REVIEW

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

Quanwu Sun[1,]*
Chuan Zhou[2,]*
Ruofei Ma[3]
Qianhong Guo[4]
Haiyun Huang[1]
Jie Hao[1]
Hong Liu[1]
Rong Shi[1]
Bo Liu[1]

[1]Department of Breast Surgery, The People's Hospital of Gansu Province, Lanzhou City, Gansu, China; [2]Department of Urology/Institute of Urology, West China School of Medicine/West China Hospital, Sichuan University, Chengdu, China; [3]Department of Abdominal Surgery, Gansu Tumor Hospital, Lanzhou City, Gansu, China; [4]Department of Oncological Surgery, The First People's Hospital of Tianshui City, Tianshui City, Gansu, China

*These authors contributed equally to this work

Correspondence: Haiyun Huang
Department of Breast Surgery, The People's Hospital of Gansu Province, No 204 Donggang West Road, Lanzhou City, Gansu 730000, China
Tel +86 093 1828 1293
Email hyhuang1968@163.com

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

tumor angiogenesis.[8,9] 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.[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.[7,11] The role of ITGB1 in malignant phenotypes of cancers has gained a lot of attention.[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.[13–17] Other studies have also shown that, in many cancer types, ITGB1 may induce resistance to radiotherapies, chemotherapies, and targeted therapies.[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,[23–26] gastric cancer,[27] breast cancer,[28–30] prostate cancer,[31] pancreatic carcinoma,[32,33] and colorectal cancer,[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,[30,36] but the conclusion was different in other studies.[28,37] Some studies could not verify a significant correlation between ITGB1 protein expression and survival of patients with breast carcinoma.[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

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 I^2 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;[24–26,28,29,33–35,39–52] 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,[24–26,39–42] 3 focused on colorectal cancer,[34,35,43] 6 focused on breast cancer,[28,29,44–47] 3 involved melanoma,[48–50] and 3 involved pancreatic cancer.[33,51,52] 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
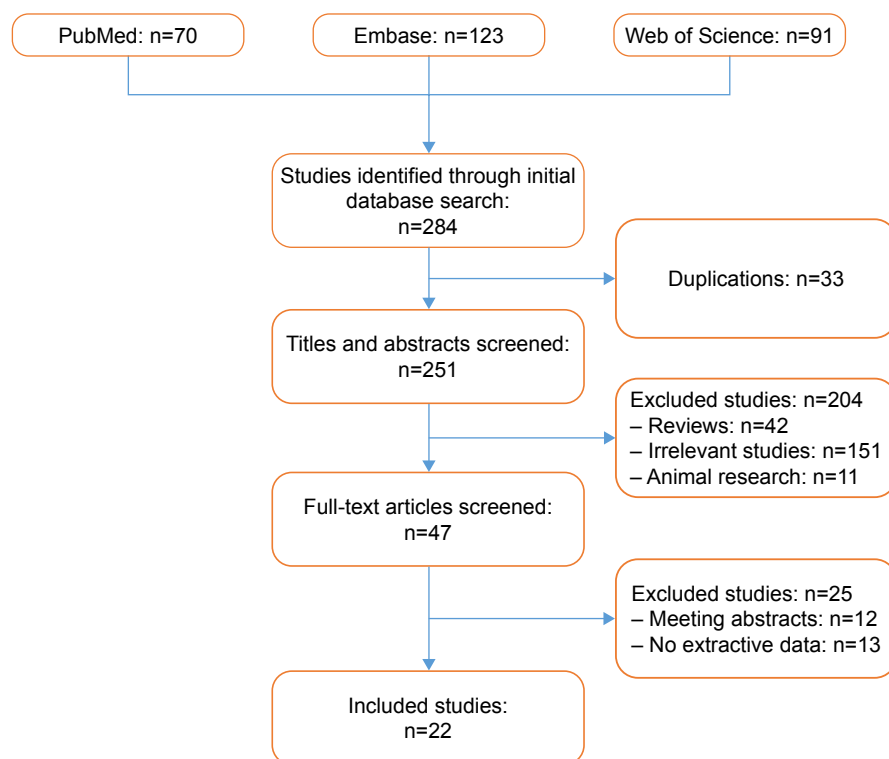
Figure 1 Flow diagram of study selection.

