Inflammation et cancer

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De mauvais pronostic

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Laboratory-Clinic Interface

The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer

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Table 1
Systemic inflammation based prognostic scores, the Glasgow Prognostic Scores.

The Glasgow Prognostic Score (GPS)	Points allocated
C-Reactive protein $\geqslant$10 mg/l and albumin $\geqslant$35 g/l	0
C-Reactive protein >10 mg/l	1
Albumin <35 g/l	1
C-Reactive protein >10 mg/l and albumin <35 g/l	2
The modified Glasgow Prognostic Score (mGPS)	
C-Reactive protein $\leqslant$ 10 mg/l and albumin $\geqslant$35 g/l	0
C-Reactive protein >10 mg/l	1
C-Reactive protein >10 mg/l and albumin <35 g/l	2

Table 2
Studies ($n = 4$) of the prognostic value of the GPS/mGPS, in unselected cohorts of patients with cancer ($n > 19{,}400$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
Crumley et al.[15]	Glasgow, UK	Gastro-oesophageal	217	1.7 (<0.001)	mGPS predicted survival independent of tumour site/stage/treatment
Proctor et al.[16]	Glasgow, UK	11 sites	9608	1.9 (<0.001)	mGPS predicted survival independent of tumour site
Proctor et al.[17]	Glasgow, UK	11 sites	8759	1.7 (<0.001)	mGPS predicted survival superior to NLR, PLR, PI, PNI
Shafique et al.[18]	Glasgow, UK	Prostate	897	1.8 (<0.05)	mGPS predicted survival superior to NLR

HR multivariate hazard ratio for incremental change of GPS/mGPS.

Table 3
Studies ($n = 28$) of the prognostic value of the GPS/mGPS in patients with operable cancer ($n > 8{,}000$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
McMillan et al.[14]	Glasgow, UK	Colorectal	316	1.7 (<0.001)	mGPS predicted survival independent of stage/treatment
Leitch et al.[19]	Glasgow, UK	Colorectal	233	2.1 (<0.001)	mGPS predicted survival superior to WCC/lymphocytes
Ishizuka et al.[20]	Tochigi, Japan	Colorectal	315	1.5 (<0.01)	GPS predicted survival independent of stage/treatment
Crozier et al.[21]	Glasgow, UK	Colorectal	188	2.2 (<0.05)	mGPS predicted survival independent of emergency presentation
Roxburgh et al.[22]	Glasgow, UK	Colorectal	244	2.3 (<0.001)	mGPS predicted survival independent of Petersen Index
Moyes et al.[23]	Glasgow, UK	Colorectal	455	1.8 (<0.01)	mGPS predicted post-operative infective complications
Roxburgh et al.[24]	Glasgow, UK	Colorectal	287	2.7 (<0.001)	mGPS predicted survival independent of tumour inflammatory infiltrate
Ishizuka et al.[25]	Tochigi, Japan	Colorectal liver	300	2.1 (<0.05)	GPS predicted survival independent of CLIP score
Ishizuka et al.[26]	Tochigi, Japan	Colorectal	156	24.5 (<0.05)	GPS predicted survival in T1/T2 stage disease
Kobayashi et al.[27]	Tokyo, Japan	Oesophageal	65	NR (<0.001)	GPS predicted survival independent of lymph node status
Polterauer et al.[28]	Vienna, Austria	Cervical	244	NR (<0.05)	GPS predicted survival independent of FIGO stage
Kobayashi et al.[29]	Tokyo, Japan	Colorectal liver	63	3.1 (<0.01)	GPS predicted survival independent of number of liver metastases
Knight et al.[30]	Manchester, UK	Pancreas	99	4.3 (<0.05)	GPS predicted post-operative morbidity
Richards et al.[31]	Glasgow, UK	Colorectal	320	1.8 (<0.001)	mGPS predicted survival independent of POSSUM
Nozoe et al.[32]	Koga, Japan	Gastric	232	4.1 (<0.001)	mGPS predicted survival independent of tumour stage
Moug et al.[33]	Kilmarnock, UK	Colorectal	206	1.6 (<0.05)	mGPS predicted survival independent of LNR
Roxburgh et al.[34]	Glasgow, UK	Colorectal	302	1.6 (<0.001)	mGPS predicted survival independent of comorbidity indices
Vashist et al.[35]	Hamburg, Germany	Oesophageal	495	3.0 (<0.001)	GPS predicted peri-operative morbidity and survival
Ishizuka et al.[36]	Tochigi, Japan	Hepatocellular	300	2.1 (<0.05)	GPS predicted survival independent of post-operative mortality
Dutta et al.[37]	Glasgow, UK	Oesophageal	112	4.3 (<0.001)	mGPS predicted survival independent of LNR, NLR and PLR
Jamieson et al.[38]	Glasgow, UK	Pancreas	135	2.3 (<0.001)	GPS predicted survival independent of margin status/adjuvant therapy
Ishizuka et al.[39]	Tochigi, Japan	Hepatocellular	398	2.5 (<0.05)	GPS predicted survival independent of CLIP score
Lamb et al.[40]	Glasgow, UK	Renal	169	5.1 (<0.001)	GPS predicted survival independent of established scoring systems
La Torre et al.[41]	Rome, Italy	Pancreas	101	1.8 (<0.01)	mGPS predicted survival independent of LNR and margin status
Wang et al.[42]	Guangzhou, China	Gastric	324	1.4 (<0.01)	GPS predicted survival independent of TNM stage, NLR and PLR
Jamieson et al.[43]	Glasgow, UK	Pancreas	173	1.8 (<0.01)	mGPS predicted survival independent of LIR
Ishizuka et al.[44]	Tochigi, Japan	Colorectal	271	2.0 (<0.05)	mGPS predicted survival in patients with normal CEA
Dutta et al.[45]	Glasgow, UK	Gastric	120	2.2 (<0.01)	mGPS predicted survival independent of LNR, NLR and PLR
Jiang et al.[46]	Tokyo, Japan	Gastric	1710	1.8 (<0.01)	mGPS predicted survival independent of TNM stage

HR, multivariate hazard ratio for incremental change of GPS/mGPS; NR, not reported; LNR, lymph node ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; CLIP, cancer of the liver Italian program; LIR, local inflammatory response; POSSUM.

Table 4
Studies ($n = 11$) of the prognostic value of the GPS/mGPS, in cancer patients receiving chemo/radiotherapy ($n > 1500$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
Forrest et al.[13]	Glasgow, UK	Lung (NSCLC)	109	1.9 (<0.01)	GPS predicted survival independent of ECOG-ps/platinum therapy
Crumley et al.,[47]	Glasgow, UK	Gastro-oesophageal	65	1.7 (<0.05)	mGPS predicted survival independent of ECOG-ps/platinum therapy
Kobayashi et al.[48]	Tokyo, Japan	Oesophageal	48	5.9 (<0.01)	GPS predicted toxicity in patients receiving neoadjuvant therapy
Sharma et al.[49]	London/Sydney	Colorectal	52	NR	GPS predicted toxicity and survival independent of stage/treatment
Ishizuka et al.[50]	Tochigi, Japan	Colorectal	112	6.0 (<0.01)	GPS predicted survival in patients receiving adjuvant therapy
Wang et al.[51]	Kaohsiung, Taiwan	Oesophageal	123	3.4 (<0.001)	GPS predicted survival in patients receiving radiotherapy
Roxburgh et al.[52]	Glasgow, UK	Colon	348	3.2 (<0.01)	mGPS predicted survival in patients receiving adjuvant therapy
Chau et al.[53]	Sydney, Australia	Various	68	4.1 (<0.01)	GPS predicted survival in patients receiving docetaxel
Hwang et al.[54]	Gwangui, South Korea	Gastric	402	1.8 (<0.01)	GPS predicted survival independent of performance status
Morimoto et al.[55]	Yokohama, Japan	Hepatocellular	81	5.5 (<0.001)	GPS predicted survival in patients receiving sorafenib
Gioulbasanis et al.[56]	Heraklion, Greece	Lung (metastatic)	96	1.9 (<0.01)	GPS) predicts toxicity and efficacy in platinum-based treatment

HR, multivariate hazard ratio for incremental change of GPS; NR, not reported.

Table 5
Studies ($n = 11$) of the prognostic value of the GPS/mGPS, in patients with inoperable cancer ($n > 2000$).

Study	Centre	Tumour site	n	HR (p-value)	Comments
Forrest et al.[57]	Glasgow, UK	Lung (NSCLC)	109	1.7 (<0.001)	GPS predicted survival independent of ECOG-ps/stage/treatment
Al Murri et al.[58]	Glasgow, UK	Breast	96	2.3 (<0.001)	GPS predicted survival independent of stage/treatment
Crumley et al.[59]	Glasgow, UK	Gastro-oesophageal	258	1.5 (<0.001)	GPS predicted survival independent of stage/treatment
Glen et al.[60]	Glasgow, UK	Pancreas	187	1.7 (<0.001)	GPS predicted survival independent of stage
Read et al.[61]	Sydney, Australia	Colorectal	84	2.3 (<0.05)	GPS independent of stage/treatment
Ramsey et al.[62]	Glasgow, UK	Renal	119	2.4 (<0.001)	GPS predicted survival independent of scoring systems
Sharma et al.[63]	Sydney, Australia	Ovarian	154	1.7 (<0.01)	GPS independent of stage/treatment
Pinato et al.[64]	London, UK	Lung (mesothelioma)	171	2.6 (<0.001)	mGPS predicted survival independent of NLR and EPS
Leung et al.[65]	Glasgow, UK	Lung (NSCLC)	261	1.7 (<0.001)	mGPS predicted survival independent of ECOG-ps/stage/treatment
Pinato et al.[66]	London, UK	Hepatocellular	578	2.7 (<0.01)	GPS predicted survival in training and validation datasets
Partridge et al.[67]	Edinburgh, UK	5 sites	102	2.7 (<0.01)	mGPS predicted survival independent of tumour site in palliative care

HR, multivariate hazard ratio for incremental change of GPS; NR, not reported; NLR, neutrophil lymphocyte ratio; EPS, European organisation for the research and treatment of cancer Prognostic Score.

Table 6
Studies ($n = 15$) of associations with the GPS/mGPS in patients with cancer ($n > 2000$).

Study	Centre	Tumour site	n	Comments
Brown et al.[68]	Glasgow, UK	Lung and colorectal	50	GPS associated with weight loss, poor performance status and biochemical disturbance
K-Korpacka[69]	Wroclaw, Poland	Gastro-oesophageal	96	GPS associated with weight loss, transferrin, IL-1, IL-6, IL-8, TNF, VEGF-A and midkine concentrations
Leung et al.[70]	Glasgow, UK	Colorectal	106	mGPS associated with plasma retinol, lutein, lycopene, alpha and beta carotene
Kerem et al.[71]	Ankara, Turkey	Gastric	60	GPS associated with weight loss, ghrelin, resistin, adiponectin and leptin
Fujiwara et al.[72]	Tokyo, Japan	Hepatocellular	66	GPS associated with blood transfusion and post-operative complications
Meek et al.[73]	Glasgow, UK	Lung (NSCLC)	56	mGPS associated with haemoglobin and IGFBP-3
Skipworth et al.[74]	Edinburgh, UK	Gastro-oesophageal	293	mGPS associated with weight loss, dietary intake, MAMC and KPS
Shimoda et al.[75]	Tochigi, Japan	Pancreas (unresectable)	83	GPS associated with responses to treatment
Diakowska et al.[76]	Wroclaw, Poland	Gastro-oesophageal	135	GPS associated with cachexia in cancer and controls
Giannousi et al.[77]	Heraklion, Greece	Lung (metastatic)	122	GPS associated with MNA, anxiety, depression and survival
Blomberg et al.[78]	Stockholm, Sweden	ENT and non-cancer	484	Combination of C-reactive protein and albumin associated with mortality following PEG
Richards et al.[79]	Glasgow, UK	Colorectal	343	mGPS associated with tumour necrosis
Naito et al.[80]	Shizuoka, Japan	Gastro-oesophageal	47	GPS associated with clinical responses to oxycodone
Leung et al.[81]	Glasgow, UK	Colorectal	108	mGPS associated with plasma B6
Richards et al.[82]	Glasgow, UK	Colorectal	174	mGPS associated with skeletal muscle index

NSCLC, non-small cell lung cancer; MNA, mini-nutritional assessment; IGFBP-3, insulin like growth factor binding protein-3.

Imaging, Diagnosis, Prognosis

Clinical Cancer Research

Prognostic Factors in Patients with Advanced Cancer: A Comparison of Clinicopathological Factors and the Development of an Inflammation-Based Prognostic System

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Glasgow prognostic score

Biomarkers

CRP and albumin were used as biomarkers of the inflammatory response and were taken by venous blood sampling at entry points to both studies. The limit of detection of CRP was less than 5mg/L, all samples (CRP and albumin) were analyzed at a central laboratory. The mGPS was calculated as follows:

- CRP $\leq$ 10mg/L = 0
- CRP > 10mg/L = 1
- CRP > 10mg/L and albumin < 35 g/L = 2

Table 1. Patient demographics—test sample and validation sample

Parameter	Test sample ($n = 1825$) n (%)	Validation sample ($n = 631$) n (%)
Age (≤65/65- 74/≥74 years)	1,014/509/302 (56/28/16)	368/148/115 (58/24/18)
Sex (M/F)	931/894 (51/49)	237/294 (53/47)
Country[a]		
Switzerland	109 (6)	61 (10)
Germany	248 (14)	0 (0)
Denmark	12 (1)	0 (0)
Australia	0 (0)	11 (2)
United Kingdom	284 (16)	52 (18)
Iceland	150 (8)	0 (0)
Austria	0 (0)	80 (13)
Italy	348 (19)	0 (0)
Norway	541 (30)	426 (68)
Sweden	133 (7)	0 (0)
Canada	0 (0)	1 (1)
Primary cancer site		
Breast	244 (13)	88 (14)
Urological	124 (7)	43 (7)
Gynaecologic	138 (8)	14 (2)
Prostate	223 (12)	69 (11)
Gastrointestinal	387 (21)	183 (29)
Haematologic	107 (6)	23 (4)
Head and Neck	90 (5)	15 (2)
Pulmonary	310 (17)	117 (19)
Others	202 (11)	79 (13)
Place of care		
Inpatient	1,510 (83)	437 (69)
Outpatient	315 (17)	194 (31)

[a]Where $n = 0$, study not recruiting in that country.

Table 2. The relationship between clinicopathological factors and survival in patients with advanced cancer—test sample ($n = 1,825$) and validation sample ($n = 631$)

	Test sample					Validation sample				
		Univariate[b]		Multivariate[b]			Univariate[b]		Multivariate[b]	
	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*	Patients *N*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≤65/65–74/≥74)	1,014/509/302	1.13 (1.05–1.21)	0.001			368/148/115	1.01 (0.88–1.14)	0.987		
Sex (male/female)	931/894	0.93 (0.82–1.06)	0.270			337/294	0.91 (0.73–1.14)	0.417		
Symptoms (EORTC QLQ-C30)[a]										
Cognitive function	1,529	0.96 (0.93–0.98)	<0.001			631	0.99 (0.99–1.00)	0.067		
Dyspnea	1,528	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.04)	0.002	631	1.01 (0.99–1.04)	0.565		
Appetite loss	1,531	1.02 (1.01–1.04)	0.002			631	1.00 (0.99–1.04)	0.836		
Quality of life	1,513	0.94(0.92–0.97)	<0.001			631	0.99 (0.99–1.00)	0.043	0.99 (0.99–0.99)	0.011
Physical functioning	1,533	0.89 (0.87–0.91)	<0.001			631	1.00 (0.99–1.03)	0.005	0.99 (0.98–1.00)	<0.001
Role functioning	1,525	0.93 (0.91–0.96)	<0.001			631	1.00 (0.99–1.03)	0.443		
Emotional functioning	1,528	0.98 (0.96–1.01)	0.157			631	1.06 (1.00–1.10)	0.042		
Social functioning	1,524	0.99 (0.97–1.01)	0.235			631	1.01 (1.01–1.05)	0.512		
Fatigue	1,531	1.05 (1.03–1.07)	<0.001			631	1.00 (0.99–1.04)	0.533		
Nausea and vomiting	1,537	1.01 (0.99–1.03)	0.237			631	1.04 (1.00–1.08)	0.118		
Pain	1,535	1.01 (0.99–1.03)	0.314			631	1.05 (1.01–1.08)	0.012	1.04 (1.00–1.09)	0.028
Insomnia	1,530	0.99 (0.98–1.01)	0.453			631	1.00 (0.99–1.02)	0.387		
Constipation	1,524	1.00 (0.98–1.01)	0.654			631	1.00 (0.99–1.00)	0.636		
Diarrhea	1,521	0.99 (0.97–1.01)	0.373			631	1.00 (0.99–1.00)	0.056		
BMI (<20/≥20)[c]	376/1403	0.84 (0.74–0.95)	0.007			104/527	0.73 (0.57–0.94)	0.015	0.76 (0.60–0.98)	0.031
Performance status (ECOG grouping)[d]										
P1 (ECOG 2)	713	1.21 (1.05–1.40)	0.007			262	1.58 (1.27–1.97)	<0.001		
P2 (ECOG 3)	549	1.98 (1.71–2.29)	<0.001	1.76 (1.50–2.06)	<0.001	83	3.74 (2.78–5.02)	<0.001	2.12 (1.48–3.04)	<0.001
P3 (ECOG 4)	179	3.61 (2.97–4.39)	<0.001	2.77 (2.17–3.52)	<0.001	13	3.75 (2.03–6.91)	<0.001		
mGPS[d]										
G1 (mGPS 1)	544	1.55 (1.32–1.84)	<0.001	1.62 (1.35–1.93)	<0.001	168	1.76 (1.39–2.22)	<0.001	1.58 (1.25–2.01)	<0.001
G_2 (mGPS 2)	1,004	2.01 (1.71–2.35)	<0.001	2.05 (1.72–2.44)	<0.001	177	2.41 (1.90–3.05)	<0.001	2.06 (1.62–2.63)	<0.001

[a]EORTC QLQ-C30 scores available on approximately 1,500 patients in test sample.

[b]HR expressed as per 10 unit change.

[c]BMI available on 1,779 patients in test sample.

[d]Using indicator variables.

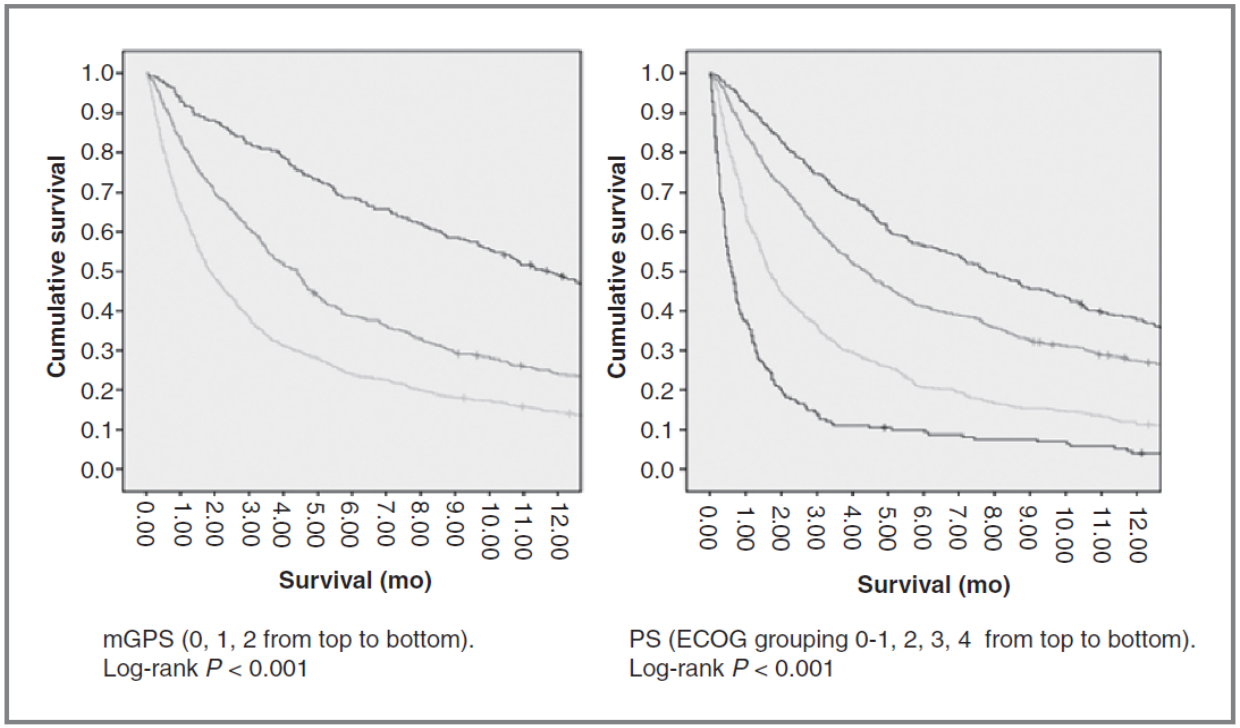

Figure 1. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Test sample ($n = 1,825$). Both mGPS and performance status predict survival $P < 0.001$.

