REVIEW

Sehreen Tory et al

**Prognostic value of transglutaminase-2 overexpression in cancer patients: A Meta‑analysis**

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**Acknowledgements**:This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Abstract:**

**Purpose**

Transglutaminase-2 (TG2) has been linked to cancer growth, proliferation, invasion, the epithelial-to-mesenchymal transition and metastasis, according to recent studies. Although the prognostic value of TG2 expression in a variety of cancer has been documented, it is still unclear because different researches have reported contradictory results. The goal of this study was to evaluate systematically the prognostic value of TG2 expression in cancer patients.

**Methods**

Web of Science, PubMed and Google scholar databases were searched up to 21 December, 2022. Eleven eligible studies were included in meta-analysis for determining the prognostic value of TG2 in cancer patients. While performing meta-analysis heterogeneity was checked by using *I2* Cochran’s Q statistic. Random effect model was used in meta-analysis. Publication bias was assessed by using contour-enhanced funnel plots and Egger’s test.

**Results**

Eight studies were used for the meta-analysis of overall survival and found that having high expression of TG2 caused poor overall survival (HR: 1.66, 95%CI: 1.07-2.56). For disease-free survival, five studies included to the analysis and meta-analysis show that having high expression of TG2 also caused poor disease-free survival (HR: 1.68, 95%CI: 1.34-2.11).

**Conclusion:**Our meta-analysis showed that high TG2 expression level causes poor overall and disease-free survival.

**Keywords**

Tissue transglutaminase, transglutaminase 2, TG2, cancer, prognosis, meta-analysis.

# Introduction

TG2 protein is a member of the TG family & participates in calcium ion (Ca2+)-dependent post-translational protein modification and cross-linking. It is found in the extracellular matrix (ECM), on the cell surface, and inside the cell, where it is mostly cytosolic. It is also present on the inner face of the plasma membrane or nuclear membrane.TG2 is widely distributed in various tissues (Iismaa et al., 2009). It can facilitate protein cross-linking and take part in signal transduction by guanidine triphosphate (GTP) enzyme activation and hydrolysis. TG2 is involved in several biological processes, including cell adhesion, motility, invasion, survival, and apoptosis, which all contribute to the development of tumors. (Huang et al., 2015). It fosters consistent interaction between cells and the ECM, resulting in increased cell survival, migration, and invasion in tumors (Huang et al., 2015). TG2 induces type 3 epithelial-mesenchymal transition, and in elevated level of TG2 is correlated with chemotherapy resistance. (Kumar et al., 2010). High expression of TG2 is found in various cancer cells and tissues, such as leukemia, breast cancer, ovarian cancer, prostate cancer, lung cancer, glioblastoma, renal cancer, epidermal squamous cell carcinoma, pancreatic cancer, cervical cancer, esophageal adenocarcinoma, oral squamous cell carcinoma, mesothelioma, gastric cancer and colon cancer (Eckert, 2019). Some authors showed that TG2 is an independent prognostic marker for cancer, but controversial results have also been found. We did a systematic review and meta-analysis to assess the prognostic value of TG2 for cancer patients in light of these conflicting results.

# Methods

**Literature search**

We searched in the Web of Science, PubMed, and Google Scholar databases up to December 21, 2022. We used (((TGM 2) OR (TGM2) OR (Transglutaminase 2) OR (TG2) OR (Tissue transglutaminase)) AND ((Cancer) OR (Malignancy) OR (Carcinoma) OR (Tumor)) AND ((Prognosis) OR (Outcome) OR (Survival) OR (Survival Time))) for Web of science & PubMed and "TGM 2'', ''Transglutaminase 2'', ''TG 2'', ''Tissue transglutaminase'', ''Cancer'', ''Malignancy'', ''Carcinoma'', ''Tumor'', ''Prognosis'', ''Outcome'', ''Survival'', ''Survival Time'' for Google scholar.

