially considered border-line eligible for antineoplastic treatments, and then subsequently face clinical worsening, which prevents them from being treated. Alternatively, some patients may not be eligible for chemotherapy-based combinations due to comorbidities or performance status, but undergo nonetheless diagnostic biopsy with the aim of detecting molecular features compatible with first-line treatment with single-agent immunotherapy or targeted therapy; in such cases, the patients receive systemic treatment; otherwise, they may receive only single-agent chemotherapy or best supportive care at the end of the diagnostic work-up, often after a long hospitalization. As a result, many patients undergo multiple diagnostic exams, including invasive procedures, potentially without getting effective antineoplastic treatments.

The poor prognosis and the troubled path of patients diagnosed with lung cancer after Emergency Department admission suggest that this particular patient population deserves particular attention and their management might benefit from improvements. Hence, our study aims to analyze the diagnostic and therapeutic care pathways and outcomes of such patients within a Comprehensive Cancer Center, in order to identify areas of improvement in these critical pathways."

2. Materials and methods

2.1. Patient population

Patients with clinical evidence of lung cancer admitted from July 2018 to June 2021 to the Comprehensive Cancer Center "IRCCS Ospedale Policlinico San Martino" in Genoa (Italy) were retrospectively screened. To be eligible, patients had to be admitted through the Emergency Department, with diagnosis of lung cancer identified after hospitalization; those with prior lung cancer diagnosis and oncological care were not eligible for inclusion. Clinical evidence of lung cancer was defined as either: 1) cyto/histologic diagnosis of lung neoplasm, including NSCLC and small cell lung cancer (SCLC); 2) clinical symptoms AND radiologic findings strongly suggestive for the presence of lung cancer (i.e.: thoracic mass with exclusion of pneumonitis, with or without lymph nodal involvement and/or distant metastases) in absence of cyto/histologic diagnosis.

2.2. Data collection

Data were obtained retrospectively from medical files collected after written consent. Patient-related data included demographics, date and duration of hospitalization, smoking habit, comorbidities (using Charlson Comorbidity Index, CCI [10] and grouped as following: cardiovascular, neurological, renal, pulmonary), emergency admission due to cancer symptoms (pain, dyspnea, neurological symptoms, newly diagnosed atrial fibrillation) or due to other reasons, Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of admission, and oncological evaluation during hospitalization. Notably, we considered CCI at hospitalization; hence, the presence of cancer (which is an item of CCI) was not taken into account. Tumor-related data comprised disease stage, histology, and molecular analyses. Finally, treatment-related data included the therapeutic approach and outcomes. Non-dichotomic variables were initially recorded as continuous and later dichotomized.

2.3. Statistical analyses

We analyzed correlations of patients' outcomes with clinical and pathological factors identified at emergency admission and after diagnosis and staging.

The main outcome was overall survival (OS), measured from the date of emergency admission to the date of death, and estimated using the Kaplan-Meier product-limit method [11]. Univariate analysis for survival was performed by using the log-rank test [12], in order to determine the potential effect on OS of stage (I-III vs. IV), gender (male vs. female), age (above vs. below median), smoking habit (ever smoker vs. never smoker), CCI (above vs. below median), comorbidities (present vs. absent and categories), cancer-related symptoms (present vs. absent), ECOG-PS (cut-off: 2), oncological evaluation (performed vs. not performed), and histology (NSCLC vs. SCLC); additionally, for patients with advanced NSCLC, we determined the effect on survival of actionable molecular targets for first-line, improvement in terms of ECOG PS during hospitalization (for patients with baseline ECOG PS = 2) and treatment initiation. In these analyses, the null hypothesis was the absence of differences in term of OS between groups differing for each aforementioned parameter, while the alternative hypothesis was the presence of an OS difference between groups differing for the parameters. Univariate Cox regression analysis was employed to detect and select individual significant covariates ($p < 0.05$) associated with different OS, to be subsequently tested in multivariate regression analysis (as reported in Table 4 and Supplementary Tables in the following sections) [13]. We assessed whether specific clinical-pathological features were associated with the probability of starting systemic treatments (as compared to receiving only best supportive care) for patients with advanced non-squamous NSCLC; more specifically, we used Fisher's exact test (two-sided) for binary variables, including actionable molecular drivers for first-line (presence vs. absence), while we employed Mann-Whitney *U* test (two-tailed) for continuous variables of two groups, including age (above vs. below median), ECOG PS (0 vs.1 vs. 2), comorbidities (0–1 vs. 2+), CCI (above vs. below median), and ECOG PS improvement during hospitalization (improvement vs. no improvement). In this case, the null hypothesis was represented by the absence of differences in terms of probability to start systemic treatment, while the alternative hypothesis was represented by a different likelihood to start systemic treatment.

Furthermore, due to the acknowledged impact of oncogenic alterations in the management of advanced, non-squamous NSCLC, we assessed whether specific clinical features were associated with different probability of harboring actionable molecular drivers for first-line; more specifically, we used Fisher's exact test (two-sided) for binary variables, including smoking status (ever vs. never-smoker), gender (male vs. female), ECOG PS (0 vs. 1 vs. 2), while we employed Mann-Whitney *U* test (two-tailed) for continuous variables of two groups, such as age. In this case, the null hypothesis was represented by the absence of differences in terms of probability to harbor actionable oncogenic alterations for first-line, while the alternative hypothesis was represented by a different likelihood to harbor such oncogenic alterations.