Table 1 Baseline characteristics of studies included in the meta-analysis

Cancer type	First author (year)	Region	Time of recruitment	No of patients	Age (years), median (range)	Test method	Rate of high ITGB1 expression (%)	Survival outcomes (HR, 95% CI), H/L	Follow-up (months), median	NOS score
Small cell lung cancer	Chang et al[25] (2012)	Korea	2000–2008	112	66 (42–88)	IHC	57.1	OS: 0.98 (0.66–1.45)	61	7
Non-small cell lung cancer	Dingemans et al[26] (2010)	the Netherlands	1995–1999	68	69.1 (44.5–90.2)	Real-time qPCR	NR	OS: 2.11 (1.21–3.69); DFS: 1.53 (0.87–2.70)	93	6
Small cell lung cancer	Lawson et al[39] (2010)	UK	1998–2005	151	67.34 (9.93)	IHC	70.2	OS: 1.67 (1.09–2.56)	72	7
Non-small cell lung cancer	Liang et al[40] (2017)	China	NR	134	NR	IHC	NR	OS: 1.56 (0.96–2.53)	NR	5
Non-small cell lung cancer	Okamura et al[41] (2007)	Japan	1997–2000	118	65 (41–79)	IHC	66.9	OS: 1.41 (0.80–2.49)	71.0	7
Lung adenocarcinoma	Zhang et al[42] (2013)	China	2004–2006	108	NR	IHC	32.4	RFS: 6.592 (4.106–10.584); OS: 6.183 (3.851–9.929)	60	7
Non-small cell lung cancer	Zheng et al[24] (2016)	China	NR	959	67 (38–90)	TCGA RNASeq database	NR	OS: 1.31 (1.10–1.55)	NR	5
Colorectal cancer	Langan et al[43] (2012)	USA	NA	30	56 (35–76)	IHC	NR	OS: 0.28 (0.06–1.27)	113	6
Colorectal cancer	Liu et al[35] (2015)	China	2001–2013	582	NR	IHC	52.6	OS: 1.537 (1.147–2.059)	100	6
Colorectal liver metastases	Vassos et al[34] (2014)	Germany	1995–2010	81	NR	IHC	45.7	OS: 1.23 (0.44–3.43); DFS: 0.95 (0.44–2.01)	55	6
HER-2-positive metastatic breast cancer	Lesniak et al[44] (2009)	Canada	1998–2002	78	NR	IHC	29.5	OS: 2.82 (1.52–4.24)	28	6
Breast cancer	McSherry et al[45] (2009)	Ireland	1988–1992	272	NR	IHC	NR	OS: 1.16 (0.62–2.19)	NR	6
Breast cancer	Petricevic et al[29] (2012)	Croatia	2002–2003	133	NR	IHC	36.4	NR	60	7
Breast cancer	dos Santos et al[46] (2012)	Brazil	1994–2010	225	55	IHC	32.9	DSS: 2.51 (1.24–3.7); DFS: 1.38 (0.86–2.23); MFS: 1.94 (1.07–3.52)	NR	7
Breast cancer	Yao et al[28] (2007)	USA	1974–1999	149	NR	IHC	10.1	OS: 1.73 (1.22–2.44); DFS: 1.88 (1.20–2.95)	60	7
Breast cancer	Yin et al[47] (2016)	China	NR	67	51	IHC	43.3	OS: 2.772 (1.011–7.600)	NR	6
Melanoma	Hieken et al[48] (1999)	USA	1976–1995	111	53	IHC	32.4	OS: 3.10 (0.9–10.73)	105	7
Melanoma	Nikkola et al[49] (2004)	Finland	1989–1995	55	47	IHC	10.7	DFS: 3.36 (2.03–5.54)	NR	6

Melanoma	Vihinen et al[50] (2000)	Finland	NR	38	NR	IHC	28.9	NR	OS: 0.43 (0.12–1.59); DFS: 0.21 (0.07–0.60)	5
Pancreatic cancer	Sawai et al[51] (2006)	Japan	NR	78	65.1	IHC	NR	17.6	Training set OS: 0.909 (0.569–1.410); validation set OS: 0.782 (0.505–1.355)	7
Pancreatic ductal adenocarcinoma	Yang et al[52] (2016)	China	2012–2014	63	NR	IHC	54.0	NR	OS: 2.375 (1.186–5.194); RFS: 2.488 (1.197–5.170)	6
Pancreatic cancer	Zhou et al[33] (2013)	China	2008–2012	54	56	RT-PCR	50	NR	OS: 3.2 (1.2–6.7); DFS: 2.5 (0.7–6.8)	6

Note: H/L is high ITGB1 expression vs low ITGB1 expression.
Abbreviations: ITGB1, integrin-beta 1; NOS, Newcastle–Ottawa Scale; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; qPCR, quantitative polymerase chain reaction; TCGA, The Cancer Genome Atlas; RT-PCR, reverse transcription polymerase chain reaction; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; DSS, disease-specific survival; MFS, metastatic-free survival; NR, not reported; NA, not applicable; HR, hazard ratio.

