Prognostic value of increased integrin-beta 1 expression in solid cancers: a meta-analysis

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Abstract: Integrin-beta 1 (ITGB1) is aberrantly overexpressed or downregulated in solid cancers; however, its prognostic value remains controversial. Therefore, we conducted a meta-analysis to explore whether ITGB1 expression is correlated with overall survival (OS) and the clinicopathological characteristics of patients with solid cancers. We systematically searched the PubMed, Embase, and Web of Science databases for eligible studies published up to June 1, 2017. In total, 22 studies involving 3,666 patients were included. A sensitivity analysis was performed to assess the validity and reliability of the pooled OS. Among the 22 studies, 7 focused on lung cancer, 3 focused on colorectal cancer, 6 focused on breast cancer, 3 involved melanoma, and 3 involved pancreatic cancer. The pooled results showed that high ITGB1 expression was significantly associated with worse OS in lung cancer (pooled hazard ratio [HR]=1.78, 95% CI: 1.19–2.65, p<0.05) and breast cancer (pooled HR=1.88, 95% CI: 1.46–2.42, p<0.01). In addition, a significant association was observed between high ITGB1 expression and disease-free survival in breast cancer (pooled HR=1.63, 95% CI: 1.17–2.25, p<0.001) and pancreatic cancer (pooled HR=2.49, 95% CI: 1.35–4.61, p<0.001). However, high ITGB1 expression was not related to OS in colorectal cancer, pancreatic cancer, or melanoma. The pooled HRs used to evaluate the prognostic value of increased ITGB1 expression in lung cancer, breast cancer, and pancreatic cancer were not significantly altered, which indicates that the pooled results were robust. The results of this study indicate that the prognostic value of decreased ITGB1 expression varies among solid cancers.

Keywords: ITGB1, solid cancer, prognosis, meta-analysis

Introduction
Cancer is a major cause of death worldwide; in 2012, 14.1 million new cancer cases and 8.2 million cancer-related deaths were reported across the world.1 Currently, several therapeutic strategies, including radical operation, chemotherapy, and radiotherapy, are available for primary solid tumors and metastatic cancers. Nevertheless, the therapeutic response differs significantly in patients. Therefore, it is imperative to develop effective and clinically applicable biomarkers to accurately evaluate the therapeutic effect and prognosis of patients with cancer.

Integrins are a family of transmembrane receptors that generally consist of non-covalently linked alpha and beta subunits. Integrins have a variety of functions in cell adhesion and contact, and anchorage-dependent cell survival, and regulate various cellular processes including tissue healing, hemostasis, immune response, cell differentiation, division, growth, recognition, and migration.2-4 Recent evidence suggests that integrins are involved in many processes associated with tumor cell adhesion to the extracellular matrix, including migration, invasion, and metastasis.5-7 Moreover, previous studies have shown that integrins play an important role in the regulation of...
Additional investigations indicate that integrins can interact with tyrosine kinase receptors, such as epidermal growth factor receptor and vascular epidermal growth factor receptor, to promote cancer cell proliferation, survival, and differentiation.\textsuperscript{10} Integrin-beta 1 (ITGB1), also known as CD29, is a member of the integrin family and is composed of alpha and beta transmembrane subunits that form at least 24 distinct heterodimeric receptors.\textsuperscript{7,11} The role of ITGB1 in malignant phenotypes of cancers has gained a lot of attention.\textsuperscript{12} Previous studies have suggested that ITGB1 is the predominantly expressed integrin in normal and tumor cells and controls various developmental processes including angiogenesis, tumor progression, and metastasis.\textsuperscript{13–17} Other studies have also shown that, in many cancer types, ITGB1 may induce resistance to radiotherapies, chemotherapies, and targeted therapies.\textsuperscript{18–22} On the basis of these findings, ITGB1 has been studied extensively in terms of the biology of solid tumors, and its aberrant expression at the protein or RNA level has been shown to correlate with poor prognosis in several types of cancer, including lung cancer,\textsuperscript{23–26} gastric cancer,\textsuperscript{27} breast cancer,\textsuperscript{28–30} prostate cancer,\textsuperscript{31} pancreatic carcinoma,\textsuperscript{32,33} and colorectal cancer,\textsuperscript{34,35} making it a potential target for antitumor therapies. Nevertheless, the prognostic significance of ITGB1 expression in patients with cancer remains inconsistent. For instance, some studies have reported that decreased ITGB1 protein expression is associated with more aggressive breast cancer types,\textsuperscript{30,36} but the conclusion was different in other studies.\textsuperscript{28,37} Some studies could not verify a significant correlation between ITGB1 protein expression and survival of patients with breast carcinoma.\textsuperscript{29,38}

