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Highly elevated systemic inflammation is a strong independent predictor of early mortality in advanced non-small cell lung cancer

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ABSTRACT

Background: Ample evidence support inflammation as a marker of outcome in non-small cell lung cancer (NSCLC). Here we explore the outcome for a subgroup of patients with advanced disease and substantially elevated systemic inflammatory activity.

Methods: The source cohort included consecutive patients diagnosed with NSCLC between January 2016 – May 2017 ($n = 155$). Patients with active infection were excluded. Blood parameters were examined individually, and cut-offs (ESR > 60 mm, CRP > 20 mg/L, WBC > 10×10^9, PLT > 400×10^9) were set to define the group of hyperinflamed patients. A score was developed by assigning one point for each parameter above cut-off (0–4 points).

Results: High systemic inflammation was associated with advanced stage and was seldom present in limited NSCLC. However, the one year survival of patients in stage IIIB-IV ($n = 93$) with an inflammation score of ≥2 was 0% compared to 33% and 50% among patients with a score of 1 and 0 respectively. The effect of a high inflammation score on overall survival remained significant in multi-variate analysis adjusted for confounding factors. The independent hazard ratio of an inflammation score ≥ 2 in multi-variate analysis (HR 3.43, CI 1.76–6.71) was comparable to a change in ECOG PS from 0 to 2 (HR 2.42, CI 1.13–5.18).

Conclusion: Our results show that high level systemic inflammation is a strong independent predictor of poor survival in advanced stage NSCLC. This observation may indicate a need to use hyperinflammation as an additional clinical parameter for stratification of patients in clinical studies and warrants further research on underlying mechanisms linked to tumor progression.

Background

Treatment options for non-small cell lung cancer (NSCLC) have expanded rapidly in recent years with the advent of targeted therapies and the introduction of immunotherapy. Overall survival has improved but the long term survival in advanced disease remains poor [1]. Tools for prognostication are important for the choice of treatment for individual patients, for evaluation of new treatment options and for prioritization strategies in face of rapidly increasing treatment costs.

Inflammation is an intrinsic part of most malignancies and has several tumor-promoting effects, including proliferation, metastasis and survival of cancer cells [2]. The tumor cells, the surrounding tissue and migratory immune cells constitute the tumor microenvironment (TME) where the localized immune response and the interplay between neo-antigens, active and regulatory T-cells and suppressing factors play a role in the inflammatory process [3, 4]. The systemic inflammation, in turn, is mediated by cytokines, proteins and circulating immune cells released from the TME as a response to the activity in and around the tumor [5]. The impact of inflammation induced by destructive tumor growth is likely quite different in localized and advanced stage cancer.

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In low stage disease surgery with curative intent will remove the tumor lesion as well as the cause of inflammation. In contrast, at high stage the tumor lesions remain in place as inflammatory foci during systemic therapy or best supportive care. Here, the general well systemic effects on organ function presumably explain the negative impact on survival.

Strong evidence links systemic inflammation to outcome in solid tumors [6–9]. A plethora of biomarkers have been used, most commonly C-reactive protein (CRP), absolute blood cell counts and ratios between white blood cell subtypes or combination indexes of several blood parameters. In lung cancer similar approaches have been used to examine survival and outcome following treatment with surgery [10, 11], radiotherapy [12, 13], chemotherapy [14], immunotherapy [15, 16] and targeted therapy [17]. Across treatment modalities, systemic inflammation has been linked to risk of recurrence or worse outcome. Although treatment selection based on systemic inflammation is theoretically feasible, it is not currently used in clinical practice.

The most common approach when establishing the cut-off levels for individual blood parameters is to use values at, or near, the upper limit of the normal reference range. Using these values in a setting with cancer patients, especially in advanced disease, leads to a large proportion of patients above cut-off [18]. This in turn means that relevant subgroups among patients with the highest degree of systemic inflammation may be obscured.

Here we aimed to investigate the prognostic impact of elevated inflammation in a consecutive cohort of NSCLC patients, with focus on patients in stage IIIB-IV. We used laboratory inflammation parameters that are part of the routine work-up at diagnosis and explored higher cut-offs to identify and analyze the fraction of patients with severe signs of tumor induced active inflammation.