Additionally, we assessed the potential correlations between clinical features which may be associated, such age and ECOG PS (0 vs.1 vs. 2), assessed by Kruskal-Wallis H test, age and CCI (above vs. below median) or age and comorbidities (0–1 vs 2+ comorbidities), both assessed by two-tailed Mann-Whitney *U* test. In these cases, the null hypothesis was represented by the absence of differences in terms of age (considered as continuous variable) among the clinically relevant categories, while the alternative hypothesis was represented by a different age among such categories.

Cox regression was carried out by considering OS from hospitalization as the outcome variable, while age (above or below median), CCI (above or below median), presence of actionable mutations for first-line treatment, and actual treatment initiation were employed as explanatory variables.

Table 1
Main clinical and tumor-related characteristics of the eligible patients (N = 124).

CLINICAL CHARACTERISTICS AT ADMISSION TO EMERGENCY DEPARTMENT	
Median age (range) – years	73 (41–97)
Male/Female (%)	81 (65.3) – 43 (34.7)
Smokers; Non-smokers; unknown (%)	95 (76.6); 8 (6.5); 21 (16.9)
Charlson Comorbidity Index, median (range)	4 (0–10)
Admission due to cancer symptoms (%)	108 (87.1)
ECOG PS at admission ≤2 vs. >2	113 (91.1); 11 (8.9)
TUMOR-RELATED CHARACTERISTICS	
Staging performed (%)	118 (95.1)
Stage I-III vs. stage IV (%)[a]	22 (18.7); 96 (81.3)
Biopsy performed (%)	104 (83.9)
NSCLC (%)[b]	93 (89.4 %)
SCLC (%)[b]	8 (7.7)
Non-diagnostic biopsy (%)[b]	3 (2.9)

Legend. CCI: Charlson comorbidity index; COPD: chronic obstructive pulmonary disease; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ED: extensive disease; LD: limited disease; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

[a] Refers to % among patients who underwent staging.

[b] Refers to % among patients who underwent biopsy.

3. Results

3.1. Patients' characteristics at hospitalization

A total of 124 patients were included in the study. Patients' characteristics are summarized in Table 1 and Supplementary Table 1. Median age was 73 years, with 33 (26.6 %) patients older than 80 years. Median CCI not counting cancer diagnosis was 4; 98 patients (79.0 %) had at least one comorbidity in the evaluated categories. Cancer symptoms were the reason of emergency admission in 108 cases (87.1 %); most common symptoms were pain (n = 52; 41.9 %), dyspnea (n = 51; 41.1 %), neurological symptoms (n = 25; 20.2 %) and newly diagnosed atrial fibrillation (n = 5; 4.0 %). Most patients (n = 113; 91 %) had ECOG PS between 0 and 2.

3.2. Staging and diagnostic procedures

Most patients (n = 118; 95.1 %) underwent systemic staging, while 104 patients (83.9 %) underwent biopsy.

Molecular analyses were performed in 89.5 % of advanced NSCLC cases, and included molecular assessment of *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement, *BRAF* mutation, *MET* amplification, *KRAS* mutation for non-squamous NSCLC, as well as PD-L1 expression for both squamous and non-squamous NSCLC, consistently with clinical practice, with a median time of 22 days from biopsy to completion. With regards to the nine patients with stage IV NSCLC for whom molecular analyses were not required, the reason was always associated with worsening of clinical conditions in the days following biopsy. Details on the observed molecular alterations are reported in Table 2.

Excluding *KRAS* mutations (for which targeted therapy is currently available in second-line) and high PD-L1 expression (which allows single-agent immunotherapy in Italy), patients with non-squamous NSCLC harboring oncogenic drivers which are currently actionable with targeted therapies in first-line accounted for 14 out of 58 patients (24.1 %).

3.3. Systemic treatment initiation

The evaluation of systemic treatment initiation was performed in the sub-group of patients affected by stage IV NSCLC/extended-disease (ED) SCLC. 66.2 % of patients received first-line therapy, with some differences depending on the potential first-line treatment that could be proposed based on histo-molecular analyses, as reported in Table 3. Slightly more than half of the patients without oncogenic drivers for first-line treatment received systemic therapy with chemotherapy and/or immunotherapy, based on PD-L1 expression (respectively, 58.1 % of patients with PD-L1<50 % and 54.5 % of patients with PD-L1 ≥50 %), while all the patients with an actionable oncogenic alteration eligible for first-line targeted therapy received systemic treatment.

3.4. Survival outcomes based on clinical and pathological characteristics at hospitalization

Median OS for the global population was 3.9 months (95 % confidence interval (CI): 2.0–5.8). The Kaplan-Meier curve is reported in Supplementary Fig. 1, while survival rates are listed in Supplementary Table 2.

Table 2
Data regarding molecular analyses performed in case of advanced NSCLC, including 65 patients with non-squamous NSCLC and 11 patients with squamous NSCLC.

