Original Study

Clinico-Pathological Features Influencing the Prognostic Role of Body Mass Index in Patients With Advanced Renal Cell Carcinoma Treated by Immuno-Oncology Combinations (ARON-1)

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Abstract

Obesity is a well-known risk factor for the development of renal cell carcinoma (RCC), one of the most frequent malignant urogenital tumors. The development of immunotherapy (IO)-based combinations for the treatment of metastatic RCC (mRCC) has led to a marked improvement of patients' outcomes and quality of life. The ARON-1 study (NCT05287464) was designed to globally analyze real-world treatment outcomes of mRCC patients receiving first-line immune-based combinations. In this sub-analysis, we investigated the role of body mass index (BMI) in patients treated by immuno-oncology combinations stratified by clinico-pathological features. According to our results, the prognostic significance and the association of BMI with treatment outcome may vary across clinico-pathological mRCC subgroups.

Background: Obesity has been associated with improved response to immunotherapy in cancer patients. We investigated the role of body mass index (BMI) in patients from the ARON-1 study (NCT05287464) treated by dual immuno-oncology agents (IO+IO) or a combination of immuno-oncology drug and a tyrosine kinase inhibitors (TKI) as first-line therapy for metastatic renal cell carcinoma (mRCC). **Patients and Methods:** Medical records of patients with documented mRCC treated by immuno-oncology combinations were reviewed at 47 institutions from 16 countries. Patients were assessed for overall survival (OS), progression-free survival (OS), and overall clinical benefit (OCB), defined as the sum of the rate of partial/complete responses and stable disease. Univariate and multivariate analyses were used to explore the association of variables of interest with survival. **Results:** A total of 675 patients were included; BMI was >25 kg/m^2 in 345 patients (51%) and was associated with improved OS (55.7 vs. 28.4 months, $P < .001$). The OCB of patients with BMI >25 kg/m^2 versus those with BMI ≤25 kg/m^2 was significantly higher only in patients with nonclear cell histology (81% vs. 65%, $P = .011$), and patients with liver metastases (76% vs. 58%, $P = .007$), Neutrophil to lymphocyte ratio >4 (77% vs 62%, $P = .022$) or treated by nivolumab plus ipilimumab (77% vs. 64%, $P = .044$). In the BMI ≤25 kg/m^2 subgroup, significant differences were found between patients with NLR >4 versus ≤4 (62% vs. 82%, $P = .002$) and patients treated by IO+IO versus IO+TKIs combinations (64% vs. 83%, $P = .002$). **Conclusion:** Our study suggests that the prognostic significance and the association of BMI with treatment outcome varies across clinico-pathological mRCC subgroups.

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Introduction

In the past 5 decades, the prevalence of obesity has reached pandemic levels worldwide.[1] Obesity contributes to a decline in both quality of life and life expectancy by increasing the risk of type 2 diabetes mellitus,[2] cardiovascular diseases,[3] and cancer.[4,5] Moreover, It has been associated with increased severity of complications from infections[6] and poor vaccine responses.[7] The molecular mechanisms of cancer development in obese patients are poorly understood and include inflammation, the alteration of adipokine (ie, leptin and adiponectin) and insulin signaling and the loss of the role of adipocytes in energy homeostasis.[8]

Obesity is a well-known risk factor for the development of RCC, one of the most frequent malignant urogenital tumors.[9,10] The development of immunotherapy (IO)-based combinations for the treatment of metastatic RCC (mRCC) has led to a marked improvement of patients' outcomes and quality of life.[11] These approaches rely on the use of 2 different immune checkpoint inhibitors (IO + IO combination), anti-programmed death (PD)-1 nivolumab and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), ipilimumab, or involve anti-PD-1 (nivolumab, pembrolizumab) or anti-PD ligand 1 (PD-L1) agents (avelumab, atezolizumab) combined with anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab) or tyrosine kinase inhibitors (TKIs, axitinib, lenvatinib, cabozantinib), defined as IO + TKI combinations.[12-20]

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A growing body of evidences suggests that overweight and obesity are associated with better outcome in mRCC patients treated with immunotherapy.[21] A potential explanation has been provided by Sanchez et al.,[22] who observed that tumours from obese RCC patients are enriched in the expression of VEGF and related proteins and show a higher proportion of plasmacytoid dendritic cells (pDCs) and mast cells and a lower proportion of innate lymphoid cells (in particular natural killer_CD56bright_cells). Interestingly, leptin levels in obese subjects have been associated to higher T cell Programmed Death (PD)-1 expression and increased response to immune checkpoint inhibitors.[23,24]

The ARON-1 study (NCT05287464) was designed to globally analyze real-world treatment outcomes of mRCC patients receiving first-line immune-based combinations. In this sub-analysis, we investigated the role of BMI in patients treated by immuno-oncology combinations stratified by clinico-pathological features.

Patients and Methods

Study Population

The ARON-1 study (NCT05287464) retrospectively collected data from patients aged ≥18 years having a cytological and/or histological confirmed diagnosis of mRCC receiving first-line immuno-combination therapies from January 1, 2016 to August 1, 2022. Forty-seven Institutions from 16 countries were involved in the ARON-1 project.

Patients' paper and electronic medical records were consulted to extract selected clinical and laboratory parameters. The dataset included data on age, gender, tumor histology, nephrectomy, International mRCC Database Consortium (IMDC) criteria, sites of metastases, type of immuno-combination and response to therapy. Patients with insufficient data on tumor assessment or response to therapy were excluded from the ARON-1study.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed following standard local procedures every 8 to 12 weeks. Physical and laboratory tests were usually carried out every 4 to 6 weeks during patients' treatment and follow-up.

