The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy

Anna J Black[1], Homayoun Zargar[1,2], Kamran Zargar-Shoshtari[3,4], Adrian S Fairey[5], Laura S Mertens[6], Colin P Dinney[7], Maria C Mir[8,9], Laura-Maria Krabbe[10,11], Michael S Cookson[12], Niels-Erik Jacobsen[5], Joshua Griffin[14], Jeffrey S Montgomery[15], Nikhil Vasdev[16,17], Evan Y Yu[18], Evanguelos Xylinas[19,20], Nicholas J Campain[21], Wassim Kassouf[22], Marc A Dall'Era[23], Jo-An Seah[24], Cesar E Ercole[8], Simon Horenblas[6], John S McGrath[21], Jonathan Aning[21,25], Shahrokh F Shariat[19, 26], Jonathan L Wright[27], Andrew C Thorpe[17], Todd M Morgan[15], Jeff M Holzbeierlein[14], Trinity J Bivalacqua[13], Scott North[28, 29], Daniel A Barocas[30], Yair Lotan[10], Petros Grivas[18,31], Andrew J Stephenson[8], Jay B Shah[7,32], Bas W van Rhijn[6], Philippe E Spiess[3], Siamak Daneshmand[33], Srikala S Sridhar[24], Peter C Black[1]

Disclosures

- I have no conflict of interest to disclose.

Neutrophil to Lymphocyte Ratio

Promise as a prognostic factor

Available in routine blood work

Value in patients receiving NAC before RC not yet established

Objectives

01

How does NLR relate to tumor response to NAC?

02

Does NLR have value as a prognostic tool in patients receiving NAC prior to RC?

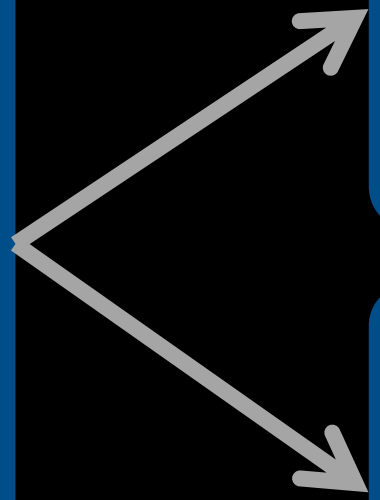
Hypothesis

A high NLR is associated with a poor response to NAC and is a poor prognostic indicator in patients receiving NAC

Methods

PATIENTS:

- Non-metastatic MIBC (cT2-4aN0M0)
- 3+ cycles of cisplatin-based NAC
- 2000-2013 at one of 19 centres across Europe and North America



NLR > 3

NLR ≤ 3

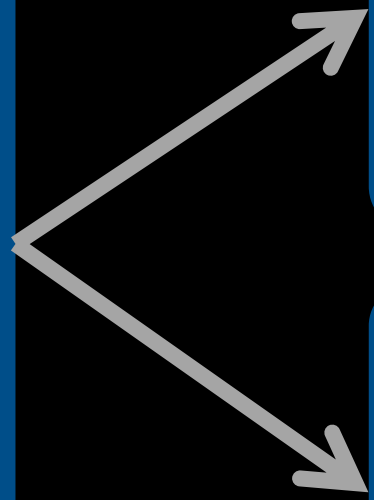
Results

1865 patients

PATIENTS:

- Non-metastatic MIBC (cT2-4aN0M0)

340 patients



NLR > 3

141

NLR ≤ 3

199

Demographics

NLR ≤ 3 patients:

slightly younger
(61.5 vs 64.5 years old)

&

higher proportion with LVI
(60.3% vs 48.2% present)