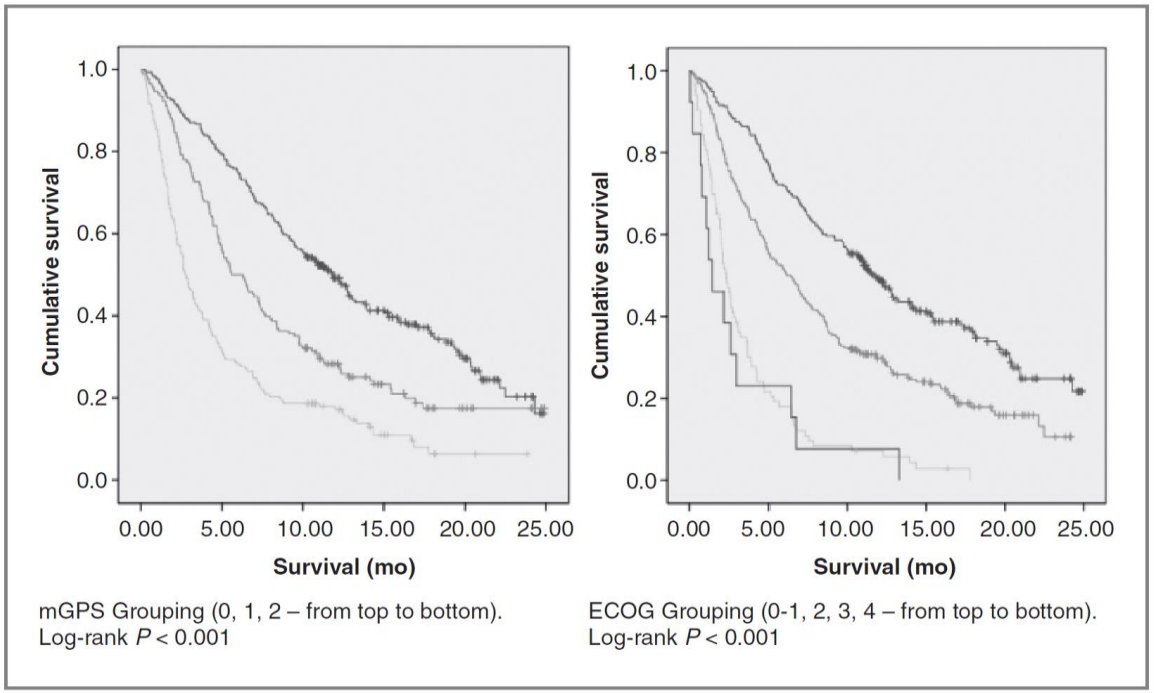

Figure 2. Kaplan–Meier curves examining the relationship between mGPS and survival, and performance status (ECOG grouping) and survival. Validation sample ($n = 631$). Both mGPS and performance status predict survival $P < 0.001$.

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Neutrophil-Lymphocyte Ratio as a Prognostic Factor in Colorectal Cancer

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TABLE I. Baseline Characteristics of Study Group

	No. of patients (%)
Age	
≥74 years	123 (53%)
<74 years	107 (47%)
Site	
Colon	142 (62%)
Rectum	88 (38%)
Dukes	
A	30 (13%)
B	80 (35%)
C	65 (28%)
D	26 (11%)
Unclassified	29 (13%)
Presentation	
Elective	189 (82%)
Emergency	41 (18%)

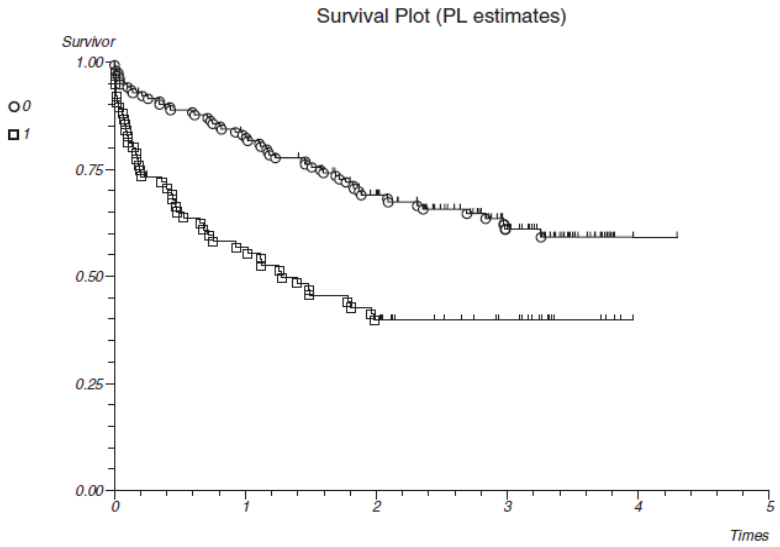

Fig. 1. Kaplan–Meier overall survival curves for patients with NLR ≥5 (1) and <5 (0) ($P = 0.0001$; log-rank test).

TABLE II. Analysis of Factors Influencing Survival

	Overall survival (univariate *P*)	Overall survival (multivariate *P*)	Cancer-specific survival (univariate *P*)	Cancer-specific survival (multivariate *P*)
Age	0.05	0.03	0.39	—
Gender (male vs. female)	0.08	—	0.007	0.18
Site (colon vs. rectum)	0.13	—	0.87	—
Anastomotic leak	0.99	—	0.99	—
Pre-operative radiotherapy	0.99	—	0.99	—
Dukes stage	0.0001	<0.0001	0.0001	<0.0001
NLR (≥5 vs. <5)	0.0001	0.15	0.0001	0.31
Presentation (emergency vs. elective)	0.0001	0.006	0.01	0.48

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The systemic inflammation-based neutrophil–lymphocyte ratio: Experience in patients with cancer

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Table 3
Studies of the prognostic value of the NLR in patients with operable cancer who received neoadjuvant therapy.

Study	Centre	Tumour site	*n*	HR (*p*-value)	Threshold	Comments
Wang [50]	Guangdong (China)	HCC	101	2.65 (<0.001)	>3	Elevated NLR independently associated with poor DFS
Halazun [51]	New York (USA)	Liver	150	19.99 (0.005)	>5	Elevated NLR associated with increased risk of recurrence and death
Bertuzzo [52]	Bologna (Italy)	Liver	219	19.14 (<0.001)	>5	Elevated NLR associated with lower OS. Elevated NLR and MVI negatively affected DFS. Elevated NLR and MVI were independent prognostic factors
Sato [53]	Shizuoka (Japan)	Oesophageal	83	2.83 (0.043)	>2.2	NLR associated with pathological response to neoadjuvant chemotherapy
Miyata [54]	Osaka (Japan)	Oesophageal	152	(Non-significant)	>4	Elevated NLR associated with survival but not independently prognostic
Sharaiha [55]	New York (USA)	Oesophageal	339	2.26 (<0.001)	>5	Elevated NLR associated with worse DFS and OS independent of tumour type

DFS, disease-free survival; OS, overall survival.

Table 4
Studies of the prognostic value of the NLR, in cancer patients receiving chemo/radiotherapy.

Study	Centre	Tumour site	*n*	HR (*p*-value)	Threshold	Comments
Carruthers et al. [56]	Glasgow (UK)	Rectal	115	4.1 (0.002)	>5	Elevated NLR > 5 associated with decreased OS, and DFS
Chua et al. [57]	Sydney (Australia)	Appendiceal	174	(0.01)	>5	Low NLR associated with improved DFS and OS. NLR, CRP and PLR all predicted OS and DFS on univariate analysis
Kishi et al. [58]	Texas (USA)	CRC Liver Metastases	290	2.22 (0.016)	>5	Pre- and post-treatment NLR independently associated with 1-, 3-, 5-year survival
Cedres et al. [59]	Barcelona (Spain)	Lung	171	1.5 (0.015)	>5	Association with T and N stage, but no association between NLR and number of metastatic sites, performance status, type of chemotherapy, use of glucocorticoids. Elevated NLR independently associated with poor OS and DFS. Patients with elevated NLR that normalised following treatment had better survival
Kao et al. [60]	Concord (Australia)	Lung	173	2.7 (<0.001)	>5	NLR < 5 associated with improved survival in those undergoing 1st line, 2nd and 3rd line chemotherapy. Normalisation of NLR after 1 cycle treatment associated with prolonged survival
Yao et al. [61]	Nanjing (China)	Lung	182	1.81 (0.008)	>2.63	Elevated NLR associated with poorer DFS and OS
Lee et al. [62]	Goyang (Korea)	Lung	199	1.05 (0.051)	>3.25	Pre- and post-treatment NLR associated with disease progression after 1st line treatment
Teramukai et al. [63]	Kyoto (Japan)	Lung	388	1.48 (0.013)	>4.74	Elevated NLR pre-treatment associated with shorter OS and DFS
Aliustaoglu et al. [64]	Istanbul (Turkey)	Gastric	168	(0.001)	>2.56	Elevated NLR was associated with OS
An et al. [65]	Guangdong (China)	Pancreatic	95	4.49 (0.013)	>5	Elevated pre-treatment NLR associated with poor OS and an independent predictor of OS in patients receiving chemotherapy
Keizman et al. [66]	Baltimore (USA)	Renal	133	(<0.001)	>3	NLR associated with OS and DFS
Chua et al. [67]	Sydney (Australia)	Various	68	2 (0.01)	>5	Combined GPS/NLR score predicted OS. NLR that normalised after three doses of chemotherapy associated with improved OS

DFS, disease-free survival; OS, overall survival.

Table 5
Studies of the prognostic value of the NLR, in cancer patients with inoperable cancer.

Study	Centre	Tumour site	*n*	HR (*p*-value)	Threshold	Comments
Kaneko et al. [68]	Tokyo (Japan)	Colorectal	50	4.39 (0.0013)	>5	NLR independently associated with OS. Elevated NLR and hypoalbuminaemia associated with poor OS and DFS
Chua et al. [67]	Sydney (Australia)	Colorectal	349	1.6 (0.01)	>5	NLR independent predictor of OS. Low/Normal NLR associated with improved clinical benefit and response to treatment
McNally et al. [69]	Ohio (USA)	HCC	103	(0.021)	>5	NLR independently associated with OS
Huang et al. [70]	Guangzhou (China)	HCC	145	(0.041)	>3.3	Elevated NLR independently associated with poor survival in patients with unresectable HCC
Jeong et al. [71]	Seoul (Korea)	Gastric	104	(0.037)	>3	Elevated NLR and mGPS were independent prognostic factors
Wang et al. [72]	Dalian (China)	Variety	497	1.35 (0.014)	>3	Elevated NLR associated with survival. NLR associated with T-stage, tumour type

DFS, disease-free survival; OS, overall survival.

FULL PAPER

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Keywords: Glasgow Prognostic Score; neutrophil-lymphocyte ratio; colorectal cancer

Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer

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Table 1. Baseline clinicopathological characteristics of patients undergoing potentially curative resection for colorectal cancer

	Number of patients ($n = 206$)	
Age		
< 65/65–74/ > 75	74 (36%)/79 (38%)/53 (26%)	
Sex		
Male/female	120 (58%)/86 (42%)	
Presentation		
Elective/emergency	187 (91%)/19 (9%)	
Site		
Colon/rectum	129 (63%) 77 (37%)	
T-stage	Colon	Rectum
T1	8 (4%)	6 (3%)
T2	12 (6%)	9 (4%)
T3	63 (31%)	49 (24%)
T4	46 (22%)	12 (6%)
TNM stage		
I	32 (16%)	
II	85 (41%)	
III	87 (42%)	
IV	2 (1%)	
Adjuvant chemotherapy		
No/yes	148 (72%)/58 (28%)	

Measurement of systemic inflammatory response (TNM I–IV)	Pre-operative ($n = 206$)	Post-operative ($n = 206$)	*P*-value*
mGPS			
0	132 (64%)	140 (68%)	0.926
1	33 (16%)	18 (9%)	
2	41 (20%)	48 (23%)	
NLR			
0 (<5)	161 (78%)	170 (82%)	0.216
1 (>5)	45 (22%)	36 (18%)	
Measurement of systemic inflammatory response (TNM I–II)	**Pre-operative ($n = 117$)**	**Post-operative ($n = 117$)**	***P*-value***
mGPS			
0	74 (63%)	82 (70%)	0.427
1	17 (15%)	10 (9%)	
2	26 (22%)	25 (21%)	
NLR			
0 (<5)	90 (77%)	93 (79%)	0.577
1 (>5)	27 (23%)	24 (21%)	

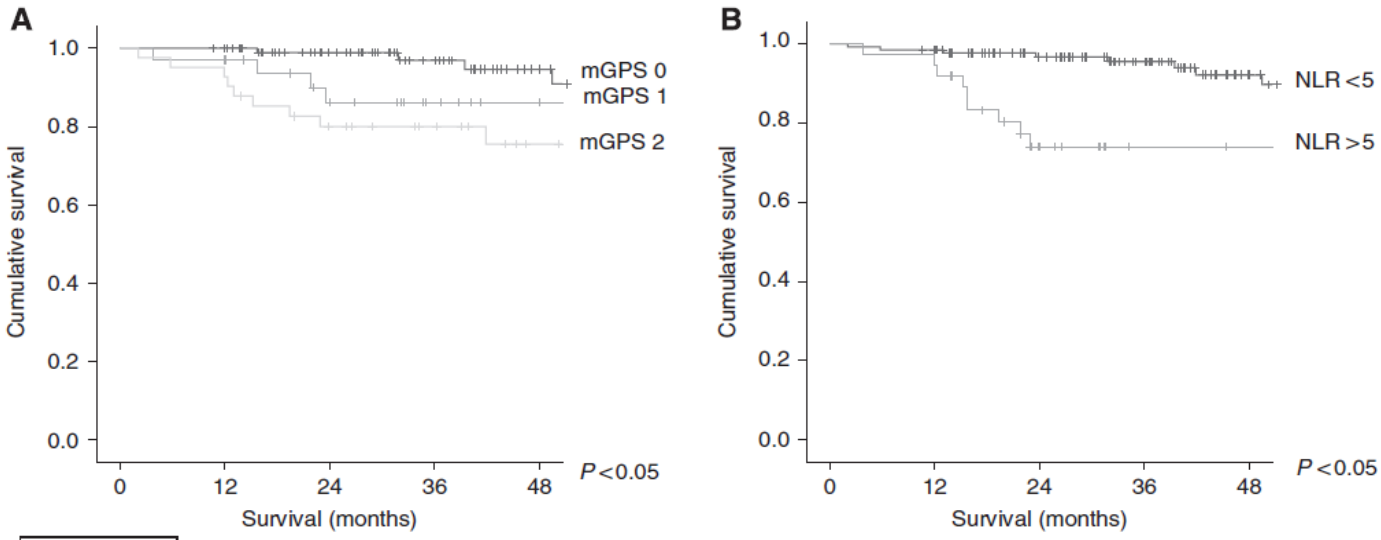
Abbreviations: mGPS = modified Glasgow Prognostic Score; NLR = neutrophil-lymphocyte ratio; TNM = tumour, node, metastasis. *Wilcoxon Rank test.

Table 2. The relationship between clinicopathological characteristics and survival in patients undergoing potentially curative resection for colorectal cancer

	All patients ($n = 206$)			Node negative ($n = 117$)		
	Cancer-specific survival Univariate analysis			Cancer-specific survival Univariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (<65/ 65–74/ >75)	0.79	0.49–1.27	0.330	0.10	0.24–1.14	0.101
Gender (male/ female)	1.24	0.58–2.63	0.570	4.23	0.92–19.41	0.064
Site (colon/ rectum)	1.03	0.49–2.19	0.930	1.55	0.49–4.80	0.450
T-stage (T1/T2/T3/ T4)	2.75	0.49–5.07	0.001	1.69	0.77–3.70	0.190
TNM stage I/II/III/IV	2.31	1.28–4.17	0.005	4.13	0.53–32.08	0.180
Pre-operative mGPS (0/ 1/2)	1.94	1.17–3.21	0.010	2.57	1.10–5.96	0.028
Pre-operative NLR (<5/ >5)	3.28	1.36–7.93	0.008	2.08	0.62–2.09	0.233
Post-operative mGPS (0/ 1/2)	3.31	2.15–5.09	<0.001	4.81	2.13–10.83	<0.001
Post-operative NLR (<5/ >5)	3.07	1.42–6.62	0.004	3.10	0.98–9.84	0.054

Abbreviations: CI = confidence intervals; HR = hazard ratio.

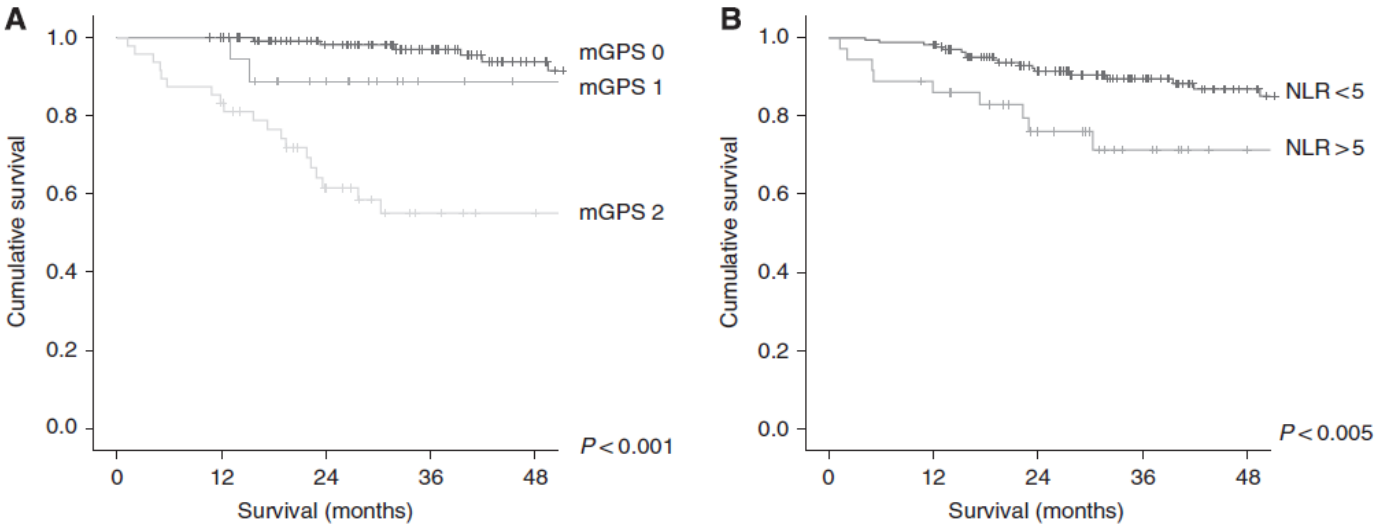
On multivariate survival analysis, comparing pre-operative mGPS with NLR, both pre-operative mGPS (HR 1.97, confidence intervals (CI) 1.16–3.34, $P < 0.05$) and NLR (HR 3.07, CI 1.23–7.63, $P < 0.05$) were independently associated with reduced cancer-specific survival (mGPS and NLR). When the same multivariate comparison was carried out on post-operative measurements, only the post-operative mGPS was independently associated with the cancer-specific survival (HR 4.81, CI 2.13–10.83, $P < 0.001$).



No. at risk	0	12	24	36	48
mGPS 0	132	125	86	54	32
mGPS 1	33	32	23	15	11
mGPS 2	41	38	29	21	13

No. at risk	0	12	24	36	48
NLR <5	161	151	111	75	43
NLR >5	45	44	27	15	13

Figure 1. The relationship between pre-operative assessment of systemic inflammation as evidence by mGPS (**A**) and NLR (**B**) and cancer-specific survival in patients undergoing potentially curative resection of CRC.



No. at risk					
	0	12	24	36	48
mGPS 0	140	120	90	59	39
mGPS 1	18	15	10	3	2
mGPS 2	48	32	20	12	9

No. at risk					
	0	12	24	36	48
NLR <5	170	141	102	65	46
NLR >5	36	26	18	9	4

Figure 2. The relationship between post-operative assessment of systemic inflammation as evidence by mGPS (**A**) and NLR (**B**) and cancer-specific survival in patients undergoing potentially curative resection of CRC.

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Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma

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Table 1 Demographics and preoperative hematology results from resected pancreatic ductal adenocarcinoma patients

No. of patients analyzed	110
Male:female ratio	65:45
Median age, y (interquartile range)	67 (61–73)
Mean interval from FBC to surgery, d (±SEM)	2.4 (.4)
Timing of preoperative FBC	
Number of patients within 24 hours of surgery	75
Within 1–2 days of surgery	17
Within 3–7 days of surgery	12
>7 days of surgery	6
Neutrophilia present (>7.5 × 10^6/mL)	
No	87 (79%)
Yes	23 (21%)
Lymphocytopenia present (<1.0 × 10^6/mL)	
No	102 (93%)
Yes	8 (7%)
Thrombocytosis present (>400 × 10^6/mL)	
No	85 (77%)
Yes	25 (23%)
Intervention for preoperative biliary drainage	
No	18 (16%)
ERCP + stent	85 (77%)
PTC ± stenting	7 (7%)

ERCP = endoscopic retrograde cholangiopancreatography; FBC = full blood count; PTC = percutaneous transhepatic cholangiography; SEM = standard error.