Study Endpoints

RECIST 1.1 criteria[25] were used to assess the response to therapy and to define the response as complete (CR), partial (PR), stable disease (SD) or progressive disease (PD). Overall clinical benefit (OCB) was calculated by the sum of CR, PR, and SD. Overall Survival (OS) was defined as the time from the start of first-

Table 1 Patients' characteristics

Patients	Overall	BMI >25	BMI ≤25	*P*
	675 (%)	345 (%)	330 (%)	
Gender				.112
Male	495 (73)	270 (78)	225 (68)	
Female	180 (27)	75 (22)	105 (32)	
Age, years (y)	64	64	63	-
Range	25 – 88	31 – 88	25 – 85	
Metastatic at diagnosis	381(56)	178 (52)	203 (62)	.154
Past nephrectomy	428 (63)	234 (68)	194 (59)	.187
Clear cell histology	573 (85)	303 (88)	270 (82)	.236
Sarcomatoid differentiation	107 (16)	48 (14)	59 (18)	.442
IMDC risk stratification				.097
Favorable risk	110 (17)	73 (21)	37 (11)	
Intermediate risk	387 (57)	197(57)	190 (58)	
Poor risk	178 (26)	75 (22)	103 (31)	
Common sites of metastasis				
Lung	468 (69)	231 (67)	237 (72)	.444
Bone	232 (34)	113 (33)	119 (36)	.656
Liver	126 (19)	50 (14)	76 (23)	.102
Brain	50 (7)	30 (9)	20 (6)	.422
Neutrophil to Lymphocyte Ratio				
>4	245 (36)			
≤4	430 (64)			
First-line therapy				.087
IO + IO	289 (43)	168 (49)	121 (37)	
IO + TKIs	386 (57)	177 (51)	209 (63)	

Statistically significant values were reported in bold. BMI = Body Mass Index; IMDC = International mRCC Database Consortium; RCC = Renal Cell Carcinoma.

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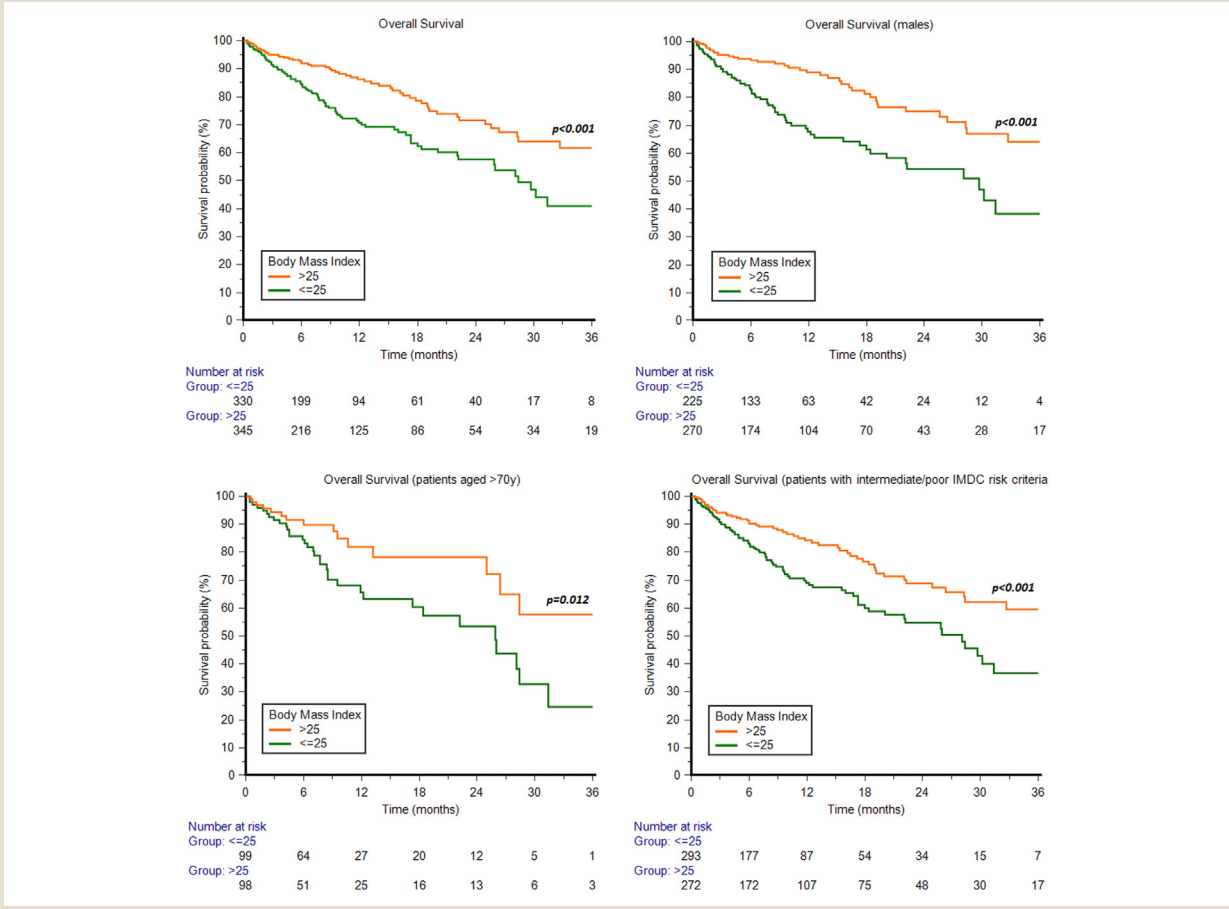
Figure 1 Median overall survival in mRCC patients treated with first-line immuno-combinations stratified by body mass index basing on gender, age, and IMDC intermediate/poor risk criteria.



line therapy until death. Progression-Free Survival (PFS) was calculated from the start of immune-combination to progression or death from any cause, whichever occurred first. Patients without disease progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit.