MOLECULAR ANALYSES PERFORMED AMONG PATIENTS WITH DIAGNOSTIC BIOPSY FOR ADVANCED NSCLC (N° = 76)	N° (% among evaluable patients)
Molecular analyses performed	68 (89.5 %)
Patients with molecular analyses among non-squamous NSCLC (%; n = 65)	58 (89.2 %)
Patients with molecular analyses among squamous NSCLC (%; n = 11)	10 (90.9 %)
MOLECULAR FINDINGS RELEVANT FOR TREATMENTS	**N° (% among tested patients)**
PD-L1 EXPRESSION ≥50 % (%; n = 68)	25 (36.8 %)
EGFR MUTATION (%; n = 58)	11 (19.0 %)
ALK REARRANGEMENT (%; n = 58)	2 (3.4 %)
ROS1 REARRANGEMENT (%; n = 58)	1 (1.7 %)
BRAF MUTATION (%; n = 58)	0 (0.0 %)
MET AMPLIFICATION (%; n = 58)	2 (3.4 %)
KRAS MUTATION (%; n = 58)	18 (31.0 %)
NTRK FUSION (%; n = 58)	0 (0.0 %)

Patients with SCLC were not included in the table as they did not undergo molecular analyses for therapeutic purposes.
Patients with squamous cell lung cancer were considered as "tested" for molecular analysis if PD-L1 expression analysis was performed; patients with non-squamous NSCLC were considered as "tested" for molecular analyses if the following analyses were performed: PD-L1 expression, *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement, *BRAF* mutation, *MET* amplification, *KRAS* mutation (not limited to G12C), *NTRK* fusion.
The following methods were used: mass spectrometry (*EGFR*, *BRAF*, *KRAS*); immunohistochemistry (PD-L1, ALK, NTRK screening); fluorescence in situ hybridization (*ROS1*, *MET*).
Since in Italy PD-L1 expression ≥50 % is required for prescribing single-agent immunotherapy, this cut-off was considered in order to define a "relevant" finding for this molecule.

Table 3
Systemic treatment initiation among patients with advanced NSCLC who underwent biopsy and molecular characterization for treatment purpose.

All patients evaluated for systemic treatment with complete molecular characterization[a] (n = 68)	Systemic antineoplastic treatment	45 (66.2 %)
	No systemic antineoplastic treatment	23 (33.8 %)
Patients with no actionable oncogenic drivers for first-line* and PD-L1 expression <50 % evaluated for systemic treatment (n = 31[b])	Single-agent chemotherapy	4 (12.9 %)
	Platinum-based doublet	8 (25.8 %)
	Platinum-based chemotherapy plus immunotherapy (anti-PD-1)	6 (19.4 %)
	No treatment	13 (41.9 %)
Patients with PD-L1 expression ≥50 % and no actionable oncogenic drivers for first-line[a] evaluated for systemic treatment (n = 22)	Single-agent immunotherapy (anti-PD-1 agent)	12 (54.5 %)
	No treatment	10 (45.5 %)
Patients with oncogenic drivers for first-line[a] evaluated for systemic treatment (n = 14)	Single-agent targeted agent (according to molecular alteration)	14 (100.0 %)
	No treatment	0 (0.0 %)

[a] For patients with squamous NSCLC and smoking history, only PD-L1 expression assessment was performed; for the other patients, PD-L1 expression and analysis for molecular alterations of *EGFR*, *ALK*, *ROS1*, *BRAF*, *KRAS, MET*, *NTRK* was performed. On the basis of drug availability, only *EGFR*, *ALK*, *ROS1*, *BRAF*, and *NTRK* were considered oncogenic drivers for first-line.
[b] Originally, 32 patients were included in this category; however, one patient was taken in charge in another hospital following initial hospitalization and no treatment data are available.

Median OS among patients with stage I-III NSCLC or limited SCLC has not been reached at the time of analysis; median OS among patients with metastatic lung cancer was 2.9 months (95 % CI: 1.8–4.0); as expected, the difference between the two groups was significant ($p < 0.001$).

Variables significantly associated with shorter OS were age above median (>73 years) in the overall population ($p = 0.0002$) and in