Table 2 Univariate survival analysis of preoperative hematologic parameters as prognostic covariates in resected pancreatic ductal adenocarcinoma (Cox proportional hazards)

	Median value (interquartile range)	Hazard ratio (95% CI)	*P*
Lymphocyte count, $\times 10^6$/mL	1.9 (1.3–2.4)	.677 (.511–.897)	.007
Neutrophil count, $\times 10^6$/mL	5.5 (4.0–7.1)	1.038 (.956–1.127)	.373
Platelet count, $\times 10^6$/mL	303 (258–375)	1.002 (1.000–1.004)	.068
N/L ratio	2.9 (1.9–4.8)	1.047 (.985–1.113)	.140
P/L ratio	159 (116–230)	1.004 (1.002–1.006)	.0001

Hazard ratios for continuous data reflect an increase in the relative risk of death with each incremental increase in a covariate value of 1 unit.
N/L ratio = neutrophil-lymphocyte ratio.

Table 5 Univariate and multivariate (Cox proportional hazards) survival analysis for prognostic factors in pancreatic ductal adenocarcinoma

	Univariate analysis	Multivariate analysis (n = 104)		
Prognostic factors	*P* value	Hazard ratio (95% CI)	Chi-square	*P* value
Continuous covariates				
Platelet-lymphocyte ratio (n = 110)*	.0001	1.004 (1.002–1.006)	14.092	.0003
Tumor size (n = 108)*	.003	1.025 (1.006–1.044)	6.214	.010
Lymph node ratio (n = 107)*	.004	6.109 (1.465–25.478)	6.508	.013
Categoric covariates				
Resection margin status				
Negative (n = 32)	.062	1.158 (.601–2.233)	.071	.661
Positive (n = 77)				
Tumor differentiation				
Well/moderate (n = 72)	.141	1.186 (.706–1.990)	1.209	.520
Poor (n = 37)				

Histologic data were incomplete for some patients, hence the overall number of patients included in the final Cox model was 104.

*Modeled as continuous covariates on both univariate and multivariate analyses— hazard ratios for continuous data reflect an increase in the relative risk of death with each incremental increase in a covariate value of 1 unit.

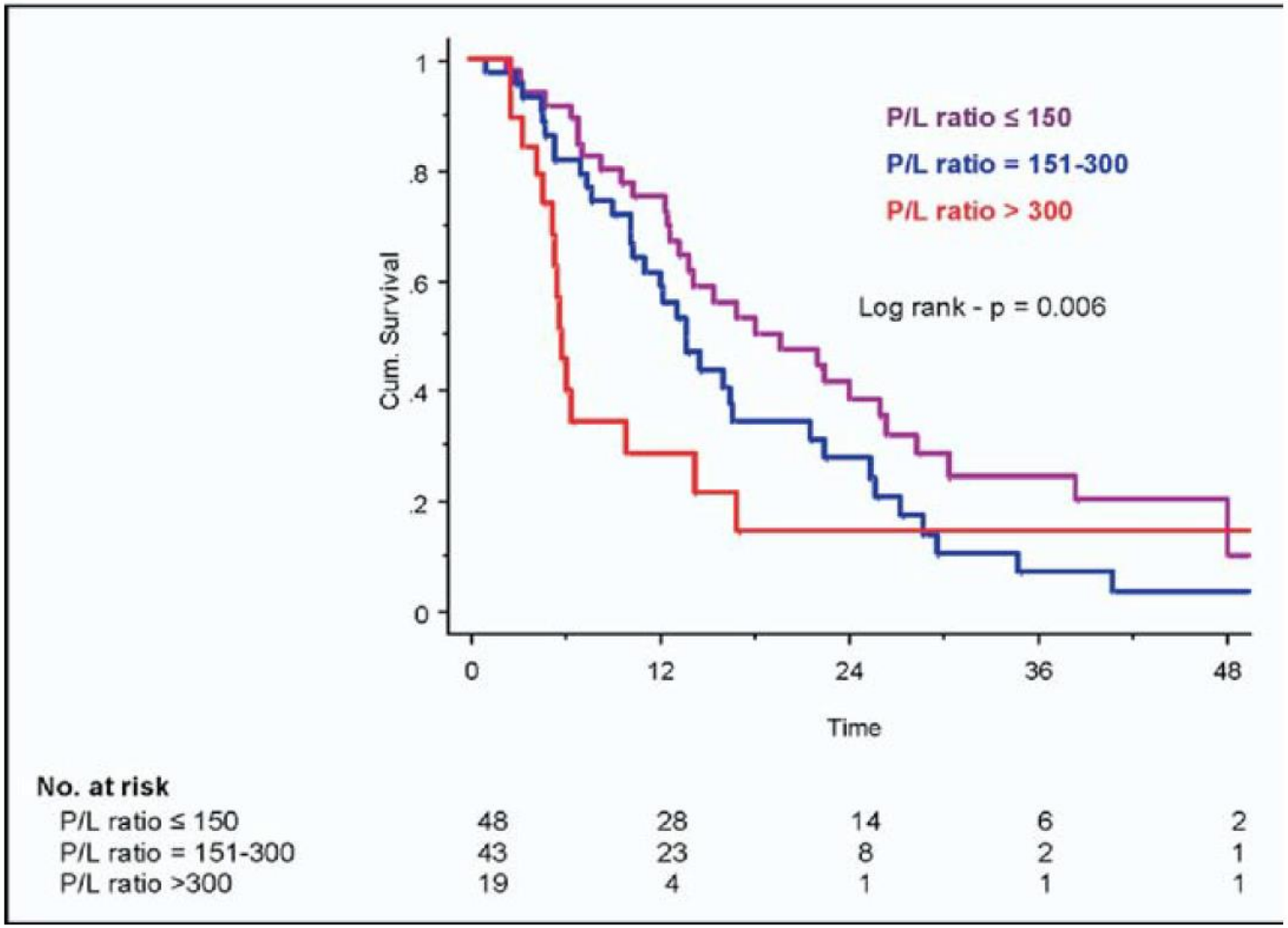

Figure 1 Kaplan-Meier cumulative survival curves for pancreatic ductal adenocarcinoma patients according to the preoperative P/L ratio. Purple line, P/L ratio ≤150; blue line, P/L ratio = 151–300; red line, P/L ratio >300. Log-rank $P = .006$.

The predictive value of pre-treatment inflammatory markers in advanced non-small-cell lung cancer

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TABLE I Definition of the prognostic index (PI)

PI	*C-Reactive protein*	*White blood cells*
0	≤10 mg/L	$\leq 11 \times 10^9$
1	≤10 mg/L	$> 11 \times 10^9$
1	>10 mg/L	$\leq 11 \times 10^9$
2	>10 mg/L	$> 11 \times 10^9$

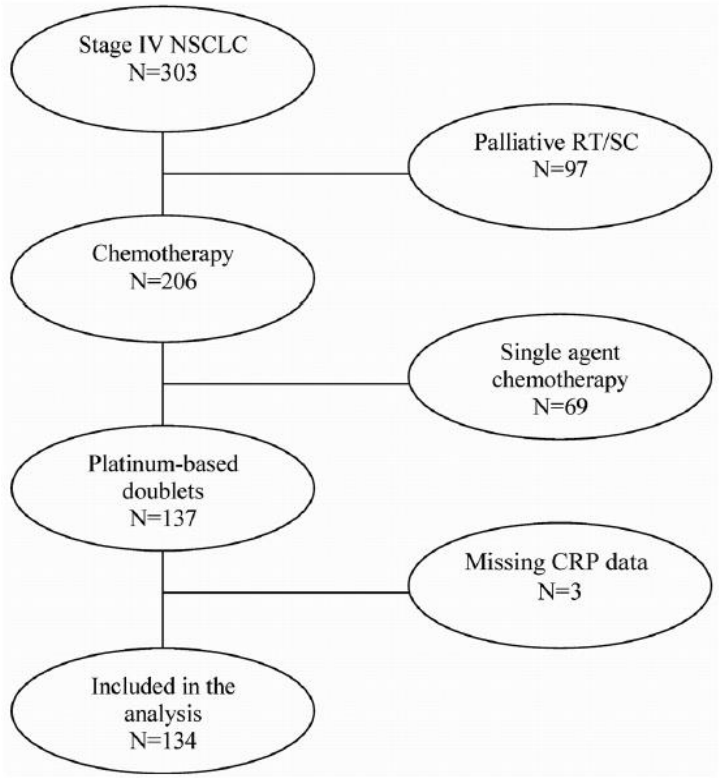

FIGURE 1 *Cohort organization chart.* NSCLC = *non-small-cell lung cancer;* RT = *radiotherapy;* SC = *supportive care;* CRP = *C-reactive protein.*

TABLE II Clinical characteristics of the study patients

Characteristic	*Patients*	
	(n)	*(%)*
Sex		
Male	71	53
Female	63	47
Smoking status		
Smoker	40	30
Ex-smoker	65	48
Never-smoker	29	22
ECOG performance status		
0–1	116	87
2	18	13
Tumour type		
Adenocarcinoma	96	72
Squamous cell carcinoma	13	10
Other	25	18
Stage		
IV (pleural effusion)	15	11
IV	119	89
Chemotherapy type		
Carboplatin–gemcitabine	71	53
Carboplatin–paclitaxel	46	34
Other platinum-based doublets	17	13
Weight loss		
<5%	86	64
≥5%	48	36

ECOG = Eastern Cooperative Oncology Group.

TABLE III Clinical difference among the prognostic index (PI) groups

Characteristic	*Patients by PI group (n)*			p *Value*
	0	*1*	*2*	*(Spearman*
	(N=46)	*(N=60)*	*(N=28)*	*correlation)*
Age				
<65	30	34	20	0.336
≥65	16	26	8	
Smoking				
Smoker or ex-smoker	30	13	0	0.002
Never-smoker	16	47	28	
ECOG performance status				
0–1	43	51	22	0.060
2	3	9	6	
Sex				
Female	28	26	9	0.013
Male	18	34	19	
Weight loss				
<5%	36	37	13	0.019
≥5%	10	23	15	

ECOG = Eastern Cooperative Oncology Group.

TABLE V Factors affecting rate of progression

Variable	*Coefficient*	*p Value*
Constant[a]	0.26	0.002
Age	0.47	0.09
Sex	1.37	0.45
Weight loss	1.11	0.81
Smoking status	0.61	0.30
ECOG performance status	2.58	0.09
Prognostic index	1.79	0.04

[a] *y* intercept.
ECOG = Eastern Cooperative Oncology Group.

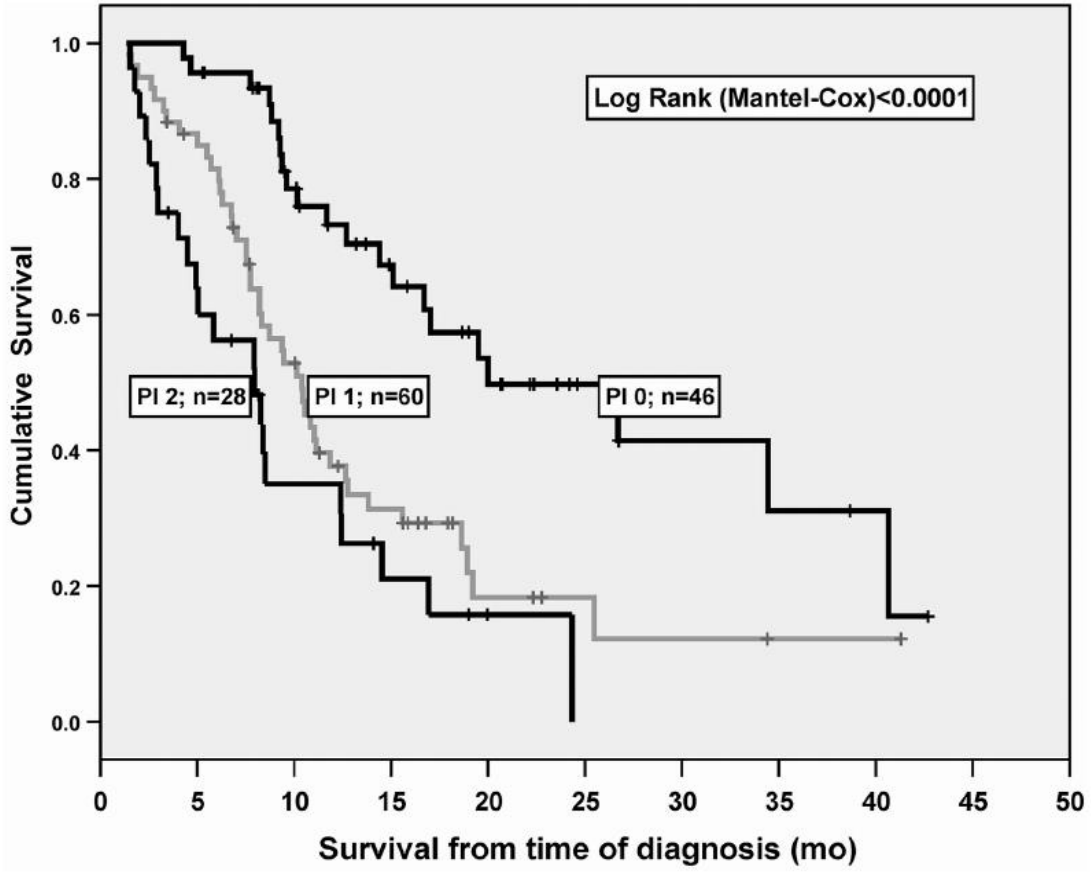

FIGURE 2 *Kaplan–Meier survival curves based on the prognostic index (PI).*

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A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study

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Introduction: Components of the systemic inflammatory response, combined to form inflammation-based prognostic scores (modified Glasgow Prognostic Score (mGPS), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Prognostic Index (PI), Prognostic Nutritional Index (PNI)) have been associated with cancer specific survival. The aim of the present study was to compare the prognostic value of these scores.

Table 1 – Systemic inflammation-based prognostic scores.

The modified Glasgow Prognostic Score	Score
C-reactive protein $\leqslant$ 10 mg/l and albumin $\geqslant$ 35 g/l	0
C-reactive protein $\leqslant$ 10 mg/l and albumin < 35 g/l	0
C-reactive protein > 10 mg/l	1
C-reactive protein > 10 mg/l and albumin < 35 g/l	2
Neutrophil Lymphocyte Ratio	
Neutrophil count:lymphocyte count < 5:1	0
Neutrophil count:lymphocyte count $\geqslant$ 5:1	1
Platelet Lymphocyte Ratio	
Platelet count:lymphocyte count < 150:1	0
Platelet count:lymphocyte count 150–300:1	1
Platelet count:lymphocyte count > 300:1	2
Prognostic Index	
C-reactive protein $\leqslant$ 10 mg/l and white cell count $\leqslant 11 \times 10^9$/l	0
C-reactive protein $\leqslant$ 10 mg/l and white cell count > 11×10^9/l	1
C-reactive protein > 10 mg/l and white cell count $\leqslant 11 \times 10^9$/l	1
C-reactive protein > 10 mg/l and white cell count > 11×10^9/l	2
Prognostic Nutritional Index	
Albumin (g/L) + 5 × total lymphocyte count × 10^9/l $\geqslant$ 45	0
Albumin (g/L) + 5 × total lymphocyte count × 10^9/l < 45	1

Table 2 – The relationship between patient characteristics, tumour site, inflammatory-based prognostic scores and survival.

			Patients $n = 8759$ (%)	Five year overall survival % (n of deaths) $n = 5163$	p-Value	Five year cancer specific survival % (n of deaths) $n = 4417$	p-Value
Age	⩽65 years		4237 (48)	52 (1977)	<0.001	55 (1808)	<0.001
	65–74 years		2620 (30)	33 (1703)		41 (1439)	
	⩾75 years		1902 (22)	21 (1483)		31 (1170)	
Sex	Male		4115 (47)	29 (2844)	<0.001	36 (2432)	<0.001
	Female		4644 (53)	49 (2319)		55 (1985)	
SIMD 2006	1 (least deprived)		1278 (15)	51 (609)	<0.001	57 (523)	<0.001
	2		1138 (13)	48 (579)		54 (495)	
	3		1391 (16)	43 (779)		48 (683)	
	4		1786 (20)	37 (1110)		44 (940)	
	5 (most deprived)		3166 (36)	33 (2086)		40 (1776)	
Tumour site	Breast		1853 (21)	79 (361)	<0.001	85 (263)	<0.001
	Bladder		437 (5)	48 (226)		63 (149)	
	Gynaecological		460 (5)	45 (248)		51 (217)	
	Prostate		456 (5)	53 (206)		64 (153)	
	Gastroesophageal		874 (10)	12 (754)		15 (697)	
	Haematological		817 (10)	48 (418)		57 (320)	
	Renal		400 (5)	38 (242)		44 (214)	
	Colorectal		996 (11)	39 (583)		45 (493)	
	Head and neck		555 (7)	34 (344)		51 (239)	
	Hepatopancreaticobiliary		474 (5)	7 (430)		8 (410)	
	Pulmonary		1437 (16)	5 (1351)		7 (1262)	
Inflammation based prognostic scores	mGPS	0	3673 (42)	61 (1349)	<0.001	68 (1083)	<0.001
		1	2436 (28)	32 (1640)		39 (1425)	
		2	2650 (30)	16 (2174)		22 (1909)	
	NLR	0	5151 (59)	51 (2401)	<0.001	58 (2021)	<0.001
		1	3608 (41)	23 (2762)		29 (2396)	
	PLR	0	2734 (31)	52 (1253)	<0.001	60 (996)	<0.001
		1	3522 (40)	42 (1993)		48 (1716)	
		2	2503 (29)	23 (1917)		28 (1705)	
	PI	0	3084 (35)	64 (1042)	<0.001	70 (832)	<0.001
		1	3460 (40)	31 (2303)		38 (1994)	
		2	2215 (25)	17 (1818)		23 (1591)	
	PNI	0	4342 (50)	57 (1806)	<0.001	63 (1487)	<0.001
		1	4417 (50)	21 (3357)		27 (2930)	

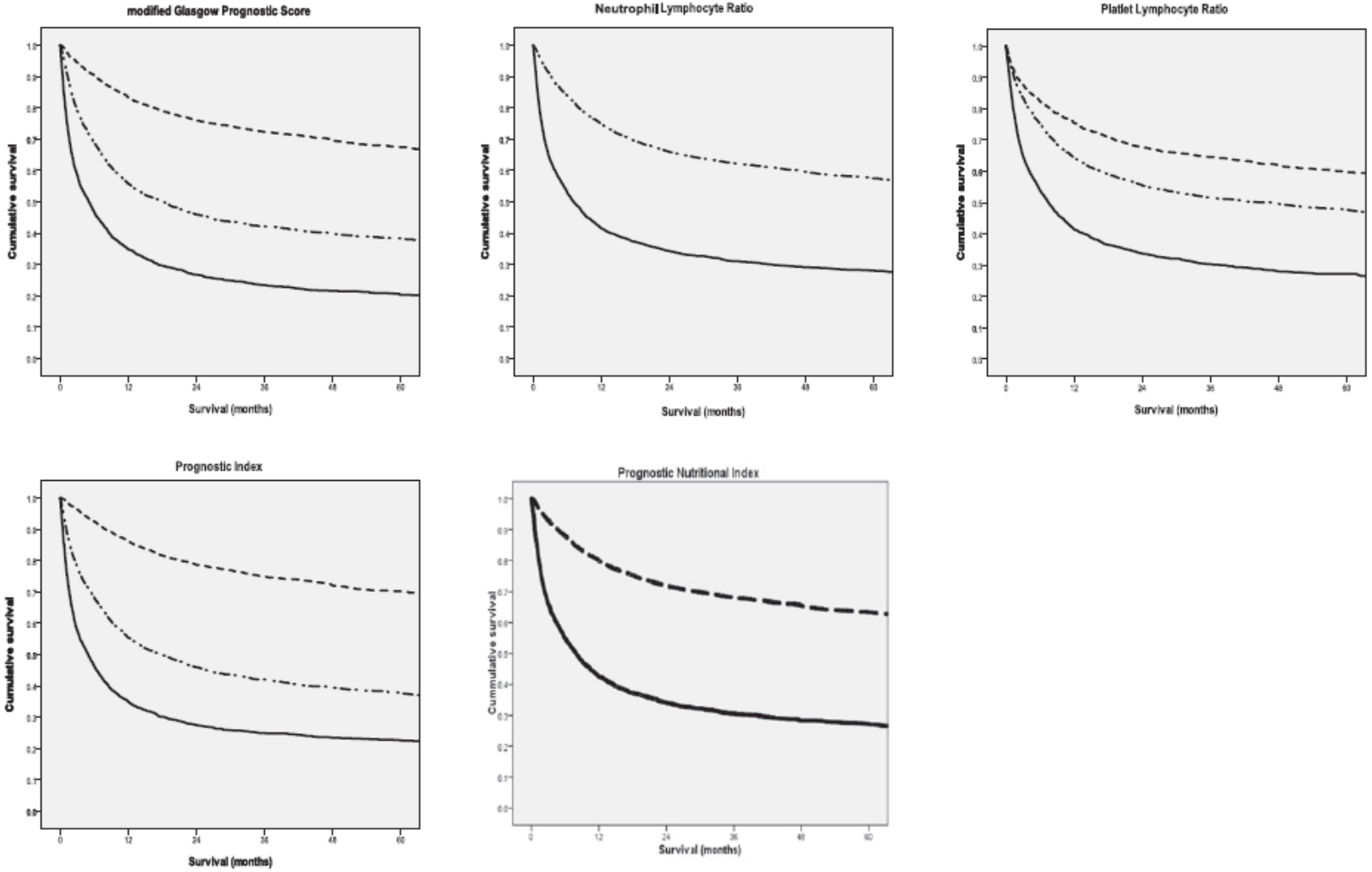

Fig. 1 – The relationship between the mGPS (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), NLR (0-top, large dash line; 1-bottom, solid line), PLR (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PI (0-top, small dash line; 1-middle, large dash line; 2-bottom, solid line), PNI (0-top, large dash line; 1-bottom, solid line) and cancer specific survival in all patients (all $p<0.001$).

