Association of CD103+ T cell infiltration with overall survival in solid tumors of the digestive tract and its potential in anti-PD-1 treatment: A review and meta-analysis

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We looked into the most recent studies of digestive tumor patients and performed a meta-analysis to explore the association of CD103+ T cell infiltration with overall survival (OS) in solid tumors of the digestive duct. Major databases were searched. The hazard ratios (HR) and 95% confidence intervals (CI) for overall survival were extracted and pooled. A total of 1915 patients from 11 cohorts were included into the present meta-analysis. The pooled HR was 0.64 (95% CI: 0.42-0.96, *P*=0.03), suggesting that high CD103+ T cell infiltration is associated with better prognosis. Yet significant heterogeneity was revealed and located in the subgroup of CD4+CD103+ T cells. The pooled result indicated that CD103+ T cell infiltration in solid tumors of the digestive duct may possess predictive value for prognosis. Preclinical studies suggested that CD103+ T cell infiltration could predict response to anti-PD-1/PD-L1 treatment.

Key words: CD103+ T cell, digestive tumor, prognosis

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INTRODUCTION

Tissue resident memory T (T_{RM}) cells, defined by expression of CD69, CD103, CD49a and CD44, are recently recognized to play a vital role in anti-tumor immunity[1]. CD103 is induced by tumor growth factor (TGF) β in the tumor microenvironment and uniquely expressed upon the surface of T_{RM} cells to bind to the epithelial marker E-cadherin, which enables T_{RM} cells to persist in epithelial tumor areas and therefore participate in local cytotoxic immune response[2-4]. Accumulating studies suggest that T_{RM} cells provide long-time protection in the peripheral tissue and respond fast to reexposure to tumor antigen[5]. CD103+ T cells are enriched among tumor-specific T cells in close contact with tumor cells, where they express chemokine receptors to facilitate T cell homing and produce high levels of cytotoxic molecules to further strengthen target cancer cell killing[3,6,7]. In the past decade or even earlier, several studies established that CD103+ T cell infiltration in varies tumors confer improved prognosis, some even independently of the infiltration of CD8+ T cells, including non-small-cell lung cancer (NSCLC), cervical cancer, endometrial adenocarcinoma, ovarian cancer, breast cancer, renal cell carcinoma, urothelial cell carcinoma of the bladder and other tumors[8-19]. However, researchers did not look into the infiltration of CD103+ T cell in digestive tumors until the past two or three years. In this systematic review and meta-analysis, we selected the latest published studies concerning CD103+ T cell infiltration in the tumors of the digestive duct and evaluated its prognostic significance.

Many researchers discovered that CD8+CD103+ tumor infiltrating lymphocytes cells highly express PD-1, and patients with dense CD8+CD103+ T cell infiltration exhibit favorable response to anti-PD-1 treatment[6,9,20]. The expansion of CD103+ T cells was observed during PD-1 blockade treatment in mouse models and promoted its efficacy compared to the control group, while depletion of CD103+ T cells showed opposite results[21-23]. Many claimed that CD103+ T cell infiltration can serve as the predictive marker for favorable response to immune checkpoint blockade treatment[1,24]. Some even hypothesized that amplifying CD103+ T cells or upregulating TGFβ might be a potential therapeutic method to improve immunotherapy efficacy.

RESULTS

Search results

As shown in Fig. 1, in the beginning, 266 studies from all databases surfaced by our searching strategy and 3 studies were found by manual search. We removed 18 duplicated studies, leaving 251 candidate studies. After preliminary screening for titles and abstracts, 233 studies were taken out according to the exclusion criteria. The remaining 18 studies were thoroughly scanned and 10 studies were deemed ineligible for our meta-analysis due to insufficient data. Eventually, 8 studies containing 11 cohorts, a total number of 1915 patients, were included into this meta-analysis[25-32].

Table 1. Characteristics of the studies included into the current meta-analysis.

