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Naples Prognostic Score is a Useful Tool to Assess the Surgical Treatment in Non-Small Cell Lung Cancer

Stefano Elia [1,2,*], Alexandro Patirelis [2], Georgia Hardavella [3,*], Antonella Santone [1], Federica Carlea [2] and Eugenio Pompeo [2]

[1] Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy
[2] Thoracic surgery unit, Tor Vergata University Hospital, Rome, Italy
[3] 9th Dept of Respiratory Medicine, Athens Chest Diseases Hospital Sotiria, Athens, Greece
* Correspondence: stefano.elia@unimol.it; Tel.: +39 0620902879

Abstract: Different prognostic scores have been applied to identify patients with non-small cell lung cancer who have a higher probability of poor outcome. In this study we evaluated whether Naples Prognostic Score, a novel index which considers both inflammatory and nutritional values, was associated with long-term survival. The study is a retrospective propensity score matching analysis of patients who underwent curative surgery for non-small cell lung cancer from January 2016 to December 2021. The score considered four pre-operative parameters: neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio, serum albumin and total cholesterol. Kaplan-Meier method and Cox regression analysis were performed to evaluate the relation between the score and disease-free survival, overall survival and cancer-related survival. A total of 260 patients were selected for the study, reduced to 154 after propensity score matching. Post-propensity Kaplan-Meier analysis showed a significant correlation between Naples Prognostic Score and overall survival (p=0.018) and cancer-related survival (p=0.007). Multivariate Cox regression analysis further validated the score as an independent prognostic indicator for both these survivals (p=0.007 and p=0.010 respectively). Naples Prognostic Score proved to be an easily achievable prognostic factor of long-term survival in patients with non-small cell lung cancer after surgical treatment.

Keywords: non-small cell lung cancer; prognosis; naples prognostic score; thoracic surgery; survival; prognostic score

1. Introduction

Lung cancer is one of the most common malignancies and the main cause of cancer death in men and women combined worldwide [1,2]. Non-small cell lung cancer (NSCLC) accounts for 84% of all lung cancers [3]. Despite the improvements in early lung cancer detection and in treatment options, about 30-50% of patients with completely surgically resected lung cancer develop recurrence [4-6] and 5-year survival ranges between 40- 90% [7].

Recently, there has been a growing interest in finding possible prognostic markers, which might impact management plans. Early identification of patients with a higher probability of a poor outcome can potentially guide an early personalized treatment. Currently, many hematological markers, which can be easily obtained in daily clinical practice, are increasingly utilized for the prognosis in several cancers, including NSCLC. In particular, systemic inflammation and nutritional status has been proven to be involved in cancer development [8,9] and related biomarkers were evaluated as possible indicators of outcome for oncologic patients [10-14].

In 2017, Galizia et al. proposed a novel score, the Naples prognostic score (NPS), based on both inflammatory and nutritional biomarkers, for patients receiving surgery for colorectal cancer [15]. The score considered pre-operative neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), serum albumin and total cholesterol and proved to have a strong association with long-term survival.

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In this retrospective study we evaluated whether NPS is associated with disease recurrence and death in a group of patients with surgically resected NSCLC.

2. Materials and Methods

2.1. Patient selection

The study is a retrospective analysis of patients who underwent surgery for NSCLC confirmed by final histology from January 2016 to December 2021. All enrolled patients were discussed in a multidisciplinary team meeting and subsequently underwent pulmonary resection (pneumonectomy, bilobectomy, lobectomy, segmentectomy, wedge resection), and lymphadenectomy. All patients' clinical pre-operative nodal and metastatic stage was N0 and M0 and clinical stage ranged from stage I to stage IIIA. Patients with a history of infection or any surgery within the previous 3 months or any malignancy within the last 5 years preceding pulmonary resection were excluded. We also excluded anyone who had a positive history for hematological, autoimmune or immunodeficiency diseases. We finally excluded patients who had incomplete pre-operative laboratory tests.

2.2. Data collection

Data about patients demographic and clinical information were collected by clinical records, including sex, age, comorbidities smoking history, type of surgery, final histology, pT and pN and pre-operative laboratory tests about neutrophils, lymphocytes, monocytes, serum albumin and total cholesterol. NPS was calculated, as stated by the original study of Galizia et al. [15] considering NLR, LMR, serum albumin and total cholesterol. According to previous studies, 1 point was assigned if NLR≤2.96, LMR≥4.44, serum albumin<4 g/dL or total cholesterol was ≤180 mg/dL. Then patients were divided into 3 groups according to their final score; group 0 for final score 0, group 1 for final score 1 or 2 and group 2 for final score 3 or 4.

