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# Prognostic and Clinicopathologic Significance of Discoidin Domain Receptors in Different Human Malignancies: A Meta-Analysis

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**Keywords**
Discoidin domain receptors · Cancer prognosis · Meta-analysis

**Abstract**
***Background:*** Discoidin domain receptors (DDRs) belong to the receptor tyrosine kinases family and are activated by different types of collagens, which play roles in various physiological processes. An abnormal expression of DDRs is reported in different types of cancers. Despite many reports about the association and roles of high DDR expression levels in cancers, the prognostic values of DDRs are still unclear. This meta-analysis was performed to evaluate the prognostic effect of DDRs in different tissue cancers. ***Method:*** A literature search was performed in several related databases to find eligible English articles. Based on our research, 20 appropriate studies with 2,602 patients were selected till October 5, 2020. The pooled hazard ratio (HR) with a corresponding 95% confidence interval (CI) was computed to evaluate the strength of correlation between DDRs and survival of cancer patients. ***Result:*** Pooling results showed that a high DDR expression was significantly associated with poorer overall survival (OS) (HR = 1.304, 95% CI 1.007–1.69, $p = 0.04$). Subgroup analysis based on cancer type revealed a significant link between a high DDR expression level and poor OS both in gastrointestinal (pooled HR = 1.78, 95% CI 1.214–2.624, $p = 0.003$) and urological cancers (pooled HR = 1.42, 95% CI 1.062–1.82, $p = 0.018$). ***Conclusion:*** Our meta-analysis results suggest that high DDRs expression has the potential to be used as a biomarker of poor prognosis in cancers.



## Introduction

Cancer is characterized by an abnormal proliferation of cells and with the ability to metastasize and invades different parts of the body. The rising trend of cancers is a big concern globally. According to this, approximately about 1,762,450 new cases related to cancers were diagnosed, and 606,880 death occurred in the USA in 2019 [1]. The assessment of cancer prognosis plays an important role in oncology and includes the prediction of pa-

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tient's survival and guide therapy [2]. Despite the recent development of multidisciplinary synthetic therapy, the prognosis of patients with late stages of malignant tumors remains unsatisfactory [3]. To this end, developing new specific biomarkers for cancer prognosis has great clinical value in the follow-up of patients which can be applied to targeted therapy of tumors and promote patient's survival.

Discoidin domain receptors (DDRs) are a family of receptor tyrosine kinases (RTKs) that are responsible for the response of collagen and an appealing anti-fibrotic target [1, 2]. These receptors are composed of 2 types, $DDR_1$ and $DDR_2$, which contain a discoidin homology domain in the extracellular region for collagen binding, then undergo autophosphorylation of intracellular catalytic domains to mediate cellular response [2], although there are limited studies that describe the signaling pathways stimulated by DDRs upon collagen attachment. DDRs are distributed in different organs; in solid tissues, $DDR_1$ is more expressed in epithelial cells, and $DDR_2$ is limited to mesenchymal cells [4]. Recently, studies have shown that the expression of DDRs upregulated in different types of malignancies such as hepatocellular carcinoma (HCC) [5, 6], gastric cancer [4], ovarian cancer [5, 7, 8], lung cancer [6, 9, 10], pancreatic carcinoma [11], and breast cancer [12, 13]. To the best of our knowledge, no systematic review and meta-analysis has been done to assess the relation between DDR expression and clinicopathologic features and prognostic value of DDRs in patients with different malignancies; so in this meta-analysis, we systematically pooled related published evidence to explain the prognostic significance of DDR expression in malignant tumors.

## Methods

The study was conducted and described according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

*Literature Search Strategy*

An electronic literature search was systematically carried out in databases including PubMed, Web of Science, Scopus, Google Scholar, and Embase to get pertinent English publication with reference to prognostic and clinicopathologic features of DDRs in malignant tumors up to October 5, 2020. The searched keywords included ("Discoidin Domain Receptor" or "DDR Proteins") AND ("cancer" or "neoplasm" or "malignancy" or "tumor" or "carcinoma") AND ("prognostic factor" or "prognosis") were used. Also, we checked reference lists in selected articles to assess the potential of the related article and increase the accuracy of the search process.

*Inclusion and Exclusion Criteria*

The inclusion criteria for our study were as follows: (1) evaluation of the expression levels of DDRs (1 or 2) in malignant tissue, (2) divided the patients into 2 groups regarding the DDRs expression levels, (3) adequate data for estimation of the hazard ratio (HR) with 95% confidence interval (CI) and the correlation between survival and DDR expression, and (4) the association between clinicopathologic features and prognostic information. The exclusion criteria were as follows: (1) unpublished studies, (2) articles such as review, case report, letter to editor, and animal studies or articles with inadequate or unavailable data, (3) overlapping articles or duplicate data, and (4) non-English articles.