Thus far, no meta-analyses of studies focusing on the investigation of the prognostic and clinicopathological significance of ITGB1 in patients with solid tumors have been performed. Furthermore, conclusions made from most studies published so far are limited by small sample sizes. Therefore, we conducted a meta-analysis to estimate the prognostic and clinicopathological value of ITGB1 in patients with solid cancers.

**Materials and methods**

**Literature search strategy and study selection**

We searched the PubMed, Embase, and Web of Science databases to identify all relevant studies that assessed the association between ITGB1 expression and survival outcome in patients with solid cancers published up to June 1, 2017. The search terms included the following terms: (“ITGB1” or “Integrin β1”), (“cancer” or “tumor” or “malignancy” or “carcinoma”), and (“prognos*”). The publication language was limited to English.

Studies were included in the analysis if they met the following inclusion criteria: 1) the studies investigated the association between ITGB1 and overall survival (OS) or disease-free survival (DFS) among patients with primary solid cancers or metastasis; 2) relevant clinicopathological characteristics were presented; 3) tumor tissues from patients with solid cancers were used for the determination of ITGB1 expression; 4) patients were grouped into high and low expression groups according to the ITGB1 protein or RNA level; and 5) sufficient information and data were available to calculate hazard ratios (HRs) with 95% CIs. The exclusion criteria were as follows: 1) studies that were published as reviews, abstracts, case reports, letters, or comments, as well as duplicate studies; 2) studies in which human cell lines or animals were used; and 3) studies that failed to provide the HRs with 95% CIs or Kaplan–Meier survival curves used to calculate the OS and DFS.

**Data extraction and quality assessment**

All the candidate publications were reviewed, and the data were extracted by 2 independent investigators. The third investigator was responsible for reconciling disagreements when the results were controversial. The following information was extracted: cancer type, first author’s name, publication year, region, number of patients, patients’ ages, test method, rate of high ITGB1 expression, clinical and pathological features, follow-up duration, OS, and DFS. If the results of both the univariate and multivariate analyses were provided in the studies, only the latter were extracted owing to their higher accuracy, since multivariate analyses account for confounding factors. Moreover, the selection of participants, comparability, and ascertainment of outcomes were assessed. The study quality was assessed using the standard Newcastle–Ottawa Scale, which ranges from 0 (minimum) to 9 (maximum). If the final score of a study was higher, it indicated that the study’s methodological quality was better. A study with a score of 6 or higher was defined as “high-quality.”

**Statistical analysis**

The meta-analysis was performed using Stata SE12.0 (Stata Corp., College Station, TX, USA). HRs and 95% CIs were used to assess the prognostic value of ITGB1, and odds ratios (ORs) with 95% CIs were used to evaluate the association between ITGB1 expression and
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Clinicopathological features of solid cancers. A sensitivity analysis was performed to assess the validity and reliability of the pooled OS in patients with lung cancer, breast cancer, and pancreatic cancer. Chi-square-based Q-tests and I² statistics were applied to evaluate study heterogeneity, with $I^2 > 50\%$ and $p < 0.05$ indicating statistical heterogeneity. If no large statistical heterogeneity was detected, a fixed-effects model was used to assess the pooled HRs; otherwise, a random-effects model was used. Egger’s test and Begg’s test should have been applied to investigate publication bias, but the tests were not conducted owing to the small number of included studies used to assess the specific outcomes of interest.