Study + year cohort	Tumor type	Sample size	Area	High CD103 infiltration	Cut-off value	Cell subgroup	HR (95%CI)	*P*	Specimen form	HR origin	Ref.
Chu 2019 STCH cohort	esophageal squamous cell carcinoma	107	China	76	37.58/field	CD103	0.406 (0.247-0.667)	<0.001	WS	OA	25
Chu 2019 SYSUCC cohort	esophageal squamous cell carcinoma	91	China	24	37.58/field	CD103	0.328 (0.141-0.763)	0.01	WS	OA	25
Hu 2019	colorectal	165	China	125	NM	CD8CD103	0.600 (0.374-0.963)	0.03	TMA	OA	27
Knief 2019	esophagogastric junction carcinoma	135	Germany	NM	NM	CD103	0.780 (0.541-1.125)	0.18	TMA	OA	28
Li 2020 Zhongshan cohort	gastric cancer	448	China	179	NM	CD8CD103	0.59 (0.40-0.86)	<0.001	TMA	KM curve	29
Solomon 2019 PAH cohort	HPV oropharyngeal cancer	177	Australia	20.4% (36)	≥30%	CD103	0.16 (0.002-1.22)	0.02	WS	OA	30
Solomon 2019 PMCC cohort	HPV oropharyngeal cancer	189	Australia	19.8% (37)	≥30%	CD103	0.13 (0.02-0.94)	0.004	WS	OA	30
Wang 2019	gastric cancer	90	China	70	29	CD8CD103	0.516 (0.285-0.934)	0.03	TMA	OA	32
Xiao 2019	oral cancer	44	China	22	median	CD103	0.25 (0.06-0.97)	0.023	WS	KM curve	31
Gu 2020 discovery cohort	gastric cancer	235	China	125	6/HPF	CD4CD103	1.72 (1.12-2.64)	<0.001	TMA	KM curve	26
Gu 2020 validation cohort	gastric cancer	234	China	124	6/HPF	CD4CD103	1.88 (1.25-2.82)	0.003	TMA	KM curve	26

WS; Whole Slides; NM, Not Mentioned; TMA, Tissue Microarrays; OA, Original Article

Study characteristics and quality assessment

The included studies are listed in Table 1, all of which, surprisingly, were newly published from 2019 to 2020. These patients were from China, Germany and Australia and were pathologically diagnosed of gastric cancer, esophageal cancer, colorectal cancer, esophagogastric junction cancer, oral cancer or oropharyngeal cancer. Sample sizes ranged from 44 to 448. Specimens were obtained before any kind of treatment. All of the researchers measured CD103+ T cells via immunohistochemistry and fluorescence immunoassay if additional markers were detected. Some used whole slides and others tissue microarrays. Different cut-off standards from each study were listed in Table 1. Cut-off values varied from 6 cells/HPF in TMA to 37.58 cells/field in WS. Some researchers investigated all CD103+ T cells, while others focused on CD8+CD103+ T cells or CD4+CD103+ T cells. Some articles provided HRs with 95% CI, while the rest did not, where we extracted survival data from Kaplan-Meier (KM) curves using the method previously described. HRs with 95%CI and P values of each cohort were listed in Table 1.

Quality assessment was done by Review Manager 5.3, and risk of bias was shown in Fig. 2.

CD103+ T cell infiltration is associated with better prognosis

The HRs for OS extracted from each study were pooled in Fig. 3. Patients were divided into CD103+ T cell high infiltration and low infiltration groups. The pooled HR was 0.64 (95% CI: 0.42-0.96, P=0.03). Apparently, the result suggested that high CD103+ T cell infiltration is associated with longer overall survival and better outcome in solid tumors of the digestive duct. However, in this meta-analysis the I^2 is 81.4% (P<0.001), meaning there is rather high heterogeneity among the included studies.

Heterogeneity from CD4+CD103+ T cell subgroup

Since significant heterogeneity occurred, we performed subgroup analysis to explore the potential cause. We divided these groups by areas, tumor types, and the measured T cell types (CD8+CD103+ T cell, CD4+CD103+ T cell or CD103+ T cell, Fig. 4). Subgroup analysis suggested that areas and tumor types were not the significant causes of heterogeneity. Namely, the associated of CD103+ T cell infiltration with OS was generally reliable among patients from different areas as well as patients with different types of solid tumors in the digestive duct. However, as depicted in Fig. 4, the subgroup analysis concerning different CD103+T cell types showed that CD8+CD103+ T cell infiltration and total CD103+ T cell infiltration are both consistently associated with better prognosis (HR=0.58,95% CI: 0.44-0.75, P<0.001; HR=0.42, 95% CI: 0.25-0.70, P=0.001), while CD4+CD103+ T cell infiltration is associated with poor prognosis (HR=1.80, 95% CI: 1.34-2.42, P<0.001).

