Korean Medication Algorithm Project for Bipolar Disorder 2022, Fifth Revision: An Executive Summary

Young Sup Woo[1], Won-Myong Bahk[1], Jong-Hyun Jeong[1], Jung Goo Lee[2], Won Kim[3], InKi Sohn[4], Sung-Yong Park[4], Se-Hoon Shim[5], Jeong Seok Seo[6], IL Han Choo[7], Chan-Mo Yang[8], Myung Hun Jung[9], Duk-In Jon[9], Moon-Doo Kim[10], Bo-Hyun Yoon[11]

[1]Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, [2]Department of Psychiatry, Haeundae Paik Hospital, College of Medicine, Inje University, Busan, [3]Department of Psychiatry, Sanggye Paik Hospital, College of Medicine, Inje University, Seoul, [4]Department of Psychiatry, Keyo Hospital, Uiwang, [5]Department of Psychiatry, Soonchunhyang University Cheonan Hospital, College of Medicine, Soonchunhyang University, Cheonan, [6]Department of Psychiatry, College of Medicine, Chung-Ang University, Seoul, [7]Department of Psychiatry, College of Medicine, Chosun University, Gwangju, [8]Department of Psychiatry, Wonkwang University Hospital, School of Medicine, Wonkwang University, Iksan, [9]Department of Psychiatry, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, [10]Department of Psychiatry, Jeju National University Hospital, Jeju, [11]Department of Psychiatry, Naju National Hospital, Naju, Korea

Objective: We revised the Korean Medication Algorithm Project for Bipolar Disorder (KMAP-BP), first published in 2002 and revised in 2006, 2010, 2014, and 2018, to reflect recent progress in the treatment of bipolar disorder.
Methods: The questionnaires consisted of 56 items for adult patients and 7 items for child/adolescent patients, and were used to obtain the consensus of experts regarding pharmacological treatment strategies for various phases of bipolar disorder. The review committee included 87 Korean psychiatrists and 40 child and adolescent psychiatry experts.
Results: For treatment of manic episodes, a combination of a mood stabilizer (MS) and atypical antipsychotics (AAP), or monotherapy with MS or AAP were recommended as first-line treatments. Combinations of MS and AAP, or AAP and lamotrigine (LMT) were recommended as first-line treatments for depressive episodes regardless of the severity. Monotherapy with MS, AAP, or LMT were also first-line treatments for mild to moderate depressive episodes. For mixed features, a combination of MS and AAP, or monotherapy with AAP or MS were recommended as first-line treatments, and a combination of AAP and LMT, or MS and LMT were the first-line treatments for depressive mixed state.
Conclusion: The recommendations of the KMAP-BP 2022 have changed from the previous version, to reflect the evolution of the social culture and healthcare system in Korea and recent evidence regarding pharmacotherapy of bipolar disorder. The KMAP-BP 2022 provides clinicians with a wealth of information regarding appropriate strategies to treat patients with bipolar disorder.

KEY WORDS: Bipolar disorder; KMAP-BP 2022; Expert consensus; Pharmacotherapy.

INTRODUCTION

Bipolar disorder is a chronic and debilitating psychiatric disorder characterized by recurring manic or hypomanic episodes that may alternate with depressive episodes [1]. Pharmacotherapy has been the cornerstone treatment for bipolar disorder since the introduction of lithium (LIT) in the late 1960s and early 1970s [2,3]. Despite substantial progress in psychopharmacology during the past several decades, a significant proportion of patients with bipolar disorder suffer from treatment failure

[4]. Moreover, rapid advances in psychopharmacology have led to changes in the pharmacological treatment strategies for bipolar disorder, but clinicians often have limited time and resources to update their knowledge of the newest evidence regarding the efficacy, safety, and tolerability of the range of interventions available for the various and complex phases of bipolar disorder. Hence, several treatment algorithms and clinical practice guidelines (CPGs) have been published in many countries over the last two decades to assist practitioners in making decisions about appropriate management for specific clinical circumstances [5-8]. While the majority of these CPGs are based on evidence obtained from well-designed controlled clinical trials and are considered useful, they may not be broadly applicable in clinical practice because of various culture-specific characteristics, such as patient-related factors, clinical environment, healthcare policy and the prevailing medical insurance system. Thus, the Korean Medication Algorithm Project (KMAP) was initiated in 2001 and has been continually revised to develop consensus-based guidelines for pharmacotherapy of major mental disorders, including schizophrenia, bipolar disorder, and major depressive disorder, that reflect the national characteristics of these disorders and their treatment [9,10]. The KMAP for Bipolar Disorder was first published in 2002 (KMAP-BP 2002), based on an expert consensus among Korean psychiatrists with experience in treating bipolar disorder [11], and the feasibility of the KMAP-BP 2002 was confirmed through additional studies showing that the algorithm could be successfully implemented in clinical settings in Korea [12-14]. Thereafter, the KMAP-BP was revised four times every four years in 2006, 2010, 2014, and 2018 [15-18]. Since publication of the KMAP-BP 2018 [18], more than 2000 articles addressing the pharmacotherapy of bipolar disorder have been published and a number of major or minor changes to standard treatment have been recommended. Therefore, the Korean College of Neuropsychopharmacology (KCNP) and the Korean Society for Affective Disorders (KSAD) have now produced a firth revision, the KMAP-BP 2022, to reflect changes in expert opinion regarding the treatment of bipolar disorder, which we report here.

METHODS

The detailed methods for the selection of the review committee, preparation of questionnaires, data analyses and development of treatment guidelines and algorithms were similar to those of previous Korean Medication Algorithm Projects [11-16,18,19].

Review Committee

The review committee included 93 Korean psychiatrists who were life-long members of the Korean College of Neuropsychopharmacology or the Korean Society for Affective Disorder, and who had more than 10 years of clinical experience in the field of bipolar disorder and had published at least one paper regarding bipolar or mood disorder during last 5 years. Additionally, 60 experts in child and adolescent psychiatry were included in the review committee for the development of the child and adolescent section. Among the 93 psychiatrists initially selected, 87 (93.5%) of the total responded to our survey, and 40 of the 60 child and adolescent psychiatrists (66.7%) responded. The respondents were employed in a wide variety of clinical settings; university hospitals (n = 92), general hospitals/psychiatric hospitals (n = 20), and private psychiatric clinics (n = 15).

Questionnaire

The KMAP-BP 2022 is a set of expert consensus guidelines modeled after the 2002, 2006, 2010, 2014, and 2018 KMAP-BP assessments. The questionnaire used in the KMAP-BP 2022 is similar to the questions used to develop the KMAP-BP 2018, with some modifications.

