JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

Impact of beta blockers on survival outcomes in ovarian cancer: a nationwide population-based cohort study

Min-Hyun Baek [iD],[1] Dae-Yeon Kim [iD],[2] Seon Ok Kim [iD],[3] Ye-Jee Kim,[3] Young-Han Park[1]

[1]Department of Obstetrics and Gynecology, Hallym University Sacred Heart Hospital, Anyang, Korea
[2]Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[3]Department of Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

OPEN ACCESS

Correspondence to
Dae-Yeon Kim
Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: kdyog@amc.seoul.kr

ORCID iDs
Min-Hyun Baek [iD]
https://orcid.org/0000-0003-0423-9038
Dae-Yeon Kim [iD]
https://orcid.org/0000-0002-8068-3475
Seon Ok Kim [iD]
https://orcid.org/0000-0001-9010-5460

ABSTRACT

Objective: The impact of beta blockers (BBs) on survival outcomes in ovarian cancer was investigated.

Methods: By using Korean National Health Insurance Service Data, Cox proportional hazards regression was performed to analyze hazard ratios (HRs) with 95% confidence intervals (CIs) adjusting for confounding factors.

Results: Among 866 eligible patients, 206 (23.8%) were BB users and 660 (76.2%) were non-users. Among the 206 BB users, 151 (73.3%) were non-selective beta blocker (NSBB) users and 105 (51.0%) were selective beta blocker (SBB) users. BB use in patients aged ≥60 years, longer duration use (≥1 year), in patients with Charlson Comorbidity Index (CCI) ≥3, and in cardiovascular disease including hypertension was associated with better survival outcome. These findings were observed in both NSBB and SBB. When duration of medication was analyzed based on number of days, NSBB (≥180 days) was associated with improved overall survival (OS) with a relatively shorter period of use compared to SBB (≥720 days). In multivariate Cox proportional hazards model, longer duration of BB medication (≥1 year) was an independent favorable prognostic factor for both OS and disease-specific survival in ovarian cancer patients.

Conclusion: In our nationwide population-based cohort study, BB use was associated with better survival outcomes in ovarian cancer in cases of long term duration of use, in older patients, and in cardiovascular and/or other underlying disease (CCI ≥3).

Keywords: Ovarian Neoplasms; Adrenergic beta-Antagonists; Survival; Treatment Outcome

INTRODUCTION

Ovarian cancer is one of the five leading cause of cancer death among all malignancies worldwide [1]. Further, it is estimated to be the 8th most common cause of death and its incidence has increased approximately 50% over the recent 10 years in Korea [2,3]. Treatment of ovarian cancer includes primary debulking surgery followed by chemotherapy. Incorporation of bevacizumab has been shown to improve survival outcome [4], but a

JOURNAL OF GYNECOLOGIC ONCOLOGY

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: B.M.H., P.Y.H.; Formal analysis: K.S.O, K.Y.J.; Funding acquisition: B.M.H.; Project administration: B.M.H.; Supervision: P.Y.H., K.D.Y.; Visualization: K.S.O., K.Y.J.; Writing – original draft: B.M.H.; Writing – review & editing: B.M.H.

majority of the patients (75%) still experience recurrence and succumb (70%) within five years [5]. Further, the use of bevacizumab is limited by its high cost and numerous adverse effects such as genitourinary fistula, gastrointestinal tract perforation, and hypertension in ovarian cancer patients [4]. Therefore, better therapeutic strategies are needed. The concept of drug repurposing is an alternative method to find promising therapeutic agents by uncovering anti-cancer effects of previously known drugs, reducing the cost, and time involved in finding investigational new drugs (INDs) [6].

Previous pre-clinical studies have shown that beta adrenergic receptors are commonly expressed on the surface of ovarian cancer cells [7]. Activation of these receptors by catecholamines produced due to chronic stress was found to be associated with carcinogenesis and tumor progression via evasion from apoptosis and acquisition of resistance to chemotherapy [8-10]. Catecholamines activate and enhance the expression of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) via the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway. These events increase invasiveness and metastatic potential of tumors leading to a higher tumor stage and worse survival outcomes in ovarian cancer [8,9,11]. Surprisingly, these pathways were found to be downregulated and even reversed when beta blockers (BBs) were administered to mice in previous preclinical studies [12-14].

Based on such promising evidence, a number of clinical studies sought to evaluate BBs for ovarian cancer treatment, but the results obtained were conflicting [14-21]. Ovarian cancer possesses a variable genetic background with characteristics differing between region and country. It is likely that each nation will need their own surveys and investigations to understand how BBs affect ovarian cancer prognosis in the context of multi-factorial social change. BBs are a treatment of choice for managing hypertension worldwide including Korea. In addition, they are widely used to control cardiac arrhythmia, congestive heart failure, anxiety, and for secondary prevention of myocardial infarction [10]. It is because they are economically and ethically sound for both patients and researchers. Above all, their safety has been widely accepted over a long history of use. The proportion of the elderly is on the rise in Korea and use of BBs is likely to increase due to higher incidence of hypertension and related heart diseases. If BBs have an anticancer effect, they can be potential therapeutic agents to relieve the financial burden involved in cancer therapy. Therefore, we performed a nationwide population-based cohort study to investigate the impact of BBs on survival outcomes in ovarian cancer.

MATERIALS AND METHODS

Data

Data collected in the South Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) database from 2002 to 2013 (released by NHIS in 2014) was used to perform the study. All individuals are enrolled in the NHIS, and NHIS-NSC represents the entire South Korean population (n=46,605,433) in terms of every demographic background with no significant differences [22]. The NHIS made available an encrypted 2.2% sample of the database (n=1,025,340) (national representative cohort) for researchers in 2002. This was constructed via random stratified sampling per 5-year age groups, gender, income status, prescriptions, diagnosis, mortality, and health insurance status. The data is renewed every year by adding random samples of newborns and deletion of individuals undergoing death or emigration.

Study cohort

The 6th edition of the Korean Classification of Disease (KCD-6), which is a Korean version of the International Classification of Disease, 10th Revision (ICD-10) has been coded to categorize all diagnoses. We only included patients who were diagnosed with ovarian cancer (C56) and had a record of hospital admission due to ovarian cancer. Only patients who were older than 20 years of age at the time of diagnosis were included. Further, only patients who had a medical record of ≥1 year & follow up of ≥3 years before & after the diagnosis were included for better data accuracy and analysis (**Fig. 1**).