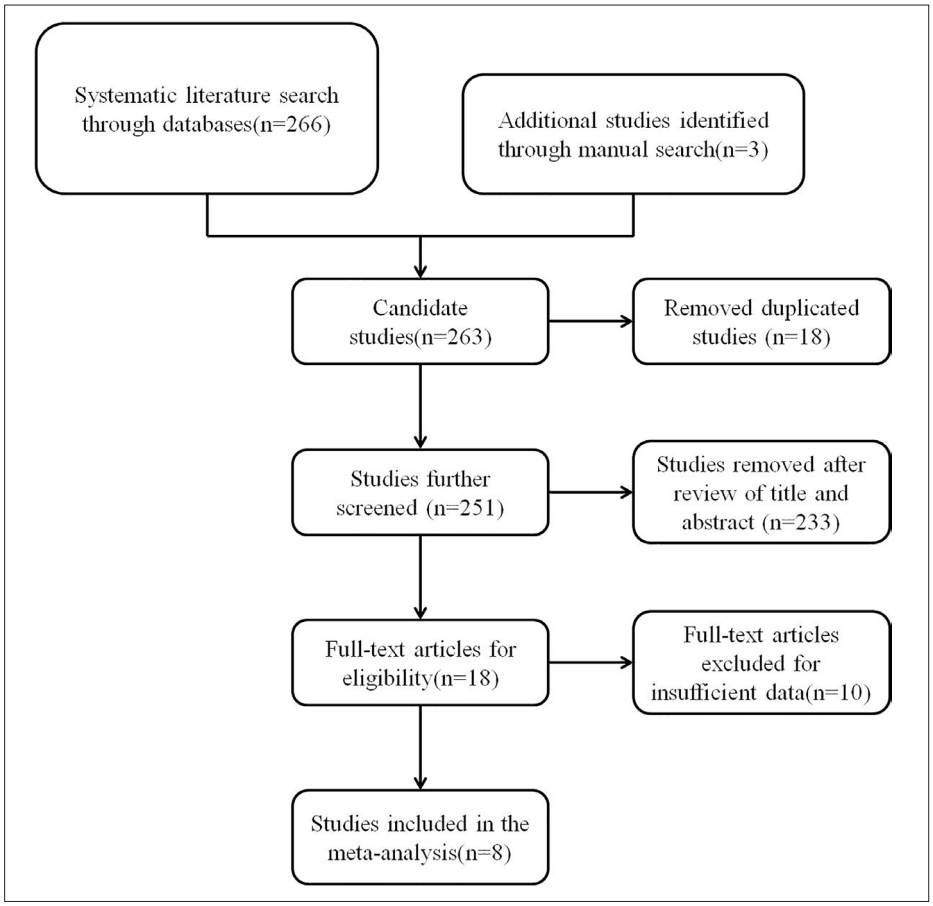

Fig. 1. Flow chart of literature search.

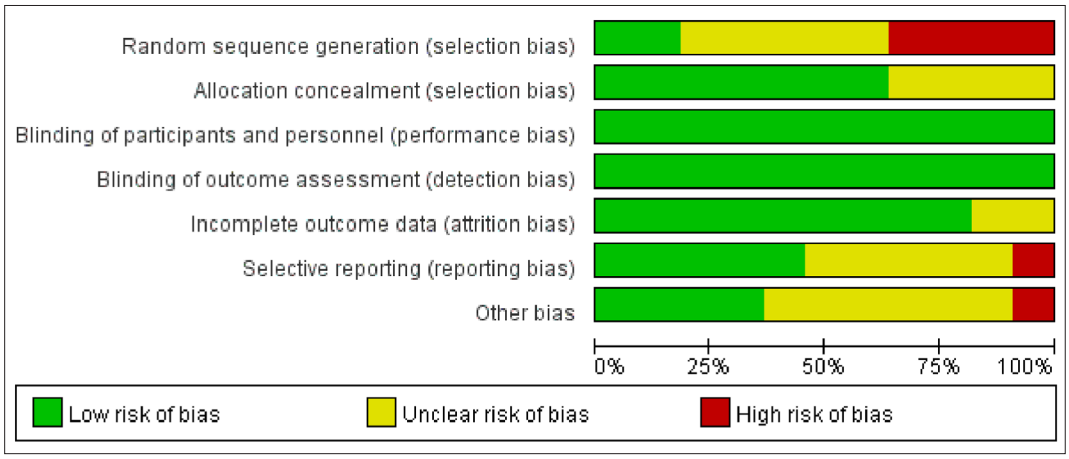

Fig. 2. Risk of bias.

CD4+CD103+ T cell infiltration is associated with worse prognosis

In order to confirm the contracted prognostic influence of CD4+CD103+ T cell infiltration and further explain the heterogeneity in our meta-analysis, a sensitivity analysis was done. We ran an influence analysis in STATA 14.0 to evaluate the influence of each cohort on the pooled result. The chart exhibited that the two cohorts from the study focusing on the prognostic value of CD4+CD103+ T cell infiltration in gastric cancer patients generated the most remotely deviated results, while the results from the remaining 9 cohorts were consistent with the pooled result.

We also drew a Galbraith Radial plot to confirm the cause of heterogeneity. Evidently, the same two cohorts identified in the influence analysis stood out in the Galbraith Radial plot. These plots demonstrated that, in contrast to CD8+CD103+ T cell, CD4+CD103+ T cell infiltration may imply poor prognosis in tumors of the digestive duct.