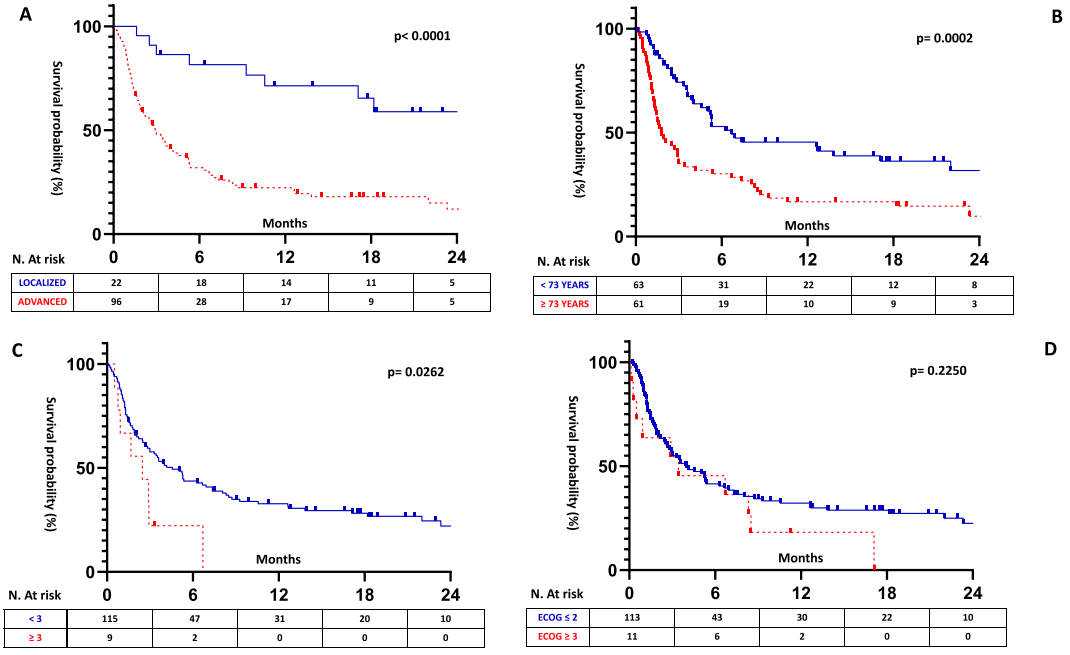

Fig. 1. A Overall survival of patients with localized lung cancer (including limited SCLC) and advanced lung cancer (including extensive SCLC) (median not reached vs. 2.9 months; $p < 0.0001$; HR = 0.24). Only patients for whom staging was completely performed were included.
Fig. 1B: Overall survival of patients aged below median (cut-off = 73 years) and patients aged above median (6.7 vs. 1.8 months; $p = 0.0002$; HR = 0.46).
Fig. 1C: Overall survival of patients with <3 or ≥3 comorbidity categories (4.6 vs. 2.5 months; $p = 0.0262$; HR = 0.45).
Fig. 1D: Overall survival of patients with ECOG PS ≤ 2 vs. ECOG ≥3 at hospitalization (4.3 vs. 3.4 months; $p = 0.2250$; HR = 0.67).

stage IV/ED subgroup ($p < 0.001$), ≥3 comorbidity categories in the overall population ($p = 0.026$) and CCI >4 in stage IV/ED subgroup ($p = 0.002$). There were no significant differences according to ECOG PS ($p = 0.225$, $p = 0.748$, $p = 0.076$ in overall population, stage I-III/LD, stage IV/ED respectively). The relevant survival curves for baseline patients' characteristics are reported in Fig. 1 (A-D) and Fig. 2 (A-C), while the univariate analyses are summarized in Table 4.

3.5. Survival outcomes of patients with advanced NSCLC based on molecular analyses and systemic treatment

Improved survival was observed among patients with actionable oncogenic drivers for first-line (*EGFR* mutations, *ALK* and *ROS1* rearrangements; $p < 0.001$); data of patients with non-squamous, advanced NSCLC according to presence of oncogenic drivers are reported in Fig. 3. Patients with advanced NSCLC who received first-line therapy (irrespective of mutational status) had longer OS than patients who did not receive systemic antineoplastic treatment ($p < 0.0001$; Fig. 4). This benefit of treatment initiation was consistent according to potential systemic treatment (Table 3). Among patients with no oncogenic targets for first-line, individuals with PD-L1 <50 % (hence potentially eligible for chemotherapy with or without immunotherapy) who actually received systemic treatment achieved improved OS compared to patients who did not receive any treatment (5.3 vs. 2.9 months); similarly, individuals with PD-L1 ≥50 % (hence potentially eligible for single-agent immunotherapy) who were treated achieved longer OS compared to patients with PD-L1≥50 % who were not treated (12.7 vs. 1.3 months). With regards to patients with oncogenic targets for first-line, all the individuals received systemic treatment, with a median OS of 23.3 months. The log-rank tests based on molecular characterization and treatment initiation are summarized in Supplementary Table 3. At the Cox regression analysis for survival of patients with advanced NSCLC, which included age (cut-off 73 years), CCI (cut-off: 4), presence of actionable molecular drivers for first-line and initiation of therapy, OS was associated only with actionable molecular drivers for first-line ($p = 0.018$) and initiation of therapy ($p < 0.001$), as reported in Supplementary Table 4.

3.6. Correlations among clinical and molecular characteristics

For these analyses, we considered only patients with diagnosis of advanced, non-squamous NSCLC. The difference between presence or absence of oncogene addiction for first-line in the likelihood of starting therapy was statistically significant ($p = 0.0027$). Then we looked for predictive factors of oncogene-addiction: smoking habit, age, gender, ECOG PS; none of them were significant in this group ($p = 0.3154$, $p = 0.4883$, $p > 0.9999$, $p = 0.7529$, respectively; Supplementary Tables 2–6).

Age was associated with likelihood of starting therapy ($p = 0.0006$), ECOG PS ($p = 0.0052$), and CCI ($p < 0.0001$), but not with