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 tumor differentiation (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.
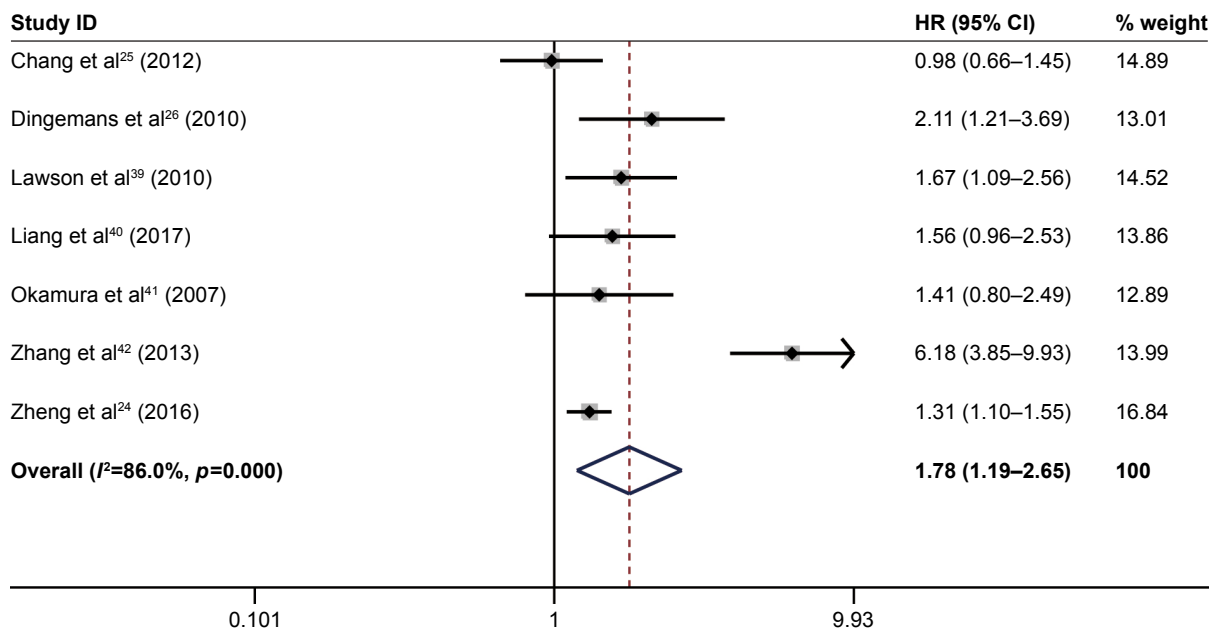
Table 2 Methodological quality assessment (risk of bias) of included studies by the Newcastle–Ottawa Scale

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Chang et al[25] (2012)	★	★	★	★	★☆	★	★	☆	7
Dingemans et al[26] (2010)	★	★	★	☆	★☆	☆	★	★	6
Lawson et al[39] (2010)	★	★	★	★	★☆	☆	★	★	7
Liang et al[40] (2017)	☆	★	★	☆	★☆	☆	★	★	5
Okamura et al[41] (2007)	★	★	★	★	★☆	☆	★	★	7
Zhang et al[42] (2013)	☆	★	★	★	★☆	★	★	★	7
Zheng et al[24] (2016)	☆	★	★	☆	★☆	☆	★	★	5
Langan et al[43] (2012)	★	★	★	☆	★☆	☆	★	★	6
Liu et al[35] (2015)	☆	★	★	★	★☆	☆	★	★	6
Vassos et al[34] (2014)	☆	★	★	★	★☆	☆	★	★	6
Lesniak et al[44] (2009)	★	★	★	★	★☆	☆	☆	★	6
McSherry et al[45] (2009)	★	★	★	★	★☆	★	☆	☆	6
Petricevic et al[29] (2012)	★	★	☆	★	★☆	★	★	★	7
dos Santos et al[46] (2012)	★	★	★	★	★☆	★	★	☆	7
Yao et al[28] (2007)	★	★	☆	★	★☆	★	★	★	7
Yin et al[47] (2016)	☆	★	★	★	★☆	★	★	☆	6
Hieken et al[48] (1999)	★	★	☆	★	★☆	★	★	★	7
Nikkola et al[49] (2004)	☆	★	★	★	★☆	★	☆	★	6
Vihinen et al[50] (2000)	☆	☆	★	★	★☆	★	☆	★	5
Sawai et al[51] (2006)	★	★	★	★	★☆	★	☆	★	7
Yang et al[52] (2016)	☆	★	★	★	★☆	★	★	☆	6
Zhou et al[33] (2013)	☆	★	★	★	★☆	★	★	☆	6

