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Efficacy of Combined Bevacizumab and Angiotensin-Converting Enzyme Inhibitors or Angiotensin II type 1 Receptor Blockers in Metastatic Colorectal Cancer Patients

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Abstract
Background: Bevacizumab, used in the treatment of metastatic colorectal cancer (mCRC), has an angiogenesis inhibitory effect. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARBs) used in the treatment of arterial hypertension demonstrate antitumoural effects through different pathways. In our study, we aimed to investigate whether ACEi or ARB has a synergistic effect on survival in patients receiving bevacizumab treatment.
Method: A total of 208 patients receiving Bevacizumab for mCRC were included in this retrospective study. We divided the patients into two groups as Renin Angiotensin System inhibitors (RASi) users and non-users. We compared the progressin-free survival (PFS) and overall survival (OS) times between the 2 groups. Kaplan-Meier and Cox regression analyses were used for statistical analyses.
Results: In this study, 53 patients with RASIs and 155 without RASIs were included. The RASIs group had a median PFS of 8.66 months, while the non-RASIs group had a median of 6.67 months ($P = 0.034$; $P < 0.05$). The RASIs group had a median OS of 24.86 months, while the non-RASIs group had a 18.71 months ($P = 0.039$; $P < 0.05$). In the RASIs group, multivariate analysis showed PFS [Hazard Ratio (HR): 1.425 (95% Confidence Interval (CI): 1.037-1.959), $P = 0.029$] and OS [HR: 1.371 (95% CI: 1.001-1.897), $P = 0.044$].
Conclusion: Bevacizumab in combination with ACEi or ARBs prolongs PFS and OS in patients with mCRC. Prioritising ACEi and ARBs in patients with mCRC and arterial hypertension provides a survival advantage. These findings should be supported through further studies involving larger patient populations and addressing other factors that may affect prognosis.

Keywords: Colorectal neoplasms, Bevacizumab, Angiotensin-converting enzyme inhibitors, Angiotensin II type 1 receptor blockers

Introduction

Colorectal cancer is the third most common cancer in the world. It ranks second in cancer-related deaths.[1] While the mean 5-year survival in non-metastatic local disease is 91%, the mean 5-year survival in patients with distant metastasis is around 13%.[2] These low 5-year survival rates in colorectal cancer patients with distant metastasis have led to new treatment requirements over the years. In addition to classical chemotherapy agents, Bevacizumab, one of the monoclonal antibody anti-vascular endothelial growth factor (VEGF) agents, is used in metastatic stage colorectal cancer due to its negative effects on tumour angiogenesis.

While the prevalence of arterial hypertension is 32-34% worldwide, it is similarly estimated to be between 30 and 35% in Turkey.[3-4] Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARBs) are safely used in antihypertensive treatment.[5] ACEi and ARBs are known to have antitumoural effects through inhibition of the renin-angiotensin system. These effects are thought to be mediated by preventing neoangiogenesis, decreasing epidermal growth factor level and increasing apoptosis.[6-7]

While ARBs only block angiotensin II type1 (AT1R) receptor, ACEi act through type1 (AT1R) and type2 (AT2R) receptors by decreasing angiotensin II synthesis.[8] It is known that blocking two different receptors separately has antitumoural effects.[9-10]

There are many diseases that have been successfully treated with the synergistic effect obtained by the combination of drugs. The anti-angiogenetic properties of bevacizumab and ACEi/ARBs are known. However, there are not enough studies investigating the synergistic effects of anti-VEGFs and ACEi/ARBs in hypotensive patients with metastatic colorectal cancer (mCRC).

Therefore, we aimed to investigate the effect of the relationship between these drugs on treatment response in patients with arterial hypertension who were prescribed ACEi or ARBs, diagnosed with mCRC, and received bevacizumab for treatment.

Methods

This retrospective study included patients who received treatment in the Medical Oncology Clinic of Marmara University Pendik Training and Research Hospital between 01.01.2012 and 31.12.2022 and were diagnosed with colorectal carcinoma by histopathological examination. The data of the patients were recorded retrospectively using patient files and hospital electronic information system.