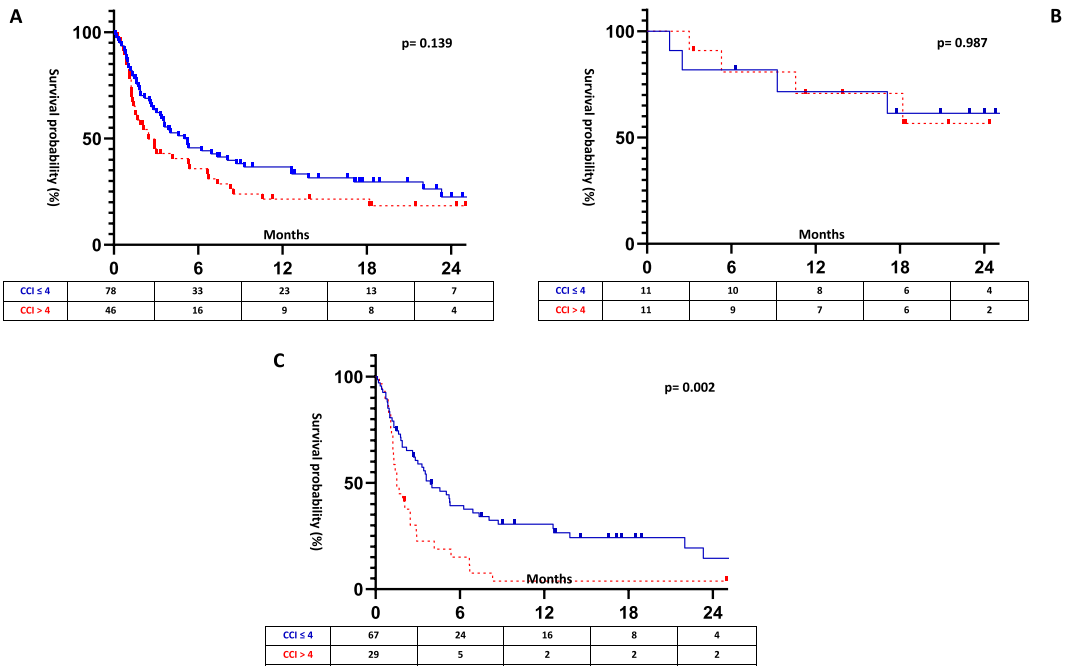

Fig. 2. A Overall survival of patients with CCI below or above median (≤4 vs. >4; 5.0 vs. 2.5 months; $p = 0.139$; HR = 0.73) within the whole study population.

Fig. 2B: Overall survival of patients with CCI below or above median (≤4 vs. >4; median values not reached; $p = 0.987$; HR = 1.01) among patients with localized lung cancer (patients with unknown stage were excluded).

Fig. 2C: Overall survival of patients with CCI below or above median (≤4 vs. >4; 3.9 vs. 1.5 months; $p = 0.002$; HR = 0.49) among patients with advanced/extensive lung cancer (patients with unknown stage were excluded).

Table 4
Univariate analyses for overall survival according to patients' characteristics at hospital admission.

PATIENTS' CHARACTERISTICS	DISEASE STAGE	P-VALUE (LOG-RANK)
Stage (I-III/LD vs IV/ED)	–	**<0.001**
GENDER (male vs. female)	Overall	0.870
	Stage I-III/LD	0.862
	Stage IV/ED	0.720
Age below median vs. below median (cut-off 73 years)	Overall	**<0.001**
	Stage I-III/LD	0.515
	Stage IV/ED	**<0.001**
Smoking habit (former/current smoker vs. never smoker)	Overall	0.445
	Stage I-III/LD	0.413
	Stage IV/ED	0.510
CCI > median value (4)	Overall	0.139
	Stage I-III/LD	0.987
	Stage IV/ED	**0.002**
Cardiovascular comorbidities	Overall	0.347
	Stage I-III/LD	0.497
	Stage IV/ED	0.416
Neurological comorbidities	Overall	0.904
	Stage I-III/LD	0.674
	Stage IV/ED	0.331
Renal comorbidities	Overall	0.440
	Stage I-III/LD	0.459
	Stage IV/ED	0.502
Pulmonary comorbidities	Overall	0.579
	Stage I-III/LD	0.657
	Stage IV/ED	0.273
≥1 comorbidity category	Overall	0.945
	Stage I-III/LD	0.559
	Stage IV/ED	0.794
≥2 comorbidity categories	Overall	0.510
	Stage I-III/LD	0.916
	Stage IV/ED	0.708
≥3 comorbidity categories	Overall	**0.026**
	Stage I-III/LD	0.698
	Stage IV/ED	0.251
Admission due to cancer symptoms	Overall	0.998
	Stage I-III/LD	0.741
	Stage IV/ED	0.936
Pain	Overall	0.324
	Stage I-III/LD	0.292
	Stage IV/ED	0.232
Dyspnea	Overall	0.294
	Stage I-III/LD	0.148
	Stage IV/ED	0.245
Neurological symptoms	Overall	0.110
	Stage I-III/LD	0.556
	Stage IV/ED	0.374
Atrial fibrillation	Overall	0.266
	Stage I-III/LD	NE
	Stage IV/ED	0.906
ECOG PS ad admission >2	Overall	0.225
	Stage I-III/LD	0.748
	Stage IV/ED	0.076
Oncological evaluation performed during hospitalization	Overall	0.467
	Stage I-III/LD	0.128
	Stage IV/ED	0.817
Histology (NSCLC vs SCLC)	Overall	0.905
	Stage I-III/LD	0.459
	Stage IV/ED	0.999

Legend: ED: extensive disease; LD: limited disease; NE: not evaluable; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

comorbidities ($p = 0.0576$). Association between likelihood of starting therapy and ECOG PS was not significant ($p = 0.1519$); same for likelihood of starting therapy and at least 2 comorbidity categories ($p = 0.7642$). Patients with advanced NSCLC and at least 3 comorbidity categories were too few ($n = 4$) for consistent statistical analyses. Notably, CCI above or below median was significantly associated with probability to start treatment ($p = 0.0003$). The reported data are represented in the **Supplementary Figs. 7–13**.

