

Differential Impact of Smoking Status on Lung Cancer Phenotype and Outcomes: a Moroccan Analysis



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BACKGROUND

- A growing concern has been raised about the lung cancer (LC) biological distinction between current smokers (CS) and never smokers (NS), implying divergence in molecular features, patterns of presentation and treatment responsiveness.
- LCINS is the fifth most common cause of cancer-related deaths worldwide.¹
- For NS symptoms are non-specifics, and often dismissed due to these patients not fitting a high-risk profile (e.g., smokers).²
- In LMI real-world settings, where routine genotyping and sequencing are not widely implemented to guide personalised therapy,³ the distinction between CS and NS becomes particularly relevant. It may serve as a pragmatic surrogate for underlying biological heterogeneity, influencing diagnostic vigilance, therapeutic choices, and prognostic modelling.

OBJECTIVE: investigate the demographic, pathological, clinical and therapeutic differences between NS and CS.

METHODS

- Retrospective registry of consecutive LC patients, diagnosed at a Moroccan academic centre serving middle and southern Morocco (Jan 2013–Dec 2022), with documented smoking status; curated for real-world clinical, pathological and treatment data with centralised quality checks.
- Maximally selected rank statistics (Lausen & Schumacher) used to identify candidate PA cut-points and to define exploratory light (LS) versus heavy smokers (HS) groups when supported by the data, in addition for dose-response assessment.
- Multivariable Cox PHM adjusted for age, sex, stage, histology and ECOG PS; proportional hazards checked with Schoenfeld residuals.
- Dose-response: Restricted cubic spline Cox models to assess nonlinear PA–mortality relationships and test for threshold effects.
- Recursive partitioning: Decision-tree analysis to compare prognostic importance of smoking versus anatomical staging (T/N categories) and to identify subgroups with differential smoking impact.
- Sensitivity analyses: Stage- and histology-stratified models, analyses after propensity matching (exploratory 1:1 matching to balance CS and NS on baseline covariates (age, sex, histology, stage, ECOG PS)