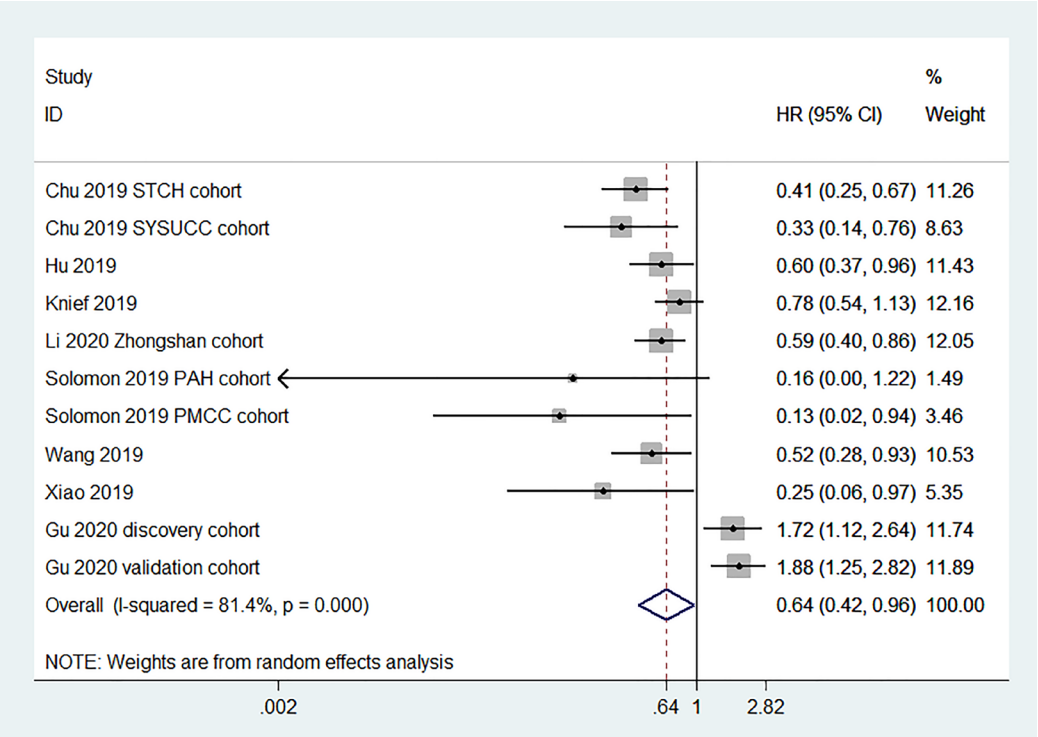

Fig. 3. Forest plot of all the included studies.

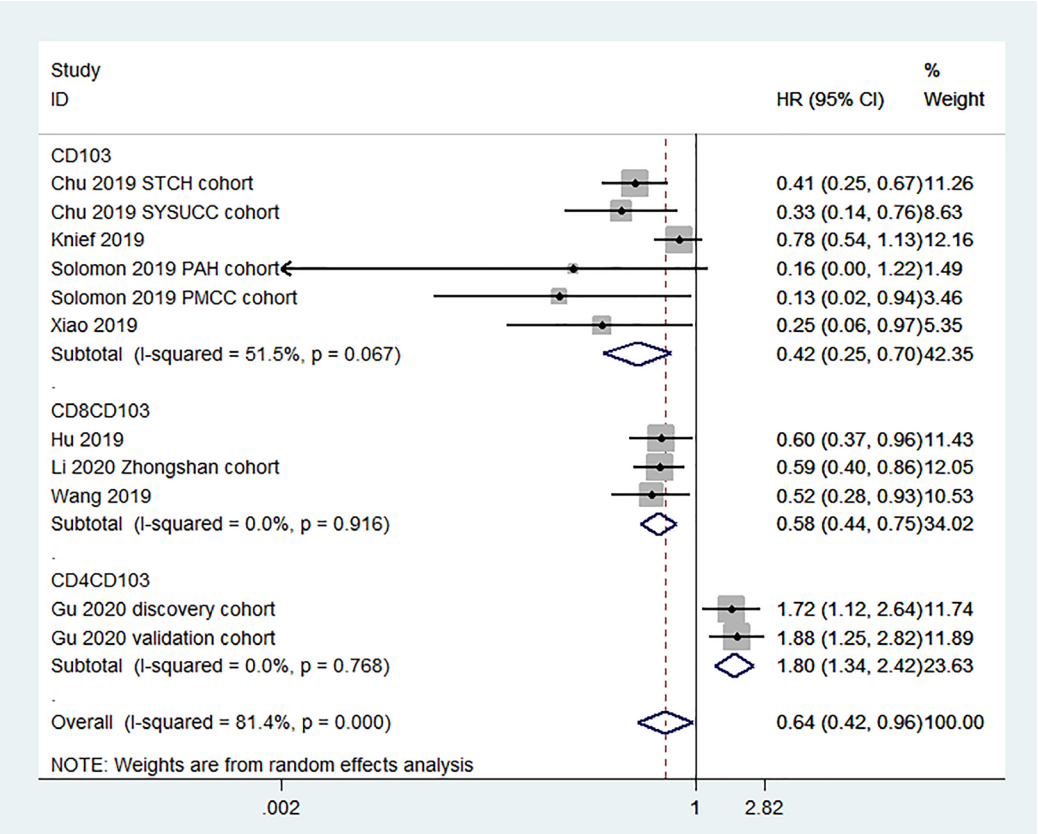

Fig. 4. Subgroup analysis by cell types.

