Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Predictive and prognostic value of inflammatory markers in LARC patients undergoing neoadjuvant chemoradiotherapy – a retrospective multicentric analysis by AIRO Gastrointestinal Study Group

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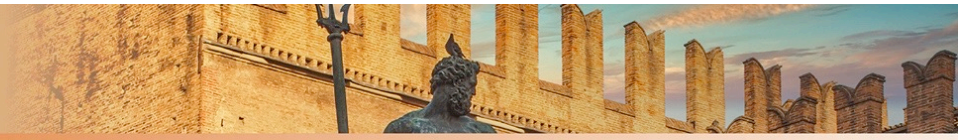


DICHIARAZIONE

Relatore: Silvia Mariani

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

15-30% pCR

Local excision

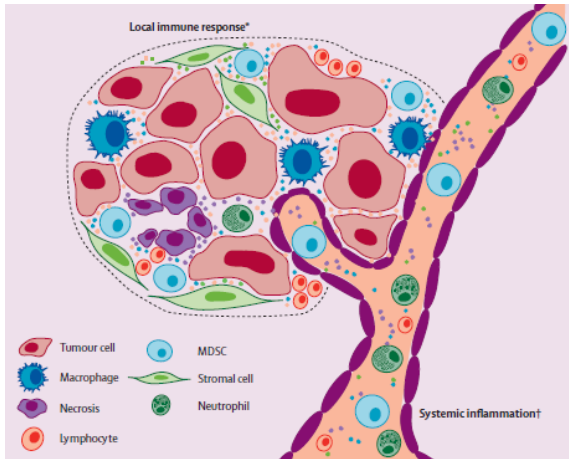
Watch & wait

Distant metastases

(65% 5yOS)

Adj CT

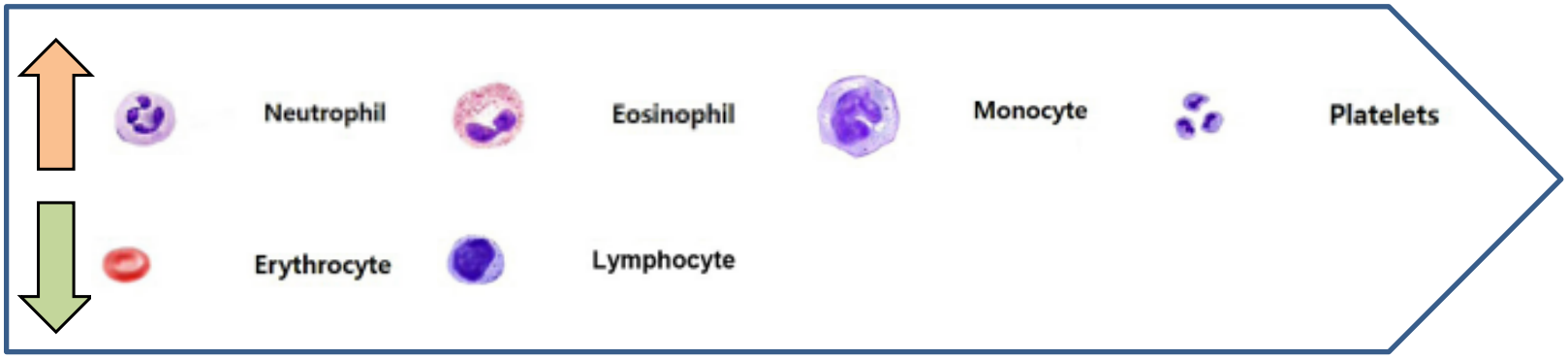
TNT



- Need for patient-tailored treatments
- Peri-tumoral environment and inflammation

