Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic role of aspartate aminotransferase-lymphocyte ratio index in patients with metastatic colorectal cancer: results from the randomized ITACa trial

Andrea Casadei Gardini,[1,]*
Emanuela Scarpi,[2,]* Elena
Orlandi,[3] Davide Tassinari,[4]
Silvana Leo,[5] Ilaria Bernardini,[6]
Fabio Gelsomino,[7] Stefano
Tamberi,[8] Silvia Ruscelli,[1]
Roberto Vespignani,[9] Sonia
Ronconi,[10] Giovanni Luca
Frassineti,[1] Dino Amadori,[1]
Alessandro Passardi[1]

[1]Department of Medical Oncology, Istituto
Scientifico Romagnolo per lo Studio e la
Cura dei Tumori (IRST) IRCCS, Meldola,
Italy; [2]Unit of Biostatistics and Clinical
Trials, IRST IRCCS, Meldola, Italy; [3]Medical
Oncology Department, Piacenza Hospital,
Piacenza, Italy; [4]Department of Oncology,
City Hospital, Rimini, Italy; [5]Medical
Oncology Unit, Vito Fazzi Hospital, Lecce,
Italy; [6]Medical Oncology Unit, Ramazzini
Hospital, Carpi, Italy; [7]Department of
Oncology and Hematology, Division of
Oncology, University Hospital Modena,
Italy; [8]Oncolgy Unit, Degli Infermi Hospital,
Faenza, Italy; [9]IT Service, IRST IRCCS,
Meldola, Italy; [10]Hematology Unit, Istituto
Scientifico Romagnolo per lo Studio
e la Cura dei Tumori (IRST) IRCCS,
Meldola, Italy

*These authors contributed equally
to this work

Correspondence: Emanuela Scarpi
Unit of Biostatistics and Clinical Trials, Istituto
Scientifico Romagnolo per lo Studio e la Cura
dei Tumori (IRST) IRCCS, Via P Maroncelli 40,
47014 Meldola, Forlì-Cesena, Italy
Tel +39 543 7391 00
Fax +39 543 7392 90
Email emanuela.scarpi@irst.emr.it

Background: The aim of this study was to investigate the role of pre-treatment aspartate aminotransferase-lynphocyte ratio (ALRI) as a predictor of prognosis and treatment efficacy in patients with metastatic colorectal cancer (mCRC) enrolled in the prospective multicenter randomized ITACa (Italian Trial in Advanced Colorectal Cancer) trial to receive first-line chemotherapy (CT) + bevacizumab (B) or CT alone.

Patients and methods: Patients randomly received CT+B or CT alone as first-line therapy. CT consisted of either FOLFOX4 or FOLFIRI at the clinician's discretion.

Results: Out of the 284 patients enrolled, increased ALRI levels were associated with shorter PFS and OS ($p<0.0001$). At baseline, median PFS was 10.3 months (95% CI 9.4–12.0) and 8.0 months (95 % CI 6.8–8.9), and median OS was 25.2 months (95 % CI 21.3–30.2) and 18.8 months (95 % CI 16.6–21.7) for patients with low (<14) and high (≥14) ALRI levels, respectively (HR 1.43, 95% CI 1.12–1.82, $p=0.004$; HR=1.51, 95% CI 1.17–1.96, $p<0.001$). Interaction tests on ALRI levels and treatment efficacy in the CT+B and the CT groups were statistically significant for PFS ($p=0.0003$), but not for OS ($p=0.228$).

Conclusion: Our results indicate that ALRI is a good prognostic and predictive marker for mCRC patients candidate for CT+B.

Keywords: metastatic colorectal cancer, bevacizumab, first line, prognosis, aspartate aminotransferase-lymphocyte ratio index, clinical outcome, rectal cancer

Introduction

Colorectal cancer (CRC) is the third most common cause of death from cancer in Western Europe and North America.[1]

Literature has shown the relationship between systemic chronic inflammation and various types of cancer, including CRC,[2] as the activation of the inflammatory cascade by malignant tumors leads to apoptosis inhibition and angiogenesis promotion, eventually causing tumor genesis, proliferation, and metastasis.[3,4]

In clinical practice, physicians commonly test the liver enzyme aspartate aminotransferase (AST), without evidence of any correlation with the response to bevacizumab (B).

To our knowledge, no population-based study has yet been conducted on the prognostic value of baseline AST-lymphocyte ratio index (ALRI) in predicting progression-free survival (PFS) in CRC patients treated with B. We think that the ALRI is an important parameter that provides data after combining the inflammatory state with a hepatic index.