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

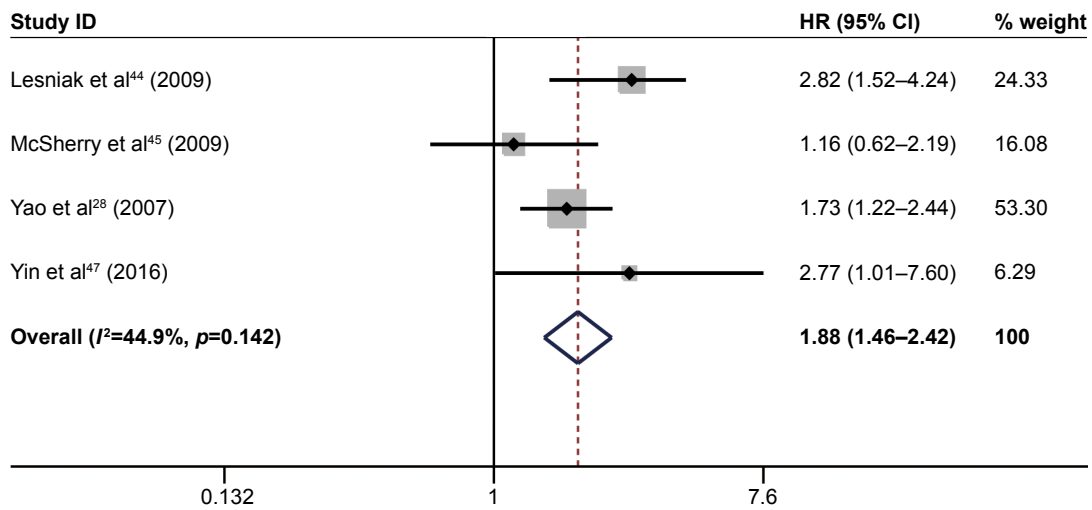| Study ID		HR (95% CI)	% weight
Chang et al[25] (2012)		0.98 (0.66–1.45)	14.89
Dingemans et al[26] (2010)		2.11 (1.21–3.69)	13.01
Lawson et al[39] (2010)		1.67 (1.09–2.56)	14.52
Liang et al[40] (2017)		1.56 (0.96–2.53)	13.86
Okamura et al[41] (2007)		1.41 (0.80–2.49)	12.89
Zhang et al[42] (2013)		6.18 (3.85–9.93)	13.99
Zheng et al[24] (2016)		1.31 (1.10–1.55)	16.84
Overall (I^2=86.0%, p=0.000)		**1.78 (1.19–2.65)**	**100**