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RESULTS

Table 1. Patient characteristics					Clinical Nodal category - no. (%)			
Variable	Overall N = 1,351 ¹	Smoking Status		p-value ²	0	1	2	3
		Current N = 1,087 ¹	Never N = 264 ¹					
Year at diagnosis - no. (%)				0.66				
2013	68 (5.0%)	59 (5.4%)	9 (3.4%)					
2014	122 (9.0%)	98 (9.0%)	24 (9.1%)					
2015	99 (7.3%)	79 (7.3%)	20 (7.6%)					
2016	112 (8.3%)	91 (8.4%)	21 (8.0%)					
2017	111 (8.2%)	95 (8.7%)	16 (6.1%)					
2018	155 (11%)	124 (11%)	31 (12%)					
2019	170 (13%)	134 (12%)	36 (14%)					
2020	153 (11%)	127 (12%)	26 (9.8%)					
2021	174 (13%)	137 (13%)	37 (14%)					
2022	187 (14%)	143 (13%)	44 (17%)					
Sex				<0.001				
Female	159 (12%)	10 (0.9%)	149 (56%)					
Male	1,192 (88%)	1,077 (99%)	115 (44%)					
Age at diagnosis - yr	61 (55, 67)	61 (56, 67)	62 (51, 70)	0.99				
PA	30 (12, 40)	37 (25, 45)	0 (0, 0)	<0.001				
Comorbidities - no. (%)								
Endocrine	92 (6.8%)	71 (6.5%)	21 (8.0%)	0.41				
Cardiac	66 (4.9%)	37 (3.4%)	29 (11%)	<0.001				
Pulmonary	87 (6.5%)	72 (6.6%)	15 (5.7%)	0.58				
Family History - no. (%)	57 (4.2%)	47 (4.3%)	10 (3.8%)	0.7				
Time from Symptoms Onset to Consultation - mth	5.0 (3.0, 8.0)	5.0 (3.0, 8.0)	5.0 (3.0, 9.0)	0.79				
Symptoms - no. (%)								
GSA	38 (7.8%)	26 (6.8%)	12 (12%)					
Weight loss	14 (2.9%)	12 (3.1%)	2 (1.9%)					
Appearance of a mass	8 (1.6%)	7 (1.8%)	1 (1.0%)					
Asthenia	1 (0.2%)	0 (0%)	1 (1.0%)					
COPD	1 (0.2%)	1 (0.3%)	0 (0%)					
Chest pain	183 (37%)	150 (39%)	33 (32%)					
Dysphagia	5 (1.0%)	4 (1.0%)	1 (1.0%)					
Dysphonia	3 (0.6%)	3 (0.8%)	0 (0%)					
Expectoration	1 (0.2%)	1 (0.3%)	0 (0%)					
Hemiparesis	2 (0.4%)	2 (0.5%)	0 (0%)					
Hemoptysis	54 (11%)	46 (12%)	8 (7.7%)					
Neurologic symptoms	150 (31%)	9 (2.3%)	1 (1.0%)					
Cough	111 (29%)	39 (38%)	39 (38%)					
None	19 (3.9%)	13 (3.4%)	6 (5.8%)					
Dyspnea grade - no. (%)				0.3				
Grade 0	204 (44%)	170 (47%)	34 (34%)					
Grade 1	19 (4.1%)	14 (3.8%)	5 (5.0%)					
Grade 2	104 (22%)	75 (21%)	29 (29%)					
Grade 3	103 (22%)	80 (22%)	23 (23%)					
Grade 4	30 (6.5%)	22 (6.0%)	8 (8.0%)					
Histology - no. (%)								
ADC	657 (50%)	499 (47%)	158 (61%)					
ASq	10 (0.8%)	7 (0.7%)	3 (1.2%)					
Carcinoma with Incomplete IHC	167 (13%)	135 (13%)	32 (12%)					
CNOS	40 (3.0%)	36 (3.4%)	4 (1.6%)					
Large Cell	4 (0.3%)	3 (0.3%)	1 (0.4%)					
Lung Neuroendocrine Tumour	146 (11%)	119 (11%)	27 (11%)					
Others	2 (0.2%)	1 (<0.1%)	1 (0.4%)					
Squamous	294 (22%)	263 (25%)	31 (12%)					
Localisation - no. (%)				<0.001				
Bilateral	2 (0.3%)	2 (0.4%)	0 (0%)					
Left	224 (36%)	180 (36%)	44 (35%)					
Mediastinum	30 (4.8%)	25 (5.0%)	5 (4.0%)					
Parenchymal	1 (0.2%)	0 (0%)	1 (0.8%)					
Pleura	21 (3.4%)	8 (1.6%)	13 (10%)					
Right	342 (55%)	281 (56%)	61 (49%)					
Sternum	1 (0.2%)	1 (0.2%)	0 (0%)					
Subclavicular	1 (0.2%)	1 (0.2%)	0 (0%)					
