Prognostic and clinicopathological value of high expression of TIM-3 in different cancer types: A meta-analysis

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Abstract
Background: This meta-analysis was performed to clarify the prognostic role of the expression of T-cell immunoglobulin mucin-3 (TIM-3) in different cancer types.

Methods: Related articles were searched from PubMed, EMBASE, Web of Science up to December 31, 2019. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were utilized to explore their associations. In addition, we conducted subgroup analyses stratified by various factors.

Results: Eventually, a total of 33 studies including 4223 patients were enrolled in this study. Results showed that patients with high TIM-3 expression had shorter overall survival (OS) (HR = 1.67, 95% CI: 1.37-2.04) and progression-free survival (HR = 1.80, 95% CI: 1.14-2.83), but subgroup analyses indicated there were no relationships between TIM-3 expression and disease-free survival or recurrence-free survival. It was reassuring that high TIM-3 expression may be associated with poor prognosis in osteosarcoma, gastric cancer, liver cancer, esophageal cancer, and lymphoma, while no prognostic significance was detected of TIM-3 expression in lung cancer, kidney cancer, or breast cancer. Furthermore, we did not find association of TIM-3 with any clinicopathological parameters.

Conclusions: High TIM-3 expression might be a potential biomarker which can be used to predict the poor prognosis of different cancer types, especially osteosarcoma, gastric cancer, liver cancer, esophageal cancer, and lymphoma.

KEYWORDS
biomarker, cancer, meta-analysis, prognosis, TIM-3

1 | BACKGROUND

Cancer remains one of the predominant causes of morbidity and mortality in the world.¹ Although great progress has been made in the diagnostic techniques and treatment methods, not all patients benefited from these interventions. Under such circumstances, the diagnosis of patients with poor prognosis plays an increasingly important role in treatment, tumor progression and prognostic estimation. So far, only tumor node metastasis (TNM) staging is the most commonly used method to predict the prognosis in different cancer types. Regretfully, some studies have suggested that many patients within the same TNM staging have different prognosis.² Thus, novel and more accurate
biomarkers to predict prognostic outcomes for cancer survivors are urgently needed.

T-cell immunoglobulin mucin-3 (TIM-3) is mainly localized on the T-cell surface as an immune checkpoint (co-inhibitory signal receptor). Lots of studies demonstrated that TIM-3 played a pivotal role in immune modulation of cancers. Moreover, previous research showed that aberrant TIM-3 expression was central to carcinogenesis and progression. Furthermore, binding of TIM-3 to its ligand galectin-9 triggers Th1 cells died and induces peripheral tolerance, suggesting an inhibitory effect of TIM-3 in immune response. In fact, TIM-3 is identified as an important negative regulatory factor of CD4+ and CD8+ T-cells. Evidence shows that TIM-3 suppresses CD4+ T-cells activation by multiple mechanisms. Moreover, overexpression of TIM-3 has a relationship with cancer-specific antigen CD8+ T-cell dysfunction in patients with malignant tumor. These observations made us speculate TIM-3 as a new biomarker.

Accumulating studies have suggested that TIM-3 is over-expressed and is related to poor prognosis in different kinds of tumor, consisting of hepatocellular carcinoma, lung carcinoma, cervical carcinoma, gastric carcinoma, renal cell carcinoma, bladder urothelial carcinoma, colon carcinoma, and so on. A previous meta-analysis including these cancers showed that TIM-3 was a potential therapeutic target and prognostic marker of patients with solid tumors. However, more and more researches have been published to explore the function of TIM-3 in cancers over the past 5 years, and new evidences have been contrary to previously published studies. Specifically, Burugu et al found that high TIM-3 expression cancer tissue was associated with good prognosis in patients. Meanwhile, previous research only discussed the prognostic significance of patients’ overall survival (OS), and so far, the relationship between high expression of TIM-3 and certain tumor types remains unclear.

Therefore, it is necessary to conduct an updated study to evaluate the prognostic value of TIM-3 in various cancer types. The objective of current research was to comprehensively and systematically assess the effects of high TIM-3 expression on OS and progression-free survival (PFS) in different cancer types.

2 MATERIAL AND METHODS

2.1 Search strategy

Our research was performed basing on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The PubMed, EMBASE and Web of Science databases were thoroughly screened up to December 31, 2019. Keywords employed in the search were “TIM-3” AND “tumor OR carcinoma OR cancer OR neoplasm OR leukemia OR lymphoma” AND “survival OR prognosis OR progress OR progression OR outcome OR death,” by searching “all fields.” Furthermore, the references of qualified articles were also checked to identify eligible studies.

2.2 Selection criteria

In our study, the inclusion criteria for a study’s selection were: (a) studies analyzed the prognostic role of TIM-3 in different kinds of cancers, (b) cancers were confirmed by histologic or pathologic examinations, (c) with enough data to extract hazard ratios (HRs) and their 95% confidence intervals (CIs) for OS and/or disease-free survival (DFS) and/or PFS and/or recurrence-free survival (RFS), and (d) researches involved human participants only. In addition, the criteria for exclusion were as follows: (a) editorials or conference abstracts, letters to the editor, case studies or nonclinical studies, (b) articles were not in English languages, and (c) articles had duplicate data or repeat analysis. Apart from the above, only the most informative recent publication or the largest sample size manuscript were eligible for inclusion if the same samples were reported in different studies.