Definition of BB use

Both brand and generic names of drugs (based on the drug formulary code of the Korean Health Insurance Review and Assessment service), the prescription date, the number of days of supply, and administration route were found in the prescription data. This was coded based on the Anatomical Therapeutic Chemical (ATC) classification system. Selective beta blockers (SBBs) are drugs that block one of the beta1/2 adrenoreceptors. Non-selective beta blockers (NSBBs) are drugs that block all subtypes of beta adrenoreceptors. BB users were defined as individuals with at least one prescription within 90 days of diagnosis. Patients were classified as non-users when there was no prescription within 90 days of diagnosis, because it is customary in Korea to prescribe for 30-90 days period for long-term users.

Mortality

In total, follow-up data for the cohort over a 12-year period until 2013 were available in the database. Follow-up was performed from the date of diagnosis until the last visit, death, or emigration, whichever was first. Information on all-cause and disease specific mortality for all individuals in the cohort was analyzed.

Confounders

Potential confounders such as co-morbidities and medications were identified by sorting based on the ICD-10 and ATC codes. Prior use of diuretics, aspirin, statins, and year of diagnosis were assessed. Information on history and diagnosis of myocardial infarction, congestive heart failure, peripheral vessel disease, cerebrovascular disease, dementia,
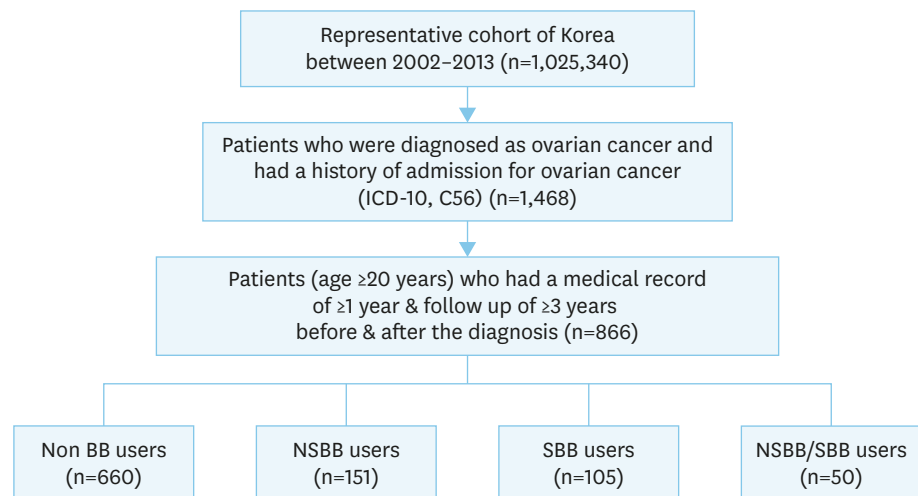
Fig. 1. Flow diagram of selection of the study patients.
BB, beta blocker; ICD-10, International Classification of Disease, 10th Revision; NSBB, non-selective beta blocker; SBB, selective beta blocker.

chronic pulmonary disease, connective tissue disease, gastric ulcer, liver disease, diabetes mellitus with/without associated complication, hemiparesis, kidney disease, hematological malignancies, acquired immune-deficiency syndrome (AIDs), and other co-existing malignancies was obtained. The Charlson Comorbidity Index (CCI) was used to categorize and measure the burden of co-morbid diseases [23]. Multivariate Cox proportional hazard model was generated to identify an independent prognostic factor.

Statistical analysis

The proportion and frequency of deaths, covariates, and amount of accumulated person-time were calculated. Survival curves were constructed using Kaplan-Meier estimates and compared with results of the log-rank test. Cox proportional hazard regression was adopted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Risk factor modeling was used to build a multivariate model including prior use of other medication, CCI, age group, and year of diagnosis. The $p<0.05$ was defined as the threshold for statistical significance. SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for statistical analysis.

Ethical approval

This study was approved from the Institutional Review Board review (No. 2016-I084) in Hallym University Sacred Heart Hospital.

RESULTS

We analyzed the mortality HRs in ovarian cancer patients based on BB medication use in various cohorts.

Impact of age

Among the 866 ovarian cancer patients, 206 (23.8%) were BB users and 660 (76.2%) were non-users. Among the 206 BB users, 151 (73.3%) were NSBB users and 105 (51.0%) were SBB users. Fifty (24.3%) patients were taking both NSBB and SBB (**Fig. 1**).

The median follow-up period was 5.98 and 6.71 years for non-users and users, respectively. In total, there was no survival difference between the 2 groups (HR=1.046; 95% CI=0.799–1.368; p=0.745). However, when patients were sub-grouped based on their age at diagnosis, BB was associated with better survival outcome in patients of age ≥60 (adjusted HR=0.579; 95% CI=0.408–0.823; p=0.002). Both NSBB (adjusted HR=0.565; 95% CI=0.377–0.848; p=0.006) and SBB (adjusted HR=0.523; 95% CI=0.332–0.827; p=0.005) were associated with better survival outcomes in patients of age ≥60 (**Table 1** and **Fig. 2A**).

Impact of duration of medication

Longer duration of BB medication (≥1 year) was associated with better survival outcome in patients with ovarian cancer regardless of BB type (adjusted HR=0.306; 95% CI=0.187–0.501; p<0.001). When patients were analyzed based on days of medication use, NSBB was associated with better survival outcome when it was used for ≥180 days (adjusted HR=0.387; 95% CI=0.179–0.837; p=0.016), while such a finding was observed in the SBB group with a longer duration of medication of ≥720 days (adjusted HR=0.275; 95% CI=0.111–0.684; p=0.005, **Table 2** and **Fig. 3**).