Clinical Tumour category - no. (%)				<0.001				
0	18 (1.4%)	8 (0.8%)	10 (4.3%)					
1	65 (5.2%)	46 (4.5%)	19 (8.1%)					
2	191 (15%)	154 (15%)	37 (16%)					
3	250 (20%)	202 (20%)	48 (21%)					
4	722 (58%)	602 (59%)	120 (51%)					
Clinical Metastasis category - no. (%)								
0	209 (17%)	177 (17%)	32 (13%)					
1	225 (18%)	181 (18%)	44 (18%)					
2	615 (49%)	496 (49%)	119 (50%)					
3	211 (17%)	167 (16%)	44 (18%)					
Initial stage at diagnosis - no. (%)								
IA	4 (0.3%)	2 (0.2%)	2 (0.8%)					
IB	1 (<0.1%)	1 (<0.1%)	0 (0%)					
IIA	11 (0.8%)	11 (1.0%)	0 (0%)					
IIB	30 (2.3%)	26 (2.5%)	4 (1.6%)					
IIIA	107 (8.2%)	93 (8.8%)	14 (5.6%)					
IIIB	176 (13%)	149 (14%)	27 (11%)					
IIIC	38 (2.9%)	32 (3.0%)	6 (2.4%)					
IVA	510 (39%)	407 (39%)	103 (42%)					
IVB	428 (33%)	336 (32%)	92 (37%)					
Initial liver metastasis - no. (%)	179 (14%)	133 (13%)	46 (19%)	0.014				
Initial bone metastasis - no. (%)	350 (27%)	270 (26%)	80 (32%)	0.031				
Initial adrenal metastasis - no. (%)	252 (19%)	219 (21%)	33 (13%)	0.008				
Initial brain metastasis - no. (%)	279 (21%)	228 (21%)	51 (20%)	0.72				
EGFR Status - no. (%)				<0.001				
Mutated	13 (1.0%)	5 (0.5%)	8 (3.0%)					
Mutated exon19	4 (0.3%)	2 (0.2%)	2 (0.8%)					
Wild type	65 (4.8%)	47 (4.3%)	18 (6.8%)					
Unknown	1,269 (94%)	1,033 (95%)	236 (89%)					
ALK Status - no. (%)				0.63				
Unknown	1,290 (95%)	1,039 (96%)	251 (95%)					
Negative	58 (4.3%)	46 (4.2%)	12 (4.5%)					
Positive	3 (0.2%)	2 (0.2%)	1 (0.4%)					
PD-L1 expression - no. (%)				0.75				
<1%	36 (2.7%)	29 (2.7%)	7 (2.7%)					
> 50%	8 (0.6%)	6 (0.6%)	2 (0.8%)					
1% - 49%	23 (1.7%)	17 (1.6%)	6 (2.3%)					
ND	1,284 (95%)	1,035 (95%)	249 (94%)					
Urgency at diagnosis - no. (%)								
CB	2 (0.2%)	2 (0.2%)	0 (0%)					
CM	13 (1.1%)	8 (0.8%)	5 (2.1%)					
Condensation Sd	23 (1.9%)	18 (1.8%)	5 (2.1%)					
HTIC	18 (1.5%)	13 (1.3%)	5 (2.1%)					
Interstitial Sd	3 (0.2%)	2 (0.2%)	1 (0.4%)					
PE	244 (20%)	175 (18%)	69 (29%)					
PT	24 (2.0%)	23 (2.3%)	1 (0.4%)					
None	813 (67%)	677 (69%)	136 (58%)					
Sd paraneoplastic	4 (0.3%)	4 (0.4%)	0 (0%)					
SVCS	67 (5.5%)	56 (5.7%)	11 (4.7%)					
SVCS + PE	11 (0.9%)	10 (1.0%)	1 (0.4%)					
ECOG PS - no. (%)				0.1				
0	11 (0.9%)	8 (0.8%)	3 (1.2%)					
1	637 (51%)	528 (52%)	109 (45%)					
2	363 (29%)	277 (27%)	86 (36%)					
3	186 (15%)	150 (15%)	36 (15%)					
4	53 (4.2%)	45 (4.5%)	8 (3.3%)					
Strategy - no. (%)				0.31				
Adjuvant	54 (4.0%)	40 (3.7%)	14 (5.4%)					
BSC	158 (12%)	133 (12%)	25 (9.6%)					
LF-U	397 (30%)	319 (29%)	78 (30%)					
NeoAdjuvant	219 (16%)	184 (17%)	35 (13%)					
Palliative	514 (38%)	405 (37%)	109 (42%)					
Progressive Site Following Systemic Therapy - no. (%)								
Lung	184 (71%)	147 (75%)	37 (60%)	0.024				
Bone	91 (35%)	64 (32%)	27 (44%)	0.11				
Liver	48 (19%)	32 (16%)	16 (26%)	0.091				
Adrenal	39 (15%)	29 (15%)	10 (16%)	0.79				