Results

Study selection and study characteristics

A total of 284 articles were primarily identified, 70 of which were from PubMed, 123 from Embase, and 91 from Web of Science. After duplicate publications were removed and the remaining abstracts and full texts meticulously reviewed, 22 publications were finally determined to be eligible for the present pooled analysis. The inclusion of the publications in the analysis was based on the selection criteria mentioned above. The detailed selection process is shown in Figure 1.

The basic characteristics of the included studies are summarized in Table 1. In all, 22 studies involving 3,666 patients were included in the current meta-analysis, the sample size of which ranged from 30 to 959. All the included studies were published in English. The recruitment period of patients ranged from 1974 to 2014. Among the 22 studies, 7 focused on lung cancer, 3 focused on colorectal cancer, 6 focused on breast cancer, 3 involved melanoma, and 3 involved pancreatic cancer. Moreover, 7 studies were performed in China and 3 studies were performed in the USA. The majority of the studies used immunohistochemistry to detect ITGB1 protein levels, while 3 studies used real-time quantitative reverse transcription polymerase chain reaction (Table 1). The study quality scores ranged from 5 to 7, which indicated that the quality of the included studies was moderate to high (Table 2).

High ITGB1 expression and OS in solid cancers

The pooled result revealed that high ITGB1 expression was significantly associated with worse OS in patients with lung cancer (pooled HR = 1.78, 95% CI: 1.19–2.65, $p < 0.05$) (Figure 2) and breast cancer (pooled HR = 1.88, 95% CI: 1.46–2.42, $p < 0.01$) (Figure 3). In addition, no significant
### Table 1 Baseline characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>First author</th>
<th>Region</th>
<th>Time of recruitment</th>
<th>No of patients</th>
<th>Age (years), median (range)</th>
<th>Test method</th>
<th>Rate of high ITGB1 expression (%)</th>
<th>Survival outcomes (HR, 95% CI), H/L</th>
<th>Follow-up (months), median</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer</td>
<td>Chang et al&lt;sup&gt;25&lt;/sup&gt; (2012)</td>
<td>Korea</td>
<td>2000–2008</td>
<td>112</td>
<td>66 (42–88)</td>
<td>IHC</td>
<td>57.1</td>
<td>OS: 0.98 (0.66–1.45)FO: 0.98 (0.66–1.45)</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Dingemans et al&lt;sup&gt;26&lt;/sup&gt; (2010)</td>
<td>the Netherlands</td>
<td>1995–1999</td>
<td>68</td>
<td>69.1 (44.5–90.2)</td>
<td>Real-time qPCR</td>
<td>NR</td>