2.3 Data collection and endpoints

All eligible articles were reviewed independently by two investigators (W.B.X. and R.D.J.) and any disagreement was resolved through a third investigator (F.Q.). Then, the following elements were gathered: year of publication, name of first author, patient’s nationality, cancer types, number of patients, sex ration, age at diagnosis, number of patients with TIM-3 overexpression, detection methods, the site of TIM-3’ expression, cut-off value, therapeutic strategy, follow-up, HRs, and 95% CIs for endpoints. The primary endpoints of this study were OS and DFE/PFS/RFS. If HRs with 95% CIs were not available directly, they were estimated from Kaplan-Meier survival curves by appropriate software (Engauge Digitizer version 10.9) according to the method described by Tierney’s. Importantly, multivariate analysis results were preferred because of the higher precision when compared with univariate analysis.

2.4 Quality assessment

Two investigators (W.B.X. and R.D.J.) independently evaluated the quality of the included researches by the Newcastle-Ottawa-Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The NOS criteria were scored based on three categories: subject selection (0-4 scores), comparability of subjects (0-2 scores), and outcome assessment (0-3 scores). Typically, a score of 6 or more points was deemed to indicate a high-quality research.

2.5 Statistical analyses

Cochran Q test and inconsistency index (I²) statistics were undertaken to assess the heterogeneity between enrolled researches. If P < .10 or I² > 50%, showing that the heterogeneity was significant, a random-effect model (DerSimonian and Laird) was utilized. Otherwise, a fixed-effect model was applied instead. Possible sources of
heterogeneity were analyzed by conducting subgroup analysis, sensitivity analysis and meta-regression. We evaluated the publication bias graphically using Begg’s funnel plot and Egger’s publication bias plot.24,25 P < .05 (two-sided) was generally considered as statistically significant. All data analyses in this study were conducted using STATA v.15.0 (StataCorp, Texas).

3 | RESULTS

As shown in Figure 1, the initial literature search obtained 2432 articles and a total of 33 studies4-6,12-18,26-48 including 4223 patients were finally included after further examination.

3.1 | Study characteristics and quality assessment

A total of 33 eligible studies were published between 2012 and 2019, and the countries included China (23), Korea (3), America (2), Japan (2), Czech (1), France (1), and Poland (1). The minimum-pooled sample size was 30 cases and the maximum was 587. All included articles in this study were retrospective studies. Of the total cancer cohort, lung cancer was the most studied carcinoma (5), followed by kidney cancer (4), esophageal cancer (3), gastric cancer (3), liver cancer (3), lymphoma (3), osteosarcoma (3), breast cancer (2), and other cancers (7). Out of the 33 studies, 17 (20/33, 60.61%) directly reported HRs and 95% CIs; for the remaining 13 studies, we used Tierney’s method to evaluate HRs and their 95% CIs. The relevance of TIM-3 and OS was reported in 31 studies, and 14 studies also examined the DFS, PFS, or RFS. The remaining 2 studies only investigated PFS. Table 1 presented the summary characteristics of the included studies. The results for quality assessment of included studies by NOS were presented in Supplementary Table S1. According to the NOS evaluation criterion, all of the included studies were high quality.

3.2 | Meta-analysis

3.2.1 | The prognostic value of TIM-3 in OS

We combined results from 31 studies to get a pooled HR and 95% CI for OS in different kinds of tumor (Figure 2). Since high significant heterogeneity ($I^2 = 81.2\%, P < .001$), a random-effect model was employed. Results showed that patients with high TIM-3 expression had shorter OS (HR = 1.67, 95% CI: 1.37-2.04).

