Peer Review File

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Reviewer: A

Comment 1: RCC is essentially a metabolic disease characterized by a reprogramming of energetic metabolism (PMID: 36960789; PMID: 30983433, PMID: 36430837,PMID: 36310399). In particular the metabolic flux through glycolysis is partitioned (PMID: 29371925, PMID: 28933387, PMID: 25945836), and mitochondrial bioenergetics and OxPhox are impaired , as well as lipid metabolism (PMID: 30538212; PMID: 32861643, PMID: 29371925, PMID: 36430448). These findings should be referenced and discussed.

Reply 1: We sincerely appreciate the valuable comments. We have checked the literature carefully and added more references on the relationship between lipid metabolism and kidney cancer in the Introduction part and Discussion part of the revised manuscript.

Changes in the text: Firstly, we added the statement "RCC, especially ccRCC, is generally considered as a metabolic disease. Among them, abnormal alterations in lipid metabolism have important effects in the occurrence and development of ccRCC" in the second paragraph of the Introduction part (see Page 3, line 67-70). Secondly, in the second paragraph of the Discussion part, we included the statement "A notable characteristic of renal cell carcinoma is the mutation of key genes involved in metabolic pathways, which directly impact the metabolic processes of renal cell carcinoma cells, with alterations in oxygen, energy, and nutrient metabolism playing a crucial role in the occurrence and progression of renal cell carcinoma" (see Page 7-8, line 236-244). Additionally, in the third paragraph of the Discussion part, we focused on discussing the role of abnormal lipid metabolism in the occurrence and development of kidney cancer (see Page 9-10, line 258-283).

Reviewer B

Comment 1: Authors should clarify the breakdown of clinical and pathological features, including whether kidney cancer include both clear cell renal cell carcinoma (ccRCC) and non-ccRCC or

not, and local or metastatic RCC, because there may be some differences of the causal relationship between kidney cancer and omega-3/6 fatty acids in various clinical and pathological features.

Reply 1: We sincerely appreciate the valuable comments. Through careful review of the literature, we discovered that ccRCC was the most common histological type of renal cell carcinoma and accounted for the majority of kidney cancers. It was named ccRCC because of its homogeneous and transparent appearance under the light microscope, which was attributed to its abundant cytoplasm containing glycogen and lipids. ccRCC is generally considered a metabolic disorder, characterized by abnormal accumulation of phospholipids, neutral lipids, and cholesterol during its development. Therefore, this study included more relevant descriptions of clear cell renal cell carcinoma. Unfortunately, due to the lack of specific differentiation of kidney cancer subtypes in the original database, we could not establish a causal relationship between omega-3/6 fatty acids and a particular subtype.

Changes in the text: Page 3, line 65-70:"Among them, clear cell renal cell carcinoma (ccRCC) is the predominant subtype of RCC, occupying 80% of RCC(18). Studies have shown that RCC, especially ccRCC, is generally considered as a metabolic disease. Among them, abnormal alterations in lipid metabolism have important effects in the occurrence and development of ccRCC".

Page 10, line 272-283:"At the same time, significant progress has been made in targeting lipid metabolism for kidney cancer treatment. Hypoxia-induced factors (HIF) played a crucial role in the pathophysiology of ccRCC, and they could influence tumorigenesis of ccRCC by controlling fatty acid metabolism(47). Multiple clinical trial studies have shown that the HIF-2α inhibitor MK-6482 and another HIF-2α antagonist PT2399 demonstrated significant therapeutic effects and good safety profiles in patients with ccRCC, making them potential treatment options for this type of cancer(48, 49). In a population-based cohort study, the use of statin medications was found to lower the risk of RCC, with a risk ratio of 0.64 (95% CI, 0.38-0.87)(50). Further research has indicated that statin drugs can inhibit the growth of RCC cells by inducing cell cycle arrest and apoptosis in a dose and time-dependent manner".

Comment 2: Authors concluded the positive relationship between an onset of kidney cancer and omega-3/6 fatty acids. On the other side, other authors reported that higher body mass index was associated with better survival in patients with metastatic RCC (mRCC) treated with immuno-

oncology (IO) drug. Authors might had better describe that they need an investigation of the relationship of survival outcome between kidney cancer and omega-3/6 fatty acids in patients with mRCC in IO era as a future direction.

Reply 2: We sincerely appreciate the valuable comments. For your comment, we have checked the literature carefully and added more references on “Prognostic impact of obesity and dyslipidemia in patients with kidney cancer” in the and Discussion part of the revised manuscript, and proposed the hypothesis that omega-3/6 fatty acids are not only related with the risk of kidney cancer, but also to their prognosis.

Changes in the text: In the third paragraph of the Discussion part, we included the statement that " PUFAs were not only associated with the risk of kidney cancer, but also possibly related to its treatment and prognosis." We supported this statement by citing relevant papers. Please refer to the revised manuscript (Page 9-10, line 257-286).