cancer initiation, promotion, progression

- Blood cells inflammatory markers



NLR – N/L

PLR – P/L

MLR – M/L

SII - PxN/L

HEI - SII, Hb, Eos

LARC
nCRT
NLR
MLR
PLR
SII

First author (year)	Patients n°	Endpoints	Evaluated markers	Cut-off	p-value	Statistics, comments
Carruthers R (2012)	115	**OS, DFS, TTLR**	**NLR ,** PLR	5	0.001, 0.002, 0.014	HR 7.0, 4.1, 3.8
Kim IY (2014)	102	**ypTNM**	**NLR**	3	0.04	HR 5.2
Shen L (2014)	199	**OS,** DFS, ypTNM	**NLR**	2.8	0.018	HR 2.123
Nagasaki T (2015)	201	**OS**, RFS	**NLR**	3	0.012	HR 3.38
Shen J (2017)	202	OS, DFS	NLR	n.s.	n.s.	-
Zhao J (2017)	100	**OS**	**LMR,** NLR, PLR	3	0.002	HR 0.43
Vallard A (2018)	257	**OS, PFS, LR,**TRG	**NLR**	2.8	0.02, 0.006, 0.03	HR 2.23, 2.21,14.7
Zhang X (2018)	76	**OS**	**NLR**	2	0.025	HR 7.707
Braun LH (2019)	220	**DFS**	**NLR,** LMR, PLR	4.06	0.017	HR 0.3
Dudani S (2019)	1237	pCR, OS, DFS	NLR, PLR	n.s.	n.s.	-
Kim TG (2019)	176	**TRG, OS, DFS** **TRG**, OS, DFS	**NLR** **PLR**	2 133.4	0.008, 0.027, 0.014 <0.001	-
Lee J H (2020)	549	OS, DFS	NLR, PLR	n.s.	n.s.	Significance only in MSI cases
Sun Y (2020)	100	**TRG**	**NLR, PLR,** SII	3.05 145.98	0.028 0.038	OR 4.025 OR 4.337
Timudom K (2020)	111	ypT, NAR	NLR, MLR, PLR	n.s.	n.s.	-
Zhang Y (2020)	472	**OS, DFS**	**NLR,** SII, MLR, PLR	2.3	0.046, 0.044	HR 1.797, 1.707
Eraslan E (2021)	188	**pCR**	**SII,** NLR, LMR, PLR	748	0.047	OR 0.471
Wang Y (2021)	273	**TRG**, OS, DFS	**PLR,** NLR, LMR	-	0.013	HR 0.992

Which markers?

With which cut-offs?

HEI (Anal cancer > CRT)

Sum of 3 scores (0-1):

- SII (=1 if >560)
- Hb (=1 if <12)
- Eos (=1 if >100)

0-1 low-risk

2-3 high-risk

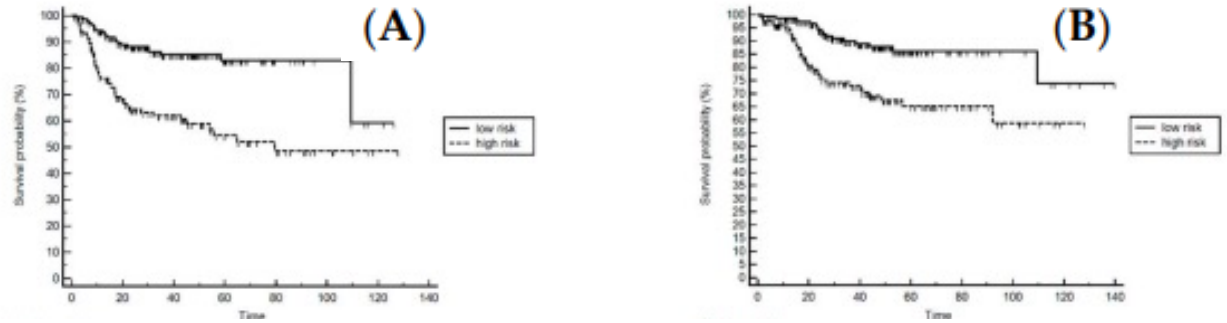
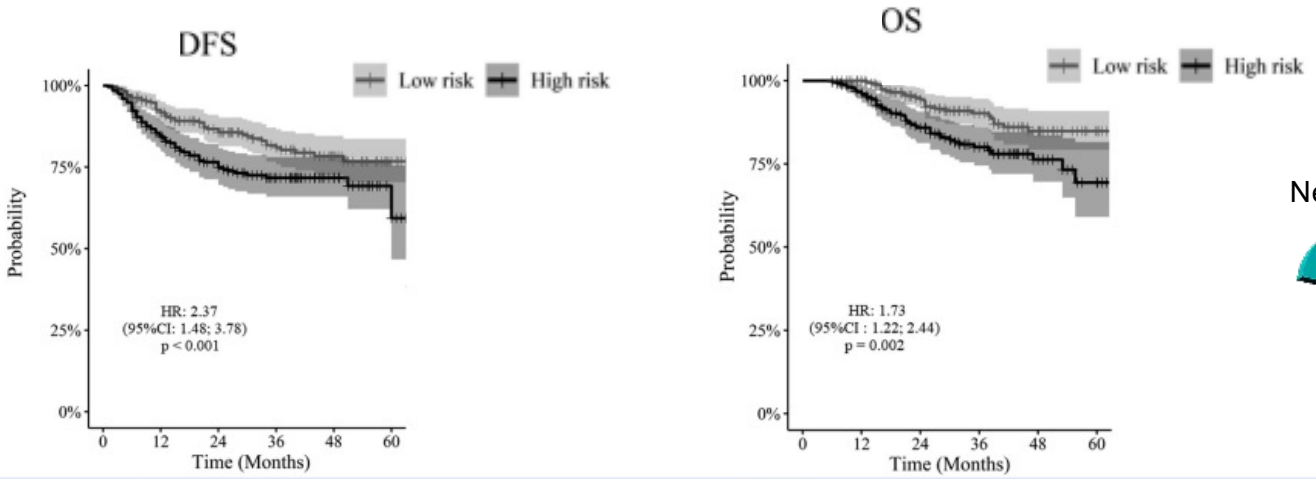


