Point-by-point Response to the reviewers' comments:

Specific Comments to Authors:

This was interesting study on relapse of depressive symptoms among patients with major depressive disorder (MDD) who were treated with ECT, and some of them developed bipolar disorder (BD) during continuation/maintenance treatment. I thought that the most significant findings of the study were the higher prevalence of depressive relapses, the shorter time to depressive relapse, and the predictive ability of the time to relapse among patients with BD. These findings may have clinical implications, but I thought their importance was rather overstated by the authors. Moreover, there were several issues in the design, results and discussion of findings of this study that need to be either clarified or acknowledged as limiting factors.

Thank you very much for your detailed review.

We have revised the manuscript following your comments. We believe that this manuscript has been improved.

METHODS The way the diagnosis of MDD and BD were made was of utmost importance in this study.

1. Diagnosis of MDD The authors state that - "Patients were diagnosed by a certified psychiatrist of the Japanese Board of Psychiatry (JBP) and cross-reviewed by another certified JBP psychiatrist at an inpatient conference based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)". This was somewhat surprising given that this was a retrospective study. The authors need to clarify whether diagnosis based on DSM criteria and made by two psychiatrists is standard practice in their set-up, or were the application of criteria and the ascertainment of diagnoses made later at the time of the conduct of the study, i.e. retrospectively. In either case use of structured diagnoses would have been better than consensus diagnoses, especially since the change of diagnosis from MDD to BD was central to this study.

P 6 lines 4-11: We routinely have weekly conferences with multiple psychiatrists of the Japanese Board of Psychiatry (JBP) to decide on diagnoses. We have revised the manuscript to clarify this issue.

2. Diagnosis of BD Though details of how the diagnosis of MDD was made are provided, there is no clarity on how the diagnosis of BD was made. It is not clear whether DSM IV criteria or structured interviews were used, whether the patients had hypomanic or manic episodes, and what was the proportion of BP I and BP II among patients who switched to BD. This appears to be a major shortcoming in a study where the change of diagnosis from MDD to BD was the major focus.

P 6 lines 7-8: We have clarified that BP was also diagnosed at weekly conferences.

P 6 lines 22-28: We have added how BP, BP1, and BP2 were diagnosed using DSM-IV-TR.

P 17 lines 3-5: We have added an explanation for not using structured interviews as a limitation.

3. Prior risk factors for BD among patients The authors state that -"We obtained patient data from medical records: age, sex, number, and date of ECT, HAMD-21, GAF, diagnosis, the onset of diseases, medication, psychotic features, and depressive symptoms. There is no mention of mixed episodes, which the authors acknowledge as limitation. It is not clear how "severe MDD" was determined - by DSM criteria or by HAM-D ratings, whether patients had high levels of anxiety symptoms, and family history of mood disorders. Prior treatment with antidepressants is not mentioned. All these could be potential risk factors of the switch to BD. More importantly, some of these patients with MDD might have had a bipolar spectrum disorder which was missed. Therefore, the lack of a validated scale such as the Mood Disorder Questionnaire or the Bipolar Spectrum Diagnostic Scale was a limiting factor.

P 6 lines 10-11: We have added an explanation for not recruiting BP patients or patients with mixed episodes initially.

We have deleted all instances of “severe” qualifying MDD from this manuscript because the referenced systemic review (*Psychiatry Res* 2020;294:113497) did not highlight the severity of MDD in the application of ECT.

P 7 lines 24-26; P 17 line 6-8: We did not analyze anxiety symptoms and the family history of BP. We have explained why we did not use anxiety symptoms. We add not using family history as a limitation.

P 7 lines 4-13: We have described how we decided to perform ECT in patients with MDD. Prior treatments with antidepressants have been highlighted in P 7 lines 9-10.

P 17 lines 3-5: We diagnosed BP based on the consensus of psychiatrists and not the scales for BP. We have clarified this as a limitation.