Agomelatine which had been withdrawn from Korean market and was then reintroduced into Korea in 2019, and esketamine, which was been introduced to Korea in 2020, were included as antidepressants. In addition, liraglutide and a bupropion/naltrexone combination therapy were included as treatment options for weight gain. To reflect findings from previous versions and address feedback from respondents, we revised the questionnaire and reduced the number of options to improve applicability to real clinical practice.

The KMAP-BP 2022 questionnaire contains 56 main questions including 208 sub-items for adult bipolar disorder, and 7 main questions including 23 sub-items for pediatric bipolar disorder.

Rating Scale

Of the 231 total sub-items in the questionnaire for adult

and child/adolescent bipolar disorder, 167 address particular clinical cases and the appropriateness of potential treatment options for these cases using a 9-point scale. This scale is based on the Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000 [12];

a score of 9 out of 9 indicates "extremely appropriate", a score of 7 or 8 indicates "usually appropriate" (first-line), a score of 4−6 indicates "equivocal appropriateness" (second-line), a score of 2 or 3 indicates "usually inappropriate" (a treatment you would rarely use), and a score
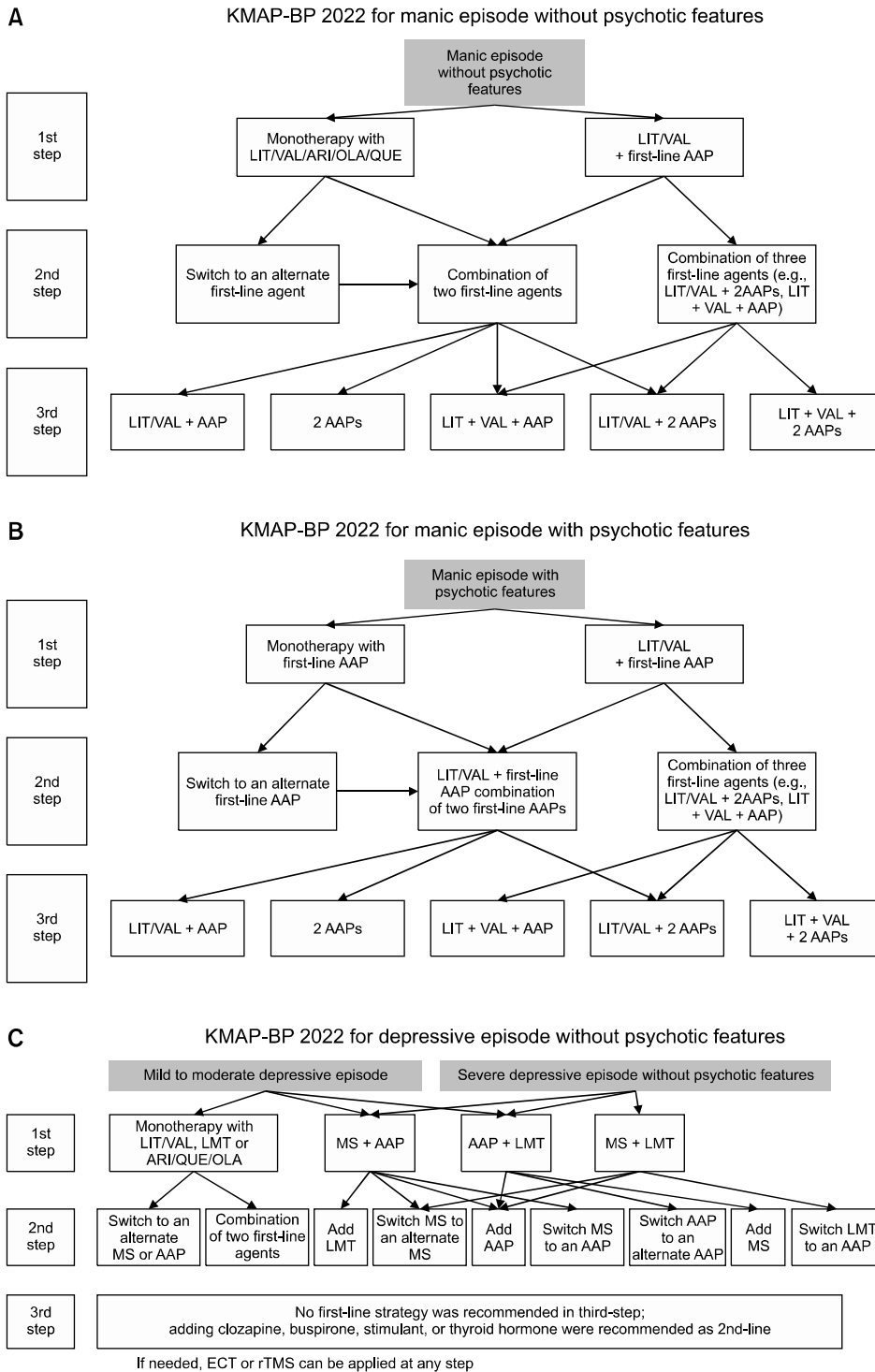

Fig. 1. The Korean Medication Algorithm for Bipolar Disorder 2022. (A) KMAP-BP 2022 for manic episode without psychotic features, (B) KMAP-BP 2022 for manic episode with psychotic features, (C) KMAP-BP 2022 for depressive episode without psychotic features, (D) KMAP-BP 2022 for depressive episode with psychotic features.

KMAP-BP, Korean Medication Algorithm Project for Bipolar Disorder; AAP, atypical antipsychotics; ARI, aripiprazole; ECT, electroconvulsive therapy; LIT, lithium; LMT, lamotrigine; MS, mood stabilizers; OLA, olanzapine; QUE, quetiapine; rTMS, repetitive transcranial magnetic stimulation; VAL, valproate.
[a]Treatment of choice.