At the multiple linear regression analysis including the aforementioned parameters, the factors significantly associated with likelihood of starting therapy were age ($p = 0.0092$) and actionable oncogenic drivers for first-line treatment ($p = 0.0183$).

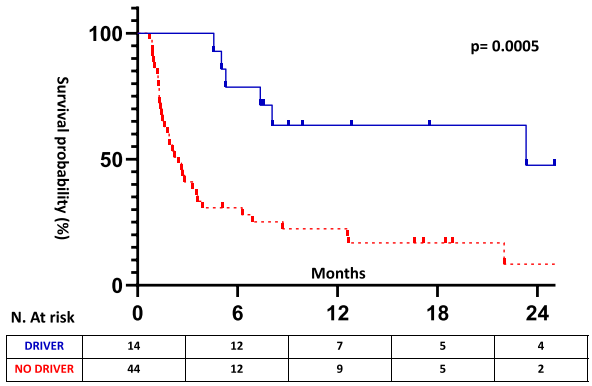

Fig. 3. Overall survival of patients with advanced NSCLC according to presence or absence of actionable oncogenic driver for first-line (23.3 vs. 2.5 months; p = 0.0005; HR = 0.26).

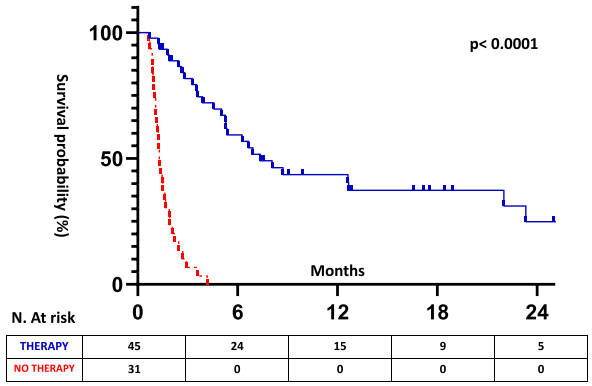

Fig. 4. Overall survival from admission to the emergency department among patients who received treatment and patients who did not receive systemic treatment for advanced lung cancer, irrespective of the specific treatment (7.3 vs. 1.3 months; p < 0.0001; HR = 0.18).

3.7. Improvement of performance status after hospitalization

When we took into account patients who had ECOG PS ≥ 2 at hospitalization, we evaluated the potential impact of PS improvement due to supportive care on the outcomes of patients with advanced NSCLC (irrespective of histology and molecular profile). PS improvement was associated with increased probability to receive systemic therapy (p = 0.0248) and with significantly increased OS (median not reached vs. 2.0 months). The reported data are represented in the supplementary figures 14-15.

4. Discussion

Diagnosis following emergency admission accounts for 5.3–34.5 % of lung cancer cases [14–17]. Several studies have identified factors strongly associated with this diagnostic route, such as older age, higher comorbidity burden, worse socioeconomic status or residence in deprived areas [18,19]. In addition, single studies also identified further factors as former-smoker status [20], presentation with respiratory symptoms [21], worse performance status [22], and Afro-American ethnicity [23]. Patients diagnosed following emergency admission had more frequently disease at advanced stage [24]. While one study concluded that emergency presentation was not an independent predictor of OS [25], others reported lower survival rates in these patients [15,17,18,22,24].

Most recent studies focused on patients' outcomes and predictive factors associated with emergency presentation of cancer, while less data about treatments received are available. A study showed that patients with emergency presentation were less likely to undergo diagnostic procedures such as mediastinoscopy or bronchoscopy, as well as surgery [21]. In another study, almost a third (29.5 %) of these patients could not receive any antitumoral treatment [26].

Our study showed that diagnosis of lung cancer following emergency admission is associated with poor OS (3.9 months) and two-years survival rate (20.7 %). Although we did not perform direct comparison between these patients and those who followed traditional route to diagnosis, a median OS shorter than 4 months from the date of emergency admission is a meaningful information.

We observed that only two-thirds of patients with advanced NSCLC were able to start first-line treatment. Our data must be considered taking into account that, at time of admission, 91.3 % of patients had ECOG PS ≤ 2, hence being potentially eligible for oncological treatments. Furthermore, we evaluated potential associations between probability to start first-line treatment and clinical

and pathological characteristics of patients with advanced NSCLC who underwent diagnostic procedures including biopsy and molecular characterization, as these patients were considered potential candidates for systemic treatment during diagnostic work-up.

In our study, the initiation of therapy was significantly associated with longer OS in both univariate and multivariate analysis. However, the benefit was weak compared to literature data. In our cohort, patients eligible to first-line chemotherapy plus immunotherapy or chemotherapy alone who started treatment had a median OS of 5.3 months, while candidates to single-agent immunotherapy achieved a median OS of 12.7 months and patients with an actionable oncogenic driver had a median OS equal to 23.3 months. In all the categories, the outcomes were lower compared to pivotal trials; however, patients with actionable oncogenic drivers achieved by far the best outcomes among individuals with advanced NSCLC. In first place, they all received targeted therapy; in second place, albeit lower than the outcomes of randomized trials, our patients with oncogene-addicted, advanced NSCLC achieved almost 2 years of survival, which is in line with the expectations for this patient category irrespective of emergency presentation. By contrast, the outcomes of patients with emergency presentation who were candidates for chemotherapy-based regimens were extremely poor. Notably, it is possible that some frail patients (due to age or ECOG PS), unfit for chemotherapy, might have undergone biopsy and molecular characterization with the hope of identifying oncogenic drivers or high PD-L1 expression. In these cases, patients who did not result eligible for single-agent immune checkpoint blockade or targeted therapy might have received single-agent chemotherapy as they were not considered eligible for combination strategies, potentially explaining their poor outcomes. On the other hand, we also observed that ECOG PS improvement during hospitalization, due to supportive care, was associated with increased probability to receive systemic antineoplastic treatment, hence supporting a proactive medical approach for symptomatic patients with cancer in order to increase access to active antineoplastic therapy and eventually survival.

