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Impact of metformin, statin, aspirin and insulin on the prognosis of uHCC patients receiving first line Lenvatinib or Atezolizumab plus Bevacizumab

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Recently, in Hepatocellular carcinoma (HCC) setting, the use of metformin has been associated to a trend toward worse response rate, overall survival and progression free survival in patients who received immunotherapy. The study population included individuals from both Eastern and Western regions with a confirmed diagnosis of HCC and receiving first line treatment with Atezolizumab plus bevacizumab or Lenvatinib. Univariate and multivariate analyses were performed by Cox proportional. For the analysis, patients were stratified based on their use of concomitant medication or not. At the time of database lock, 319 deaths were observed: 209 in the Lenvatinib cohort, 110 in the Atezolizumab plus bevacizumab cohort. In the Atezolizumab plus Bevacizumab arm, 50 (16.5%) patients were on chronic metformin use. At the univariate analysis for OS, patients who used metformin showed significantly shorter OS compared to patients who did not use metformin (HR 1.9,

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95% CI 1.1–3.2). Multivariate analysis confirmed that patients in metformin group had significantly shorter OS compared to patients in no-metformin group (HR 1.9; 95% CI 1.1–3.1). At the univariate analysis for PFS, patients in metformin group had significantly shorter PFS compared to patients in no-metformin group (HR 1.6, 95% CI 1.0–2.6). Multivariate analysis confirmed that patients in metformin group had significantly shorter PFS compared to patients in no-metformin group (HR 1.7; 95% CI 1.1–2.7; *p* = 0.0147). No differences were reported in terms of ORR and DCR between patients in metformin group and those in no-metformin group. In the Lenvatinib cohort, 65 (15%) patients were recorded to chronically use metformin. No statistically significant differences in terms of both OS and PFS were found between patients in metformin group and patients in no-metformin group. This analysis unveils a negative prognostic role associated with metformin use specifically within the Atezolizumab plus Bevacizumab group.

Keywords Advanced HCC, Atezolizumab, Bevacizumab, Lenvatinib BMI

Hepatocellular Carcinoma (HCC) is currently a global health challenge and represents the sixth most common cancer and the third leading cause of cancer-related death worldwide[1]. Recently, immunotherapy has become an important part of the therapeutic armamentarium for advanced HCC. The combination of Atezolizumab and bevacizumab has been settled as the new first-line standard of care, along with Lenvatinib and Sorafenib, for patients affected by advanced HCC[2]. Furthermore, the dual immune checkpoint inhibitors blockade has been recently tested in the HIMALAYA trial, thus leading to positive results[3]. In all the aforementioned studies, no preplanned subgroup analyses highlighted different efficacy basing on clinical factors, including etiology. In recent years, a growing body of evidence has emerged that suggest that patients affected by advanced HCC arising from metabolic dysfunction related steatosis liver disease (MASLD) and metabolic dysfunction related steatohepatitis (MASH) may be less responsive to immunotherapy[4–7]. However, MASLD/MASH is considered a frequent manifestation of metabolic disease, and therefore several comorbidities need to be taken into account in the clinical decision-making process for these patients. Among others, diabetes is a frequent manifestation and metformin is one of the most commonly used drugs for this type of disease. Discordant evidences about the metformin's antineoplastic properties have been highlighted[8–10]. Recently, Kang and collaborators conducted a retrospective analysis on 111 patients affected by advanced HCC who received immune checkpoint inhibitors (ICIs) and demonstrated that the use of metformin was associated with a trend towards worse objective response rates (ORR), overall survival (OS), and progression-free survival (PFS), even without reaching statistical significance[11]. Building upon these findings, the aim of the present study was to investigate the potential prognostic role of metformin use and other concomitant medications (such as statins, insulin, and aspirin) in a cohort of advanced HCC patients who received Lenvatinib or Atezolizumab plus Bevacizumab as first-line treatment.

