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

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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

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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. neversmoker), 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	
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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/extendeddisease (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 \geq 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 <u>ADVANCED NSCLC</u> (N $^{\circ}$ = 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 \geq 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 \geq 50 % is required for prescribing single-agent immunotherapy, this cut-off was considered in order to define a

Since in faily PD-L1 expression \geq 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.

	1 5	1 1
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 %	Single-agent chemotherapy	4 (12.9 %)
evaluated for systemic treatment $(n = 31^{b})$	Platinum-based doublet	8 (25.8 %)
	Platinum-based chemotherapy plus	6 (19.4 %)
	immunotherapy (anti-PD-1)	
	No treatment	13 (41.9
		%)
Patients with PD-L1 expression \geq 50 % and no actionable oncogenic drivers for first-line ^a	Single-agent immunotherapy (anti-PD-1 agent)	12 (54.5
evaluated for systemic treatment $(n = 22)$		%)
	No treatment	10 (45.5
		%)
Patients with oncogenic drivers for first-line ^{n} evaluated for systemic treatment (n = 14)	Single-agent targeted agent (according to	14 (100.0
	molecular alteration)	%)
	No treatment	0 (0.0 %)
		2 (210 /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 \leq 2 vs. ECOG \geq 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 \geq 50 % (hence potentially eligible for single-agent immunotherapy) who were treated achieved longer OS compared to patients with PD-L1 \geq 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 ($\leq 4 \text{ vs.} > 4$; 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.

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Age below median vs. below median (vs. 16%) (vs. 16%)(720)Age held, to median vs. below median (vs. 16%) (vs. 16%)0.001Age held, former/varrent smoker vs. never smoker)(36%) (vs. 16%)Age held, former/varrent smoker vs. never smoker)(36%) (vs. 16%)Age held, former/varrent smoker vs. never smoker vs. never smoker vs. 16%)0.031Age held, former/varrent smoker vs. never smoker vs. 16%)0.031Age held, former/varrent smoker vs. 16%)0.032Age held, former/varrent smoker vs. 16%)0.032Age held, former/varrent smoker vs. 16%)0.031Age held, former/varrent smoker smok		Stage I-III/LD	0.862
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<table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-container><table-container><table-container><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container>		Stage I-III/LD	0.515
		Stage IV/ED	<0.001
<table-row> Singe II/LD 613 C1> anclian value (A) 631 Oteral 0.831 C2> anclian value (A) 0.831 Carabose constructions 0.832 Carabose constructions 0.832 Carabose constructions 0.831 Singe IV/LD 0.831 Namo for the second s</table-row>	Smoking habit (former/current smoker vs. never smoker)	Overall	0.445
Sign IVEDSign IVEDSign IVEDCC> media value (4)Sign IVED097Sign IVEDSign IVED097Cardiovascular comobiditiesSign IVED0416Maren IVEDSign IVED0416<		Stage I-III/LD	0.413
