Dear Editor

Thank you so much for your comments:

Kindly find the response here:

1 In page 3 line 5, "the other" should be revised as "another" to denote relationship between 2 systems.

We edited it

2 in page 5 from "EPO is one method of enhancing Hb levels" to the end of the paragraph is advised to write as "Erythropoietin (EPO) is a hematopoietic growth factor, the major function of which is to stimulate the proliferation and differentiation of erythroidpoiesis. EPO treatment is an effecient approach to increase Hb levels in patients with CHF in whom the anemia is caused by the reduced EPO production.[6]. EPO can also infuence other cellular processes, such as cell integrity and angiogenesis[7]. EPO have been demonstrated to improve both renal and cardiac function. EPO has an ability to decrease marrow inflammation, which can reverse the myelosuppressive effects of cardiac dysfunction and coexisting uremia [6]. Furthermore, EPO may prevent myocardial ischemic injury in CHF patients by inhibiting apoptosis of cardiac myocytes [6]. Iron therapy was unable to provide such effects on hematopoiesis due to the lack of hematological and immunological regulatory ability and its limited bioavailability [6]"

We edited it

3 In page 5, "It is important to investigate EPO's role in treating patients with CRS. EPO is routinely prescribed to treat anemia in patients with end-stage renal disease (ESRD) and has been beneficial in patients with CHF. Accordingly, it is reasonable to assume that EPO would be beneficial in patients with CRS. Given the prevalence of CRS, finding a treatment modality that demonstrably improves outcomes would significantly impact clinical practice and potentially decrease mortality and hospitalizations for those patients." is advised to write

as "It is of great significance to investigate the role of EPO in the treatment of patients with CRS. Recombinant human erythropoietin (rhEPO) is a drug routinely prescribed to treat anemia in patients with end-stage renal disease (ESRD), and rhEPO treatment has been demonstrated to be beneficial for improving patients' life quality and survival. It is reasonable to assume that rhEPO treatment is beneficial for patients with CRS. Given the high prevalence of CRS, searching for a treatment modality that can improve therapeutic responses is of high significance in clinical practice and will significantly decrease the mortality and hospitalization of CRS patients."

In the following paragraph, EPO as a drug used to treat anemia in CHF should be revised as "rhEPO"

We edited it

4 "Several studies are currently in progress examining the benefits of EPO in patients with CRS." is advised to write as "Several studies are ongoing to examine the benefits of rhEPO treatment in patients with CRS." We edited it.

5 Grammar error: Out of the 43 articles assessed for eligibility, of which 34 articles were excluded (seven were incorrect study designs, three were not retrievable, and one was an abstract). "of which" should be deleted. We edited it.

6 Table 1 (1) make the title succinct and put it on the top of the table; (2) make the content succinct by using abbreviations; (3) combine some columns such as "**Author/Year of publication**", "Jackevicius/2015[12]"; (4) list the first author as the representative. (5) the column "EPO dosage and period of treatment" is better written as "EPO doses/treatment duration". (6) separate the column "Average Hb level before EPO therapy, after EPO therapy, and after no EPO therapy (g/dL)" as

| Hb level (g/dL) Prior and Post EPO treatment | | | | | |
|--|----------------|------------|----|-----|--|
| Prior treatment | Post treatment | After | no | EPO | |
| | | treatment? | | | |

We edited it

(7) what is the meaning for "After no EPO therapy"? without EPO treatment or discontinuation of EPO treatment? (8) combine the columns "EPO's effect on Hb level ", "EPO's effect on major cardiovascular (CV) event risk", and "EPO's effect on hospitalization rate" as

| EPO treatment effects on | | | | |
|--------------------------|-----------------|-----------------------|--|--|
| Hb levels | Major CV events | Hospitalization rates | | |

(8) Make the contents succinct, such as "EPO supplementation increased Hb levels" to "increased Hb levels", "EPO increases cFGFR23 and iFGFR23. cFGFR23 was associated with an increased risk of CV events and increased mortality risk; however, the underlying mechanism is unknown." to "Increased cFGF23 and iFGF23 levels, increased risk of CV events and mortality".

We edited it

(9) Deeper discussion of the reviewed articles are need in the Discussion section by summarizing the reported studies. EPO has multiple functions on hematopoietic and immune regulation via the activation of JNK-STAT signaling pathway, and red blood cells play roles not only in the transportation of oxygen and carbon dioxide but also in the participation of defence and coagulation processes. The functional properties of JNK-STAT signaling pathway and red blood cells likely have impacts on the therapeutic outcomes and adverse effects. In addition, low and high Hb levels are associated with an increase in cardiovascular events.

We added this:

In summary, this systematic review studied the overall significance of EPO when managing patients with CRS. The literature demonstrates that not only does EPO increase patients baseline hemoglobin levels, but it also lowers the risk of major CV events from occurring in patients with CRS. EPO improves the heart failure aspect of CRS by both improving cardiac remodeling and overall myocardial function, and by doing so EPO is able to minimize the cardiovascular mortality as well. Moreover, the reviewed literature does not demonstrate a clear effect of EPO on hospitalization rates and hence this effect should be further analyzed in future studies. Lowering hospitalization rates would potentially decrease healthcare expenses and, more importantly, improve the quality of life of patients with this condition. In conclusion, the literature included in this review clearly demonstrates how EPO has several significant benefits when used to treat patients with CRS.