D   KMAP-BP 2022 for depressive episode with psychotic features
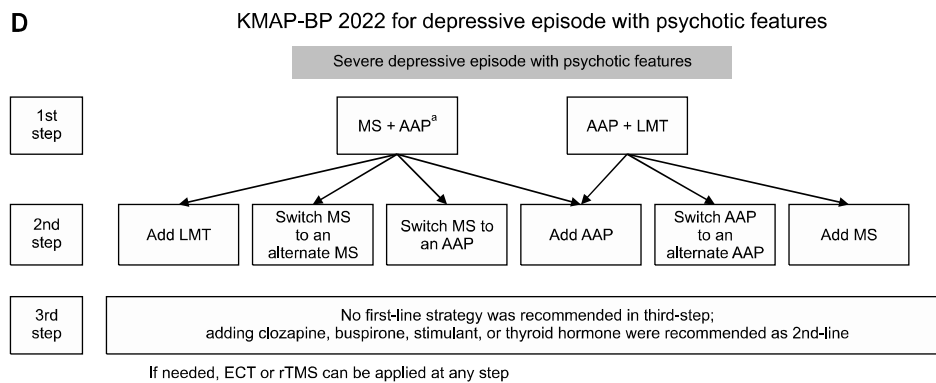

Fig. 1. Continued.

of 1 indicates "extremely inappropriate" (a treatment you would never use). The reviewers were asked to consider ideal treatment options rather than those actually practiced and to choose "q" if they had little experience or did not have available information for a particular question. The questionnaire includes 24 multiple-choice questions that ask the responder to select one or more treatment options, and 40 open-ended questions.

Medication Categories

The medications were categorized as follows: typical antipsychotics (e.g., haloperidol, chlorpromazine, molindone, perphenazine, pimozide, etc.), atypical antipsychotics (AAPs; e.g., aripiprazole [ARI], olanzapine [OLA], quetiapine [QUE], risperidone [RIS], and ziprasidone [ZIP]); other AAPs that were not approved for treating bipolar disorder by the Korean Ministry of Food and Drug Safety (e.g., amisulpride, blonanserin, paliperidone, and zotepine), mood stabilizers (MSs; e.g., LIT, valproic acid [VAL], and carbamazepine [CBZ]), and antidepressants (ADs; e.g., agomelatine, bupropion, desvenlafaxine, duloxetine, escitalopram, fluoxetine, milnacipran, mirtazapine, moclobemide, paroxetine, sertraline, tianeptine, tricyclic antidepressants, venlafaxine, and vortioxetine). Clozapine (CLZ) and lamotrigine (LMT) were not included in any of the categories and were treated as a category per se. Medications not available in Korea (e.g., asenapine, cariprazine and lurasidone) were not included in this survey.

Data Analyses and Development of the Treatment Guidelines and Algorithms

The rating scores were assumed to be randomly distributed and the rating scores on the 9-point scale were divided into three groups (1−3, 4−6, and 7−9). A lack of a significant difference among groups was interpreted as reflecting a lack of consensus by the experts. The presence or absence of a consensus for each of the options/questions was determined using the chi-square test to identify significant differences. Then, the means and 95% confidence intervals (CIs) of the scores were calculated and divided into three categories based on the lowest CI score: $\geq$ 6.5 for first-line/preferred treatments, < 6.5 and $\geq$ 3.5 for second-line/reasonable treatments, and < 3.5 for third-line/inappropriate treatments. The first-line treatment options that received scores of from 9 $\geq$ 50% of the experts were defined as the treatment of choice (TOC; i.e., the most strongly recommended treatment). The SPSS software package (version 22; IBM Co., Armonk, NY, USA) was used for the preference ranking and multiple response analyses. After the advisory committee and the executive committee discussed these results and reviewed the clinical evidence while considering the context of Korean clinical practice, the executive committee drew up the fifth revised KMAP-BP algorithms (Fig. 1).

Ethics

The present study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board or Ethics Committee at each respective study site. The Institutional Review Board waived the requirement for informed consent for this survey. All respondents received a predetermined fee for their participation. The revision process was funded entirely by KCNP and KSAD without external financial support.

RESULTS

Manic Episodes

Step 1. Initial treatment

The combination of an MS and an AAP (MS + AAP) was the TOC for manic episodes with psychotic features and the first-line strategy for manic episodes without psychotic features. Monotherapy with an AAP was the first-line strategy for manic episodes both with and without psychotic features. Monotherapy with an MS was also the first-line treatment for manic episodes without psychotic features (Table 1). Three medications, ARI, OLA and QUE, were the first-line medications for manic episodes both with and without psychotic features, while LIT was an additional first-line recommendation for manic episodes without psychotic features, and RIS was included among the first-line agents for manic episode with psychotic features. When combined with LIT or VAL, ARI, OLA, QUE and RIS were recommended as the first-line AAPs for manic episodes both with and without psychotic features; among these, OLA and QUE were the TOC when used in combination with LIT for manic episodes with psychotic features, and QUE was the TOC for combination with VAL for manic episodes with psychotic features (Table 1).

Step 2. Inadequate response to treatment in Step 1

In cases where patients responded poorly to initial monotherapy with one of the MSs, augmentation with an AAP was recommended as the TOC for partial response, and as the first-line for non-response. Combinations of two MSs were recommended as the first-line when the patient showed partial response to MS monotherapy, and switching from an MS to an alternate first-line MS or an AAP was the first-line treatment when the patient was non-responsive to MS monotherapy.

If the patient showed partial response to AAP monotherapy, adding an MS was the TOC for both types of manic episode. A combination of two AAPs was recommended as the first-line treatment for partially responsive psychotic mania; when monotherapy with an AAP resulted in no response, adding an MS was the TOC. Switching to an MS or another AAP was the first-line strategy for mania without psychotic features, and adding an MS or another AAP and switching to an alternate AAP were the first-line options for psychotic mania.

In cases where patients showed partial or non-response to the initial combined treatment with a MS and an AAP, the recommended first-line strategies for both types of mania were to switch the AAP to another AAP, and the MS to another MS, and add another AAP. Switching the MS in an MS/AAP combination therapy to an AAP (to instead use a combination of two AAPs) was the first-line treatment for non-responders with non-psychotic mania and partial or non-responders with psychotic mania. Adding another MS (a combination of two MSs and an AAP) was the first-line recommendation for partial or non-responders with non-psychotic mania and partial responders with psychotic mania. Switching the AAP to a MS (combination of two MSs) was the first-line for non-psychotic mania of non-response.

Step 3. Inadequate response to treatment in Step 2

When treatment using a combination of LIT, VAL, and one AAP failed at Step 2, switching the AAP to another AAP or adding another AAP (combination of LIT, VAL and two AAPs), and switching LIT or VAL to another AAP (combination of LIT or VAL and two AAPs) were recommended as first-line treatments for mania with or without psychotic features.