Furthermore, subgroup analyses stratified by cancer types, publication year, sample size, region, type of TIM-3, expression site of TIM-3, analysis of survival and treatment modality were conducted (Table 2).
| Author (year) | Country | Cancer types | Number of patients (M/F) | Mean Age (years) | Percentage of high Tim-3 expression | The site of Tim-3 expression | Cut-off value | Treatment strategy | Follow-up (months) | Endpoint | HR for OS (95% CI) | HR for DFS/RFS/PFS (95% CI) | NOS score |
|--------------|---------|--------------|-------------------------|-----------------|-------------------------------------|--------------------------|---------------|-------------------|-------------------|-----------|--------------------|---------------------------|-----------|
| Jia K 2019    | Poland  | Lung cancer  | 139 (30/109)           | 64              | 7.19%                               | TILs                     | ≥10% in TILs  | Surgery           | NA                | OS and RFS | 1.18 (0.59, 2.35) | 2.56 (0.87, 7.52)           | 9         |
| Su H 2018     | China   | Lung cancer  | 223 (120/103)          | 61              | 52.02%                              | Tumor cells, or TILs     | ≥24% in tumor cells, and ≥ 11% in TILs | Surgery           | 76        | 2.04 (1.30, 3.21) | 2.32 (1.44, 3.73)           | 8         |
| Soo RA 2017   | South Korea | Lung cancer | 89 (64/25)             | 62              | NA                                  | Tumor cells              | ≥5% in tumor cells | Chemotherapy      | 13        | OS and RFS | 1.00 (1.00, 1.00) | 1.00 (0.99, 1.00)           | 7         |
| Xu L 2015     | China   | Lung cancer  | 85 (34/51)             | NA              | 73%                                 | CD3(+) and CD56 (+) T-cells | NA             | Surgery           | NA                | OS        | 1.22 (0.34, 4.35) | NA                         | 6         |
| Zhuang X 2012 | China   | Lung cancer  | 30 (23/7)              | 60              | 50.00%                              | Tumor cells, or TILs     | ≥25% of tissue specimens | Surgery           | 34        | OS      | 3.95 (0.67, 23.29) | NA                         | 8         |
| Pu F 2019     | China   | Osteosarcoma | 38 (12/26)             | 18              | 63.16%                              | Tumor cells              | score > 1.1 | Surgery           | 60        | OS       | 2.85 (0.73, 11.13) | NA                         | 8         |
| Ge W 2017     | China   | Osteosarcoma | 120 (77/43)            | NA              | NA                                  | Serum                    | NA             | Surgery-plus-chemotherapy | 37.1 | OS | 2.12 (1.36, 3.31) | NA                         | 7         |
| Liu H 2016    | China   | Osteosarcoma | 56 (NA)                | NA              | 50.00%                              | CD8(+) T                 | NA             | Surgery           | 39        | OS       | 1.63 (0.49, 5.45) | NA                         | 7         |
| Chen BJ 2019  | America | Diffuse large B-cell lymphoma | 70 (32/38) | 69 | 32.86% | Tumor cells | score ≥ 80 | Chemotherapy | 44 | OS and PFS | 3.49 (1.67, 7.31) | 3.35 (1.57, 7.17) | 8 |
| Horlad H 2016 | Japan   | Adult T-cell leukemia/lymphoma | 58 (24/34) | NA | 43.10% | Tumor cells | ≥50% in tumor cells | Chemotherapy | NA | OS | 1.83 (0.89, 3.76) | NA                         | 7         |
| Zhou J 2019   | China   | Chordoma     | 93 (53/40)             | 45.8            | 73.12%                              | TILs                      | 278.2 cells/mm² | Surgery-plus-radiation | 36.9 | OS and RFS | 1.45 (1.10, 1.92) | 0.43 (0.22, 0.82) | 6 |
| Gravelle P 2016 | France  | Follicular lymphoma | 46 | 55 | 63.04% | Tumor cells | Cut-off value at 10% | Chemotherapy | NA | PFS | NA | 5.60 (1.48, 21.20) | 7 |
| Wang Q 2019   | America | Renal cell carcinoma | 182 (135/47) | 59 | 32.97% | Serum | ≥5908 pg/mL | Surgery-plus-chemotherapy | 66.1 | OS and RFS | 1.65 (0.61, 4.43) | 6 |
TABLE 1 (Continued)

| Author (year) | Country | Cancer types | Number of patients (M/F) | Mean Age (years) | Percentage of high Tim-3 | The site of Tim-3 expression | Cut-off value | Treatment strategy | Follow-up (months) | Endpoint | HR for OS (95% CI) | HR for DFS/RFS/PFS (95% CI) | NOS score |
|---------------|---------|--------------|--------------------------|------------------|--------------------------|-----------------------------|---------------|-------------------|-------------------|----------|-------------------|-----------------------------|-----------|
| Zhang X 2019  | China   | Renal cell carcinoma | 163 (107/56) | NA | 56.44% | Tumor cells | intensities ≥1+ | Surgery | 36 | OS and DFS | 0.54 (0.25, 1.17) | 0.67 (0.28, 1.61) | 8 |
| Komohara Y 2015 | Japan | Renal cell carcinoma | 91 (59/32) | NA | 68.48% | Tumor cells | score 1.2 | Surgery | NA | OS and DFS | 3.70 (0.38, 36.47) | 6.10 (1.33, 27.92) | 6 |
| Wu J 2017    | China   | Prostate cancer | 139 (0/139) | 66 | 25.18% | Tumor cells | ≥ weak staining | Surgery | 21.1 | OS | 0.34 (0.13, 0.85) | NA | 8 |
| Yang M 2015  | China   | Bladder urothelial carcinoma | 100 (68/32) | 65.32 | 50.00% | Tumor cells | H-score ≥ 100 | Surgery-plus-chemotherapy | 44 | OS and DFS | 5.51 (1.52, 19.96) | 5.43 (1.48, 19.86) | 9 |
| Yuan J 2014  | China   | Renal cell carcinoma | 137 (107/30) | 57 | 20.44% | Tumor cells | HSCORE > 3 + 4+ | Surgery | 70 | PFS | NA | 2.23 (1.24, 4.00) | 6 |
| Byun KD 2018 | South Korea | Breast Cancer | 109 (0/109) | 50 | 84.40% | TILs | ≥24% TILs express TIM-3 | Surgery | 76 | OS and DFS | 0.11 (0.03, 0.39) | 0.11 (0.03, 0.36) | 6 |
| Cheng S 2018 | China   | Breast Cancer | 42 (42/0) | NA | 42.86% | Tumor cells | NA | Surgery | 49 | OS | 2.00 (1.10, 3.61) | NA | 6 |
| Fucikova J 2019 | Czech | Ovarian Cancer | 80 (0/80) | 61 | 31.25% | CD8(+) T | ≥31.3% CD8(+) T expressed | Chemotherapy | NA | OS | 1.41 (1.07, 1.85) | NA | 7 |
| Cao Y 2013    | China   | Cervical Cancer | 43 (0/43) | 39 | 65.12% | Tumor cells | IRS scores2 and 3 | Surgery | 45.2 | OS | 2.78 (0.70, 11.07) | NA | 9 |
| Wang Y 2018  | China   | Gastric cancer | 587 (401/186) | 61.6 | 49.91% | Tumor cells | >5 stained cells/high-power field | Surgery-plus-chemotherapy | 48 | OS | 1.39 (1.08, 1.81) | NA | 6 |
| Cheng G 2015 | China   | Gastric cancer | 52 (41/11) | 64.5 | NA | CD8(+) T | NA | Surgery | NA | OS | 4.57 (1.05, 19.93) | NA | 6 |
| Jiang J 2013  | China   | Gastric Cancer | 305 (231/74) | 64 | 60.00% | Tumor cells | HSCORE > 0 | Surgery | 40 | OS | 1.83 (1.25, 2.67) | NA | 9 |