We investigated the prognostic and predictive roles of baseline ALRI in metastatic CRC (mCRC) patients treated with first-line chemotherapy (CT)+B or CT alone in the Phase III prospective multicenter randomized ITACa trial (Italian Trial in Advanced Colorectal Cancer; EudraCT no 2007-004539-44 and on ClinicalTrials.gov NCT01878422).[5]

Patients and methods
The ITACa trial

Patients randomly received CT+B or CT alone as first-line therapy. CT consisted of either FOLFOX4 (a 2-hour infusion of 85 mg/m² oxaliplatin on day 1 and a 2-hour infusion of 100 mg/m² leucovorin followed by 400 mg/m² bolus 5-FU and a 22-hour infusion of 600 mg/m² 5-FU on days 1–2 every 2 weeks) or FOLFIRI (a 2-hour infusion of 100 mg/m² leucovorin followed by 400 mg/m² bolus 5-FU and a 22-hour infusion of 600 mg/m² 5-FU on days 1–2 every 2 weeks with the addition of a 90-minute infusion of 180 mg/m² irinotecan on day 1) at the clinician's discretion. A 30–90-minute intravenous infusion of 5 mg/kg B was administered on day 1 of each 2-week cycle.

Treatment continued until either progressive disease (PD) or unacceptable toxicity or withdrawal of consent. Tumor assessment was performed before the start of treatment and repeated every 8 weeks until PD. Responses were defined according to the Response Evaluation Criteria in Solid Tumors guidelines (per investigator assessment). The National Cancer Institute Common Toxicity Criteria were used for evaluating adverse events.

The ITACa trial was approved by the local ethics committee (Comitato Etico Area Vasta Romagna) on September 19, 2007 and registered in our National Clinical Trials Observatory (Osservatorio delle Sperimentazioni Cliniche) and in the European Clinical Trials Database (EudraCT no 2007-004539-44) before patient recruitment began. Registration on ClinicalTrials.gov (NCT01878422) was not mandatory but was carried out at a later date (June 7, 2013). All patients provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki under good clinical practice conditions and after full approval of the ethics committees of all participating centers (Comitato Etico Area Vasta Romagna e IRST, Comitato Etico Provinciale di Modena, Comitato Etico AUSL di Piacenza, Comitato Etico Interaziendale AOU "Maggiore della Carità" di Novara, Comitato Etico Interaziendale dell'A.S.O. Santa Croce e Carle di Cuneo, Comitato Etico della Provincia di Modena, Comitato Etico della Provincia di Ferrara, Comitato Etico Unico per la Provincia di Parma, Comitato Etico

Indipendente Azienda USL di Bologna, Comitato Etico della ASL LE di Lecce, Comitato Etico Provinciale di Belluno per la Sperimentazione Clinica).

Statistical analysis

PFS and overall survival (OS) were, respectively, the primary and one of the secondary endpoints of the ITACa study. Information on AST and lymphocyte counts from blood tests carried out at baseline (before systemic treatment) was collected subsequently for the purpose of this post hoc analysis. ALRI was calculated as AST/lymphocyte count. The aim of this analysis was to evaluate the association between baseline ALRI levels and PFS and OS in the intent-to-treat population.

PFS was defined as the time from the date of random assignment to the date of either first documentation of PD, or last tumor evaluation, or death from any cause. Patients undergoing curative metastasectomy were censored at the date of surgery. OS was defined as the time from the date of random assignment to the date of death or last follow-up visit. PFS and OS were estimated by Kaplan–Meier method and curves were compared using the log rank test. Cox regression model was used to estimate HRs, their 2-sided 95% CI, and HR adjusted by center, baseline characteristics (gender, age, Eastern Cooperative Oncology Group performance status [ECOG PS], KRAS status, and tumor localization), CT regimen, and ITACa treatment. Cox regression model was also used to evaluate the effect on PFS and OS of the interaction between ALRI levels and treatment, including ALRI levels, treatment, and treatment-by-ALRI levels. X-tile 3.6.1 software (Yale University, New Haven, CT, USA) was used for bioinformatics analysis of baseline data to determine the cutoff value for pretreatment levels of ALRI. ALRI ≥ 14 was considered as a high level.

Patient characteristics were compared with χ^2 test, and median values were compared using nonparametric ranking test (median test). All p-values were based on 2-sided testing. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Inc., Cary, NC, USA).

