30870-ANSWERING REVIEWERS

Dear editor and reviewers

We appreciate deeply the time and consideration that editor and reviewers have given to this manuscript. We agree with many of the reviewer's comments and we now realize that there are some points that we need to explain more clearly. The manuscript has also been enriched by your suggestions.

I would appreciate if you consider our paper for the publication in World Journal of Gastrointestinal Oncology.

Thank you for your consideration.

Sincerely,

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Reviewer #1

This review focused on the clinical significance of immune cells, especially TILs, in gastric cancer. This article was interesting and useful for realizing the TILs on gastric cancer and immunotherapy. But I have some comments as bellow. #1. It was very confuse to realize about relationship between TILs and prognosis of gastric cancer. So, the authors should summarized in one table about relationship between TILs and prognosis of gastric cancer. #2. The authors should make correlation chart of cancer cells and TILs including CD8 T cell , CD4 T cell, memory T cell, NK cell, other immune cells. #3. Immunotherapy targeting for PD-1 and PD-L1 is current topics. So the authors should described the novel reports about these current immunotherapy more in detail.

Reply) Thank you for thoughtful comments. According to reviewer's suggestion, the authors have provided Tables 1 and 2 for the prognostic impact of TILs and their subset in the revised manuscript. Plus, we added the paragraph for immunotherapy targeting for PD-1/PD-L1, and the title is "Roles of programmed cell death protein in immune cells of gastric cancer". Please, see the revised manuscript.

Reviewer #2

Review paper of clinical significance of tumour infiltrating lymphocytes in gastric cancer. Well laid out manuscript, clearly written. Included discussion relating to current evidence of TILs in gastric cancer. There is not a lot of information, but I suppose this reflects the paucity of information in the literature. Do the authors have any personal research to add to the manuscript? Could the authors add some data from laboratory studies to augment the manuscript?

Reply) For better comprehension, the authors have provided the summarized research data and our new research results on TILs and PD-1/PD-L1 in the revised manuscript.

Table 2 Lymphocyte subtypes associated with the prognosis of gastric cancer

References	**Lymphocyte subtypes**	**Sample size**	**Patient group**	**Criteria (Cut-off)**	**Prognostic role**
Lee *et al*[17]	CD3+, CD8+,CD45RO+	220	G	High density	Increased OS
Thompson *et al*[18]	CD8+	43	G/GEJ	High density	Decreased PFS and OS
Kawazoe *et al*[33]	CD8+	487	G	High density	Increased OS
Wakatsuki *et al*[30]	CD45RO+	101	G	High numbers	Increased PFS and OS
Chiaravalli *et al*[34]	CD3+, CD8+	96	MSI –H G	High numbers	Increased OS
Kim *et al*[22]	CD8+, FOXP3+	99	MSI –H G	High density	Increased OS
Liu *et al*[23]	CD8+/ FOXP3+ ratio	166	G	High ratio	Increased OS
Shen *et al*[26]	FOXP3+/CD8+ ratio	133	G	High ratio	Decreased OS
Wang *et al*[5]	FOXP3+	107	G	High expression	Increased OS
Haas *et al*[20]	FOXP3+	52	G	High numbers	Increased OS
Mizukami *et al*[24]	FOXP3+	120	G	Diffuse pattern	Decreased OS
Perrone *et al*[25]	FOXP3+	110	G	High numbers	Decreased RFS and OS
Zhou *et al*[27]	FOXP3+	133	G	High numbers	Decreased OS

Choi *et al*[19]	FOXP3+/CD4+ ratio	28	G	High ratio	Increased OS
Kim *et al*[21]	FOXP3+/CD4+ ratio	180	G	High ratio	Decreased OS
Dong *et al*[35]	CD20+	100	G	High density	Increased OS
Ishigami *et al*[31]	NK cells	146	G	High numbers	Increased OS
Rosso *et al*[36]	NK cells	72	G	High concentration	Increased DFS and OS
Ishigami *et al*[37]	NK cells	169	G	High numbers	Increased OS
Ubukata *et al*[28]	Th1/Th2 ratio	157	G	High ratio†	Increased OS
Liu *et al*[29]	Th22, Th17	32	G	High numbers†	Decreased OS

†Peripheral blood

G: gastric cancer; OS: overall-survival; G/GEJ: gastric/gastro-esophageal junction cancer; PFS: progression-free survival; MSI-H: microsatellite instability-high; RFS: relapse-free survival; DFS: disease-free survival.

Impact of TILs on subtypes of gastric cancer - “Meanwhile, recent data showed an independent association between high TILs and favorable RFS or DFS in 120 patients with EBV-associated gastric cancer (EBVaGC), suggesting that TILs exhibit a host cellular immune response against tumors and immunotherapy may have a potential role in patients with EBVaGC”

Roles of programmed cell death protein in immune cells of gastric cancer – “Indeed, we already evaluated the tissue samples that were obtained from patients included in a previous study of EBVaGC. We found that intratumoral PD-L1 was significantly associated with DFS in these patients group. These observations have given rise to the hypothesis that specific inhibitors for PD-L1 or PD-1 would be potential therapeutic candidates that can affect a variety of gastric cancer.”