¹ n (%); Median (Q1, Q3)

² Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test; NA

*: The TNM Classification of Malignant Tumours, 9th edition, was used to (re)classify the data for disease stage ECOG denotes Eastern Cooperative Oncology Group; PS denotes performance status; EGFR denotes epidermal growth factor receptor; ALK denotes anaplastic lymphoma kinase; PD-L1 denotes programmed death-ligand 1; IHC denotes immunohistochemistry; CB denotes Claude Bernard; MC denotes medullary compression; ICHT denotes intracranial hypertension; ILD denotes interstitial lung disease; PE denotes pleural effusion; PT denotes Pancoast-Tobias; GSA denotes general state alteration; COPD denotes chronic obstructive pulmonary disease; ADC denotes adenocarcinoma; ASq denotes adenosquamous cell carcinoma; NOS denotes not otherwise specified; NEC denotes neuroendocrine carcinoma; Sd denotes syndrome; SVCS denotes superior venacava syndrome

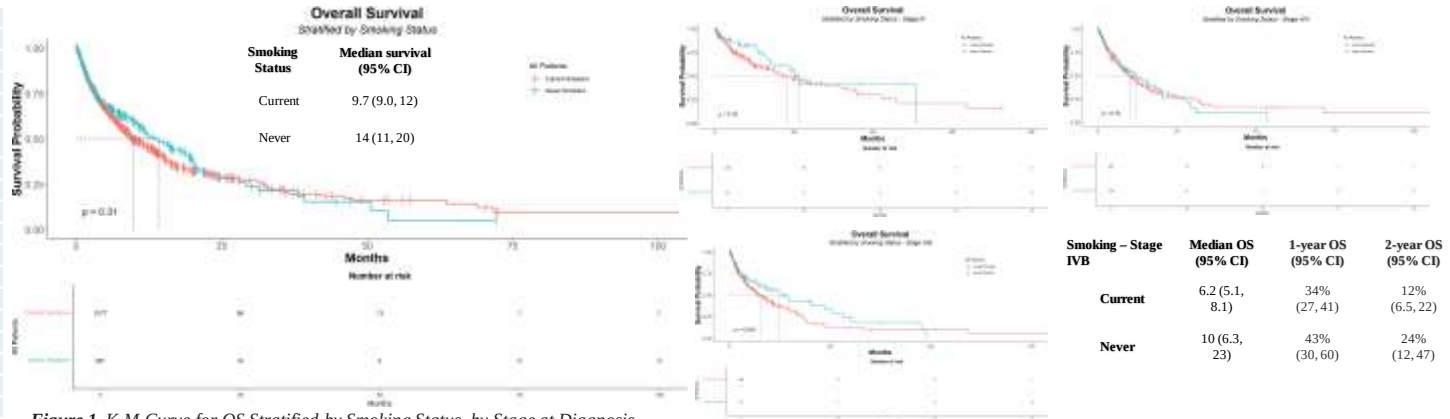


Figure 1. K-M Curve for OS Stratified by Smoking Status, by Stage at Diagnosis

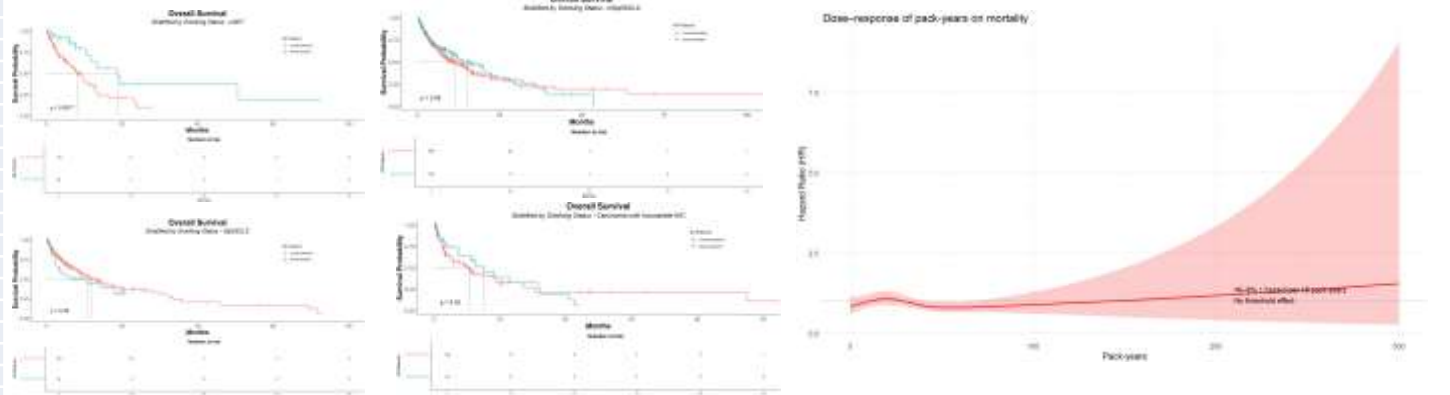


Figure 2. K-M Curve for OS Stratified by Smoking Status, by Histology; With the exception of LNET, where the OS was favoured, NS compared to CS (aHR, 0.39; 95% CI, 0.2 to 0.79; p=0.007), no statistical difference was observed across other histologic types, following adjustment for age and stage.

KEY TAKEAWAY:

- Clinically, NS presented with cough (p=0.03) and quicker clinical deterioration (p=0.04); pleural predominant disease with an oligometastatic liver (p=0.01) and bone (p=0.03) involvement, as well as higher rates of oligo-progression following systemic platinum-based chemotherapy; conversely, CS more often had chest pain (p=0.04), haemoptysis (p=0.02), right lower lobe primaries (p<0.001) and initial adrenal metastases (p=0.008).
- No overall survival (OS) difference was concluded between CS and NS.
- By stage, survival was comparable for I/II, III and IVA, but in stage IVB CS had poor OS (6.2 m (95% CI, 5.1 - 8.1) vs. 10 m (95% CI, 6.3 - 23) for NS (aHR, 0.7; 95% CI, 0.5 to 0.97; p=0.047))
- Recursive partitioning analysis, only in pts with stage I/II and IVB, smoking had greater prognostic impact than N0-1 vs. N2 vs. N3 categories.
- All findings were consistent following propensity-score matching.

CONCLUSION

Supported by the distinct clinical presentations and metastatic patterns, the results argue for stage- and histology-specific risk stratification and for integrating smoking intensity into prognostic and treatment algorithms, despite the lack of a uniform OS disadvantage of CS compared to NS.

References: **1.** LoPiccolo, J., et al. Lung cancer in patients who have never smoked — an emerging disease. Nat Rev Clin Oncol 21, 121–146 (2024); **2.** Caswell D, et al. Lung cancer in never smokers: from early detection to prevention Trends in Cancer, 2026; 12, 310-319; **3.** Tafenzi HA, et al. Thoracic cancer management in Morocco: from diagnosis to follow-up and everything in between. J Thorac Oncol 2026;21:103561

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