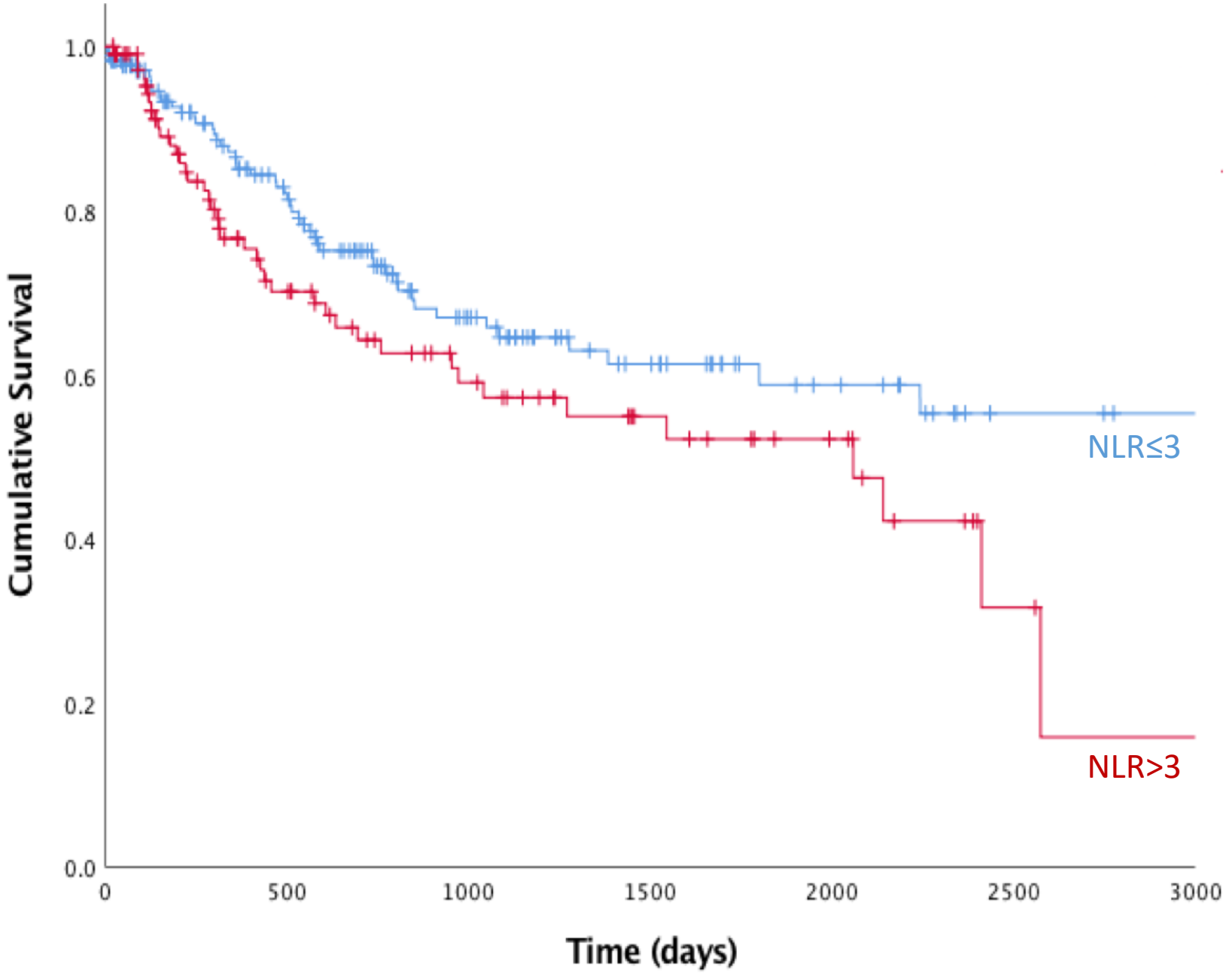
		NLR ≤ 3	NLR > 3	Total	P-value
Age (Mean, STD) (n=338)		61.5 ± 9.3	64.5 ± 9.2	62.8 ± 9.4	0.003
Sex (n, %)	Male	150 (75.4%)	113 (80.1%)	263 (77.4%)	0.301
	Female	49 (24.6%)	28 (19.9%)	77 (22.6%)	
Race (n, %)	Caucasian	131 (65.8%)	102 (72.3%)	233 (68.5%)	0.882
	Black	16 (8.0%)	9 (6.3%)	25 (7.4%)	
	Asian	5 (2.5%)	4 (2.8%)	9 (2.6%)	
	Hispanic	3 (1.5%)	3 (2.1%)	6 (1.8%)	
	Unknown	44 (22.1%)	23 (16.3%)	67 (19.7%)	
Smoker (n, %)	Never	56 (28.1%)	47 (33.3%)	103 (30.2%)	0.741
	Prior	91 (45.7%)	64 (45.4%)	155 (45.6%)	
	Current	36 (18.1%)	30 (21.3%)	66 (19.4%)	
	Unknown	16 (8.0%)	-	16 (4.7%)	
ECOG (n, %)	0	99 (49.7%)	63 (44.7%)	162 (47.6%)	0.057
	1	32 (16.1%)	28 (19.9%)	60 (17.6%)	
	2	1 (0.5%)	5 (3.5%)	6 (1.8%)	
	3	-	1 (0.7%)	1 (0.3%)	
	Unknown	67 (33.7%)	44 (31.2%)	111 (32.6%)	
Hydronephrosis (n, %)	No	129 (64.8%)	76 (53.9%)	205 (60.3%)	0.110
	Unilateral	61 (30.6%)	57 (40.5%)	128 (34.7%)	
	Bilateral	6 (3.0%)	8 (5.7%)	14 (4.1%)	
Clinical T-Stage (n, %)	T2	119 (59.8%)	75 (53.2%)	194 (57.1%)	0.376
	T3	61 (30.7%)	47 (33.3%)	108 (31.8%)	
	T4a	19 (9.5%)	19 (13.5%)	38 (11.2%)	
Histology (n, %)	Pure UC	164 (82.4%)	113 (80.1%)	277 (81.5%)	0.682
	UC with squamous differentiation	12 (6.0%)	14 (9.9%)	26 (7.6%)	
	UC with glandular differentiation	5 (2.5%)	3 (2.1%)	8 (2.4%)	
	Micropapillary	3 (1.5%)	-	3 (0.9%)	
	Sarcomatoid	1 (0.5%)	1 (0.7%)	2 (0.6%)	
	Small cell	3 (1.5%)	3 (2.1%)	6 (1.8%)	
	Unknown	11 (5.5%)	7 (5.0%)	18 (5.3%)	
Lymphovascular Invasion (TURBT) (n, %)	Present	120 (60.3%)	68 (48.2%)	188 (55.3%)	0.030
	Absent	43 (21.6%)	43 (30.5%)	86 (25.3%)	
	Unknown	36 (18.1%)	30 (21.3%)	66 (19.4%)	
Hemoglobin (Mean, STD)		12.6 ± 2.6	12.9 ± 1.9	12.7 ± 2.3	0.253
Platelets (Mean, STD)		279.5±115.9	297.2±118.1	286.7±116.8	0.171