Methods

Patients and procedures

The study encompassed a diverse population drawn from both Eastern and Western regions, spanning Japan, Portugal, Germany, and Italy. Participants were required to have a confirmed diagnosis of hepatocellular carcinoma (HCC), validated either through histological examination or appropriate imaging studies, in accordance with international guidelines. These individuals were classified as being at stage B or C according to the Barcelona Clinic Liver Cancer (BCLC) staging system and were considered unsuitable candidates for loco-regional therapies.

Baseline characteristics were documented by each participating institution and subsequently verified through centralized review. Patients were assigned to receive either Atezolizumab plus Bevacizumab, administered from August 2018 to March 2023, or Lenvatinib, administered from November 2017 to April 2023, as their primary treatment. Lenvatinib dosing followed the protocol established by the REFLECT trial: patients received a daily oral dose of 12 mg if their baseline body weight was ≥ 60 kg or 8 mg if it was < 60 kg. Atezolizumab plus Bevacizumab treatment adhered to the regimen outlined in the IMbrave150 trial: patients received intravenous infusions of 1200 mg of atezolizumab alongside 15 mg/kg of body weight of bevacizumab every 3 weeks. Treatment response was evaluated using computed tomography or magnetic resonance imaging scans and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on local review, following modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1 guidelines. Patients continued treatment until either clinical benefit was observed as determined by the treating physician or until unacceptable toxicity occurred.

Adverse events (AEs) were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Management of AEs allowed for treatment interruptions and/or dose reductions as deemed necessary.

Ethical approval for the study was obtained from the respective Ethics Committees at each participating center, and the study was conducted in compliance with Good Clinical Practice guidelines, the Declaration of Helsinki, local laws, and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 concerning the protection of natural persons with regard to the processing of personal data. The protocol number assigned by the ethics committee was 113/INT/2021.

Statistical analysis

Demographic, clinical, and pathological characteristics of the patients were gathered and summarized utilizing descriptive statistics. Categorical variables underwent comparison via the Fisher exact test, while continuous variables were compared using the t-test. Survival curves for overall survival (OS) and progression-free survival (PFS) were generated using Kaplan–Meier estimates.

Univariate and multivariate analyses were conducted utilizing Cox proportional hazards models to examine potential associations between patients' baseline characteristics and survival outcomes (OS and PFS). Overall response and objective response rate were computed. Objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) and partial response (PR), while disease control rate (DCR) encompassed ORR plus the proportion of stable disease (SD).

For analysis purposes, patients were stratified based on their use of concomitant medication. In particular, patients were categorized into either the metformin group or the no-metformin group. Concomitant medication usage was determined at baseline before initiating first-line treatment. A significance level of $p < 0.05$ was considered statistically significant.

Statistical analysis was conducted using the MedCalc package (MedCalc® version 16.8.4).

Results

Study population

Overall, 730 consecutive patients with HCC met inclusion criteria and were included in the analysis. Among them, 430 (59%) patients received Lenvatinib and 300 (41%) patients received Atezolizumab plus Bevacizumab.

At the time of database lock, 319 deaths were observed: 209 in the Lenvatinib cohort, 110 in the Atezolizumab plus bevacizumab cohort. The median follow-up was 14.7 months (95% CI 12.4–51.1) for Atezolizumab plus Bevacizumab patients and 21.0 months (95% CI 18.4–55.3) for Lenvatinib patients. The two cohorts of patients were almost homogeneous, except for the proportion of patients with diabetes (42.5% in Lenvatinib cohort vs. 35% in Atezolizumab plus Bevacizumab cohort), BCLC B (45% in Lenvatinib cohort vs. 38% in Atezolizumab plus Bevacizumab cohort), portal vein's involvement (15.5% in Lenvatinib cohort vs. 26.5% in Atezolizumab plus Bevacizumab cohort), and NLR ≥ 3 (24% in Lenvatinib cohort vs. 14% in Atezolizumab plus Bevacizumab cohort).

The complete baseline characteristics in the two cohorts of patients are reported in Table 1.