<td>OS: 2.11 (1.41–3.69); DFS: 1.53 (0.87–2.70)</td>
<td>93</td>
<td>6</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Liang et al&lt;sup&gt;28&lt;/sup&gt; (2017)</td>
<td>China</td>
<td>NR</td>
<td>134</td>
<td>NR</td>
<td>IHC</td>
<td>NR</td>
<td>OS: 1.56 (0.96–2.53)</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Okamura et al&lt;sup&gt;29&lt;/sup&gt; (2007)</td>
<td>Japan</td>
<td>1997–2000</td>
<td>118</td>
<td>65 (41–79)</td>
<td>IHC</td>
<td>66.9</td>
<td>DFS: 1.53 (0.87–2.70)</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>Zhang et al&lt;sup&gt;30&lt;/sup&gt; (2016)</td>
<td>China</td>
<td>2004–2006</td>
<td>108</td>
<td>NR</td>
<td>IHC</td>
<td>NR</td>
<td>DFS: 3.36 (2.03–5.54)</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Zheng et al&lt;sup&gt;31&lt;/sup&gt; (2016)</td>
<td>China</td>
<td>NR</td>
<td>959</td>
<td>67 (38–90)</td>
<td>TCGA RNASeq database</td>
<td>NR</td>
<td>DFS: 3.36 (2.03–5.54)</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Langan et al&lt;sup&gt;32&lt;/sup&gt; (2012)</td>
<td>USA</td>
<td>NA</td>
<td>30</td>
<td>56 (35–76)</td>
<td>IHC</td>
<td>NR</td>
<td>OS: 0.28 (0.06–1.27)</td>
<td>113</td>
<td>6</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Liu et al&lt;sup&gt;33&lt;/sup&gt; (2013)</td>
<td>China</td>
<td>2001–2013</td>
<td>582</td>
<td>NR</td>
<td>IHC</td>
<td>53.6</td>
<td>OS: 1.537 (1.147–2.059)</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>Colorectal liver metastases</td>
<td>Vassos et al&lt;sup&gt;34&lt;/sup&gt; (2014)</td>
<td>Germany</td>
<td>1995–2010</td>
<td>81</td>
<td>NR</td>
<td>IHC</td>
<td>45.7</td>
<td>DFS: 0.95 (0.44–2.01)</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>dos Santos et al&lt;sup&gt;38&lt;/sup&gt; (2012)</td>
<td>Brazil</td>
<td>1994–2010</td>
<td>225</td>
<td>55</td>
<td>IHC</td>
<td>32.9</td>
<td>DFS: 3.36 (2.03–5.54)</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Yao et al&lt;sup&gt;39&lt;/sup&gt; (2007)</td>
<td>USA</td>
<td>1974–1999</td>
<td>149</td>
<td>NR</td>
<td>IHC</td>
<td>10.1</td>
<td>DFS: 1.88 (1.20–2.95)</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Yin et al&lt;sup&gt;40&lt;/sup&gt; (2016)</td>
<td>China</td>
<td>NR</td>
<td>67</td>
<td>51</td>
<td>IHC</td>
<td>43.3</td>
<td>DFS: 1.22 (1.67–4.05)</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Hieken et al&lt;sup&gt;41&lt;/sup&gt; (1999)</td>
<td>USA</td>
<td>1976–1995</td>
<td>111</td>
<td>53</td>
<td>IHC</td>
<td>32.4</td>
<td>DFS: 1.73 (1.22–2.44)</td>
<td>105</td>
<td>7</td>
</tr>
</tbody>
</table>
Increased integrin-beta 1 expression in solid cancers