CC1> median value (4)Overall0.139Singe I/LD0.002Cardiovascular conorbiditiesNeurological conorbidities0.407Neurological conorbiditiesSinge I/LD0.407Neurological conorbiditiesSinge I/LD0.401Neurological conorbiditiesSinge I/LD0.401Neurological conorbiditiesSinge I/LD0.401Neurological conorbiditiesSinge I/LD0.401Neurological conorbiditiesSinge I/LD0.401Neurological conorbiditiesSinge I/LD0.502Neurological conorbiditiesSinge I/LD0.502Neurological conorbiditiesSinge I/LD0.502Neurological conorbiditiesSinge I/LD0.502Neurological conorbiditiesSinge I/LD0.502Neurological conorbidity categoriesSinge I/LD0.50220 conorbidity categoriesSinge I/LD0.50220 conorbidity categoriesSinge I/LD0.50220 conorbidity categoriesSinge I/LD0.50221 conorbidity categoriesSinge I/LD0.50222 conorbidity categoriesSinge I/LD0.50223 conorbidity categoriesSinge I/LD0.50224 conorbidity categoriesSinge I/LD0.50225 conorbidity categoriesSinge I/LD0.50226 conorbidity categoriesSinge I/LD0.50226 conorbidity categoriesSinge I/LD0.50227 conorbidity categoriesSinge I/LD0.50228 conorbidity categoriesSinge I/LD0.		Stage IV/ED	0.510
Singe I/LDSinge I/LD0.097Singe I/LD0.347Singe I/LD0.347Any Control0.347Any Control0.347Any Control0.341Any Control0.341<	CCI > median value (4)	Overall	0.139
Seq IV/EDNew Coveral0.002Cardiovascular conorbiditiesSinge IV/ED0.497Neurological conorbiditiesSinge I/I/LD0.904Neurological conorbiditiesSinge I/I/LD0.31Renal conorbiditiesOverall0.404Agee I/I/LD0.3310.51Agee I/I/LD0.590.51Pulnonary conorbiditiesOverall0.57Munoary conorbidities0.6270.57Pulnonary conorbidities0.590.57Pulnonary conorbidity categories0.590.59Punonary conorbidity categoriesSinge I/I/LD0.59Punonary conorbidity categorie		Stage I-III/LD	0.987
Cardiosscular comorbiditiesOverall0.347Stage I/I/L06.467Neurological comorbiditiesOverall0.641Renal comorbiditiesStage I/I/L00.674Renal comorbiditiesStage I/I/L00.469Ages I/I/L00.4590.502Pulnonary comorbiditiesStage I/I/L00.502Pulnonary comorbiditiesOverall0.502Pulnonary comorbiditiesOverall0.579Stage I/I/L00.5790.579Stage I/I/L00.5790.579Pulnonary comorbidity categoryOverall0.579PattersStage I/I/L00.579PattersStage I/I/L00.579PattersOverall0.579PattersStage I/I/L00.579PattersStage I/I/L00.579PattersStage I/I/L00.510PattersStage I/I/L00.510PattersStage I/I/L00.510PattersStage I/I/L00.510PattersStage I/I/L00.510PattersStage I/I/L00.510PattersStage I/I/L00.510PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L00.521PattersStage I/I/L0<		Stage IV/ED	0.002
Singe LII/LD0.497Neurological comorbiditiesSinge LV/ED0.416Neurological comorbiditiesNeurological comorbidities0.674Renal comorbiditiesSinge IV/ED0.531Pulmonary comorbiditiesOveral0.469pulmonary comorbiditiesOveral0.579Pulmonary comorbiditiesOveral0.579pulmonary comorbiditiesOveral0.579pulmonary comorbiditiesOveral0.579pulmonary comorbidity categorySinge III/LD0.551pulmonary comorbidity categorySinge III/LD0.591page III/LD0.5910.591page III/LD0.5920.591page III/LD0.5920.591page III/LD0.5920.591page III/LD0.5910.591page III/LD0.5920.591page III/LD0.5920.591page III/LD0.5920.591page III/LD0.5920.591page III/LD0.5920.591page III/LD0.592<	Cardiovascular comorbidities	Overall	0.347
