Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Extensive myocardial calcification in critically ill patients receiving extracorporeal membrane oxygenation: A case report and literature review." . (No.: 71494). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made the following corrections which we hope meet with approval. Revised parts are marked in red in the paper. The main corrections in the paper and the responses to the reviewer's comments are as flowing:

Responses to the reviewer's comments:

Reviewer #1:

1.The LV systolic and diastolic functions of the index case need to be clearly mentioned both during

index visit and follow up.

Response: We have re-written this part according to the reviewer's suggestion. Repeat echocardiography 1 d later demonstrated a left ventricular ejection fraction (LVEF) of 35% with moderate diastolic dysfunction, but the left ventricular end diastolic diameter showed no obvious change.

2. Is there any difference in literature regarding myocardial calcification after VA or VV ECMO...effect of type of ECMO can be added in discussion.

Response: The brief summary of the literature on myocardial calcification after VA or VV ECMO was added in the discussion section.

3. Few areas need language clarity and i have highlighted 10 comments/corrections in the manuscript word file attached. Please respond to each one of them.

Response: We are sorry for the grammatical and spelling errors, and we have had the manuscript edited and proofread by MedE Medical Editing Group.

Reviewer #2:

1.The case is of an adolescent with "fulminant myocarditis". What caused the myocarditis? Why was it necessary to treat the patient with ECMO?

Response: Laboratory result: anti-Epstein–Barr virus antibodies IgG and IgM were positive. We think Epstein–Barr virus caused the myocarditis. On the day after admission, the patient had a cardiac arrest due to acute left ventricular failure and malignant arrhythmia. He developed acute renal failure following cardiogenic shock. Repeat echocardiography 1 day later demonstrated a LVEF of 35%. Emergency VA-ECMO was carried out and bedside continuous renal replacement therapy was performed to optimize fluid management.

2.Why did the patient develop severe hypocalcaemia? With infusion of calcium to correct this, was there any overshoot? What happened to renal function? Could the authors please describe the state of inflammatory markers? How was the patient treated apart from ECMO?

Response: Multiple causes including cardiogenic shock, rhabdomyolysis, and acute renal failure may jointly lead to severe hypocalcaemia. In literature review, intravenous supplementation of a large amount of exogenous calcium possibly further aggravated calcium deposition in the necrotic area of myocardia. He developed acute renal failure following cardiogenic shock. Laboratory examination results were as follows: glutamic oxaloacetic transaminase 1080 U/L, glutamic pyruvate transaminase 1450 U/L, creatine kinase 12 000 U/L, creatine kinase isoenzyme 2880 U/L, lactic dehydrogenase 19300 U/L, serum myoglobin 1400 ng/mL, troponin I 4.01 mg/L, white blood cell count 17.6×109/L, plasma C-reactive protein 33.0 mg/L, serum procalcitonin 0.15 ng/mL. Emergency VA-ECMO was carried out and bedside continuous renal replacement therapy was performed to optimize fluid management. In addition, comprehensive treatment such as antiviral, myocardial nutrition, arrhythmia prevention and nutritional support were administered.

3.Did the patient, by any chance, receive warfarin or any other vitamin K analog, given that these induce calcification by inhibiting matrix Gla protein activation?

Response: The patient did not receive warfarin or any other vitamin K analogue during hospitalization.

4.I find the description of the echocardiography result extraordinarily poor. For example, was there what happened to overall left ventricular function? Was there any evidence of constrictive or restrictive physiology?

Response: Repeat echocardiography 1 d later demonstrated a left ventricular ejection fraction (LVEF) of 35% with moderate diastolic dysfunction. Echocardiography (2 mo after hospital admission) showed a LVEF of 56%, and mild diastolic dysfunction. In addition, the echocardiography was 'blind' to myocardial calcification, and we have added a four chamber echo view (Figure 2C).

5.Might the patient have been septic? Was any effort made to quantify and specifically localise calcium? For example, was there any valvular calcification?

Response: There was no evidence of sepsis before myocardial calcification was found. CT, not MRI, is the gold standard for detecting myocardial calcification. Echocardiography would likely be “blind” to this injury. Repeated CT examination showed that myocardial calcification was mainly concentrated in the left ventricle, and the heart valve and right ventricle were not involved.

6.Why was there no cardiac MRI? What happened to the extent of myocardial calcification in the long term? If the patient recovered despite the calcification, is the calcification important?? Did the patient TRULY recover completely?? Was any study made regarding long-term calcification/fibrosis?

Response: We have added cardiac MRI view. The MRI performed 50 days after admission showed high signal intensity in the left ventricular wall, suggesting myocardial fibrosis/scarring resulting from myocardial injury/necrosis. We are aware that MRI is not usually used for diagnosing myocardial calcification. Two years later, CT still showed obvious myocardial calcification in left ventricle (Figure 2.D). The patient TRULY recovered

completely, but the acute mortality of similar patients reported in the literature was about 50%. Therefore, it is necessary to monitor the symptoms of cardiomyopathy secondary to cardiac calcifications, and develop specific treatment and follow-up guidelines. We failed to find any other reports regarding long-term calcification/fibrosis.

We have responded to all the comments by the reviewers and editors, and we hope all the responses will meet with your approval.

Thank you very much for the comments and suggestions.