Treatment & Outcomes

	NLR ≤ 3	NLR > 3
Complete response:	24.1%	16.3%
Partial response:	17.6%	14.9%
Residual MIBC:	55.3%	68.1%

		NLR ≤ 3	NLR > 3	Total	P-value
NAC Regimen (n, %)	DDMVAC	47 (23.6%)	48 (34.0%)	95 (27.9%)	0.079
	MVAC	55 (27.6%)	26 (18.4%)	81 (23.8%)	
	GC	95 (47.7%)	66 (46.8%)	161 (47.4%)	
	Other cis containing	2 (1.0%)	1 (0.7%)	3 (0.9%)	
NAC Number of Cycles (n, %)	3	71 (35.7%)	53 (37.6%)	124 (36.5%)	0.060
	4	113 (56.8%)	67 (47.5%)	180 (52.9%)	
	>4	15 (7.5%)	21 (14.9%)	36 (10.6%)	
Pathological T-Stage (n, %)	ypT0	53 (26.6%)	25 (17.7%)	78 (22.9%)	0.074
	ypTa	5 (2.5%)	2 (1.4%)	7 (2.1%)	
	ypTis	26 (13.1%)	10 (7.1%)	36 (10.6%)	
	ypT1	11 (5.5%)	9 (6.4%)	20 (5.9%)	
	ypT2	36 (18.1%)	34 (24.1%)	70 (20.6%)	
	ypT3	49 (24.6%)	38 (27.0%)	87 (25.6%)	
	ypT4	17 (8.5%)	22 (15.6%)	39 (11.5%)	
	ypTx	2 (1.0%)	1 (0.7%)	3 (0.9%)	
Pathological N-Stage (n, %)	ypN0	148 (74.4%)	99 (70.2%)	247 (72.6%)	0.148
	ypN1	19 (9.5%)	11 (7.8%)	30 (8.8%)	
	ypN2	18 (9.0%)	24 (17.0%)	42 (12.4%)	
	ypN3	4 (2.0%)	5 (3.5%)	9 (2.6%)	
	ypNx	10 (5.0%)	2 (1.4%)	12 (3.5%)	
Response to NAC (n, %)	ypT0N0	48 (24.1%)	23 (16.3%)	71 (20.9%)	0.071
	ypTa/Tis/T1N0	35 (17.6%)	21 (14.9%)	56 (16.5%)	
	ypT2-T4Nany or ypTanyN1-3	110 (55.3%)	96 (68.1%)	206 (60.6%)	
	Unknown*	6 (3.0%)	1 (0.7%)	7 (2.1%)	
Lymphovascular Invasion (RC) (n, %)	Absent	34 (17.1%)	27 (19.1%)	61 (17.9%)	0.831
	Present	18 (9.0%)	13 (9.2%)	31 (9.1%)	
	Unknown	147 (73.9%)	101 (71.6%)	248 (72.9%)	
Surgical Margin (n, %)	Positive	5 (2.5%)	10 (7.1%)	15 (4.4%)	0.053
	Negative	183 (92.0%)	129 (91.5%)	312 (91.8%)	
	Unknown	11 (5.5%)	2 (1.4%)	13 (3.8%)	