Use of statins, aspirin, insulin and metformin and clinical outcome in Atezolizumab plus Bevacizumab group

In the Atezolizumab plus bevacizumab cohort, there were no statistically significant differences observed in overall survival (OS) and progression-free survival (PFS) between patients who chronically used statins, aspirin, or insulin compared to those who did not. Within the Atezolizumab plus bevacizumab arm, 50 (16.5%) patients were on chronic metformin therapy. Baseline characteristics were similar between patients in the metformin and no-metformin groups, except for etiology (viral etiology: 24% vs. 58%, $p = 0.000011$; MASH etiology: 50% vs. 18%, $p = 0.000005$; in the metformin and no-metformin groups, respectively), statin use (36% vs. 9% in metformin vs. no-metformin groups, $p = 0.000007$), aspirin use (26% vs. 12.5% in metformin vs. no-metformin groups, $p = 0.026006$), and insulin use (22% vs. 8.5% in metformin vs. no-metformin groups, $p = 0.009734$). Univariate analysis revealed that patients using metformin had significantly shorter OS [14.9 months (95% CI 6.4–16.3) vs. 19.7 (95% CI 16.0–30.4); HR 1.87 (95% CI 1.08–3.24) $p = 0.0248$] (Fig. 1A) and PFS [4.5 months (95% CI 2.9–14.2) vs. 5.8 (95% CI 4.1–34.0); HR 1.61 (95% CI 0.99–2.62) $p = 0.0212$] (Fig. 1B) compared to those not using metformin. Multivariate analysis confirmed that patients in the metformin group had significantly shorter OS (HR 1.79; 95% CI 1.10–3.12; $p = 0.035$) (Table 2) and PFS (HR 1.78; 95% CI 1.13–2.77; $p = 0.014$) (Table 3) compared to those in the no-metformin group. To exclude the bias of diabetes, it is included in the multivariate analysis.

There were no differences in terms of objective response rate (ORR) and disease control rate (DCR) between the metformin and no-metformin groups ($p = 0.722399$ and $p = 0.866298$, respectively). Additionally, no significant differences in adverse events were detected between the two groups (Supplementary table).

Use of statins, aspirin, insulin and metformin and clinical outcome in Lenvatinib group

In the Lenvatinib group of patients, no statistically significant differences in terms of both OS and PFS were observed in patients who were on chronic use of statins, aspirin, or insulin compared to those who were not.

In the Lenvatinib cohort, 65 (15%) patients were recorded to chronically use metformin.

At the univariate analysis, no statistically significant differences in terms of OS were found between patients in metformin group and patients in no-metformin group [respectively, 16.6 months (95% CI 14.8–51.3) vs. 19.5 (95% CI 15.1–36.2); HR 1.2 (95% CI 0.8–1.8) p = 0.3164] (Table 4).

The multivariate analysis confirmed that the use of metformin was not a prognostic factor for OS in the cohort of patients who received Lenvatinib (Table 4).

At the univariate analysis, no statistically significant differences in terms of PFS were found between patients in metformin group and patients in no-metformin group [respectively, 4.7 months (95% CI 3.7–24.2) vs. 4.4 months (95% CI 3.8–41.8); HR 1.0 (95% CI 0.8–1.4) $p = 0.8542$] (Table 5).

The multivariate analysis confirmed that the use of metformin was not a prognostic factor for PFS in the cohort of patients who received Lenvatinib (Table 5).

No differences were reported in terms of ORR and DCR between patients in metformin group and those in no-metformin group ($p = 0.661410$ and $p = 0.669873$, respectively) (Supplementary table).