Despite our encouraging findings underline the need for proactive medical approaches, our analysis has serious limitations based on the small number of patients, and nature of mono-centric, retrospective study. However, to our knowledge, this is the first study evaluating in detail molecular diagnostics and treatment of patients with lung cancer diagnosis following emergency admission.

Data availability

This specific manuscript has not been associated with publicly available repositories, since all the collected data have been included in the main article and supplementary material and are therefore accessible within the publication.

CRediT authorship contribution statement

Giacomo Vallome: Data curation, Writing – original draft. **Iacopo Cafaro:** Data curation, Writing – original draft. **Annarita Bottini:** Data curation. **Chiara Dellepiane:** Conceptualization, Writing – review & editing. **Giovanni Rossi:** Conceptualization, Writing – review & editing. **Elisa Bennicelli:** Data curation, Writing – review & editing. **Francesca Parisi:** Data curation. **Lodovica Zullo:** Methodology, Resources. **Marco Tagliamento:** Conceptualization. **Alberto Ballestrero:** Formal analysis. **Emanuela Barisione:** Data curation, Formal analysis. **Ines Maria Grazia Piroddi:** Data curation. **Fabrizio Montecucco:** Data curation, Formal analysis, Investigation. **Federico Carbone:** Data curation, Formal analysis, Writing – review & editing. **Paolo Pronzato:** Conceptualization, Formal analysis. **Matteo Lambertini:** Data curation, Formal analysis, Investigation, Methodology. **Francesco Spagnolo:** Investigation, Methodology, Resources. **Giulia Barletta:** Data curation, Investigation. **Lucrezia Barcellini:** Data curation, Formal analysis. **Michele Ferrante:** Data curation. **Simone Nardin:** Data curation, Formal analysis. **Simona Coco:** Methodology, Project administration, Resources, Software. **Silvia Marconi:** Methodology, Software. **Linda Zinoli:** Methodology, Software. **Paolo Moscatelli:** Conceptualization, Data curation. **Eleonora Arboscello:** Conceptualization, Investigation. **Lucia Del Mastro:** Conceptualization, Formal analysis. **Andrea Bellodi:** Conceptualization, Investigation. **Carlo Genova:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The Authors declare the following potential conflicts of interest.

Matteo Lambertini: advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences. Speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Knight, Daiichi Sankyo and Takeda. Research funding (to the Institution) and travel Grants from Gilead outside the submitted work.

Francesco Spagnolo: advisory role for Novartis, Pierre Fabre, MSD, Philogen. Speaker honoraria from Novartis, Pierre Fabre, MSD, BMS, Sanofi, Merck, Sun Pharma.

Carlo Genova: Advisory role for AstraZeneca, Bristol Myers Squibb, Novartis, Roche, Sanofi, Takeda;

Speaker honoraria from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, Sanofi, Takeda, Thermofisher. Research Funding from the Italian Ministry of Health and from Bristol Myers Squibb outside the submitted work.

The other Authors declare no conflict of interest.

Acknowledgements

The Authors wish to thank the Italian Ministry of Health for research grants supporting our studies involving immunotherapy in

non-small cell lung cancer (5x1000 funds; CO-2016-02361470; Ricerca Corrente 2022–2024) and for the project "Organizational innovations and new needs of care for end-of-life cancer patients" (Ricerca Finalizzata 2018).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21177.