Table 1. Mortality HRs in ovarian cancer patients using BBs, based on age at diagnosis

Variables	No.	Number of deaths (%)	Median years of follow-up	Crude HR	95% CI	p value	Adjusted HR*	95% CI	p value
Overall									
No BB use	660	210	5.98	1 (reference)			1 (reference)		
BB use	206	71	6.71	1.046	0.799–1.368	0.745			
NSBB	151	48	6.36	0.951	0.695–1.301	0.754			
SBB	105	36	7.39	1.005	0.705–1.431	0.980			
20–39 years (n=216)									
No BB use	198	19	6.48	1 (reference)			1 (reference)		
BB use	18	3	6.15	1.679	0.496–5.676	0.405	0.769	0.222–2.669	0.680
NSBB	17	3	6.66	1.755	0.519–5.934	0.366	0.814	0.234–2.830	0.747
SBB	1	0	3.36	-			-		
40–59 years (n=350)									
No BB use	280	83	5.98	1 (reference)			1 (reference)		
BB use	70	16	7.28	0.696	0.407–1.189	0.185	1.020	0.559–1.860	0.949
NSBB	51	10	7.17	0.584	0.303–1.126	0.108	0.829	0.399–1.724	0.615
SBB	39	9	7.92	0.687	0.345–1.367	0.285	1.024	0.478–2.196	0.951
≥60 years (n=300)									
No BB use	182	108	5.39	1 (reference)			1 (reference)		
BB use	118	52	6.13	0.604	0.434–0.842	0.003	0.579	0.408–0.823	0.002
NSBB	83	35	5.75	0.580	0.396–0.849	0.005	0.565	0.377–0.848	0.006
SBB	65	27	7.12	0.534	0.350–0.815	0.004	0.523	0.332–0.827	0.005

BB, beta blocker; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NSBB, non-selective beta blocker; SBB, selective beta blocker.
*Adjusted for comorbidity level, prior use of diuretics (yes/no), year of diagnosis, aspirin (yes/no), and statins (yes/no). Comorbidity was computed using the CCI score categorized into low (0), medium (1–2), or high (3+).
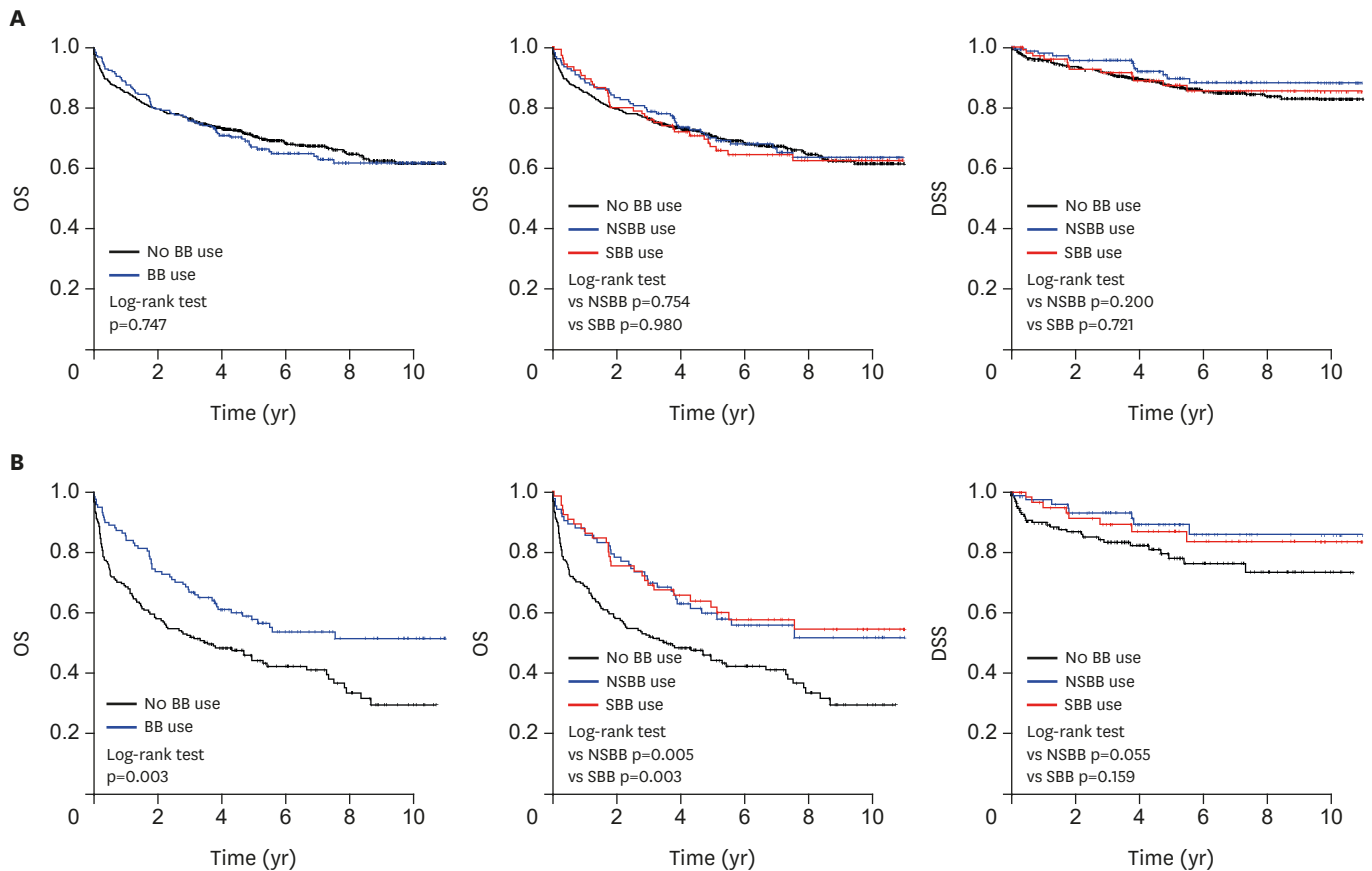
Fig. 2. (A) OS and DSS in patients with ovarian cancer based on BB use (NSBB or SBB) and no BB use. (B) OS and DSS in patients (age ≥60) with ovarian cancer based on BB use (NSBB or SBB) and no BB use.
BB, beta blocker; DSS, disease-specific survival; NSBB, non-selective beta blocker; OS, overall survival; SBB, selective beta blocker.