	Lenvatinib (n = 430)	Atezolizumab plus bevacizumab (n = 300)	*P*
Sex			
Male	358 (83)	233 (78)	0.068537
Female	72 (17)	67 (22)	
Viral			
Y	249 (58)	157 (52.5)	0.129097
N	178 (41)	142 (47)	
Na	3 (1)	1 (0.5)	
Nash			
Y	121 (28)	69 (23)	0.122745
N	305 (70.5)	229 (76)	
Na	4 (1.5)	2 (1)	
Diabetes			
Y	182 (42.5)	105 (35)	0.045443
N	246 (57)	194 (64.5)	
Na	2 (0.5)	1 (0.5)	
Metformin			
Y	65 (15)	50 (16.5)	0.606169
N	363 (84.5)	249 (83)	
Na	2 (0.5)	1 (0.5)	
Statin			
Y	37 (8.5)	41 (13.5)	1.000000
N	227 (53)	258 (86)	
Na	166 (38.5)	1 (0.5)	
Aspirin			
Y	47 (11)	45 (15)	0.425474
N	219 (51)	254 (84.5)	
Na	164 (38)	1 (0.5)	
Insulin			
Y	29 (7)	32 (10.5)	1.000000
N	237 (55)	267 (89)	
Na	164 (38)	1 (0.5)	
Child			
A	387 (90)	266 (88.5)	0.274485
B	31 (7)	29 (9.5)	
Na	12 (3)	5 (2)	
BCLC			
B	193 (45)	115 (38)	0.047178
C	227 (53)	184 (61.5)	
Na	10 (2)	1 (0.5)	
ECOG			
0	328 (76.5)	221 (73.5)	0.482295
> 0	100 (23)	77 (25.5)	
Na	2 (0.5)	2 (1)	
PVT			
Y	66 (15.5)	80 (26.5)	0.000050
N	319 (74)	177 (59)	
Na	45 (10.5)	43 (14.5)	
AFP			
> 400	117 (27.5)	93 (31)	0.241967
≤ 400	303 (70.5)	197 (65.5)	
Na	10 (2)	10 (3.5)	
NLR			
≥ 3	102 (24)	43 (14)	0.035902
< 3	249 (58)	163 (54.5)	
Na	79 (18)	94 (31.5)	
Albumin			
Continued			

	Lenvatinib (n = 430)	Atezolizumab plus bevacizumab (n = 300)	*P*
≤ 3.5	139 (32)	83 (27.5)	0.187623
> 3.5	276 (64.5)	208 (69.5)	
Na	15 (3.5)	9 (3)	
Bilirubin			
> 2	38 (9)	19 (6)	0.208849
≤ 2	374 (87)	274 (91.5)	
Na	18 (4)	7 (2.5)	
EHD			
Y	164 (38)	102 (34)	0.274458
N	265 (61.5)	196 (65)	
Na	1 (0.5)	2 (1)	

Table 1. Baseline patients' characteristics in the two cohorts (Lenvatinib and Atezolizumab plus Bevacizumanb).