(Continues)
| Author | Year | Country | Cancer types | Number of patients (M/F) | Mean Age (years) | Percentage of high Tim-3 expression | The site of Tim-3 expression | Cut-off value | Treatment strategy | Follow-up (months) | Endpoint | HR for OS (95% CI) | HR for DFS/RFS/PFS (95% CI) | NOS score |
|--------|------|---------|---------------|-------------------------|----------------|------------------------------------|--------------------------|----------------|------------------|----------------|----------|----------------|---------------------------|---------|
| Li F   | 2018 | China   | Hepatocellular carcinoma | 84 (69/15) | 55.04 | 60.71% | Serum | sTim-3 (>3000 pg/mL) | NA | 52 | OS | 2.77 (1.47, 5.22) | NA | 7 |
| Yan W  | 2015 | China   | Hepatocellular carcinoma | 69 (57/12) | 50 | 59.42% | CD68(+) T-cells | NA | NA | NA | OS | 1.08 (0.43, 2.72) | NA | 7 |
| Li H   | 2012 | China   | Hepatocellular Carcinoma | 99 (91/8) | 51 | 57.58% | CD4(+) and CD8(+) T-cells | NA | Surgery | 36 | OS | 1.98 (0.82, 4.77) | NA | 6 |
| Zhao Y | 2019 | China   | Esophageal squamous cell carcinoma | 183 (36/147) | NA | 47.54% | Tumor cells | Score 3 | Surgery | NA | OS and RFS | 2.62 (1.57, 4.37) | 4.01 (2.45, 6.55) | 7 |
| Hong MH| 2019 | South Korea | Esophageal squamous cell carcinoma | 396 (370/26) | 64 | 50.76% | TILs | ≥1% of immune cells | Surgery-plus-chemoradiation | 24.8 | OS and PFS | 1.60 (1.13, 2.27) | 1.52 (1.10, 2.10) | 8 |
| Shan B | 2016 | China   | Esophageal squamous cell carcinoma | 64 (48/16) | 57.5 | 56.25% | Tumor cells | score 3 | Surgery | 31 | OS | 2.87 (1.22, 6.76) | NA | 8 |
| Zhou E | 2015 | China   | Colon cancer | 201 (116/85) | 65 | 58.71% | Tumor cells | score ≥ 200 | Surgery | 61 | OS | 2.73 (1.27, 5.88) | NA | 8 |
| Peng PJ | 2017 | China   | Pancreatic cancer | 50 (30/20) | 55.06 | 72.00% | Tumor cells | score (+), (++), (+++) | Surgery | NA | OS | 1.40 (0.44, 4.45) | NA | 8 |

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NA, not available; NOS, Newcastle-Ottawa-Scale; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; TILs, tumor infiltrating lymphocytes; TIM-3, T-cell immunoglobulin mucin-3.
When the models were switched from random-effect to fixed-effect model, we found that high TIM-3 expression levels were significantly associated with worse OS regardless of publication year, sample size, region, type of TIM-3, analysis of survival, and treatment modality. It should be noted that in the analysis stratified by cancer types, high TIM-3 expression levels were correlated with poor OS in osteosarcoma (HR = 2.11, 95% CI: 1.42-3.15), gastric cancer (HR = 1.55, 95% CI: 1.26-1.92), liver cancer (HR = 2.03, 95% CI: 1.30-3.18), esophageal cancer (HR = 1.95, 95% CI: 1.49-2.57), and lymphoma (HR = 2.51, 95% CI: 1.50-4.20), but were not correlated with lung cancer (P = .155), kidney cancer (P = .511), and breast cancer (P = .631). The outcome of subgroup analysis also showed that high TIM-3 expression levels on tumor cells (HR = 1.72, 95% CI: 1.27-2.32), serum (HR = 2.45, 95% CI: 1.76-3.40), and CD8(+) T-cells (HR = 1.47, 95% CI: 1.13-1.92) had connections with poor OS. But high TIM-3 expression levels in tumor infiltrating lymphocytes (TILs) did not have a prognostic value for OS (P = .961).

3.2.2 The prognostic value of TIM-3 in DFS/PFS/RFS

Fourteen studies were included to investigate the prognostic value of TIM-3 in DFS/PFS/RFS. In the case of the obvious heterogeneity (I² = 88.1%, P = 0), a random-effects model was applied. Figure 3 showed that high TIM-3 expression was relevant with shorter DFS/PFS/RFS (HR = 1.67, 95% CI: 1.12-2.49).