A significant association was found between high ITGB1 expression and OS in colorectal cancer (pooled HR = 1.06, 95% CI: 0.48–2.32, \( p < 0.001 \)) (Figure 4), pancreatic cancer (pooled HR = 1.41, 95% CI: 0.76–2.61, \( p < 0.0001 \)) (Figure 5), or melanoma (pooled HR = 0.79, 95% CI: 0.06–11.08, \( p = 0.01 \)) (Figure 6).

High ITGB1 expression and DFS in solid cancers

The pooled result revealed that high ITGB1 expression was significantly associated with worse DFS in patients with breast cancer (pooled HR = 1.63, 95% CI: 1.17–2.25, \( p < 0.001 \)) (Figure 7) and pancreatic cancer (pooled HR = 2.49, 95% CI: 1.35–4.61, \( p < 0.001 \)) (Figure 8). In addition, no significant association was found between high ITGB1 expression and DFS in lung cancer (pooled HR = 3.20, 95% CI: 0.77–13.40, \( p < 0.01 \)) (Figure 9) or melanoma (pooled HR = 0.88, 95% CI: 0.06–13.25, \( p = 0.05 \)) (Figure 10).

High ITGB1 expression and clinicopathological factors in lung cancer

Considering that the biology, pathology, clinical courses, and treatments vary enormously among different types of solid cancers, we assessed the associations between high ITGB1 expression and clinicopathological characteristics in lung cancer, breast cancer, and pancreatic cancer. However, high expression of ITGB1 was not evaluated in colorectal cancer and melanoma owing to limited data on the clinicopathological features. Six studies reported a relationship between high ITGB1 expression and clinicopathological factors in lung cancer, including 2 studies that investigated tumor differentiation, N stage, T stage, and age (Table 3). Except for T stage (\( I^2 = 0, \ p = 0.50 \)) and age (\( I^2 = 5\%, \ p = 0.305 \)), significant heterogeneity was observed between high ITGB1 expression and tumor differentiation (\( I^2 = 85\%, \ p = 0.01 \)) and N stage (\( I^2 = 74.7\% \ p = 0.047 \)). The pooled analysis showed no significant association between high ITGB1 expression and clinicopathological factors in breast cancer (OR = 0.69, 95% CI: 0.10–4.98, \( p = 0.712 \)), N stage (OR = 0.40, 95% CI: 0.16–1.01, \( p = 0.053 \)), or age (OR = 0.98, 95% CI: 0.70–1.37, \( p = 0.921 \)) (Table 3), while high ITGB1 expression showed a strong association with worse T stage (OR = 0.64, 95% CI: 0.41–0.98, \( p = 0.041 \)) (Table 3).

High ITGB1 expression and clinicopathological factors in breast cancer

A total of 6 studies identified an association between ITGB1 expression and clinicopathological factors in breast cancer.
Table 2 Methodological quality assessment (risk of bias) of included studies by the Newcastle–Ottawa Scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed cohort</td>
<td>Non-exposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Outcome of interest</td>
</tr>
<tr>
<td>Chang et al²⁵ (2012)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Dingemans et al²⁶</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Lawson et al²⁷ (2010)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Liang et al²⁸ (2017)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Okamura et al²¹ (2007)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Zhang et al²² (2013)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Zheng et al²³ (2016)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Langan et al²⁴ (2012)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Liu et al²⁵ (2015)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Vassos et al²⁶ (2014)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Lesniak et al²⁷ (2009)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
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<tr>
<td>McSherry et al²⁸ (2009)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
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<tr>
<td>Petricevic et al²⁹ (2012)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
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<tr>
<td>dos Santos et al³⁰ (2012)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Yao et al³¹ (2007)</td>
<td>★</td>
<td>★</td>
<td>☆</td>
<td>★☆</td>
</tr>
<tr>
<td>Yin et al³² (2016)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Hieken et al³³ (1999)</td>
<td>★</td>
<td>★</td>
<td>☆</td>
<td>★☆</td>
</tr>
<tr>
<td>Nikkola et al³⁴ (2004)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
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<tr>
<td>Vihinen et al³⁵ (2000)</td>
<td>☆</td>
<td>☆</td>
<td>★</td>
<td>★☆</td>
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<tr>
<td>Sawai et al³⁶ (2006)</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
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<tr>
<td>Yang et al³⁷ (2016)</td>
<td>☆</td>
<td>☆</td>
<td>★</td>
<td>★☆</td>
</tr>
<tr>
<td>Zhou et al³⁸ (2013)</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★☆</td>
</tr>
</tbody>
</table>

Notes: For each domain, either a “star” or “white star” is assigned, with a “star” indicating that the study design element was considered adequate and less likely to introduce bias. A maximum of 2 stars could be given for Comparability. A study could receive a maximum of 10 stars.

No significant heterogeneity was identified between high ITGB1 expression and N stage ($I^2=2\%$, $p=0.36$), tumor grade ($I^2=0$, $p=0.636$), T stage ($I^2=0$, $p=0.639$), metastasis ($I^2=0$, $p=0.357$), estrogen receptor (ER) ($I^2=14.8\%$, $p=0.279$), progesterone receptor (PR) ($I^2=43.6\%$, $p=0.183$), or human epidermal growth factor receptor (HER) ($I^2=29.9\%$, $p=0.232$); therefore, a fixed-effects model was used for the analysis (Table 3). The pooled analysis revealed no significant association between high ITGB1 expression and overall survival ($HR=1.78$ (95% CI 1.19–2.65), $p=0.000$).

Figure 2 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in lung cancer.

Note: Weights are from random effects analysis.