Table 2. Mortality HRs in ovarian cancer patients using BBs, based on duration of use

Variables	No.	Number of deaths (%)	Median years of follow-up	Crude HR	95% CI	p value	Adjusted HR*	95% CI	p value
Overall									
Nonusers	660	210	5.98	1 (reference)			1 (reference)		
Current users with <1 years BB use	119	52	6.08	1.475	1.089–1.998	0.012	1.045	0.758–1.439	0.789
Current users with ≥1 years BB use	87	19	7.12	0.581	0.363–0.930	0.024	0.306	0.187–0.501	0.000
Current users with <1 years NSBB use	99	38	6.28	1.222	0.865–1.726	0.256	0.845	0.583–1.225	0.374
Current users with ≥1 years NSBB use	52	10	6.57	0.516	0.274–0.974	0.041	0.292	0.151–0.563	0.000
Current users with <1 years SBB use	69	27	7.15	1.213	0.812–1.810	0.346	0.754	0.492–1.154	0.193
Current users with ≥1 years SBB use	36	9	7.49	0.663	0.340–1.292	0.227	0.340	0.169–0.683	0.002
Current BB users									
<180 days	96	44	6.32	1.580	1.141–2.186	0.006	1.111	0.788–1.566	0.547
≥180 & <720 days	47	15	5.27	0.977	0.579–1.650	0.932	0.528	0.308–0.904	0.020
≥720 days	63	12	8.34	0.485	0.271–0.868	0.015	0.279	0.153–0.511	0.000
Current NSBB users									
<180 days	90	36	6.38	1.295	0.909–1.844	0.152	0.913	0.624–1.337	0.641
≥180 & <720 days	28	7	5.29	0.722	0.340–1.534	0.398	0.387	0.179–0.837	0.016
≥720 days	33	5	7.43	0.386	0.159–0.936	0.035	0.235	0.095–0.579	0.002
Current SBB users									
<180 days	52	21	6.08	1.273	0.813–1.993	0.292	0.705	0.438–1.133	0.149
≥180 & <720 days	29	10	7.39	1.025	0.543–1.932	0.940	0.718	0.373–1.384	0.322
≥720 days	24	5	8.82	0.522	0.215–1.267	0.150	0.275	0.111–0.684	0.005

BB, beta blocker; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NSBB, non-selective beta blocker; SBB, selective beta blocker.
*Adjusted for age (20–39, 40–59, 60–79, ≥80 years), comorbidity level, prior use of diuretics (yes/no), year of diagnosis, aspirin (yes/no), and statins (yes/no). Comorbidity was computed using the CCI score categorized into low (0), medium (1–2), or high (3+).

Impact of CCI

There was no survival difference between the CCI 0 (adjusted HR=1.080; 95% CI=0.119–9.812; p=0.946) and 1–2 (adjusted HR=0.561; 95% CI=0.217–1.451; p=0.233) groups of ovarian cancer patients using BB medication. However, BB medication use was associated with better survival outcomes in ovarian cancer patients with CCI ≥3 (adjusted HR=0.690; 95% CI=0.502–0.949; p=0.023). Both NSBB (adjusted HR=0.633; 95% CI=0.438–0.913; p=0.014) and SBB (adjusted HR=0.642; 95% CI=0.424–0.971; p=0.036) were associated with better survival outcomes in patients with CCI ≥3 (**Table 3** and **Fig. 4A**).

Impact of hypertension

BB medication was associated with better survival outcome in ovarian cancer patients with hypertension (adjusted HR=0.647; 95% CI=0.452–0.926; p=0.017). Both NSBB (adjusted HR=0.632; 95% CI=0.414–0.964; p=0.033) and SBB (adjusted HR=0.564; 95% CI=0.365–0.873; p=0.010) were associated with better survival outcome in patients with hypertension (**Table 3** and **Fig. 4B**).

Impact of cardiovascular disease

Patients with ovarian cancer were considered as also having cardiovascular disease when they had more than one condition among hypertension, myocardial infarction, angina pectoris, and congestive heart failure. BB medication was associated with better survival outcome in ovarian cancer patients with cardiovascular disease (adjusted HR=0.655; 95% CI=0.463–0.927; p=0.017). Both NSBB (adjusted HR=0.613; 95% CI=0.406–0.926; p=0.020) and SBB
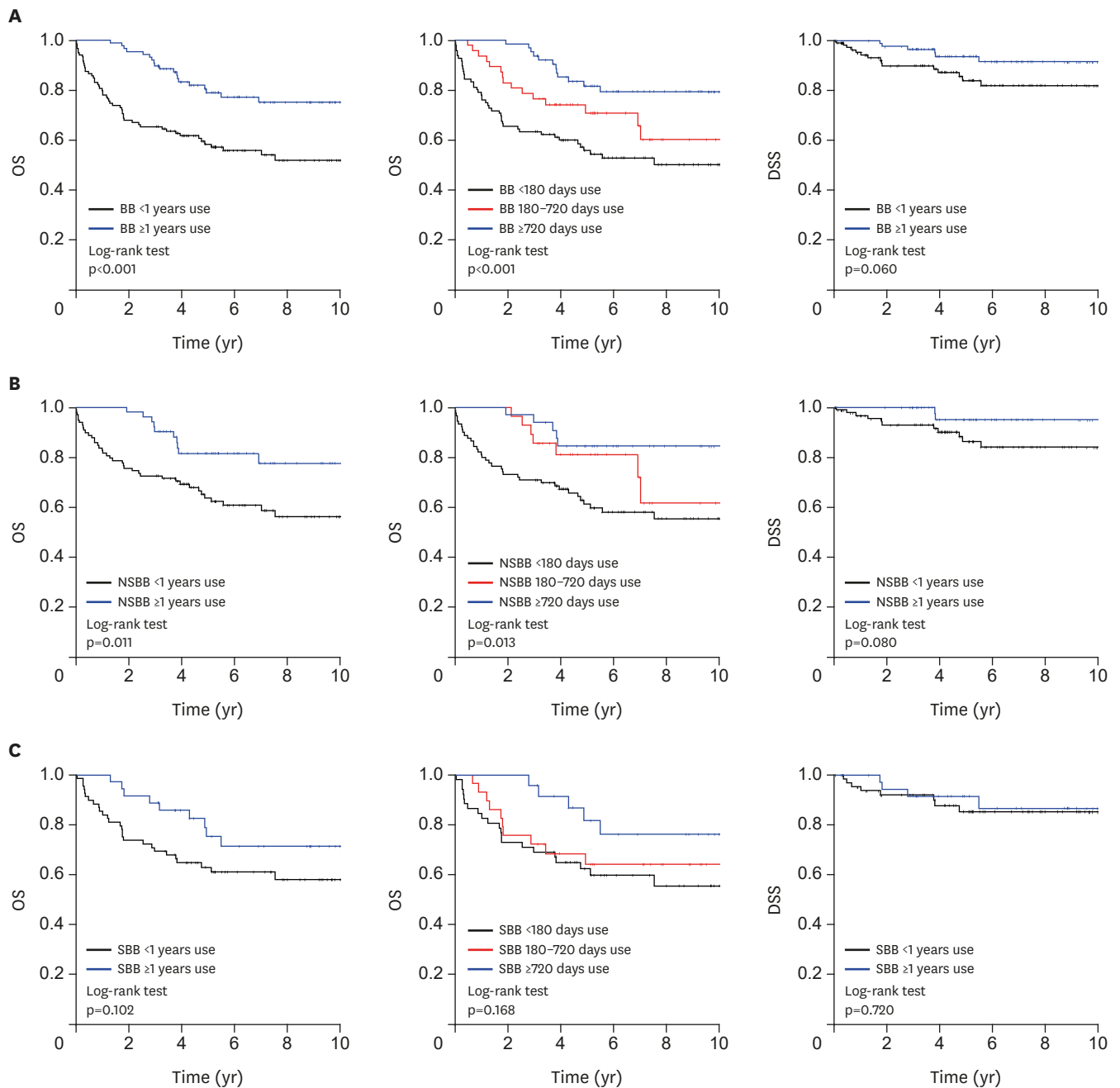
Fig. 3. OS and DSS of patients with ovarian cancer based on duration of use of (A) BB, (B) NSBB, or (C) SBB.
BB, beta blocker; DSS, disease-specific survival; NSBB, non-selective beta blocker; OS, overall survival; SBB, selective beta blocker.