**Inclusion and Exclusion criteria**

The inclusion criteria were as follows: (I) TG2 expression was detected in human primary cancer tissue by using the immunohistochemical method. (II) Correlation of TG2 expression with overall survival (OS) and/or disease-free survival (DFS) (III) Patients were divided into TG2 high and TG2 low groups based on TG2 expression. (IV) Availability of the hazard ratio (HR) with 95% CI. We excluded those articles where HR with a 95% CI was not reported. We discovered that there are a number of ways to measure TG2 expression, including immunohistochemistry (IHC) and real-time polymerase chain reaction (RT-PCR), but immunohistochemistry is the technique that is most frequently used in the field of prognosis analyses. This was discovered after conducting a preliminary analysis of the published papers. For the purpose of this meta-analysis, we confined our consideration to articles in which the IHC method was used for the detection of TG2 because the RT-PCR technique was only utilized in a single paper.

Exclusion criteria: (I) animal studies (II) non-English and not full free text (III) thesis or dissertation (IV) review, conference paper, letter, editorial, abstract, book, document, case report, comment, and duplicate articles. We did not make limitations for sample size and did not include the cancer genome (TCGA) database for our analysis.

**Data Extraction and Analysis**

Two authors independently screened the title, abstract, and full text of potentially eligible studies twice at two different time points. Any disagreements were resolved by a third author. The titles and abstracts of the articles were examined, and irrelevant ones were excluded. The full texts of the remaining articles were reviewed to find relevant studies that met the inclusion criteria. We collected the following information from the included studies: First author, publication year, country, study period, sample size, cancer-type, TG2 high patients group, TG2 low patients group, outcome measure. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline is aimed at improving systematic reviews and formed the basis for the selection protocol used in the current study.

**Statistical Analysis**

For all meta-analyses, Rstudio statistical software (version 1.0.143) and the Meta package (reference: Schwarzer G. meta: an R package for meta-analysis; R news 2007; 7:40–5) were used. *I*2 and Cochran’s *Q* statistics were used to assess heterogeneity. A level less than 25% indicated low heterogeneity, whereas levels between 35% and 50% showed moderate heterogeneity, and those above 50% showed high heterogeneity. A p-value of less than 0.05 for Cochran’s Q statistic indicates heterogeneity. Due to the large degree of heterogeneity, a random-effects model was applied, which does not adjust heterogeneity but is a more conservative approach when heterogeneity exists. Publication bias was assessed by using contour-enhanced funnel plots and Egger’s test.

**Results**

**Literature search and selection**

After retrieving 1280 papers from three databases, we removed 318 that were duplicates and read the titles and abstracts of the remaining 962. 591 were deemed irrelevant; 161 were reviews; 101 were theses or dissertations; 38 were books, documents, letters, case reports, abstracts, editorials, comments, and conference papers; and 23 were not written in English. After reading the full texts of 48 articles, we eliminated 37 from further consideration on the basis of various criteria: (1) no reported HR with 95% CI; (2) no prognostic relation of TG2 with cancer; (3) analysis of the cancer genome database only; (4) analysis of animal tissue; (5) different survival analyses; (6) insufficient patient information; and (7) different detecting methods. Eleven papers were included in the end tally for this meta-analysis and review (Figure 1).

**Characteristics of included studies**

We included 2714 patients from 11 articles in this meta-analysis. Among the 11 studies, 4 were conducted in Korea, 3 in China, 1 in Canada, 1 in the USA, 1 in Germany, and 1 in Spain. Seven types of cancer were investigated: three in NSCLC, two in breast cancer, two in renal cell carcinoma, and one each of ovarian cancer, laryngopharyngeal squamous cell carcinoma, colon cancer, and urothelial cancer. IHC detected TG2 expression in tissue in all 11 studies. Except for those, we got one article (Miyoshi et al., 2010)(Miyoshi et al., 2010) using RT-PCR to detect TG2 expression and we excluded this. From Fernández- Aceñero et al., 2019(Fernández-Aceñero et al., 2016), we took the epithelial expression of TG2, and they did immunohistochemistry on 172 samples out of 198. So for their study, our sample size was 172 instead of 198. As for survival outcome measures, six studies reported OS, three studies reported DFS, and two studies reported both OS and DFS. (Table 1)