Material and methods

Patients

All patients undergoing diagnostics for thoracic malignancies at Gävle Hospital were asked to participate in a regional biobanking study, U-CAN [19]. The study was approved by the Regional Ethics Committee (reference number 2015/142). The included patients were diagnosed between January 2016 and May 2017, with an inclusion rate of 95%. Patients with small cell lung cancer and patients without a histolopathological diagnosis were excluded. In total 155 patients with non-small lung cancer (NSCLC) were evaluated for inflammation biomarkers; Of these, 4 were excluded due to concurrent active infection leaving 151 patients eligible for review of clinical data and further analysis.

Data collection

Patient charts were retrospectively reviewed and medical data collected. Date of diagnosis was defined as the date of obtaining tissue confirming the diagnosis of NSCLC. Overall survival (OS) was determined as time elapsed between the date of diagnosis and date of death. Follow-up on survival data was done in May 2018. Results from blood samples taken before the start of treatment, as part of routine diagnostics, were used for the analysis. Peripheral blood parameters evaluated in this study were erythrocyte sedimentation rate (ESR, reference interval 2 – 22 mm), C-reactive protein (CRP, ref 0 – 5 mg/L), white blood cell count (WBC, ref 3.5 – 8.8 $\times$ 10^9/L) and platelet count (PLT, ref 145 – 348 $\times$ 10^9/L). The staging was done according to the 7th edition of the TNM classification guidelines [20].

Statistical analysis

Descriptive statistics were performed using proportions for categorical variables and means with standard deviations for continuous variables. The variables of interest were then aggregated into two groups, and presented in Kaplan-Meier curves, together with a total risk score. The risk score was based on the cut off from the four inflammation markers. In a final step, the separate markers and the overall risk score were included in Cox regression models adjusted for potential other confounders (gender, age, PS, stage, and smoking history). All analyses were conducted using R 3.5.1, and a p-value below 5% was considered statistically significant.

Results

Blood parameters, cut-offs and inflammation score

Blood parameters were examined individually to decide cut-offs with the aim to target the quartile of patients with the highest values for each biomarker. The cut-off levels were arbitrarily set at even rounded numbers based on clinical experience and guidance from published papers that included data on high stage subgroups [18, 21–23]. Cut-off levels were set at ESR >60 mm, CRP>20 mg/L, WBC>10 $\times$ 10^9 and PLT > 400 $\times$ 10^9. An inflammation score was determined giving one (1) point for each peripheral blood parameter above cut-off for a total between zero (0) and four (4) points. In this scoring system high level inflammation was defined as a score of two points and above (2+).

Patient characteristics and inflammation scores in full cohort

Detailed patient characteristics are shown in **Table 1** (n = 151) stratified according to inflammation scores 0, 1 and 2+. The median value and interquartile range of each inflammation parameter are shown for patients stratified in the 0, 1 and 2+ groups, as well as for the cohort in total. Thus, the chosen cut-offs were found to define the top 22% (ESR), 17% (PLT), 31% (WBC) and 24% (CRP) of patients in the total cohort respectively.

There were obvious differences in regard to clinical characteristics between the patients with high levels of systemic inflammation (2+) compared to patients with inflammation score 0 or 1. Poor performance status, ECOG PS 3–4, was seen in 32% of patients in the score 2+ group and in only 6% in the score 0 group. Active treatments were given to over 90% of patients with a score of 0 or 1 compared to 55% of the patients with a score of 2+. Never smokers and EGFR mutations were more common in patients with inflammation score 0 or 1 with the overwhelming majority of the score 2+ group being current or former smokers (94%). Moreover, 84% of patients with score 2+ were diagnosed in stage IIIb-IV in comparison to 52% and 64% of patients with score 0 or 1 respectively. A BMI cut-off of < 18.5 was used to mark malnourishment, a factor that could possibly impact survival outcomes and treatment efficacy in NSCLC [24]. However, the prevalence of BMI < 18.5 was lowest in the group with a score of 2+ at 6.5% compared to score 0 (8.3%) and score 1 (19%).

Notably, high levels of systemic inflammation (2+), was rarely present in low stage disease, only in 5 of 58 patients (8.6%) in stage I-IIIA. In contrast, score 2+ was present in 26 of 93 (28%) of patients in stage IIIB and IV. Thus, the impact of our definition of high inflammation will be less relevant at lower stages, as a stratifying parameter. For this reason we chose to limit further analysis to patients with advanced disease.

