26th December 2018

Dear Editor,

Title: Clinical significance of exosomes as potential biomarkers in cancer

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Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 42936

Thanks for revising the manuscript. Improvements have been made based on the suggestions of reviewers.

Responses to the Reviewer #1

Comment 1) Analysis was not done on the base of individual exosome but done on the base of study.

Response: Thanks for the reviewer's suggestion. We now analyze the exosomal biomarkers based on cancer type. We focused on cancer types with more than three biomarkers was studied. Therefore, we meta-analyzed biomarkers in colon, pancreatic, liver, gastric, prostate and lung cancer separately. The results obtained may give us insight on which exosomal biomarker or biomarkers can be used in diagnosis and prognosis of a cancer.

Comment 2) The figures and tables (especially table2) is raw, needs simplification.

Response: Thanks for the reviewer's suggestion. In the tables, isolation methods of exosomes and source of exosomes in different studies were included since it is currently lack of a standard protocol for detection of exosomal biomarkers. For the isolating methods, ultracentrifugation or the use of commercial isolation kits are commonly used. Ultracentrifugation gives highly pure exosomes but the isolation efficiency is relatively low; whereas the use of commercial kits maximizes the efficiency with the loss of purity. For the source of exosomes, serum or plasma are the common sources of exosomes, but urine and saliva may also be used in cancer diagnosis. Therefore, it is necessary to include the details of detection method in the table to develop a standardized protocol in cancer diagnosis and prognosis.

Responses to the Reviewer #2

Comment 1) The heterogeneity of cancer group for example in prognosis part - GI cancers (11 studies were about colorectal or colon cancer; 5 studies were related to liver cancer; 5 studies were about pancreatic cancer and 4 studies were related to gastric cancer) with I^2 of >90%.

Response: Thank you for the reviewer's comment. Since 47 biomarkers from 30 studies covering 14 cancer types were recruited in this systematic review, there was great heterogeneity of cancer group. Therefore, we now separate the exosomal prognostic biomarkers based on cancer type. Then we focused on cancer types with more than three biomarkers was studied in our meta-analysis.

Comment 2) Most of the included studies are retrospective type

Response: Thank you for the reviewer's comment. Most of the studies were retrospective that is performed on stored samples. The main disadvantage of retrospective study is the lack of complete clinicpathological information, which lowers the quality of study. Further large prospective studies are greatly needed to clarity the performance of exosomal biomarkers in cancer diagnosis and prognosis.

Sincerely,

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