Table 3. Mortality HRs in ovarian cancer patients using BBs, based on the CCI, presence of hypertension, and cardiovascular disease

Variables	No.	Number of deaths (%)	Median years of follow-up	Crude HR	95% CI	p value	Adjusted HR*	95% CI	p value
CCI 0 (n=131)									
No BB use	111	5	6.06	1 (reference)			1 (reference)		
BB use	20	1	8.63	0.814	0.093–7.110	0.853	1.080	0.119–9.812	0.946
NSBB	12	1	7.18	1.537	0.179–13.221	0.695	2.659	0.250–28.321	0.418
SBB	9	0	9.80	-		-			
CCI 1–2 (n=219)									
No BB use	186	34	5.97	1 (reference)			1 (reference)		
BB use	33	6	7.45	0.946	0.397–2.257	0.901	0.561	0.217–1.451	0.233
NSBB	24	4	7.28	0.856	0.303–2.417	0.770	0.600	0.196–1.838	0.371
SBB	18	3	8.45	0.821	0.252–2.680	0.744	0.404	0.116–1.410	0.155
CCI ≥3 (n=516)									
No BB use	363	171	5.78	1 (reference)			1 (reference)		
BB use	153	64	5.78	0.810	0.608–1.080	0.151	0.690	0.502–0.949	0.023
NSBB	115	43	5.75	0.703	0.504–0.983	0.039	0.633	0.438–0.913	0.014
SBB	78	33	6.71	0.793	0.546–1.151	0.223	0.642	0.424–0.971	0.036
No hypertension (n=573)									
No BB use	506	128	6.07	1 (reference)			1 (reference)		
BB use	67	14	7.39	0.730	0.420–1.268	0.264	0.604	0.341–1.071	0.084
NSBB	59	12	7.17	0.710	0.393–1.283	0.257	0.578	0.312–1.069	0.080
SBB	18	4	9.02	0.738	0.272–1.997	0.549	0.615	0.218–1.733	0.358
Hypertension (n=293)									
No BB use	154	82	4.92	1 (reference)			1 (reference)		
BB use	139	57	5.87	0.642	0.458–0.901	0.010	0.647	0.452–0.926	0.017
NSBB	92	36	5.55	0.617	0.417–0.913	0.016	0.632	0.414–0.964	0.033
SBB	87	32	6.89	0.534	0.354–0.804	0.003	0.564	0.365–0.873	0.010
No cardiovascular disease (n=527)									
No BB use	470	113	6.07	1 (reference)			1 (reference)		
BB use	57	13	7.28	0.844	0.475–1.500	0.564	0.638	0.351–1.159	0.140
NSBB	51	12	7.17	0.881	0.486–1.598	0.678	0.640	0.344–1.190	0.159
SBB	16	3	9.17	0.630	0.200–1.985	0.430	0.484	0.143–1.644	0.245
Cardiovascular disease (n=339)									
No BB use	190	97	5.47	1 (reference)			1 (reference)		
BB use	149	58	6.10	0.653	0.472–0.904	0.010	0.655	0.463–0.927	0.017
NSBB	100	36	5.88	0.601	0.410–0.881	0.009	0.613	0.406–0.926	0.020
SBB	89	33	6.99	0.590	0.397–0.876	0.009	0.597	0.390–0.913	0.017

CCI score: 1, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, gastric ulcer, mild liver disease, and diabetes mellitus without complication; 2, diabetes mellitus with retinopathy, neuropathy, and nephropathy, hemiparesis, kidney disease (≥ moderate), and non-metastatic solid tumor, leukemia, lymphoma, and multiple myeloma; 3, liver disease (≥ moderate); 6, metastatic solid tumor, and acquired immunodeficiency syndrome.
BB, beta blocker; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; NSBB, non-selective beta blocker; SBB, selective beta blocker.
*Adjusted for age (20–39, 40–59, 60–79, ≥80 years), year of diagnosis, prior use of diuretics (yes/no), aspirin (yes/no), and statins (yes/no).

(adjusted HR=0.597; 95% CI=0.390–0.913; p=0.017) were associated with better survival outcome in patients with cardiovascular disease (**Table 3** and **Fig. 4C**).

Multivariate Cox proportional hazards model and disease-specific survival (DSS)
Kaplan Meier survival curve was generated according to DSS. NSBB was associated with better DSS outcome in ovarian cancer patients with CCI ≥3 (p=0.011, **Fig. 4A**). Although not statistically significant, BB use was associated with a tendency of better DSS outcome which is in accordance to the results with overall survival (OS) (**Figs. 2**-**4**).