Patient follow-up data were collected from outpatient clinic records, medical inpatient records or virtual consultations. We measured the disease-free survival (DFS), as the time from the day of surgery to recurrence, and the overall survival (OS) as the time from surgery to patients' death. We also evaluated the cancer-related survival (CRS), considering only deaths due to NSCLC.

2.3. Objective

The main goal of this retrospective study was to investigate whether the NPS is related to long-term survival in operated patients with NSCLC. Particularly, we evaluated if patients within a higher Naples group presented an increased tendency to recurrence or a poorer prognosis. We also assessed if NPS has a higher prognostic value compared to its single biomarkers.

2.4. Statistics

Statistical analysis was performed using the SPSS (IBM Corp. Released 2016. IBM SPSS Statistics, Version 26.0, Armonk, NY, USA: IBM Corp.) and a *p*-value less than 0.050 was considered statistically significant.

Continuous variables were reported as median and interquartile range (IQR), categorical ones as whole number and percentage.

Receiver operating characteristics (ROC) curves were performed to evaluate the ability of NPS groups, NLR, LMR, serum albumin and total cholesterol to predict prognosis by comparing their Areas under curves (AUCs)

Prognostic factors evaluation was initially based on survival curves using the Kaplan-Meier method and log rank test for DFS, OS and CRS. Afterwards, univariate Cox regression was performed. The covariates taken into consideration were: age (median, ≤72 vs >72 years), gender (male vs female), smoking history (never smoked vs former or current smoker), surgical procedure (major, including pneumonectomy, bilobectomy and lobectomy, vs sublobar, including both

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segmentectomy and wedge resection), side of surgery (right vs left), lobe affected by malignancy (upper or middle vs lower), pT (1 vs 2, 3 or 4), pN (0 vs 1 or 2), histology (adenocarcinoma vs squamous cell carcinoma) and Naples group. Factors significantly affecting survival at univariate analysis underwent multivariate analysis.

After this preliminary analysis, we performed a propensity score matching to reduce possible selection bias. The two considered populations were Naples groups 0 and 1 vs Naples group 2 and they were selected and matched one by one. This division was made according to the results of Kaplan-Meier analysis, with similar survivals for group 0 and 1, and after taking into consideration previous studies [16-18]. The covariates considered for this model were: age (≤72 vs >72 years old), gender, smoking history, type of surgery (major vs sublobar resection), pT (T1 vs T2-3-4), pN (N0 vs N1-2) and histology. In order to verify the homogeneity between the two groups, the standardized difference was calculated for each covariate before and after matching. Subsequently, we repeated Kaplan Meier and Cox regression analysis with the new population.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical features of the enrolled population, consisting of 260 patients, are summarized in Table 1. Median age of patients submitted to surgery was 72 (IQR 65-77) and 64.6% of them were male. Half of the population was a former smoker while only a minority (37/260, 14.2%) denied any smoking history. The most common type of surgery was lobectomy (187/260, 71.9%) followed by wedge resection (51/260, 19.6%), segmentectomy (10/260, 3.8%), pneumonectomy (8/260, 3.1%) and bilobectomy (4/260, 1.5%). Final histology showed lung adenocarcinoma in 184 patients (70.8%). With regard to pathological staging, the majority of the cases were in stage I or II; 115/260 (44.2%) patients were pT1 and 103/260 (39.6%) pT2 while 212/260 (81.5%) had no regional lymph nodes involved in the pathology review.

With reference to NPS, 86/260 patients (33.1%) had a NLR > 2.96 and 205/260 (78.8%) a LMR < 4.44. Regarding nutritional markers, serum albumin was < 4g/dL in 99/260 patients (38.1%) and half of them had total cholesterol ≤ 180 mg/dL (127/260, 48.8%). Therefore, 28/260 patients belonged to Naples group 0, 146/260 to group 1 (56/260 with a score of 1 and 90/260 with a score of 2) and 86/260 to group 2 (63/260 with a score of 3 and 23/260 with a score of 4).

Table 1. Demographic and clinical characteristics of the enrolled population. IQR: interquartile range.