Survival and inflammation in advanced stage

Clinical characteristics for the 93 patients in stage IIIB and IV are displayed in **Table 2**, as well as the median values and inter-quartile ranges for the inflammatory parameters. Survival illustrated by Kaplan-Meier curves for stage IIIB and IV are presented for individual blood parameters in **Fig. 1**. Each inflammatory parameter was significantly associated with survival at the defined cut-offs. ESR showed the highest univariate impact (HR 3.80, CI 2.07 – 6.97) followed by CRP (HR 2.95,CI 1.78 – 4.89), WBC (HR 2.79, 1.71 – 4.53) and PLT (HR 1.91, CI 2.78 – 3.28). **Fig. 2** shows the survival impact after stratification for

Table 1
Patient characteristics for the entire cohort of patients with NSCLC diagnosed 2016–2017 ($n = 151$) as well as separated by inflammation score.

	Score 0		Score 1		Score 2+		Total	
	n	%	n	%	n	%	n	%
Gender								
Male	50	59.5	18	50	21	67.7	89	58.9
Female	34	40.5	18	50	10	32.3	62	41.1
Age at diagnosis								
<75	46	54.8	15	41.7	20	64.5	81	53.6
>75	38	45.2	21	58.3	11	35.5	70	46.4
BMI								
<18.5	7	8.3	7	19.4	2	6.5	16	10.6
>18.5	77	91.7	29	80.6	28	90.3	134	88.7
Smoking status								
Former	34	40.5	15	41.7	16	51.6	65	43
Current	38	45.2	16	44.4	13	41.9	67	44.4
Never	12	14.3	5	13.9	2	6.5	19	12.6
Performance status								
0	25	29.8	9	25	6	19.4	40	26.5
1	37	44	8	22.2	5	16.1	50	33.1
2	17	20.2	18	50	10	32.3	45	29.8
3–4	5	6	1	2.8	10	32.3	16	10.6
Histology								
Non squamous	74	88.1	33	91.7	27	87.1	134	88.7
Squamous	10	11.9	3	8.3	4	12.9	17	11.3
Stage at diagnosis								
IA-IIA	22	26.2	9	25	2	6.5	33	21.9
IIB-IIIA	18	21.4	4	11.1	3	9.7	25	16.6
IIIB-IV	44	52.4	23	63.9	26	83.9	93	61.6
ALK								
Negative	82	97.6	36	100	31	100	149	98.7
Positive	2	2.4	0	0	0	0	2	1.3
EGFR								
Negative	78	92.9	31	86.1	30	96.8	139	92.1
Positive	6	7.1	5	13.9	1	3.2	12	7.9
Treatment								
Yes	78	92.9	34	94.5	17	54.8	129	85.4
No	5	6	2	5.5	14	45.2	21	13.9
ESR, median, IQR	24	12–38	29	13.5–49.5	74	63–84.75	32	15–60
ESR <60	69	100	20	80	7	25	96	78.1
ESR 60+	0	0	6	20	21	75	27	21.9
PLT, median, IQR	280	235–333.25	291	220.5–333.25	343	296.5–445.5	292	240–353
PLT, <400	74	88.1	33	91.7	19	61.3	126	83.4
PLT, >400	10	11.9	3	8.3	12	38.7	25	16.6
WBC, median, IQR	7.8	6.3–9.0	9.75	7.925–12.1	12.8	10.9–15.35	8.6	6.9–19.5
WBC, <10	78	92.9	19	52.8	7	22.6	104	68.9
WBC, >10	6	7.1	17	47.2	24	77.4	47	31.1
CRP, median, IQR	3.6	1.7–7.15	7.7	2.4–20.0	62	27.5–80.5	6.6	2.3–19.5
CRP, <20	78	98.7	25	75.8	5	16.7	108	76.1
CRP, >20	1	1.3	8	24.2	25	83.3	34	23.9

inflammation scores 0, 1 and 2+. For high level inflammation (2+) the hazard ratio was 5.61 (CI 3.07 – 10.23). Notably, the one year survival of patients with an inflammation score of two or higher (2+) was 0% compared to 50% among patients with a score 0.

