Tumor-stroma ratio (TSR) as a potential novel predictor of prognosis in digestive system cancers: A meta-analysis

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ABSTRACT

Main problem: The tumor-stroma ratio (TSR) has been reported as a prognosis predictor in multiple cancers. The aim of this meta-analysis was to investigate the potential value of TSR as a prognostic predictor of cancer in the digestive system.

Methods: We searched PubMed, Embase, Elsevier and Web of Science. All studies exploring the association of TSR with overall survival (OS) or disease-free survival (DFS), and lymph node metastasis (LNM) were identified.

Results: In total, eight studies were eligible for analysis, and they included 1959 patients. Meta-analysis showed that the low TSR in the tumor could predict poor overall survival (OS) (pooled Hazard Ratio [HR]: 2.15, 95%CI: 1.80–2.57, P < 0.00001, fixed effects). For disease-free survival (DFS), low TSR was also a significant predictor (pooled Hazard Ratio [HR]: 2.31, 95%CI: 1.88–2.83, P < 0.00001, fixed effects). In addition, low TSR was correlated with tumor stage.

Discussion: The tumor-stroma ratio (TSR) may potentially serve as a poor prognostic predictor for the metastasis and prognosis of cancer.

1. Introduction

Cancer is a large public health problem and a major cause of deaths worldwide. In 2015, 1,658,370 individuals developed cancer, and 589,430 people died of cancer in the United States, according to the American National Center for Health Statistics [1]. Furthermore, digestive system cancers are the deadliest forms of cancer, including many organs cancer in our body [2]. Reflecting the complex initiation and progression mechanism, the 5-year survival rate is low in most tumors. Consequently, we developed a novel prognostic marker to assist clinical application in multiple cancers.

The tumor-stroma ratio (TSR) is the proportion of tumor cells in the stroma. Tumors are complex tissues that are composed of carcinoma cells and surrounding stroma; thus, the tumor stroma is associated with tumor initiation, progression, and metastasis, and it holds prognostic value [3–4]. Recently, the tumor to stroma ratio of (TSR) has been demonstrated to be a novel and practical prognostic predictor in many neoplasms, such as breast cancer [5], esophageal cancer [6], colon cancer [7], and hepatocellular carcinoma [8]. Those studies have shown that a low TSR is a poor prognostic marker [5.6.7.8]. So we need performed a meta-analysis to explore the relation of TSR with OS and DFS.

2. Evidence acquisition

2.1. Search strategies

We searched MEDLINE, Embase, Elsevier and Web of science. Search terms included “carcinoma-stroma ratio (CSR)”, “tumor-stroma ratio (TSR)”, “tumor-stroma percentage (TSP)”, “cancer”, “tumor”, “carcinoma”, “neoplasms”, “survival”, “prognosis”, and “outcome”. Systematic reviews and meta-analyses were manually retrieved and served as references for the included studies. The language was restricted to English. The literature search was completed on November 31, 2016.

2.2. Inclusion criteria

The inclusion criteria included 1) a clear relationship between TSR and overall survival or TSR and disease-free survival; 2) multivariate analysis as the analysis method; 3) studies reported on hazard ratio (HR) and 95% confidence interval (CI); and 4) studies published in English.
2.3. Exclusion criteria

The exclusion criteria included 1) metastatic cancers in organs not related to the primary cancers; 2) studies investigating the structure, mechanism and functions; 3) studies in which it was impossible to obtain available data; 4) duplicate publications; and 5) non-English-language studies.

2.4. Data extraction

According to the aforementioned inclusion and exclusion criteria, two investigators reviewed all eligible studies and extracted the necessary data. Any disagreement was resolved by discussions among all coauthors. The following information was collected: name of the first author, year of publication, country, number of patients, tumor type, stage, overall survival (OS), disease-free survival (DFS), analysis methods, hazard ratio (HR) with 95% confidence interval (CI), and follow-ups.

2.5. Statistical analysis

The meta-analysis was conducted using the RevMan version 5.3 software (Cochrane Collaboration). Heterogeneity was measured using Q and I² tests, and I² > 50% and P < 0.10 indicated heterogeneity [9]. When I² < 50%, no statistically significant heterogeneity was considered. The fixed-effects model was used to pool the results, and the random-effects model was used. Pooled hazard ratios (HRs) were extracted from the published data; the log HR and standard error (SE) were used to aggregate the survival results. P < 0.05 was defined as statistically significant.

3. Evidence synthesis

3.1. Search results

A total of 322 articles were found in the selected databases. A total of 25 articles were excluded as duplication, and 282 articles were excluded after screening the titles and abstracts, leaving 15 articles for further evaluation. As a result, 8 articles fulfilled the inclusion criteria and were included in the meta-analysis [6–8,10–14]; this process is shown in Fig. 1.

3.2. Characteristics of the included studies

A total of eight studies that included 1959 patients were enrolled in the present meta-analysis. The number of patients in each study ranged from 81 to 710. Among these studies, three studies were conducted in the UK, two were conducted in the Netherlands, two were conducted in China, and one was conducted in the Republic of Korea. Among these eight studies, four studies on colorectal cancer, one study on esophageal adenocarcinoma, one study on esophageal squamous cell carcinoma, one study on hepatocellular carcinoma, and one study on gastric signet ring cell carcinoma were observed. In total, eight studies focused on OS, and five studies focused on DFS. The hazard ratios (HRs) and corresponding 95% confidence intervals were obtained though multivariate analysis. Most of studies were divided into two groups: high stroma ratio and low stroma ratio of TSR, and the cutoff values were all set to 50%. Concerning the methodological quality of these studies, the NOS scores of all included studies were ≥ 6. Detailed patient characteristics are shown in Table 1.

4. Meta-analysis

4.1. Association between TSR and OS

Eight eligible studies showed that the low TSR, reflecting rich stroma, was associated with the high risk of OS (pooled Hazard Ratio [HR]: 2.15, 95%CI: 1.80–2.57, P < 0.00001, fixed effects, I² = 0%, P_h = 0.58) (Table 3, Fig. 2). In the subgroup analysis, potential heterogeneity was detected using the region, sample size, cancer type, clinical stage, and NOS score (Table 2). And we found that rich stroma had significantly poor prognostic in all subgroups.

4.2. Association between TSR and DFS

Five studies described the relation between TSR and DFS. An analysis of 1402 patients to evaluate this association showed that a low TSR was significantly correlated with the poor outcome of DFS (pooled
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