Publication bias

In order to discover potential publication bias, we drew a funnel plot and conducted Egger's and Begg's test via STATA 14.0. The generated *P* value was 0.125, meaning there was no significant publication bias among the included studies. There was no need for further trim and fill analysis.

DISCUSSION

Over the last decade, the function of CD103+ T cells in anti-tumor immunity has been researched in NSCLC, ovarian cancer, breast cancer, endometrial adenocarcinoma and other tumors. However, little attention was drawn to its role in digestive tumors until the past three years. To our knowledge, this is the first systematic review and meta-analysis to focus on the prognostic value of CD103+ T cells in solid tumors of the digestive duct. In this meta-analysis, 11 cohorts from 8 recently published studies were deemed eligible according to our inclusion and exclusion criteria. A total of 1915 patients from China, Germany and Australia suffering from gastric cancer, esophageal cancer, esophagogastric junction cancer, colorectal cancer, oral cancer and oropharyngeal cancer were included into this study. We extracted HRs with 95% CI from the original studies and reached the result that dense CD103+ T cell infiltration is associated with favorable clinical outcome in patients with digestive tumors (HR: 0.64 ,95% CI: 0.42-0.96, *P*=0.03). Significant heterogeneity was found and subgroup analysis revealed that the prognostic value of CD4+CD103+ T cells was inconsistent with either CD8+CD103+ T cells or CD103+ T cells, which was further confirmed by sensitivity analysis. Egger's and Begg's test discovered no significant publication bias. It is worth pointing out that all the included studies were extremely up-to-date and published no later than 2019, because the function of CD103+ T cell in cancer immunity did not draw serious attention until the past three years. We believe our work is innovative and holds clinical significance.

During literature search, we also noticed some studies focusing on CD103+ T cell infiltration in digestive tumors, yet lacking sufficient data to be included into our meta-analysis. In line with the pooled results, a recent study investigated fresh surgical samples of human esophageal cancer and reported that CD8+CD103+ tumor infiltrating lymphocyte (TIL) infiltration is associated with better prognosis. This specific subgroup of TILs display potent proliferation and cytotoxic cytokine secretion ability, and elicit robust anti-tumor immunity after PD-1 blockade treatment regardless of chemotherapy[20]. Another team from Germany looked into CD103+ T cells in resected pancreatic duct adenocarcinoma and proposed that high ratio of intraepithelial to total CD103+ T cells, instead of the actual numbers of CD103+ T cells or CD103+ intraepithelial lymphocytes, indicates improved overall survival in pancreatic cancer patients. Their work emphasized the distribution of CD103+ T cells rather than the number[33]. As immunotherapy in intrahepatic cholangiocarcinoma (ICC) patients yields fruitful clinical benefits, a group of researchers tended extra attention to T_{RM} cells in surgical samples of 33 ICC patients and observed higher infiltration of CD103+CD8+ TILs in intratumoral areas than in stroma. They noticed that, when compared to CD103+ T cells, CD103+ T cells exhibited stronger tumor specificity, proliferation and activation[34]. These findings imply that the anti-tumor potential of CD103+ T cells is particularly contributed to the intratumoral subgroup rather than total 103+ T cells. Interestingly, all the studies included in the current meta-analysis investigated the numbers of intratumoral CD103+ T cells except one on human oral cancer, which stated that stromal, instead of intratumoral CD8+CD103+ TILs were correlated with a favorable prognosis[31].

Up until now, the mechanism underlying the role of CD103+ T cell in anti-tumor immunity still remain largely unknown. Through accumulating evidence from studies around the globe, a gradually cleared theory is being formed and consented among scientists investigating CD103+ T cells. It has been established that T_{RM} cells, distinctively expressing CD103, respond much faster to reexposure of cognate antigens than circulating memory cells[35]. Upon activation, T_{RM} cells take up local immunosurveillance and trigger recruitment of various immune cells by secretion of cytokines[21]. The cytotoxic functions of CD8+CD103+ TILs are hinted through observed expression of granzyme A, granzyme B, perforin, and TIA-1, a marker for potential cytotoxicity[9,36,37]. Functional studies proved that CD8+CD103+ TILs are capable of producing interferon (IFN) γ and tumor necrosis factor (TNF) α in tumor microenvironment, which is enhanced upon binding of CD103 to tumor cell E-cadherin[38]. When compared to CD103+CD8+ T cells, intratumoral CD103+CD8+ T cells presented higher cytotoxicity[29].

