



# Utility of serum markers in the assessment of perioperative and postoperative morbidity and mortality after radical cystectomy for muscle invasive bladder cancer



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## INTRODUCTION AND OBJECTIVES

Despite significant improvements in surgical techniques, radical cystectomy (RC) remains a highly morbid operation and greater than one-half of patients experience complications during their hospital stay and after discharge<sup>1</sup>. The ability to predict complications and create prevention strategies is crucial in the surgical decision-making process and to optimise treatment outcomes. Methods of risk assessment include surrogates of comorbidity, such as the American Society of Anesthesiologists (ASA) Physical Status Classification and the Charlson Comorbidity Index (CCI) and it was reported previously that such tools possess a moderate capacity to predict post-RC outcomes, with a focus on mortality<sup>2</sup>. Recently, there is growing interest in the association of preoperative inflammation and immuno-nutritional serum markers with postsurgical complications and survival outcomes. The aim of this study was to investigate and compare the ability of preoperative Controlling Nutritional Status (CONUT), Prognostic Nutritional Index (PNI), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), systemic immune-inflammation index (SII), albumin, fibrinogen and PCR to predict perioperative and postoperative morbidity and mortality after RC.

## MATERIALS AND METHODS

We retrospectively evaluated 164 patients who underwent open RC for muscle-invasive bladder cancer (MIBC) at our Institute between December 2004 and June 2018. We excluded those patients who received neoadjuvant therapy and those in whom postoperative complications were not recorded or records were incomplete (table 1). Covariates were analyzed to determine associations with complication rates (according to the Clavien-Dindo system), mean hospitalization length, 30-days readmission rates and 90-days mortality. A multivariable binomial logistic regression determined associations with postsurgical outcomes taking into account age, sex, urinary diversion, pT stage and each serum marker, or American Society of Anesthesiologists (ASA) classification and Charlson Comorbidity Index (CCI).

In all patients, blood samples were evaluated before surgery. CONUT score was calculated from the serum albumin concentration, total lymphocyte count, and total cholesterol concentration, PNI was calculated based on the serum albumin concentration and total lymphocyte count, while NLR, PLR, LMR and SII were obtained with different combinations of peripheral neutrophil, lymphocyte ratio and platelet count.

## RESULTS

Cut-off values to discriminate threshold of CONUT score, PNI, NLR, PLR, LMR and SII were determined calculating the ROC curve and the maximum Youden index. We included 164 patients underwent RC for MIBC. The mean age at surgery was 72.1 years (range, 46-88) and the majority of urinary diversions were ileal conduit (78.1%). Overall, 44(26.8%) patients experienced a major complication (Clavien grade $\geq$ 3) and there were 9(5.5%) deaths within 3 months of surgery. ASA, CONUT, NLR, PLR, SII and PCR showed statistically significant differences in distribution of complications (all  $p < 0.05$ ) (table 2,3). There were no differences in mean hospitalization length while CONUT, PNI, fibrinogen, PCR, SII and CCI were statistically associated with 30-days readmission. Fibrinogen was the only serum marker associated with 90-days mortality ( $p=0.01$ ). Multivariable binomial logistic regression analysis confirmed the association of CONUT, SII, ASA, NLR, PCR and fibrinogen with surgical complications (all  $p < 0.05$ ).