After multi-variate adjustment (**Table 3**) for confounding factors (stage, gender, age, BMI, smoking status and ECOG PS), an independent impact was confirmed for the individual laboratory parameters: ESR (HR 2.12, CI 1.02 – 4.37), CRP (HR 2.50, CI 1.36 – 4.58) and WBC (HR 2.23, CI 1.28 – 3.88), but not for PLT. The adjusted hazard ratio for inflammation score 1 was not significant at 1.22 (CI 0.59 – 2.51). However, high inflammation Score (2+) independently exhibited a significant survival impact at HR 3.43 (CI 1.76 – 6.71). Notably, the hazard ratio of an inflammation score of 2+, in multi-variate analysis, was higher than the independent impact of a change in ECOG PS from 0 to 2 (HR 2.42 CI 1.13 – 5.18).

Discussion

In this single center study on NSCLC we show a strong, independent, correlation between high levels of inflammatory activity, using routine laboratory parameters, and poor survival in stage IIIB-IV disease. A high inflammation score was comparable to a deterioration of PS from ECOG 0 to ECOG 2.

The strength of the study is that it is based on patients in daily practice with a high inclusion rate limiting selection biases incurred by referral to specialist centres, clinical study inclusion or other patient characteristics. Notably, also patients with ECOG PS 2 and higher were included in the study population. The parameters used are readily available, cheap and require no complicated calculations.

The effect of inflammation on outcome is well established in several treatment modalities in NSCLC. However, by using low cut-offs the impact of hyperinflammation might be obscured. When using cut-offs near the normal range, the majority of patients fall into the "inflamed" subgroup of patients. In the study by Koch et al. on advanced stage NSCLC [22], using CRP > 10 and WBC >8.8, almost two thirds (206/289 and 181/289) of patients were above the cut-off, and in multivariate analysis the HR for CRP was 1.5 (CI 1.11 – 2.02). In the same study, in patients treated with first line chemotherapy, stratifying for different CRP levels, the median survival at CRP < 10 (11.3 months) was somewhat reduced to 8.2 months (HR 1.38) at CRP 10 – 49 and notably fell to only 3.6 months (HR 2.61) in the 27% of patients with CRP > 50. In our study, the median survival in stage IIIB-IV was approximately 5 months for patients with an inflammation score ≤2 comprising treated and untreated patients and all ECOG PS.

Table 2
Patient characteristics for the cohort of stage IIIB/IV patients with NSCLC diagnosed 2016–2017 ($n = 93$).

	Score 0		Score 1		Score 2+		Total	
	n	%	n	%	n	%	n	%
Gender								
Male	27	61.4	12	52.2	18	69.2	57	61.3
Female	17	38.6	11	47.8	8	30.8	36	38.7
Age at diagnosis								
<75	26	59.1	9	39.1	17	65.4	52	55.9
>75	18	40.9	14	60.9	9	34.6	41	44.1
BMI								
<18.5	6	13.6	6	26.1	2	7.7	14	15.1
>18.5	38	86.4	17	73.9	24	92.3	79	84.9
Smoking status								
Former	18	40.9	7	30.4	14	53.8	39	41.9
Current	17	38.6	11	47.8	11	42.3	39	41.9
Never	9	20.5	5	21.7	1	3.8	15	16.1
Performance status								
0	13	29.5	7	30.4	3	11.5	23	24.7
1	18	40.9	3	13.0	5	19.2	26	28.0
2	8	18.2	12	52.2	9	34.6	29	31.2
3–4	5	11.4	1	4.3	9	34.6	15	16.1
Histology								
Non squamous	39	88.6	21	91.3	24	92.3	84	90.3
Squamous	5	11.4	2	8.7	2	7.7	9	9.7
ALK								
Negative	42	95.5	23	100.0	26	100.0	91	97.8
Positive	2	4.5	0	0.0	0	0.0	2	2.2
EGFR								
Negative	39	88.6	18	78.3	25	96.2	82	88.2
Positive	5	11.4	5	21.7	1	3.8	11	11.9
Treatment								
Yes	40	90.9	21	91.3	14	53.8	75	80.6
No	4	9.1	2	8.7	12	46.2	18	19.4
ESR, median, IQR	26	14–40	29	17–37	72	60–80	35	18–60
ESR < 60	40	100.0	15	93.8	7	29.2	62	77.5
ESR > 60	0	0.0	1	6.2	17	70.8	18	22.5
PLT, median, IQR	290	237–347	291	217–329	348	299–446	308	248–368
PLT, <400	37	84.1	21	91.3	15	57.7	73	78.5
PLT, >400	7	15.9	2	8.7	11	42.3	20	21.5
WBC, median, IQR	7.2	6.2–8.5	9.2	8.1–12.3	12.4	11–15.4	8,6	7.0–11.2
WBC, <10	41	93.2	13	56.5	6	23.1	60	64.5
WBC, >10	3	6.8	10	43.5	20	76.9	33	35.5
CRP, median, IQR	4.8	2.3–10.5	7.4	3.0–27.3	62	32–79	9,8	2.9–34.0
CRP, <20	42	97.7	13	65.0	4	16.0	59	67.0
CRP, >20	1	2.3	7	35.0	21	84.0	29	33.0

