Dear reviewer:

Thank you for your decision and constructive comments on my manuscript. We have carefully considered the suggestion of the reviewer and made some changes. We have tried our best to improve. The revised sections are marked in red. Revision notes, point-to-point, are given as follows:

Reviewer 1#

1. The theme regarding the ageing subset of patient remains ambiguous.

Response: We acknowledge the reviewer’s comment regarding the ambiguity surrounding the theme regarding the ageing subset of patients. We apologize for any confusion caused. To address this concern, we further clarify and provide more specific information on the treatment of spinal cord injuries in the elderly population. Please see the revised manuscript of line 85-95, 128-133, 232-234, 244-246, 249-250, 263-265, 279-282, 297-301.

2. For one the review fails to explain whether the elderly patients were impacted by traumatic SCI when they were younger or when they were senior citizens. If they had traumatic SCI when they were younger, then it becomes imperative to focus on therapeutic strategies for that specific age range. However, if it the latter then how much of the therapeutic strategy such as stem plant implant going to being negatively impacted by the age of the patient.

Response: Thank you for your valuable feedback. The elderly patients mentioned in our review refer to individuals who sustain SCI during their senior years. Here is the revised introduction: “Therefore, how to treat late-life SCI in an aging society becomes a very delicate issue.” Please see the revised manuscript of line 52-53.

However, the analysis of SCI in elderly rats has led to the conclusion that age is a factor influencing functional recovery, as it is associated with increased axonal injury and demyelination [15]. This is consistent with the observed higher activation of microglial cells, oxidative stress, and expression of inflammation-related genes in elderly rats following SCI compared to young rats [16-18]. This increases the likelihood of axonal growth impairment occurring after stem cell transplantation into the injured area. Please see the revised manuscript of line 89-95.

3. It is already well established that cellular functions reduce with age, in this case, do the authors think that subjecting an elderly patient through vigorous surgical transplants is the best course of therapy. In conclusion, the review would read better if the theme of age is omitted or have data that addresses the questions mentioned above.

Response: We appreciate the reviewer's feedback and concerns regarding the impact of age on stem cell transplantation. While it is true that cellular functions tend to decline with age, it is important to note that the impact of aging on stem cell transplantation outcomes is still an area of active research. Research has discovered that aging-related secretory phenotype manifests in the spinal cord of aged mice following injury, enhancing the suitability of the injury microenvironment for cell transplantation in aged mice [12-14]. This suggests that the aged spinal cord may provide a favorable environment for stem cell transplantation in older individuals. Please see the revised manuscript of line 85-89.

Reviewer 2#

1. The major concern is that this combinatory approach is not approved for clinical treatment of SCI patients, nor for SCI in aging patients. This approach is still in research stage. The authors are confused with concept of approved clinical treatment and bio-medical research. Currently there is no approved stem cells or fibrin treatment for SCI patient, regardless of age.

Response: Thank you for bringing this important point to our attention. You are correct in stating that currently there is no approved stem cell or fibrin treatment specifically for SCI patients, regardless of their age. To address this issue, we revised the review: “Meanwhile, we explore the potential of stem cell transplantation combined with fibrin scaffold for the treatment of SCI.” “Research advances in stem cell transplantation combined with fibrin scaffold for spinal cord injury in an aging society.” “Meanwhile, we summarized the potential that different types of stem cells combined with fibrin scaffolds in the treatment of SCI, especially in the elderly.” Please see the revised manuscript of line 1-2, 33-34, 118-120.

2. The authors need to be careful for literature review. For example, the authors reviewed that (Line 130.) “King et al. [18] injected fibrin/fibronectin into the injured part of the human spinal cord” In fact, King et al did not inject fibrin/fibronectin into human spinal cord. They injected into rat spinal cord.

Response: We appreciate the reviewer's attention to detail and apologize for the error in our literature review. To address this issue, we revised the review to accurately reflect the study by King *et al.* as follows: King *et al.* [22] injected fibrin/fibronectin into the injured part of the young adult male rat spinal cord. Please see the revised manuscript of line 140.

3. The English writing is not smooth and need to be reviewed and corrected by a native English speaker.

Response: Thank you for your feedback and for pointing out the grammar issues in the manuscript. We appreciate your careful review and your valuable suggestions. In response to your comments, we have carefully reviewed the manuscript and made the necessary revisions to address the grammar problems. We have carefully proofread the entire document and have made sure that the grammar is now correct and consistent throughout.

4. Line 63, “resulting in a glial/fibrotic scar cavity at the center of the SCI site” Glial scar is a tough solid physical tissue and is not a cavity.

Response: I apologize for the incorrect terminology. It is true that glial scars are not cavity but rather dense, solid tissue that forms at the center of the SCI site. The sentence should be revised as follows: “resulting in the formation of a glial/fibrotic scar at the center of the SCI site.” Please see the revised manuscript of line 61.

5. Line 238, “The combination of MSCs and fibrin scaffold can promote the migration and differentiation of the patients’ mesenchymal cells into neurons,” No approved result showing mesenchymal stem cells can trans-differentiate into neurons without re-programming genes.

Response: MSCs have been shown to have the potential to differentiate into multiple cell types, including neuronal cells, under certain conditions. However, the process of MSCs differentiating into neurons typically requires specific induction protocols or genetic modification to reprogram the cells. Here are the revised sections: “The combination of MSCs and a fibrin scaffold can promote the migration of rats’ mesenchymal cells across the blood-brain barrier, facilitate the reconstruction of the neural glial cell pool, and induce differentiation into neuron-like cells and oligodendrocyte-like cells [38, 52].” Please see the revised manuscript of line 252-255.

6. Line 299. “our research on fibrin scaffold combined with stem cell transplantation is still in the preliminary exploration stage,” This is correct, fibrin and stem cell transplantation are still in the research stage, but not approved for clinical application except that fibrin is used in clinical to seal the tissue and stop bleeding.

Response: Thank you for the clarification. “Our research on fibrin scaffold combined with stem cell transplantation is still in the preliminary exploration stage,” is indeed correct. Both fibrin scaffold and stem cell transplantation are still in the preliminary exploration stage of research.

7. Fig. 1B, there are no transplanted cells in the lesion site showed.

Response: We have revised the figure.