Statistical Analysis

The Kaplan-Meier method with Rothman's 95% confidence intervals (CI) was used to analyze OS and PFS. Comparisons between survival distributions were carried out by using the log-rank test. Cox proportional hazards models were used to compare the multivariable effects on patients' survival and to calculate hazard ratios (HRs) and 95% CIs. A survival receiver operating characteristic (ROC) analysis was adopted to identify potential cut-offs that better stratify patients in risk groups. The χ^2 test was used to compare each group for categorical variables. Statistical differences were considered significant when the *P*-value was <.05, and all *P* values were 2-sided.

BMI was defined as a person's weight in kilograms divided by the square of height in meters. Based on the World Health Organization (WHO) classification, patients were included in the overweight/obesity group when BMI was>25 kg/m^2.

MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium) was employed for data analysis. The research was carried out in accordance with the approval by the ethical committee of the Marche Region.

Results

Study Population

Our analysis included 675 patients. The median follow-up time was 18.1 months (95% CI 14.4−67.8); 495 patients (73%) were males. The median age was 64 years (range 25-88). Tumor histology was clear cell RCC in 573 patients (85%); in the 102 nonclear cell RCC patients, papillary type I or II histology was observed in 27 cases and chromophobe RCC in 11 (Table 1); sarcomatoid differentiation was reported in 107 patients (16%). Previous nephrectomy was performed in 428 patients (63%). Distant metastases confined to the lungs were identified in 468 patients (69%). Stratifying by IMDC criteria, 110 patients (17%) were at favorable-risk, 387 (57%) at intermediate-risk, and 178 (26%) at poor-risk.

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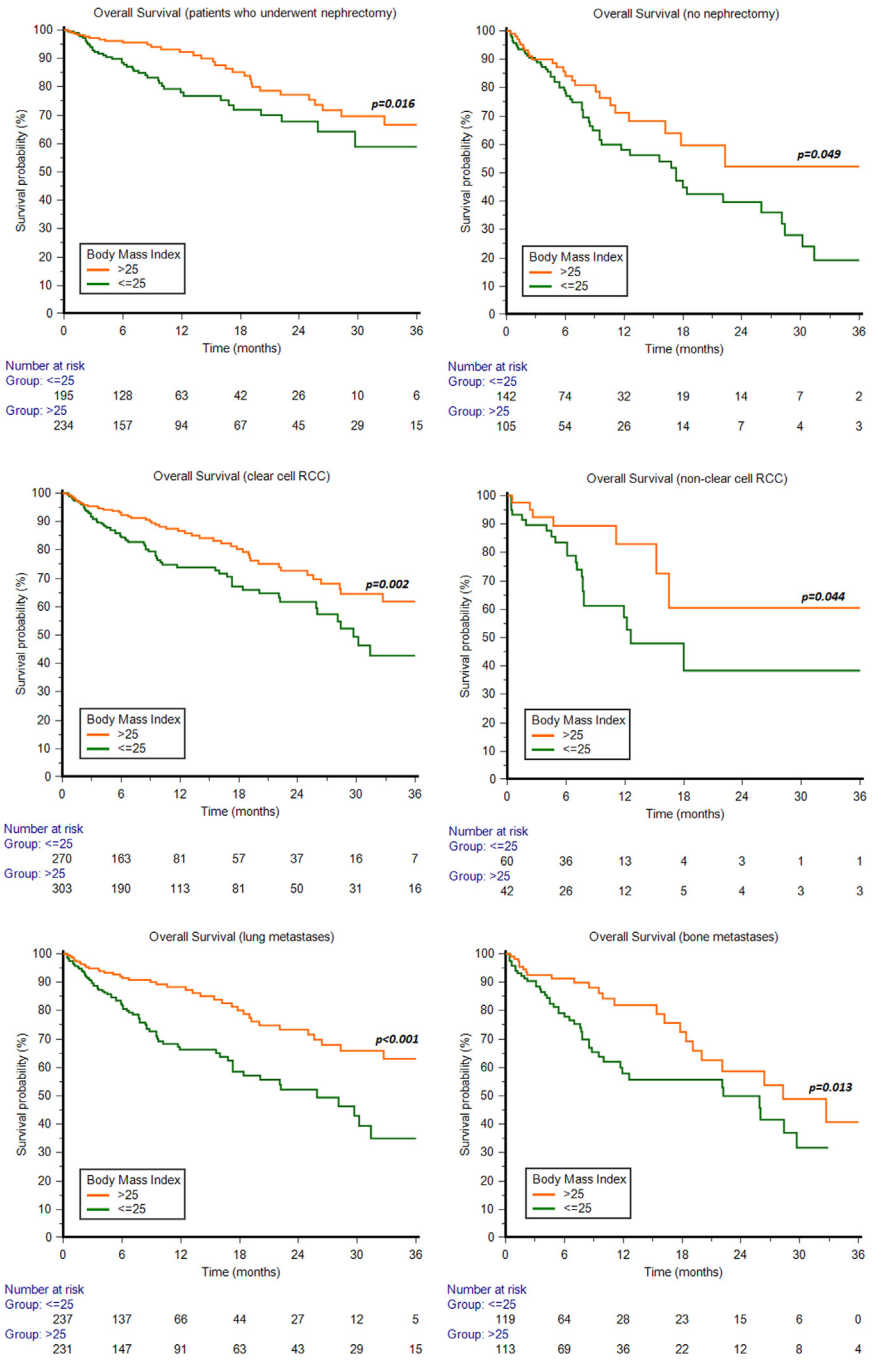
Figure 2 Median overall survival in mRCC patients treated with first-line immuno-combinations stratified by body mass index basing on nephrectomy status, tumor histology and presence of lung or bone metastases.