Variable	
Median age, years (IQR)	72 (65-77)
Gender, n (%)	
Male	168 (64.6%)
Female	92 (35.4%)
Median number of comorbidities (IQR)	3 (IQR 2-5)
Smoking history, n(%)	
Never smoked	37 (14.2%)
Former smoker	130 (50.0%)
Current smoker	93 (35.8%)
Surgical procedure, n(%)	
Pneumonectomy	8 (3.1%)
Bilobectomy	4 (1.5%)
Lobectomy	187 (71.9%)
Segmentectomy	10 (3.8%)
Wedge resection	51 (19.6%)
Side of surgery, n(%)	

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Right	151 (58.1%)
Left	109 (41.9%)
Lobe (pneumonectomies excluded), n(%)	
Upper	151 (58.1%)
Middle/lingula	11 (4.2%)
Lower	90 (37.7%)
Final histology, n (%)	
Lung adenocarcinoma	184 (70.8%)
Lung squamous carcinoma	76 (29.2%)
pT, n(%)	
1	115 (44.2%)
2	103 (39.6%)
3	29 (11.2%)
4	13 (5.0%)
pN, n(%)	
0	212 (81.5%)
1	29 (11.2%)
2	19 (7.3%)
Neutrophil/lymphocyte ratio, n(%)	
≤ 2.96	174 (66.9%)
>2.96	86 (33.1%)
Lymphocyte/monocyte ratio, n(%)	
<4.44	205 (78.8%)
≥4.44	55 (21.2%)
Serum albumin, n(%)	
<4.0 g/dL	99 (38.1%)
≥4.0 g/dL	161 (61.9%)
Total cholesterol, n(%)	
≤ 180 mg/dL	127 (48.8%)
> 180 mg/dL	133 (51.2%)
NAPLES score, n (%)	
0	28 (10.8%)
1	56 (21.5%)
2	90 (34.6%)
3	63 (24.2%)
4	23 (8.8%)
NAPLES group, n(%)	
0	28 (10.8%)
1	146 (56.2%)
2	86 (33.1%)
Median follow-up, months (IQR)	26 (15-40)
Recurrence, n(%)	
Yes	93 (35.8%)
No	167 (64.2%)
Median time to recurrence, months (IQR)	16 (8-29)
Status, n(%)	
Alive	216 (83.1%)
Dead	44 (16.9%)
Cancer-related death, n(%)	

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Yes	24 (54.5%)
No	20 (45.5%)
Median time to death, months (IQR)	13 (6-22)

3.2. Follow-up

Median follow up was 26 months (IQR 15-40 months). 93/260 patients (35.8%) presented recurrence during this period, with a median time to recurrence of 16 months (IQR 8-29 months). A total of 44/260 deaths (16.9%) occurred and more than half of them were due to lung cancer (24/44, 54.5%). Median time to death for these patients was 13 months (IQR 6-22 months).

3.3. ROC curves

NPS was found to have the largest AUC for all the considered outcomes when compared to NLR, LMR, serum albumin and total cholesterol. In particular, the AUC values were 0.58 (95% CI 0.51-0.66, p=0.025) for risk of recurrence, 0.67 (95 CI 0.59-0.76, p<0.001) for risk of death and 0.71 (95% CI 0.60-0.81, p=0.001) for risk of cancer-related death. AUCs for the other variables are reported in Figure 1.

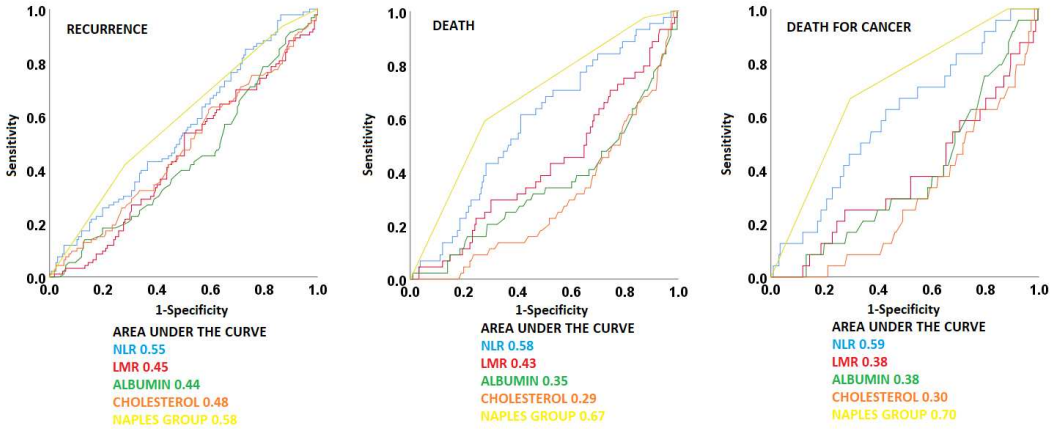

Figure 1. Receiver operating characteristics (ROC) curver for Naples Prognostic Score and its variables.