Neurological comorbidities0veral0.416Neurological comorbidities0veral0.674Real comorbidities0veral0.440Nage IV/ED0.5020.502Pulmoary comorbiditiesStage IV/ED0.502Pulmoary comorbiditiesStage IV/ED0.573Stage IV/ED0.5730.573Stage IV/ED0.2730.573Stage IV/ED0.2730.573Stage IV/ED0.2730.553Stage IV/ED0.5740.574Stage IV/ED <td< td=""><td></td><td>Stage I-III/LD</td><td>0.497</td></td<>		Stage I-III/LD	0.497
Neurological comorbiditiesOverall0.904Stage IVLD0.674Renal comorbidities0.440Renal comorbidities0.430Pulmonary comorbidities0.502Pulmonary comorbidities0.671Stage IV/ED0.657Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.671Stage IV/ED0.510Stage IV/ED0.510Stage IV/ED0.510Stage IV/ED0.510Stage IV/ED0.510Stage IV/ED0.510Stage IV/ED0.741Stage IV/ED0.741Stage IV/ED0.681Stage IV/ED0.681Stage IV/ED0.691Stage IV/ED0.292Stage IV/ED0.510Stage IV/ED0.521Stage IV/ED0.521Stage IV/ED0.521Stage IV/ED0.521Stage IV/ED0.521Stage IV/ED0.521Stage IV/ED0.292Stage IV/ED0.292		Stage IV/ED	0.416
Stage III/LD6.674NameName0.331Renal comorbidities0.9000.469NameName0.502Pulmonary comorbidities0.5020.502Pulmonary comorbidities0.5020.502Stage III/LD0.5030.502Stage III/LD0.5030.503Stage III/LD0.7040.503Stage III/LD0.6980.503Stage III/LD0.6980.503Stage III/LD0.5040.503Stage III/LD0.5040.504Stage III/LD0.5040.504Stage III/LD0.3040.504Stage III/LD0.3040.504Stage III/LD0.3240.504Stage III/LD0.5040.504Stage III/LD0.5050.504Stage III/LD0.5050.504Stage III/LD0.5050.504Stage III/LD0.5050.504Stage III/LD0.5050.504Stage III/LD0.5050.504Stage III/LD0.5050.505Stage III/LD0.5050.505Sta	Neurological comorbidities	Overall	0.904
Stage IV/ED0.331Real conorbidities0.440Auge III/LD0.450Pulnonary conorbidities0.502Pulnonary conorbidities0.602Stage IV/ED0.657Stage IV/ED0.27321 comorbidity category0.94121 comorbidity categories0.941Stage IV/ED0.55920 comorbidity categories0.59121 comorbidity categories0.79423 comorbidity categories0.79424 comorbidity categories0.91625 comorbidity categories0.92126 comorbidity categories0.92127 comorbidity categories0.92128 comorbidity categories0.92129 comorbidity categories0.92120 comorbidity categories0.92120 comorbidity categories0.92121 comorbidity categories0.92122 comorbidity categories0.92123 comorbidity categories0.92124 comorbidity categories0.92125 comorbidity categories0.92126 comorbidity categories0.92127 comorbidity categories0.92128 comorbidity categories0.92129 comorbidity categories0.92129 comorbidity categories0.92120 c		Stage I-III/LD	0.674
Renal comorbiditiesOverallOverall0.440Stage I-II/LD0.459Pulmonary comorbidities5kage I-II/LD0.502Pulmonary comorbidities0.5020.50221 comorbidity categoryStage I-II/LD0.65722 comorbidity category0.7040.51022 comorbidity categories0.7080.70822 comorbidity categories0.7080.70823 comorbidity categories0.7080.70824 comorbidity categories0.7080.70825 comorbidity categories0.7080.70826 comorbidity categories0.7080.70827 comorbidity categories0.7080.70828 comorbidity categories0.7080.70829 comorbidity categories0.7080.70829 comorbidity categories0.7080.70820 comorbidity categories0.7080.70820 comorbidity categories0.7080.70820 comorbidity categories0.7080.70820 comorbidity categories0.7080.70820 comorbidity categories0.7080.70821 comorbidity categories0.7080.71822 comorbidity categories0.7080.71823 comorbidity categories0.7280.71824 comorbidity categories0.7280.71825 comorbidity categories0.7280.71826 comorbidity categories0.7280.71827 comorbidity categories0.7280.71828 comorbidity categories0.728		Stage IV/ED	0.331