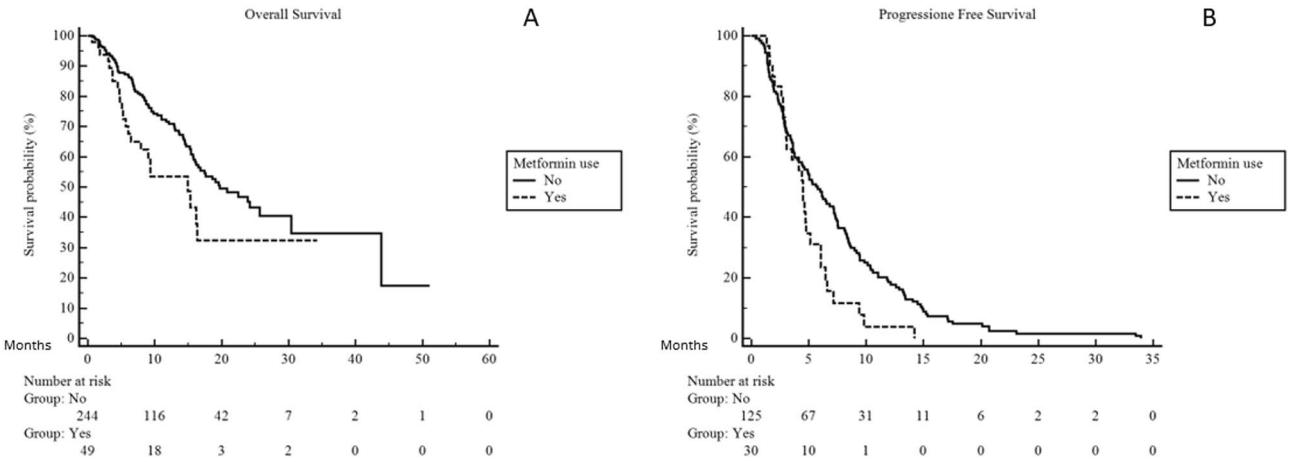

Fig. 1. Kaplan Meier curves for OS (**A**) and PFS (**B**) in Metformin and no-Metformin groups of patients treated with Atezolizumab plus bevacizumab.

Discussion

This analysis has highlighted, for the first time, the use of metformin as a negative prognostic factor in a cohort of patients who received atezolizumab plus bevacizumab for advanced HCC. Conversely, the utilization of metformin was found to have no prognostic impact in a cohort of patients with advanced HCC who received Lenvatinib as a first-line treatment. Recently, Kang and colleagues performed an analysis on a cohort of patients treated with immunotherapy for advanced HCC and highlighted worse survival outcomes in patients included in the metformin group compared to those in the no-metformin groups, even without reaching the statistical significance[11]. Our study encompassed a larger patient sample receiving first-line treatment for advanced HCC (Atezolizumab plus Bevacizumab or Lenvatinib), whereas the previous study focused exclusively on patients who received immunotherapy in either the first or subsequent lines of treatment. However, our findings provide substantial support, based on a larger patient cohort, to the notion that individuals receiving immunotherapy for advanced HCC and using metformin as a chronic medication exhibit inferior survival outcomes when compared to those not taking metformin chronically. Preclinical evidence provides a biological rationale for the anticancer properties of metformin. Metformin has been demonstrated to improve the restoring of CD8 + tumor infiltrating lymphocytes (TILs) from immune exhaustion[12]and to reduce hypoxic status in tumor microenvironment and improve intra-tumoral T cell function[13]. In addition, metformin could inhibit the differentiation of naïve CD4 + T cells into regulatory T cells (Tregs), thus blocking the activation of myeloid-derived suppressor cells

Variables	Univariate analysis			Multivariate analysis		
	Hr	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.37	0.86–2.19	0.1846	1.38	0.87–2.13	0.23
Male	1			1		
Viral						
N	1.23	0.84–1.80	0.2805			
Y	1					
Nash						
Y	1.23	0.78–1.95	0.3744	1.19	0.71–1.94	0.64
N	1			1		
Diabetes						
Y	1.39	0.93–2.09	0.1100	1.21	0.88–2.15	0.33
N	1			1		
Metformin						
Y	1.87	1.08–3.24	0.0248	1.79	1.10–3.12	0.035
N	1			1		
Statin						
Y	1.03	0.59–1.80	0.9057			
N	1					
Aspirin						
N	1.02	0.60–1.71	0.9541			
Y	1					
Insulin						
Y	1.49	0.78–2.83	0.2274			
N	1					
Child						
B	3.49	1.57–7.76	0.0021	2.13	1.11–3.73	0.02
A	1			1		
BCLC						
C	1.28	0.88–1.88	0.1975			
B	1					
ECOG						
0	1.08	0.68–1.71	0.7321			
> 0	1					
Portal vein thrombosis						
Y	1.63	1.03–2.60	0.0371			
N	1					
AFP						
> 400	1.53	1.00–2.34	0.0495	1.25	0.84–1.91	0.39
≤ 400	1			1		
NLR						
≥ 3	1.46	0.75–2.84	0.2134			
< 3	1					
Albumin						
≤ 3.5	3.49	2.19–5.56	< 0.0001			
> 3.5	1					
Continued						

Variables	Univariate analysis			Multivariate analysis		
	Hr	95% CI	P value	HR	95% CI	P value
Bilirubin						
>2	2.22	0.87–5.69	0.0971			
≤2	1					
ALT						
>30	2.00	1.37–2.92	0.0003	1.56	0.90–2.14	0.12
≤30	1			1		
AST						
>2	2.59	1.70–	<0.0001	2.12	1.14–	0.009
≤288	1	3.95		1	3.56	
Extra hepatic disease						
Y	1.22	0.82–1.82	0.3215			
N	1					

Table 2. Uni and multi-variate analysis for OS in the cohort of patients treated with Atezolizumab plus bevacizumab.