3.4. Survival analysis

We analyzed the influence of each NPS parameter on survival with Kaplan-Meier curves. There was no statistical significance between NLR and survival while patients with LMR<4.44 showed a shorter disease-free survival (p=0.031). At the analysis of nutritional markers, both serum albumin and total cholesterol resulted in affecting OS (p=0.003 and p<0.001 respectively) and CRS (p=0.020 and p=0.004 respectively) while they had no influence on DFS.

After this preliminary analysis, we performed Kaplan-Meier curves to evaluate differences among the Naples groups on survival. A statistically significant difference was found among groups in the DFS (p=0.037), as shown in Figure 2. Recurrence occurred in 6/28 patients in group 0 (21.4%), 48/146 patients in group 1 (32.9%) and 39/86 patients in group 2 (45.3%). 5-year DFS was 55.8% for group 0, 44.4% for group 1 and 37.8% for group 2.

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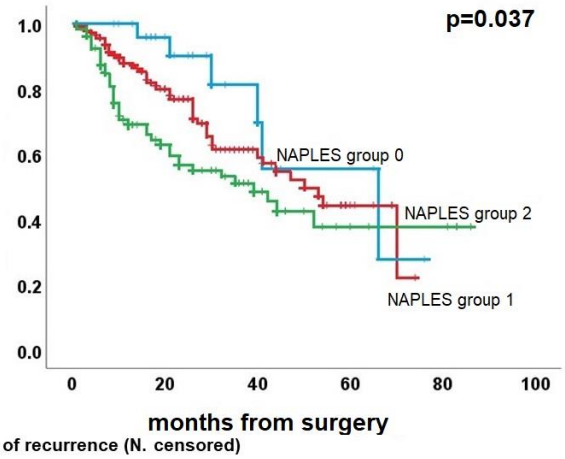
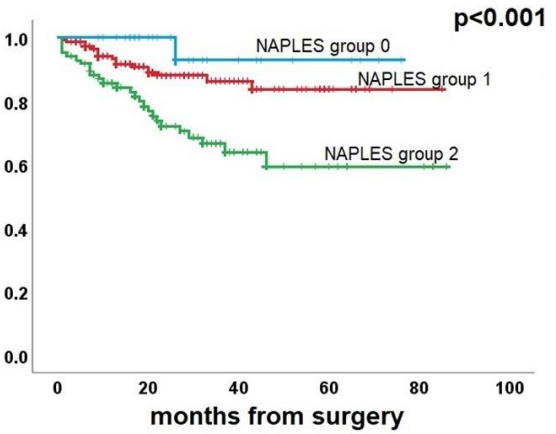


N. patients at risk of recurrence (N. censored)

Time (months)	0	20	40	60	74 76 80 86
NAPLES group 0	28(0)	17(9)	5(18)	3(19)	0(21)
NAPLES group 1	146(0)	79(42)	28(77)	7(92)	0(98)
NAPLES group 2	86(0)	40(18)	18(32)	5(42)	4(43) 0(47)

Figure 2. Kaplan Meier curve for disease-free survival.

NPS also affected OS, as reported in Figure 3 (p<0.001). We recorded 1 case of death in group 0 (1/28, 3.6%), 17 cases in group 1 (17/146, 11.6%) and 26 cases in group 2 (26/86, 30.2%). 5-year OS was 92.9% for group 0, 83.8% for group 1 and 59.4% for group 2.



N. patients at risk of recurrence (N. censored)

Time (months)	0	20	40	60	76 80 86
NAPLES group 0	28(0)	17(11)	7(20)	4(23)	0(27)
NAPLES group 1	146(0)	92(40)	36(94)	11(118)	1(128) 0(129)
NAPLES group 2	86(0)	50(18)	20(41)	7(53)	4(56) 0(60)

Figure 3. Kaplan Meier curve for overall survival.