Figure 1. Kaplan–Meier curves for disease-free (**A**) and overall (**B**) survival in high- and low-risk groups according the HEI index.



New markers?

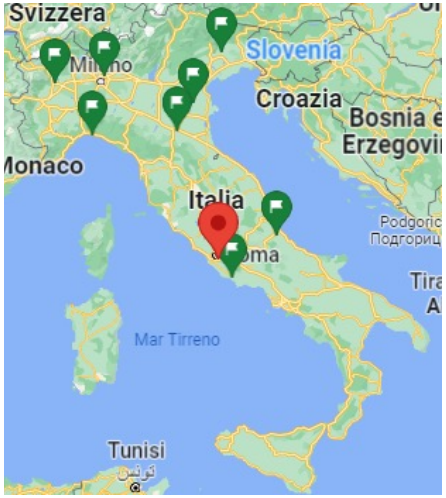
Rimini M, Cancers 2021
Franco P, CTRO 2022

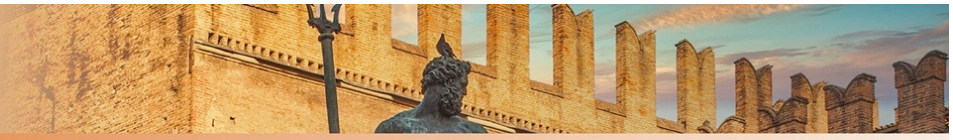
AIM

To evaluate
- predictive role (pCR) and
- prognostic role (OS, DFS) of
- several baseline combined inflammatory markers in a
- large Italian retrospective multicentric cohort of LARC patients

AIRO Gastrointestinal Study Group - 9 centers

- Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma
- Centro di Riferimento Oncologico, Aviano
- Policlinico S. Orsola Malpighi, Bologna
- Policlinico SS. Annunziata, Chieti
- IRCCS Ospedale Policlinico S. Martino, Genova
- Ospedale Civile ASL TO4, Ivrea
- Ospedale S. Maria Goretti, Latina
- A.O. San Gerardo, Monza
- Ospedale S. Maria della Misericordia, Rovigo





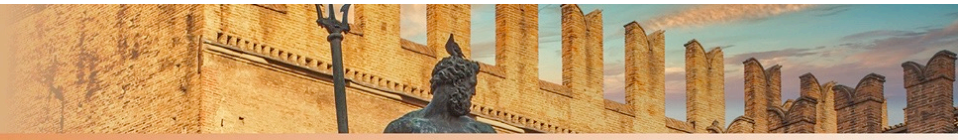
SELECTION CRITERIA

- M0 LARC patients
- Treated between 2008-2019 (Rome) or 2002-2019 (remaining 8 centers)
- Long-course RT w/ concomitant CT
- Delayed surgery
- +/- adjuvant CT
- Follow-up ≥2 years in the absence of events