Mean and median BMI were 26 kg/m^2 and 25 kg/m^2, respectively, ranging from 14 to 45 kg/m^2; BMI was >25 kg/m^2 in 345 patients (51%) and ≤25 kg/m^2 in 330 patients (49%).

IO + IO combination was the first-line therapy in 289 patients (43%), while 386 patients (57%) received IO + TKI combinations. Patients' characteristics are summarized in Table 1. No significant differences were found in terms of clinico-pathological features between patients with BMI>25 kg/m^2 versus ≤25 kg/m^2 (Table 1).

Survival Analysis

In the overall study population, the median OS was 41.0 months (95% CI 28.4-55.7); 150 patients had died at the time of analy-

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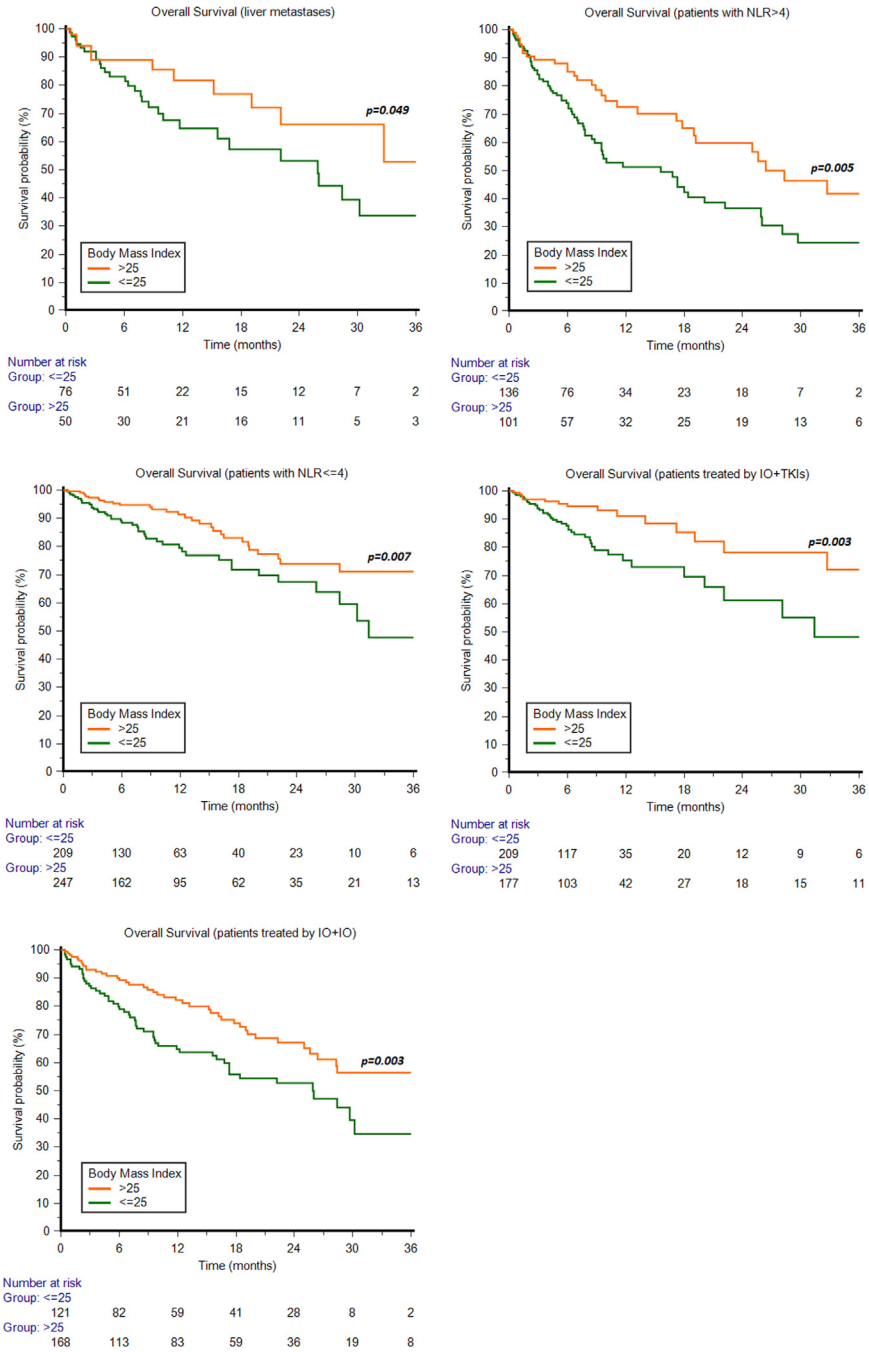
Figure 3 Median overall survival in mRCC patients treated with first-line immuno-combinations stratified by body mass index basing on the presence of liver metastases, neutrophil to lymhocyte ratio and type of first-line immuno-combination.



sis, 92 and 58 patients in the BMI $\leq$ 25 kg/m^2 and >25 kg/m^2 subgroups, respectively. The median OS was longer in patients with BMI > 25 kg/m^2 compared to those with BMI $\leq$ 25 kg/m^2 (55.7 months, 95% CI 36.5-55.7, vs. 28.4 months, 95% CI 22.2-41.0, $P < .001$, Figure 1). Interestingly, BMI > 25 kg/m^2 was associated with a significantly longer median OS in male patients (55.7 months, 95% CI 36.5-55.7, vs. 29.7 months, 95% CI 20.1-31.4, $P < .001$, Figure 1) but not in females (not reached, NR, 95% CI NR-NR, vs. 28.4 months, 95% CI 17.3-41.0, $P = .864$).