Finally, a significant difference was found in the CRS with p=0.001 (Figure 4). Deaths due to cancer were 8/146 in group 1 (5.5%) and 16/86 in group 2 (18.6%) while no cases were registered in group 0. 5-year CRS was 100.0% for group 0, 91.4% for group 1 and 72.2% for group 2.

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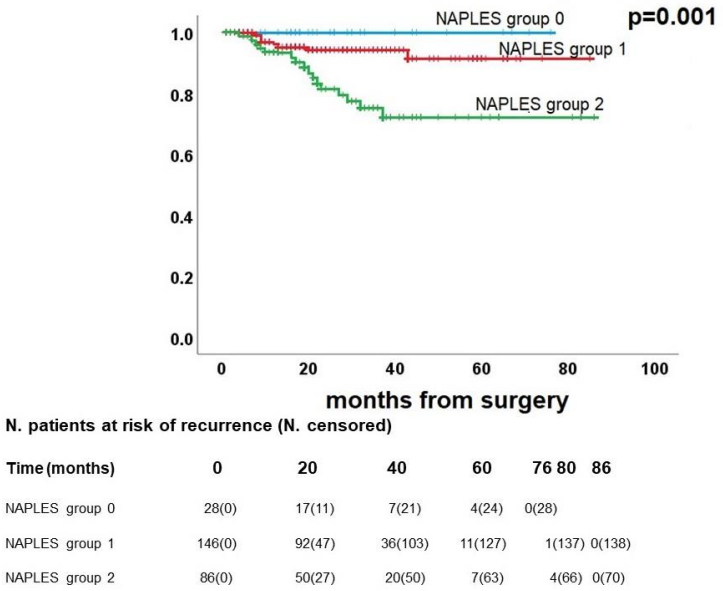

N. patients at risk of recurrence (N. censored)

Time (months)	0	20	40	60	76 80	86
NAPLES group 0	28(0)	17(11)	7(21)	4(24)	0(28)	
NAPLES group 1	146(0)	92(47)	36(103)	11(127)	1(137)	0(138)
NAPLES group 2	86(0)	50(27)	20(50)	7(63)	4(66)	0(70)

Figure 4. Kaplan Meier curve for cancer-related survival.

Cox regression analysis (Table 2) showed that a higher Naples group was a predictor of shorter DFS only at univariate analysis (p=0.011). Conversely, at multivariate analysis, a higher Naples group was associated with worse OS (HR=2.5, 95% CI 1.4-4.3, p<0.001) together with a pT>1 (HR=3.5, 95% CI 1.5-7.9, p=0.003) Similarly, a decreased CRS was associated with higher Naples group (HR=3.5, 95% CI 1.6-7.9, p=0.002), pT>1 (HR=4.0, 95% CI 1.2-13.8, p=0.027), and the presence of metastatic regional lymph nodes at final histology (HR=2.8, 95% CI 1.3-6.3, p=0.015).

Table 2. Cox regression analysis. CI: confidence interval; F: female; HR: hazard ratio; M: male.

	Disease Free Survival			**Overall Survival**			**Cancer related Survival**		
	Univariable	**Multivariable**		**Univariable**	**Multivariable**		**Univariable**	**Multivariable**	
	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value
Age (≤ 72 vs > 72) years	**0.019**	1.4 (0.9-2.1)	0.14	0.057	-	-	0.11	-	-
Gender (M vs F)	0.13	-	-	0.10	-	-	0.10	-	-
Smoking history (never vs former/current)	0.84	-	-	0.080	-	-	0.41	-	-
Surgical procedure (major vs sublobar)	**0.028**	1.7 (1.1-2.7)	**0.020**	0.98	-	-	0.78	-	-

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Side of surgery (right vs left)	0.057	-	-	0.67	-	-	0.51	-	-
Lobe (upper and middle vs lower)	0.66	-	-	0.33	-	-	0.25	-	-
pT (1 vs 2-3-4)	**<0.001**	2.2 (1.4-3.5)	**0.001**	**<0.001**	3.5 (1.5-7.9)	**0.003**	**0.003**	4.0 (1.2-13.8)	**0.027**
pN (0 vs 1-2)	**0.030**	1.4 (0.8-2.3)	0.19	**0.009**	1.8 (0.9-3.4)	0.072	**0.002**	2.8 (1.2-6.3)	**0.015**
Histology (adenocarcinoma vs squamous)	**0.013**	1.4 (0.9-2.2)	0.15	0.067	-	-	0.19	-	-
NAPLES group	**0.011**	1.3 (0.9-1.9)	0.13	**<0.001**	2.5 (1.4-4.3)	**0.001**	**0.001**	3.5 (1.6-7.9)	**0.002**