PROCEDURES

- Pre-CRT blood sample with CBC
- Markers calculation
- Endpoints: pCR, OS, DFS
- Regression analysis (continuous variables)
- Cut-off search
- Univariate and multivariate analysis

Inflammatory marker	Laboratory parameters	Formula
Neutrophil to lymphocyte ratio (**NLR**)	Neutrophils; Lymphocytes	Neutrophils/Lymphocytes
Platelet to lymphocyte ratio (**PLR**)	Platelets; Lymphocytes	Platelets/Lymphocytes
Monocyte to lymphocyte ratio (**MLR**)	Monocytes; Lymphocytes	Monocytes/Lymphocytes
Systemic index of inflammation (**SII**)	Platelets; Neutrophils; Lymphocytes	Platelets × (Neutrophils/ Lymphocytes)
Hemo-eosinophils inflammation index (**HEI**)	SII (=0 if SII/560 ≤1, =1 if SII/560 >1); Hemoglobin (Hb) (=0 if Hb/12 ≥1, =1 if Hb/12 <1); Eosinophils (=0 if eosinophils/100 <1, =1 if eosinophils/100 ≥1)	SII + Hb + Eosinophils scores



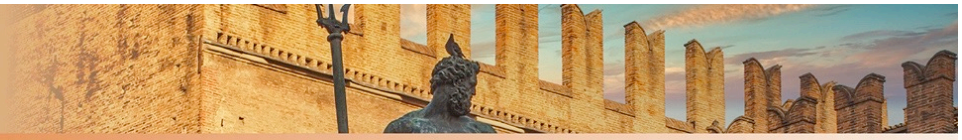
808 patients
out of 1262

	N (%)
GENDER	
Male	**493 (61.0)**
Female	315 (39.0)
AGE, years	
Median (range)	**64 (26-88)**
≥65	403 (49.9)
CEA, ng/ml	
Median (range)	3.1 (0.1-316)
≥5	156 (19.3)
cT	
1-2	58 (7.2)
3	**557 (68.9)**
4	**168 (20.8)**
cN	
0	155 (19.2)
+	**644 (79.7)**

RT DOSE, Gy	
Median (range)	**55 (30.8-56)**
≥55	488 (60.4)
CONCOMITANT CT	
single agent	**595 (73.6)**
double agent	201 (24.9)
SURGICAL INTERVAL, w	
Median (range)	11 (2-41)
≥12	320 (39.6)

pCR	**22%**
5yDFS	84%
5yOS	**63.1%**

53.5 mo
median FUP
(6-198)



Regression analysis (inflammatory markers as continuous variables)

	pCR – OR (95% CI) p value	DFS - HR (95% CI) p value	OS - HR (95% CI) p value
NLR	**0.86 (0.75-0.97) p=0.02**	1.01 (0.94-1.08) p=0.82	**1.08 (0.99-1.17) p=0.09**
PLR	**0.99 (0.99-1.00) p=0.008**	0.99 (0.99-1.00) p=0.28	0.99 (0.99-1.00) p=0.34
MLR	0.43 (0.13-1.42) p=0.16	**1.92 (1.04-3.56) p=0.037**	**2.45 (1.10-5.47) p=0.03**
SII	**0.99 (0.99-1.00) p=0.013**	1.00 (1.00-1.00) p=0.51	1.00 (1.00-1.00) p=0.33
HEI	p=0.84 13 (26.5) 73 (25.5) 72 (25.4) 20 (21.3)	**p=0.054** 1.00 1.09 (0.68-1.74) 0.97 (0.60-1.56) 1.53 (0.91-2.57)	p=0.30 1.00 0.92 (0.49-1.76) 1.02 (0.54-1.93) 1.43 (0.71-2.89)

Logistic regression for pCR prediction

		Univariate		Multivariate	
Variable	**Value**	**OR (95% IC)**	**p value**	**OR (95% IC)**	**p value**
GENDER	Male	1.13 (0.85-1.50)	p=0.39		
AGE, years	≥65	**1.25 (0.96-1.64)**	**p=0.10**	-	-
cT	3 4	0.62 (0.37-1.04) 0.53 (0.29-0.96)	p=0.11		
cN	positive	0.96 (0.67-1.35)	p=0.8		
N extra	yes	0.99 (0.68-1.43)	p=0.95		
CT scheme	double agent	1.00 (0.75-1.34)	p=0.99		
RT dose, Gy	≥55	**1.29 (0.98-1.69)**	**p=0.07**	-	-
SURGICAL INTERVAL, w	≥12	1.19 (0.90-1.58)	p=0.23		
NLR	>1.2	**0.34 (0.16-0.72)**	**p=0.005**	-	-
PLR	>200	**0.53 (0.34-0.83)**	**p=0.005**	**-**	**-**
SII	>500	**0.56 (0.40-0.79)**	**p=0.001**	**0.53 (0.37-0.75)**	**p<0.0001**