Similar to OS analyses, we also performed subgroup analyses for DFS/PFS/RFS (Table 2). Findings from the subgroup analysis suggested that high TIM-3 expression had significantly shorter PFS (HR = 2.13, 95% CI: 1.27-3.58) but was insignificantly correlated with DFS (P = .887) or RFS (P = .176). Besides, we performed stratified analyses to investigate the relationship between high TIM-3 expression levels and DFS/PFS/RFS in cancer types. The results showed that high TIM-3 expression levels were related with poor DFS/PFS/RFS in lymphoma (HR = 3.80, 95% CI: 1.96-7.36) but was insignificantly correlated with lung cancer (P = .170), kidney cancer (P = .142), and esophageal cancer (P = .068).

3.3 TIM-3 expression and the association with clinicopathological factors

To determine the clinical prognostic value of TIM-3, we investigated the association between TIM-3 expression and clinicopathological factors in different cancer types (Table 3). Unfortunately, final analysis indicated that there were no significant association between TIM-3 expression and clinical variables, including age, sex, smoking history, tumor size, pT stage, pN stage, and TNM stage.
# Table 2

Subgroup analyses and meta-regression of OS and DFS/PFS/RFS for different cancer types

| Subgroup                          | N | HR (95% CI)       | P value* | Heterogeneity | Metaregression |
|-----------------------------------|---|-------------------|---------|---------------|----------------|
|                                   |   |                   |         | i²            | Ph            | Model | P value* |
| **Different cancer types—DFS/PFS/RFS** |   |                   |         |               |                |       |          |
| Outcome                           |   |                   |         |               |                |       |          |
| DFS                               | 2 | 0.76 (0.02, 35.46) | .887    | 94.7%         | 0.000          | R     | .565     |
| PFS                               | 7 | 1.80 (1.14, 2.83)  | .012    | 83.4%         | 0.000          | R     | .249     |
| RFS                               | 5 | 1.76 (0.78, 3.99)  | .176    | 86.7%         | 0.000          | R     | .249     |
| **Cancer types**                  |   |                   |         |               |                |       |          |
| Lung cancer                       | 3 | 1.66 (0.81, 3.41)  | .170    | 86.6%         | 0.001          | R     | .249     |
| Kidney cancer                     | 4 | 1.75 (0.83, 3.71)  | .142    | 61.9%         | 0.048          | R     | .249     |
| Esophageal cancer                 | 2 | 2.42 (0.94, 6.26)  | .068    | 90.4%         | 0.001          | R     | .249     |
| Lymphoma                          | 2 | 3.80 (1.96, 7.36)  | <.001   | 0.0%          | 0.511          | F     |          |
| Other cancer                      | 3 | 0.61 (0.09, 3.95)  | .605    | 89.7%         | 0.000          | R     |          |
| **Different cancer types—OS**     |   |                   |         |               |                |       |          |
| Cancer types                       |   |                   |         |               |                |       |          |
| Lung cancer                       | 5 | 1.38 (0.89, 2.14)  | .155    | 66.6%         | 0.018          | R     | .541     |
| Osteosarcoma                      | 3 | 2.11 (1.42, 3.15)  | <.001   | 0.0%          | 0.834          | F     |          |
| Kidney cancer                     | 3 | 1.61 (0.39, 6.65)  | .511    | 81.1%         | 0.005          | R     |          |
| Breast cancer                     | 2 | 0.50 (0.03, 8.38)  | .631    | 93.9%         | 0.000          | R     |          |
| Gastric cancer                    | 3 | 1.55 (1.26, 1.92)  | <.001   | 41.9%         | 0.179          | F     |          |
| Liver cancer                      | 3 | 2.03 (1.30, 3.18)  | <.001   | 26.9%         | 0.255          | F     |          |
| Esophageal cancer                 | 3 | 1.95 (1.49, 2.57)  | <.001   | 39.2%         | 0.193          | F     |          |
| Lymphoma                          | 2 | 2.51 (1.50, 4.20)  | <.001   | 33.4%         | 0.221          | F     |          |
| Other cancers                     | 7 | 1.53 (1.02, 2.30)  | .041    | 65.2%         | 0.008          | R     |          |
| **Publication year**              |   |                   |         |               |                |       |          |
| 2012-2015                         | 9 | 2.00 (1.52, 2.63)  | <.001   | 0.0%          | 0.582          | F     | .279     |
| 2016-2019                         | 22| 1.57 (1.25, 1.96)  | <.001   | 83.7%         | 0.000          | R     |          |
| **Sample size**                   |   |                   |         |               |                |       |          |
| < 100                             | 18| 1.81 (1.40, 2.35)  | <.001   | 72.8%         | 0.000          | R     | .348     |
| ≥ 100                             | 13| 1.48 (1.08, 2.04)  | .015    | 77.1%         | 0.000          | R     |          |
| **Region**                        |   |                   |         |               |                |       |          |
| Asia                              | 27| 1.63 (1.30, 2.03)  | <.001   | 80.7%         | 0.000          | R     | .591     |
| Non-Asia                          | 4 | 1.93 (1.17, 3.19)  | .010    | 65.5%         | 0.033          | R     |          |
| **Type of TIM-3**                 |   |                   |         |               |                |       |          |
| TIM-3                             | 28| 1.58 (1.28, 1.94)  | <.001   | 79.4%         | 0.000          | R     | .178     |
| sTIM-3                            | 3 | 2.45 (1.76, 3.40)  | <.001   | 0.0%          | 0.628          | F     |          |
| **Expression site of TIM-3**      |   |                   |         |               |                |       |          |
| Tumor cells                       | 16| 1.72 (1.27, 2.32)  | <.001   | 81.4%         | 0.000          | R     | .618     |
| TILs                              | 4 | 1.01 (0.57, 1.81)  | .961    | 81.7%         | 0.001          | R     |          |
| Tumor cells or TILs               | 2 | 2.12 (1.37, 3.30)  | .001    | 0.0%          | 0.479          | F     |          |
| Serum                             | 3 | 2.45 (1.76, 3.40)  | <.001   | 0.0%          | 0.628          | F     |          |
| CD8(+) T-cells                    | 3 | 1.47 (1.13, 1.92)  | .004    | 16.3%         | 0.303          | F     |          |
| Other cells                       | 3 | 1.43 (0.81, 2.52)  | .221    | 0.0%          | 0.624          | F     |          |
| **Analysis of survival**          |   |                   |         |               |                |       |          |
| Univariate                        | 15| 1.85 (1.33, 2.56)  | <.001   | 69.1%         | 0.000          | R     | .482     |
| Multivariate                      | 16| 1.57 (1.21, 2.03)  | .001    | 74.1%         | 0.000          | R     | .482     |
| **Treatment modality**            |   |                   |         |               |                |       |          |
| Surgery                           | 19| 1.57 (1.13, 2.18)  | .007    | 64.4%         | 0.000          | R     | .765     |
| Surgery-plus-other                | 6 | 1.72 (1.36, 2.18)  | <.001   | 47.4%         | 0.091          | R     |          |
| Chemotherapy                      | 4 | 1.52 (1.00, 2.30)  | .048    | 84.6%         | 0.000          | R     |          |
| NA                                | 2 | 1.84 (0.74, 4.60)  | .191    | 63.4%         | 0.098          | R     |          |