Another option is to combine several biomarkers into indexes as a method to select the patient group at highest risk. Sandfeld et al. [18] compared several indexes and combined them into composite indexes which reached a HR of 3.7 for the highest strata. Our study attempted to combine these two approaches using higher laboratory cut-offs as well as a combined parameter score to define the patients with high systemic inflammation.

Patients with high levels of inflammation represent a distinct subgroup of NSCLC with markedly worse survival. In our study the 2+ inflammation score identifies 30% of the patients in stage IIIB and IV. In this group many patients present with ECOG PS 3 – 4 and are thus not eligible for treatment. There is a clear confounding overlap between high PS and high inflammation but the impact of inflammation remain independently significant in multivariate analysis. Furthermore, even among patients with high levels of inflammation that present with more favorable characteristics (ECOG PS 0 – 1) and receiving treatment, survival is poor with a 1 year OS of 0% (**Fig. 2**).

The main weakness of this study is that it is a single center study with a relatively small patient cohort remaining after exclusion due to missing data. The number of patients with complete pre-treatment differential white blood cell counts were too few to compare our inflammation score with established indexes such as the neutrophil/lymphocyte ratio or the systemic immune-inflammation index [25]. Not having pre-treatment neutrophil levels has a further impact in that they are highly prevalent in the immune landscape of NSCLC [26]. Still, this is somewhat mitigated by our use of WBC which will largely be made up of neutrophils [27]. The cut-off levels chosen are arbitrary and are by no means definitive when it comes to defining an optimal definition of high level of inflammation. Furthermore, the individual impact of each parameter is different though they are given the same weight in the scoring system. Finally, high inflammatory activity could influence the efficacy of immunotherapy treatment [16, 28] though such effects could not be evaluated here. No patient in the subgroup with high inflammation received checkpoint inhibitors due to lack of treatment indications in the first line at the time of the study, and poor survival excluded second line use.

The clinical impact of high level systemic inflammation is large enough to warrant further studies to better understand the underlying biological mechanisms from histopathologic, genetic and immune response perspectives. In clinical studies patients with ECOG PS 2 and above are normally excluded and the resulting treatment groups are adjusted for ECOG PS status. However, as the effect of hyper-inflammation is of similar independent magnitude this might be an additional parameter to account for when evaluating treatment outcome.

A more radical concept would be to explore whether or not these patients benefit at all from chemotherapy. A subgroup of patients with high inflammatory activity and resulting poor outcome can readily be identified by the use of simple laboratory parameters used in routine practice. Given the quality of life impact and risk of complications for