Abbreviation: HR, hazard ratio.
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Figure 3 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in breast cancer.
Abbreviation: HR, hazard ratio.

Study ID | HR (95% CI) | % weight
--- | --- | ---
Lesniak et al³ (2009) | 2.82 (1.52–4.24) | 24.33
McSherry et al³⁶ (2009) | 1.16 (0.62–2.19) | 16.08
Yao et al³⁷ (2007) | 1.73 (1.22–2.44) | 53.30
Yin et al³⁷ (2016) | 2.77 (1.01–7.60) | 6.29
**Overall (I²=44.9%, p=0.142)** | **1.88 (1.46–2.42)** | **100**

Figure 4 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in colorectal cancer.
Abbreviation: HR, hazard ratio.

Study ID | HR (95% CI) | % weight
--- | --- | ---
Langan et al³⁸ (2012) | 0.28 (0.06–1.27) | 18.04
Liu et al³⁹ (2015) | 1.54 (1.15–2.06) | 53.09
Vassos et al⁴⁰ (2014) | 1.23 (0.44–3.43) | 28.87
**Overall (I²=57.5%, p=0.095)** | **1.06 (0.48–2.32)** | **100**

Figure 5 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in pancreatic cancer.
Abbreviation: HR, hazard ratio.

Study ID | HR (95% CI) | % weight
--- | --- | ---
Yang et al⁴² (2016) | 2.38 (1.19–5.19) | 22.89
Zhou et al⁴³ (2013) | 3.20 (1.20–6.70) | 20.52
Sawai et al⁴⁴ (2006) | 0.91 (0.57–1.41) | 28.69
Sawai et al⁴⁴ (2006) | 0.78 (0.51–1.36) | 27.90
**Overall (I²=76.0%, p=0.006)** | **1.41 (0.76–2.61)** | **100**
Figure 6 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in melanoma.
Note: Weights are from random effects analysis.
Abbreviation: HR, hazard ratio.

Figure 7 Results of pooled hazard ratios of disease-free survival of patients with high integrin-beta 1 (ITGB1) expression level in breast cancer.
Abbreviation: HR, hazard ratio.

Figure 8 Results of pooled hazard ratios of disease-free survival of patients with high integrin-beta 1 (ITGB1) expression level in lung cancer.
Note: Weights are from random effects analysis.
Abbreviation: HR, hazard ratio.
significant relationship between increased ITGB1 expression and N stage (OR=0.79, 95% CI: 0.52–1.19, p=0.262), tumor grade (OR=1.20, 95% CI: 0.74–1.94, p=0.462), T stage (OR=0.78, 95% CI: 0.51–1.19, p=0.25), ER (OR=1.45, 95% CI: 0.90–2.35, p=0.462), PR (OR=1.15, 95% CI: 0.74–1.80, p=0.527), or HER (OR=1.70, 95% CI: 0.98–2.93, p=0.057), while high ITGB1 expression demonstrated a strong association with metastasis (OR=1.99, 95% CI: 1.18–3.38, p=0.010) (Table 3).

**ITGB1 expression and clinicopathological factors in pancreatic cancer**

Only 2 studies reported a relationship between ITGB1 expression and age in pancreatic cancer. No significant heterogeneity was detected in the studies regarding age (I²=0, p=0.459); therefore, a fixed-effects model was applied. The pooled results showed that high ITGB1 expression was not significantly correlated with age (OR=1.35, 95% CI: 0.65–2.80, p=0.417) (Table 3).

**Sensitivity analysis**

Sensitivity analyses were performed to evaluate the stability of the pooled results for OS in lung cancer (Figure 11), breast cancer (Figure 12), and pancreatic cancer (Figure 13). The results of the sensitivity analyses showed that the pooled HRs for OS did not change substantially, which indicates that the conclusions from our meta-analysis were relatively reliable.

**Publication bias**

Begg’s and Egger’s tests were used to assess publication bias in our meta-analysis. The results revealed that there was no significant bias in the pooled HRs for OS in lung cancer (Begg’s test, z=1.05, p=0.293; Egger’s test, t-bias=1.10, p=0.262).