0.101   1   9.93

Figure 2 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in lung cancer.
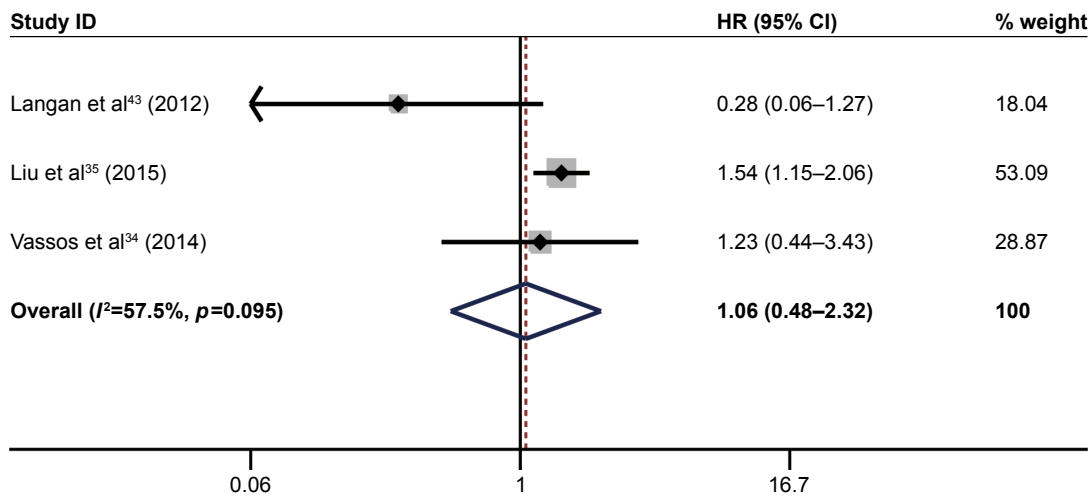**Note:** Weights are from random effects analysis.
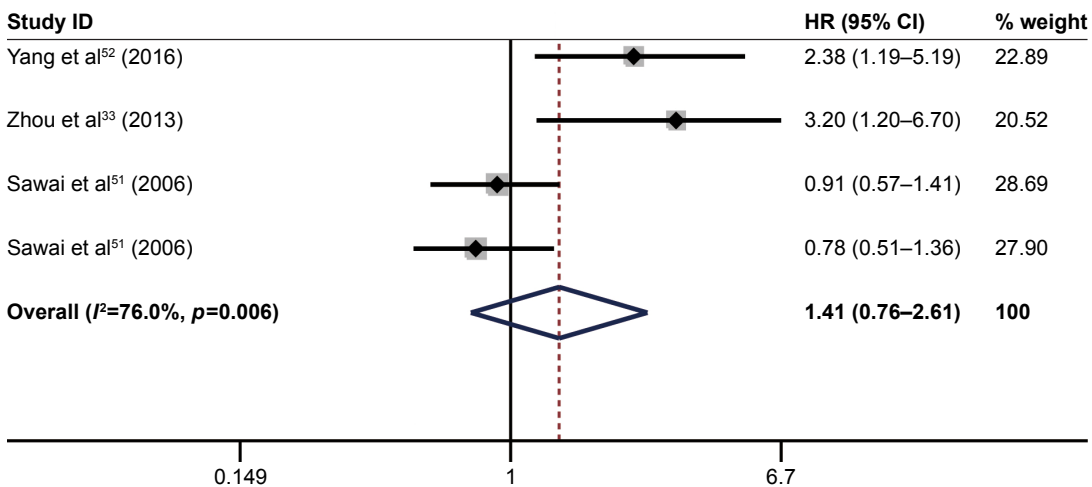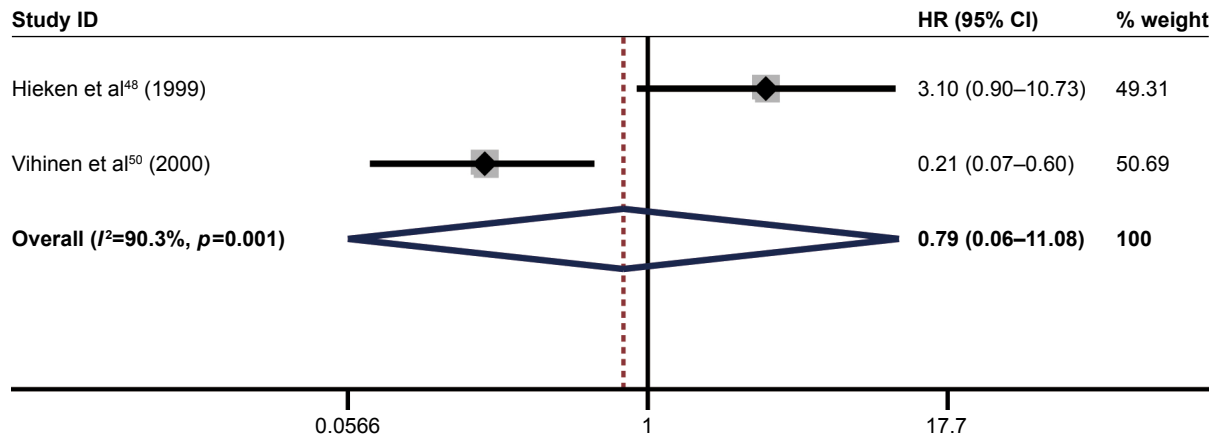**Abbreviation:** HR, hazard ratio.

Study ID		HR (95% CI)	% weight
Lesniak et al[44] (2009)		2.82 (1.52–4.24)	24.33
McSherry et al[45] (2009)		1.16 (0.62–2.19)	16.08
Yao et al[28] (2007)		1.73 (1.22–2.44)	53.30
Yin et al[47] (2016)		2.77 (1.01–7.60)	6.29
Overall (*I*²=44.9%, *p*=0.142)		1.88 (1.46–2.42)	100

0.132   1   7.6

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
Langan et al[43] (2012)		0.28 (0.06–1.27)	18.04
Liu et al[35] (2015)		1.54 (1.15–2.06)	53.09
Vassos et al[34] (2014)		1.23 (0.44–3.43)	28.87
Overall (*I*²=57.5%, *p*=0.095)		1.06 (0.48–2.32)	100

