Dear editors and dear reviews:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for your positive and constructive comments and suggestions on our manuscript entitled “Acute pulmonary embolism from upper limb venous thrombosis following breast cancer surgery two case reports”.(Manuscript NO: 71898, Case Report)

We have studied reviewer's comments carefully and have made revision which marked in red in the paper. We have tried our best to revise our manuscript according to the comments. We would like to submit for your kind consideration.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Reply to referee Reviewer #1

Point 1:

Referee:Both patient seems to have developed respiratory compromise within short period of time from surgery, indicating pulmonary embolism of existing upper extremity thrombosis. Do authors suggest patient developed upper extremity thrombosis due to surgery or they feel likely there was an existing thrombosis due to cancer that was exacerbated by surgery?

Response: We are also interested in this question. First, on admission, there were no signs of venous thrombosis such as pain and unilateral edema, and the D-dimer concentration was normal. Therefore, the diagnosis of venous thrombosis was ruled out. Second, we think that pathophysiologic explanations of the etiology of thrombosis in cancer include known hypercoagulability (eg, pro-coagulants such as tissue factor expressed by cancer cell),vessel wall damage, and vessel stasis from direct compression. The incidence of cancer-associated thrombosis is further increased by the presence of additional risk factors, such as surgical procedures, prolonged immobilization and so on. Therefore, we think that these patients developed upper extremity thrombosis that was induced by surgery on the basis of hypercoagulability due to cancer.

Point 2:

Referee:Authors needs to specify in both cases if preoperatively there was any complaints from patient or physical exam finding of arm swelling/pain and if yes any preop imaging was done to evaluate that.

Response: Thank you for your suggestion. As suggested by reviewer, we have added the content which marked in red in the paper. (page 4, line 112) (page 7, line 182)

Point 3:

Referee:explain in detail what kind of post op bleeding complication patient 2 had while on anticoagulation?

Response: Thank you for your precious comments which are very helpful for improving our paper. We have revised the manuscript accordingly. We've changed [However, she had to stop the anticoagulant drug due to bleeding in the surgical area 2 days after treatment (Figure 2D)] to [However, she had to stop Enoxaparin due to bleeding in the surgical area 2 days after treatment (Figure 2D) .The patient developed a drop hemoglobin level from from 122g/L to 88g/L. Bleeding in the surgical field did not require invasive intervention and blood transfusion, nor did it affect the overall clinical outcome.] and the content is highlighted in red. (page 8, line 220)

Point 4:

Referee:If available longer term follow up information on patients would be helpful. were they kept on anticoagulation indefinite?

Response: We appreciate the reviewer's positive advice. We have added more follow-up the information on patients. The precedent version of the "Outcome and follow-up" has been replaced, becoming [The rivaroxaban dosing was lowered from 15mg twice daily to 20mg every day after 21 days which made routine laboratory tests when upon discharge unnecessary. Color flow Doppler ultrasound performed was negative for thrombus in the brachial vein at 4 weeks after Modified radical mastectomy. During this period, she received adjuvant chemotherapy consisting of four cycles of cyclophosphamide plus epirubicin, followed by four cycles of docetaxel. Treatment duration was for a minimum of 6 months.] (case 1) and [Six days after restarting anticoagulation, the patient was discharged in stable condition. Rivaroxaban was given at a dose of 15 mg twice-daily for the initial three weeks followed by a 20 mg once-daily dosing thereafter. At 6 months, the patient returns for outpatient follow-up. She has remained on anticoagulant treatment and denies bleeding episodes. The thrombosis of the vena basilica was ruled out using colour venous ultrasonography. Laboratory investigations demonstrated the concentration of D-dimer was normal. During anticoagulant therapy, this patient received six cycles of doxorubicin plus cyclophosphamide chemotherapy.] (case 2) respectively.

Point 5:

Referee:Is there any existing literature on risk of upper extremity DVT in breast cancer in patients who have not undergone recent surgery? if yes include in manuscript.

Response: It would be an interesting research. However, we found no relevant literature. Results from numerous studies have identified planted central catheters (PICCs) which can be inserted in the cephalic, basilic, or brachial vein are the most important cause for development of an upper-extremity extremity DVT. We would focus on related Literature.

Point 6:

Referee:authors have used "pulmonary thrombosis" term few times, unless clinically felt clot formed in pulmonary artery " pulmonary embolism" term is more appropriate. kindly change it.

Response: We agree with the comment. We have changed [pulmonary thrombosis] to [“pulmonary embolism” or “PE”] which highlighted in red in the paper.

Point 7:

Referee:authors have used Novel anticoagulants. they are not novel any longer. more appropriate term is Direct oral anticoagulants (DOACs).

Response: We thank the reviewer for pointing this out. We’ve changed [Novel Oral Anti-Coagulants] to [Direct oral anticoagulants (DOACs)] which marked in red in the paper.(page 8, line 226)

Reply to referee Reviewer #2

Point 1:

Referee:The authors should provided the details of known risk factors.

Response: This suggestion is apprecisted. Obesity , inpatient status, venous catheterization, prolonged operative time, and so on were found to be independent risk factors for VTE after MRM. Many of the risk factors for development of VTE are common to patients with breast cancer. For these two patients, more advanced age, overweight (Body Mass Index BMI $\geqslant$24 kg/m^2) , hospitalization and surgery were

shown to be associated with increased risk for venous thrombosis. We have made revision which marked in red in the paper. (page 4, line 117) (page 7, line 186)

Point 2:

Referee:the dose and duration of anti-coagulant

Response: We are grateful for the suggestion. To be more clearly and in accordance with the reviewer concerns, we have added a more detailed anticoagulation agents which marked in red in the paper. (page 6, line 157) (page 8, line 219)

Case 1: Upon diagnosis of PE, 5,000 IU Enoxaparin subcutaneously every 12 hours was administered for the initial management. Five days later, anticoagulation agent was changed to rivaroxaban (15mg PO twice daily). The rivaroxaban dosing was lowered from 15mg twice daily to 20mg every day after 21 days which made routine laboratory tests when upon discharge unnecessary.

Case 2: The patient was treated with Enoxaparin (6,150 IU subcutaneously twice-daily dose). However, she had to stop Enoxaparin due to bleeding in the surgical area 2 days after treatment. After the bleeding had stopped, anticoagulant drugs was transitioned to Rivaroxaban (15mg PO twice daily)which is direct oral anticoagulants (DOACs). Rivaroxaban was given at a dose of 15 mg twice-daily for the initial three weeks followed by a 20 mg once-daily dosing thereafter.

Point 3:

Referee: followup CT/US should be provided.

Response: As suggested by the reviewer, we have added more follow up information on patients.

Case 1: Color flow Doppler ultrasound performed was negative for thrombus in the brachial vein at 4 weeks after Modified radical mastectomy. During this period, she received adjuvant chemotherapy consisting of four cycles of cyclophosphamide plus epirubicin, followed by four cycles of docetaxel. Treatment duration was for a minimum of 6 months.

Case 2: At 6 months, the patient returns for outpatient follow-up. She has remained on anticoagulant treatment and denies bleeding episodes. The thrombosis of the vena basilica was ruled out using colour venous ultrasonography. Laboratory investigations demonstrated the concentration of D-dimer was normal. During anticoagulant therapy, this patient received six cycles of doxorubicin plus cyclophosphamide chemotherapy.

We would like to thank the referee again for taking the time to review our manuscript. We sincerely hope this manuscript will be finally acceptable to be published on "World Journal of Clinical Cases".