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**Figure 9** Results of pooled hazard ratios of disease-free survival of patients with high integrin-beta 1 (ITGB1) expression level in pancreatic cancer.

**Note:** Weights are from random effects analysis.

**Abbreviation:** HR, hazard ratio.

**Figure 10** Results of pooled hazard ratios of disease-free survival of patients with high integrin-beta 1 (ITGB1) expression level in melanoma.

**Note:** Weights are from random effects analysis.

**Abbreviation:** HR, hazard ratio.
Table 3  Meta-analysis results of the associations of integrin-beta 1 with clinicopathological parameters

<table>
<thead>
<tr>
<th>Clinicopathological parameter</th>
<th>No of studies</th>
<th>Reference no</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I² (%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor differentiation (moderate–well vs poor)</td>
<td>2</td>
<td>637</td>
<td>0.69 (0.10–4.98)</td>
<td>0.712</td>
<td>85.0</td>
</tr>
<tr>
<td>N stage (N0 vs N+)</td>
<td>2</td>
<td>663</td>
<td>0.40 (0.160–1.01)</td>
<td>0.053</td>
<td>74.7</td>
</tr>
<tr>
<td>T stage (T1–2 vs T3–4)</td>
<td>2</td>
<td>663</td>
<td>0.64 (0.41–0.98)</td>
<td>0.041</td>
<td>0.0</td>
</tr>
<tr>
<td>Age (&lt;60 vs ≥60 years)</td>
<td>2</td>
<td>665</td>
<td>0.98 (0.70–1.37)</td>
<td>0.921</td>
<td>5.0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N stage (N0 vs N+)</td>
<td>3</td>
<td>399</td>
<td>0.79 (0.52–1.19)</td>
<td>0.262</td>
<td>2.0</td>
</tr>
<tr>
<td>Tumor grade (I–II vs III–IV)</td>
<td>3</td>
<td>424</td>
<td>1.20 (0.74–1.94)</td>
<td>0.462</td>
<td>0.0</td>
</tr>
<tr>
<td>T stage (T1 vs T2–3)</td>
<td>3</td>
<td>424</td>
<td>0.78 (0.51–1.19)</td>
<td>0.250</td>
<td>0.0</td>
</tr>
<tr>
<td>Metastasis (yes vs no)</td>
<td>2</td>
<td>292</td>
<td>1.99 (1.18–3.38)</td>
<td>0.010</td>
<td>0.0</td>
</tr>
<tr>
<td>ER (+ vs –)</td>
<td>2</td>
<td>352</td>
<td>1.45 (0.90–2.35)</td>
<td>0.126</td>
<td>14.8</td>
</tr>
<tr>
<td>PR (+ vs –)</td>
<td>2</td>
<td>352</td>
<td>1.15 (0.74–1.80)</td>
<td>0.527</td>
<td>43.6</td>
</tr>
<tr>
<td>HER (+ vs –)</td>
<td>2</td>
<td>357</td>
<td>1.70 (0.98–2.93)</td>
<td>0.057</td>
<td>29.9</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&lt;60 vs ≥60 years)</td>
<td>2</td>
<td>117</td>
<td>1.35 (0.65–2.80)</td>
<td>0.417</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor; OR, odds ratio.

$p = 0.320$). Publication bias was not observed when assessing for potential bias in the pooled HRs for the correlation between high ITGB1 expression and DFS, owing to the limited number of studies investigating this relationship.

 Discussion

Studies have shown conflicting results regarding the role of ITGB1 in the carcinogenesis of solid cancers; 28–30 therefore, its prognostic value in patients with solid cancers is also inconsistent and remains unknown. Although several previous studies reported that ITGB1 could induce resistance to chemotherapy and radiation in several human cancers, 53,54 the impact of increased ITGB1 expression on the prognosis of patients with solid cancers has not been fully explored. Hence, we combined 22 publications involving 3,666 patients to perform the first meta-analysis that evaluated the association between ITGB1 and OS and DFS in patients with solid cancers. In addition, we explored the relationship between low ITGB1 expression and the clinicopathological features of solid cancers.