**Heterogeneity and Publication Bias**

While evaluating heterogeneity according to I2 and Cochran’s Q, for the analysis of OS, there was heterogeneity (I2=83.3%, Q=41.8, p<0.001), and for DFS, no significant heterogeneity was found (I2=3.0%, Q=4.1, p=0.389). Contour-enhanced funnel plots were drawn, and Egger’s test was used to determine whether there was a publication bias in the meta-analysis. For DFS, as the funnel plot seemed almost symmetrical, and according to Egger’s test (p=0.437), there was no publication bias (Figure 2). For OS, the funnel plot was nearly symmetrical (Figure 3), but Egger’s test results (p=0.031) show a weak bias.

**Relationship between TG2 expression and overall survival**

Eight studies were included in the meta-analysis, and according to the results of the analysis, there was a significant relation between TG2 expression and overall survival (OS) (Figure 4). When the HR obtained as a result of the meta-analysis using the random effects model was examined, it was seen that having high expression of TG2 caused poor overall survival (HR: 1.66, 95% CI: 1.07-2.56, Z: 2.27, p<0.023.

**Relationship between TG2 expression and Disease-free survival:**

While evaluating the association for disease-free survival (DFS), five studies were included in the meta-analysis. According to the results of the analysis, there was also a relation between TG2 expression and DFS (Figure 5). When the HR obtained the result of the meta-analysis by using the random-effects model, it was seen that having high expression of TG2 caused poor DFS (HR: 1.68, 95%CI: 1.34–2.11, p<0.001).

# Discussion

TG2 is a member of the transglutaminase (TG) family and an 80-kDa multifunctional protein that consists of four domains encoded by a single gene, TGM2, located on chromosome 20q11–12 in humans. TG2 is also known as tissue transglutaminase and is present in both extracellular (cell surface and extracellular matrix) and intracellular compartments (mostly in the cytosol), but also in the plasma membrane, nucleus, and mitochondria (Nurminskaya & Belkin, 2012). TG2 protein has many functions, such as cross-linking, GTP hydrolysis activities, protein disulfide isomerase, protein kinase, and as a scaffolding factor. Among them, Ca2+-dependent post-translational modification of target proteins is the primary function of TG2. TG2 acts as GTPase when Ca2+ concentration is low. As a GTPase, TG2 is involved in α1- adrenergic receptor-mediated transmembrane signaling (Lee & Park, 2017). TG2 is widely expressed in various organs, including the liver, heart, and intestine, as well as blood cells such as erythrocytes (Fesus & Piacentini, 2002). TG2 has been linked to many human diseases, including celiac disease, cancer, fibrosis, cardiovascular disease, and neurological disorders (Szondy et al., 2017). TG2 expression has been shown to be increased in breast cancer (Assi et al., 2013), pancreatic cancer (Verma et al., 2008), colon cancer (Kotsakis et al., 2011), lung cancer (Jeong et al., 2013), ovarian cancer (Khanna et al., 2011), glioblastoma cancer(Yuan et al., 2007), laryngeal cancer(Jin et al., 2012), esophageal adenocarcinomas (Leicht et al., 2014), colorectal cancer(Kang et al., 2018), melanoma (Kok et al., 2006), mesothelioma (Adhikary et al., 2018), and renal cell carcinoma(Hidaka et al., 2012). Transglutaminase 2 (TG2) has been identified as a critical regulator of cancer cell survival that promotes epithelial to mesenchymal transition, invasion and migration, angiogenesis, metastasis, inflammation, and drug resistance. It also promotes the survival and stemness of cancer stem cells (Eckert, 2019). However, Choi et al., did not find an effect of TG2 on EMT marker expression in squamous lung cancer (Choi et al., 2011). TG2 activates various carcinogenic pathways, such as the nuclear factor kappa-light-chain-enhancer of activated B cells/NF-κB, focal adhesion kinase/FAK, protein kinase B/Akt, β-catenin, Ras homolog family member A (RhoA)(Sima et al., 2022). Some studies showed that high TG2 expression was a prognostic factor in cancer patients. In the case of gallbladder cancer,