Multivariate Cox proportional hazards analysis was performed according to both OS and DSS to identify an independent prognostic factor in ovarian cancer patients regardless of
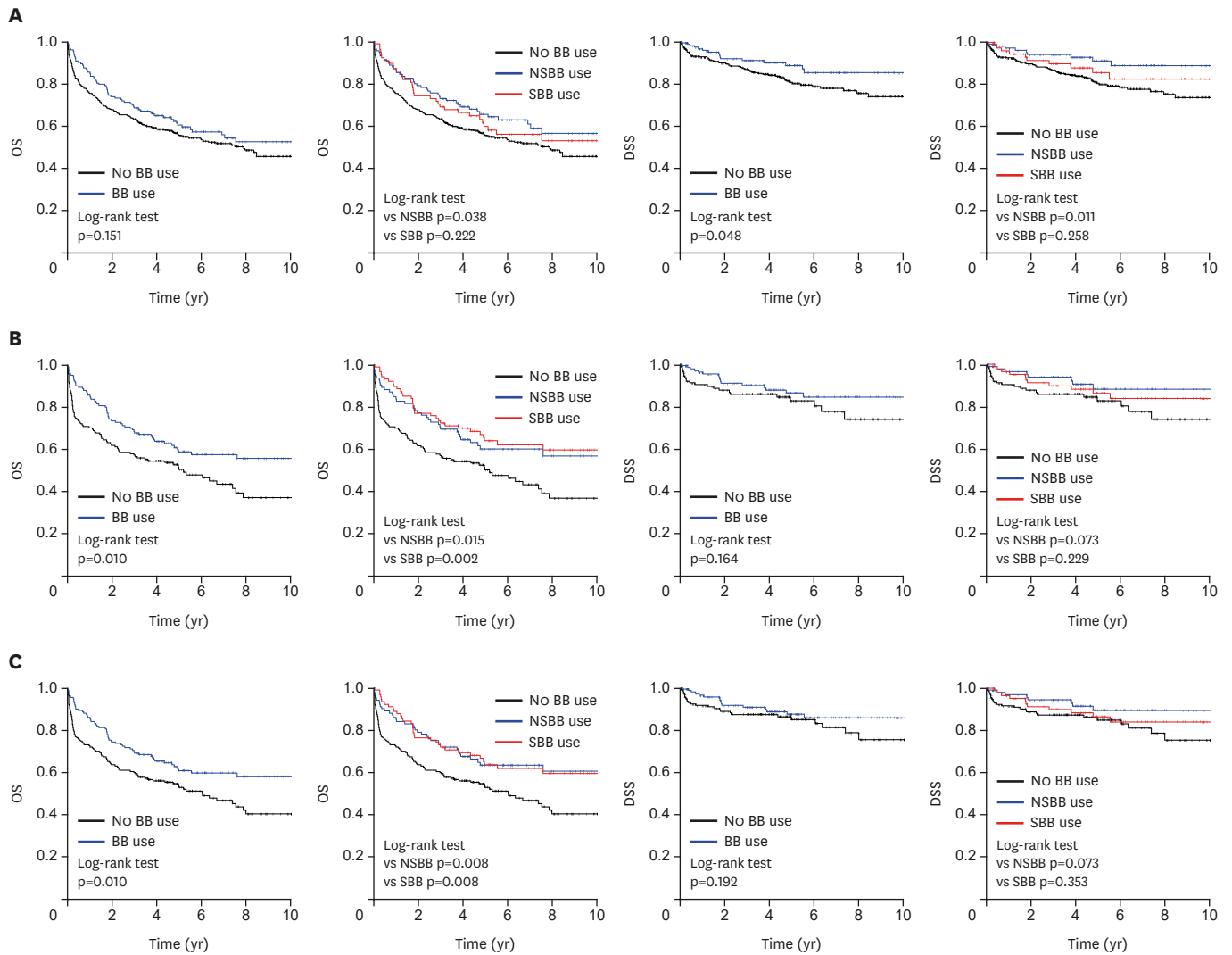
Fig. 4. OS and DSS of patients with ovarian cancer based on BB use (NSBB or SBB) and no BB use in (A) CCI ≥3, (B) hypertension, and (C) cardiovascular disease. BB, beta blocker; CCI, Charlson Comorbidity Index; DSS, disease-specific survival; NSBB, non-selective beta blocker; OS, overall survival; SBB, selective beta blocker.

BB related underlying diseases. Age ≥60 and CCI ≥3 were independent prognostic factors for both lower OS and DSS. Hypertension and cardiovascular disease were not independent prognostic factors for both OS and DSS. Longer duration of both NSBB and SBB medication (≥1 year) was an independent favorable prognostic factor for OS in ovarian cancer patients (HR=0.266; 95% CI=0.163–0.435; p<0.001), while only NSBB medication (≥1 year) was an independent favorable prognostic factor for DSS (HR=0.178; 95% CI=0.043–0.746; p=0.018, **Table 4**).

Table 4. Multivariate Cox proportional hazards model in ovarian cancer patients using BBs