4. Definitions of relapse and grouping of patients The authors have defined relapse on the basis of depressive episodes. The patient groups with/without relapse were then divided into those who switched to BD and those who retained the diagnosis of MDD. But this is not clearly stated. For example at the beginning of the section on "Groups A, B, and others" the authors simply state that - " Fifty-six subjects who did not experience relapse after the first course of ECT were classified as A, B, and others." - with no mention of depressive episodes being the indicator of relapse. This creates a lot of confusion as I have mentioned later in the results section. "Group B: Eleven subjects with BP, whose diagnoses were changed from MDD to BP owing to the appearance of manic symptoms during their first course of ECT or during subsequent maintenance therapy with antidepressants, which then persisted after treatment was discontinued, were maintained in remission using mood stabilizers." Note that the DSM 5 now specifies that - A full hypomanic/manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative or a bipolar diathesis. Although applying this criteria to diagnose BD was not possible because DSM IV criteria were used. Nevertheless, information on the nature of episodes (mania or hypomania), and on how long did full episodes persist after discontinuing antidepressants is required to confirm the diagnosis of BD. If such information is not available this should be acknowledged as a limitation. "Group D: Twenty-one subjects with BP, whose diagnoses were changed from MDD to BP because mania appeared during C/M-ECT with antidepressants and then persisted after treatment was discontinued, were maintained in remission by mood stabilizers and C/M-ECT was discontinued." The standard practice for ECT-induced mania is to continue ECTs because they are effective treatments for hypomania/mania. The same considerations for proper diagnosis of BD also apply to this group.

To reduce confusion, we have moved the “Definitions of remission and relapse” and “Criterion for changing diagnosis” paragraphs to just after the “Participants”. We have also added an explanation of the footnote for figure 2. We moved description of excluded subjects with schizophrenia, epilepsy, chronic pain, or Alzheimer's disease during the follow-up from “Group classification” section in methods to “Characteristics of the participants” in results. We corrected some classification errors.

As the reviewer pointed out, we used DSM-IV and not DSM-5. Thus, the decisions on hypomanic episodes were simple in this study.

Page 8 lines 22-23; P 9 lines 11-12: We have added the number of patients with BP1 and BP2 in groups B and D.

P 14 lines 19-24 We have added a paragraph on ECT–induced mania to the Discussion section.

5. Follow-up regimens Maintenance pharmacotherapy with TCAs which have the highest rates of switch for the majority of patients was somewhat surprising. It is not made clear whether this had something to do with the severity of depression, psychotic features, or lack of response to prior antidepressants. The authors justify this by quoting - "Sackeim et al.reported that nortriptyline has an advantage in increasing remission compared to venlafaxine when concomitantly administered with ECT to patients with MDD[22]." However the more recent PRIDE study (Kellner et al. 2016) obtained similar response rates with the combination of c/m ECT and venlafaxine. The authors state that - "When 36of the subjects experienced a relapse, a second course of ECT was administered, and remission was achieved. Subsequently, the treatment was changed to C/M-ECT using antidepressants. If no relapse was observed, the intervals of C/M-ECTs was gradually increased from one to six months. The phrase - the treatment was changed to C/M-ECT using antidepressants is not clear. should it be C/M-ECT with antidepressants?

According to a Danish report on treatment-resistant depression (Journal of Affective Disorders. 2021;287:204–213), the most common treatment combined with ECT was TCA, followed by SNRI. Thus, the choice of TCA for ECT may be common.

P 10 line 6: Venlafaxine was not available in Japan during the study period.

P 10 line 12: We changed to “C/M-ECT with antidepressants” as the reviewer suggested.

RESULTS

6. Diagnostic group-specific characteristics (MDD vs. BP) . BP subjects MDD subjects BP subjects p-values HAMD-21 on discharge 7.13±5.03 6.77±4.14 7.72±6.26 0.008 It appeared that the MDD group was more severely ill and had psychotic features more often. This is somewhat contrary to findings in literature which suggest that MDD with onset before 25 years, 3 or more episodes and psychotic symptoms is more likely to switch to BD. Along with the rather late onset, low prevalence of psychotic symptoms and h/o switch on antidepressants , the BD group of this study appeared to be somewhat atypical. Perhaps they were suffering from a bipolar spectrum disorder which was unmasked by ECT or antidepressants (often referred to as latent bipolars). Or, they had only mild and transient switches that did not were not typical BP I or BP II disorder. However, without further details about the BD group such as onset, duration, course of manic/hypomanic episodes it is difficult to decide. It is also not clear why a manic symptom rating scale was not used.

P 15 lines 8-11: Our patients were relatively old. This may be the reason our MDD group had more severe illness and more frequent psychotic features. We have added this to the Discussion section. Thank you.

P8 lines 23-25; P 9 lines 9-13: We discontinued the ECT and antidepressants and used mood stabilizers after manic episodes were confirmed.

P 17 lines 5-6: As described above, we did not highlight the BP scales as our limitation. It is difficult to diagnose BP without manic episodes with or without such scales.