Table 3 – The relationship between inflammation-based prognostic scores and survival. Adjusted for age, sex, deprivation and stratified by tumour site.

		Overall survival		Cancer specific survival	
		HR	*p*-Value	HR	*p*-Value
All patients (n = 8759)					
mGPS	0	1	<0.001	1	<0.001
	1	1.74	<0.001	1.85	<0.001
	2	2.91	<0.001	3.06	<0.001
NLR	0	1	<0.001	1	<0.001
	1	1.93	<0.001	1.97	<0.001
PLR	0	1	<0.001	1	<0.001
	1	1.22	<0.001	1.31	<0.001
	2	1.89	<0.001	2.08	<0.001
PI	0	1	<0.001	1	<0.001
	1	2.03	<0.001	2.15	<0.001
	2	2.87	<0.001	3.03	<0.001
PNI	0	1	<0.001	1	<0.001
	1	2.24	<0.001	2.34	<0.001
Patients sampled within two months following cancer diagnosis (n = 4674)					
mGPS	0	1	<0.001	1	<0.001
	1	1.65	<0.001	1.74	<0.001
	2	2.35	<0.001	2.44	<0.001
NLR	0	1	<0.001	1	<0.001
	1	1.76	<0.001	1.77	<0.001
PLR	0	1	<0.001	1	<0.001
	1	1.19	<0.001	1.24	<0.001
	2	1.71	<0.001	1.82	<0.001
PI	0	1	<0.001	1	<0.001
	1	1.78	<0.001	1.87	<0.001
	2	2.44	<0.001	2.51	<0.001
PNI	0	1	<0.001	1	<0.001
	1	1.98	<0.001	2.01	<0.001

Table 4 – The relationship between inflammation-based prognostic scores and survival in colorectal cancer patients sampled within two months following cancer diagnosis. Adjusted for age, sex, deprivation and Dukes stage.

$n = 374$		Overall survival		Cancer specific survival	
		HR	*p*-Value	HR	*p*-Value
mGPS	0	1	<0.001	1	<0.001
	1	1.81	0.004	1.91	<0.001
	2	2.30	<0.001	2.51	<0.001
NLR	0	1	0.102	1	0.146
	1	1.27	0.102	1.25	0.146
PLR	0	1	0.786	1	0.560
	1	1.16	0.487	1.30	0.281
	2	1.13	0.596	1.23	0.403
PI	0	1	<0.001	1	<0.001
	1	1.69	0.012	1.92	<0.001
	2	2.83	<0.001	3.07	<0.001
PNI	0	1	0.059	1	0.095
	1	1.33	0.059	1.31	0.095

In summary, the results of the present study show that systemic inflammation-based scores mGPS, NLR, PLR, PI and PNI have prognostic value in a variety of cancers. However, in terms of differentiating good from poor prognostic groups in a variety of tumour sites and the existing validated literature, the mGPS is superior. A measurement of systemic inflammation, in particular the mGPS, should be included in the routine assessment of all patients with cancer.

Marqueurs circulants de l'inflammation

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Circulating levels of immune and inflammatory markers and long versus short survival in early-stage lung cancer

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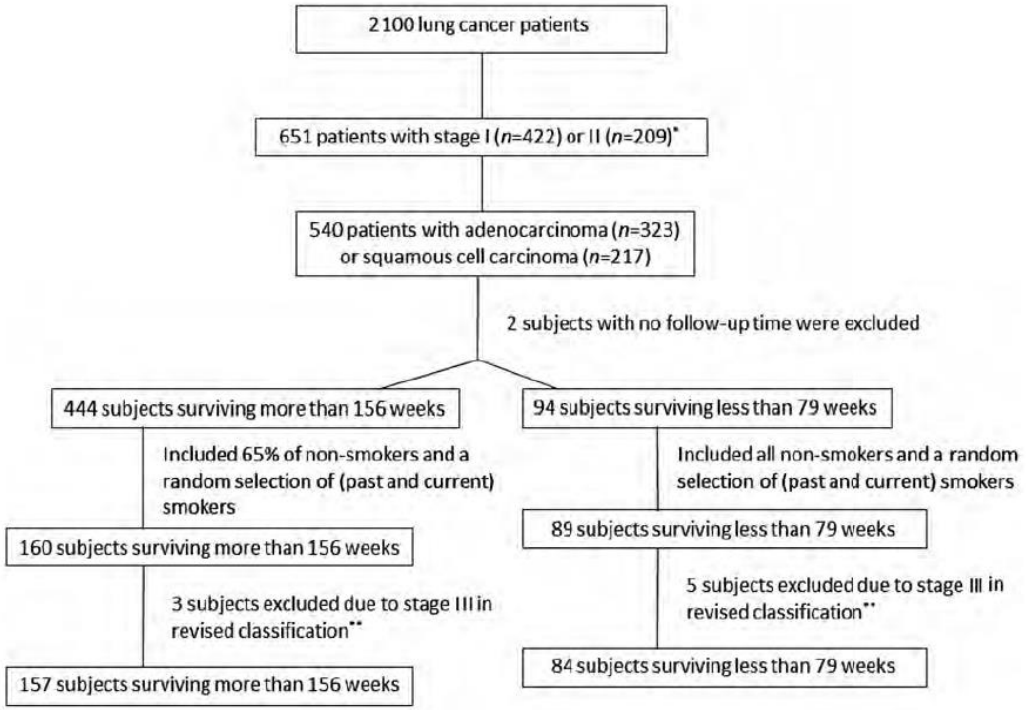

Figure 1. Flow diagram of study participants.

Table 1. Distribution of characteristics of lung cancer patients by survival status.

Characteristics	LS (>156 weeks) ($n = 157$)	SS (<79 weeks) ($n = 84$)
Median follow-up time (weeks), (IQR)	341.0 (289.4–389.1)	44.6 (20.6–61.3)
Age (years), *n* (%)		
<65	56 (35.7)	20 (23.8)
65 to <70	41 (26.1)	16 (19.0)
70 to <75	44 (28.0)	20 (23.8)
≥75	16 (10.2)	28 (33.3)
Sex, *n* (%)		
Males	123 (78.3)	68 (81.0)
Females	34 (21.7)	16 (19.0)
Stage[a], *n* (%)		
IA	43 (27.4)	16 (19.0)
IB	38 (24.2)	26 (31.0)
IIA	51 (32.5)	17 (20.2)
IIB	25 (15.9)	25 (29.8)
Histology, *n* (%)		
Adenocarcinoma	89 (56.7)	46 (54.8)
Squamous cell carcinoma	68 (43.3)	38 (45.2)
Smoking status, *n* (%)		
Never smoker	22 (14.0)	5 (6.0)
Former smoker	73 (46.5)	38 (45.2)
Current smoker	62 (39.5)	41 (48.8)
COPD (self-reported), *n* (%)		
No	113 (75.8)	52 (71.2)
Yes	36 (24.2)	21 (28.8)
COPD (spirometer-based), *n* (%)		
Normal or mild	81 (81.0)	28 (57.1)
Moderate or severe	19 (19.0)	21 (42.9)
Surgery, *n* (%)		
No	5 (3.2)	13 (15.5)
Yes	152 (96.8)	71 (84.5)
Chemotherapy treatment, *n* (%)		
No	111 (70.7)	55 (65.5)
Yes	46 (29.3)	29 (34.5)
Radiation treatment, *n* (%)		
No	119 (76.3)	59 (72.0)
Yes	37 (23.7)	23 (28.0)

Percentages might not add up to 100% because of rounding.
Patients treated according to standard practice at clinical site where they were seen; details of chemotherapy regimens not known.
LS, long survivors; SS, short survivors; IQR, interquartile range.
[a]Staging according to the 2010 classification for lung cancer (AJCC Cancer Staging Manual. 7 edn. New York: Springer-Verlag; 2010).

Table 2. Adjusted analysis for the associations between inflammatory circulating markers and survival status[a].

Markers	Median			Q2 versus Q1		Q3 versus Q1		Q4 versus Q1		P^{c}_{trend}	Q-value[d]
	LS	SS	P-value*	OR[b]	(95% CI)	OR[b]	(95% CI)	OR[b]	(95% CI)		
CCL15	1957.03	2317.34	2.8×10^{-4}	2.60	(1.02–6.66)	3.82	(1.48–9.88)	4.93	(1.9–12.8)	7.4×10^{-4}	0.042
IL-8	7.30	9.77	0.002	0.62	(0.24–1.57)	1.41	(0.59–3.35)	3.05	(1.31–7.1)	0.002	0.064
CRP[e]	25 256 000.00	66 605 000.00	0.007	0.98	(0.38–2.5)	2.72	(1.17–6.31)	3.08	(1.17–8.08)	0.004	0.071
IL-2Ra	3.20	6.25	0.020	–	–	1.12	(0.52–2.43)	2.58	(1.26–5.29)	0.023	0.249
TNF-a	8.56	9.44	0.007	1.72	(0.73–4.02)	1.27	(0.53–3.09)	2.92	(1.25–6.78)	0.029	0.249
IL-6	4.51	5.64	0.048	2.48	(0.95–6.47)	3.78	(1.45–9.83)	2.84	(1.08–7.43)	0.030	0.249
TRAIL	21.52	16.53	0.085	1.04	(0.46–2.34)	0.74	(0.32–1.71)	0.38	(0.15–0.95)	0.031	0.249
IL-6R	15 793.15	16 987.09	0.034	1.04	(0.43–2.48)	1.68	(0.72–3.93)	2.07	(0.91–4.75)	0.049	0.326
CXCL13	24.59	30.04	0.001	0.92	(0.39–2.21)	1.07	(0.46–2.53)	2.25	(0.97–5.24)	0.052	0.326
TNFRII	5369.65	6910.59	0.006	0.95	(0.38–2.36)	1.44	(0.6–3.49)	2.08	(0.86–5.05)	0.060	0.341
CCL19	59.72	67.90	0.031	1.14	(0.49–2.66)	1.21	(0.51–2.84)	2.02	(0.87–4.67)	0.109	0.566
G-CSF	89.84	101.34	0.219	1.07	(0.46–2.48)	1.08	(0.45–2.56)	1.89	(0.84–4.27)	0.136	0.645
TNFRI	1234.41	1377.58	0.009	2.01	(0.83–4.89)	1.64	(0.67–4.04)	2.13	(0.87–5.2)	0.167	0.700
EGFR	37 460.37	36 289.72	0.159	0.89	(0.4–1.97)	0.66	(0.29–1.5)	0.61	(0.26–1.41)	0.185	0.700
SAA[e]	48 800 000.00	142 200 000.00	0.085	1.18	(0.47–2.98)	2.77	(1.16–6.63)	1.21	(0.43–3.42)	0.197	0.700

Markers ordered from the most significant association to the least significant according to P_{trend}.
LS, long survivors; SS, short survivors.

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Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma

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Table 1 Characteristics of the patients and controls

	CRC patients ($n = 116$)	Healthy controls ($n = 86$)
Age, mean (s.d.)	67.9 (11.2)	67.3 (10.6)
BMI, mean (s.d.)	26.6 (4.5)	27.4 (3.6)
White blood cell count, mean (s.d.)	6.9 (2.1)	6.9 (1.5)
Gender		
Male	58 (50%)	45 (52.3%)
Female	58 (50%)	41 (47.7%)
Preoperative RT/CRT		
Yes	0 (0%)	
No	116 (100%)	
Tumour location		
Proximal colon	49 (42.2%)	
Distal colon	27 (23.3%)	
Rectum	40 (34.5%)	
WHO grade		
Grade 1	16 (13.8%)	
Grade 2	86 (74.1%)	
Grade 3	14 (12.1%)	
TNM stage (n = 115)		
Stage I	19 (16.5%)	
Stage II	46 (40.0%)	
Stage III	32 (27.8%)	
Stage IV	18 (15.7%)	

Abbreviations: BMI = body mass index; CRC = colorectal cancer; RT/CRT = radiotherapy or chemoradiotherapy; s.d. = standard deviation.

Table 2 Serum cytokine and chemokine levels in colorectal cancer patients compared with healthy controls

Cytokine	CRC patients ($n = 116$) pg ml^{-1}, median (IQR)	Healthy controls ($n = 86$) pg ml^{-1}, median (IQR)	*P*-value
IL-1ra	63.8 (37.9–98.2)	62.7 (43.8–75.9)	0.296
IL-4	0.88 (0.75–1.13)	0.83 (0.72–0.99)	0.127
IL-6	4.89 (3.44–8.92)	3.57 (2.62–4.54)	1.3E – 7
IL-7	5.53 (3.99–7.46)	4.71 (3.43–5.61)	2.9E – 4
IL-8	12.3 (9.13–18.1)	8.30 (6.94–10.5)	7.3E – 11
IL-9	9.18 (5.57–13.9)	7.39 (6.06–12.0)	0.221
IL-12	30.1 (15.7–40.9)	23.9 (14.3–34.6)	0.068
IFN-γ	31.7 (24.1–43.4)	28.7 (23.1–34.4)	0.068
Eotaxin	132.6 (91.0–181.4)	136.5 (108.8–211.3)	0.081
IP-10	918.5 (670.2–1212.3)	885.8 (694.0–1352.7)	0.869
MCP-1	16.6 (10.8–23.7)	22.3 (15.2–32.2)	0.002
MIP-1β	64.6 (50.2–81.9)	69.6 (55.8–87.1)	0.118
PDGF-BB	8595.5 (5570.3–11352.0)	7623.5 (5312.4–9330.2)	0.041

Abbreviations: CRC = colorectal cancer; IFN-γ = interferon gamma; IL = interleukin; IP-10 = IFN-γ-induced protein 10 kDa; IQR = interquartile range; MCP-1 = monocyte chemotactic protein-1; MIP-1β = macrophage inflammatory protein-1β; PDGF-BB = platelet-derived growth factor, subtype BB. *P* values are for Mann–Whitney *U*-test.

Table 3 Serum cytokine levels of CRC patients in WHO Grades 1–3

Cytokine	Grade 1 ($n=16$) pg ml^{-1}, median (IQR)	Grade 2 ($n=86$) pg ml^{-1}, median (IQR)	Grade 3 ($n=14$) pg ml^{-1}, median (IQR)	*P*-value
IL-1ra	38.4 (31.1–85.5)	65.8 (41.6–98.4)	80.8 (54.1–122.3)	0.032
IL-4	0.88 (0.60–1.04)	0.86 (0.75–1.17)	1.00 (0.84–1.14)	0.210
IL-6	4.08 (2.51–4.55)	4.98 (3.46–8.71)	7.87 (4.03–21.3)	0.016
IL-7	4.90 (3.04–7.42)	5.53 (4.26–7.62)	5.92 (3.83–7.05)	0.501
IL-8	9.10 (8.15–13.4)	12.4 (9.64–16.9)	18.8 (11.5–29.4)	0.020
IL-9	5.86 (3.35–11.5)	9.27 (6.12–14.3)	12.0 (7.55–20.4)	0.064
IL-12	26.1 (13.4–31.3)	32.5 (15.7–41.0)	29.4 (12.8–55.3)	0.524
IFN-γ	26.3 (17.4–35.3)	32.4 (24.9–45.9)	31.8 (25.4–48.6)	0.077
Eotaxin	121.7 (79.2–176.1)	141.2 (103.2–181.8)	109.1 (66.5–194.2)	0.558
IP-10	864.5 (706.8–1481.6)	924.0 (651.3–1160.4)	1041.5 (670.3–2561.9)	0.425
MCP-1	13.0 (10.1–19.5)	17.2 (10.5–25.5)	17.0 (12.9–24.5)	0.286
MIP-1β	52.7 (43.5–69.3)	65.2 (51.1–81.9)	64.8 (47.2–91.4)	0.312
PDGF-BB	8485.0 (2958.5–12079.4)	8569.9 (5796.2–12406.0)	8687.1 (7206.7–10056.2)	0.772

Abbreviations: CRC = colorectal cancer; IFN-γ = interferon gamma; IL = interleukin; IP-10 = IFN-γ-induced protein 10 kDa; IQR = interquartile range; MCP-1 = monocyte chemotactic protein-1; MIP-1β = macrophage inflammatory protein-1β; PDGF-BB = platelet-derived growth factor, subtype BB. *P* values are for Kruskal–Wallis test.

Table 4 Serum cytokine levels of CRC patients in different TNM stages

Cytokine	Stage I ($n=19$) pg ml^{-1}, median (IQR)	Stage II ($n=46$) pg m^{-1}, median (IQR)	Stage III ($n=32$) pg ml, median (IQR)	Stage IV ($n=18$) pg ml^{-1}, median (IQR)	*P*-value
IL-1ra	47.9 (33.0–89.1)	60.0 (36.2–91.3)	63.6 (36.6–98.2)	92.7 (75.9–107.0)	0.039
IL-4	0.90 (0.64–1.08)	0.82 (0.71–1.17)	0.85 (0.74–1.02)	1.06 (0.91–1.12)	0.176
IL-6	4.33 (3.17–6.59)	4.69 (3.38–9.24)	4.73 (3.10–8.59)	7.72 (4.79–12.6)	0.055
IL-7	5.56 (3.37–7.59)	5.03 (3.65–7.40)	5.39 (4.06–7.38)	7.04 (5.87–9.21)	0.060
IL-8	9.20 (8.09–12.5)	12.1 (8.97–18.8)	12.1 (9.43–14.2)	20.4 (14.4–60.1)	6.99E − 5
IL-9	8.00 (3.75–20.4)	8.63 (4.94–13.6)	7.79 (4.67–13.1)	10.9 (8.57–20.4)	0.298
IL-12	24.6 (15.7–31.5)	31.6 (15.4–40.3)	33.0 (11.8–47.5)	30.3 (17.1–42.4)	0.662
IFN-γ	33.9 (20.1–45.1)	31.5 (22.0–46.1)	29.0 (25.2–40.1)	32.3 (28.9–43.4)	0.573
Eotaxin	167.9 (72.2–184.4)	142.8 (106.3–178.2)	124.9 (92.0–171.5)	129.4 (78.0–182.8)	0.644
IP-10	885.2 (722.4–1605.4)	901.7 (654.6–1270.5)	893.8 (585.4–1130.3)	1015.9 (770.1–1461.1)	0.600
MCP-1	14.1 (11.0–23.7)	16.9 (9.36–27.0)	14.8 (10.8–18.9)	24.3 (14.9–41.2)	0.073
MIP-1β	66.1 (42.2–85.6)	62.3 (47.3–82.2)	63.8 (52.3–80.6)	72.8 (50.7–82.8)	0.900
PDGF-BB	8246.5 (4762.9–12395.9)	8474.3 (4689.3–11502.6)	8150.2 (5859.2–10066.8)	10495.6 (8115.8–15109.7)	0.085

Abbreviations: CRC = colorectal cancer; IFN-γ = interferon gamma; IL = interleukin; IP-10 = IFN-γ-induced protein 10 kDa; IQR = interquartile range; MCP-1 = monocyte chemotactic protein-1; MIP-1β = macrophage inflammatory protein-1β; PDGF-BB = platelet-derived growth factor, subtype BB. *P* values are for Kruskal–Wallis test.

Table 5 Logistic regression model for predicting colorectal cancer

	Coefficient	OR	95% CI	*P*-value
IL-1ra	−3.76	0.023	0.002–0.225	0.0011
IL-6	3.95	52.1	4.29–632.4	0.0019
IL-8	9.07	8665.4	201.1–373433.1	2.3E−6
IP-10	−3.21	0.041	0.0052–0.315	0.0022
MCP-1	−3.53	0.029	0.0057–0.149	2.1E−5
Constant	9.28			

Abbreviations: CI = confidence interval; IL = interleukin; IP-10 = IFN-γ-induced protein 10 kDa; MCP-1 = monocyte chemotactic protein-1; OR = odds ratio. The data shown are on the basis of the 115 colorectal cancer patients and 84 controls. All the cytokine/chemokine levels were logarithmically transformed. A receiver operating characteristics curve for the model is presented in Figure 1.