0.06   1   16.7

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

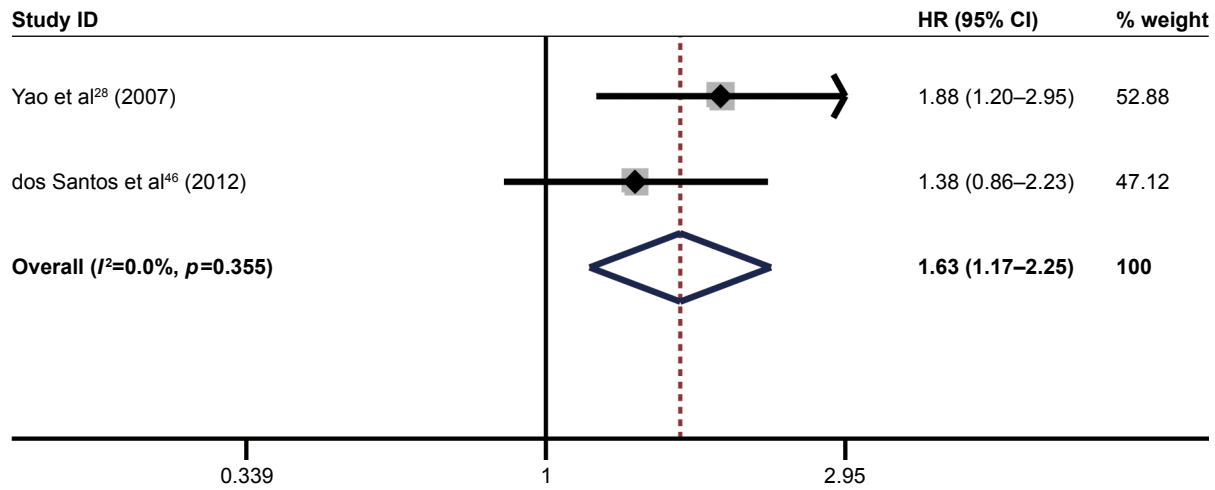| Study ID		HR (95% CI)	% weight
Yang et al[52] (2016)		2.38 (1.19–5.19)	22.89
Zhou et al[33] (2013)		3.20 (1.20–6.70)	20.52
Sawai et al[51] (2006)		0.91 (0.57–1.41)	28.69
Sawai et al[51] (2006)		0.78 (0.51–1.36)	27.90
Overall (*I*²=76.0%, *p*=0.006)		1.41 (0.76–2.61)	100

0.149   1   6.7

Figure 5 Results of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in pancreatic cancer.
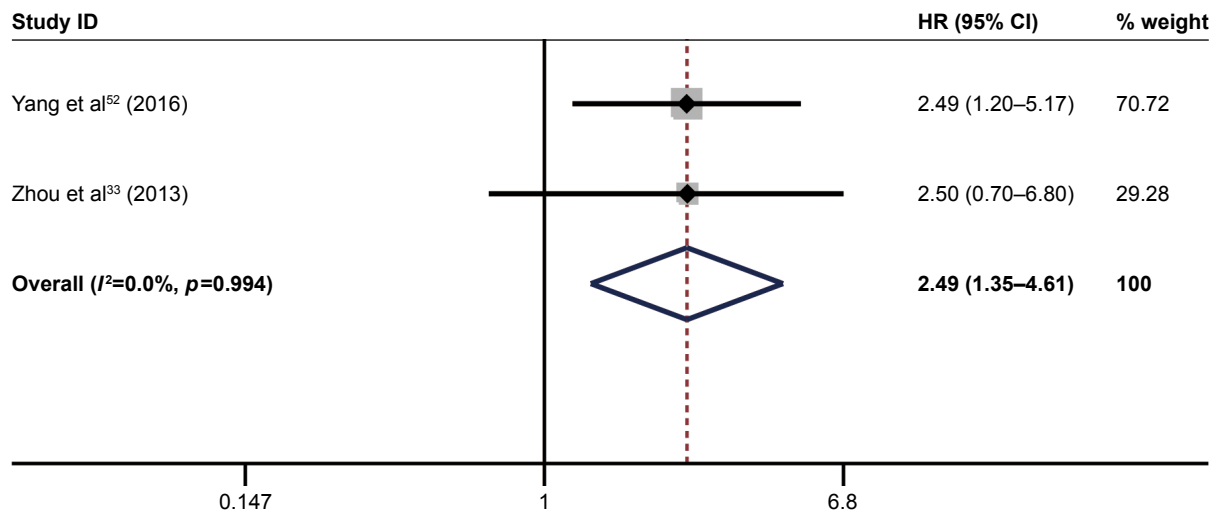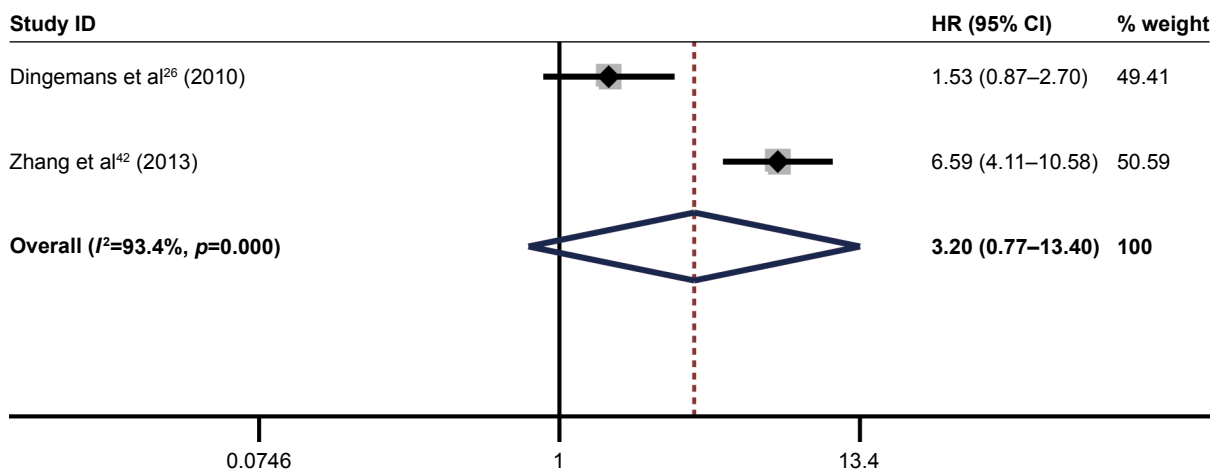**Note:** Weights are from random effects analysis.
Abbreviation: HR, hazard ratio.