The pooled results of the meta-analysis revealed that high ITGB1 expression was significantly associated with worse OS in lung cancer and breast cancer. Moreover, the results showed that high ITGB1 expression was not related to OS in colorectal cancer, pancreatic cancer, or melanoma. In addition, the pooled result revealed that high ITGB1 expression

**Figure 11**  Sensitivity analysis of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in lung cancer.

**Figure 12**  Sensitivity analysis of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in breast cancer.
was significantly associated with worse DFS in breast cancer and pancreatic cancer. The sensitivity analyses demonstrated that the pooled HRs used to evaluate the prognostic value of increased ITGB1 expression in lung cancer, breast cancer, and pancreatic cancer were not significantly altered, which indicates that the pooled results were robust. Considering the above findings, we believe that the prognostic value of increased ITGB1 expression varies according to cancer type in patients with solid cancer.

In addition, we investigated the relationship between ITGB1 expression and clinicopathological characteristics to further validate the pooled results of the association between OS and ITGB1 expression. Increased ITGB1 expression was significantly associated with worse T stage in lung cancer. However, the results showed no significant association between high ITGB1 expression and tumor differentiation and N stage. In addition, high ITGB1 expression strongly correlated with metastasis in breast cancer. Similarly, the results revealed no significant relationship between increased ITGB1 expression and N stage, tumor grade, T stage, ER, PR, or HER in breast cancer. This result should be interpreted with caution. On the one hand, the prognostic value and association between ITGB1 expression and the clinicopathological features of lung cancer and breast cancer may vary with the subtype of cancer. On the other hand, the included sample size was relatively small, which may have led to statistical bias. Previous studies have verified that ITGB1 overexpression promoted lymph-node metastasis in lung cancer. In addition, Klahan et al reported that knockdown of ITGB1 inhibited the migration and invasion of breast cancer cells. Therefore, to date, the published literature supports the notion that the effects of ITGB1 on the biological functions of solid cancer cells vary according to the type of malignant cells, which is consistent with the results of our meta-analysis.

Our study had several significant limitations; therefore, the results should be interpreted with caution. First, only English language publications were included in this meta-analysis, which may have introduced publication bias. Second, only 3 studies on colorectal cancer, melanoma, and pancreatic cancer were included; therefore, it was difficult to accurately assess the association between ITGB1 expression and survival in these 3 cancer types. Third, although the HRs with 95% CIs in most of the included studies were calculated via a multivariate analysis, the variables added into the Cox proportional hazard models varied across studies. Fourth, all the included studies failed to carefully describe the location of the ITGB1 expression in the tumor specimens; therefore, further studies should be performed to determine whether the increased ITGB1 expression appears at cell-matrix attachment sites or in the epithelial or stromal regions. Fifth, this meta-analysis did not explore the correlation between increased ITGB1 expression and ER+/HER2+ and triple-negative breast cancers owing to the unavailability of data. Sixth, our study failed to determine whether high ITGB1 expression was associated with the type of metastasis. Last but not least, the sample size and the number of the included studies for the pooled estimate of clinicopathological parameters were rather small, which may have affected the reliability of the pooled ORs for the associations between high ITGB1 expression and clinicopathological parameters.

**Conclusion**

The prognostic significance of increased ITGB1 expression varies according to cancer type. Overall, high ITGB1 expression was significantly associated with a worse OS in lung cancer and breast cancer and a worse DFS in breast cancer and pancreatic cancer. However, high ITGB1 expression was not related to OS in colorectal cancer, pancreatic cancer, or melanoma. Further high-quality clinical studies that overcome the aforementioned limitations need to be performed to validate the prognostic value of increased ITGB1 expression in patients with solid cancer.
Disclosure

The authors report no conflicts of interest in this work.

References