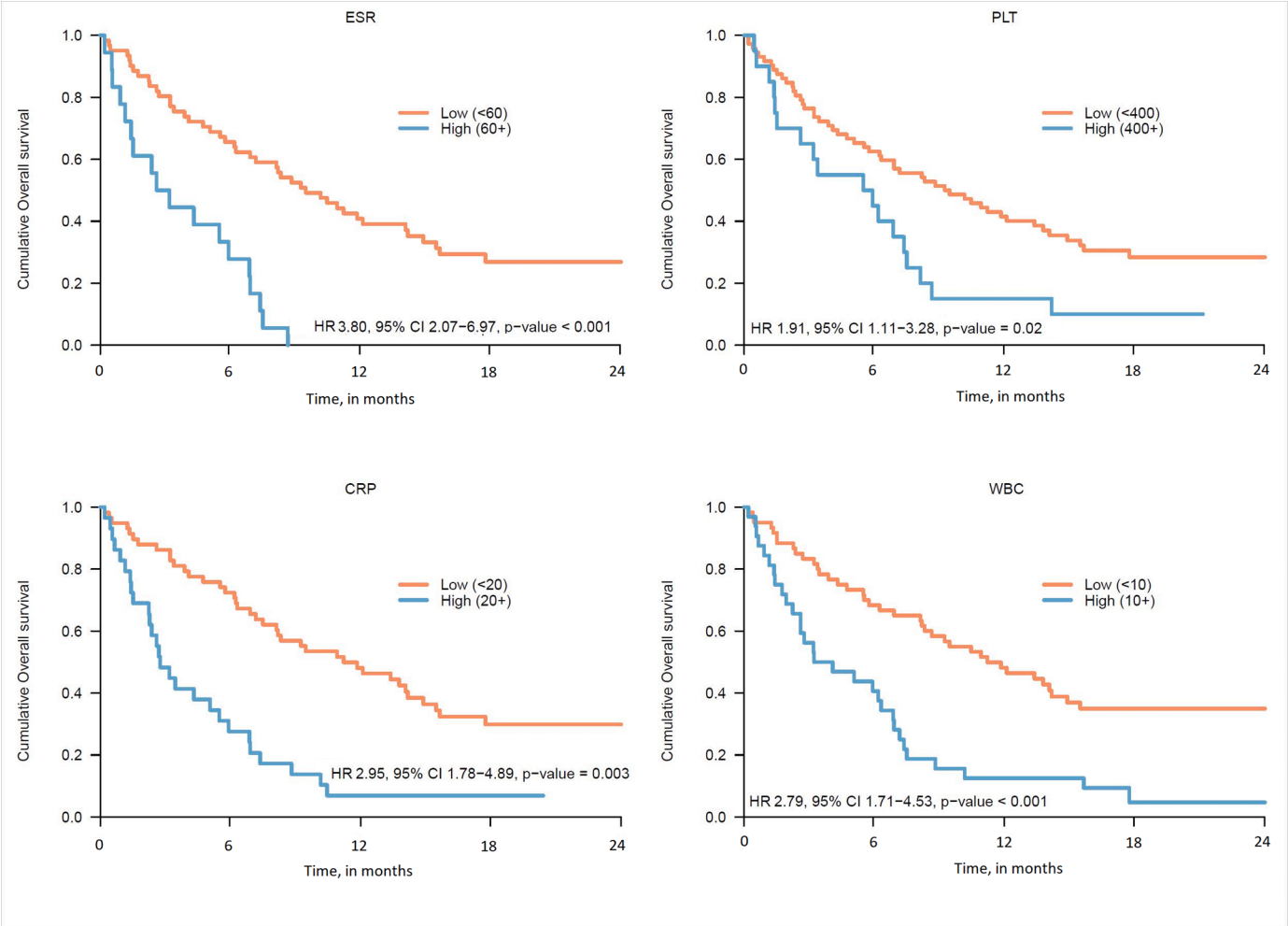

Fig. 1. Kaplan-Meier curves for the individual blood parameters comparing survival outcome in stage IIIB/IV NSCLC patients for high vs low values.