3.5. Propensity score matching

The standardized difference before and after matching for each covariate is reported in Table 3. Propensity score matching extrapolated a final population of 154 patients, 77 belonging to Naples group 0 or 1 and 77 to Naples group 2.

Table 3. Standardized differences before and after propensity score matching.

	Before matching				**After matching**			
	Naples group 0-1	**Naples group 2**	**p-value**	**Standardized difference**	**Naples group 0-1**	**Naples group 2**	**p-value**	**Standardized difference**
Gender male, n(%)	102 (58.6)	66 (76.7)	0.004	0.39	59 (76.6)	57 (74.0)	0.71	0.06
Age>72 years, n(%)	71 (40.8)	47 (54.7)	0.035	0.28	39 (50.6)	38 (49.4)	0.87	0.02
Smoker (former or current), n(%)	143 (82.2)	80 (93.0)	0.019	0.33	71 (92.2)	71 (92.2)	1.00	0.00
Type of resection, n(%)			0.13	0.19			0.57	0.09
Sublobar	36 (20.7)	25 (29.1)			17 (22.1)	20 (26.0)		

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Major	138 (79.3)	61 (70.9)			60 (77.9)	57 (74.0)		
pT, n(%)			0.008	0.36			1.00	0.00
T1	87 (50.0)	28 (32.6)			25 (32.5)	25 (32.5)		
T2-T3-T4	87 (50.0)	58 (67.4)			52 (67.5)	52 (67.5)		
pN, n(%)			0.77	0.04			0.52	0.10
N0	141 (81.0)	71 (82.6)			62 (80.5)	65 (84.4)		
N1-N2	33 (19.0)	15 (17.4)			15 (19.5)	12 (15.6)		
Histology, n(%)			0.41	0.11			0.86	0.02
Adenocarcinoma	126 (72.4)	58 (67.4)			54 (70.1)	53 (68.8)		
Squamous cell carcinoma	48 (27.6)	28 (32.6)			23 (29.9)	24 (31.2)		

As shown in Figure 5, DFS did not present significant differences between Naples groups 0 and 1 vs group 2. In detail, Naples groups 0 and 1 had a 5-year DFS rate of 38.0%, and Naples group 2, had 41.2% (p=0.34). On the other hand, a significant difference was confirmed between group 0-1 and group 2 in OS (p=0.018), with a 5-year survival rate of 83.5% and 61.1% respectively (Figure 6), and in CRS (p=0.007), showing 5-year survival rates of 95.3% for Naples group 0 and 1 and 74.7% for Naples group 2 (Figure 7).

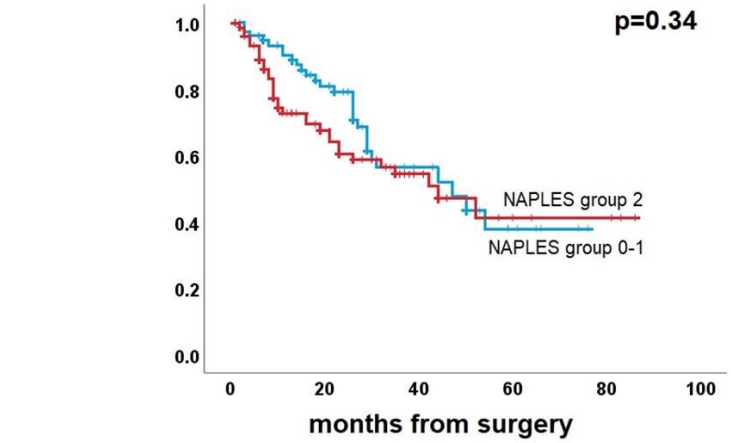

Figure 5. Post-propensity Kaplan Meier curve for disease-free survival.