Logistic regression for DFS prediction

		Univariate		Multivariate	
Variable	**Value**	**HR (95% IC)**	**p value**	**HR (95% IC)**	**p value**
GENDER	Male	**1.19 (0.97-1.47)**	**p=0.09**	-	-
AGE, years	≥65	**1.56 (1.27-1.90)**	**p<0.0001**	**1.50 (1.16-1.94)**	**p=0.002**
cT	3 4	0.79 (0.55-1.14) 0.99 (0.66-1.47)	p=0.12		
cN	positive	**1.37 (1.04-1.79)**	**p=0.025**	-	-
N extra	yes	**1.42 (1.12-1.79)**	**p=0.003**	**1.41 (1.06-1.88)**	**p=0.02**
CT scheme	double agent	0.89 (0.71-1.12)	p=0.31		
RT dose, Gy	≥55	**1.31 (1.06-1.61)**	**p=0.001**	**1.43 (1.07-1.90)**	**p=0.015**
SURGICAL INTERVAL, w	≥12	**1.34 (1.08-1.65)**	**p=0.007**	-	-
HEI	3	**1.49 (1.11-2.01)**	**p=0.009**	**1.39 (1.00-1.96)**	**p=0.005**
MLR	>0.18	**1.59 (1.14-2.22)**	**p=0.006**	**1.49 (1.03-2.14)**	**p=0.03**

Logistic regression for OS prediction

		Univariate		Multivariate	
Variable	**Value**	**HR (95% IC)**	**p value**	**HR (95% IC)**	**p value**
GENDER	Male	1. 1.26 (0.95-1.67)	p=0.39		
AGE, years	≥65	**1.98 (1.51-2.61)**	**p<0.0001**	**2.00 (1.46-2.75)**	**p<0.0001**
cT	3 4	0.90 (0.53-1.53) 1.19 (0.67-2.11)	p=0.11		
cN	positive	1.34 (0.93-1.93)	p=0.12		
N extra	yes	1.14 (0.80-1.63)	p=0.46		
CT scheme	double agent	0.92 (0.69-1.24)	p=0.60		
RT dose, Gy	≥55	**0.72 (0.55-0.94)**	**p=0.01**	**0.73 (0.53-0.99)**	**p=0.04**
SURGICAL INTERVAL, w	≥12	1.03 (0.76-1.40)	p=0.85		
MLR	>0.35	**1.61 (1.17-2.22)**	**p=0.004**	**1.49 (1.08-2.06)**	**p=0.01**
NLR	>2.5	**1.36 (1.00-1.85)**	**p=0.05**	-	-

Multivariate analysis

pCR

Variable	Value	OR (95% IC)	p value
SII	>500	0.53 (0.37-0.75)	p<0.0001

DFS

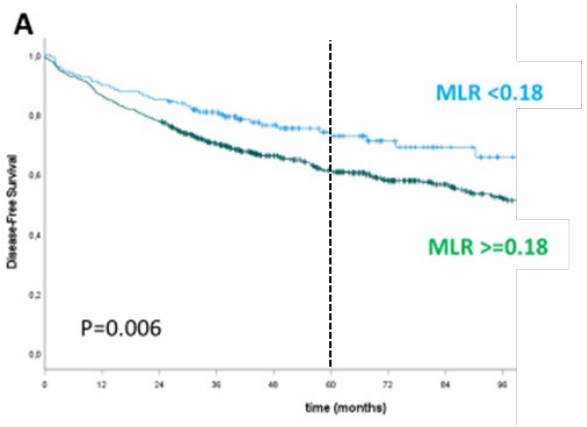
Variable	Value	HR (95% IC)	p value
AGE, years	≥65	1.50 (1.16-1.94)	p=0.002
N extra	yes	1.41 (1.06-1.88)	p=0.02
RT dose, Gy	≥55	1.43 (1.07-1.90)	p=0.015
HEI	3	1.39 (1.00-1.96)	p=0.05
MLR	>0.18	1.49 (1.03-2.14)	p=0.03