If a patient showed an inadequate response a combination of LIT or VAL and two AAPs at Step 2, switching one

Table 1. Preferred initial treatment strategies and medications for mania and hypomania

Diagnostic features	First-line strategies	First-line medications
Mania without psychotic features	MS + AAP	Monotherapy: ARI, LIT, OLA, QUE, or VAL
	MS or AAP monotherapy	Combination therapy: LIT/VAL + ARI/OLA/QUE/RIS
Mania with psychotic features	MS + AAP[a]	Monotherapy: ARI, OLA, QUE, or RIS
	AAP monotherapy	Combination therapy: LIT + OLA[a]/QUE[a] /ARI/RIS, VAL + QUE[a]/ARI/OLA/RIS
Hypomania	MS or AAP monotherapy	Monotherapy: ARI, LIT, QUE, or VAL
	MS + AAP	

AAP, atypical antipsychotics; ARI, aripiprazole; LIT, lithium; MS, mood stabilizers; OLA, olanzapine; QUE, quetiapine; RIS, risperidone; VAL, valproate. [a]Treatment of choice.

of the pre-existing AAPs to another AAP, or LIT or VAL to alternate MS, and adding another MS (combination of two MSs and two AAPs) were recommended as the first-line strategy for both types of mania. Switching one of the pre-existing AAPs to an MS (combination of two MSs and an AAP) was also the first-line strategy for non-psychotic mania.

If Step 2 treatment with a combination of two AAPs failed, adding an MS (combination of an MS and two AAPs), switching one of the pre-existing AAP to an alternate AAP or an MS were the recommended first-line treatment strategies for both types of mania.

Hypomanic Episode

The recommended first-line strategy for hypomania episodes was monotherapy with an MS or an AAP, or a combination of an MS and an AAP (Table 1). The preferred medications were ARI, LIT, QUE, and VAL.

In cases where patients showed partial or no response to initial MS monotherapy, switching the MS to another MS or an AAP, and augmentation with an AAP were recommended as the first-line treatment. If patients partially responded to AAP monotherapy, adding an MS was the TOC and adding an AAP was the first-line strategy. In cases of a non-response to initial AAP monotherapy, switching the AAP to another AAP or an MS, and adding a MS were recommended as the first-line treatment. The first-line treatment options for an inadequate response to the combination of an MS and an AAP was switching the MS to another MS or an AAP (combination of two AAPs), switching the AAP to another AAP, or adding another AAP (combination of an MS and two AAPs) or MS (combination of two MSs and an AAP).

Depressive Episodes

Step 1. Initial treatment

Monotherapy with an MS, AAP, or LMT, or a combination of an AAP with an MS or LMT were the first-line recommendations as the initial treatment strategy for mild to moderate depression (Table 2). The first-line recommendation for initial treatment of severe depressive episode without psychotic features was the combination of two agents comprising an MS, AAP, or LMT. The combination of an MS and AAP was the TOC for patients with depressive episode with psychotic features, and the combination of an AAP with LMT was also recommended as the first-line treatment strategy (Table 2). The first-line recommendations included ARI, LIT, LMT, OLA, QUE, and VAL for monotherapy of psychotic and non-psychotic depression, and monotherapy for psychotic depression, while ARI, OLA, QUE, and RIS were the first-line AAPs for combined therapy of psychotic depression.

Step 2. Inadequate response to treatment in Step 1

When the response to the initial treatment strategy was insufficient, adding an AAP or LMT was the first-line second step treatment for partial or non-responders with mild to moderate depression to initial MS monotherapy. In addition, switching the MS to LMT or another MS was the first-line recommendation for non-responders, and adding another MS was also the first-line recommendation for partial responders. When treatment with AAP monotherapy was not effective at Step 1, adding an MS or LMT was recommended as the first-line for the case of both partial and non-responders. Switching the AAP to an MS or LMT was the first-line recommendation for non-res-

Table 2. Preferred initial treatment strategies and medications for bipolar depression

Diagnostic features	First-line strategies	First-line MS	First-line AAP
Mild to moderate depression	MS, LMT or AAP monotherapy MS + AAP AAP + LMT	Monotherapy: LIT, LMT, or VAL Combination therapy: LIT, LMT, or VAL	Monotherapy: ARI, QUE, or OLA Combination therapy: ARI, QUE, or OLA
Severe depression without psychotic features	MS + AAP AAP+LMT MS+LMT		
Severe depression with psychotic features	MS + AAP[a] AAP + LMT	LIT, LMT, or VAL	Monotherapy: ARI, QUE, or OLA Combination therapy: ARI, QUE, OLA, or RIS

AAP, atypical antipsychotics; ARI, aripiprazole; LIT, lithium; LMT, lamotrigine; MS, mood stabilizers; OLA, olanzapine; QUE, quetiapine; RIS, risperidone; VAL, valproate.
[a]Treatment of choice.

ponders, while the addition of another AAP (combination of two AAPs) was recommended for partial responders. In cases of inadequate response to LMT monotherapy, adding an MS or an AAP was the first-line strategy for both partial and non-responders, and switching from LMT to an MS or an AAP was also a first-line option for non-responders.

In cases where patients with severe depressive episodes did not respond or only partially responded to initial combined treatment with an MS and an AAP, the first-line recommendations were adding LMT (combination of an MS, an AAP and LMT), another AAP (combination of a MS and two AAPs) or another MS (combination of an AAP and two MSs) or switching the AAP to an alternate AAP. Switching the MS to an alternate MS or LMT was the first-line treatment for non-responders. If initial treatment with the combination of an AAP and LMT showed an insufficient response, adding an MS (combination of an AAP, LMT and an MS) or an AAP (combination of two AAPs and LMT), or switching the AAP to another AAP were recommended as the first-line treatment for both partial and non-responders. When the combination of a MS with an AD did not result sufficient response, adding an AAP (combination of a MS, an AD and an AAP) or LMT (combination of a MS, an AD and LMT) was the first-line strategy. For non-responders, switching the MS to an alternate MS or LMT was recommended, and adding another MS (combination of two MSs and an AD) was the first-line recommendation for partial responders. If combination of an MS and LMT resulted in only partial or no response, adding an AAP was recommended as the first-line option. In addition, switching LMT to an AAP, and MS to an alternate MS were the first-line treatments for non-responders. If the initial strategy for severe depressive episodes with psychotic features was the combination of an AAP and an AD, adding an MS, LMT or another AAP was recommended for both partial and non-responders. Switching the AAP to an alternate AAP was also included among the first-line treatments for non-responders.