Abbreviations: CI, confidence interval; DFS, disease-free survival; Fixed, fixed-effects model; HR, hazard ratio; NA, not available; N, number of studies; OS, overall survival; Ph, P value of Q test for heterogeneity test; PFS, progression-free survival; R, random-effects model; RFS, recurrence-free survival; sTIM-3, soluble TIM-3; TILs, tumor infiltrating lymphocytes; TIM-3, T-cell immunoglobulin mucin-3.

*Statistically significant (P < .05).
3.4 | Meta-regression

For the sake of exploring the sources of heterogeneity between studies, a meta-regression was performed, including outcome, cancer types, publication year, sample size, region, type of TIM-3, expression site of TIM-3, analysis of survival, and treatment modality. Table 2 displayed the results of meta-regression. And our results suggested these variables did not significantly contribute to the heterogeneity.

3.5 | Sensitivity analyses and publication bias

To confirm the reliability and stability of the results, sensitivity analysis of the OS group was conducted by excluding individual study in each turn (Figure 4). The sensitivity analyses indicated that the results of meta-analysis were basically stable. In addition, we applied Begg's funnel plot and Egger's test to assess the publication bias for OS (Figure 5A). The P values of Begg’s and Egger’s test for OS were .032 and <.001, revealing significant publication bias. To further evaluate possible publication bias, we drew a filled funnel plot (Figure 5B). Trim-and-fill analysis showed that the result remained stable (updated pooled HR = 1.50, 95% CI: 1.25-1.82).

4 | DISCUSSION

TIM-3 has been researched for a number of years, but it is still a popular studying topic currently. Accumulating evidence indicated that play a critical role in migration, invasion and metastasis of tumor cells. First, on the T-cell surface, binding of TIM-3 and its ligands galectin-9 leads to the death of T-cell, thereby suppressing the innate immune response. Second, high levels of Tim-3 expression correlate with suppression of natural killer cells (NK), dendritic cells (DCs) and...
macrophage, this can block antitumor responses. Furthermore, the broad expression of Tim-3 on diverse tumor cells causes low levels of IFN-γ and TNF-α that can promote tumor progression. So, some study have shown that cancer cells could escape host immune defenses by expressing TIM-3 to modulate T-cells activation state. What is more interesting, in both solid and hematologic cancer, co-blockade of the TIM-3 and Programmed death 1 protein (PD-1) pathways is better than block PD-1 pathway alone at promoting antitumor effect of the general immune system. These reports pointed out high expression of TIM-3 to be a putative predictor related to poor OS and PFS. Therefore, above results indicated that TIM-3 may be a potential target candidate in different cancer types.

In the present study, our data showed that high TIM-3 expression had significantly shorter OS and PFS in cancer patients, but was insignificantly correlated with DFS/RFS. It was reassuring that high-level expression of TiM-3 may be a general poor prognostic biomarker in osteosarcoma, gastric cancer, liver cancer, esophageal cancer and lymphoma. Although some findings suggested that high TIM-3 expression indicated longer OS in breast cancer (HR = 0.11, 95% CI: 0.03-0.39) and renal cell carcinoma (HR = 0.54, 95% CI: 0.25-1.17), we found no relationship between TIM-3 and breast cancer/kidney cancer/lung cancer. The possible reasons might include: (a) the function of TIM-3 may vary depending upon tumor stages; (b) due to the heterogeneous nature of cancer. Our study demonstrated that overexpression of TIM-3 in tumor cells, serum and CD8(+) T-cells maybe prognostic role of site. More interestingly, sTim-3 overexpressed in serum was associated with poor prognosis. Previous studies have shown the levels of serum sTim-3 may parallel the levels of Tim-3 expressed on cells. Because of more simplistic detection method, we reasoned the sTim-3 overexpressed in serum maybe a more appropriate prognostic factor. Therefore, these may point the way for future research directions. However, it should be noted that some studies related to
patients with TIM-3 expression between clinicopathological parameters and clinical outcome. Some studies also indicated opposite results, such as a poor survival of high TIM-3 in hepatocellular carcinoma with higher tumor grades and TIM-3 expression was not related to tumor grades in pancreatic cancer. Regrettably, we did not find correlation of TIM-3 with any clinicopathological features.