In the 197 patients aged >70 years, BMI confirmed its prognostic significance for OS (NR, 95% CI NR-NR, vs. 25.9 months, 95% CI 12.2-31.4, $P = .012$, Figure 1).

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Table 2 Overall Clinical Benefit in mRCC Patients Treated With Immuno-Combinations Stratified by Body Mass Index

Patients	Overall Clinical Benefit (%)	Overall Clinical Benefit (%)		*P*
		BMI >25	BMI ≤25	
Overall population	79	82	76	.073
Gender				
Male	79	81	77	.489
Female	77	83	73	.089
Patients aged >70 y	80	82	78	.481
Previous nephrectomy				
Yes	81	84	78	.281
No	74	76	71	.424
Tumor histology				
Clear cell RCC	80	82	78	.481
Non-clear cell RCC	72	81	65	**.011**
Sarcomatoid differentiation	67	72	63	.175
IMDC risk stratification				
Good risk	95	95	93	.553
Intermediate/poor risk	76	78	74	.509
Common sites of metastasis				
Lung	76	81	72	.134
Bone	70	73	67	.356
Liver	64	76	58	**.007**
Brain	69	68	70	.760
Neutrophil to lymphocyte ratio				
>4	68	77	62	**.022**
≤4	83	84	82	.707
First-line therapy				
IO + IO	71	77	64	**.044**
IO + TKIs	84	86	83	.559

Statistically significant values were reported in bold.
Abbreviations: BMI = Body Mass Index; IMDC = International mRCC Database Consortium.

By stratifying patients according to IMDC prognostic criteria, no significant differences were found between patients with BMI > 25 kg/m^2 versus ≤25 kg/m^2 in the good risk subgroup (36.5 months, 95% CI 25.6-36.5, vs. NR, 95% CI NR−NR, $P = .848$). Otherwise, patients with intermediate/poor IMDC risk criteria showed a longer median OS in the subgroup of patients with BMI > 25 kg/m^2 (55.7 months, 95% CI 32.7-55.7, vs. 28.1 months, 95% CI 20.1-31.4, $P < .001$, Figure 1).

The median OS was longer in patients with BMI > 25 kg/m^2 independently from nephrectomy status (patients who underwent nephrectomy: 55.7 months, 95% CI 55.7-55.7, vs. 41.0 months, 95% CI 29.7−41.0, $P = .016$, Figure 2; patients without nephrectomy: 36.5 months, 95% CI 16.2-36.5, vs. 17.3 months, 95% CI 9.7-26.0, $P = .049$, Figure 2) and tumor histology (clear cell RCC: 55.7 months, 95% CI 55.7-55.7, vs. 29.7 months, 95% CI 25.9-41.0, $P = .002$, Figure 2; nonclear cell RCC: 36.5 months, 95% CI 15.2−36.5, vs. 12.6 months, 95%CI 7.8−18.0, $P = .044$, Figure 2). Of note, no significant interaction between BMI and OS was observed in patients with sarcomatoid differentiation (BMI>25 kg/m^2: NR, 95% CI NR−NR;BMI < 25 kg/m^2: 41 months, 95% CI 9.6-41.0, $P = .423$) or brain metastases (BMI > 25 kg/m^2:22.1 months, 95% CI 11.1-22.1; BMI < 25 kg/m^2: 16.8 months, 95% CI 6.0−41.0, $P = .784$), while patients with lung (NR, 95% CI NR−NR, vs. 25.9 months, 95% CI 17.3-31.4, $P < .001$, Figure 2), bone (28.3 months, 95%CI 19.1−55.7, vs. 22.2 months, 95% CI 11.7-29.7, $P = .013$, Figure 2) or liver metastases (55.7 months, 95% CI 22.1−55.7, vs. 25.9 months, 95% CI 15.6-30.2, $P = .049$, Figure 3) showed a longer median OS in patients with BMI > 25 kg/m^2.

On the basis of the well-known correlation between overweight/obesity and inflammatory status,[26,27] we further investigated the potential influence of neutrophil to lymphocyte ratio (NLR) on the prognostic significance of BMI. The best cut-off for the NLR was calculated by ROC curve and resulted >4; NLR was >4 in 245 patients (36%) and ≤4 in 430 patients (64%). Interestingly, no correlation was found between BMI and NLR status. Indeed, the median OS was longer in patients with BMI>25 kg/m^{2}versus ≤25 kg/m^2 in both NLR > 4 (28.3 months, 95% CI 19.0-32.7 vs. 15.6 months, 95% CI 8.8-20.1, $P = .005$, Figure 3) and NLR ≤ 4 subgroups (55.7 months, 95% CI 36.5-55.7, vs. 31.4 months, 95% CI 28.4-41.0, $P = .007$, Figure 3).

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Table 3 Univariate and Multivariate Analyses of Predictors of Overall Survival and Progression-Free Survival in mRCC Patients Treated With Immunocombinations

	Univariate Cox Regression		Multivariable Cox regression	
OS	**HR (95%CI)**	***P-Value***	**HR (95%CI)**	***P-Value***
Gender (females vs. males)	1.13 (0.80-1.61)	.489		
Age (≥70y vs. <70y)	1.38 (0.98-1.94)	.068		
Body mass Index (>25 vs. ≤25)	0.52 (0.38-0.73)	**<.001**	0.68 (0.48−0.95)	**.025**
IMDC prognostic group	2.28 (1.74-3.00)	**<.001**	1.54 (1.15−2.56)	**.004**
Nephrectomy (yes vs no)	0.36 (0.26-0.50)	**<.001**	0.57 (0.41−0.81)	**.002**
Histology (ccRCC vs. nccRCC)	0.54 (0.36-0.81)	**.003**	0.56 (0.37−0.84)	**.005**
Sarcomatoid features (yes vs no)	1.45 (0.97-2.16)	.067		
Bone metastases (yes vs. no)	1.78 (1.29-2.45)	**<.001**	1.52 (1.09−2.12)	**.013**
Liver metastases (yes vs. no)	1.47 (1.02-2.11)	**.038**	0.97 (0.67−1.42)	.878
Brain metastases (yes vs. no)	1.99 (1.24-3.18)	**.004**	2.04 (1.27−3.30)	**.003**
NLR (>4 vs. ≤4)	3.42 (2.46-4.77)	**<.001**	2.40 (1.68−3.42)	**<.001**