Study ID		HR (95% CI)	% weight
Hieken et al[48] (1999)		3.10 (0.90–10.73)	49.31
Vihinen et al[50] (2000)		0.21 (0.07–0.60)	50.69
Overall (*I*²=90.3%, *p*=0.001)		0.79 (0.06–11.08)	100

0.0566 1 17.7

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.

Study ID		HR (95% CI)	% weight
Yao et al[28] (2007)		1.88 (1.20–2.95)	52.88
dos Santos et al[46] (2012)		1.38 (0.86–2.23)	47.12
Overall (*I*²=0.0%, *p*=0.355)		1.63 (1.17–2.25)	100

0.339 1 2.95

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.

Study ID		HR (95% CI)	% weight
Yang et al[52] (2016)		2.49 (1.20–5.17)	70.72
Zhou et al[33] (2013)		2.50 (0.70–6.80)	29.28
Overall (*I*²=0.0%, *p*=0.994)		2.49 (1.35–4.61)	100

0.147 1 6.8

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.

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.

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 (I^2=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,
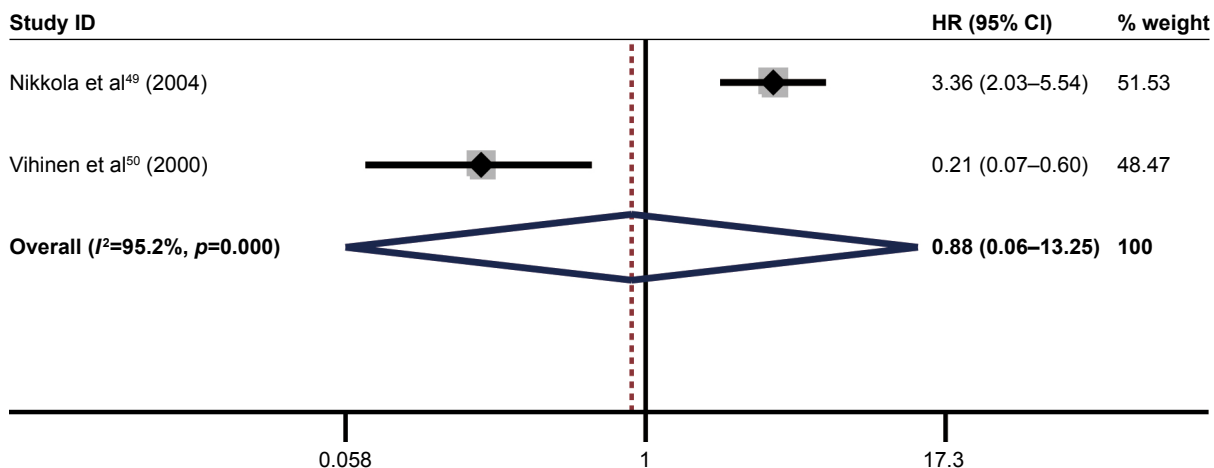
Figure 10 Results of pooled hazard ratios of disease-free survival of patients with high integrin-beta 1 (ITGB1) expression level in melanoma.
Note: Weights are from random effects analysis.
Abbreviation: HR, hazard ratio.