(MDSCs) and reverting the M2-like polarization of tumor associated macrophages (TAMs)[14]. These evidence seems to suggest that the combination of immunotherapy and metformin could act in synergism and potentially enhancing the anticancer response. In the field of HCC, additional factors contribute to shaping the overall scenario. Unlike other oncologic diseases, HCC develops within the context of hepatopathy, which can have various underlying etiologies. These different etiologies have been shown to exert distinct effects on the immune microenvironment, resulting in diverse carcinogenic pathways[4–7]. In addition both preclinical and retrospective clinical data support the hypothesis that patients with MASH-related HCC could be less responsive to immune checkpoint inhibitors[7]. Wabitsch and colleagues recently confirmed that patients with MASH-related HCC are less responsive to immunotherapy, due to aberrant activation and exhaustion of CD8 + T cells[15]. In the same work, authors demonstrated that metformin treatment restores the motility and metabolism of CD8 + T cells, thus enhancing the anti-tumor immune responses[15], which is inconsistent with the present analysis. As expected, in our analysis the proportion of MASH-related HCC in the metformin-group of patients is higher, which could have influenced the results reported. Nevertheless, after correction for etiology, the multivariate analysis confirmed the negative prognostic factor of the chronic use of metformin in the cohort of patients who received Atezolizumab plus Bevacizumab. Several further speculations on the negative prognostic impact of the chronic use of metformin could be done. First of all, a possible explanation could be based on the changes in gut microbiota induced by metformin. Indeed, previous, extensive researches underscored the critical role of gut microbiota in the efficacy of ICIs in several oncologic settings. More specifically, strong evidence indicates that metformin exposure significantly interferes with human intestinal microbiota and gut metabolome, even if the specific mechanisms are not completely highlighted yet[16–19].

Another consideration is that metformin has been shown to negatively modulate the immune system by increasing the peripheral proportions of CD4 + and CD8 + regulatory T cells while decreasing CD4 + T helper cell 17 levels[20]. In the context of ICI immunotherapy, metformin may unintentionally dampen the desired anti-tumor immune response elicited by ICIs. Therefore, this interaction could potentially contribute to poorer outcomes in patients using metformin concurrently with ICIs.

Additionally, studies suggest that metformin may have proangiogenic effects in hypoxic conditions[21]. It is also important to note that, in diabetic contexts, metformin has been reported to enhance the angiogenic function of endothelial progenitor cells[22]. This dual role of metformin introduces the possibility that its proangiogenic effect might contribute to the adverse association between metformin use and less favorable prognoses in patients undergoing ICI therapy. However, further research is needed to confirm this speculative link. Finally, we have to consider that it is convincible that the underlying diabetes's biological mechanisms could have contributed

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* Value
Sex						
Female	1,04	0.70–1.56	0.8376	0.92	0.57–1.62	0.84
Male	1			1		
Viral						
N	1.06	0.77–1.46	0.7150			
Y	1					
Nash						
Y	1.03	0.70–1.52	0.8750			
N	1					
Diabetes						
Y	1.20	0.85–1.70	0.2867	1.29	0.82–1.83	0.33
N	1			1		
Metformin						
Y	1.61	0.99–2.62	0.0212	1.78	1.13–2.77	0.014
N	1			1		
Statin						
Y	1.32	0.76–2.28	0.2686			
N	1					
Aspirin						
N	1.36	0.79–2.35	0.2036			
Y	1					
Insulin						
Y	1.12	0.63–1.99	0.6912			
N	1					
Child						
B	1.93	0.91–4.12	0.0210	1.93	1.05–3.14	0.018
A	1			1		
BCLC						
C	1.22	0.88–1.69	0.2378			
B	1					
ECOG						
> 0	1.05	0.73–1.52	0.7848			
0	1					
Portal vein thrombosis						
Y	1.12	0.77–1.64	0.5345			
N	1					
AFP						
> 400	1.45	1.01–2.09	0.0295	1.67	0.97–2.14	0.06
≤ 400	1					
NLR						
≥ 3	1.36	0.82–2.28	0.2067			
< 3	1					
Albumin						
≤ 3.5	1.48	1.00–2.20	0.0301			
> 3.5	1					
Continued						