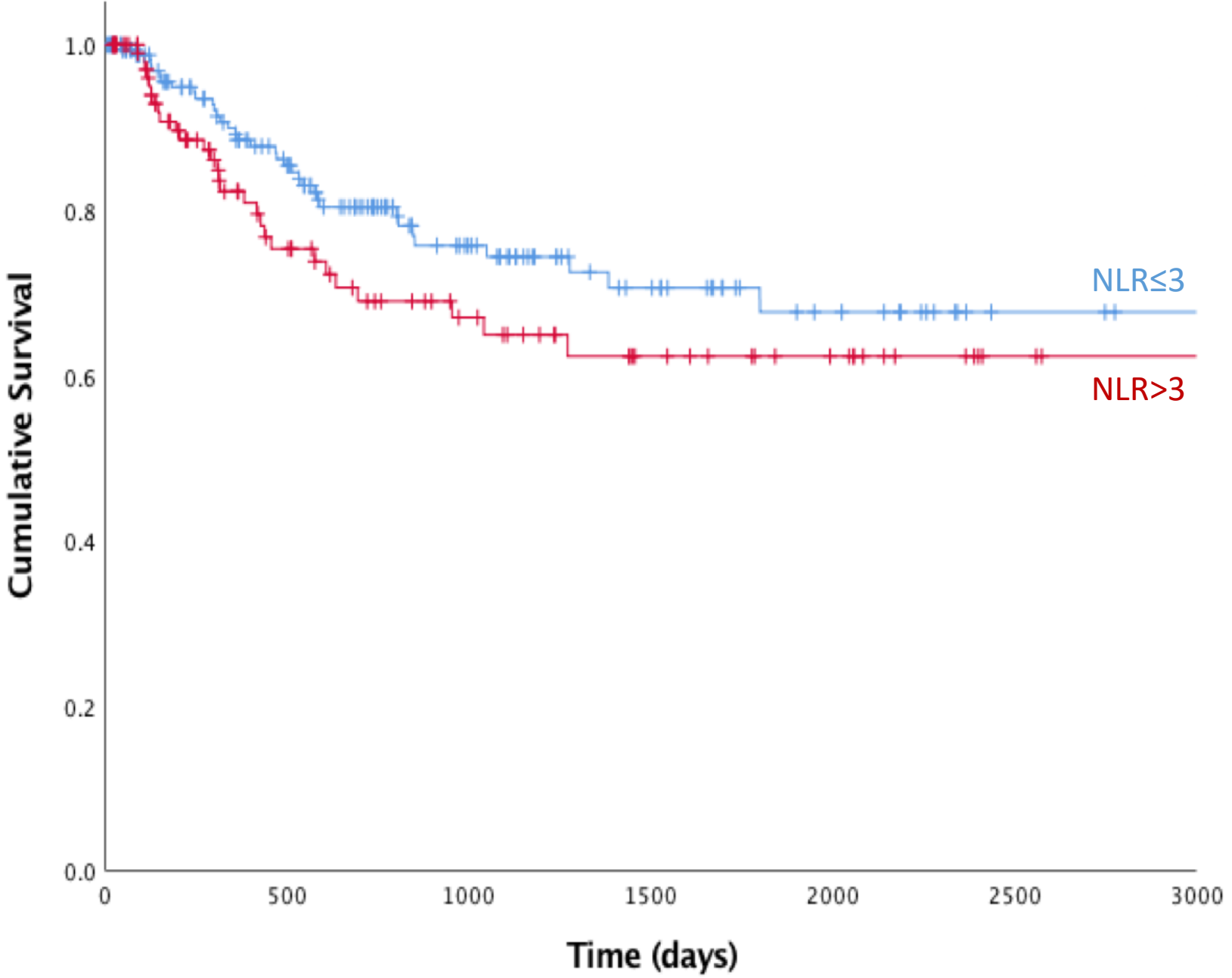
Overall Survival



Number at Risk	NLR ≤ 3	199	108	58	35	21	10	8
	NLR > 3	141	53	33	20	13	4	1

$p = 0.048$

Disease-Specific Survival



Number at Risk	NLR ≤ 3	199	108	58	35	21	10	8
	NLR > 3	141	53	33	20	13	4	1

$p = 0.113$

Response to NAC

Worse pathological response predicted by:

NLR > 3

Female sex (p = 0.06)

	OR	95% confidence interval		P value
NLR (pre-NAC) Ref: ≤3 >3	 0.43	 0.22	 0.82	 0.01
Age continuous	0.99	0.96	1.02	0.45
Sex Ref: Male Female	 0.45	 0.20	 1.04	 0.06
Smoker Ref: No Ever smoker	 1.24	 0.63	 2.40	 0.54
Hydronephrosis Ref: No Yes	 0.59	 0.30	 1.16	 0.13
cT stage Ref: T2 T3 T4	 1.35 1.66	 0.45 0.52	 4.09 5.26	 0.59 0.39
Histology Ref: Pure UC Other	 0.56	 0.23	 1.35	 0.20
Lymphovascular invasion Ref: Absent Present	 1.50	 0.78	 2.85	 0.22
Hemoglobin Continuous	1.07	0.92	1.25	0.40
Platelets Continuous	1.00	0.997	1.004	0.73

Disease Specific Survival

Worse disease specific survival predicted by:

NLR > 3

Non-smoker

	HR	95% confidence interval		P value
NLR (pre-NAC)				
Ref: ≤3				
>3	2.40	1.29	4.47	0.006
Age continuous	1.01	0.98	1.04	0.566
Sex				
Ref: Male				
Female	0.96	0.45	2.06	0.923
Smoker				
Ref: No				
Ever smoker	0.43	0.23	0.79	0.006
Hydronephrosis				