Step 3. Inadequate response to treatment in Step 2

Use of CLZ, buspirone, thyroid hormone, or a psychostimulant were recommended as the second-line treatment options when treatment at Step 2 failed to produce a response. Figure 1C and 1D presents the algorithm for treating bipolar depression.

Mixed Features

In the KMAP-BP 2022, bipolar disorder with mixed features was subdivided into three types: mixed features with predominant manic symptoms (mania with mixed features/mixed mania), mixed features with predominant depressive symptoms (depression with mixed features/mixed depression), and mixed features without predominance, in which with the severity of manic and depressive symptoms are similar.

Step 1. Initial treatment

The initial treatment strategies for mania with mixed features and mixed features without predominance were identical. The combination of an MS and an AAP and monotherapy with an AAP or an MS were the first-line treatment strategies (Table 3). Among these, a combination of an MS and an AAP was the TOC for mixed mania. In case of mixed depression, combination of a MS and an AAP, a MS and LMT, and an AAP and LMT, and monotherapy with a MS or an AAP were the first-line. The preferred medication as monotherapy was ARI, LIT, OLA, QUE, and VAL for all types of mixed features. RIS for mixed mania and LMT for mixed depression also included as the first-line.

Step 2. Inadequate response to treatment in Step 1

If patients with mixed mania responded insufficiently to initial MS monotherapy, adding an AAP (TOC) or another MS (first-line) was recommended. In cases of an in-

Table 3. Preferred initial treatment strategies for mixed features

Diagnostic features	First-line strategies	First-line medications
Mixed mania	MS + AAP[a] AAP or MS monotherapy	VAL, LIT, ARI, OLA, QUE, RIS
Mixed depression	MS + AAP AAP + LMT AAP monotherapy MS + LMT MS monotherapy	LIT, VAL, LMT, ARI, OLA, QUE
Mixed features without predominance	MS + AAP AAP monotherapy MS monotherapy	LIT, VAL, ARI, OLA, QUE

AAP, atypical antipsychotics; ARI, aripiprazole; LIT, lithium; LMT, lamotrigine; MS, mood stabilizers; OLA, olanzapine; QUE, quetiapine; RIS, risperidone; VAL, valproate.
[a]Treatment of choice.

sufficient response to initial treatment with AAP mono-therapy, adding a MS or adding another AAP was the first-line recommendation. When there was insufficient treatment response for the combination of an MS and an AAP, switching the MS to an AAP (combination of two AAPs) or an alternate MS, switching the AAP to another AAP, or adding another MS or AAP (combination of two MSs and an AAP or a MS and two AAPs) were recommended first-line treatments.

The recommended strategy at Step 2 varied from the initial treatment strategy when patients with depression and mixed features did not show a sufficient response. In cases of an insufficient response to monotherapy, adding another MS, an AAP or LMT to MS monotherapy, adding an MS, or LMT or an alternate AAP to AAP monotherapy, or adding an MS or an AAP for LMT monotherapy were recommended as the first-line strategies. If patients responded poorly to a combination of an MS and an AAP, switching the AAP to another AAP or the MS to another MS, and adding LMT (combination of a MS, an AAP and LMT) or another MS (combination of two MSs and an AAP) or AAP (combination of a MS and two AAPs) were recommended as first-line treatments. Switching the MS to an AAP or adding an AAP were recommended in cases of a poor response to the combination of MS and LMT. If the combination of an AAP and LMT failed, then adding an MS or another AAP, or switching the AAP to an alternate AAP were first-line treatments. When AD was used in combination with an MS as the first-step and failed to produce an adequate response, switching the AD to an AAP or adding an AAP or LMT were recommended. If treatment at Step 1 used a combination of AD and an AAP, then adding an MS or LMT was considered as the first-line of second-step strategy.

Switching to or adding another first-line medication was recommended in cases where the initial treatment produced an insufficient response in patients with mixed features without predominance. If monotherapy with an MS failed, adding an AAP or another MS was the first-line treatment option at Step 2. When AAP monotherapy failed at Step 1, adding an MS or another AAP was the first-line strategy. If first-line monotherapy with LMT did not produce a sufficient response, adding an MS or an AAP was the first-line combination treatment. When combination of an MS and an AAP failed to achieve an adequate response, adding LMT or another MS or AAP, and

switching the MS to another MS or the AAP to another AAP were recommended as first-line treatments. After the combination of MS and LMT as the initial strategy, adding an AAP, and switching the MS or LMT to AAP was the first-line option as the next step strategy. When the combination of AAP and LMT treatment was unsuccessful, switching the LMT to a MS, and AAP to an alternate AAP, and adding a MS were recommended. Switching AD to an AAP or adding an AAP for the unsuccessful initial combination of MS and AD, and switching AD to MS or adding a MS for an unsuccessful initial combination of AAP and AD were recommended as the next step.

Rapid Cycling

The first-line treatment strategies for rapid cycling were monotherapy with an AAP or a MS, and the combination of a MS and an AAP for both untreated manic and depressive phase of rapid cycling. Combinations of LMT and an AAP or a MS were also recommended as first-line treatments for untreated depressive phase of rapid cycling. When patients in the manic phase had an insufficient response to MS monotherapy, the TOC was the combination of an MS and an AAP, and the first-line strategy was combination of two MSs. When patients in the depressive phase did not respond to a combination of an MS and an AD, adding an AAP or LMT were recommended as first-line options. The first-line medications for all phases (manic, depressive, mixed, and hypomanic) of rapid cycling were ARI, LIT, OLA, QUE, and VAL: RIS was the first-line medication for manic and mixed phases and LMT was the first-line medication for treatment of the depressive phase.

When manic breakthrough occurred during rapid cycling, adding an AAP to initial monotherapy with LIT, VAL, CBZ or a combination of LIT and VAL were recommended as the TOC. The combination of two MSs (e.g., LIT and VAL, CBZ and LIT or VAL) was the first-line strategy. In cases of manic breakthrough during AAP monotherapy, adding VAL was the TOC and adding LIT or another AAP was the first-line strategy.

For patients in a depressive phase who had previously experienced SSRI-induced manic/hypomanic switch or cycle acceleration associated with SSRI treatment, the recommended first-line strategies were a combination of LIT or VAL and an AAP, LMT or an alternate MS, and combination of an MS or an AAP with LMT, or an AAP with LMT.

Maintenance Therapy

The first-line strategy to prevent manic episodes included monotherapy with a MS or an AAP, and combination therapy with a MS and an AAP (Table 4). The preferred AAP was ARI, QUE, or OLZ for both monotherapy and in combination with a MS. Monotherapy with an MS, an AAP, or LMT, a combination of two of these three medications, or a combination of two MSs were all recommended as first-line maintenance therapy to prevent a depressive episode (Table 4).