OS

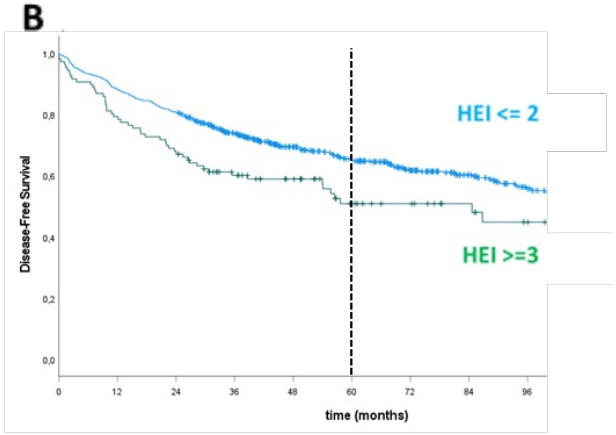
Variable	Value	HR (95% IC)	p value
AGE, years	≥65	2.00 (1.46-2.75)	p<0.001
RT dose, Gy	≥55	0.73 (0.53-0.99)	p=0.04
MLR	>0.35	1.49 (1.08-2.06)	p=0.01

Kaplan-Meier analysis

DFS stratified by MLR (A) and HEI (B)

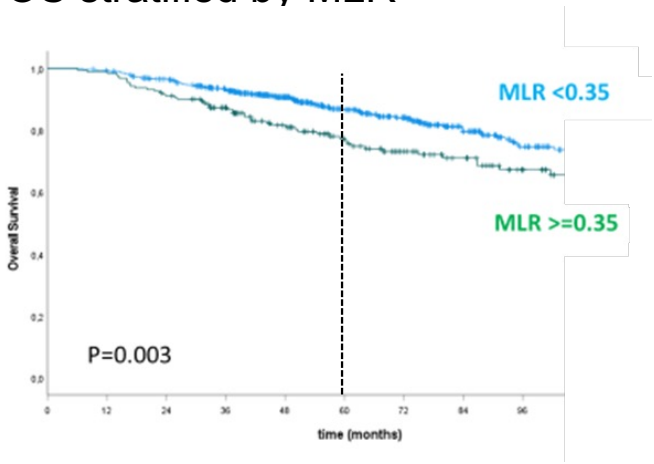


5yDFS 72.7% vs 61.0%

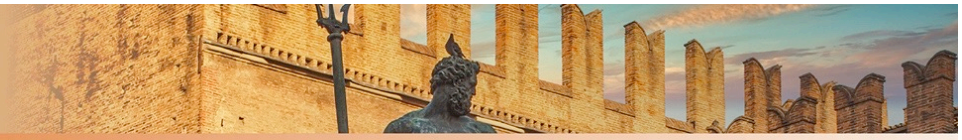


5yDFS 65.0% vs 50.8%

OS stratified by MLR



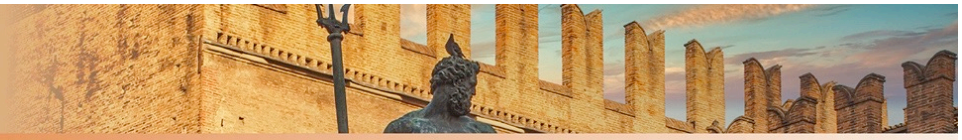
5yOS 86.5% vs 76.5%



Conclusions

- Baseline inflammatory markers do have some predictive and prognostic role in LARC
- Higher SII values -> lower pCR probability
- Higher HEI and MLR values -> worse DFS
- Higher MLR -> worse OS
- Available data are not univocal and are all retrospective in nature (confounding factors?)
- Immune response may change over the course of the disease, also as a result of treatments
- Baseline inflammatory markers are inexpensive and easy to obtain

- Prospective studies evaluating pre- and post-treatment inflammation markers may be the key to getting to the point of including these parameters in the therapeutic work-up of LARC patients



Thank you for your kind attention!