Stage I-II/,DStage IV,ED0.502Pulmonary comorbiditiesOverall0.579Stage I-II/,DD0.5790.571Stage I-VED0.2730.571Stage I-VED0.2730.591Stage I-II/,DD0.5590.591Stage I-II/,DD0.5510.591Stage I-II/,DD0.5100.510Stage I-II/,DD0.5100.510Stage I-II/,DD0.5100.510Stage I-II/,DD0.5100.510Stage I-II/,DD0.5100.510Stage I-II/,DD0.5100.510Stage I-II/,DD0.5100.510Stage I-III/,DD0.9160.510Stage I-III/,DD0.5210.510Stage I-III/,DD0.2250.510Stage I-III/,DD0.2260.511Stage I-III/,DD0.2320.511Stage I-III/,DD0.2320.521Stage I-III/,DD0.2320.521Stage I-III/,DD0.2320.521Stage I-III/,DD0.2320.551Stage I-III/,DD0.2320.551Stage I-III/,DD0.5560.551Stage I-III/,DD0.5560.556Stage I-III/,DD0.5610.556Stage I-III/,DD0.5260.556Stage I-III/,DD0.5560.556Stage I-III/,DD0.5560.566Stage I-III/,DD0.5260.566Stage I-III/,DD0.5660.566Stage I-III/,DD0.5660.566Stage I-III/,DD<	Renal comorbidities	Overall	0.440
Pulmonary comorbiditiesSingle IV/ED0.502Pulmonary comorbidities0.657Stage II/LD0.657Stage IV/ED0.27321 comorbidity category0.287Stage IV/ED0.94522 comorbidity categories0.91622 comorbidity categories0.91632 comorbidity categories0.91632 comorbidity categories0.91633 comorbidity categories0.92134 comorbidity categories0.92135 comorbidity categories0.92136 comorbidity categories0.92136 comorbidity categories0.92137 comorbidity categories0.92136 comorbidity categories0.92136 comorbidity categories0.92137 comorbidity categories0.92138 comorbidity categories0.92139 comorbidity categories0.92130 comorbidity categories0.92130 comorbidity categories0.92130 comorbidity categories0.92130 comorbidity categories0.92130 comorbidity categories0.92130 comorbidity categories0.92230 comorbidity categories0.93231 comorbidity categories0.93232 comorbidity categories0.93233 comorbidity categories0.93234 comorbidity categories0.93235 comorbidity categories0.93235 comorbidity categories0.93235 comorbidity categories0.93235 comorbidity categories0.93235 co		Stage I-III/LD	0.459
Pulmonary conorbiditiesOverall0.579Stage I/I/LD0.55721 comorbidity categoryGage I/I/LD0.55921 comorbidity categoriesStage I/I/LD0.55922 comorbidity categoriesOverall0.01623 comorbidity categoriesStage I/I/LD0.51024 comorbidity categoriesStage I/I/LD0.01625 comorbidity categoriesOverall0.02626 comorbidity categoriesStage I/I/LD0.69827 comorbidity categoriesStage I/I/LD0.69828 comorbidity categoriesStage I/I/LD0.69829 comorbidity categoriesStage I/I/LD0.31429 comorbidity categoriesStage I/I/LD0.32420 comorbidity categoriesStage I/I/LD0.32421 comorbidity categoriesStage I/I/LD0.32422 comorbidity categoriesStage I/I/LD0.32423 comorbidity categoriesOverall0.32424 comorbidity categoriesStage I/I/LD0.32425 comorbidity categoriesStage I/I/LD0.32426 comorbidity categoriesStage I/I/LD0.32427 comorbidity categoriesStage I/I/LD0.32428 comorbidity categoriesStage I/I/LD0.32429 comorbidity categoriesStage I/I/LD0.324<		Stage IV/ED	0.502
Stage II/LD0.65721 comorbidity categoryStage IV/ED0.9452 comorbidity categoryStage IV/ED0.7942 comorbidity categoriesOveral 00.7942 comorbidity categoriesStage I/I/LD0.9162 comorbidity categoriesStage I/I/LD0.7082 comorbidity categoriesStage I/I/LD0.7082 comorbidity categoriesStage I/I/LD0.6982 comorbidity categoriesOveral0.6982 comorbidity categoriesStage I/I/LD0.6982 comorbidity categoriesStage I/I/LD0.9812 comorbidity categoriesStage I/I/LD0.9812 comorbidity categoriesStage I/I/LD0.9812 comorbidity categoriesStage I/I/LD0.9812 comorbidity categoriesStage I/I/LD0.9362 comorbidity categoriesStage I/I/LD0.9363 comorbidity categoriesStage I/I/LD0.936	Pulmonary comorbidities	Overall	0.579