Patients were divided into two groups of 65+ years old and less than 65 years old. The cecum, ascending colon and transverse colon were grouped as right side and descending colon, sigmoid colon and rectum were grouped as left side. Patients with radiological distant metastasis at the time of diagnosis were grouped as denovo metastatic. Patients without Kirsten Rat Sarcoma/Neuroblastoma Rat Sarcoma (KRAS/NRAS) or v-raf murine sarcoma viral oncogene homolog B (BRAF) mutation were classified as wild type and those with mutation were classified as non-wild type. The performance scores of the patients were calculated using the Eastern Cooperative Oncology Group Performance Score (ECOG PS). Patients were divided into two groups of ECOG PS of 0-1 and ECOG PS of 2. Treatment responses of the patients were evaluated as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) according to Response Evaluation Criteria in Solid Tumours (RESIST) version 1.1. Objective response rate (ORR) was found as the sum of CR and PR.

Progression-free survival (PFS) was calculated as the time in months from the patient's first treatment dose to disease progression or the day of the last visit if the patient was still receiving treatment. If the patient died while on treatment, the last date was considered as the date of death. Overall survival (OS) was calculated as the time in

months from the first treatment dose until the date of death or until the date of the last visit if the patient was still alive.

Bevacizumab treatment was administered in combination with cytotoxic chemotherapy regimens at doses of 5mg/kg in 14-day regimens and 7.5mg/kg in 21-day regimens. These regimens were 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) capecitabine, oxaliplatin (CapeOX), 5-fluorouracil, leucovorin (FUFA), single agent capecitabine, single agent Irinotecan. In the first series of Wild type mCRCs involving the left colon, cetuximab or panitumumab was preferred in combination with cytotoxic chemotherapies in the absence of any contraindication. When progression developed under treatment, we switched to bevacizumab treatment with different cytotoxic chemotherapy. In these patients, PFS and OS were calculated from the date of initiation of bevacizumab. In patients with CR, PR or SD treatment response under bevacizumab, bevacizumab was administered as maintenance therapy with capacitabine or FUFA according to the first treatment until progression.

ACEi and ARB group drugs were categorized as Renin Angiotensin System inhibitors (RASIs). Patients were divided into two groups as RASIs users (RASIs) and non-users (non-RASIs). OS and PFS were compared between the two groups.

SPSS version 22.0 (IBM corp.) was used for all statistics. Categorical variables were calculated using chi-square. Survival curves were obtained using the Kaplan-Meier method. 95% confidence intervals (CI) were calculated using the Brookmeyer and Crowley method and survival differences between groups were compared using the log-rank test. Univariate analysis was used to examine the prognostic significance of any factor. Prognostic factors with *P*-value <0.5 in univariate analysis were analysed in multivariate analysis. Hazard ratios (HRs) for these comparisons were calculated using a Cox proportional hazards model. $P < 0.05$ was considered statistically significant.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Marmara University School of Medicine, İstanbul, Turkiye, number: 03.11.23.1456.

Results

A total number of 1422 patients with colorectal carcinoma diagnosed by histopathological methods were screened. In this study, 409 patients were accepted as metastatic disease confirmed by imaging methods. Bevacizumab was used in 324 patients. 71 patients had missing data. 15 patients were excluded because they used Bevacizumab for less than 3 months. 13 patients were excluded because they were referred to surgery and did not receive bevacizumab treatment after surgery. Nine patients were not included in the study: 2 patients refused treatment voluntarily; 1 patient had enteroentero fistula; 1 patient had enterocutaneous fistula; 2 patients had pulmonary embolism; 2 patients had intestinal obstruction; 1 patient had bleeding from the stoma. Five patients were excluded from the study because they began taking ACE or ARB to manage high blood pressure, while three patients started these medications for proteinuria. Additionally, two patients were not included in the study as they died from non-cancer related reasons.

A total number of 208 patients were included in the study: 86 patients had a diagnosis of hypertension; 39 patients were using ACEi and 14 patients were using ARB. Fifty-three patients using ACEi or ARB were divided into two groups of RASIs and 155 patients not using ACEi or ARB were divided into two groups of non-RASIs. The characteristics of the patients and tumours according to the groups are summarised in table 1.