Results
Patient characteristics

Between November 14, 2007 and March 6, 2012, 284 patients diagnosed with CRC were available for baseline AST and lymphocyte analysis (Figure 1); the study sample included 170 (59.8%) males and 114 (40.2%) females with a median age at diagnosis of 66 years (range 33–83). Median follow-up

```
┌──────────────┐        ┌─────────────────────────────────┐
│  Enrollment  │        │ Assessed for eligibility (n=376) │
└──────────────┘        └─────────────────────────────────┘
                                        │
                                        │      ┌──────────────────────────────────────┐
                                        ├─────▶│ Excluded (n=6)                        │
                                        │      │ • Not meeting inclusion criteria (n=1)│
                                        │      │ • Declined to participate (n=5)       │
                                        │      │ • Other reasons (n=0)                 │
                                        │      └──────────────────────────────────────┘
                                        ▼
                            ┌──────────────────────┐
                            │  Randomized (n=370)   │
                            └──────────────────────┘
```
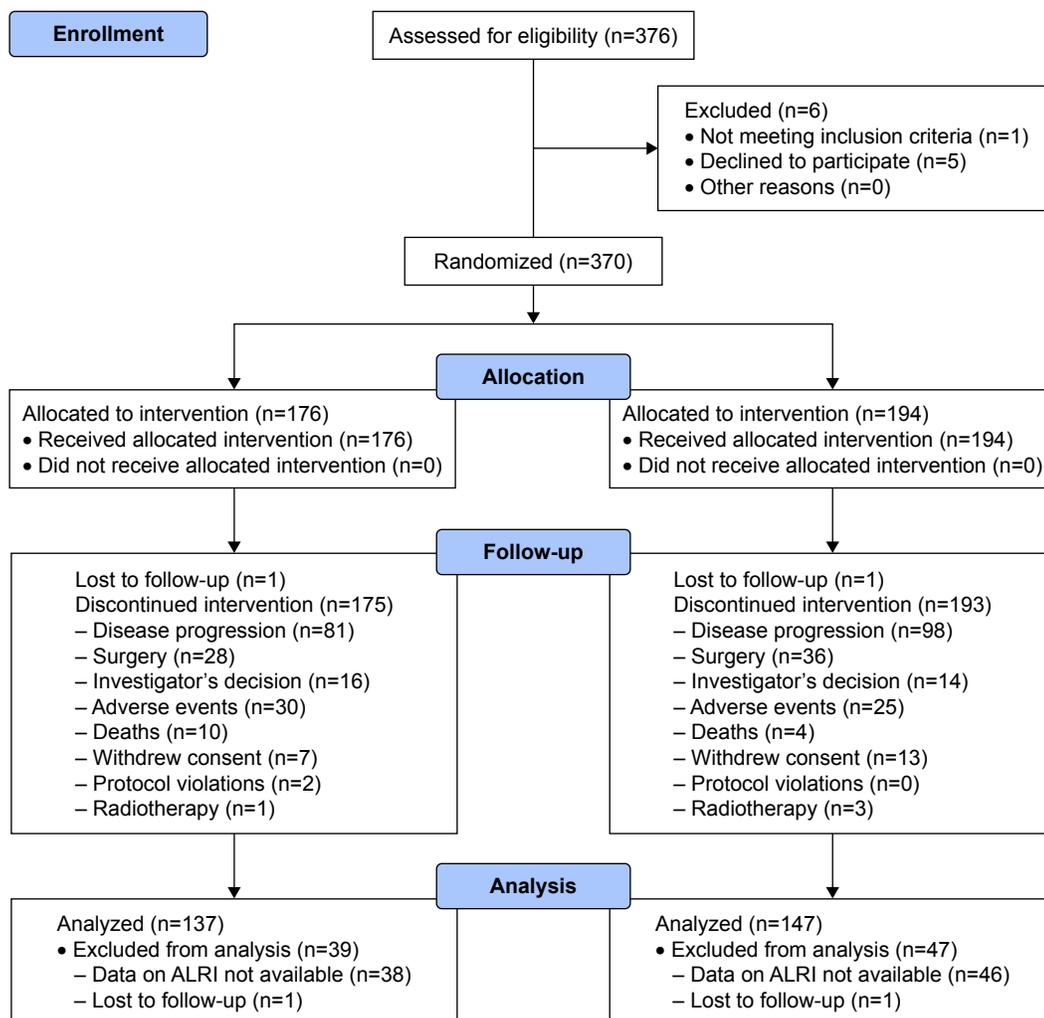

Figure 1 Flow chart of the study.
Abbreviation: ALRI, aspartate aminotransferase-lymphocyte ratio index.

was 36 months (range 1–65). Overall, median PFS was 9.1 (95% CI 8.4–9.8) and median OS was 21.4 months (95% CI 19.9–24.5). The 2 groups of patients were comparable with regard to age, gender, tumor localization, stage at diagnosis, KRAS status, and ITACa treatment. A considerable proportion of patients with high ALRI had performance status 1–2.

ALRI values and clinical outcome in all patients

Considering ALRI as a continuous variable, we observed that increased ALRI levels were associated with decreased PFS (HR 1.02, 95% CI 1.01–1.02, $p<0.0001$) and OS (HR 1.02, 95% CI 1.02–1.03, $p<0.0001$).

The 2 groups of patients were comparable for all the major clinical characteristics investigated, except for EOCG and CT regimen (Table 1).