Stage IV/ED 0.273 ≥1 conorbidity category 0.945 Stage III/LD 0.559 Stage III/LD 0.510 2 conorbidity categories 0.946 2 conorbidity categories 0.916 2 conorbidity categories 0.926 3 conorbidity categories 0.926 2 conorbidity categories 0.927 2 conorbidity categories 0.928 Admission due to cancer symptoms 0.928 Atmission due to cancer symptoms 0.928 Atmission due to cancer symptoms 0.928 Pain 0.928 Atma Atma 0.928 Pain 0.928 Pain 0.928 Pain 0.928 Pain 0.924 Pain 0.926 Pain 0.928 Pain 0.928 Pain 0.928 Pain 0.924 Pain 0.926 Pain 0.926 Pain 0.926 Pain 0.926		Stage I-III/LD	0.657
≥1 comorbidity category Overall 0.945 Stage I-II/LD 0.559 ≥2 comorbidity categories 0.704 ≥2 comorbidity categories 0.916 ≥3 comorbidity categories 0.926 ≥3 comorbidity categories 0.6698 ≥3 comorbidity categories 0.226 Admission due to cancer symptoms 0.589 Admission due to cancer symptoms 0.741 Admission due to cancer symptoms 0.741 Pain 0.741 Ages V/ED 0.324 Pain 0.324 Ages V/ED 0.322 Pain 0.929 Ages V/ED 0.324 Pain 0.294 Ages V/ED 0.324 Pain 0.292 Pain 0.294 Ages V/ED 0.292 Pain 0.294 Ages V/ED 0.294 Pain 0.294 Ages V/ED 0.294 Pain 0.294		Stage IV/ED	0.273
Stage IV/ED0.759≥2 comorbidity categories0verall0.764≥2 comorbidity categoriesStage IV/ED0.916≥3 comorbidity categories0verall0.026≥3 comorbidity categories0verall0.026Admission due to cancer symptomsStage IV/ED0.251Admission due to cancer symptomsStage IV/ED0.261Admission due to cancer symptomsStage IV/ED0.936Admission due to cancer symptomsStage IV/ED0.936PainStage IV/ED0.9360.936Admission due to cancer symptomsStage IV/ED0.936Atrian fibrillationStage IV/ED0.936Atrian fibrillation0.9360.936Atrian fibrillation0.9360.936Atrian fibrillation0.9360.936Atrian fibrillation >2Stage IV/ED0.936Atrian fibrillat	≥ 1 comorbidity category	Overall	0.945
22 comorbidity categories 0veral 0.794 32 comorbidity categories 0veral 0.916 33 comorbidity categories 0veral 0.026 34 comorbidity categories 0.026 35 comorbid		Stage I-III/LD	0.559
≥2 comorbidity categories 0,s10 Stage III/LD 0,916 Stage IV/ED 0,708 ≥3 comorbidity categories 0,048 Stage III/LD 0,048 Stage III/LD 0,048 Stage III/LD 0,948 Stage III/LD 0,948 Stage III/LD 0,366 Pain 0,741 Stage III/LD 0,336 Pain 0,244 Pain 0,244 Stage III/LD 0,232 Dyspnea 0,245 Dyspnea 0,244 Neurological symptoms 0,244 Neurological symptom 0,245 Neurological symptom 0		Stage IV/ED	0.794
Stage III/LD 0.916 Stage IV/ED 0.708 ≥3 comorbidity categories 0veral 0.026 Admission due to cancer symptoms Stage IV/ED 0.51 Admission due to cancer symptoms 0veral 0.998 Pain Stage IV/ED 0.324 Pain 0.828 0.929 pain Stage IV/ED 0.324 pain 0.828 0.232 pain Stage IV/ED 0.324 pain 0.929 0.232 pain 0.232 0.232 pain 0.234 0.234 page IV/ED 0.232 0.234 page IV/ED 0.234 0.234 page IV/ED 0.234 0.234 Neurological symptoms 0.426 0.234 Neurological symptoms 0.426 0.245 Atrial fibrillation 0.266 0.246 ECOG PS ad admission >2 0.906 0.256 Cocogle evaluation performed during hospitalization 0.427 0.256	≥ 2 comorbidity categories	Overall	0.510