Table 4. Postoperative complications according to risk grouping

Grouping	Complication according to Clavien Grade						p
	0	1	2	3	4	5	
CCI							
0	19.3(6)	45.2(14)	22.6(7)	12.9(4)	0(0)	0(0)	0.09
1	4(1)	40(10)	24(6)	32(8)	0(0)	0(0)	
$\geq 2$	7.4(8)	38.9(42)	24.1(26)	15.7(17)	8.3(9)	5.6(6)	
ASA score							
< 3	11.1(10)	48.9(44)	24.4(22)	11.1(10)	2.2(2)	2.2(2)	0.01
$\geq 3$	6.8(5)	29.7(22)	23(17)	25.7(19)	9.6(7)	5.4(4)	
Albumine							
low	7.9(3)	28.9(11)	23.7(9)	28.9(11)	7.9(3)	2.6(1)	0.32
normal	9.5(12)	43.7(55)	23.8(30)	14.3(18)	4.8(6)	4(5)	
CONUT							
low	12.2(12)	40.8(40)	28.6(28)	11.2(11)	5.1(5)	2(2)	0.03
high	4.5(3)	39.4(26)	16.7(11)	27.3(18)	6.1(4)	6.1(4)	
PNI							
low	7.4(5)	35.3(24)	22.1(15)	26.5(18)	7.4(5)	1.5(1)	0.13
high	10.4(10)	43.8(42)	25(24)	11.5(11)	4.2(4)	5.2(5)	
NLR							
low	11.2(12)	40.2(43)	28(30)	11.2(12)	5.6(6)	3.7(4)	0.049
high	5.3(3)	40.4(23)	15.8(9)	29.8(17)	5.3(3)	3.5(2)	
PLR							
low	9.4(6)	32.8(21)	34.4(22)	10.9(7)	6.3(4)	6.3(4)	0.048
high	9(9)	45(45)	17(17)	22(22)	5(5)	2(2)	
LMR							
low	6.8(6)	44.3(39)	17(15)	22.7(20)	6.8(6)	2.3(2)	0.08
high	11.8(9)	35.5(27)	31.6(24)	11.8(9)	3.9(3)	5.3(4)	
SII							
low	9(8)	42.7(38)	29.2(26)	8.9(8)	5.6(5)	4.5(4)	0.043
high	9.3(7)	37.3(28)	17.3(13)	28(21)	5.3(4)	2.7(2)	
Fibrinogen							
normal	11.8(10)	44.7(38)	24.7(21)	15.3(13)	3.5(3)	0(0)	0.06
high	6.3(5)	35.4(28)	22.8(18)	20.3(16)	7.6(6)	7.6(6)	
PCR							
normal	12.3(9)	47.9(35)	26(19)	9.6(7)	2.7(2)	1.4(1)	0.03
high	6.5(6)	34(31)	22(20)	24.2(22)	7.7(7)	5.5(5)	

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Table 1. Clinical and pathological features of population study

	Total
n. patients	164
Mean age at RC ( $\pm$ SD)	72.1 $\pm$ 8.7
Sex	
male (ref. female)	93(71)
ASA score	
$\geq 3$ (ref. < 3)	74(90)
Charlson Comorbidity Index (CCI)	
0	31
1	25
$\geq 2$	108
pT stage	
$\geq 3$ (ref. < 3)	97(67)
pN stage	
$\geq 1$ (ref. X or 0)	47(117)
Grading	
high (ref. low)	152(12)
LVI	
with (ref. without)	73(91)
Adjuvant CT	
with (ref. without)	53(111)
Mean hospitalization time ( $\pm$ SD)	24.9 $\pm$ 9.4
Mean BMI ( $\pm$ SD)	25.7 $\pm$ 4.4
Surgical Margins (R)	
positive (ref. negative)	11(153)
Urinary diversion	
Ureterocutaneostomy	24
Ileal conduit	128
Orthotopic diversion	12

Table 2,3. Mortality rates at 90-days, Readmission rates at 30-days

	Mortality at 90 days			p	Readmission at 30 days			p
	yes	no			yes	no		
total	9	155			46	118		
CONUT				0.16				0.002
low	3	95			18	80		
high	6	60			28	38		
PNI				0.87				0.02
low	3	65			26	42		
high	6	90			20	76		
NLR				0.78				0.2
low	5	102			26	81		
high	4	53			20	37		
PLR				0.72				0.38
low	4	60			15	49		
high	5	95			31	69		
LMR				0.73				0.33
low	4	84			28	60		
high	5	71			18	58		
Fibrinogen				0.0015				0.001
normal	1	84			14	71		
high	8	71			32	47		
PCR				0.31				0.002
normal	2	71			11	62		
high	7	84			35	56		
Albumin				0.74				0.11
normal	6	120			31	95		
low	3	35			15	23		
SII				0.70				0.02
normal	4	59			18	71		
high	5	96			28	47		
ASA score				0.32				0.8
1,2	3	87			24	66		
3,4	6	68			22	52		
CCI				0.74				0.001
0	0	31			1	20		
1	0	24			8	17		
$\geq 2$	8	100			27	81		

Table 5. Multivariable analysis adjusted for age, sex, pT and urinary diversion

variable	HR(95% IC)	p
SII	2.39(1.65 - 3.13)	0.02
CONUT	2.87(2.10 - 3.65)	0.008
PLR	1.29(0.52 - 2.06)	0.51
NLR	2.55(1.75 - 3.35)	0.022
LMR	1.63(0.87 - 2.39)	0.21
PCR	3.67(2.85 - 4.49)	0.002
Fibrinogen	2.27(1.52 - 3.01)	0.03
Albumine	2.05(0.96 - 2.84)	0.08
PNI	1.98(0.94 - 2.73)	0.073
ASA	3.80(3.02 - 4.59)	0.0008
CCI	1.59(0.77 - 2.37)	0.24

## CONCLUSIONS

Preoperative inflammation and immuno-nutritional serum markers based on standard laboratory measurements may be simple and inexpensive potentially effective risk-assessment tools to predict outcomes after RC. Further investigations should be necessary to confirm these results.

## REFERENCES

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