Variables	BB use			NSBB use			SBB use		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
OS (281 events)									
Duration of medication									
No	1			1			1		
<1 year	0.873	0.635–1.201	0.405	0.666	0.464–0.956	0.028	0.677	0.441–1.041	0.076
≥1 year	0.266	0.163–0.435	<0.001	0.289	0.150–0.558	<0.001	0.253	0.127–0.504	<0.001
Age (≥60 years)	2.470	1.857–3.286	<0.001	2.632	1.961–3.532	<0.001	2.526	1.867–3.416	<0.001
CCI									
0	1			1			1		
1–2	3.416	1.445–8.077	0.005	2.986	1.257–7.093	0.013	3.682	1.443–9.393	0.006
≥3	8.631	3.798–19.616	<0.001	7.265	3.178–16.608	<0.001	9.476	3.861–23.260	<0.001
Hypertension	1.389	0.812–2.378	0.230	1.349	0.774–2.349	0.291	1.218	0.707–2.099	0.477
Cardiovascular disease	0.842	0.497–1.428	0.524	0.806	0.467–1.388	0.436	0.931	0.546–1.587	0.793
Prior use of diuretics	2.560	1.955–3.353	<0.001	2.606	1.976–3.437	<0.001	2.506	1.890–3.321	<0.001
Prior use of statins	0.370	0.269–0.509	<0.001	0.367	0.261–0.516	<0.001	0.312	0.216–0.451	<0.001
DSS (100 events)									
Duration of medication									
No	1			1			1		
<1 year	0.766	0.430–1.363	0.364	0.590	0.306–1.140	0.116	0.619	0.284–1.351	0.228
≥1 year	0.258	0.108–0.619	0.002	0.178	0.043–0.746	0.018	0.361	0.125–1.042	0.060
Age (≥60 years)	1.893	1.170–3.063	0.009	1.999	1.216–3.288	0.006	1.772	1.070–2.936	0.026
CCI									
0	1			1			1		
1–2	2.734	0.930–8.035	0.067	2.476	0.837–7.321	0.101	3.246	0.952–11.063	0.060
≥3	5.202	1.869–14.477	0.002	4.610	1.642–12.940	0.004	6.704	2.077–21.641	0.001
Hypertension	2.149	0.648–7.127	0.211	1.892	0.566–6.326	0.300	1.953	0.582–6.548	0.278
Cardiovascular disease	0.383	0.119–1.236	0.108	0.386	0.119–1.245	0.111	0.412	0.127–1.334	0.139
Prior use of diuretics	4.149	2.626–6.555	<0.001	4.072	2.563–6.471	<0.001	4.226	2.630–6.790	<0.001
Prior use of statins	0.321	0.182–0.566	<0.001	0.324	0.176–0.595	<0.001	0.291	0.155–0.545	<0.001

BB, beta blocker; CCI, Charlson Comorbidity Index; CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; NSBB, non-selective beta blocker; OS, overall survival; SBB, selective beta blocker.

DISCUSSION

Immune-suppression by both physical and psychological stress is a contributory cause of tumorigenesis and disease progression [24]. Previous epidemiologic studies have shown that prolonged exposure of beta adrenergic receptors on ovarian cancer cell surfaces to catecholamines due to chronic stress causes further tumor growth [25]. There have been several retrospective and small pilot clinical studies and preclinical studies investigating the potential role of BBs, but the results were inconsistent.

First, small cohorts in single retrospective center studies with different approaches, patient characteristics, and confounders between the series may have been obstacles to elucidation of the clinical impact of BBs in ovarian cancer [15,16,20]. Second, most previous studies did not further analyze the effect of NSBBs and SBBs in ovarian cancer [15,16,18]. Further, there was no specific mention of "duration" or a clear "definition" of BB medication use in the majority of the previous series [15-17,20]. Tumorigenesis and disease progression in ovarian cancer due to stress responses is considered a "chronic process" and the duration of use among long-term BB users is important to verify efficacy. We additionally analyzed the effect of NSBBs and SBBs. Further, we strictly defined BB users on the basis of at least one prescription within 90 days of diagnosis.

Finally, there has been no analysis to find a sub-group of patients who could more benefit from BB use. Johannesdottir et al. [18] found no promising effect of BB use on OS in ovarian cancer in their population-based cohort study by using the Danish cancer registry. However, BB use showed a tendency of association with improved survival outcomes in ovarian cancer when administered in an elderly group in the above study in accordance with the results in our series, although they found no statistical significance. A relatively short period of median BB use of 19 months and no subgroup analysis of BBs was a major shortcoming of the above series, preventing conclusions about the association of long term BB use with better prognosis. Above all, 2.55 years is a relatively short follow-up period to truly understand the long-term survival effect of BB medication in ovarian cancer. In our study, the effect of BB was analyzed with 6.71 years of long-term follow up in BB users and 5.98 years in non-users. In addition, duration of medication use was categorized into several groups for better analysis. Also, multivariate analysis according to DSS in addition to OS was performed to truly know the effect of BB.

In our study, BB use in elderly patients (≥60 years) and over a long term (≥1 year) showed prognostic improvement in ovarian cancer. Further, BB medication use was associated with better survival outcomes in ovarian cancer patients with cardiovascular and/or other underlying disease (CCI ≥3). Prolonged exposure to catecholamine due to chronic stress has been correlated with tumorigenesis and disease progression in epidemiologic research [25]. Elderly patients also tend to have a higher incidence of chronic cardiovascular disease, which may lead to longer intake of BBs compared to younger groups. Further, these patients are more prone to stress and may have been exposed for a longer period. Social isolation is an additional problem among the elderly and network support to enable them to deal with stress better by decreasing depression and eventually lowering circulating and disease-related norepinephrine levels should be considered [10]. BBs show their anticancer effects biologically or immunologically and by reducing disease-associated chronic stress psychologically [17]. We consider exposure to BBs for a long period of time due to higher incidence of chronic medical conditions and multiple psycho-social effects to be of paramount importance in their anticancer effects. BBs can be beneficial agents for improving oncologic outcomes in patients with ovarian cancer, particularly in the elderly (≥60 years), considering the above background.

NSBB use (≥180 days) was associated with improved OS with a relatively shorter medication period than SBB use (≥720 days) in our series. Further, only NSBB medication (≥1 year) was an independent favorable prognostic factor for DSS in multivariate analysis. The reason for NSBBs showing an improved anticancer effect in comparison to SBBs has not been elucidated. We speculate that this may be because NSBBs cover a broad spectrum of beta adrenergic receptors compared to SBBs. NSBBs show anticancer effects by blocking the adrenergic receptor b2 (ADRB2) pathway which activates PKA and increases VEGF and MMP expression [13].

Retrospective study design was a limitation of the present study. BB was used because of its related underlying disease, and bias may still remain even confounders were meticulously adjusted by various methods. Further, detailed subtypes of ovarian cancer could not be identified from the current database. However, high general applicability and low selection bias compared to previous series was a strength of this study. Social characteristics which can be potential confounders were systematically adjusted based on the CCI system. Furthermore, confirmatory analysis was performed by generating multivariate Cox proportional hazards model by adopting both OS and DSS to minimize above mentioned problem.