	Univariate Cox Regression		Multivariable Cox regression	
PFS	**HR (95%CI)**	***P-Value***	**HR (95%CI)**	***P-Value***
Gender (females vs. males)	1.02 (0.77-1.36)	.882		
Age (≥70y vs. <70y)	1.07 (0.81-1.41)	.642		
Body mass Index (>25 vs. ≤25)	0.79 (0.61-1.02)	.068		
IMDC prognostic group	1.64 (1.34-2.01)	**<.001**	1.30 (1.04-1.63)	**.020**
Nephrectomy (yes vs. no)	0.58 (0.45-0.75)	**<.001**	0.82 (0.61-1.09)	.165
Histology (ccRCC vs. nccRCC)	0.74 (0.53-1.02)	.069		
Sarcomatoid features (yes vs. no)	1.67 (1.22-2.27)	**.001**	1.54 (1.12-2.12)	**.008**
Bone metastases (yes vs. no)	1.62 (1.26-2.09)	**<.001**	1.54 (1.18-2.01)	**.002**
Liver metastases (yes vs. no)	1.32 (0.98-1.78)	.069		
Brain metastases (yes vs. no)	1.57 (1.03-2.37)	**.034**	1.45 (0.93-2.26)	.098
NLR (>4 vs. ≤4)	1.76(1.26-2.37)	**<.001**	1.50 (1.14-1.98)	**.004**

Statistically Significant Values Were Reported in Bold.
Abbreviations: ccRCC = clear cell Renal Cell Carcinoma; CI = confidence interval; HR = hazard ratio; nccRCC = non-clear cell Renal Cell Carcinoma; NLR = Neutrophil to Lymphocyte Ratio; OS = overall survival; PFS = progression-free survival.

Interestingly, the favorable prognostic impact of higher BMI on survival was independent from the type of first-line therapy (IO+TKIs: 55.7 months, 95% CI 36.5-55.7, vs. 31.4 months, 95% CI 22.1-31.4, $P = .003$, Figure 3; IO + IO: NR, 95% CI NR−NR, vs. 25.9 months, 95% CI 16.7-41.0, $P = .003$, Figure 3).

In the overall study population, the median PFS was 15.2 months (95% CI 12.3-18.7) and the difference between patients with BMI > 25 kg/m^2 (15.9 months, 95% CI 12.9-23.9) vs. ≤25 kg/m^2 (14.1 months, 95% CI 9.6−20.1) was borderline significant ($P = .066$, Figure 4). Analogously to OS, we investigated the prognostic role of BMI in distinct subgroups. Subgroup analyses showed that BMI was significantly associated with PFS only in patients with non-clear histology (BMI > 25 kg/m^2: 15.2 months, 95% CI 8.3-15.2; BMI ≤ 25 kg/m^2: 6.9 months, 95% CI 4.4-25.1, $P = .046$, Figure 4) or NLR >4 (BMI > 25 kg/m^2: 15.8 months, 95% CI 10.4-23.9; BMI ≤ 25 kg/m^2: 6.9 months, 95% CI 5.5-9.7, $P = .014$, Figure 4), while no statistically significant differences were observed in all the other subgroups analyzed.

In the overall study population, the OCB was 79% and was not significantly higher in patients with BMI > 25 kg/m^2 (82% vs. 76%, $P = .073$, Table 2, Figure S1). On the other hand, the differences between the OCB of patients with BMI >25 kg/m^2 compared to those with BMI ≤ 25 kg/m^2 were statistically significant in 4 distinct subgroups: (1) patients with non-clear cell histology (81% vs. 65%, $P = .011$, Table 2, Figure S1); (2) patients with liver metastases (76% vs. 58%, $P = .007$, Table 2, Figure S1); (3) patients with NLR > 4 (77% vs. 62%, $P = .022$, Table 2, Figure S1); (4) patients treated by first-line IO + IO combination (77% vs. 64%, $P = .044$, Table 2, Figure S1). Of note, in patients treated by IO+IO combination the rate of patients with NLR > 4 was significantly higher in the subgroup of patients with BMI ≤ 25 (49%) compared to those with BMI > 25 (30%, $P = .006$).

Interestingly, in patients with BMI ≤ 25 kg/m^2 we observed a significant difference in terms of OCB between patients with NLR