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* Value
Bilirubin						
> 2	3.89	1.10–13.85	< 0.0001			
≤ 2	1					
ALT						
> 30	1.17	0.85–1.61	0.3403			
≤ 30	1					
AST						
> 28	1.02	0.70–1.50	0.9050			
≤ 28	1					
Extra hepatic disease						
Y	1.22	0.86–1.74	0.2400			
N	1					

Table 3. Uni and multi-variate analysis for PFS in the cohort of patients treated with Atezolizumab plus bevacizumab.

to the survival outcomes, which constitutes a bias difficult to eliminate, since deeper investigations focused on that are needed in order to clarify the complex link between HCC, immune response to immune checkpoint inhibitors, diabetes and chronic use of metformin.

Concerning the absence of prognostic impact of metformin use in patients who received Lenvatinib, several considerations could be done. In a previous work, the concomitant use of metformin and sorafenib was associated with worse OS and PFS in a cohort of patients affected by advanced HCC, due to a competitive action on PI3K and MAPK signaling exerted by metformin, which leads to the development of resistance to sorafenib[23,24]. Although belonging to the same class of drugs, Lenvatinib and Sorafenib present different target spectra, which could explain the varying results when combined with metformin. In a recent work, Chen and colleagues showed that Lenvatinib and Metformin both suppress the activation of AKT signaling pathway thus leading to the nuclear aggregation of downstream effector FOXO3. Finally, interactions between metformin and oncologic treatments depend also to the timing, since the pathways and, consequently, the biological behavior of an HCC arising in a

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Sex						
Female	1,21	0.81–1.80	0.3448	1.48	0.96–2.28	0.0793
Male						
Viral						
Y	1.24	0.94–1.64	0.1262			
N						
Nash						
N	1.12	0.82–1.53	0.4860			
Y						
Diabetes						
N	1.20	0.91–1.58	0.2030			
Y						
Metformin						
N	1.21	0.83–1.76	0.3164			
Y						
Statin						
N	1.15	0.71–1.87	0.5602			
Y						
Aspirin						
N	1.02	0.60–1.71	0.9541			
Y						
Insulin						
Y	1.59	0.86–2.94	0.1359			
N						
Child						
B	8.76	4.27–17.98	< 0.0001	3.50	1.97–6.24	< 0.0001
A						
BCLC						
C	1.60	1.21–2.11	0.0009			
B						
ECOG						
> 0	1.73	1.22–2.44	0.0019	1.58	1.07–2.34	0.0218
0						
Portal vein thrombosis						
Y	1.36	0.91–2.05	0.1000			
N						
AFP						
> 400	3.07	2.16–4.36	< 0.0001	2.28	1.59–3.27	< 0.0001
≤ 400						
NLR						
≥ 3	1.54	1.07–2.21	0.0099	1.68	1.19–2.37	0.0034
< 3						
Continued						

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Albumin						
≤ 3.5	2.29	1.67–3.14	< 0.0001			
> 3.5						
Bilirubin						
> 2	1.43	0.89–2.30	0.1375			
≤ 2						
ALT						
> 22	1.70	1.27–2.26	0.0003	0.73	0.49–1.08	0.1148
≤ 22						
AST						
> 56	3.54	2.45–5.12	< 0.0001	1.70	1.16–2.50	0.0071
≤ 56						
Extra hepatic disease						
Y	1.53	1.14–2.04	0.0041			
N						

Table 4. Uni and multi-variate analysis for OS in the cohort of patients treated with Lenvatinib.

patient already treated with metformin is different from that of an HCC arising in a patient who, at some point, undergoes treatment with metformin.