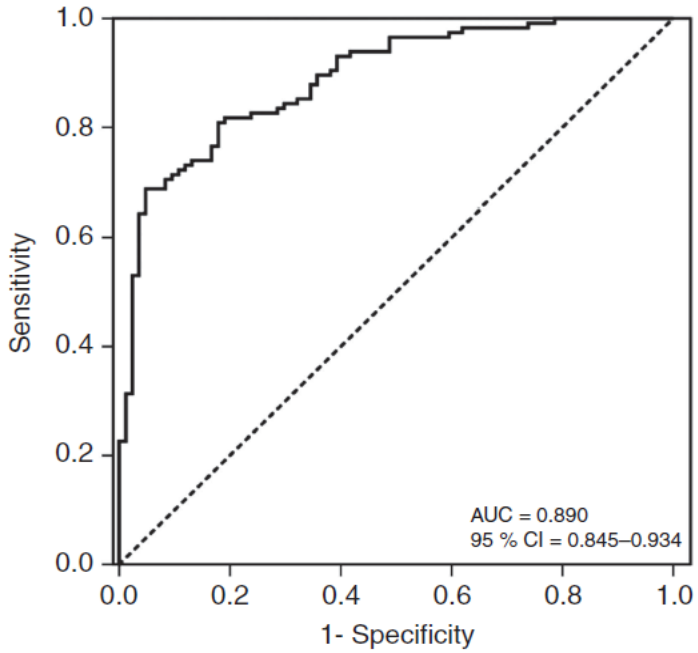


Figure 1 A receiver operating characteristics curve for serum cytokine/chemokine profile in discriminating CRC patients from healthy controls. The profile achieved an excellent discriminatory capability. Several probability cutoff values were tested, and the sensitivities and specificities were calculated: cutoff 0.349 (sensitivity 0.930, specificity 0.607), cut-off 0.500 (sensitivity 0.826, specificity 0.738), cut-off 0.545 (sensitivity 0.809, specificity 0.821), and cut-off 0.690 (sensitivity 0.687, specificity 0.952). Abbreviations: AUC = area under curve; CI = confidence interval.

Conclusion

Dysregulation of the immune cell and inflammatory responses in the patient with cancer

- tumor cells produce proinflammatory/ inflammatory cytokines and tumor burden is associated with an increased release of such cytokines.
- resection of the primary tumor does not significantly alter systemic inflammatory response status

Mécanisme

Review

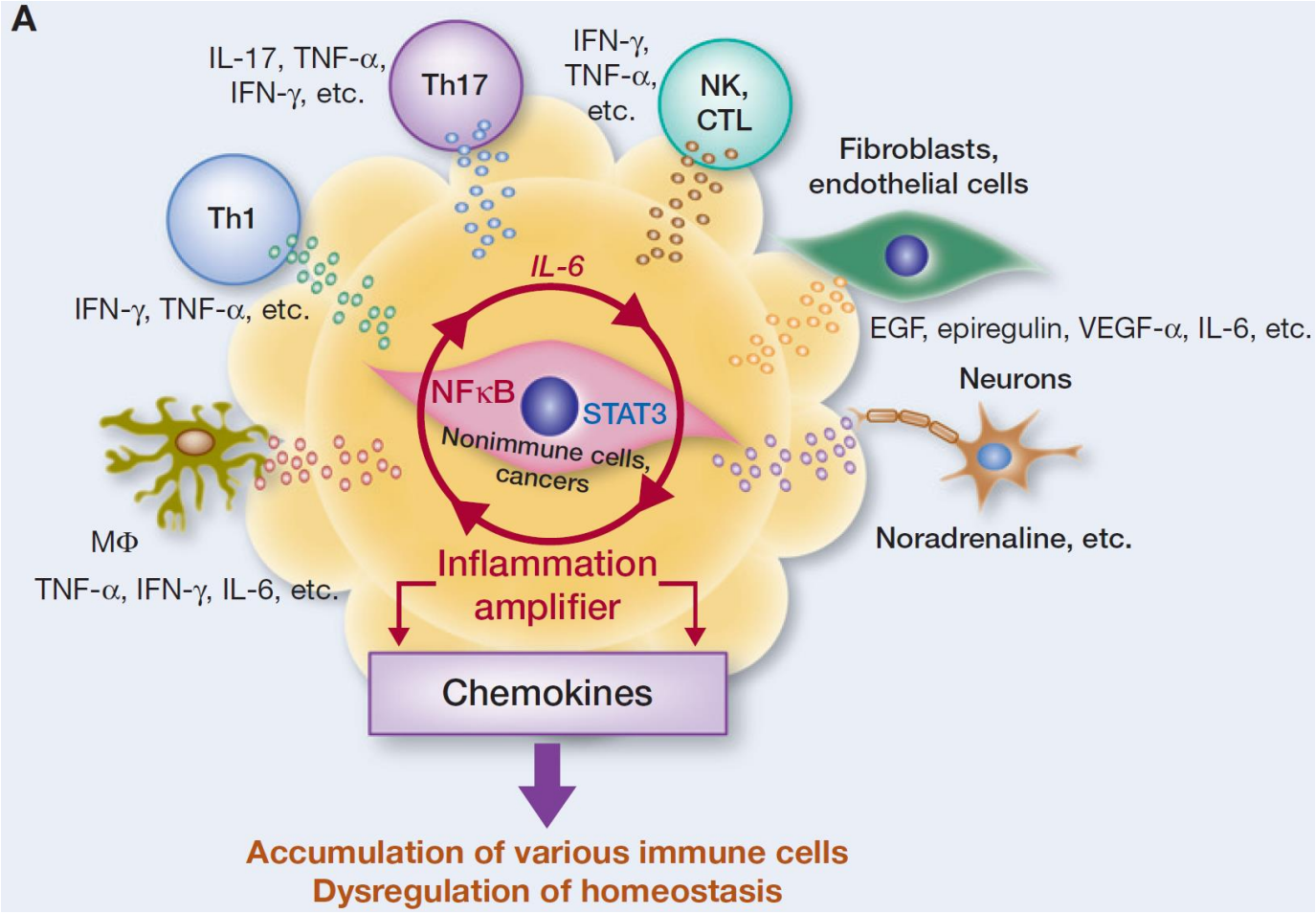
Cancer Research

Inflammation Amplifier, a New Paradigm in Cancer Biology

Toru Atsumi[1], Rajeev Singh[1], Lavannya Sabharwal[1], Hidenori Bando[1], Jie Meng[1], Yasunobu Arima[1], Moe Yamada[1], Masaya Harada[1], Jing-Jing Jiang[1], Daisuke Kamimura[1], Hideki Ogura[1], Toshio Hirano[2], and Masaaki Murakami[1]

Abstract

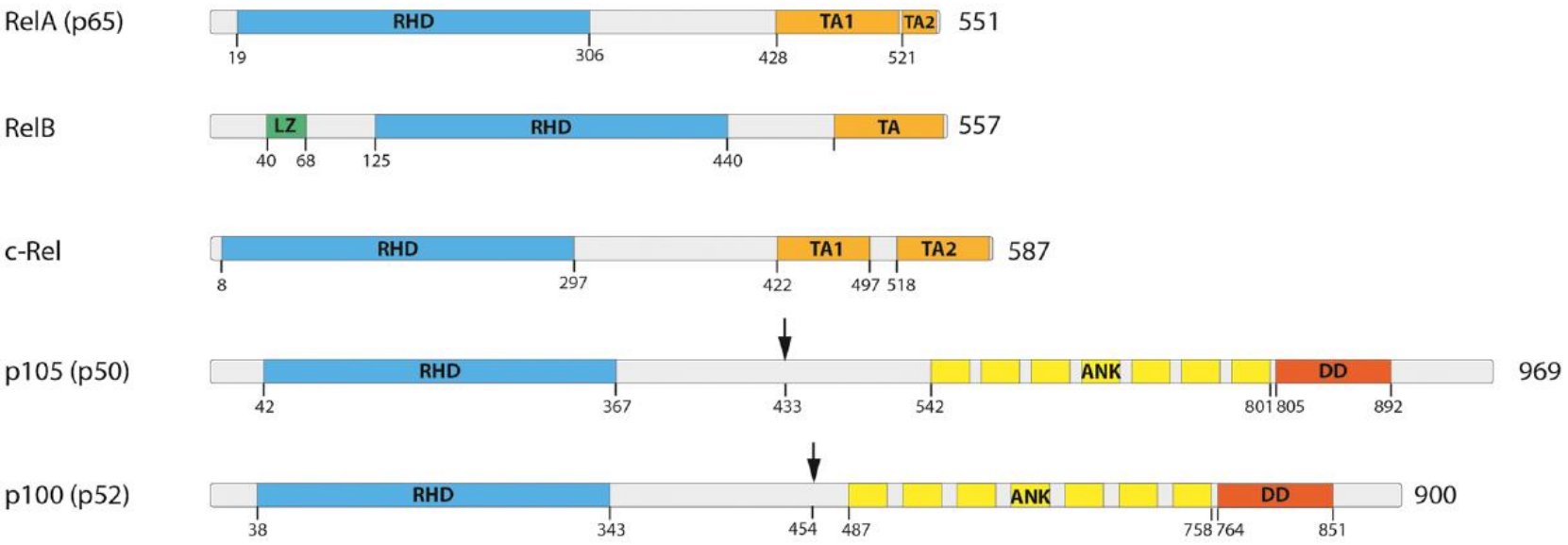
Tumor-associated inflammation can induce various molecules expressed from the tumors themselves or surrounding cells to create a microenvironment that potentially promotes cancer development. Inflammation, particularly chronic inflammation, is often linked to cancer development, even though its evolutionary role should impair nonself objects including tumors. The inflammation amplifier, a hyperinducer of chemokines in nonimmune cells, is the principal machinery for inflammation and is activated by the simultaneous stimulation of NF-κB and STAT3. We have redefined inflammation as local activation of the inflammation amplifier, which causes an accumulation of various immune cells followed by dysregulation of local homeostasis. Genes related to the inflammation amplifier have been genetically associated with various human inflammatory diseases. Here, we describe how cancer-associated genes, including interleukin (IL)-6, Ptgs2, ErbB1, Gas1, Serpine1, cMyc, and Vegf-α, are strongly enriched in genes related to the amplifier. The inflammation amplifier is activated by the stimulation of cytokines, such as TNF-α, IL-17, and IL-6, resulting in the subsequent expression of various target genes for chemokines and tumor-related genes like BCL2L11, CPNE7, FAS, HIF1-α, IL-1RAP, and SOD2. Thus, we conclude that inflammation does indeed associate with the development of cancer. The identified genes associated with the inflammation amplifier may thus make potential therapeutic targets of cancers. *Cancer Res; 74(1); 8–14. ©2013 AACR.*


A
IL-17, TNF-α, IFN-γ, etc.
Th17
IFN-γ, TNF-α, etc.
NK, CTL
Fibroblasts, endothelial cells
Th1
IFN-γ, TNF-α, etc.
IL-6
EGF, epiregulin, VEGF-α, IL-6, etc.
NFκB
STAT3
Nonimmune cells, cancers
Neurons
MΦ
TNF-α, IFN-γ, IL-6, etc.
Noradrenaline, etc.
Inflammation amplifier
Chemokines
Accumulation of various immune cells
Dysregulation of homeostasis

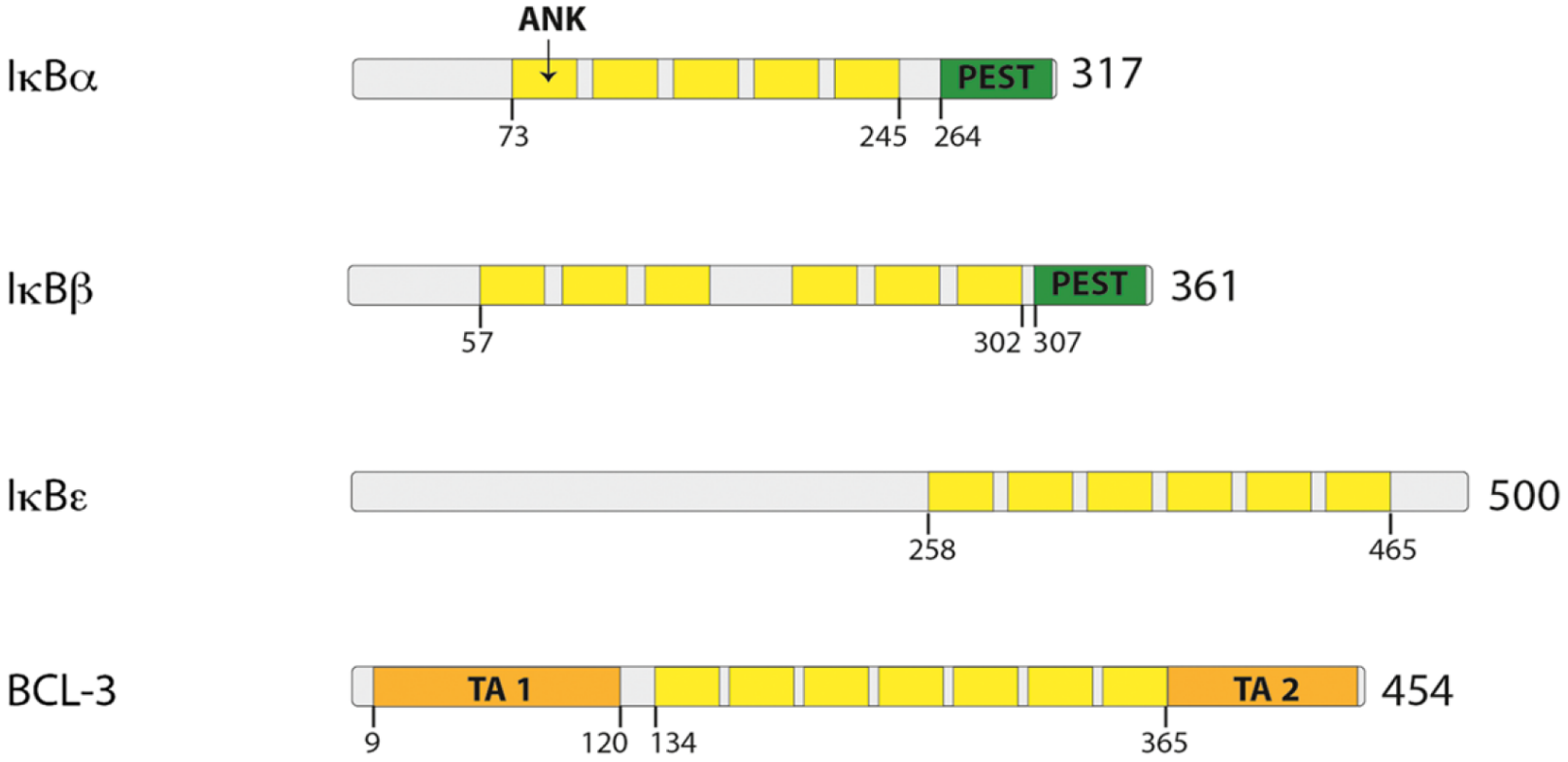
NF-κB

immunoglobulin kappa light-chain of activated B cells

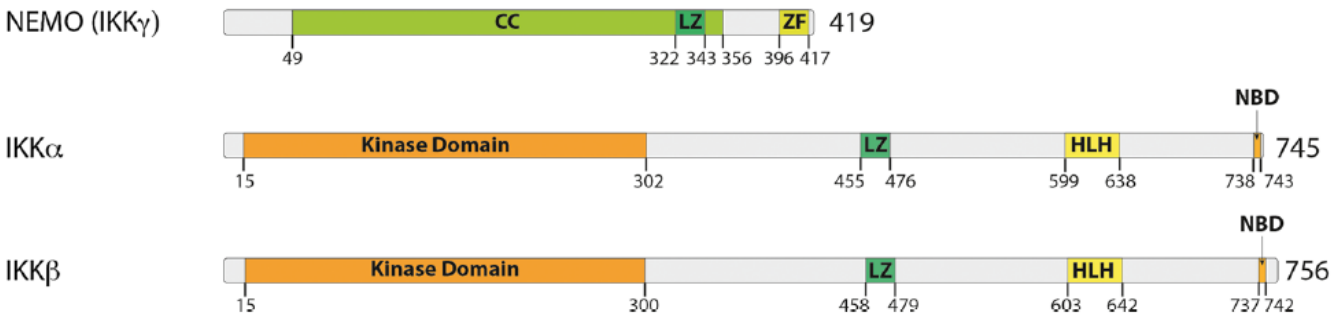
The five members of the NF-κB family of proteins: RelA (p65), RelB, c-Rel,NF-κB1 (p105), and NF-κB2 (p100). p105 and p100 are processed to their shorter forms p50 and p52, respectively. All members of the NF-κB family harbor an N-terminal Rel homology domain (RHD), which mediates DNA contact and homo- and heterodimerization. Three family members (RelA, RelB and c-Rel) contain C-terminal transactivation domains (TAs), which are essential for transcriptional activity



The IκB family of proteins consists of four members: IκBα, IκBβ, IκBε and BCL-3. These proteins are characterized by the presence of ankyrin (ANK) repeats, which mediate binding of IκBs to the NF-κB family of proteins. Based on the presence of ankyrin repeats, p100 and p105 can also be included into the IκB family – as their DNA-binding RHD domain is covalently linked to an IκB-like inhibitory domain. In addition to the ANK repeats IκBα and IκBβ contain PEST domains, which are enriched in proline, glutamate, serine and threonine and are required for constitutive turnover. BCL-3 differs from other IκB family members by containing TA domains, which mediate transcriptional activity when BCL-3 is associated with NF-κB dimers that bind to DNA.



The three most important members of IκB kinase (IKK) complex: NF-κB Essential Modulator (NEMO or IKKγ), IκB kinase α, (IKKα or IKK1) and IκB kinase β (IKKβ or IKK2). Further abbreviations: leucin-zipper-like motif (LZ), death domain (DD), coiled-coil domain (CC), zinc-finger domain (ZF), helix-loop-helix domain (HLH), NEMO-binding domain (NBD). It is important to note that the total number of amino acids of protein as well as the start and end of some domains can differ between publications and databases



Signaling pathways activating NF-κB

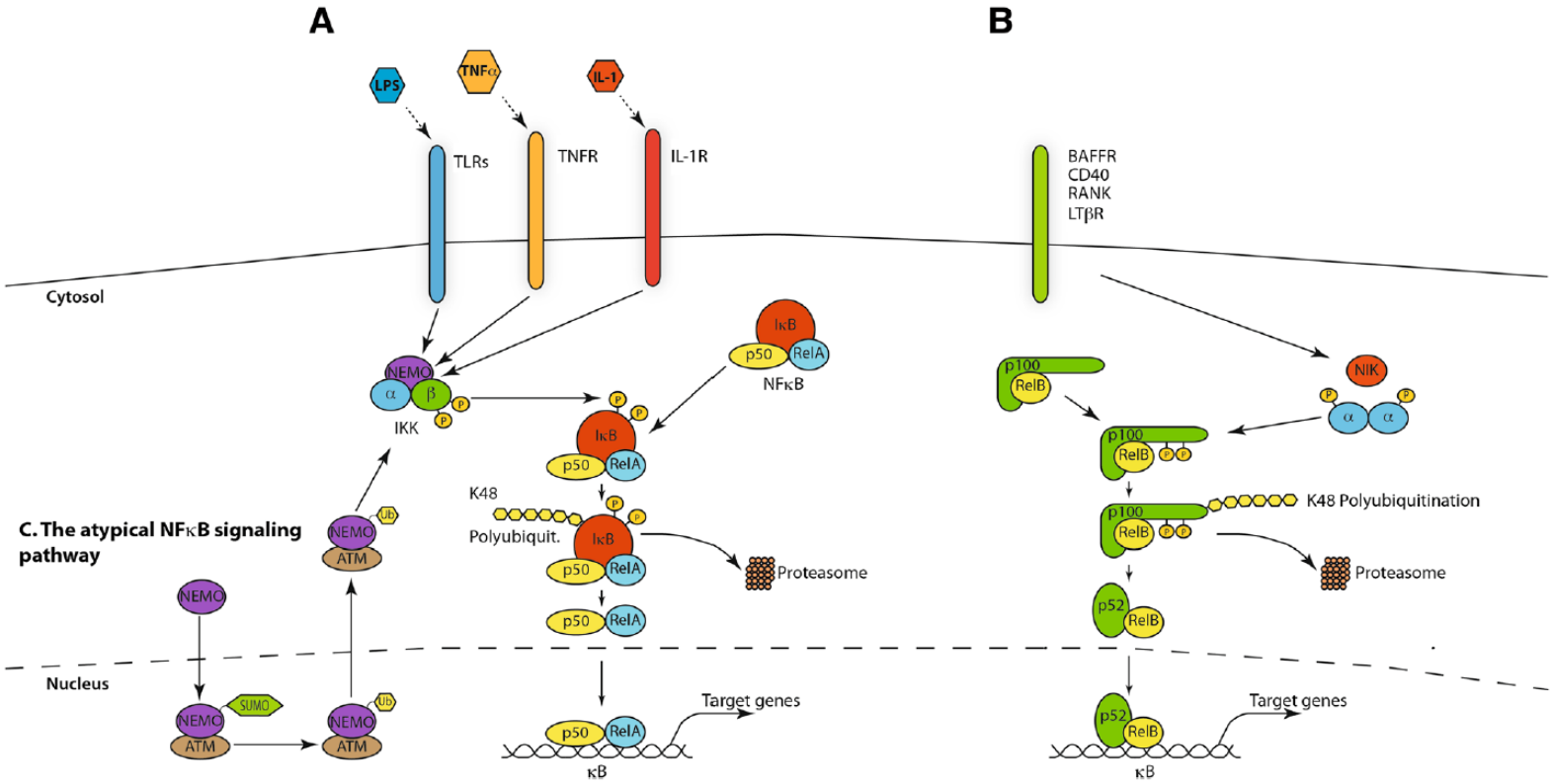


Figure 2 The canonical, non-canonical and the atypical NF-κB signaling pathway. (A) In the canonical NF-κB signaling pathway lipopolysaccharides (LPS), tumor necrosis factor α (TNFα) orinterleukin-1 (IL-1) activate Toll-like receptors (TLRs), tumor necrosis factor receptor (TNFR) and interleukin-1 receptor (IL-1R), respectively. Through a variety of adapter proteins and signaling kinases this leads to an activation of IKKβ in the IKK complex, which can then phosphorylate IκBα on Serine residues S32 and S36. This phosphorylation is a prerequisite for its subsequent polyubiquitination, which in turn results in proteasomal degradation of IκBα. NF-κB homo- or heterodimers can then translocate to nucleus and activate target gene transcription. **(B)** In the non-canonical NF-κB signaling pathway, activation of B-cell activation factor (BAFFR), CD40, receptor activator for nuclear factor kappa B (RANK) or lymphtoxin β-receptor (LTβR), leads to activation of IKKα by the NF-κB-inducing kinase (NIK). IKKα can the phosphorylate p100 on serine residues S866 and S870. This phosphorylation leads to polyubiquitination of p100 and its subsequent proteasomal processing to p52.p52-RelB heterodimers can then activate transcription of target genes. **(C)** In the atypical NF-κB signaling pathway, genotoxic stress leads to a translocation of NEMO to the nucleus where it is sumoylated and subsequently ubiquitinated. This process is mediated by the ataxia telangiectasia mutated (ATM) checkpoint kinase. NEMO and ATM can then return to the cytosol where they activate IKKβ.