Patients were 22-85 years old. The mean age of the patients was 60.01 years. The RASIs group had a greater mean age (64.3

vs 58.5). In this study, 126 cases were male and 82 were female. The ECOG PS was 0 or 1 in 199 patients and 2 in 9. In 56 cases, the tumour was on the right and in 152, on the left. During diagnosis, 121 patients had distant metastases; during follow-up, 87 did. Totally, 81 were wild type, without KRAS, NRAS, or BRAF mutations. Also, 116 patients had mutated KRAS, NRAS, or BRAF. Mismatch repair (MMR) status showed 179 individuals with microsatellite stability (MSS) and 8 with instability.

Patients' responses to Bevacizumab and cytotoxic chemotherapy are summarised in table 2. In the non-RASIs group, 53 ORRs were obtained, including 3 CRs and 50 PRs. In the RASIs group, 25 ORRs were obtained, 2 of which were CR and 23 of which were PR.

The median PFS was 8.66 (%95CI 6.71-10.57) months in the RASIs group and 6.67 (%95CI 5.90-7.61) months in the non-RASIs group. There was a statistically significant difference between the PFS of the two groups (P = 0.034; P < 0.05). Median OS in the RASIs group was 24.86 (%95CI 19.49-30.25) months, while median OS in the non-RASIs group was 18.71 (%95CI 16.26-21.17) months (Table 3). There was a statistically significant difference between OSs of the two groups (P = 0.039; P < 0.05). In the whole group, median PFS and OS were 7.24 (%95CI 1.36-13.2) and 20.28 (%95CI 3.51-37.05) months, respectively. Kaplan-Meier curves showed the PFS and OS of the groups (Figures 1 and 2).

Prognostic factors of the patients were analysed by univariate and multivariate analysis (tables 4 and 5). In univariate analysis, median PFS was 8.66 months [HR: 1.368, (95% CI: 0.997-1.876), P = 0.052)] and OS was 24.86 months [HR: 1.378, (95% CI: 1.006-1.889), P = 0.046)] in RASIs group. In multivariate analysis, PFS [HR: 1.425, (95% CI: 1.037-1.959), P = 0.029)], OS [HR: 1.371, (95% CI: 1.001-1.897), P = 0.044)] were detected in RASIs group. In univariate analysis, PFS was 8.26 months [HR: 0.713, (95% CI 0.539-0.942), P = 0.018] and OS was 20.52 months [HR: 1.012, (95% CI: 0.767-1.336), P = 0.932] in the non-wild type group. In multivariate analysis, PFS [HR:0.708, (95% CI 0.534-0.940), P = 0.017], OS [HR:1.070, (95% CI:0.801-1.430), P = 0.646] were detected in the non-wild type group.

Discussion

In our investigation focusing on prognosis of mCRC patients, the multivariate analyses unveiled pivotal insights into prognostic factors for PFS and OS. Notably, RASIs exhibit a statistically significant influence on both PFS and OS, highlighting the potential interplay between these cardiovascular medications and cancer outcomes. ECOG score and RAS/RAF status also emerge as candidate prognostic factors, although statistical significance was not reached in this specific analysis. The suppression of RAS using ACEi or ARB might contribute to potential antitumoural effects of bevacizumab. These findings signify the importance of RASIs in the context of mCRC management, offering a tailored perspective for clinicians when making informed decisions for patients concurrently using ACEIs or ARBs.

The incidence of colorectal cancer and arterial hypertension increases with ageing.[4,11] In addition, bevacizumab frequently causes hypertension.[12] Thus, the possibility of arterial hypertension is increased in the colorectal cancer patient population receiving bevacizumab. In these patients, preference of ACEi and ARB should be considered as a priority since they provide survival advantage in addition to antihypertensive effect.

The relationship between the RAS system and cancer has been investigated in previous years. In many studies, inhibition of RAS in different cancer types has provided favourable effects on cancer prognosis. [13-16] In our study, RAS inhibition increased survival and our study supports these data.