In cases when acute treatment of manic symptoms with AAP in combination with a MS was successful, 73.6% of experts recommended not discontinuing the AAP during maintenance therapy. The mean recommended duration to maintain AAP was minimum 16.1 weeks to maximum 42.3 weeks after reaching remission. When the use of AD was constrained during the maintenance phase, bupropion should be considered. In cases when acute treatment of depression with AD combined with a MS or AAP was successful, 26.4% of the experts maintained AD as long as possible for patients with psychotic depression, while 19.5% did so for non-psychotic severe depression, and 13.8% for mild to moderate depression. The experts recommended discontinuing the AD after a minimum of 9.3 weeks to a maximum of 20.8 weeks after reaching remission for mild to moderate depression, a minimum of 11.1 weeks to a maximum of 26.0 weeks for non-psychotic severe depression, and a minimum of 11.0 weeks to a maximum of 25.9 weeks for psychotic depression.

When remission of a mixed state was attained through polypharmacy, the percentage of experts who recommended not discontinuing AAP was 77.0% for mixed mania, 74.7% for mixed depression, and 79.3% for mixed

Table 4. Preferred treatment strategies for maintenance

Episode	First-line strategies
Preventing manic relapse	MS monotherapy
	MS + AAP
	AAP monotherapy
Preventing depressive relapse	MS + AAP
	MS + LMT
	LMT monotherapy
	AAP monotherapy
	MS monotherapy
	AAP + LMT
	2MS

AAP, atypical antipsychotics; LMT, lamotrigine; MS, mood stabilizers.

features without predominance, respectively. About 88.5% of experts recommended not discontinuing an MS during the maintenance phase for mixed mania, 90.8% for mixed depression, and 88.5% for mixed features without predominance. For cases of remission due to a combination of ADs and an MS or AAP, most experts recommended discontinuing AD therapy; the recommended duration of AD therapy for a mixed state was a minimum of 6.7 weeks to a maximum of 16.6 weeks for mixed mania, a minimum of 9.6 weeks to a maximum of 24.1 weeks for mixed depression, and a minimum 8.0 weeks to maximum 19.5 weeks for mixed features without predominance.

The maintenance treatment strategies for bipolar II disorder were similar to those for bipolar I disorder. Monotherapy with an MS or AAP, or a combination of an MS and an AAP were also recommended as maintenance therapy for bipolar II disorder with a history of recent hypomanic episodes; ARI, LIT, OLA, QUE, RIS, and VAL were recommended for these cases. In cases of bipolar II disorder with a history of recent depressive episodes, monotherapy with an MS, an AAP or LMT, and combination of an MS and LMT or an AAP, and LMT and an AAP were recommended. The TOC for maintenance after depressive episodes was ARI, and LIT, LMT, OLA, QUE, and VAL were the first-line medications. When AD maintenance was needed, bupropion was preferred.

Pharmacotherapy Considering Safety, Tolerability, and Physical Comorbidities

When significant weight gain associated pharmacotherapy has occurred, the TOC was behavioral and diet modifications, and switching to another medication with a low risk of weight gain was also a recommended strategy. If additional medications were needed to counteract the weight gain, bupropion, Contrave® (Orexigen Therapeutics, La Jolla, CA, USA) (a combination of bupropion and naltrexone), liraglutide, metformin, naltrexone, orlistat and topiramate were preferred. When patients expressed concerns about potential weight gain, ARI, LMT and ZIP were the first-line treatments. For patients who failed to attenuate continuous weight gain with behavioral and diet modifications, the experts recommended pharmacological interventions when the criteria for overweight were met. For patients who comorbid with metabolic disorders, ARI, LMT and ZIP were the first-line recommendations when considering both efficacy and safety/tolerability.

When patients experienced signs or symptoms of hyperprolactinemia including amenorrhea or galactorrhea during treatment with AAP, reduction of the current does was the first strategy to be considered, and switching the AAP to an alternate AAP with a low risk for hyperprolactinemia, and adding ARI were considered alternative strategies.

If benign skin rashes appeared during LMT treatment, the preferred strategy was discontinuation of LMT, and reducing the dose and close monitoring could be an alternative strategy.

Both ARI and LMT were first-line treatments for patients with comorbid cardiovascular disease. Recommended medications were ARI and LIT for patients with hepatic comorbidities, ARI, LMT, QUE and VAL for renal comorbidities, and ARI and VAL for cerebrovascular comorbidities.

Pharmacological Management of Special Populations

For women of child-bearing age, ARI was the first-line medication. No first-line recommendation was made for women with bipolar disorder during pregnancy or lactation. For geriatric bipolar patients, monotherapy with AAP or an MS, and a combination of an MS and an AAP were recommended as first-line treatment for acute mania (Table 5); these included ARI, LIT, OLA, QUE, RIS, and VAL as first-line medications to treat manic symptoms. The recommended first-line strategies for geriatric bipolar depression were monotherapy with an AAP, an MS or LMT, and a combination of two of MS, AAP, or LMT. The recommended first-line MSs for bipolar depression were LIT, LMT and VAL, and the recommended first-line AAPs were ARI, OLA and QUE. In cases where cognitive impairment was comorbid with bipolar disorder, ARI was recommended as the first-line treatment option.

In children (age $\leq$ 12 years), the first-line treatment strategies were monotherapy with an AAP and a combination of a MS and an AAP for both manic and depressive episodes (Table 5). In adolescents (age 13−18 years), combination of an MS and an AAP was the TOC, and monotherapy with an AAP or a MS was the firs-line recommendation for manic episode (Table 5). For cases of depressive episode in adolescents, monotherapy with an AAP and a combination with an MS were the first-line strategies. Monotherapy with an MS for adolescents with bipolar depression was graded as the first-line, but did not reach consensus. Among AAPs, ARI and RIS were the first-line options for children and adolescents, and QUE was also recommended as the first-line agent for adolescents with manic or depressive episodes, while ARI was the TOC for depression in children and adolescents. Among

Table 5. Preferred initial treatment strategies and medications for pediatric and geriatric bipolar patients

Clinical features	First-line strategies	First-line MSs	First-line AAP
Mania in the elderly	AAP monotherapy MS monotherapy MS + AAP	VAL, LIT	ARI, QUE, OLA, RIS
Depression in the elderly	MS + AAP AAP monotherapy MS monotherapy LMT monotherapy AAP + LMT MS + LMT	LIT, VAL, LMT	ARI, QUE, OLA
Mania in children	MS + AAP AAP monotherapy	VAL	RIS, ARI
Depression in children	AAP monotherapy MS + AAP	No first-line recommendation	ARI*, RIS
Mania in adolescents	MS + AAP[a] MS monotherapy AAP monotherapy	LIT, VAL	ARI, QUE, RIS
Depression in adolescents	AAP monotherapy MS+AAP MS monotherapy[b]	LIT, VAL	ARI[a], QUE, RIS

AAP, atypical antipsychotics; ARI, aripiprazole; LIT, lithium; LMT, lamotrigine; MS, mood stabilizers; OLA, olanzapine; QUE, quetiapine; RIS, risperidone; VAL, valproate.
[a]Treatment of choice, [b]Non-consensus.