Post-translational modifications of RelA, IκBα and IκBβ

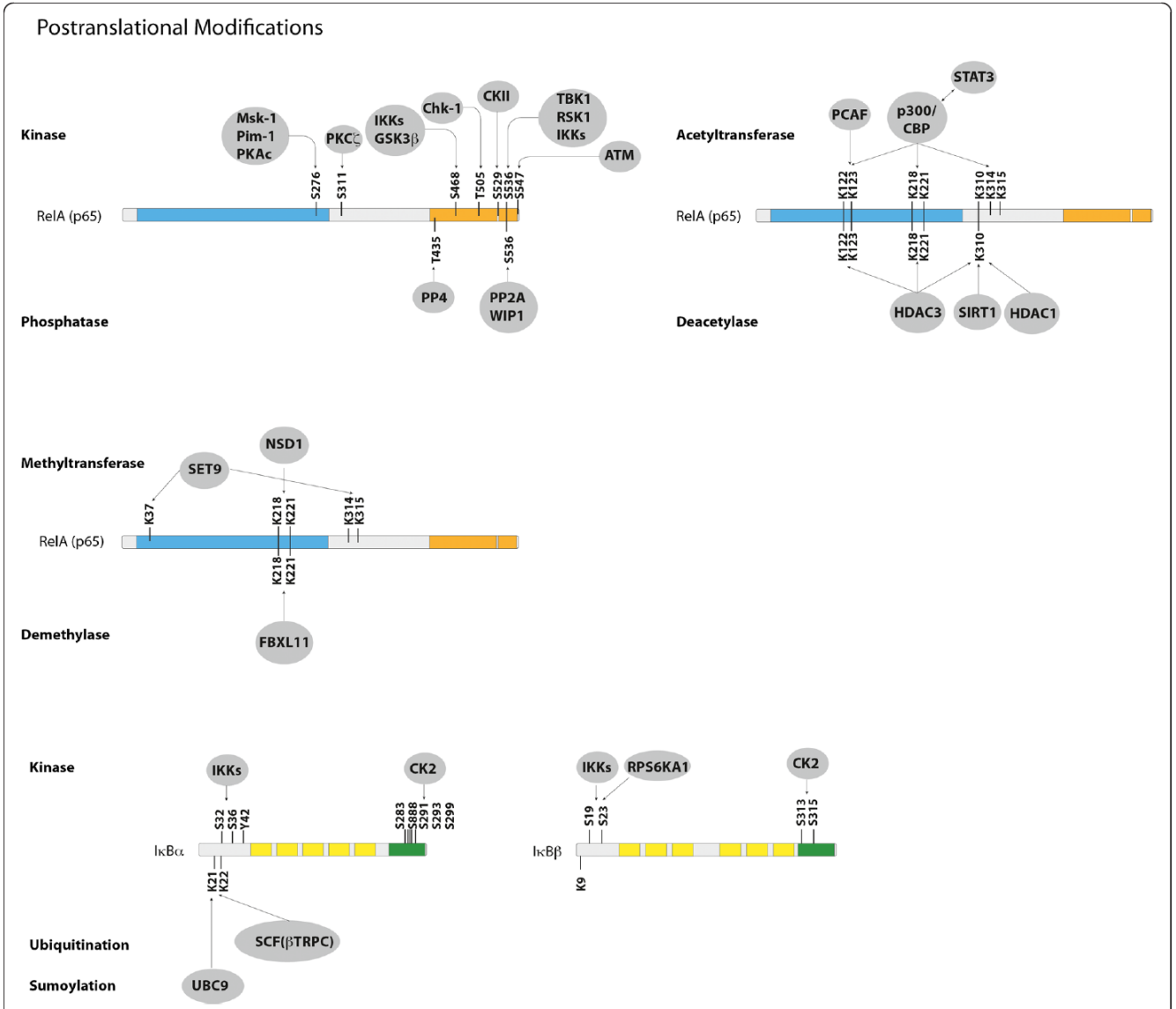


Figure 3 Post-translational modifications of RelA, IκBα and IκBβ. Phosphorylations, acetylations and methylations of RelA are shown, as well as phosphorylations, ubiquitination and sumoylation of IkBα and IkB.

Table 1 Positions of Phosphorylations of RelA and corresponding kinases

Kinase	p65 target residue	Effect of phosphate	References
unknown	S205	stimulates transcriptional activity	[54]
MSK1	S276	stimulates transcriptional activity	[55]
PIM1	S276	stimulates transcriptional activity	[56]
PKAc	S276	stimulates transcriptional activity	[57,58]
unknown	S281	stimulates transcriptional activity	[54]
PKCζ	S311	stimulates transcriptional activity	[59]
GSK-3β	S468	stimulates transcriptional activity	[60]
IKK2	S468; S536	stimulates transcriptional activity and nuclear import	[61,62]
IKKε	S468;S536	stimulates transcriptional activity	[63,64]
CKII	S529	stimulates transcriptional activity	[65]
CaMKIV	S535	stimulates transcriptional activity	[66]
TBK1	S536	stimulates transcriptional activity	[67]
IKK1	S536	stimulates transcriptional activity and stabilization	[68]
RSK1	S536	decreases IκBα -mediated nuclear export	[69]
ATM	S547	Increased expression of specific genes	[70]
unknown	T254	stabilization and nuclear localization	[71]
unknown	T435	stimulates transcriptional activity	[72]
CHK1	T505	pro-apoptotic effect	[73]

Network of NF-κB interactors

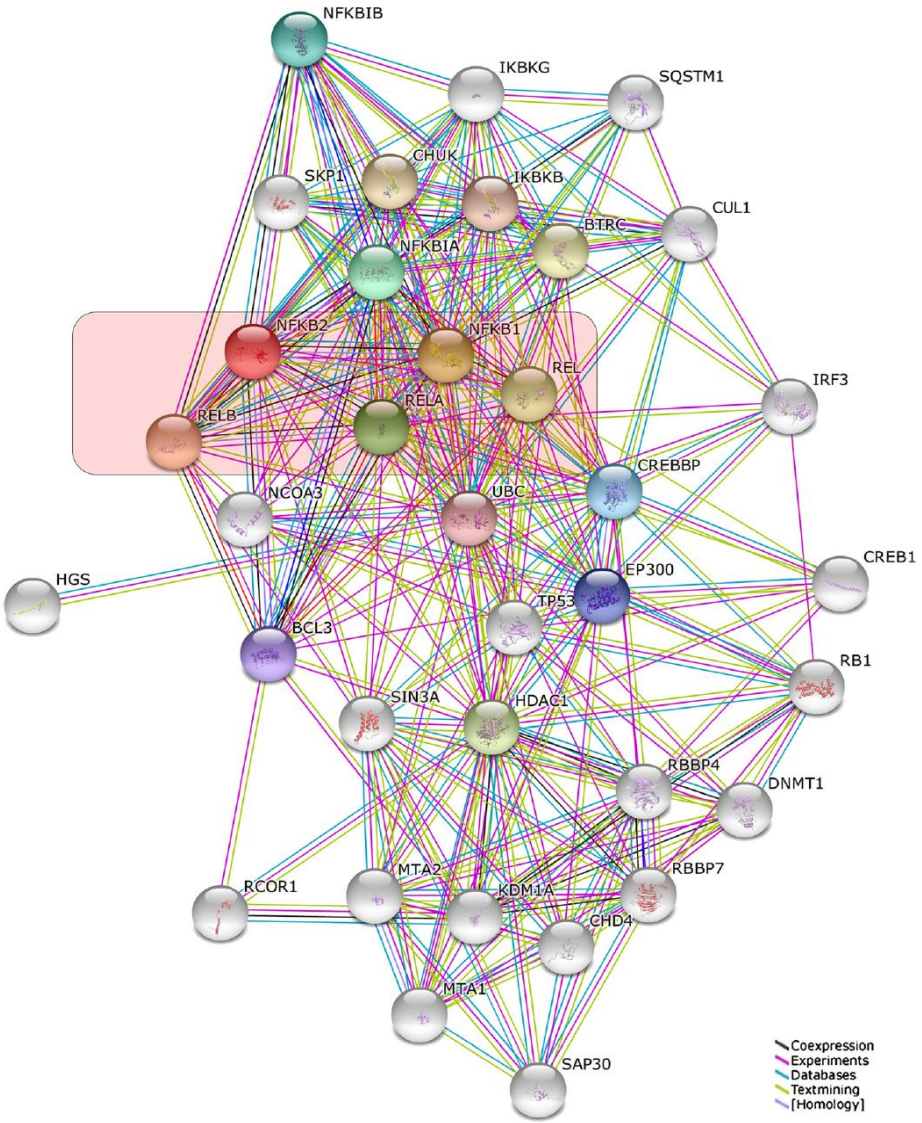


Figure 4 Network of NF-κB interactors. Evidence view of the STRING database output depicting functional and physical interactors of the NF-κB proteins, RelA, Rel (c-Rel), RelB, NFKB1 and NFKB2 obtained from: http://string-db.org/. The five NF-κB proteins are highlighted in red.

Crosstalk of the NF-κB pathway with other signaling pathways

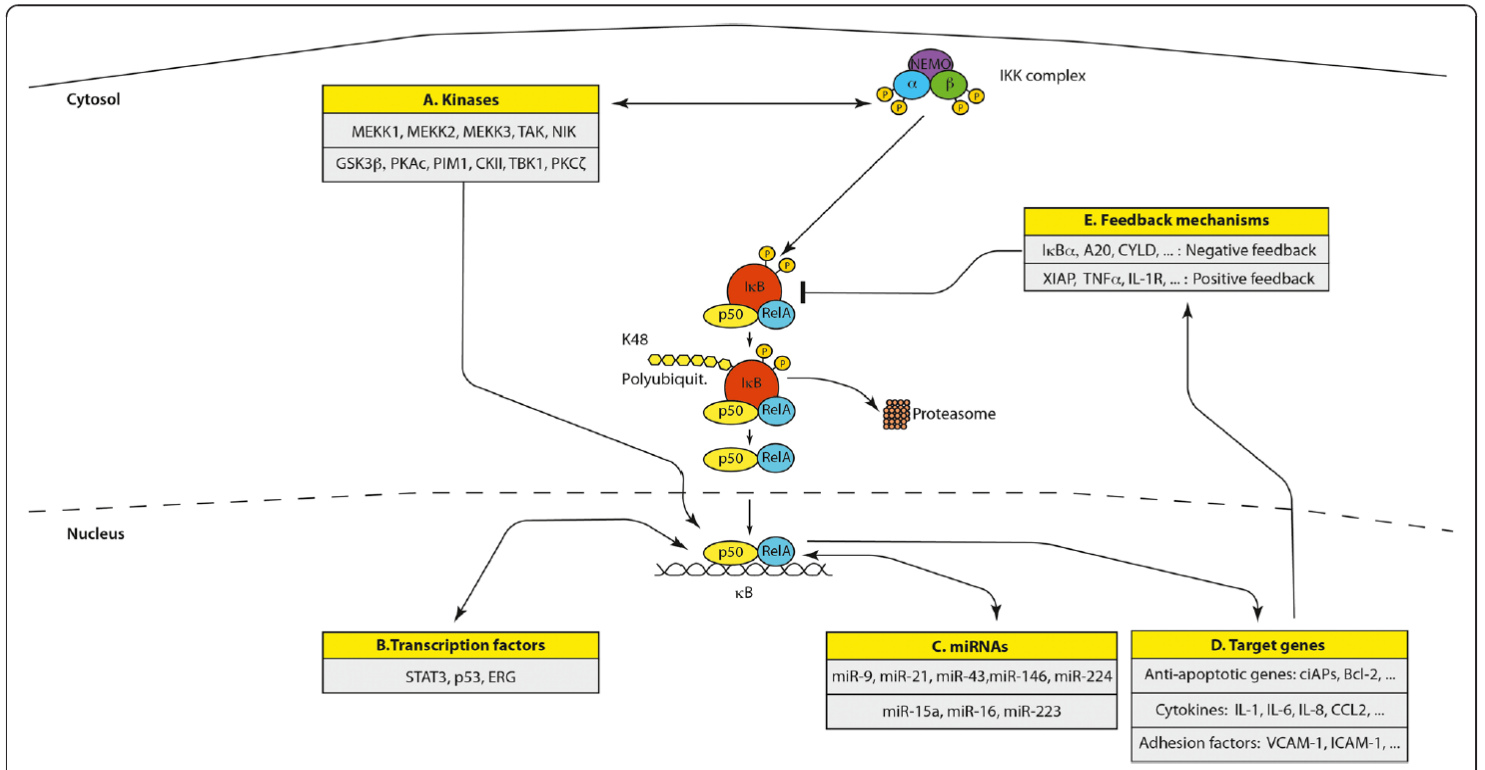


Figure 5 Crosstalk of the canonical NF-κB pathway with other signaling processes. (A) Many different kinases can phosphorylate and activate the IKKα and IKKβ subunits of the IKK complex or can enhance NF-κB transcriptional activity. Important examples are glycogen synthase kinase 3β (GSK3β), Protein Kinase B (PKB or Akt), Protein Kinase R (PKR), Protein Kinase C (PKC), Mitogen-Activated Type 3-Protein Kinase 7 (MAP3K7 or TAK1), p38 MAP Kinases or c-Jun N-terminal kinases (JNKs). **(B)** Various transcription factors such as p53, Ets Related Gene (ERG) or Signal Transducer and Activator of Transcription 3 (STAT3) can influence the transcriptional activity of NF-κB or directly activate transcription of NF-κB target genes. **(C)** microRNAs (miRNAs) can be target genes of the NF-κB signaling pathways or can affect the expression of NF-κB family members or effector molecules of the NF-κB activation pathway. **(D)** Prominent target genes of the NF-κB signaling pathway include anti-apoptotic genes as the Baculoviral IAP repeat-containing proteins (BIRCs or cIAPs) and the B-cell lymphoma 2 gene (Bcl-2), cytokines such as Interleukin-1 (IL-1), IL-6, IL-8 and chemokine (C-C motif) ligand 2 (CCL2), adhesion factors including the Vascular Cell Adhesion Molecule 1 (VCAM-1) and the Intercellular Cell Adhesion Molecule 1 (ICAM-1). **(E)** Another layer of complexity of NF-κB signaling are positive and negative feedback mechanism. Examples for positive feedback molecules are the X-linked inhibitor of apoptosis protein (XIAP) as well as TNFα or IL-1. Important negative feedback circuits are generated by the NF-κB target genes IκBα, Cylindromatosis (CYLD) or A20.

Research Article

Cancer Prevention Research

Knockout of the Tumor Suppressor Gene *Gprc5a* in Mice Leads to NF-κB Activation in Airway Epithelium and Promotes Lung Inflammation and Tumorigenesis

Jiong Deng[1], Junya Fujimoto[1], Xiao-Feng Ye[1], Tao-Yan Men[1], Carolyn S. Van Pelt[2], Yu-Long Chen[1], Xiao-Feng Lin[1], Humam Kadara[1], Qingguo Tao[1], Dafna Lotan[1], and Reuben Lotan[1]

Cancer Prev Res; 3(4); 424–37.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

JAKs and STATs in Immunity, Immunodeficiency, and Cancer

John J. O'Shea, M.D., Steven M. Holland, M.D., and Louis M. Staudt, M.D., Ph.D.

THIS PAST YEAR MARKED THE 20TH ANNIVERSARY OF THE DISCOVERY OF the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway.[1] Arising from efforts to understand the molecular mechanisms of

From the Molecular Immunology and Inflammation Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases (J.J.O.), the Laboratory of

N Engl J Med 2013;368:161-70.