The present study has several limitations, primarily stemming from its retrospective and multicenter nature. Selection bias among patients cannot be entirely ruled out, and it's important to consider the absence of centralized imaging review for the evaluation of PFS. Finally, data about doses and schedule of use of metformin as well as data on concomitant medications for diabetes and cardiovascular comorbidity were unavailable, due to the large retrospective and multicentric design of the study. Thus, bias related to the prognostic incidence of diabetes as well as other cardiovascular disease has not been included in the analysis, which means that come biases could not be completely excluded. Further investigations and prospective validations on external cohort are needed in order to verify our results. Nevertheless the present study represents the first analysis focusing on the role of metformin in a large cohort of patients with advanced HCC, who underwent first-line therapy with either Lenvatinib or Atezolizumab plus Bevacizumab. This analysis unveils a negative prognostic role associated with metformin use specifically within the Atezolizumab plus Bevacizumab group. Our findings corroborated in a larger sample size the earlier study by Kang and colleagues adding a crucial piece to the complex puzzle of the interaction between metformin and immunotherapy for patients dealing with advanced HCC.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex						
Female	1.77	1.17–2.68	0.0006	1.75	1.24–2.47	0.0015
Male						
Viral						
Y	1.12	0.89–1.43	0.3410			
N						
Nash						
N	1.13	0.87–1.45	0.3685			
Y						
Diabetes						
N	1.12	0.88–1.42	0.3423			
Y						
Metformin						
N	1.03	0.76–1.39	0.8542			
Y						
Statin						
N	1.26	0.81–1.95	0.3536			
Y						
Aspirin						
Y	1.36	0.84–2.19	0.1605			
N						
Insulin						
Y	1.60	0.90–2.87	0.0518			
N						
Child						
B	1.95	1.09–3.50	0.0021	1.87	1.19–2.93	0.0068
A						
BCLC						
C	1.07	0.84–1.35	0.5966			
B						
Ecog						
> 0	1.08	0.82–1.43	0.5886			
0						
Portal vein thrombosis						
Y	1.06	0.76–1.49	0.7159			
N						
AFP						
> 400	1.63	1.22–2.18	0.0002	1.56	1.19–2.04	0.0013
≤ 400						
NLR						
≥ 3	1.28	0.97–1.69	0.0619			
< 3						
Albumin						
≤ 3.5	1.43	1.10–1.87	0.0044			
> 3.5						
Bilirubin						
> 2	1.04	0.71–1.53	0.8226			
≤ 2						
ALT						
> 22	1.00	0.78–1.29	0.9873			
≤ 22						
AST						
> 56	1.22	0.92–1.16	0.1382			
≤ 56						
Extra hepatic disease						
Continued						

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Y	1.09	0.85–1.38	0.4946			
N						
HFSR						
N	1.42	1.05–1.91	0.0219	0.83	0.62–1.11	0.2031
Y						
Hypertension						
N	1.41	1.10–1.82	0.0122	0.86	0.67–1.10	0.2337
Y						
Fatigue						
Y	1.04	0.83–1.32	0.7242			
N						
Diarrhea						
N	1.39	1.05–1.84	0.0386			
Y						
Decrease appetite						
N	1.02	0.81–1.29	0.8373			
Y						
Proteinuria						
N	1.00	0.77–1.31	0.9715			
Y						

Table 5. Uni and multi-variate analysis for PFS in the cohort of patients treated with Lenvatinib.

Data availability

Data available on request from the authors (contact: margherita.rimini@gmail.com).

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Competing interests

The authors declare no competing interests.

Institutional review board and informed consent

The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent for treatment was obtained for all patients.

Additional information

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