In the study conducted by Moriyama et al. in patients receiving anti-VEGF therapy

regardless of cancer type, those receiving RASi and those not receiving RASi were compared and no significant difference was found between the two groups.[17] In our study, only patients with metatatic colorectal carcinoma were included, and the use of ACEi or ARB with Bevacizumab, an anti-VEGF, was found to be significant in terms of survival.

In the study by Osumi et al., patients who used angiotensin II type 1 receptor blockers (ARB) and bevacizumab only in first and second line treatment in patients with mCRC were analysed and PFS and OS of patients who used bevacizumab with ARB were found to be longer than those who used bevacizumab only.[18] In our study, patients using ACEi and ARBs were evaluated together, and patients who received bevacizumab in all series were included in the study regardless of the order of treatment. In our study, PFS and OS were found to be longer in the RASi group. In this respect, our study may be an example for more patient groups.

In our study, PFS was longer in the non-Wild type while OS was similar (PFS 8.26 vs 6.22 months, OS 20.52 vs 19.62 months). The reason for this is that in our centre, panitumub or cetuximab is used in the first series in patients with wild type tumours located in the left colon and cetuximab treatment is switched to bevacizumab in the following series in the presence of progression.

The side-effect profile of bevacizumab treatment has been described in many studies. The most common side effects include hypertension, proteinuria, thromboembolic events, gastrointestinal system perforations and bleeding. [19-20] In our study, grade 3-4 hypertension was observed in 5 patients, grade 3-4 proteinuria in 3 patients, enteric fistula in 2 patients, intestinal obstruction in 2 patients, pulmonary embolism in 2 patients and bleeding in 1 patient. In terms of complications, complications were observed in our patient population at rates similar to the literature.

The present study had certain limitations. As a retrospective study, we could not include all patients due to missing data, which resulted in a smaller patient group. Due to missing data entries, we could not record other events that may affect the prognosis and treatment-related side effects (especially grade 1-2) in detail. Despite the limitations, this study includes the largest number of patients with mCRC.

Conclusion

According to our results, the use of ACEi/ARB in combination with Bevacizumab therapy has a favourable effect on survival in patients with mCRC. Studies involving larger patient populations and addressing other factors that may affect prognosis are needed to support these findings.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author.

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Authors' Contribution

AK.G: Study design, data gathering, drafting and reviewing the manuscript; N.M: Study design, reviewing the manuscript; İ.Ç, N.S, E.K, and P.E: Data gathering, drafting;Y.A: Study design, Data gathering, reviewing; AÇ adn R.A: Study design, reviewing the manuscript; S.I: Data gathering, drafting; M.S: Study design, reviewing the manuscript; ÖE: Data gathering, drafting; İV.B:Study design, reviewing the manuscript; O.K:Study design, reviewing the manuscript.

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

None declared.

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Table 1. Basic characteristics of patients and tumours (non-RASIs group: Patients not using ACEi and ARBs, RASIs group: Patients using ACEi and ARBs)

	Non-RASIs (n=155)	**RASIs (n=53)**	**Total (n=208)**	***P***
Age (Range)	58.5(22-82)	64.3(48-85)	60.01(22-85)	0.003
Gender (%)				
Male	97 (62.6)	29 (54.7)	126 (60.5)	0.061
Female	58 (37.4)	24 (45.3)	82 (39,5)	
ECOG PS (%)				
0-1	150 (96.7)	49 (92.4)	199 (95.7)	0.080
2	5 (3.3)	4 (7.6)	9 (4.3)	
Location (%)				
Right side	43 (27.7)	13 (24.5)	56 (26.9)	0.349
Left side	112 (72.3)	40 (75.5)	152 (73.1)	
Denovo met. (%)	89 (57.4)	32 (60.3)	121 (58.2)	0.420
Mutation (%)				
Wild type	59 (38)	21 (39.6)	81 (38.6)	0.419
Non-Wild type	88 (56.7)	28 (52.8)	116 (55.7)	
Unknown	8 (5.3)	4 (7.5)	12 (5.7)	
MMR status (%)				
MSI	6 (3.8)	2 (3.7)	8 (3.9)	0.912
MSS	133 (85.8)	46 (86.7)	179 (86)	
Unknown	16 (10.3)	5 (9.4)	21 (10.1)	