≥3 comorbidity categories 0.708 ≥3 comorbidity categories 0.026 Stage I/II/LD 0.698 Admission due to cancer symptoms 0.998 Admission due to cancer symptoms 0.998 Stage I/II/LD 0.996 Pain 0.996 Age I/II/LD 0.936 Pain 0.222 Stage I/II/LD 0.232 Dyspnea 0.986 Age IV/ED 0.232 Dyspnea 0.484 Stage I/I/LD 0.245 Neurological symptoms 0.484 Neurological symptoms 0.484 Atrial fibrillation 0.484 Atrial fibrillation 0.374 ECOG PS ad admission >2 Stage I/II/LD 0.374 ECOG PS ad admission >2 Stage I/II/LD 0.966 Oncological evaluation performed during hospitalization Overall 0.906 Oncological evaluation performed during hospitalization Stage I/II/LD 0.487 Histology (NSCLC vs SCLC) Overall 0.405 Stage I/II/LD		Stage I-III/LD	0.916
Sign or Sign of Sign o		Stage IV/ED	0.708
Stage I-III/LD0.698Admission due to cancer symptoms0.251Admission due to cancer symptoms0.998Stage I-III/LD0.741Stage I-III/LD0.334Pain0.0verall0.324DyspneaStage I-III/LD0.292DyspneaStage I-III/LD0.245Meuropical symptoms0.2480.244Neuropical symptoms0.2480.245Atrial fibrillation0.2480.245Atrial fibrillation0.2460.245Atrial fibrillation0.2460.245Atrial fibrillation0.2560.266ECOG PS ad admission >20.2660.266Oncological evaluation performed during hospitalization0.2670.266Oncological evaluation performed during hospitalization0.2670.266Histology (NSCLC vs SCLC)0.2760.2760.266Histology (NSCLC vs SCLC)0.2670.2760.267Stage I-III/LD0.2660.2660.266Stage I-III/LD0.2660.2660.266Histology (NSCLC vs SCLC)0.2760.2760.266Histology (NSCLC vs SCLC)0.2760.2760.276Stage I-III/LD0.2670.2660.266Stage I-III/LD0.2660.2660.266Histology (NSCLC vs SCLC)0.2760.2760.276Stage I-III/LD0.2760.2760.276Stage I-III/LD0.2660.2760.276Stage I-III/LD0.2660.2760.276	\geq 3 comorbidity categories	Overall	0.026
Admission due to cancer symptoms 0.251 Admission due to cancer symptoms 0.998 Stage I-III/LD 0.741 Bage IV/ED 0.324 Pain 0.0281 0.324 Dyspnea Stage I/II/LD 0.2292 Dyspnea Stage I/II/LD 0.232 Neurological symptoms 0.245 0.245 Neurological symptoms 0.245 0.245 Atrial fibrillation 0.245 0.245 Atrial fibrillation 0.245 0.245 ECOG PS ad admission >2 Stage I/II/LD 0.374 Oncological evaluation performed during hospitalization Neurological evaluation performed during hospitalization Neurological I/ILD 0.374 Oncological evaluation performed during hospitalization Stage I/II/LD 0.374 Histology (NSCLC vs SCLC) 0.374 0.374 Histology (NSCLC vs SCLC) 0.374 0.374		Stage I-III/LD	0.698
Admission due to cancer symptoms Overall Overall 0.998 Stage III/LD 0.741 0.936 Pain Overall 0.324 Overall 0.292 0.292 Bage III/LD 0.292 0.292 Dyspnea Overall 0.292 Dyspnea Overall 0.294 Neurological symptoms Overall 0.294 Neurological symptoms Stage I/II/LD 0.148 Atrial fibrillation 0.294 0.294 Atrial fibrillation 0.294 0.294 ECOG PS ad admission >2 Stage I/II/LD 0.266 Stage I/II/LD 0.266 0.266 Stage I/II/LD 0.266 0.266 ECOG PS ad admission >2 Overall 0.202 Oncological evaluation performed during hospitalization Overall 0.202 Overall 0.206 0.266 Stage I/II/LD 0.266 0.266 Stage I/II/LD 0.266 0.266 Stage I/II/LD 0.267 0.266 </td <td></td> <td>Stage IV/ED</td> <td>0.251</td>		Stage IV/ED	0.251