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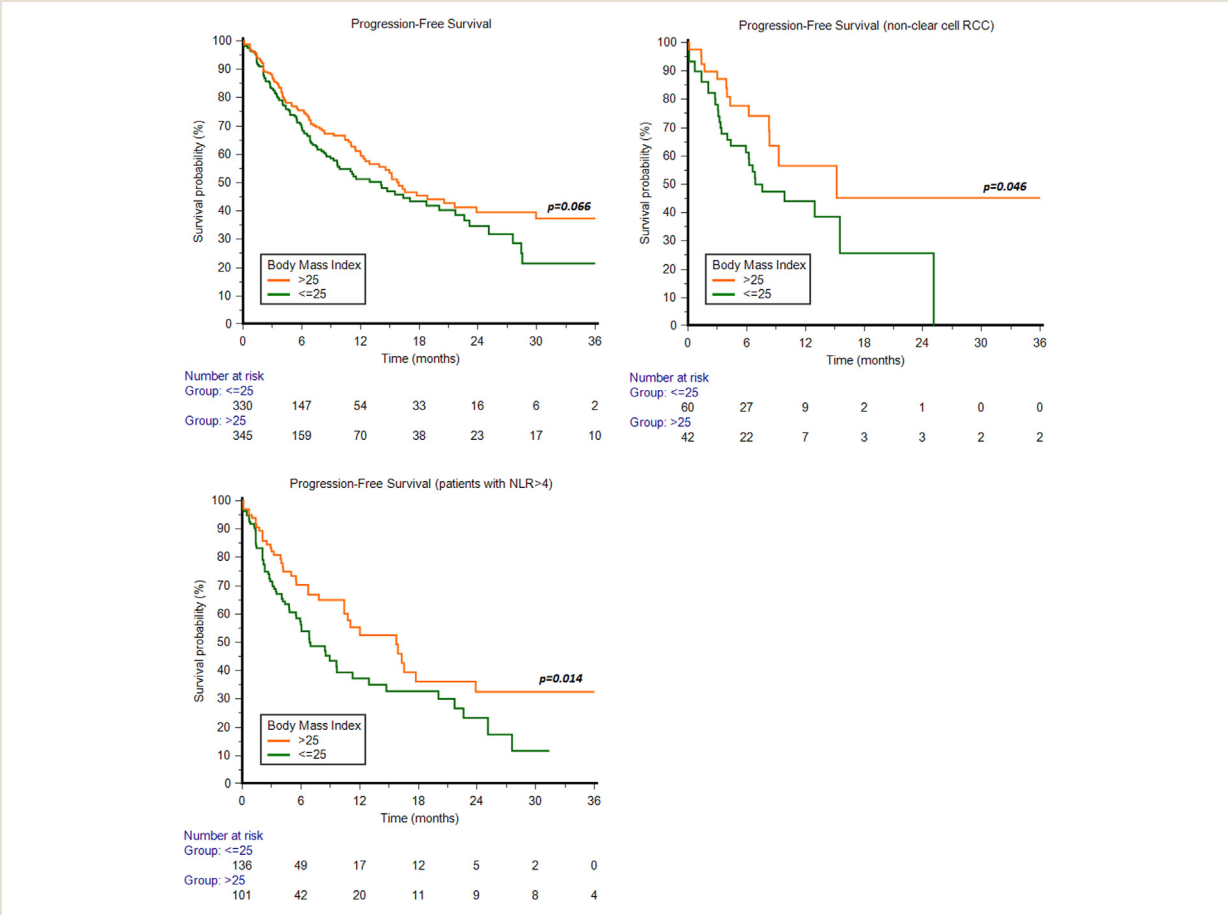
Figure 4 Median progression-free survival in mRCC patients treated with first-line immuno-combinations stratified by body mass index basing on non-clear cell histology and neutrophil to lymhocyte ratio.



> 4 versus ≤4 (62% vs. 82%, $P = .002$, Figure S1) and basing on type of first-line immuno-oncology combination (IO+IO: 64%; IO+TKIs: 83%, $P = .002$, Figure S1).

Univariate and Multivariate Analyses

At univariate analysis, BMI, IMDC group, previous nephrectomy, tumor histology, the presence of bone or liver or brain metastases and NLR were significant predictors of OS, and their prognostic role was confirmed at multivariate analysis, with the exception of liver metastases (Table 3).

As for PFS, IMDC group, previous nephrectomy, the presence of bone or brain metastases and NLR were significantly correlated with PFS at univariate analysis, while nephrectomy status and brain metastases did not prove to be associated with PFS at multivariate analysis (Table 3).

Discussion

Life style plays a crucial role in the outcome of cancer patients treated by immunotherapy. Tobacco use,[28,29] dietary patterns,[30-32] gut microbioma[33] and obesity[22-24] have been correlated with the prognosis of patients treated by immune checkpoint inhibitors, highlighting the necessity of assessing and potentially modifying patients' life style in order to improve their outcome.

The role of overweight and obesity has been investigated in mRCC patients. In 2021, our group has published the results of a retrospective study including 224 mRCC patients treated with cabozantinib as second- or third-line therapy. We observed an advantage in terms of both OS (30.7 vs. 11.0 months, $P = .003$) and PFS (9.9 vs. 7.6 months, $P < .001$) in patients with BMI ≥ 25. Furthermore, BMI was a significant predictor of both OS and PFS at multivariate analysis.[34]

More recently, Herrmann et al.[35] have observed a correlation between higher BMI and the response to first scan in mRCC patients treated by nivolumab, with longer OS observed in patients with weight gain compared to weight loss. In the same view, BMI >25 kg/m^2 was associated with improved OS in patients treated with nivolumab plus ipilimumab.[36]

The ARON-1 study has been designed to investigate for the presence of factors influencing the prognosis of mRCC patients treated with first-line immuno-oncology combinations. In this subanalysis, we assessed the role of BMI in patients treated by first-line immuno-combinations. BMI >25 kg/m^2 was associated with

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improved OS in the overall study population. Otherwise, it was not prognostic in the subpopulations located at the extremes of the survival spectrum of mRCC, represented by patients with good risk IMDC criteria, brain metastases or sarcomatoid differentiation.