Table 3 Meta-analysis results of the associations of integrin-beta 1 with clinicopathological parameters

Clinicopathological parameter	No of studies	Reference no	OR (95% CI)	p-value	Heterogeneity test	
					I² (%)	p-value
Lung cancer						
Tumor differentiation (moderate–well vs poor)	2	637	0.69 (0.10–4.98)	0.712	85.0	0.010
N stage (N0 vs N+)	2	663	0.40 (0.160–1.01)	0.053	74.7	0.047
T stage (T1–2 vs T3–4)	2	663	0.64 (0.41–0.98)	0.041	0.0	0.5
Age (<60 vs ≥60 years)	2	665	0.98 (0.70–1.37)	0.921	5.0	0.305
Breast cancer						
N stage (N0 vs N+)	3	399	0.79 (0.52–1.19)	0.262	2.0	0.360
Tumor grade (I–II vs III–IV)	3	424	1.20 (0.74–1.94)	0.462	0.0	0.636
T stage (T1 vs T2–3)	3	424	0.78 (0.51–1.19)	0.250	0.0	0.639
Metastasis (yes vs no)	2	292	1.99 (1.18–3.38)	0.010	0.0	0.357
ER (+ vs −)	2	352	1.45 (0.90–2.35)	0.126	14.8	0.279
PR (+ vs −)	2	352	1.15 (0.74–1.80)	0.527	43.6	0.183
HER (+ vs −)	2	357	1.70 (0.98–2.93)	0.057	29.9	0.232
Pancreatic cancer						
Age (<60 vs ≥60 years)	2	117	1.35 (0.65–2.80)	0.417	0.0	0.459

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
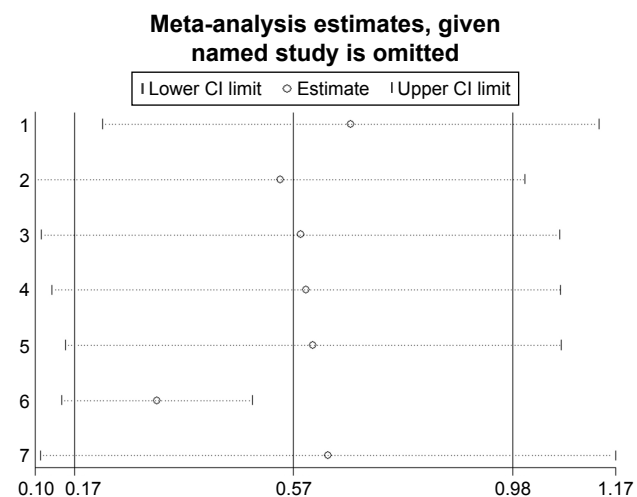
Figure 11 Sensitivity analysis of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in lung cancer.
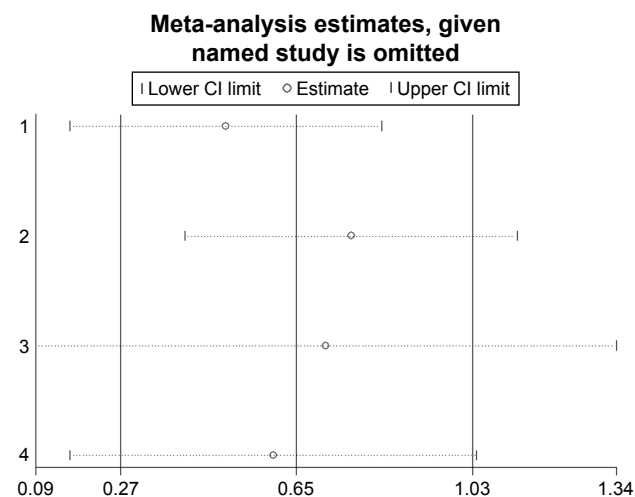
Figure 12 Sensitivity analysis of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in breast cancer.

Meta-analysis estimates, given named study is omitted
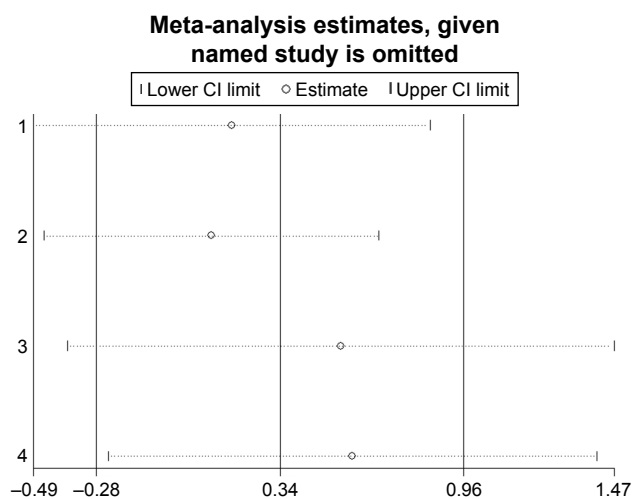
Figure 13 Sensitivity analysis of pooled hazard ratios of overall survival of patients with high integrin-beta 1 (ITGB1) expression level in pancreatic cancer.

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.[42,55] Bredin et al found that ITGB1 was involved in lung cancer cell migration in vitro,[56] and upregulation of ITGB1 was identified as an important factor for gefitinib resistance in

a lung cancer cell line.[57] In addition, the overexpression of ITGB1 was found to promote the invasion and metastasis of lung cancer.[25] 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.

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