At baseline, median PFS was 10.3 months (95% CI 9.4–12.0) and 8.0 months (95% CI 6.8–8.9) for patients with low (<14) and high (≥14) ALRI levels, respectively (HR 1.43, 95% CI 1.12–1.82, $p=0.004$) (Figure 2A). Median OS was 25.5 months (95% CI 21.3–30.2) and 18.8 months (95% CI 16.6–21.7) for patients with low and high baseline ALRI levels, respectively (HR 1.51, 95% CI 1.17–1.96, $p<0.001$) (Figure 2B). ALRI, AST, and lymphocyte values were associated with different toxicities (Table 2).

Following adjustment for clinical covariates (age, gender, ECOG, tumor localization, CT regimen, KRAS status, ITACa treatment, and LDH level and liver metastasis), multivariate analysis confirmed ALRI as an independent prognostic factor for predicting PFS (HR 1.35, 95% CI 1.02–1.79, $p=0.034$) and OS (HR 1.35, 95% CI 1.01–1.83 $p=0.048$) (Table 3).

Table 1 Patient characteristics (n=284)

Patient characteristics	ALRI		p-values
	<14	≥14	
	n (%)	n (%)	
Median age, years (range)	66 (34–83)	65 (33–81)	0.771
Gender			0.904
Male	86 (60.6)	84 (59.2)	
Female	56 (39.4)	58 (40.8)	
Performance status ECOG			0.005
0	123 (86.6)	103 (72.5)	
1–2	19 (13.4)	39 (27.5)	
Tumor localization			0.893
Rectum	37 (26.1)	38 (26.8)	
Colon	105 (73.9)	104 (73.2)	
Stage at diagnosis			0.646
I–III	35 (25.9)	31 (22.8)	
IV	100 (74.1)	105 (77.2)	
CT regimen			0.028
FOLFOX4	97 (68.3)	78 (54.9)	
FOLFIRI	45 (31.7)	64 (45.1)	
KRAS status[a]			0.387
Wild type	95 (66.9)	87 (61.3)	
Mutated	47 (33.1)	55 (38.7)	
ITACa treatment			0.812
CT+B	67 (47.2)	70 (49.3)	
CT	75 (52.8)	72 (50.7)	

Note: [a]Mandatory as consequence of amendment no 1 of May 3, 2009.
Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; B, bevacizumab; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ITACa, Italian Trial in Advanced Colorectal Cancer; n, number.

ALRI values and clinical outcome in patients treated with CT+B

Considering ALRI as a continuous variable, we observed also in patients undergoing CT+ B that increased ALRI levels were associated with decreased PFS (HR 1.01, 95% CI 1.01–1.02, p=0.001) and OS (HR 1.02, 95% CI 1.01–1.03, p<0.0001).

At baseline, median PFS was 11.3 months (95% CI 9.1–13.4) and 9.2 months (95% CI 6.8–11.3) for patients with low and high ALRI levels, respectively (p=0.304; HR 1.20, 95% CI 0.85–1.69, p=0.304) (Figure 3A). On the other hand, median OS was 22.7 and 15.9 months for patients with low and high baseline ALRI, respectively (HR 1.36, 95% CI 0.95–1.96, p=0.095) (Figure 3B).

ALRI values and clinical outcome in patients treated with CT alone

Considering ALRI as a continuous variable, we observed also in patients undergoing CT alone that increased ALRI levels were associated with decreased PFS (HR 1.04, 95% CI 1.03–1.05, p<0.0001) and OS (HR 1.03, 95% CI 1.02–1.04, p<0.0001).

At baseline, median PFS was 10.0 months (95% CI 9.0–11.8) and 7.0 months (95% CI 5.9–8.4) for patients with low and high ALRI levels, respectively (p=0.002; HR 1.71, 95% CI 1.22–2.41, p=0.002) (Figure 3C). Median OS was 27.1 and 20.2 months for patients with low and high baseline ALRI levels, respectively (p=0.007; HR 1.64, 95% CI 1.14–2.36, p=0.007) (Figure 3D).

Interaction tests on ALRI levels and treatment efficacy in the CT+B and CT only groups were statistically significant for PFS (p=0.0003) but not for OS (p=0.228).

Figure 4 shows the Kaplan–Meier curves of PFS of patients treated with CT+B and CT alone with respect to ALRI levels.