After all, a prospective clinical trial may be the definite way to know whether BB truly has an anticancer effect on ovarian cancer without any potential bias. The only prospective randomized trial of BB use in ovarian cancer treatment was recently reported by Jang et al. [26], and propranolol (NSBB) was associated with significant decrease in postoperative cancer antigen levels (CA-125), but not with disease-free survival. A small number of patients (n=22) from a single institution with a short follow-up duration (median, 17 months) was a major shortcoming of this series. Above all, there was no analysis of important parameters such as overall response rate, severe adverse events, and quality of life of the patients, making it difficult to draw conclusions. At the same time, Al-Niaimi et al. [21] reported improved survival outcomes due to perioperative metoprolol (SBB) intake with "Minnesota protocol" among a subgroup of patients who were considered "at risk". SBBs were tested in patients with no cardiovascular disease including hypertension, potentially repositioning BBs as a new targeted agent in ovarian cancer treatment. Currently, a pilot and prospective study on feasibility of propranolol (NSBB) use in ovarian cancer treatment is ongoing (NCT01308944, NCT01504126, and NCT02013492). Results of these studies will provide a better picture of the anticancer effects of BBs and will be a basis for further well-designed multicenter clinical trials.

In conclusion, BB use was associated with better survival outcomes in ovarian cancer in cases of long-term use, in presence of hypertension, in cardiovascular and/or other underlying disease (CCI ≥3), and in older patients. If BBs are found to show survival improvement in ovarian cancer, they may be re-positioned as new targeted agents, relieving the economic burden involved in cancer treatment for both government and patients by substituting conventional targeted agents.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30.
   PUBMED | **CROSSREF**

2. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH. Prediction of cancer incidence and mortality in Korea, 2017. Cancer Res Treat 2017;49:306-12.
   PUBMED | **CROSSREF**

3. Lim MC, Moon EK, Shin A, Jung KW, Won YJ, Seo SS, et al. Incidence of cervical, endometrial, and ovarian cancer in Korea, 1999–2010. J Gynecol Oncol 2013;24:298-302.
   PUBMED | **CROSSREF**

4. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83.
   PUBMED | **CROSSREF**

5. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115:1234-44.
   PUBMED | **CROSSREF**

6. Chong CR, Sullivan DJ Jr. New uses for old drugs. Nature 2007;448:645-6.
   PUBMED | **CROSSREF**

7. Rains SL, Amaya CN, Bryan BA. Beta-adrenergic receptors are expressed across diverse cancers. Oncoscience 2017;4:95-105.
   PUBMED

8. Armaiz-Pena GN, Allen JK, Cruz A, Stone RL, Nick AM, Lin YG, et al. Src activation by β-adrenoreceptors is a key switch for tumour metastasis. Nat Commun 2013;4:1403.
   PUBMED | **CROSSREF**

9. Lutgendorf SK, Cole S, Costanzo E, Bradley S, Coffin J, Jabbari S, et al. Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. Clin Cancer Res 2003;9:4514-21.
   PUBMED

10. Bunch KP, Annunziata CM. Are beta-blockers on the therapeutic horizon for ovarian cancer treatment? Cancer 2015;121:3380-3.
    PUBMED | CROSSREF

11. Sood AK, Bhatty R, Kamat AA, Landen CN, Han L, Thaker PH, et al. Stress hormone-mediated invasion of ovarian cancer cells. Clin Cancer Res 2006;12:369-75.
    PUBMED | CROSSREF

12. Lee JW, Shahzad MM, Lin YG, Armaiz-Pena G, Mangala LS, Han HD, et al. Surgical stress promotes tumor growth in ovarian carcinoma. Clin Cancer Res 2009;15:2695-702.
    PUBMED | CROSSREF

13. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med 2006;12:939-44.
    PUBMED | CROSSREF

14. Hefner J, Csef H. The clinical relevance of beta blockers in ovarian carcinoma: a systematic review. Geburtshilfe Frauenheilkd 2016;76:1050-6.
    PUBMED | CROSSREF

15. Diaz ES, Karlan BY, Li AJ. Impact of beta blockers on epithelial ovarian cancer survival. Gynecol Oncol 2012;127:375-8.
    PUBMED | CROSSREF

16. Heitz F, du Bois A, Harter P, Lubbe D, Kurzeder C, Vergote I, et al. Impact of beta blocker medication in patients with platinum sensitive recurrent ovarian cancer-a combined analysis of 2 prospective multicenter trials by the AGO Study Group, NCIC-CTG and EORTC-GCG. Gynecol Oncol 2013;129:463-6.
    PUBMED | CROSSREF

17. Watkins JL, Thaker PH, Nick AM, Ramondetta LM, Kumar S, Urbauer DL, et al. Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. Cancer 2015;121:3444-51.
    PUBMED | CROSSREF

18. Johannesdottir SA, Schmidt M, Phillips G, Glaser R, Yang EV, Blumenfeld M, et al. Use of β-blockers and mortality following ovarian cancer diagnosis: a population-based cohort study. BMC Cancer 2013;13:85.
    PUBMED | CROSSREF

19. Minlikeeva AN, Freudenheim JL, Cannioto RA, Szender JB, Eng KH, Modugno F, et al. History of hypertension, heart disease, and diabetes and ovarian cancer patient survival: evidence from the ovarian cancer association consortium. Cancer Causes Control 2017;28:469-86.
    PUBMED | CROSSREF

20. Heitz F, Hengsbach A, Harter P, Traut A, Ataseven B, Schneider S, et al. Intake of selective beta blockers has no impact on survival in patients with epithelial ovarian cancer. Gynecol Oncol 2017;144:181-6.
    PUBMED | CROSSREF

21. Al-Niaimi A, Dickson EL, Albertin C, Karnowski J, Niemi C, Spencer R, et al. The impact of perioperative β blocker use on patient outcomes after primary cytoreductive surgery in high-grade epithelial ovarian carcinoma. Gynecol Oncol 2016;143:521-5.
    PUBMED | CROSSREF

22. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15.
    PUBMED

23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
    PUBMED | CROSSREF

24. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol 2005;67:259-84.
    PUBMED | CROSSREF

25. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005;5:243-51.
    PUBMED | CROSSREF

26. Jang HI, Lim SH, Lee YY, Kim TJ, Choi CH, Lee JW, et al. Perioperative administration of propranolol to women undergoing ovarian cancer surgery: a pilot study. Obstet Gynecol Sci 2017;60:170-7.
    PUBMED | CROSSREF