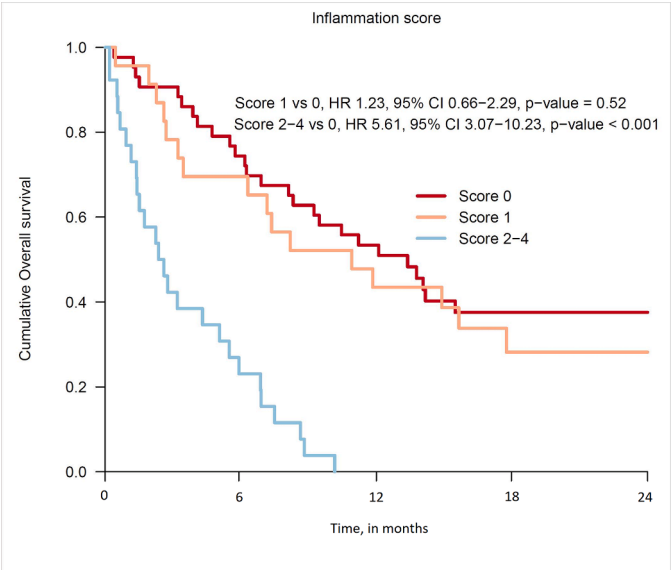

Fig. 2. Kaplan-Meier curves for the inflammation score comparing survival outcome in stage IIIB/IV NSCLC patients with inflammation score 0 vs score 1 vs score 2+.

patients undergoing chemotherapy the benefit of treatment seems low and other treatments or best supportive care may be better options.

Conclusion

A high level of systemic inflammation has a dramatic effect, comparable to ECOG PS 2 in multivariate analysis, on survival outcomes in advanced stage NSCLC.

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Disclosure statements

The authors report no conflicts of interest.

CRediT authorship contribution statement

Johan Isaksson: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Resources, Visualization, Writing – original draft. **Leo Wennström:** Investigation, Formal analysis, Data curation, Writing – review & editing. **Eva Branden:** Methodology, Supervision, Writing – review & editing. **Hirsh Koyi:** Methodology, Supervision, Writing – review & editing. **Anders**

Table 3
Multivariate cox-regression analysis for individual blood parameters as well as inflammation score adjusted for confounding factors in patients with NSCLC diagnosed 2016–2017.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Stage group												
IV	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
IIIB	1.31	0.58–2.97	1.26	0.54–2.95	1.39	0.61–3.18	1.19	0.52–2.72	1.37	0.60–3.15	1.68	0.73–3.89
Gender												
Male	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Female	1.06	0.63–1.80	0.96	0.56–1.66	1.19	0.69–2.03	0.97	0.57–1.67	1.11	0.66–1.89	1.16	0.69–1.96
Age at diagnosis												
<75	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
>75	0.70	0.42–1.18	0.65	0.37–1.16	0.66	0.39–1.13	0.82	0.48–1.41	0.60	0.35–1.01	0.73	0.43–1.25
BMI												
>18.5	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
<18.5	0.94	0.47–1.88	1.02	0.45–2.31	1.07	0.52–2.18	1.09	0.54–2.20	1.14	0.56–2.32	1.24	0.61–2.52
Smoking status												
Never	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
Former	4.31	1.76–10.56	4.73	1.75–12.84	4.40	1.80–10.76	5.06	2.02–12.63	3.72	1.51–9.17	3.72	1.50–9.22
Current	4.14	1.68–10.20	3.70	1.34–10.21	3.91	1.59–9.61	3.71	1.49–9.22	3.28	1.32–8.12	3.40	1.38–8.41
Performance status												
0	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.	1.00	ref.
1	2.00	0.96–4.17	1.74	0.80–3.79	1.79	0.84–3.79	1.84	0.86–3.93	2.39	1.13–5.09	1.94	0.89–4.21
2	3.21	1.53–6.74	3.41	1.42–8.18	2.98	1.41–6.31	2.14	0.98–4.65	3.14	1.48–6.66	2.42	1.13–5.18
3–4	11.16	4.70–26.52	8.30	2.91–23.67	9.34	3.77–23.16	8.20	3.35–20.05	9.56	3.97–23.00	6.47	2.51–16.3
ESR												
Low			1.00	ref.								
High			2.12	1.02–4.37								
PLT												
Low					1.00	ref.						
High					1.64	0.88–3.04						
CRP												
Low							1.00	ref.				
High							2.50	1.36–4.58				
WBC												
Low									1.00	ref.		
High									2.23	1.28–3.88		
Scoring group												
0											1.00	ref.
1											1.22	0.59–2.51
2–4											3.43	1.76–6.71

Berglund: Methodology, Validation, Formal analysis, Data curation, Visualization, Writing – review & editing. **Patrick Micke:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Johanna Sofia Margareta Mattsson:** Methodology, Writing – review & editing. **Linda Willén:** Conceptualization, Methodology, Validation, Writing – review & editing. **Johan Botling:** Methodology, Validation, Investigation, Resources, Supervision, Project administration, Funding acquisition, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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