No pts at risk									
ALRI <14	142	109	60	34	25	18			
ALRI ≥14	142	90	36	28	12	8			
	142	132	116	95	72	58	49	36	31
	142	118	100	71	53	32	26	19	16
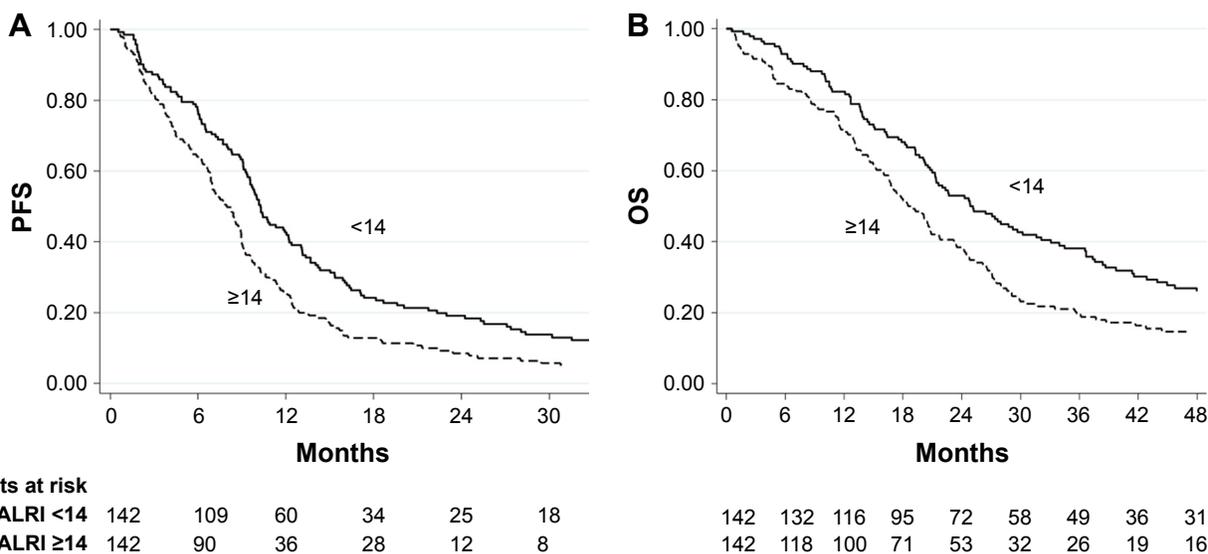
Figure 2 Kaplan–Meier curves of PFS (**A**), OS (**B**).
Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; PFS, progression-free survival; OS, overall survival.

Table 2 Comparison of median values of ALRI, AST and lymphocytes as a function of toxicity

	Number of patients	ALRI median value (range)	p-values	AST median value (range)	p-values	Lymphocyte median value (range)	p-values
Nausea			0.623		0.970		0.733
G_0	153	14.9 (1.3–172.3)		21 (9–193)		1.55 (0.43–10.40)	
G_1+G_2	124	13.2 (3.2–141.0)		21 (8–100)		1.64 (0.58–10.51)	
G_3+G_4	7	15.0 (9.3–28.6)		24 (14–28)		1.57 (0.98–2.07)	
Vomiting			0.852		0.929		0.687
G_0	217	14.0 (2.1–172.3)		21 (9–193)		1.63 (0.43–5.85)	
G_1+G_2	60	13.8 (1.4–82.6)		20 (8–100)		1.50 (0.87–10.51)	
G_3+G_4	7	15.0 (9.2–29.7)		24 (16–35)		1.60 (0.82–2.07)	
Diarrhea			0.032		0.194		0.540
G_0	150	14.9 (3.0–172.3)		22 (9–193)		1.57 (0.43–10.51)	
G_1+G_2	117	13.9 (1.3–141.0)		21 (10–88)		1.57 (0.61–10.40)	
G_3+G_4	17	11.4 (4.3–33.3)		20 (8–43)		1.93 (0.72–3.75)	
Stomatitis			0.230		0.073		0.468
G_0	220	14.0 (1.3–172.3)		20 (8–193)		1.55 (0.43–10.51)	
G_1+G_2	57	13.8 (4.8–102.3)		23 (11–96)		1.64 (0.77–4.75)	
G_3+G_4	7	21.0 (12.6–31.0)		30 (17–83)		1.57 (1.25–2.68)	
Fatigue			0.010		0.0004		0.220
G_0	159	13.2 (2.1–169.8)		20 (8–117)		1.54 (0.43–5.85)	
G_1+G_2	106	14.4 (1.3–141.0)		22 (9–142)		1.64 (0.56–10.51)	
G_3+G_4	19	20.1 (5.1–172.3)		28 (11–193)		1.46 (0.86–2.44)	
Anemia			0.221		0.187		0.857
G_0	224	13.8 (1.3–172.3)		21 (8–193)		1.60 (0.43–10.51)	
G_1+G_2	54	17.1 (3.5–102.3)		23 (10–96)		1.53 (0.72–3.75)	
G_3+G_4	6	11.4 (4.2–55.4)		16 (12–51)		1.63 (0.92–2.87)	
Neutropenia			0.791		0.683		0.182
G_0	101	14.8 (3.0–172.3)		20 (9–193)		1.51 (0.43–3.50)	
G_1+G_2	58	12.5 (3.5–70.5)		20 (10–117)		1.67 (0.58–3.75)	
G_3+G_4	124	14.7 (1.3–102.3)		22 (8–100)		1.57 (0.72–10.51)	
Thrombocytopenia			0.595		0.367		0.691
G_0	219	14.1 (1.3–172.3)		21 (8–193)		1.60 (0.43–10.51)	
G_1+G_2	59	13.2 (6.3–102.3)		23 (12–88)		1.60 (0.86–3.98)	
G_3+G_4	6	19.3 (6.3–33.3)		24 (17–33)		1.47 (0.72–3.15)	
Febrile neutropenia			0.515		0.820		0.202
G_0	278	14.1 (1.3–172.3)		21 (8–193)		1.57 (0.43–10.51)	
G_1+G_2	2	10.3 (3.5–17.0)		20 (10–30)		2.32 (1.76–2.89)	
G_3+G_4	4	11.5 (8.7–17.2)		23 (18–28)		1.90 (1.57–2.36)	
Hemorrhage			0.863		0.713		0.596
G_0	249	13.9 (1.3–172.3)		21 (8–193)		1.57 (0.43–10.51)	
G_1+G_2	35	15.6 (4.3–74.7)		22 (9–142)		1.68 (0.97–3.75)	
G_3+G_4	0	–		–		–	
Hypertension			0.096		0.429		0.077
G_0	226	14.7 (1.3–172.3)		21 (8–193)		1.57 (0.43–10.40)	
G_1+G_2	51	11.2 (2.0–82.6)		20 (10–100)		1.69 (0.77–10.51)	
G_3+G_4	7	17.1 (6.4–102.3)		25 (16–88)		1.46 (0.86–2.97)	
Thrombosis			0.379		0.335		0.361
G_0	232	14.1 (1.3–172.3)		21 (8–193)		1.57 (0.43–10.51)	
G_1+G_2	19	14.6 (4.8–82.6)		21 (12–100)		1.31 (0.56–2.55)	
G_3+G_4	33	11.9 (3.0–50.0)		20 (9–73)		1.73 (0.72–3.50)	
Proteinuria			0.001		0.005		0.514
G_0	221	13.2 (1.4–169.8)		20 (8–117)		1.60 (0.43–10.51)	
G_1+G_2	63	16.9 (4.2–172.3)		25 (11–193)		1.60 (0.61–3.50)	
G_3+G_4	0	–		–		–	
Neurologic system			0.028		0.168		0.044
G_0	183	15.0 (1.3–172.3)		22 (8–193)		1.58 (0.43–10.40)	
G_1+G_2	83	13.9 (3.2–102.3)		20 (10–88)		1.55 (0.58–10.51)	
G_3+G_4	18	9.8 (3.5–50.0)		18 (10.83)		1.88 (1.17–4.75)	

Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; AST, aspartate aminotransferase.

Table 3 Multivariate analysis of PFS and OS

	PFS		OS	
	HR (95% CI)	p-values	HR (95% CI)	p-values
ALRI (≥14 vs <14)	1.35 (1.02–1.79)	0.034	1.35 (1.01–1.83)	0.048
Age (continuous variable)	1.00 (0.98–1.01)	0.818	0.99 (0.98–1.01)	0.222
Gender (male vs female)	0.81 (0.62–1.07)	0.139	0.87 (0.65–1.16)	0.349
ECOG PS (1–2 vs 0)	1.33 (0.94–1.88)	0.109	2.18 (1.50–3.18)	<0.0001
Tumor localization (colon vs rectum)	0.98 (0.72–1.34)	0.908	1.09 (0.79–1.51)	0.585
CT regimen (FOLFIRI vs FOLFOX4)	1.27 (0.95–1.70)	0.104	1.07 (0.79–1.44)	0.659
KRAS status (mutated vs wild type)	0.98 (0.75–1.30)	0.910	1.17 (0.87–1.56)	0.296
ITACa treatment (CT+B vs CT)	0.84 (0.64–1.11)	0.230	1.19 (0.89–1.59)	0.228
LDH (>UNL vs ≤UNL)	1.20 (0.90–1.60)	0.202	1.30 (0.96–1.76)	0.095
Liver metastasis				
Only 1 lesion <5 cm vs no liver mts	0.55 (0.28–1.06)	0.076	0.62 (0.30–1.27)	0.191
Multiple liver lesions or 1 liver lesion ≥5 cm vs no liver mts	1.09 (0.78–1.52)	0.624	1.15 (0.81–1.64)	0.437

Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ITACa, Italian Trial in Advanced Colorectal Cancer; LDH, lactate dehydrogenase; PFS, progression-free survival; OS, overall survival; UNL, upper normal limit.
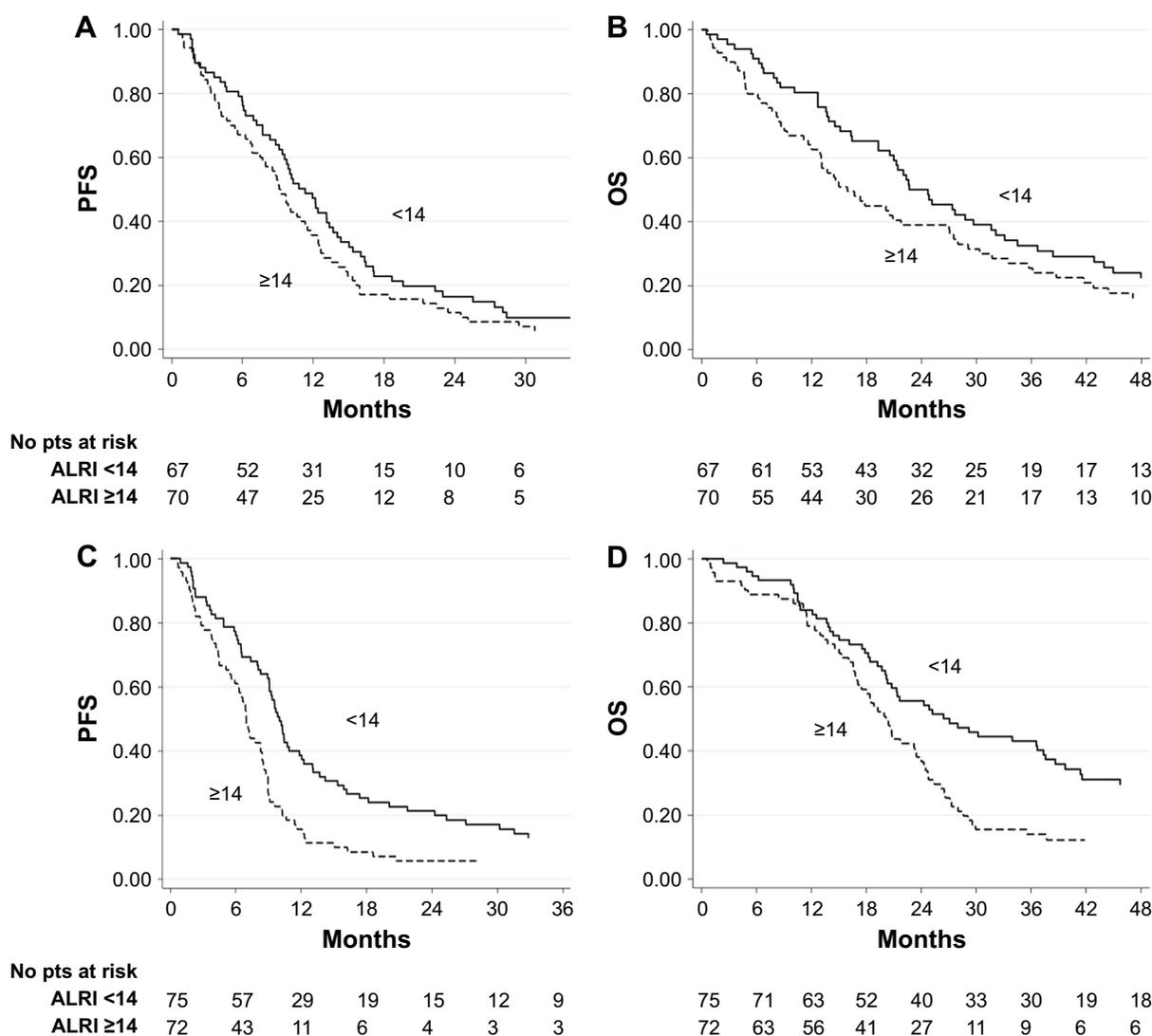
Figure 3 Kaplan–Meier curves of PFS (**A**) and OS (**B**) of patients treated with CT+B, Kaplan–Meier curves of PFS (**C**) and OS (**D**) in patients treated with CT.
Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; B, bevacizumab; CT, chemotherapy; OS, overall survival; PFS, progression-free survival.
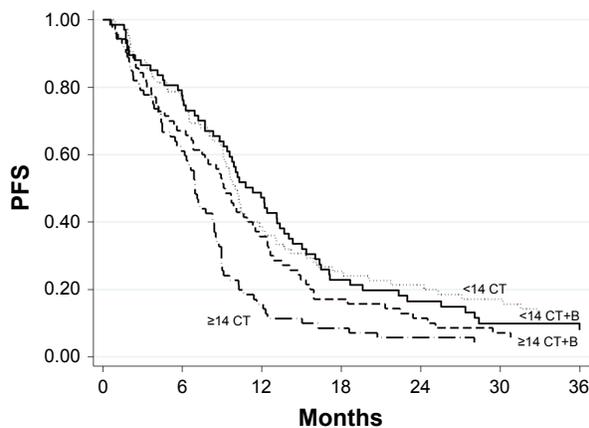
Figure 4 Kaplan–Meier curves of PFS of patients treated with CT+B and CT on the basis of ALRI levels.
Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; B, bevacizumab; CT, chemotherapy; PFS, progression-free survival.