To our best acknowledge, it was the first systematic and comprehensive study to investigate the prognostic roles of high TIM-3 expression in different tumors. A previous meta-analysis covered seven studies including 869 patients from 2012 to 2015, and only explored the influence of TIM-3 in patients' OS and four clinicopathological parameters. Our research combined 33 individual studies from 2012 to 2019 and enrolled 4223 patients. More importantly, our results are different from and even partially opposite to previous meta-analysis. Overall, our study seems to be more comprehensive and accurate.

Lastly, several inevitable limitations should be mentioned: (a) related studies were too few in some cancer types, (b) all the included studies were retrospective researches rather than prospective articles, (c) only 4 of 33 studies were focused on the western population and the impact of ethnicity could not be evaluated, and (d) some HRs with 95% CIs were extracted from the Kaplan-Meier curves, which might influence the credibility of our results.

5 | CONCLUSION

This study indicated that high TIM-3 expression might be a potential biomarker which can be used to predict the poor prognosis of different cancer types, especially osteosarcoma, gastric cancer, liver cancer, esophageal cancer, and lymphoma. However, further exploration was restricted due to the limited studies. Hence, randomized controlled trials and large sample size studies are urgently needed to verify our findings.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

(I) Conception and design: Zhengjun Kang; (II) Administrative support: Zhengjun Kang; (III) Provision of study materials or patients: Wenbo Xu and Feng Qi; (IV) Collection and assembly of data: Wenbo Xu, D Rui; (V) Data analysis and interpretation: Wenbo Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

ETHICS STATEMENT

Ethical approval or informed consent was not required for this meta-analysis.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020.
2. Van Schil PE, Rami-Porta R, Asamura H. The 8(th) TNM edition for lung cancer: a critical analysis. Ann Transl Med. 2018;6:87.
3. Das M, Zhu C, Kuchroo VK. Tim-3 and its role in regulating anti-tumor immunity. Immunol Rev. 2017;276:97-111.
4. Wu J, Lin G, Zhu Y, et al. Low TIM3 expression indicates poor prognosis of metastatic prostate cancer and acts as an independent predictor of castration resistant status. Sci Rep. 2017;7:8869.
5. Byun KD, Hwang HJ, Park KJ, et al. T-cell immunoglobulin mucin 3 expression on tumor infiltrating lymphocytes as a positive prognosticator in triple-negative breast cancer. J Breast Cancer. 2018;21:406-414.
6. Zhang X, Yin X, Zhang H, et al. Differential expression of TIM-3 between primary and metastatic sites in renal cell carcinoma. BMC Cancer. 2019;19:49.
7. Huang YH, Zhu C, Kondo Y, et al. CEACAM1 regulates TIM-3-mediated tolerance and exhaustion. Nature. 2015;517:386-390.
8. Zhu C, Anderson AC, Schubart A, et al. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nat Immunol. 2005;6:1245-1252.
9. Anderson AC. Tim-3, a negative regulator of anti-tumor immunity. Curr Opin Immunol. 2012;24:213-216.
10. Huang X, Bai X, Cao Y, et al. Lymphoma endothelium preferentially expresses Tim-3 and facilitates the progression of lymphoma by mediating immune evasion. J Exp Med. 2010;207:505-520.
11. Fourcade J, Sun Z, Benallaoua M, et al. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients. J Exp Med. 2010;207:2175-2186.
12. Li H, Wu K, Tao K, et al. Tim-3/galectin-9 signaling pathway mediates T-cell dysfunction and predicts poor prognosis in patients with hepatitis B virus-associated hepatocellular carcinoma. Hepatology. 2012;56:1342-1351.
13. Zhuang X, Zhang X, Xia X, et al. Ectopic expression of TIM-3 in lung cancers: a potential independent prognostic factor for patients with NSCLC. Am J Clin Pathol. 2012;137:978-985.
14. Cao Y, Zhou X, Huang X, et al. Tim-3 expression in cervical cancer promotes tumor metastasis. PLoS One. 2013;8:e53834.
15. Jiang J, Jin MS, Kong F, et al. Decreased galectin-9 and increased Tim-3 expression are related to poor prognosis in gastric cancer. PLoS One. 2013;8:e81799.
16. Komohara Y, Morita T, Annan DA, et al. The coordinated actions of TIM-3 on cancer and myeloid cells in the regulation of tumorigenicity and clinical prognosis in clear cell renal cell carcinomas. Cancer Immunol Res. 2015;3:999-1007.
17. Yang M, Yu Q, Liu J, et al. T-cell immunoglobulin mucin-3 expression in bladder urothelial carcinoma: clinicopathologic correlations and association with survival. J Surg Oncol. 2015;112:430-435.
18. Zhou E, Huang Q, Wang J, et al. Up-regulation of Tim-3 is associated with poor prognosis of patients with colon cancer. Int J Clin Exp Pathol. 2015;8:8018-8027.
19. Zhang Y, Cai P, Liang T, Wang L, Hu L. TIM-3 is a potential prognostic marker for patients with solid tumors: a systematic review and meta-analysis. Oncotarget. 2017;8:31705-31713.
20. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P). Syst Rev. 2015;4:1.
21. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-605.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-1558.