MSs, LIT and VAL were the first-line recommendations for adolescents with mania or depression: VAL was the first-line for mania in children, but there was no first-line recommendation among MSs for children with depression.

DISCUSSION

The most remarkable change from the 2018 version of the KMAP-BP [18], was increased preference for mono-therapeutic approaches at the first step for mixed-state and rapid-cycling bipolar disorder, and at the second step for mania and depression. Monotherapy with MSs was newly included in the first-line strategy for manic mixed state and mixed state without predominance. Monotherapy with either an AAP or MS was also added to the first-line strategy for depressive mixed states, and for untreated manic or depressive phases of rapid cycling. Moreover, trying another monotherapy with an MS or an AAP after initial failure of MS or AAP monotherapy in non-psychotic mania was considered a second-line treatment strategy in the previous version of the KMAP-BP, but was considered a first-line option in this version. In the KMAP-BP 2018, only a combination of an MS and an AAP was considered a first-line option when initial mono-therapy for non-psychotic mania failed to produce an adequate response. Additionally, for non-responsive mild-to-moderate MDE, switching from an initial MS to another MS or LMT (i.e., trying another monotherapy) was also included as the first-line strategy.

The increased preference for monotherapy with AAP or MSs for mixed-state bipolar disorder in the KMAP-BP 2022 could be understandable given recent evidence-based guidelines recommending monotherapy for the treatment of this condition. In recent recommendations from Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) for the management of patients with bipolar disorder with mixed presentation [20] there were no first-line recommended agents for both manic mixed and depressive mixed state, although the authors recommended asenapine, cariprazine, VAL and ARI as second-line treatments for manic mixed state, and cariprazine, lurasidone for depressive mixed state [20]. For Diagnostic and Statistical Manual of Mental Disorders, 4th edition mixed episodes, which correspond to mixed state without predominance in this study, asenapine and ARI were recommended as

first-line treatments [20]. It is noteworthy that, in contrast with the CANMAT and ISBD recommendations, the KMAP-BP 2022 recommended a combination of an MS and AAP as the first-line treatment for all three types of mixed state. The CANMAT and ISBD recommended combination treatment as the third-line option for all three types of mixed state (e.g., a combination of OLA with LIT or VAL for manic mixed state, OLA and fluoxetine for depressive mixed state, and LIT + VAL/carbamazepine for mixed state without predominance). The only exception was the combination of OLA with LIT or VAL as the second-line for mixed state without predominance [20]. However, this discrepancy may reflect the particular circumstances in Korea where several first-line agents recommended by CANMAT and ISBD, including asenapine, cariprazine and lurasidone, are unavailable. Hence, the World Federation of Societies of Biological Psychiatry guidelines for the treatment of mixed state bipolar disorder, which recommend monotherapy with OLA and a combination of OLA and VAL as grade 2 for manic mixed state, and monotherapy with ARI or paliperidone for manic mixed state, a combination of QUE for depressive symptoms of manic mixed state and ziprasidone combination for depressive mixed state as grade 3 [6], combination strategies were preferred comparably to monotherapy in KMAP-BP 2022.

It is interesting that monotherapy was newly added as a first-line strategy for rapid cycling in the KMAP-BP 2022. Published studies examining the pharmacological treatment of rapid cycling are lacking, and there is therefore no clear consensus with respect to its optimal pharmacological management [21]. Given treatment of rapid cycling may require combination treatments more often than monotherapies, it has been suggested that pharmacotherapy for rapid cycling should be based on effectiveness in the maintenance phase [7]. However, in a recent systematic review [22], the role of combination therapy was unclear, and the usefulness of AAPs, VAL and LMT monotherapy in rapid cycling was suggested.

When initial monotherapy for manic or depressive episodes resulted in an insufficient response, switching to or adding on an alternate agent could be the next step. Combination treatment may be more efficacious for manic episodes, but may also be more burdensome than the continuation of MS or AAP monotherapy when either monotherapy has not been successful [23,24]. The KMAP-BP

2022 recommended switching drug regimens only when initial monotherapy produced no response for both manic and depressive episodes, while combination therapy was recommended when initial monotherapy produce either no or a partial response. Because it is still unclear whether MS and AAP combinations are more beneficial than monotherapy for both manic and depressive episodes, the context of the treatment goals should be considered when determining whether an agent should be switched within any current treatment regimen or another agent added. When a partial response has occurred, it may be rational to apply a combination strategy to minimize the risk of loss of any therapeutic benefit from the initial monotherapy, or to combine agents with predominantly efficacious for different phases of bipolar disorder. However, as switching drugs is reported to be preferred over combination strategies in principle [7], the changes in the KMAP-BP 2022 to include more monotherapeutic recommendations appear to reflect increasing concerns regarding the safety of polypharmacy.

Other notable changes in the KMAP-BP 2022, as compared to the previous version, include blurring the traditional boundary between MSs and AAPs. In the KMAP-BP 2018, the 'gold standard' combination was the combination of MSs and AAPs. For example, when the initial combination of an MS and AAP fails, the recommended strategies at Step 2 were to combine an MS and an alternate AAP, an AAP and an alternate MS, two MSs and an AAP, or two AAPs and a MS; all combinations included at least one AAP and one MS. In the KMAP-BP 2018, when initial treatment with a combination of an MS and an AAP for MDE fails, adding another AAP was included as a first-line treatment option, but adding another MS was a second-line option. Moreover, for treatment of bipolar disorder with mixed features, monotherapy with an AAP was the first-line treatment for manic mixed state, but monotherapy with an MS was a second-line option in the KMAP-BP 2018. However, these preferences regarding the use of MSs and AAPs has largely disappeared from the KMAP-BP 2022, except for recommendations to use AAP when psychotic features are present.