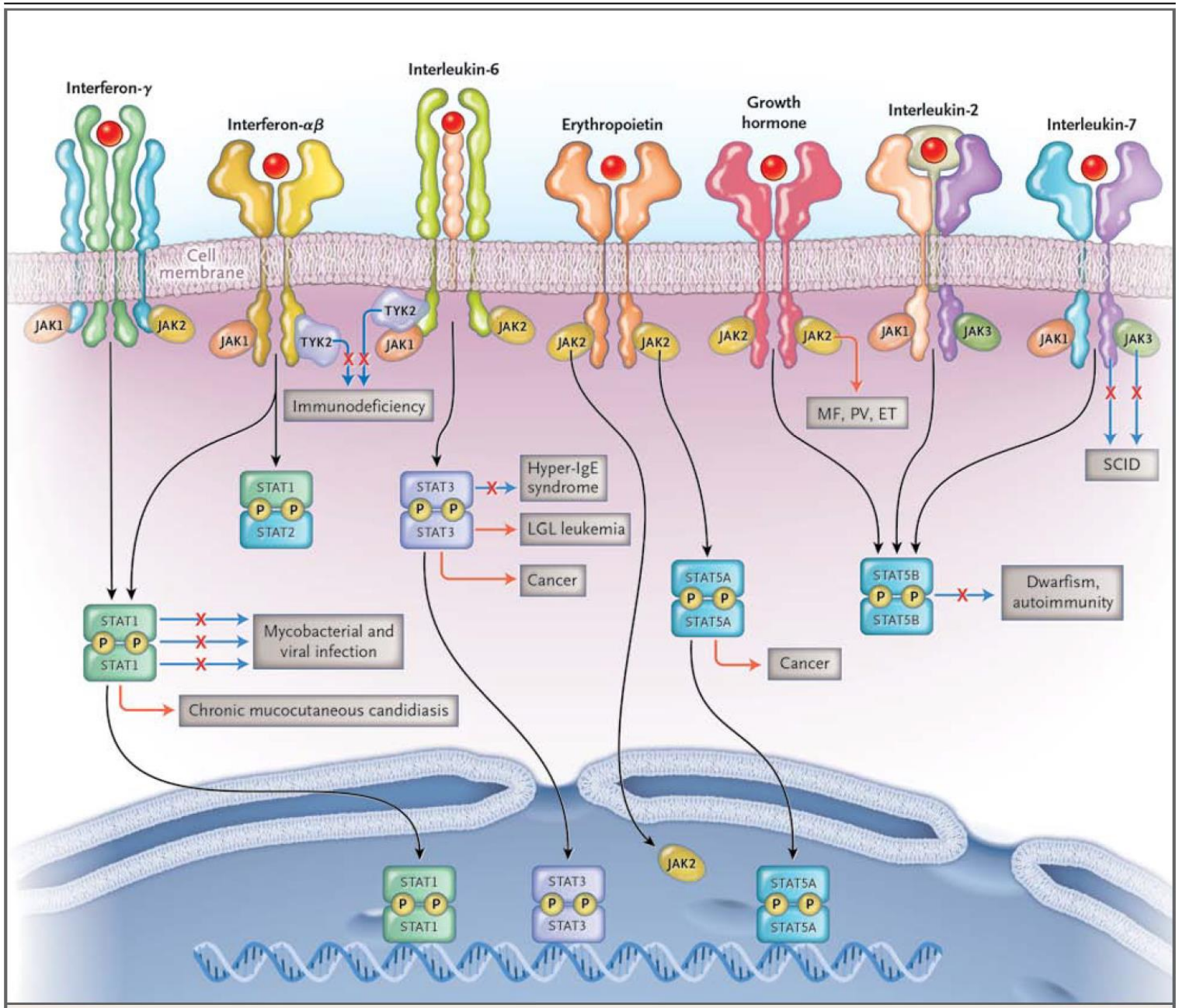
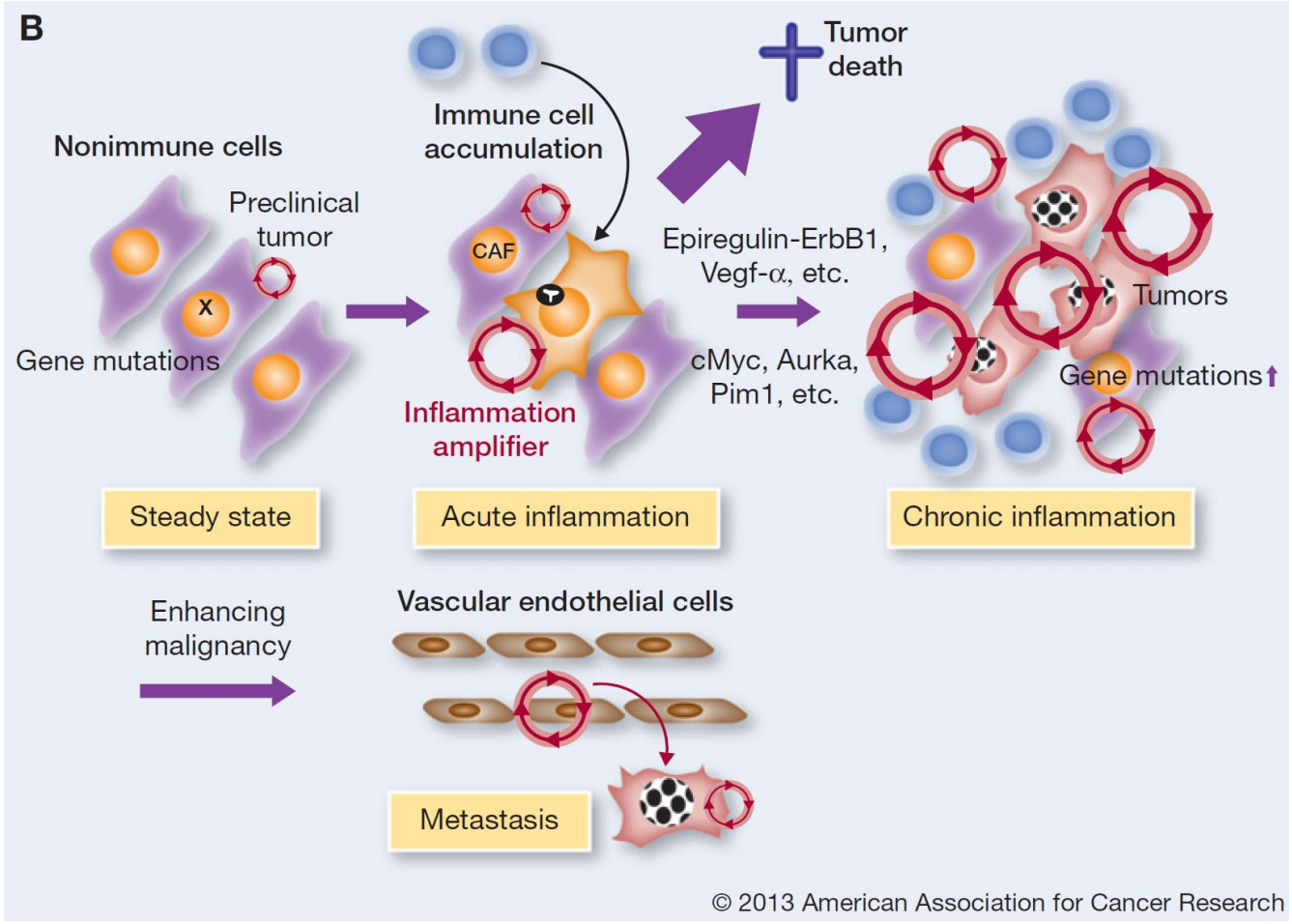


Figure 1. **Disorders Associated with Mutations of JAKs and STATs.**

Table 2. STAT-Related Disorders.*

STAT	Activating Cytokines	Disorders Caused by Loss-of-Function Mutations	Disorders Caused by Gain-of-Function (Activating) Mutations
STAT1	Interferons, other cytokines	Mycobacterial infections, viral infections	Chronic mucocutaneous candidiasis, fungal infections, aneurysms
STAT3†	Interleukin-6 and many other interleukins	Hyper-IgE syndrome	Large granular leukemia, ABC diffuse large-B-cell lymphoma, other cancers
STAT4‡	Interleukins 12, 23, α, β		
STAT5A	Prolactin, other hormonelike cytokines, interleukin-2, other cytokines		Multiple cancers
STAT5B	Growth hormone, other hormonelike cytokines, interleukin-2, other cytokines	Immunodeficiency, growth failure, autoimmunity	
STAT6§	Interleukins 4 and 13		

* STAT denotes signal transducer and activator of transcription.


B
Tumor death
Immune cell accumulation
Nonimmune cells
Preclinical tumor
X
Gene mutations
CAF
Inflammation amplifier
Epiregulin-ErbB1, Vegf-α, etc.
cMyc, Aurka, Pim1, etc.
Tumors
Gene mutations
Steady state
Acute inflammation
Chronic inflammation
Enhancing malignancy
Vascular endothelial cells
Metastasis
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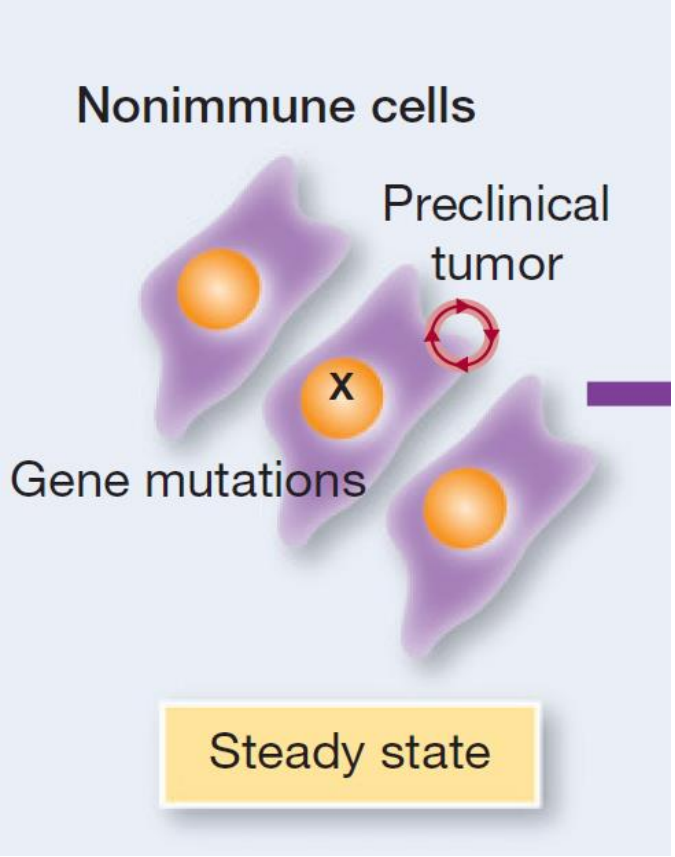
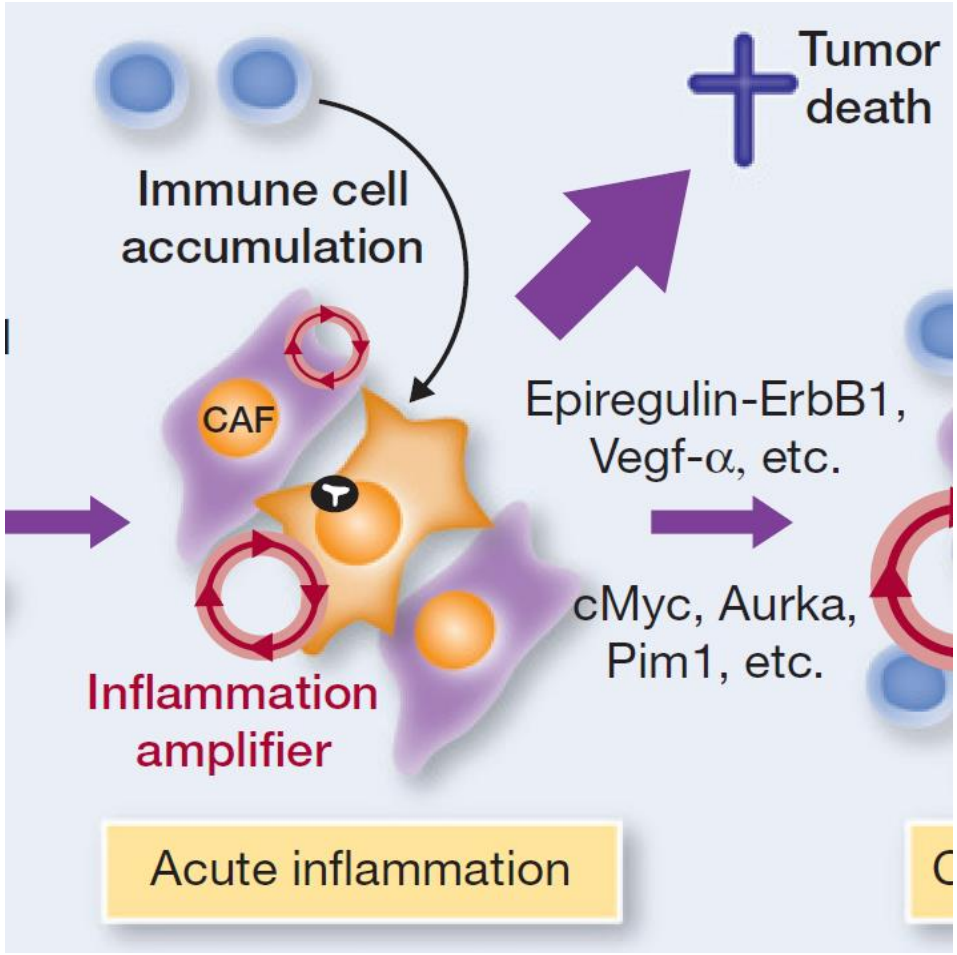
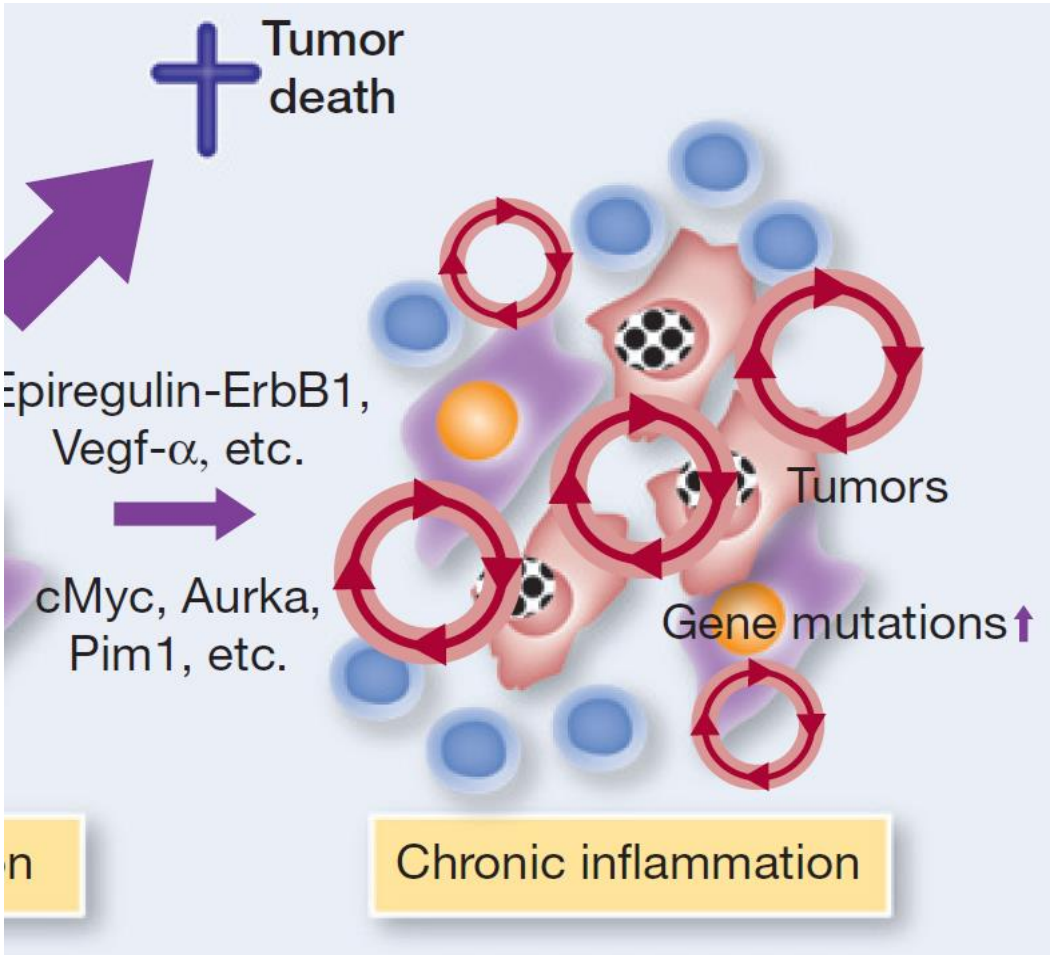
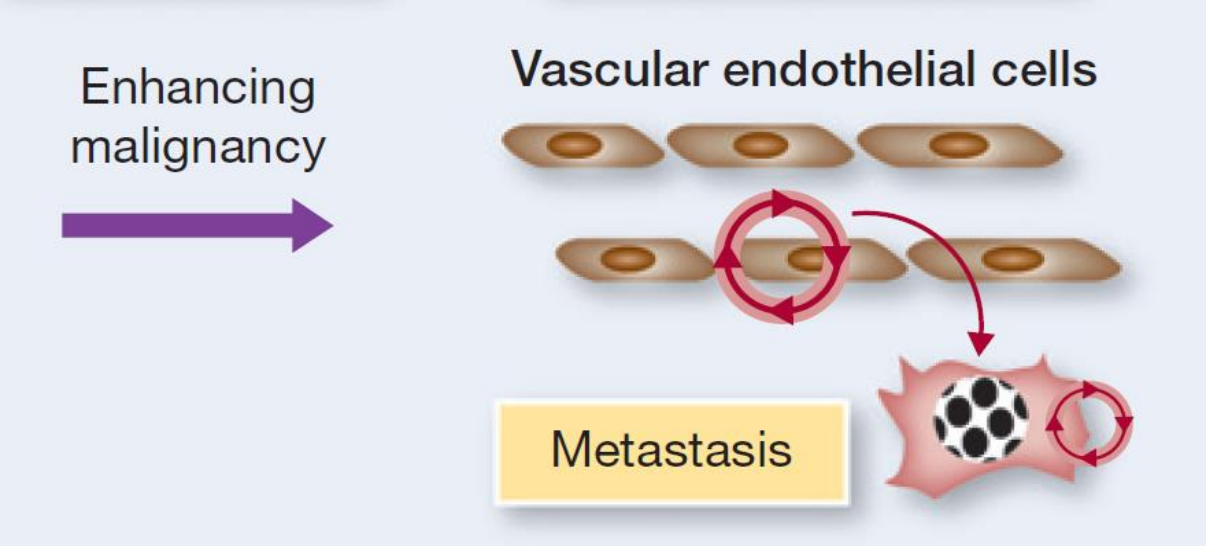

Nonimmune cells
Preclinical tumor
X
Gene mutations
Steady state


Tumor death
Immune cell accumulation
CAF
Epiregulin-ErbB1, Vegf-α, etc.
cMyc, Aurka, Pim1, etc.
Inflammation amplifier
Acute inflammation


Tumor death
Epiregulin-ErbB1, Vegf-α, etc.
cMyc, Aurka, Pim1, etc.
Tumors
Gene mutations
Chronic inflammation


Enhancing
malignancy
Vascular endothelial cells
Metastasis

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PLOS ONE

C-Reactive Protein, Interleukin 6 and Lung Cancer Risk: A Meta-Analysis

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PLoS ONE 7(8): e43075. (

Table 1. Characteristics of studies on CRP and lung cancer risk.

First author	Year	Study	Country	Study design	Age, y	N. of participant	N. of Cases	Measure, mg/l	RR (95% CI)
Il'yasova (29)	2005	HABCS	US	Co	70–79	Total: 2438	42	ln CRP	1.64 (1.20–2.24)
Trichopoulos (30)	2006	EPICN	Greece	NCC	20–86	Control:996	72	1 SD of CRP*	1.31 (1.11–1.53)
Suzuki (31)	2006	JACC	Japan	NCC	40–79	Control: 425	209	<0.36	1.0
								0.36–0.81	1.13 (0.67–1.91)
								0.82–1.72	0.66 (0.38–1.16)
								>1.73	1.19 (0.70–2.02)
Siemes (32)	2006	Rotterdam	Netherlands	Co	≥55	Total: 6273	117	ln CRP	1.51 (1.21–1.88)
Allin (33)	2009	CCHS	Danish	Co	≥35	Total: 10121	255	<1	1.0
								1–3	1.5 (0.7–3.2)
								3–10	2.2 (1.0–4.6)
Heikkila (12)	2009	BWHHS	UK	Co	60–80	Total: 3274	23	ln CRP	1.03 (0.71–1.51)
Heikkila (12)	2009	CCS	UK	Co	45–59	Total: 1144	57	ln CRP	1.17 (0.91–1.50)
dos Santos Silva (34)	2010	NPHS-II	UK	Co	56.0†	Total:1868	35	0.037–1.340	1.0
								1.341–2.83	0.79 (0.24–2.62)
								2.84–6.38	1.18 (0.41–3.41)
								6.39–123.4	1.50 (0.55–4.08)
Chaturvedi (35)	2010	PLCO Trial	US	NCC	55–74	Control:670	592	<1.0	1.0
								1.1–2.7	1.22 (0.83–1.78)
								2.8–5.5	1.54 (1.08–2.21)
								>5.6	1.98 (1.35–2.89)
Van Hemelrijck (36)	2011	AMORIS	Sweden	Co	≥20	Total: 102749	516	Men<10	1.0
								10–15	1.34 (0.96–1.88)
								15–25	2.48 (1.46–4.19)
								25–50	2.02 (1.10–3.72)
								>50	1.38 (0.57–3.36)
								Women<10	1.0
								10–15	1.10 (0.76–1.60)
								15–25	1.99 (1.06–3.77)
								25–50	0.76 (0.24–2.38)
								>50	1.84 (0.76–4.48)

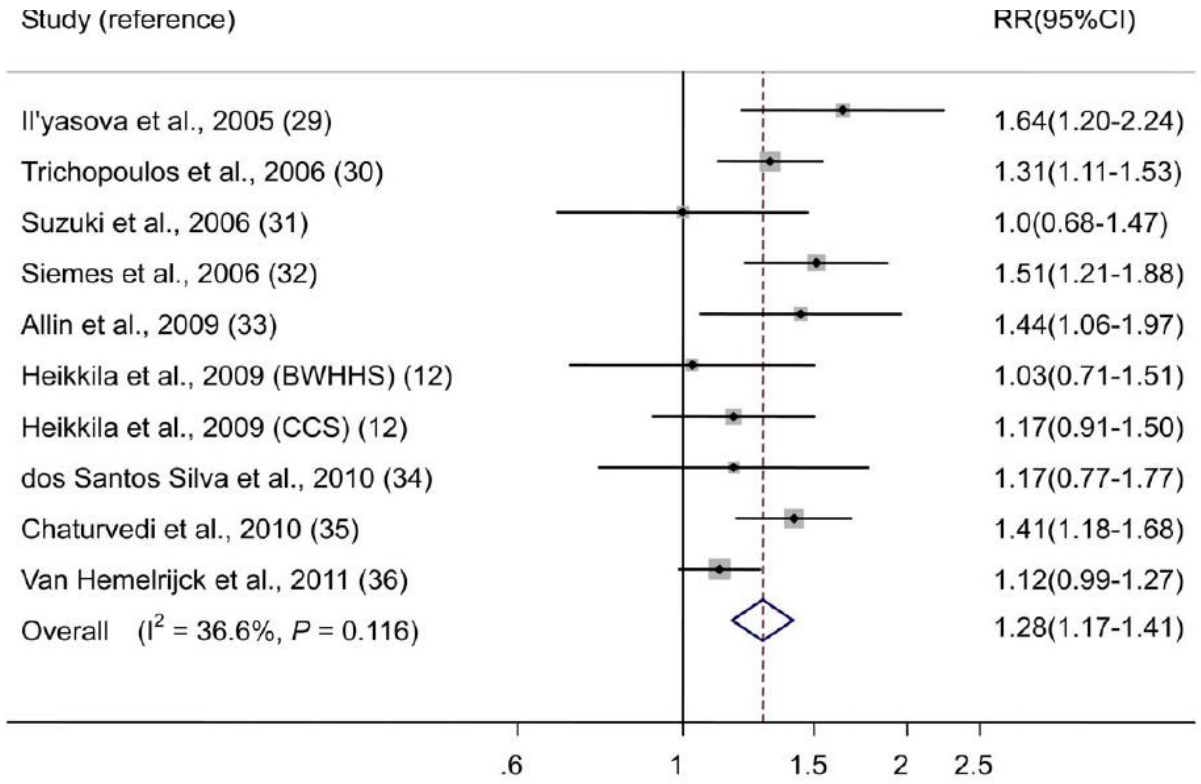

Figure 2. In studies on CRP, risk estimates of lung cancer associated with one unit change in ln CRP. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); horizontal lines indicate 95% confidence intervals (CIs); diamonds indicate summary risk estimate with its corresponding 95% confidence interval. Abbreviation: BWHHS, British Women's Heart and Health Study; CCS, Caerphilly Cohort Study.
doi:10.1371/journal.pone.0043075.g002

Table 3. Characteristics of studies on IL-6 and lung cancer risk.