24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-1101.

25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-634.

26. Yuan J, Jiang B, Zhao H, Huang Q. Prognostic implication of TIM-3 in clear cell renal cell carcinoma. Neoplasma. 2014;61:35-40.

27. Cheng G, Li M, Wu J, et al. Expression of Tim-3 in gastric cancer tissue and its relationship with prognosis. Int J Clin Exp Pathol. 2015;8:9452-9457.

28. Yan W, Liu X, Ma H, et al. Tim-3 fosters HCC development by enhancing TGF-beta-mediated alternative activation of macrophages. Gut. 2015;64:1593-1604.

29. Gravelle P, Do C, Franchet C, et al. Impaired functional responses in follicular lymphoma CD8(+)TIM-3(+) T lymphocytes following TCR engagement. Onco Targets Ther. 2016;5:e1224044.

30. Liu H, Zhi L, Duan N, Su P. Abnormal expression of TIM-3 antigen on peripheral blood T cells is associated with progressive disease in osteosarcoma patients. FEBS Open Bio. 2016;6:807-815.

31. Shan B, Man H, Liu J, et al. TIM-3 promotes the metastasis of esophageal squamous cell carcinoma by targeting epithelial-mesenchymal transition via the Akt/GSK-3beta/Snail signaling pathway. Onco Rep. 2016;36:1551-1561.

32. Ge W, Li J, Fan W, Xu D, Sun S. Tim-3 as a diagnostic and prognostic biomarker of osteosarcoma. Tumour Biol. 2017;39:1010428317715643.

33. Peng PJ, Li Y, Sun S. On the significance of Tim-3 expression in pancreatic cancer. Saudi J Biol Sci. 2017;24:1754-1757.

34. Li F, Li N, Sang J, et al. Highly elevated soluble Tim-3 levels correlate with increased hepatocellular carcinoma risk and poor survival of hepatocellular carcinoma patients in chronic hepatitis B virus infection. Cancer Manag Res. 2018;10:941-951.

35. Su H, Xie H, Dai C, et al. Characterization of TIM-3 expression and its prognostic value in patients with surgically resected lung adenocarcinoma. Lung Cancer. 2018;121:18-24.

36. Wang Y, Zhao E, Zhang Z, Zhao G, Cao H. Association between Tim3 and Gal9 expression and gastric cancer prognosis. Anti-TIM3 antibody promotes T cell IFN-gamma-mediated antitumor immunity and suppresses established tumors. Cancer Res. 2017;77:1157-1169.

37. Jia K, He Y, Dziedziszko R, et al. T cell immunoglobulin and mucin-domain containing-3 in non-small cell lung cancer. Transl Lung Cancer Res. 2019;8:895-906.

38. Fucikova J, Rakova J, Hensler M, et al. TIM-3 dictates functional orientation of the immune infiltrate in ovarian cancer. Front Immunol. 2019;10:2030-2040.

39. Zhou J, Jiang Y, Zhang H, et al. Clinicopathological implications of TIM3 (+) tumor-infiltrating lymphocytes and the miR-455-Sp/Galectin-9 axis in skull base chordoma patients. Cancer Immunol Immunother. 2019;68:1157-1169.

40. Zhao Y, Chen D, Wang W, et al. Significance of TIM-3 expression in resected esophageal squamous cell carcinoma. Ann Thorac Surg. 2019;109:1551-1557.

41. Horlad H, Ohnishi K, Ma C, et al. TIM-3 expression in lymphoma cells predicts chemoresistance in patients with adult T-cell leukemia/lymphoma. Onco Lett. 2016;12:1519-1524.

42. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21:1559-1573.

43. Anderson AC, Anderson DE, Bregoli L, et al. Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells. Science. 2007;318:1141-1143.

44. Sakuishi K, Ngiow SF, Sullivan JM, et al. TIM3(+)FOXP3(+) regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. Onco Targets Ther. 2013;6:23849.

45. Sakuishi K, Apetoh L, Sullivan JM, Blazar BR, Kuchroo VK, Anderson AC. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med. 2010;207:2187-2194.

46. Zhao Q, Munger ME, Veenstra RG, et al. Coexpression of Tim-3 and PD-1 identifies a CD8+ T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia. Blood. 2011;117:4501-4510.

47. Wang Y, Zhao E, Zhang Z, Zhao G, Cao H. Association between Tim3 and Gaal9 expression and gastric cancer prognosis. Onco Rep. 2018;40:2115-2126.

48. Chen BJ, Dashnamoorthy R, Galera P, et al. The immune checkpoint molecules PD-1, PD-L1, TIM-3 and LAG-3 in diffuse large B-cell lymphoma. OncoTarget. 2019;10:2030-2040.

49. Liu H, Zhi L, Duan N, Su P. Abnormal expression of TIM-3 antigen on peripheral blood T cells is associated with progressive disease in osteosarcoma patients. FEBS Open Bio. 2016;6:807-815.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.