Host immune status is also crucial in mRCC patients, being associated with tumor response to therapy.[37] In a pancancer analysis, Yoo et al.[38] showed that the difference between BMI groups in terms of response rate was larger in patients with higher tumor mutational burden (TMB), with patients characterized by BMI < 25 showing the worst responses. Interestingly, high TMB has been correlated with inflammation and immune signatures in human cancers,[39] thus providing a potential explanation for our results, which show worst OCB in patients with BMI < 25 and concomitant NLR > 4 and in patients with BMI ≤ 25 treated by IO + IO, characterized by a +19% rates of patients with NLR > 4.

Our study presents several limitations, mainly due to its retrospective nature. A centralized review of radiological imaging was not performed. Furthermore, we had no available data on the concomitant medications or comorbidities that could affect the efficacy of first-line therapy. As a consequence, our results should be interpreted with caution and are in need of a larger prospective validation.

Nevertheless, our data clearly suggest that the correlation of BMI with both the prognosis and tumor response varies across clinicopathological mRCC subgroups. Further studies investigating the biological and immunological characteristics of mRCC patients stratified by BMI are warranted in order to clarify (and potentially modify) the mechanisms underlying these distinct clinical behaviours.

Clinical Practice Points

- Obesity has been associated with improved response to immunotherapy in cancer patients.
- In the current study, we investigated the role of Body Mass Index (BMI) in patients from the ARON-1 study (NCT05287464) treated by dual immuno-oncology agents (IO+IO) or a combination of immuno-oncology drug and a Tyrosine Kinase Inhibitors (TKI) as first-line therapy for metastatic Renal Cell Carcinoma (mRCC).
- Our study suggests that the prognostic significance and the association of BMI with treatment outcome may vary across clinicopathological mRCC subgroups.
- Further studies investigating the biological and immunological characteristics of mRCC patients stratified by BMI are warranted in order to clarify (and potentially modify) the mechanisms underlying these distinct clinical behaviors.

Credit Author Statement

Matteo Santoni, Francesco Massari: conceptualization, methodology, software, data curation, writing – original draft, visualization, investigation, validation. All authors: visualization, investigation, software, validation. **Camillo Porta:** visualization, investigation, software, validation, supervision.

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Disclosure

The authors have stated that they have no conflicts of interest.

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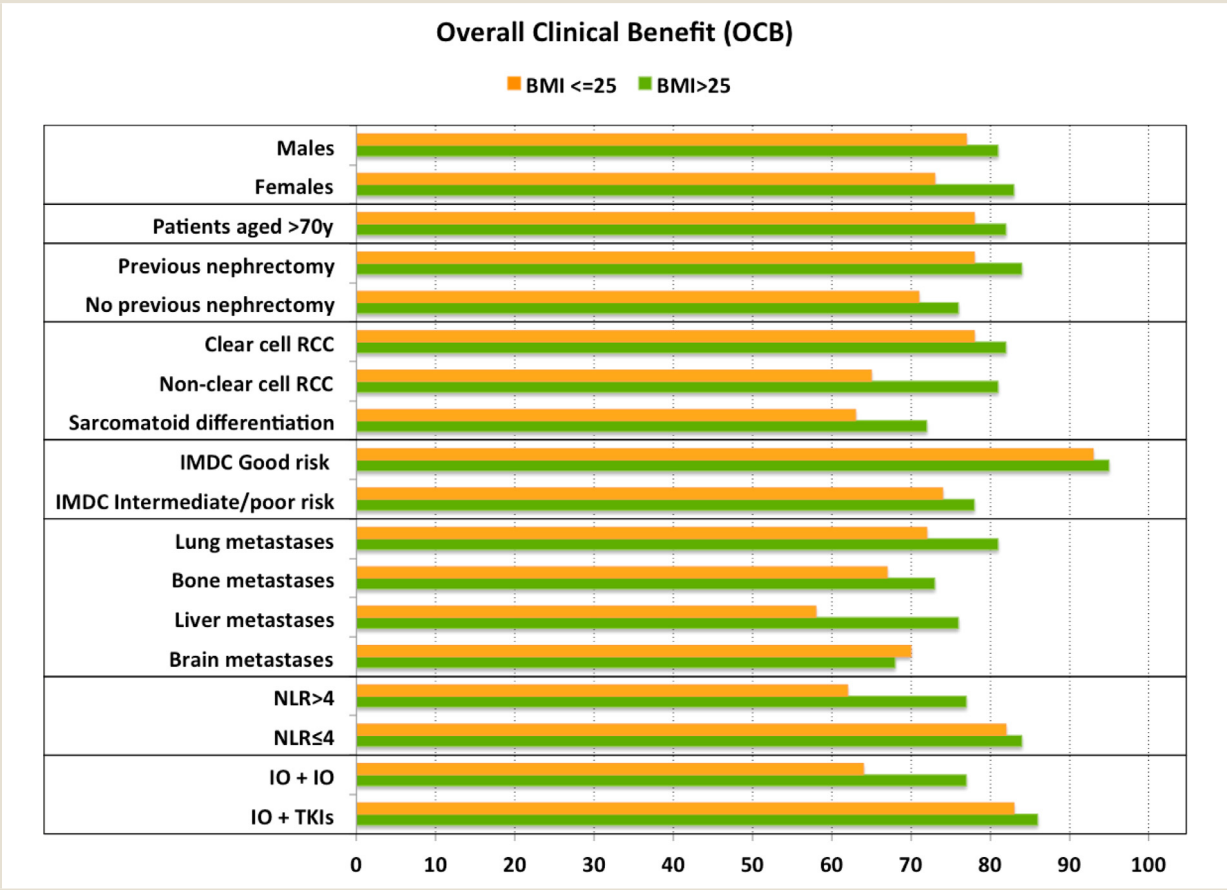
Clinico-Pathological Features Influencing the Prognostic Role

Supplementary material

Figure S1 Overall clinical benefit stratified by body mass index in different clinico-pathological RCC subpopulations.



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