The first decade of the 21st century witnessed the ground shaking revolution of immunotherapy in the battle against human cancers, as PD-1 blockade treatment reshaped the entire oncology field and benefited numerous lives. Naturally, the discussion over CD103+ T cell in anti-tumor immunity is brought under the background of cancer immunotherapy. We found quite a lot of studies implying a better response to PD-1 blockade in patients with dense CD103+ T cell infiltration. A previous study discovered increased infiltration of CD103+ T cells in colorectal cancers with microsatellite instability (MSI) in comparison to microsatellite stable (MSS) ones. Researchers found nearly thirty folds greater numbers of CD103+ T cells in tumor areas than in healthy epithelium from the same patient[39]. The works of this team provides new enlightments for patients with colorectal cancer today, as MSH-high cancers are known to respond well to immunotherapy. The highlights of the study on intrahepatic cholangiocarcinoma mentioned above showed that ICCs with high proportions of CD69+CD103+ T cells presented higher CD8+ TIL infiltration, higher tumoral PD-L1 expression, and stronger T cell inflamed gene signature. Whereas ICCs with low proportions of CD69+CD103+ T cells exhibited enrichment of genes related to the Wnt/β-catenin and TGF-β pathways, notoriously acknowledged

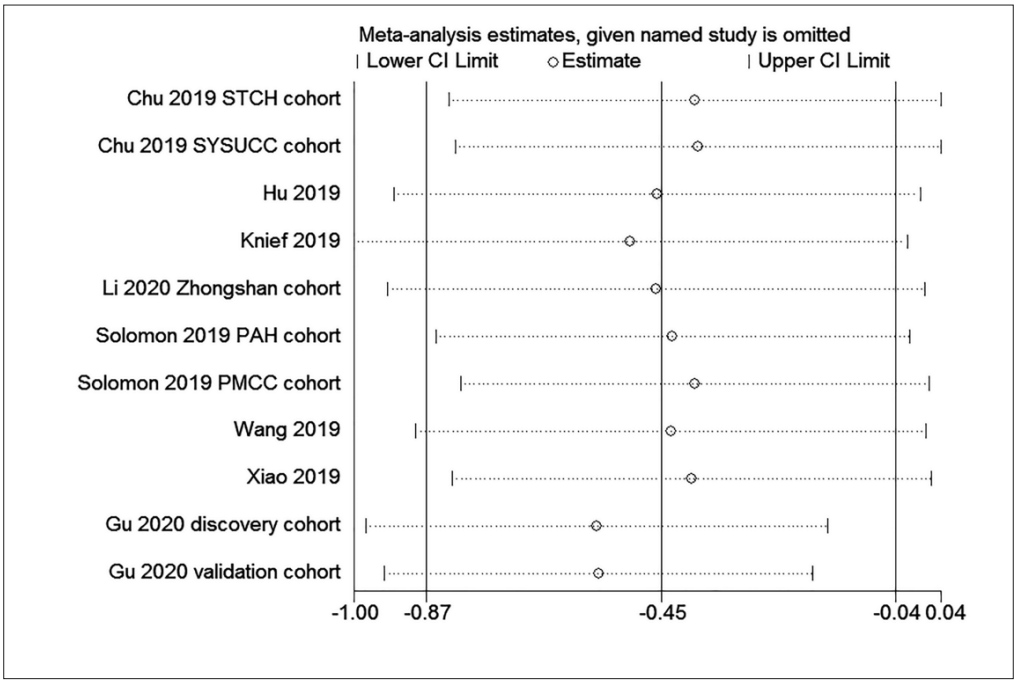

Fig. 5. Influence analysis mentioned in the text.