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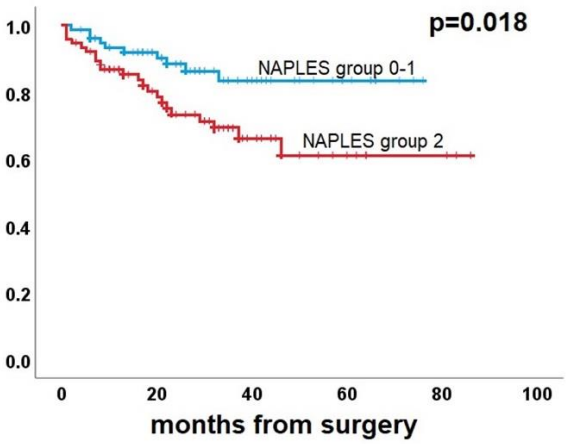
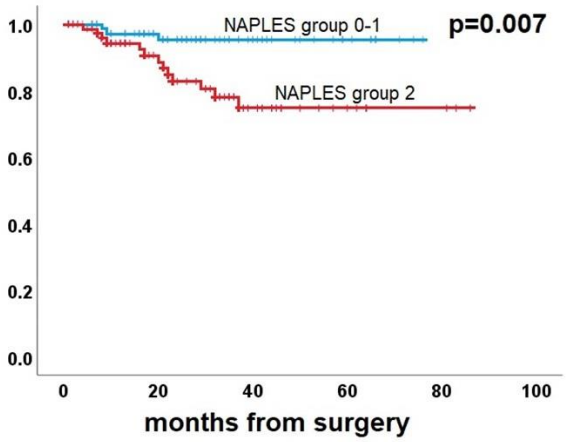


N. patients at risk of recurrence (N. censored)

Time (months)	0	20	40	60	76 80	86
NAPLES group 0-1	77(0)	53(17)	20(47)	9(58)	0(67)	
NAPLES group 2	77(0)	46(16)	19(37)	6(49)	3(52)	0(55)

Figure 6. Post-propensity Kaplan Meier curve for overall survival.



N. patients at risk of recurrence (N. censored)

Time (months)	0	20	40	60	76 80	86
NAPLES group 0-1	77(0)	53(21)	20(54)	9(65)	0(74)	
NAPLES group 2	77(0)	46(24)	19(45)	6(58)	3(61)	0(64)

Figure 7. Post-propensity Kaplan Meier curve for cancer-related survival.

The Cox regression analysis (Table 4) showed that NPS did not affect DFS at univariate analysis (p=0.34). Conversely, it resulted in being a significant prognostic factor at multivariate analysis for OS (HR=2.5, 95% CI 1.2-5.2, p=0.018) together with pT (HR=5.2, 95% CI 1.6-17.0, p=0.007) and the only one for CRS (HR=5.2, 95% CI 1.5-18.2, p=0.010).

Table 4. Post-propensity Cox regression analysis. CI: confidence interval; F: female; HR: hazard ratio; M: male.

	Disease Free Survival		Overall Survival		Cancer related Survival	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable

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	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value
Age (≤ 72 vs > 72) years	0.11	-	-	0.78	-	-	0.80	-	-
Gender (M vs F)	0.42	-	-	0.77	-	-	0.50	-	-
Smoking history (never vs former/current)	0.59	-	-	0.64	-	-	0.60	-	-
Surgical procedure (major vs sublobar)	**0.013**	2.1 (1.2-3.6)	**0.006**	0.72	-	-	0.76	-	-
Side of surgery (right vs left)	0.53	-	-	0.81	-	-	0.93	-	-
Lobe (upper and middle vs lower)	0.68	-	-	0.12	-	-	0.24	-	-
pT (1 vs 2-3-4)	**0.011**	2.3 (1.3-4.4)	**0.007**	**0.008**	5.2 (1.6-17.0)	**0.007**	**0.046**	7.0 (0.9-53.7)	0.061
pN (0 vs 1-2)	0.31	-	-	0.077	-	-	**0.027**	2.7 (0.9-7.4)	0.061
Histology (adenocarcinoma vs squamous)	0.26	-	-	0.99	-	-	0.84	-	-
NAPLES group (0-1 vs 2)	0.34	-	-	**0.023**	2.5 (1.2-5.2)	**0.018**	**0.015**	5.2 (1.5-18.2)	**0.010**

4. Discussion

Systemic inflammation has been proven to play a key role in tumorigenesis and several studies demonstrated that some inflammatory biomarkers from routinary laboratory tests could be a predictor of long-term outcome in patients with NSCLC. For example, neutrophils stimulate angiogenesis by secreting proangiogenic factors and are involved in the production of growth factors. Consequently, neutrophilia is usually related to a poorer prognosis [19]. Monocytes stimulate tumor angiogenesis by producing vascular endothelial growth factor (VEGF) and they can also differentiate into tumor-associated macrophages, thus favoring the creation of tumor micro-enviroment [20,21].