Ref: No				
Yes	0.62	0.32	1.23	0.17
Histology				
Ref: Pure UC				
Other	1.60	0.82	3.12	0.17
cT stage				
Ref: T2				
T3	1.68	0.63	4.52	0.30
T4	2.00	0.70	5.69	0.19
Lymphovascular invasion				
Ref: Absent				
Present	0.76	0.39	1.46	0.41
Hemoglobin				
Continuous	0.91	0.79	1.04	0.18
Platelets				
Continuous	1.00	0.997	1.003	0.96

Overall Survival

Worse overall survival predicted by:

NLR > 3

Age

	HR	95% confidence interval		P value
NLR (pre-NAC) Ref: ≤3 >3	 1.83	 1.10	 3.03	 0.02
Age continuous	1.03	1.00	1.06	0.03
Sex Ref: Male Female	 1.12	 0.60	 2.05	 0.75
Smoker Ref: No Ever smoker	 0.69	 0.41	 1.18	 0.18
Hydronephrosis Ref: No Yes	 0.61	 0.35	 1.09	 0.10
Histology Ref: Pure UC Other	 1.169	 0.640	 2.137	 0.28
cT stage Ref: T2 T3 T4	 T3: 1.08 T4: 1.41	 0.52 0.64	 2.26 3.10	 0.84 0.40
Lymphovascular invasion Ref: Absent Present	 0.82	 0.48	 1.39	 0.46
Hemoglobin Continuous	 0.93	 0.83	 1.05	 0.23
Platelets Continuous	 1.00	 0.998	 1.002	 0.96

Limitations

- Retrospective nature
- No comparison cohort that was not treated with NAC
  - Impossible to determine if NLR is predictive of response to NAC

Conclusion

NLR is a simple and inexpensive risk factor that can be used to assess prognosis in patients with MIBC