First author	Year	Study	Country	Study design	Age, y	N. of participant	N. of Cases	Measure, pg/ml	RR (95% CI)
Il'yasova (29)	2005	HABCS	US	Co	70–79	Total: 2438	42	ln IL-6	1.43 (0.91–2.26)
Heikkila (12)	2009	BWHHS	UK	Co	60–80	Total: 3274	23	ln IL-6	0.61 (0.31–1.22)
Heikkila (12)	2009	CCS	UK	Co	45–59	Total: 1144	57	ln IL-6	1.07 (0.81–1.43)
Pine (37)	2011	NCI-MD	US	CC	66.6†	Control:296	70	<1.4	1.0
								1.4–2.1	0.98 (0.51–1.86)
								2.1–3.8	2.28 (1.29–4.06)
								>3.8	3.29 (1.88–5.77)
Pine (37)	2011	PLCO Trial	US	NCC	55–74	Control:595	532	<2.7	1.0
								2.7–4.0	1.14 (0.79–1.65)
								4.0–6.6	1.25 (0.88–1.78)
								>6.6	1.48 (1.04–2.10)

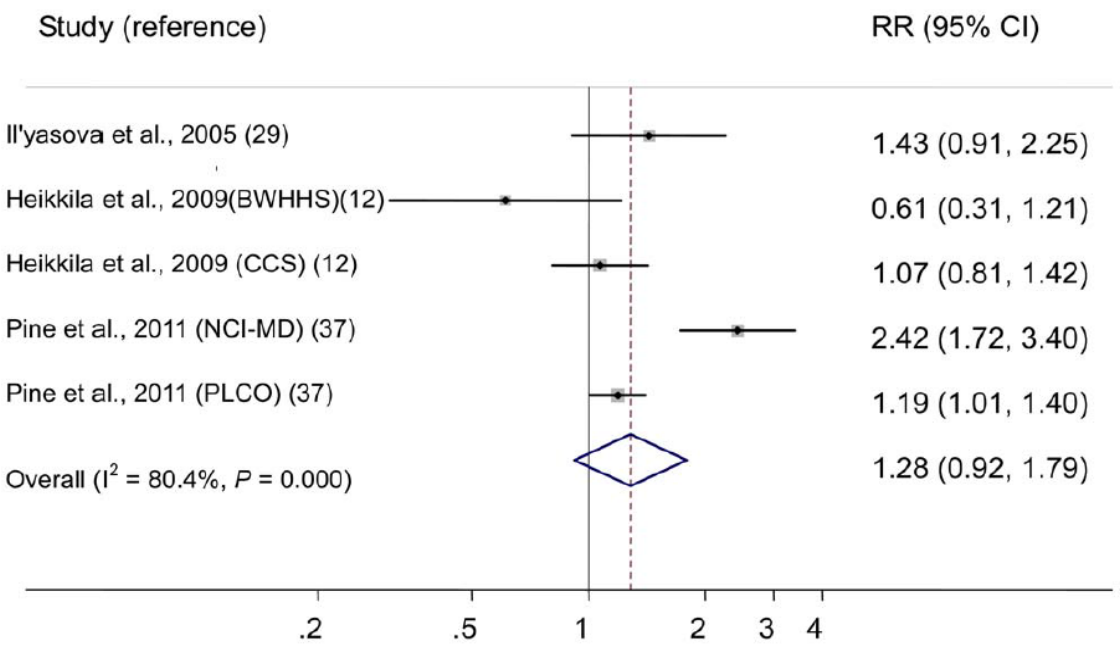

Figure 3. In studies on IL-6, risk estimates of lung cancer associated with one unit change in ln IL-6. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); horizontal lines indicate 95% confidence intervals (CIs); diamonds indicate summary risk estimate with its corresponding 95% confidence interval. Abbreviation: BWHHS, British Women's Heart and Health Study; CCS, Caerphilly Cohort Study; NCI-MD, National Cancer Institute-Maryland; PLCO, prospective Prostate, Lung, Colorectal, and Ovarian.

IJC
International Journal of Cancer

Circulating interleukin-6 level is a prognostic marker for survival in advanced nonsmall cell lung cancer patients treated with chemotherapy

Chin Hao Chang[1], Chin Fu Hsiao[2], Yu Min Yeh[3,4], Gee Chen Chang[5,6], Ying Huang Tsai[7], Yuh Min Chen[8,9], Ming Shyan Huang[10], Hui Ling Chen[2], Yao Jen Li[11,12], Pan Chyr Yang[13], Chien Jen Chen[11,12], Chao A. Hsiung[2]* and Wu Chou Su[3,4]*

Int. J. Cancer: **132**, 1977–1985 (2013)

Table 1. Baseline characteristics of lung cancer patients as stratified according to interleukin-6 level[1]

Characteristic	Patients with low IL-6 Level[2] ($N = 81$)	Patients with Intermediate IL-6 Level[2] ($N = 83$)	Patients with High IL-6 Level[2] ($N = 81$)
Median of survival time (month)	17.9	13.0	9.2
Age (year)	62.7 ± 12.5	62.1 ± 12.8	61.6 ± 11.5
Sex (no. in %)			
Female	41 (50.6)	39 (47.0)	35 (43.2)
Male	40 (49.4)	44 (53.0)	46 (56.8)
Smoking history (no. in %)			
No	47 (58.0)	42 (50.6)	43 (53.1)
Yes	34 (42.0)	41 (49.4)	38 (46.9)
Cell type (no. in %)			
Adenocarcinoma	56 (69.1)	52 (62.7)	59 (72.8)
Squamous/poorly differentiated	25 (30.9)	31 (37.3)	22 (27.2)
Stage (no. in %)			
3B	22 (27.2)	18 (21.7)	11 (13.6)
4	59 (72.8)	65 (78.3)	70 (86.4)
The date of recruitment (no. in %)			
Before the first day of first-line chemotherapy	43 (53.1)	36 (43.4)	33 (40.7)
After the first day of first-line chemotherapy	38 (46.9)	47 (56.6)	48 (59.3)

[1]IL-6 denotes Interleukin-6. Plus–minus values are ± SD. [2]Patients were categorized according to tertiles of IL-6 concentration. Each patient was classified as "low IL-6 level" (first tertile, 0–2.01 pg/mL), "intermediate IL-6 level" (second tertile, 2.01–25.16 pg/mL) or "high IL-6 level" (third tertile, >25.16 pg/mL).

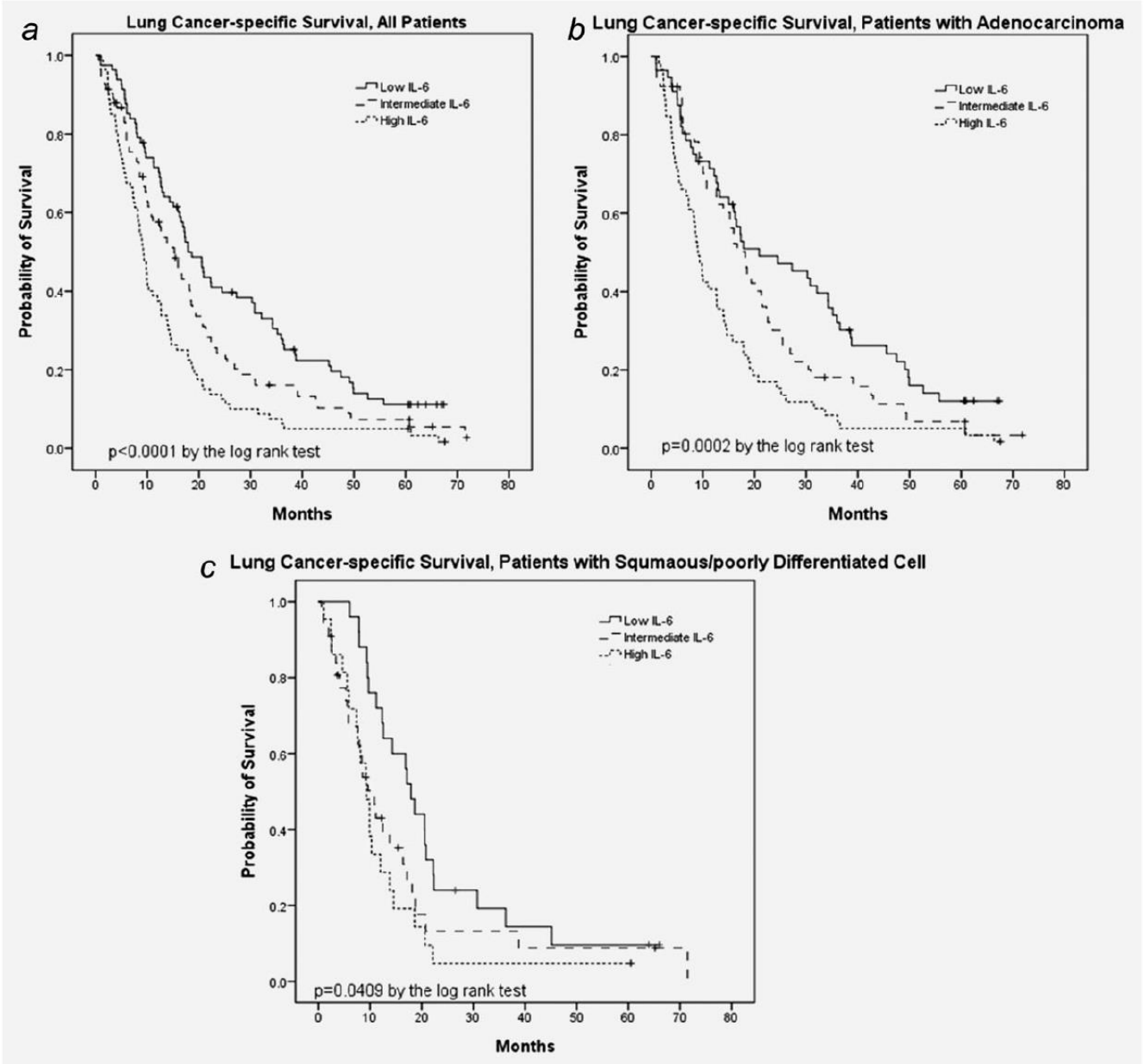

Figure 1. Kaplan-Meier Survival Estimates by Tertiles of Plasma IL-6 Concentration. Kaplan-Meier curves for lung cancer-specific survival are shown for all patients (Panel *a*), patients with adenocarcinoma (Panel *b*) and patients with squamous/poorly differentiated cell (Panel *c*). Patients were trichotomized according to tertiles of plasma IL-6 levels. The tertile cut-off points were 2.01 and 25.16 pg/mL for all patients ($N = 245$), adenocarcinoma ($N = 167$) and squamous/poorly differentiated cell ($N = 78$), respectively.

Table 2. Multivariate analysis of lung cancer-specific survival for all patients and stratified by histologic type of lung cancer[1]

	All Patients ($N = 245$)			Adenocarcinoma ($N = 167$)			Squamous/poorly differentiated ($N = 78$)		
Variable	Hazard Ratio[2]	95% CI	*p* Value	Hazard Ratio[2]	95% CI	*p* Value	Hazard Ratio[2]	95% CI	*p* Value
Sex (male *vs.* female)	0.97	(0.64, 1.47)	0.88	0.90	(0.56, 1.45)	0.67	1.23	(0.48, 3.17)	0.67
Smoking history (yes *vs.* no)	1.20	(0.80, 1.82)	0.38	1.15	(0.71, 1.87)	0.58	1.19	(0.49, 2.90)	0.70
Histologic type (squamous/poorly differentiated *vs.* adenocarcinoma)	1.31	(0.96, 1.79)	0.09	–	–	–	–	–	–
Stage (4 *vs.* 3B)	1.41	(0.99, 2.01)	0.06	1.06	(0.67, 1.67)	0.81	2.48	(1.34, 4.57)	0.004
IL-6 level[3]									
Intermediate *vs.* low	1.44	(1.03, 2.01)	0.03	1.34	(0.88, 2.04)	0.17	2.68	(1.38, 5.19)	0.003
High *vs.* low	2.10	(1.49, 2.96)	0.0001	2.16	(1.42, 3.27)	0.0001	2.96	(1.44, 6.07)	0.003

[1]IL-6 denotes Interleukin-6 and CI, confidence interval. [2]Hazard ratios were calculated with the use of a Cox proportional-hazards model, with age, sex, smoking history (yes or no), histological type (squamous/poorly differentiated or adenocarcinoma), stage and IL-6 level (high, intermediate or low) as covariates. [3]Patients were trichotomized according to tertiles of plasma IL-6 levels. The tertile cut-off points were 2.01 and 25.16 pg/mL for all patients, adenocarcinoma and squamous/poorly differentiated cell.

Table 4. Response to advanced nonsmall cell lung cancer patients treated with chemotherapy as stratified according to interleukin-6 level

Response	Group 1[1] Low IL-6 Level[2] (*N* = 32)	Group 2[1] Intermediate IL-6 Level[2] (*N* = 39)	*p* Value[3]	Group 3[1] High IL-6 Level[2] (*N* = 35)	*p* Value[3]
Overall (no. %)			0.86		0.08
Complete response (CR)	1 (3.1)	0 (0.0)		0 (0.0)	
Partial response (PR)	12 (37.5)	17 (43.6)		10 (28.6)	
Stable disease (SD)	13 (40.6)	14 (35.9)		9 (25.7)	
Progression disease (PD)	6 (18.8)	8 (20.5)		16 (45.7)	
Combination 1 (no. %)			0.95		0.07
CR + PR	13 (40.6)	17 (43.6)		10 (28.6)	
SD	13 (40.6)	14 (35.9)		9 (25.7)	
PD	6 (18.8)	8 (20.5)		16 (45.7)	
Combination 2 (no. %)			1.00		0.02
CR + PR + SD	26 (81.2)	31 (79.5)		19 (54.3)	
PD	6 (18.8)	8 (20.5)		16 (45.7)	

[1]There were 6, 8 and 13 inevaluable patients in Groups 1, 2 and 3, respectively. [2]Patients were categorized according to tertiles of IL-6 concentration. Each patient was classified as "low IL-6 level" (first tertile, 0–2.01 pg/mL), "intermediate IL-6 level" (second tertile, 2.01–25.16 pg/mL) or "high IL-6 level" (third tertile, >25.16 pg/mL). [3]Using Fisher's exact test for comparing with Group 1.

Ann Thorac Cardiovasc Surg 2011; 17: 454–460

doi: 10.5761/atcs.oa.10.01627

Original Article

Does Postoperative Serum Interleukin-6 Influence Early Recurrence after Curative Pulmonary Resection of Lung Cancer?

Hidefumi Kita, MD,[1] Yuji Shiraishi, MD,[1] Kenichi Watanabe, MD,[2] Kazuharu Suda, MD,[3] Kouki Ohtsuka, MD,[4] Yoshihiko Koshiishi, MD,[5] and Tomoyuki Goya, MD[6]

Table 1 Comparisons of the non-recurrence group and the recurrence group

	Rec (–)	Rec (+)	p value*	p value**	Odds ratio (95% CI)**
Number	78	29			
Age (Years)	66.5 ± 1.2	66.5 ± 1.8	0.998	0.925	-
Gender Male/Female	47/31	22/7	0.134	0.334	-
Histological type					
Ad/Sq/LC/Others	51/19/2/6	22/5/0/2	0.724	0.146	-
Pathological stage					
I A / I B	37/26	3/11			
II A / II B	1/7	2/5	0.005	0.006	1.346 (1.091–1.661)
III A / III B	4/3	5/3			
VATS/TH	23/55	2/27	0.019	0.073	-
MLA –/+	37/41	14/15	0.938	0.951	-
QOH (ml)	91.1 ± 11.3	147.2 ± 28.9	0.030	0.173	-
OT (minutes)	201.8 ± 8.0	241.5 ± 13.5	0.012	0.437	-
IL-6 (pg/ml)					
Preoperatively	3.5 ± 0.7	4.3 ± 0.9	0.495	0.704	-
POD 0	155.6 ± 13.6	147.5 ± 10.8	0.727	0.357	-
POD 1	81.2 ± 7.5	128.4 ± 19.5	0.007	0.003	1.008 (1.003–1.013)
POD 2	52.1 ± 4.6	56.9 ± 7.0	0.584	0.059	-

Rec (–), The non-recurrence group; Rec (+), The recurrence group
Ad /Sq /LC, Adenocarcinoma / Squamous cell carcinoma / Large cell carcinoma
VATS: The VATS group; TH: The thoracotomy group; MLA: Mediastinal lymphadenectomy; QOH: quantity of hemorrhage; OPT: operating time: 95% CI: 95% confidence interval
*Results of univariate analysis, ** Results of Cox's proportional hazards regression

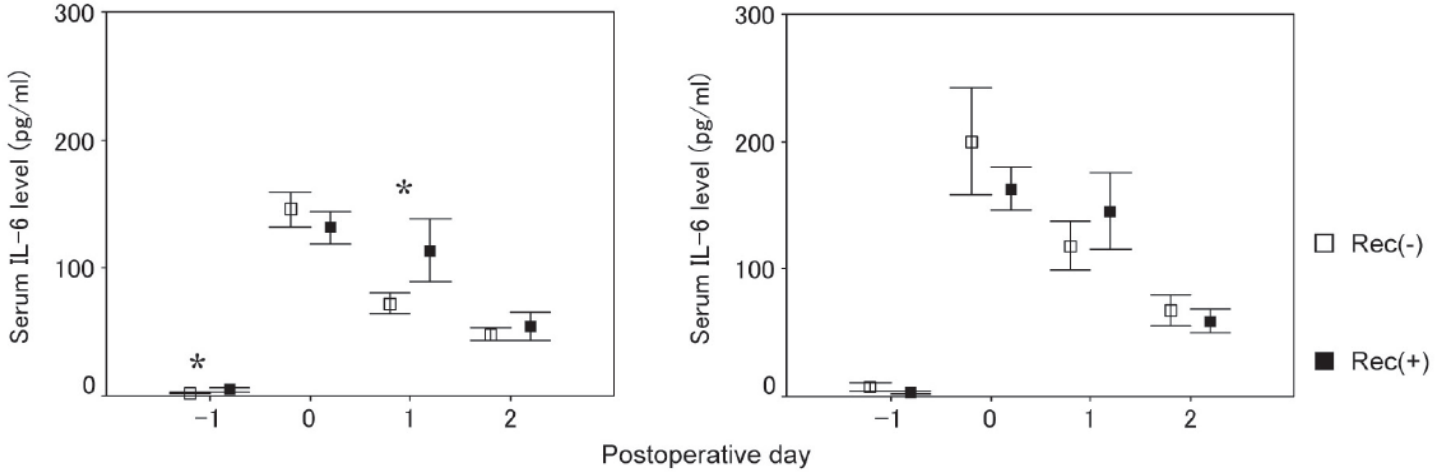

Fig. 1 Changes in the levels of serum IL-6 in the non-recurrence group (Rec (–)) and the recurrence group (Rec (+)). Comparisons of the Rec (–) (n = 63) and the Rec (+) (n = 14) with confirmed pathological stage I A + I B are shown A. Comparisons of the Rec (–) (n = 15) and the Rec (+) (n = 15) with confirmed pathological stage II + III are shown B. Data are mean ± standard error. Asterisk (*) denotes $p < 0.05$ at that time. Serum IL-6 levels preoperatively and on POD 1 were significantly higher in the Rec (+) than in the Rec (–) with confirmed pathological stage I A + I B ($p = 0.011, 0.043$). The others were not significantly difference between two groups. Serum IL-6 levels preoperatively, on POD0, POD 1 and POD2 were not significantly difference between two groups with confirmed pathological stage II + III.