Gupta et al., found that patients with TG2 positivity had shorter survival times than patients with TG2 negativity(Gupta et al., 2020). Similarly, patients with low TG2 expression had longer overall survival and disease-free survival in NSCLC patients than TG2 high-expression patients (Chihong et al., 2017). Miyoshi et al.analyzed TG2 expression in 91 paired cases of colorectal cancer (CRC) and noncancerous regions and showed a poorer overall survival rate in the high TG2 expression group than in the low expression group(Miyoshi et al., 2010). Strong epithelial TG2 expression has been linked to a poor prognosis in renal cell carcinoma(Park et al., 2015). In breast cancer patients, stromal TG2 expression was inversely correlated with disease-free survival (Assi et al., 2013) and high expression was significantly linked to poor patient survival(Hwang et al., 2008). But Krafft et al., did not find a prognostic role for TG2 expression in bladder cancer(Krafft et al., 2019) . For this contradictory result, we conducted this meta-analysis to understand the prognostic role of TG2 in cancer patients. In this study, we included 11 studies and a total of 2714 cancer patients. In our meta-analysis, which was performed by using studies that examined the relationship between TG2 expression level and survival and also reported contradictory results in the literature; it was shown that a high TG2 expression level causes poor overall and disease-free survival.

# Acknowledgments: This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Disclosure:** The author reports no conflicts of interest in this work.

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| --- | --- | --- | --- | --- | --- | --- | --- |
| 1st Author & year | Country | Study period | Sample size | Cancer type | TG2  High | TG2  Low | Outcome |
| (Choi et al., 2011) | Korea | 2000-2003 | 429 | NSCLC | 181 | 248 | DFS |
| (Jeong et al., 2013) | Korea | 2004-2011 | 120 | NSCLC | 56 | 64 | OS,DFS |
| (Chihong et al., 2017) | China | 2006-2010 | 194 | NSCLC | 75 | 119 | OS,DFS |
| (Assi et al., 2013) | Canada | NR | 253 | Breast | 199 | 54 | DFS |
| (Xu et al., 2022) | China | 2012-2015 | 210 | Breast | 126 | 84 | OS |
| (Park et al., 2015) | Korea | 1995-2005 | 638 | CCRCC | 54 | 554 | OS |
| (Kim et al., 2017) | Korea | 1992-2015 | 351 | RCC | 205 | 146 | OS |
| (Fernández-Aceñero et al., 2016) | Spain | 2003-2009 | 172 | Colon | 105 | 67 | OS,DFS |
| (Krafft et al., 2019) | Germany | NR | 106 | Urothelial | 38 | 62 | OS |
| (Jin et al., 2012) | China | 1997-2003 | 148 | LSCC | 70 | 78 | OS |
| (Hwang et al., 2008) | USA | NR | 93 | Ovarian | 61 | 32 | OS |

**Table 1: Characteristics of included studies:**

**Abbreviations:** OS, Overall survival; DFS, Disease free survival; NR, Not reported; NSCLC, Non-small cell lung cancer; RCC, Renal cell carcinoma; LSCC, Laryngeal squamous cell carcinoma: CCRCC, Clear cell renal cell carcinoma.

**Figure legends:**

**Figure1.**The PRISMA flow diagram.

**Figure: 2** The Funnel plot of the association between TG2 expression and disease-free survival (DFS) showing almost symmetrical with no publication bias

**Figure 3.**The Funnel plot of the association between TG2 expression and overall survival (OS) is nearly symmetrical with a weak bias

**Figure 4.**The Forest plot of TG2 expression for overall survival (OS) shows having high expression of TG2 caused poor overall survival

**Figure 5.**The Forest plot of TG2 expression for Disease-free survival (DFS) shows having high expression of TG2 caused poor disease-free survival