7. Figure 2 The depiction of patients in the figure and the descriptions of groups earlier in the methods section are somewhat confusing. According to the authors 56 patients did not relapse. What they seem to mean is that these 56 patients did not have any further depressive episodes after initial remission and subsequent treatment with antidepressants or mood stabilizers but this is not clearly stated in the methods section. Moreover, 11 patients developed manic symptoms and diagnosis was changed to BD. This is technically a recurrence, but this group cannot be equated with the group A, that is patients with MDD without relapse of depression. There are similar issues with group C and D. This becomes even more confusing when the authors compare MDD and BD for differences in prevalence of relapse and period until relapse. Here they are combining groups B (without relapse) and D (with relapse). Firstly the section is titled " Differences in relapse duration between diagnostically changed and unchanged groups". But what is included is a comparison of "percentage of relapses". Then they state that - "A higher percentage of relapses was found in subjects whose diagnosis was changed from MDD to BP (65.6%: Group D/Groups B + D) than in those whose diagnosis remained MDD (15.1%: GroupC/Groups A+C)" Although it appears that they are comparing only group C with D with respect to depressive relapses, this is not clearly stated. Moreover, in the methods section they mention that " Relapse was defined as symptoms that meet the diagnostic criteria of MDD." So these patients (groups c and d) actually developed depressive episodes not just depressive symptoms. However, there are no details about the number and duration of depressive episodes in them. Similarly, the section titled "Period until relapse" refers to the time to depressive relapse following ECT, and should be changed. This section compared group C (8 patients)with group D (21 patients). I wonder how valid is the roc analysis given these small numbers. DISCUSSION The authors state that - "In the current study, a large proportion (84.9%, 45/53) of patients with MDD remained in remission for three years with only a single antidepressant. Thus, an adequate dose of antidepressant monotherapy can maintain remission, with good tolerability, if the diagnosis of MDD is appropriate." However 43% of their patients with MDD had psychotic symptoms. The standard treatment (apart from ECT) of these patients is a combination of antidepressants and antipsychotics. Therefore, the fact that 85% remained in remission was somewhat surprising. Certain statements made in the discussion section were not backed by the findings of the study. These included - " With such limitations, we concluded that C/M-ECT was commonly required in patients who were initially diagnosed with severe MDD, with the diagnosis being subsequently changed to BP. Although C/M-ECT combined with an antidepressant plus lithium certainly prevents both BP and MDD relapses, it could develop several side effects and lead to a lost opportunity to validate the diagnosis for remission." " Appropriate withdrawal from C/M-ECT and multiple dosing regimens certainly contributes to

improvements in patients' quality of life and suppression of medical and social welfare costs." Similar conclusions made in the Abstract and the Core Tip are somewhat over-rated and should be toned down given the limitations of the study Other statements are quite unclear and also somewhat contradictory, such as - " It is reasonable that in patients who experience a relapse within one month after the course of ECT, even if they do not have a manic episode, changes in the treatment strategy from MDD to BP should be considered." It is not clear how the treatment can be changed if there is no manic episode, which also means that a diagnosis of BD cannot be made.

As answered to the comment 4, we have moved the "Definitions of remission and relapse" and "Criterion for changing diagnosis" paragraphs to just after the "Participants". We have also added an explanation of the footnote for figure 2. We moved description of excluded subjects with schizophrenia, epilepsy, chronic pain, or Alzheimer's disease during the follow-up from "Group classification" section in methods to "Characteristics of the participants" in results. We corrected some classification errors.

P 8 lines 17-19: Patients in group A remained in remission with the concomitant use of lithium and some antidepressants.
P 8 lines 24-25: Patients in group B were maintained in remission with mood stabilizers.

P 6 lines 18-19: We defined "relapse" as the "recurrence of five or more symptoms that are part of the diagnostic criteria for MDD" in this study, and we did not include manic symptoms as a criterion for "relapse."

P 13 Line 9: The title of the section has been changed to "Higher risk of relapse among patients with diagnostic changes than those without." Thank you.

The duration of depressive symptoms after relapse has not been highlighted in the manuscript. The duration from onset to the first ECT has been presented in Table 1.

P 13 lines 24-25: There were mistakes in the group description in the sensitivity analysis. This may have been the reason the results were confusing. We have verified them. Thank you.

Our study participants were few, but the ROC analysis showed statistically significant results with moderate accuracy. This number may have been sufficiently large in this study.

P 15 lines 17-20: The standard therapy for psychotic depression is antidepressant-antipsychotic co-treatment. However, no standard therapy has been established for MDD manifesting with psychotic symptoms after ECT. We have clarified this in the Discussion section. Thank you.

We have toned down the descriptions in the abstract, conclusion, and core tip.