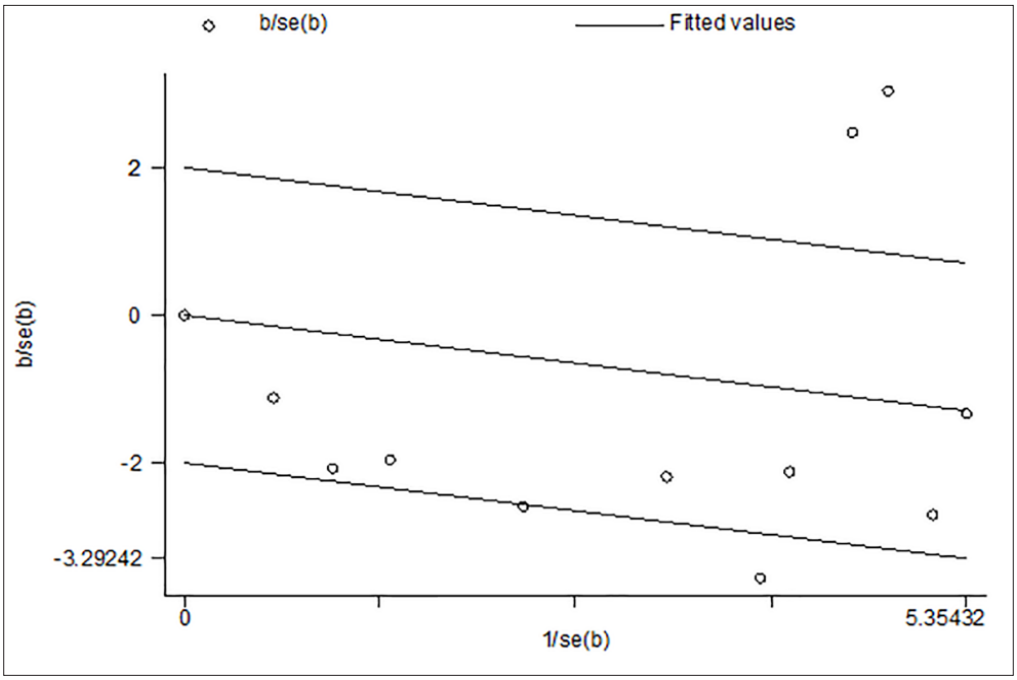

Fig. 6. Galbraith Radial plot mentioned in the text.

to be responsible for immune treatment tolerance[34]. In cytotoxicity experiments, after PD-1 neutralization, freshly isolated CD103+ TILs successfully killed autologous tumor cells and this cytotoxic activity was inhibited by CD103 blockade[6,9]. CD103+CD8+ TILs expressed dominant PD-1 and T-bet, rendering them to be better armed for immunotherapy. Consistently, researchers found that compared to CD103+CD8+ TILs, PD-1 antibody induced stronger IFNγ secretion in CD103+CD8+ TILs (ref.[24]). Similar results were observed in another study focusing on human gastric cancer, suggesting that CD103+CD8+ T cells are primely responsive to PD-1 blockade and possess the potential to predict immunotherapy efficacy[29]. In spite of expressing cell exhaustion markers, the cytotoxic potency of CD103+CD8+ TILs could be restored after PD-1 blockade administration and CD103+ T cell expansion was observed during anti PD-1treatment[20,22]. Similar expansion of CD103+ T cells after PD-1 blockage were found in a xenograft mouse model of renal cancer, and the favorable treatment efficacy was reversed with depletion of CD103+ T cells, suggesting an indispensible character of CD103+ T cells in immunotherapy and its potential to optimize treatment efficacy[19]. These findings sparkled novel ideas of future techniques to better expand

CD103+ T cells like local immunization by mucosal vaccine[21,40]. Given the fact that CD103+ T cells are vigorous participants in tumor immunity, we recommend that early detection via immunohistochemistry upon surgical resection be conducted.

Several limitations are obvious in our study. To begin with, we intended to evaluate the association of CD103+ T cell infiltration with overall survival in tumors of the digestive duct, but only 11 cohorts from 8 studies fit our criteria. It is understandable as we mentioned that the issue of CD103+ T cell in tumors of the digestive duct did not draw focus until the past three years. The total number of patients was 1915, still not enough for a statistically solid meta-analysis. The tumor types covered gastric cancer, esophageal cancer, esophagogastric junction cancer, colorectal cancer, oral cancer and oropharyngeal cancer, which means our study lacks data of patients suffering from other digestive tumors, such as pancreatic cancer, liver cancer and gallbladder cancer. The patients in our meta-analysis were mainly from China, and only 501 out of 1915 were from Germany and Australia. Although subgroup analysis revealed no significant heterogeneity among patients from different areas, we still worry about potential geographic and racial bias. Our conclusion is yet to be further strengthened in more trials concerning other digestive tumors with patients from around the globe. In addition, all the included studies used different cut-off values to divide patients into high and low CD103+ T cell infiltration groups, sometimes even within the same tumor type, making it difficult to compare the result of one study to another. We believe that different tumors exhibit their own basic CD103+ T cell infiltration levels. For studies focusing on the same type of tumor, the researchers used different specimen forms of either whole tissue slides or tissue microarrays. They also adopted different methods to observe and calculate cell numbers. Therefore, it is fairly reasonable for researchers to come up with a unique cut-off value in each study.