AST and lymphocyte values and clinical outcome in all patients

Considering ALRI as a continuous variable, we observed that increased AST levels were associated with decreased PFS (HR 1.01, 95% CI 1.01–1.02, p=0.0002) and OS (HR 1.02, 95% CI 1.01–1.02, $p<0.0001$). Among basal characteristics, we observed that AST levels were higher in patients with liver disease (Table 4).

Considering lymphocyte as a continuous variable, we observed that increased lymphocyte levels were associated with decreased PFS (HR 0.84, 95% CI 0.72–0.99, p=0.036), but not OS (HR 0.91, 95% CI 0.77–1.06, p=0.214).

Discussion

Our study showed that high levels of ALRI at baseline were associated with shorter PFS and OS than low ALRI levels. To our knowledge, our study is the first to have assessed the prognostic value of ALRI in patients with CRC, potentially representing a noninvasive predictor of prognosis for CRC patients. However, the cutoff value of ALRI in our report was different from what was previously reported in other diseases.[6,7] ALRI was evaluated in particular in patients with

hepatocellular carcinoma, as levels of AST are higher and lymphocyte levels are lower due to cirrhosis.

AST plays a role in the metabolism of amino acids in the liver, and thus its increase becomes a biochemical marker of liver failure.[8] Lymphocytes play a role in the antitumor immune response, and their presence relates to a reduced risk of relapse in several situations.[9] Increased serum AST may be a result of the progression of liver diseases, as intracellular AST is released when the hepatic parenchymal cells are injured. Conversely, decreased lymphocytes can reduce the antitumor immunity of the patients. For this reason, ALRI may be used for predicting response and OS.

B, a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor, was found to improve survival in both first- and second-line settings when added to CT.[10] There is no current validated clinical or biological factor that can predict response to B. A positive result to the interaction test indicates that the ALRI index may be predictive of B efficacy. We hypothesize that B may be capable of contrasting the negative predictive value of high baseline levels of ALRI. In fact, among patients with high ALRI levels, PFS was lower in those treated with CT alone than in those treated with CT+B.

With regard to toxicity, it is noteworthy that high values of ALRI and AST were mostly associated with a higher incidence of fatigue, probably as result of a greater amount of liver disease at baseline, which may induce higher chemo-related toxicity.

In conclusion, pretreatment levels of ALRI may constitute a marker of aggressiveness in CRC patients. Elevated ALRI levels prior to treatment seem to be indicators of poor prognosis.

Author contributions

The study was conceptualized and designed by Andrea Casadei Gardini. All authors assisted with collection and assembly of data. Andrea Casadei Gardini, Emanuela Scarpi, and Alessandro Passardi analyzed and interpreted the data.

Table 4 Liver disease and median value of AST

	Number of patients	AST median value (range)	p-values	Lymphocyte median value (range)	p-values	ALRI median value (range)	p-values
Overall			<0.0001		0.229		0.003
No liver disease +1 single liver lesion <5 cm	81	17 (9–117)		1.51 (0.56–10.40)		12.70 (1.35–80.15)	
Multiple lesions (including 1 liver) or 1 single hepatic lesion ≥5 cm	203	23 (8–193)		1.62 (0.43–10.51)		15.20 (2.05–172.32)	

Abbreviations: ALRI, aspartate aminotransferase-lymphocyte ratio index; AST, aspartate aminotransferase.

All authors were involved in manuscript writing. All authors finally approved the manuscript. The corresponding author had the final responsibility to submit for publication. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Acknowledgments

Disclosure

The authors report no other conflicts of interest in this work.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9–29.
2. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883–899.
3. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454:436–444.
4. Ko E, Jung G. Positive association of long telomeres with the invasive capacity of hepatocellular carcinoma cells. *Biochem Biophys Res Commun*. 2014;447(2):358–363.
5. Passardi A, Nanni O, Tassinari D, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. *Ann Oncol*. 2015;26(6):1201–1207.
6. Jin J, Zhu P, Liao Y, Li J, Liao W, He S. Elevated preoperative aspartate aminotransferase to lymphocyte ratio index as an independent prognostic factor for patients with hepatocellular carcinoma after hepatic resection. *Oncotarget*. 2015;6(22):19217–19227.
7. Yang Z, Zhang J, Lu Y. Aspartate aminotransferase-lymphocyte ratio index and systemic immune-inflammation index predict overall survival in HBV-related hepatocellular carcinoma patients after transcatheter arterial chemoembolization. *Oncotarget*. 2015;6(40):43090–43098.
8. Okuda M, Li K, Beard MR, et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology*. 2002;122(2):366–375.
9. Pagès F, Galon J, Dieu-Nosjean MC, Tartour E, Sautès-Fridman C, Fridman WH. Immune infiltration in human tumors: a prognostic factor that should not be ignored. *Oncogene*. 2010;29:1093–1102.
10. Hurwitz HI, Tebbutt NC, Kabbinavar F, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *Oncologist*. 2013;18(9):1004–1012.