RASIs: Renin angiotensin system inhibitors; ACEi: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II type 1 receptor blocker; ECOG PS: The Eastern Cooperative Oncology Group performance score; MMR: Mismatch-repair; MSI: Microsatellite instability; MSS: Microsatellite stable; Met.: Metastatic

Table 2. Response evaluation to bevacizumab and cytotoxic therapy (non-RASIs group: Patients not using ACEi and ARBs, RASIs group: Patients using ACEi and ARBs)

	Non-RASIs (n=155)	**RASIs (n=53)**	**Total (n=208)**
Complete response	3	2	5
Partial response	50	23	73
Stable disease	31	13	44
Progressive disease	71	15	86
Objective response rate	53 (%34)	25 (%47)	78 (%37.5)

RASIs: Renin angiotensin system inhibitors; ACEi: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II type 1 receptor blockers

Table 3. PFS and OS of RASIs and non-RASIs groups (non-RASIs group: Patients not using ACEi and ARBs, RASIs group: Patients using ACEi and ARBs)

PFS	**Median (%95 CI)**	***P*-value**	**OS**	**Median (%95 CI)**	***P*-value**
RASIs	8.66 (6.71-10.57)	0.034	RASIs	24.86 (19.49-30.25)	0.039
Non-RASIs	6.67 (5.90-7.61)		Non-RASIs	18.71 (16.26-21.17)	
Overall	7.24 (1.36-13.2)		Overall	20.28 (3.51-37.05)	

PFS: Progession-free survival; OS: Overall survival; RASIs: Renin angiotensin system inhibitors; ACEi: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II type 1 receptor blockers; CI: Confidence interval

Table 4. Univariate analyses of prognostic factors for PFS and OS

	PFS			**OS**		
	Univariate			**Univariate**		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
RASIs	1.36	0.99-1.87	0.052	1,37	1.00-1.88	0.046
Age <65	1.04	0.78-1.38	0.775	1,06	0.80-1.41	0.618
Gender-Male	0.98	0.74-1.30	0.913	0,90	0.68-1.19	0.462
Loc.-Right side	0.95	0.70-1.30	0.791	1,01	0.74-1.37	0.952
ECOG PS 0-1	0.60	0.29-1.24	0.173	0,53	0.26-1.09	0.089
Non-Wild type	0.71	0.53-0.94	0.018	1,01	0.76-1.33	0.932
Denovo met.	0.86	0.65-1.14	0.324	0,95	0.72-1.26	0.768

RASIs: Renin angiotensin system inhibitors; PFS: Progession-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG PS: The Eastern Cooperative Oncology Group performance score; Met.:Metastatic; Loc: Localization

Table 5. Multivariate analyses of prognostic factors for PFS and OS

	PFS			**OS**		
	Multivariate			**Multivariate**		
	HR	95% CI	P-value	HR	95% CI	P-value
RASIs	1.42	1.03-1.95	0,029	1.37	1.00-1.89	0.044
ECOG PS 0-1	0.60	0.29-1.24	0,170	0.52	0.25-1.09	0.084
Non-Wild type	0.70	0.53-0.94	0,017	1.07	0.80-1.43	0.646
Denovo met.	0.92	0.69-1.21	0,569	0.91	0.68-1.21	0.547

PFS: Progession-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG PS: The Eastern Cooperative Oncology Group performance score; Met.: Metastatic