References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, 2022, CA. Cancer J. Clin. 72 (2022) 7–33, https://doi.org/10.3322/caac.21708.
[2] 2022_AIOM_NDC-Web.Pdf.
[3] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics. CA, Cancer J. Clin. 61 (2011) 69–90, https://doi.org/10.3322/caac.20107.
[4] L. Guida, NEOPLASIE DEL POLMONE, 2021.
[5] K.C. Thandra, A. Barsouk, K. Saginala, J.S. Aluru, A. Barsouk, Epidemiology of lung cancer, Contemp. Oncol. Poznan Pol. 25 (2021) 45–52, https://doi.org/10.5114/wo.2021.103829.
[6] U. Malapelle, S. Pilotto, F. Passiglia, F. Pepe, P. Pisapia, L. Righi, A. Listì, P. Bironzo, L. Belluomini, F. Tabbò, et al., Dealing with NSCLC EGFR mutation testing and treatment: a comprehensive review with an Italian real-world perspective, Crit. Rev. Oncol. Hematol. 160 (2021), 103300, https://doi.org/10.1016/j.critrevonc.2021.103300.
[7] C. Genova, E. Rijavec, F. Biello, G. Rossi, G. Barletta, M.G. Dal Bello, I. Vanni, S. Coco, A. Alama, F. Grossi, New systemic strategies for overcoming resistance to targeted therapies in non-small cell lung cancer, Expet Opin. Pharmacother. 18 (2017) 19–33, https://doi.org/10.1080/14656566.2016.1261109.
[8] A. Indini, E. Rijavec, M. Ghidini, C. Bareggi, D. Gambini, B. Galassi, P. Antonelli, G. Bettio, C. Di Nubila, F. Grossi, Pharmacotherapeutic advances with anaplastic lymphoma kinase inhibitors for the treatment of non-small cell lung cancer, Expet Opin. Pharmacother. 21 (2020) 931–940, https://doi.org/10.1080/14656566.2020.1738387.
[9] N. Niranjan, K.B. Sriram, New lung cancer diagnosis after emergency department presentation in a tertiary hospital: patient characteristics and outcomes, Hosp. Pract. 1995 50 (2022) 356–360, https://doi.org/10.1080/21548331.2022.2121573.
[10] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.
[11] J.P. Klein, M.L. Moeschberger, Survival Analysis: Techniques for Censored and Truncated Data, Springer Science & Business Media, 2005, ISBN 978-0-387-95399-1.
[12] D. Collett, Modelling Survival Data in Medical Research, fourth ed., Chapman and Hall/CRC, New York, 2023, 978-1-00-328252-5.
[13] T. Emura, S. Matsui, H.-Y. Chen, Compound.Cox: univariate feature selection and compound covariate for predicting survival, Comput. Methods Programs Biomed 168 (2019) 21–37, https://doi.org/10.1016/j.cmpb.2018.10.020.
[14] J. Barrett, W. Hamilton, Pathways to the diagnosis of lung cancer in the UK: a cohort study, BMC Fam. Pract. 9 (2008) 31, https://doi.org/10.1186/1471-2296-9-31.
[15] D. Fujimoto, R. Shimizu, T. Morimoto, R. Kato, Y. Sato, M. Kogo, J. Ito, S. Teraoka, T. Otoshi, K. Nagata, et al., Analysis of advanced lung cancer patients diagnosed following emergency admission, Eur. Respir. J. 45 (2015) 1098–1107, https://doi.org/10.1183/09031936.00068114.
[16] P.P. Melling, A.C. Hatfield, M.F. Muers, M.D. Peake, C.J. Storer, C.E. Round, R.A. Haward, S.M. Crawford, Lung cancer referral patterns in the former yorkshire region of the UK, Br. J. Cancer 86 (2002) 36–42, https://doi.org/10.1038/sj.bjc.6600029.
[17] R.D. Neal, V.L. Allgar, N. Ali, B. Leese, P. Heywood, G. Proctor, J. Evans, Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes, Br. J. Gen. Pract. J. R. Coll. Gen. Pract. 57 (2007) 212–219.
[18] R. Raine, W. Wong, S. Scholes, C. Ashton, A. Obichere, G. Ambler, Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics, BMJ 340 (2010) b5479, https://doi.org/10.1136/bmj.b5479.
[19] V. Sikka, J.P. Ornato, Cancer diagnosis and outcomes in Michigan EDs vs other settings, Am. J. Emerg. Med. 30 (2012) 283–292, https://doi.org/10.1016/j.ajem.2010.11.029.
[20] P. Murchie, S.M. Smith, M.S. Yule, R. Adam, M.E. Turner, A.J. Lee, S. Fielding, Does emergency presentation of cancer represent poor performance in primary care? Insights from a novel analysis of linked primary and secondary care data, Br. J. Cancer 116 (2017) 1148–1158, https://doi.org/10.1038/bjc.2017.71.
[21] P. Beckett, L.J. Tata, R.B. Hubbard, Risk factors and survival outcome for non-elective referral in non-small cell lung cancer patients–analysis based on the national lung cancer audit, Lung Cancer Amst. Neth 83 (2014) 396–400, https://doi.org/10.1016/j.lungcan.2013.10.010.
[22] S. Yap, D. Goldsbury, M.L. Yap, S. Yuill, N. Rankin, M. Weber, K. Canfell, D.L. O'Connell, Patterns of care and emergency presentations for people with non-small cell lung cancer in new south wales, Australia: a population-based study, Lung Cancer Amst. Neth 122 (2018) 171–179, https://doi.org/10.1016/j.lungcan.2018.06.006.
[23] L. Elliss-Brookes, S. McPhail, A. Ives, M. Greenslade, J. Shelton, S. Hiom, M. Richards, Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets, Br. J. Cancer 107 (2012) 1220–1226, https://doi.org/10.1038/bjc.2012.408.
[24] A.M. Pollock, N. Vickers, Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east england: ecological study, BMJ 317 (1998) 245–252, https://doi.org/10.1136/bmj.317.7153.245.
[25] S.W. Hargarten, M.J. Richards, A.J. Anderson, Cancer presentation in the emergency department: a failure of primary care, Am. J. Emerg. Med. 10 (1992) 290–293, https://doi.org/10.1016/0735-6757(92)90004-h.
[26] S. McPhail, L. Elliss-Brookes, J. Shelton, A. Ives, M. Greenslade, S. Vernon, E.J.A. Morris, M. Richards, Emergency presentation of cancer and short-term mortality, Br. J. Cancer 109 (2013) 2027–2034, https://doi.org/10.1038/bjc.2013.569.