The term 'mood stabilizer' has been widely used in the psychiatric literature despite the absence of a consensus definition [25]. Traditionally, 'mood stabilizer' has been used to refer LIT, VAL, and carbamazepine, with LMT having also been included recently [26]. Generally, agents

with efficacy in each of four distinct uses—acute manic and depressive symptoms, and prevention of manic and depressive symptoms—are considered MSs [27]. Some studies that aimed to determine which agents meet the definition of MS reported that only LIT fulfilled the above definition and some have arguably achieved it prematurely [27,28]. More recent studies have expanded the definition of MSs to include some AAPs [26,29,30]. The results from this study could be interpreted as supporting the latter contention. Moreover, when examining the AAP and MS recommendations/preferences presented in the KMAP-BP over time, there were differences between 2002 and 2006, but the differences disappeared in 2010 and thereafter [31].

A more substantive change in KMAP-BP 2022 was with respect to the use of ADs. Recommendations for use of ADs have gradually decreased in the KMAP-BPs: the use of an AD in combination with other agents as a first-line treatment appeared in the KMAP-BP 2002, but did not appear in the KMAP-BP 2006 or subsequent editions, especially for mild-to-moderate MDE [31]. From 2002 to 201, adjunctive ADs were included in first-line strategies for severe MDE (with or without psychotic features) in the KMAP-BP, and ADs in combination with AAPs was a first-line combination for severe MDE with psychotic features in the 2018 version. However, use of ADs was not included among the first-line options in the 2022 version.

These changes in the recommendations presented in the KMAP-BP over time reflect the controversy and debate surrounding the use of ADs for bipolar depression due to potentially increased risk of harm, such as affective switching, higher suicide risk, and increased risk of development of mixed states, and a limited evidence for their efficacy [32,33]. Moreover, two recent meta-analyses [34,35] reported that adjunctive ADs in bipolar depression yield only small, non-significant benefits without increased risk of switching into mania. The authors of a recent meta-analysis concluded that their findings supported of guideline recommendations to use adjunctive AD as a second-line or lower-category treatment [35].

The main limitation of this study is that it was based on consensus data from Korean experts rather than on evidences from clinical trials. However, data derived from rigorously designed randomized controlled trials have limitations regarding generalizability and characteristics of the sample, and may be unrepresentative of real-world

clinical practice. Moreover, most clinical trials originate from Western countries, and data and treatment guidelines devised in Western countries are not automatically applicable to Korean patients. Accordingly, the KMAP-BP 2022 recommended a variety of treatment options based on expert consensus which reflect the unique characteristics of the Korean healthcare environment, clinical experience, and experimental evidence. It would be helpful for clinicians in that KMAP-BP 2022 suggest treatment options for clinical situations with limited evidence-based data, as well. Another limitation is the representativeness of the review committee. There are 3,940 psychiatrists in Korea, and a total of 127 psychiatrists may be not enough to reach a valid consensus. Finally, the study algorithm did not include novel pharmacological agents such as lurasidone, asenapine, and cariprazine that have been recommended in foreign clinical practice guidelines [5,7,36] because they are not available in South Korea. Hence, this guideline may have limited applicability for clinicians in other countries, although it could be informative in some countries with similar restricted access to newer drugs.

To our knowledge, the KMAP-BP is the only set of treatment guidelines for bipolar disorder in Asia, with the exception of one Japanese guideline published in 2013 [37]. Thus, despite these limitations, we expect the KMAP-BP 2022 will provide clinically meaningful information regarding appropriate strategies to treat patients with bipolar disorder.

■ **Author Contributions**

Conceptualization: Young Sup Woo, Bo-Hyun Yoon, Won-Myong Bahk. Data curation: Young Sup Woo, Won-Myong Bahk, Jong-Hyun Jeong, Jung Goo Lee, Won Kim, InKi Sohn, Sung-Yong Park, Se-Hoon Shim, Jeong Seok Seo, IL Han Choo, Chan-Mo Yang, Myung Hun Jung, Duk-In Jon, Moon-Doo Kim, Bo-Hyun Yoon. Formal analysis: Young Sup Woo, Jeong Seok Seo, Bo-Hyun Yoon, Won-Myong Bahk. Funding acquisition: Won-Myong Bahk. Investigation: Young Sup Woo, Won-Myong Bahk, Jong-Hyun Jeong, Jung Goo Lee, Won Kim, InKi Sohn, Sung-Yong Park, Se-Hoon Shim, Jeong Seok Seo, IL Han Choo, Chan-Mo Yang, Myung Hun Jung, Duk-In Jon, Moon-Doo Kim, Bo-Hyun Yoon. Methodology: Young Sup Woo, Won-Myong Bahk, Jong-Hyun Jeong, Jung Goo Lee, Won Kim, InKi Sohn, Sung-Yong Park, Se-Hoon Shim, Jeong Seok Seo, IL Han Choo, Chan-Mo Yang, Myung Hun Jung, Duk-In Jon, Moon-Doo Kim, Bo-Hyun Yoon. Project administration: Young Sup Woo, Bo-Hyun Yoon, Won-Myong Bahk. Writing—original draft: Young Sup Woo. Writing—review & editing: Bo-Hyun Yoon, Won-Myong Bahk.

■ **ORCID**

Young Sup Woo	https://orcid.org/0000-0002-0961-838X
Won-Myong Bahk	https://orcid.org/0000-0002-0156-2510
Jong-Hyun Jeong	https://orcid.org/0000-0003-3570-7607
Jung Goo Lee	https://orcid.org/0000-0003-3393-2667
Won Kim	https://orcid.org/0000-0002-5478-7350
InKi Sohn	https://orcid.org/0000-0002-5724-5901
Sung-Yong Park	https://orcid.org/0000-0002-8685-620X
Se-Hoon Shim	https://orcid.org/0000-0002-3137-6591
Jeong Seok Seo	https://orcid.org/0000-0002-4880-3684
IL Han Choo	https://orcid.org/0000-0001-6547-9735
Chan-Mo Yang	https://orcid.org/0000-0002-4959-7595
Myung Hun Jung	https://orcid.org/0000-0003-2393-3930
Duk-In Jon	https://orcid.org/0000-0002-1565-7940
Moon-Doo Kim	https://orcid.org/0000-0002-6441-630X
Bo-Hyun Yoon	https://orcid.org/0000-0002-3882-7930

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