We could not ignore the high heterogeneity we found in our meta-analysis, which lied among different subgroups of CD103+ T cells. No significant heterogeneity was found among the HRs of CD8+CD103+ T cell and CD103+ T cell infiltration. But apparently, the prognostic value of CD4+CD103+ T cells was quite the opposite of the pooled result. It is worth noticing that the researchers of this particular study discussing CD4+CD103+ T cells in gastric cancer were from the same team that almost simultaneously published another essay discussing CD8+CD103+ T cells in gastric cancer[26]. Providing the fact that these two highly qualified studies both came from the same lab, we do believe that the inconsistent prognostic values of CD8+CD103+ T cells and CD4+CD103+ T cells in gastric cancer is substantial. This team proved that the cytotoxic potency of CD8+ T cells are inhibited in patients with high CD4+CD103+ T cell infiltration, displaying impaired ability to produce granzyme B, IFNγ, TNFα and perforin. Such contradiction calls for more research into this specific subgroup of CD103+ T cells, not only in gastric cancer, but also in other tumors. Nonetheless, with all the studies currently accessible, we consider our conclusion that dense CD103+ T cell infiltration predicts better clinical outcome stands reliable.

CONCLUSIONS

In conclusion, the current meta-analysis indicates that CD103+ T cell infiltration is associated with favorable prognosis in solid tumors of the digestive duct, but the prognostic value of the CD4+CD103+ T cell subgroup calls for further research. Therefore we recommend CD103+ T cell infiltration evaluation by immunohistochemistry before anti-tumor treatment as a potential prognostic marker for patient survival. Preliminary function experiments and mouse models suggest that CD103+ T cells could also predict anti-PD-1/PD-L1 treatment response and are promising candidates to be targeted in cancer immunotherapy for enhanced efficacy.

Search strategy and selection criteria

Several major medicine related databases were searched, including PubMed, EMBASE, Cochrane Library, Web of Science, Wan fang Database, and China National Knowledge Infrastructure (CNKI) network until February 28, 2021. To identify studies referring to the prognostic significance of CD103+ T cells in tumors of the digestive duct, we adopted a comprehensive search strategy, combining text word and MeSH with the key words “prognosis” or “prognostic” and “CD103” and “cancer” or “tumor” or “neoplasm” or “carcinoma” or “malignancy” and “digestive” or “oral” or “pharyngeal” or “esophageal” or “gastric” or ”pancreatic” or “liver” or “gallbladder” or “colon” or “rectal”. We also performed a manual search while screening the references of eligible studies in case any study was missed out. When the original article did not provide sufficient data for our analysis, we tried to contact the authors for details. The entire searching process was done under the guidance of PRISMA 2009 statement.

Ethical approval was not required for this meta-analysis because all the studies included in this meta-analysis were previously published high qualified studies, and the ethical approval of each study can be found in the original article respectively. All of the included studies were conducted according to the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion criteria were as follows: only human studies were included; the patients were pathologically diagnosed of a certain solid tumor of the digestive duct; overall survival was observed; CD103+ T cell infiltration was evaluated; sufficient data were displayed such as HR or Kaplan-Meier curves. If duplicate studies occurred, only the most recent one was included.

Exclusion criteria were as follows: random cohorts pulled from public databases like the Cancer Genome Atlas (TCGA) or Surveillance, Epidemiology, and End Results (SEER) were excluded due to lack of detailed information. Studies focused on hematological malignancies of the digestive duct were excluded, such as lymphoma

or melanoma. In addition, reviews, letters, case reports, conference abstracts, nonhuman experimental studies and studies without sufficient exactable data were excluded.

After initial search, duplicate studies would be removed. Abstracts and titles would be screened and whole paper would be scanned to select the eventually qualified studies to be included into this meta-analysis.

Quality assessment and data extraction

We assessed the quality of each included study according to Cochrane Handbook for Systematic Reviews of Interventions, using Review Manager 5.3 (the Cochrane Collaboration, Copenhagen, Denmark). Risk of bias was evaluated by two different reviews independently. Should disagreement occurred, a third reviewer would join to reach consensus.

Data extraction was also done by two reviews independently, collecting the surname of the first author, year of publication, patient area, type of tumor, sample size, specimen type of whole slide (WS) or tissue microarray (TMA), cut-off value, HR with 95% CI and P value. The extracted data were double checked by both reviews. Should disagreement occurred, a third reviewer would join to reach consensus.

Statistical analysis

The extracted data were processed using STATA 14.0 software (IBM Corp., Armonk, NY, USA). The HRs with 95% CI for OS were pooled. If a certain study did not provide HR and 95% CI directly, survival data were then extracted from the Kaplan-Meier curves, according to the established statistical methods from Tierney et al.[41]. Random effects model was applied unless there was no significant heterogeneity, in which case fixed effects model would be applied. If heterogeneity among the included studies occurred, further subgroup analysis would be done to find the factors that had significant influence on the pooled result. Heterogeneity was evaluated by Galbraith Radial plot. Sensitivity analysis was also done to explore the influence of each cohort on the pooled HR. Publication bias was evaluated Egger's and Begg's test. A funnel plot was drawn. If significant publication bias was found, trim and fill analysis would be performed to determine whether the pooled result was stable.

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