Stage FII/LD 0.41 Stage IV/ED 0.936 Pain 5tage IV/ED 0.324 Dyspnea Stage IV/ED 0.292 Dyspnea Overal 0.294 Neurological symptoms Stage III/LD 0.148 Neurological symptoms Stage I-III/LD 0.245 Atrial fibrillation 0.100 0.100 Atrial fibrillation 0.556 0.374 ECOG PS ad admission >2 Stage I-III/LD 0.266 Overall 0.200 0.266 Grage I-III/LD 0.266 0.266 Marcial fibrillation 0.266 0.266 Atrial fibrillation 0.266 0.266 Oncological evaluation performed during hospitalization 0.276 0.276 Overall 0.2076 0.266 0.276 Histol	Admission due to cancer symptoms	Overall	0.998
Stage IV/ED 0.936 Pain Overall 0.324 Stage III/LD 0.292 Dyspnea Stage IV/ED 0.232 Dyspnea Overall 0.294 Neurological symptoms Stage III/LD 0.148 Neurological symptoms Overall 0.101 Atrial fibrillation 0.556 0.374 Atrial fibrillation 0.556 0.374 Atrial fibrillation 0.366 0.374 Atrial fibrillation 0.366 0.374 Atrial fibrillation 0.374 0.366 Atrial fibrillation 0.366 0.374 Atrial fibrillation 0.366 0.374 Atrial fibrillation 0.374 0.366 Bage IV/ED 0.906 0.374 Atrial fibrillation 0.906 0.374 <td></td> <td>Stage I-III/LD</td> <td>0.741</td>		Stage I-III/LD	0.741
Pain Overall 0.324 Stage I-III/LD 0.292 byspnea Stage I/V/ED 0.292 Dyspnea Overall 0.294 Neurological symptoms Overall 0.294 Neurological symptoms Overall 0.294 Atrial fibrillation 0.245 0.245 Atrial fibrillation 0.100 0.556 Atrial fibrillation 0.266 0.374 ECOG PS ad admission >2 Overall 0.266 COG PS ad admission >2 Overall 0.225 If this provide during hospitalization Overall 0.225 Neurological evaluation performed during hospitalization Stage I/II/LD 0.748 Histology (NSCLC vs SCLC) Overall 0.467 Histology (NSCLC vs SCLC) Overall 0.459	Del.	Stage IV/ED	0.936
Stage I-II/LD 0.292 Stage IV/ED 0.292 byspnea 0.294 Neurological symptoms 0.148 Neurological symptoms 0.245 Atrial fibrillation 0.10 Atrial fibrillation 0.566 Stage III/LD 0.374 Atrial fibrillation 0.266 Stage III/LD 0.266 <	Pain	Overall	0.324
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byspilea Overal 0.294 Stage I-III/LD 0.245 Neurological symptoms Overal 0.10 Atrial fibrillation 0.566 51328 I-III/LD 0.566 Atrial fibrillation 0.245 0.245 0.245 ECOG PS ad admission >2 Stage I-III/LD 0.374 ECOG PS ad admission >2 Overall 0.266 Stage I-III/LD 0.906 0.255 Function 0.225 0.266 Oncological evaluation performed during hospitalization Overall 0.225 Neurological evaluation performed during hospitalization Overall 0.266 Histology (NSCLC vs SCLC) Overall 0.467 Kage I-III/LD 0.128 0.128 Kage I-III/LD 0.261 0.261 Histology (NSCLC vs SCLC) 0.467 0.261	Drome oo	Stage IV/ED	0.232
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Oncological evaluation performed during hospitalization Overall 0.467 Histology (NSCLC vs SCLC) Overall 0.905 Histology (NSCLC vs SCLC) Overall 0.905 Stage III/LD 0.459 Stage IV/ED 0.609		Stage IV/ED	0.076
Histology (NSCLC vs SCLC) Overall 0.459	Oncological evaluation performed during hospitalization	Overall	0.467
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Histology (NSCLC vs SCLC) 0.017 Stage I-III/LD 0.905 Stage I-III/LD 0.459		Stage IV/ED	0.817
Stage I-III/LD 0.459	Histology (NSCLC vs SCLC)	Overall	0.905
		Stage I-III/LD	0.459
Stage IV/ED 0.999		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 twoyears 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 \leq 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, 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.

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Appendix A. Supplementary data

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

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