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Tumor angiogenesis and growth seems to be also promoted by an increased number of platelets, which release VEGF and whose proliferation is stimulated by pro-inflammatory cytokines [22,23]. On the contrary, lymphocytes react against cancer, by inhibiting cellular proliferation and migration and their high levels may correlate with a positive prognosis [24].

Based on the above, new prognostic tools such as pre-operative NLR, LMR and platelet to lymphocyte ratio (PLR) started to be used, achieving a strong correlation with all lung and other types of cancer prognosis [8,25,26]

Systemic inflammation might be usually related to a nutritional impairment due to an increase of catabolic processes and energy consumption. Therefore, low levels of nutritional markers such as serum albumin, whose synthesis is inhibited by systemic inflammation [27], or cholesterol, which is a pivotal component of cellular membranes and is involved in cell homeostasis [28], could be considered as a bad prognosticator [29-30]. Pre-operative nutritional scores, such as the Prognostic Nutritional Index (PNI) or the Controlling Nutritional Status (CONUT) score are independent prognostic factors in lung cancer [31,32].

In 2017, Galizia et al. assessed the Naples Prognostic Score which was a new prognostic tool considering comprehensively both inflammatory (NLR and LMR) and nutritional biomarkers (serum albumin and total cholesterol) [15]. NPS proved to be a prognostic factor for colorectal cancer in terms of OS and DFS. NPS was also applied in pancreatic cancer [18], osteosarcoma [33], endometrial cancer [34], gastric [35] and esophageal cancer [36], showing a significant correlation with DFS [33,34], OS [18,33-35] or CRS [36].

To the best of our knowledge, only a few studies analyzed the role of NPS in NSCLC. Guo et al. evaluated patients with unresectable stage III NSCLC and showed NPS was an independent prognostic factor for both DFS and OS [37]. Similar results were obtained by Zou et al. who studied NPS in patients with locally advanced NSCLC following neo-adjuvant therapy [38]. To the best of our knowledge our study involved operated NSCLC patients and was the first one to show a correlation between NPS and CRS in these patients. Operated early stage NSCLC patients were also studied by Dahu Ren et al [39] who found a strong correlation of NPS with recurrence free survival (RFS) and OS while Li et al [16] found it with DFS and OS. Finally, Peng et al reported NPS as a significant prognosticator for both DFS and OS in all patients with NSCLC [40]. Our study proved a strong association between NPS groups and OS and CRS, as shown at Kaplan-Meier analysis and multivariate Cox regression. These results were confirmed after propensity score matching which balanced potential confounding factors regarding clinical and pathological features of the enrolled population between Naples group 0-1 vs 2. Regarding DFS, NPS proved to be a significant indicator of prognosis only in the pre-propensity analysis at Kaplan-Meier and univariate Cox regression. Unlike the above studies, we took into account also CRS, which evaluates only deaths due to cancer and is more specific than OS.

Our findings confirm that NPS may be a strong predictor of long-term survival outcomes in patients with NSCLC following surgical resection. NPS is simple to use in daily clinical practice as it utilizes parameters that are readily available in patients due to undergo thoracic surgery with curative intent. Following extensive validation, it may be encountered in combination with clinical and radiological aspects to inform the decision-making process with regard to treatment and interventions.

This study has some limitations. It is a single-center retrospective study, thus making possible selection bias. We addressed this by performing propensity score matching which reduced the differences in clinical and pathological features between the groups. Another limitation is the small sample, further reduced after propensity score matching, therefore reducing the possibility to generalize the results. Further larger multicentric studies are needed to validate these findings.

5. Conclusions

NPS is an easily obtainable index which considers comprehensively inflammatory and nutritional status of patients with NSCLC. It was proved to be a significant prognostic factor of long-term survival outcomes in patients with NSCLC after surgical treatment. If validated by further

studies, NPS could be considered to tailor an individualized treatment in patients with a higher risk of poor outcome.

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