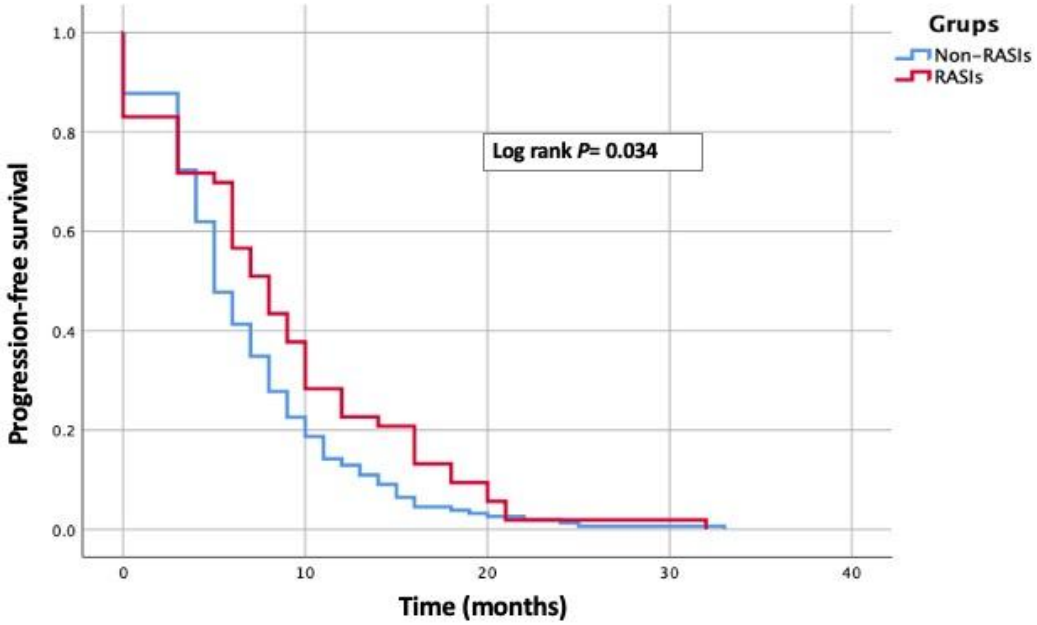

Figure 1. Kaplan-Meier curves were used to demonstrate the difference in PFS between the two groups.
PFS: Progession-free survival; RASIs: Renin angiotensin system inhibitors

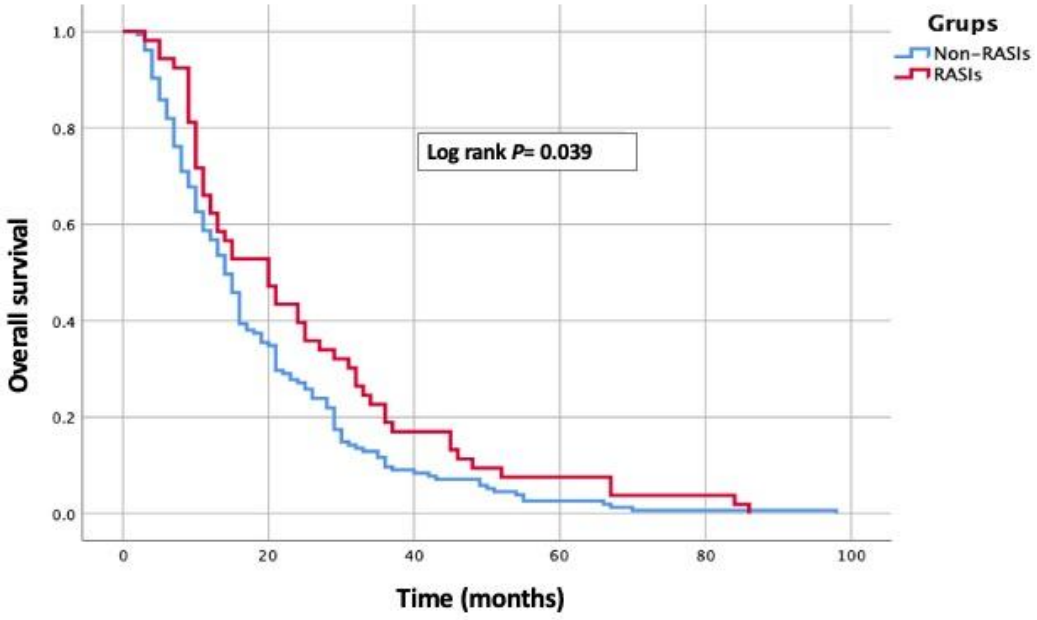

Figure 2. Kaplan-Meier curves were used to demonstrate the difference in OS between the two groups.
OS: Overall survival; RASIs: Renin angiotensin system inhibitors