*Data Extraction*

Two independent investigators (Mohammad-Hassan Arjmand and Milad Shahini Shams Abadi) carried out data extraction from all appropriate publications. Any disagreement was resolved through consulting with a third author (Sheida Shabanian). The following information was recorded from each study including first author name, publication year, region, cancer type, sample size, source of DDR, DDR isoform, and DDR detection assay. Moreover clinicopathologic parameters such as gender, tumor size, tumor stage, lymph node metastasis (LNM), distance metastasis, and HR with its 95% CI for overall survival (OS) were collected. The quality assessment of included articles was evaluated according to the Newcastle-Ottawa Scale (NOS) [14] by 2 authors independently (M.-H.A. and M.S.S.A.). A score with higher or equal to 6 points could be reflected as high quality (Table 1). If the HR and 95% CI were not directly reported and only Kaplan-Meier curves were shown in some articles, the HR and 95% CI were calculated as reported by Parmar's formula [15].

*Statistical Analysis*

All analyses were performed using Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA), a computer program. The $p$ value <0.05 showed that the result had a statistical significance. The effects of DDR expression on the OS of patients in various cancers were reported as HRs with 95% CIs. The association between DDR expression and clinicopathologic parameters was considered by odd ratios (ORs) and corresponding 95% CIs. The heterogeneity was evaluated by Cochrane's $Q$ test and the $I^2$ index among different studies. If $I^2$ >50% and $p < 0.05$ among studies, the random-effects model was selected. Otherwise, the fixed-effects model was applied. The publication bias was measured by using a funnel plot and Egger's linear regression test. Sensitivity analysis was also performed to consider the stability of the collected results.

## Results

*Literature Search and Data Characteristics*

A total of 146 relevant studies were identified from electronic databases. After assessment of titles and abstracts, 105 studies were removed because they were basic research, reviews, animal studies, case report, or duplicate articles. After that, the remaining 41 studies were read completely, and 21 articles were excluded due to inade-

**Table 1.** Characteristics of included studies in the meta-analysis

| Study year | Country | DDR isoform | Age (high/low) | Tumor type | Tumor size (high/low) | Sample size | Male (high/low) Female (high/low) | TNM stage (high/low) | DDR expression | | | | | | Survival analysis | HR (CI) | Method | Sample type | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | high | | | low | | | | | | | |
| | | | | | | | | | total | LNM | DM | total | LNM | DM | | | | | |
| Lin et al. [21] | China | DDR1 | NR | HCC | NR | 15 | NR | NR | – | – | – | – | – | – | OS | 1.8 (0.43–7.39) | qRT-PCR | Tissue | 6 |
| Sugimoto et al. [22] | Japan | DDR1 | 72/66 | EsoC | NR | 60 | 19/34 3/4 | 0/I/II (4/34) III/IV (18/4) | 22 | 17 | – | 38 | 36 | – | RFS | 4.27 (1.16–20.52) | IHC | Tissue | 6 |
| Ramalho et al. [7] | Brazil | DDR2 | NR | OvaC | NR | 78 | Female | I/II (1/13) III/IV (10/54) | 11 | – | – | 67 | – | – | OS | 1.73 (0.51–5.89) | IHC | Tissue | 6 |
| Li et al. [17] | China | DDR2 | NR | GBC (SC/ADC) | >3 cm (27/12) ≤3 cm (13/17) | 69 | NR | I/II (12/17) III/IV (28/12) | 42 | 29 | – | 27 | 11 | – | OS | 1.72 (0.95–3.10) | IHC | Tissue | 6 |
| Li et al. [17] | China | DDR2 | NR | GBC (AC) | >3 cm (30/26) ≤3 cm (46/44) | 146 | NR | I/II (37/40) III/IV (39/30) | 66 | 39 | – | 80 | 37 | – | OS | 1.39 (0.95–2.05) | IHC | Tissue | 6 |
| Velmurugan et al. [24] | Taiwan | DDR2 | NR | OSCC | NR | 268 | NR | I/II (80/21) III/IV (96/57) | 176 | 34 | 1 | 78 | 27 | 0 | OS | 2.08 (1.42–3.05) | IHC | Tissue | 6 |
| Hur et al. [4] | South Korea | DDR1 | ≥70 (25/30) <70 (77/70) | GC | NR | 202 | 68/72 34/28 | NR | 102 | – | – | 100 | – | – | OS | 1.47 (0.85–2.54) | IHC | Tissue | 6 |
| Sasaki et al. [23] | Japan | DDR2 | ≥65 (3/12) <65 (17/31) | CRC | ≥5 cm (13/27) <5 cm (7/16) | 63 | 12/27 8/16 | I/II (2/11) III/IV (18/32) | 20 | 17 | – | 43 | 25 | – | OS | 3.681 (0.976–13.87) | IHC | Tissue | 6 |
| Wang et al. [16] | China | DDR1 | ≥30 (6/13) <30 (31/31) | OsteoC | ≥5 cm (18/10) <5 cm (19/34) | 81 | 21/19 16/25 | I/II (24/36) III/IV (23/8) | 37 | – | 10 | 44 | – | 0 | OS | 1.378 (0.81–2.34) | IHC | Tissue | 6 |
| Song et al. [18] | China | DDR1 | ≥60 (35/22) <60 (36/26) | RC | >7 cm (19/8) ≤7 cm (52/40) | 119 | 50/31 21/17 | I/II (44/39) III/IV (24/8) | 71 | 12 | 2 | 48 | 2 | 1 | OS | 0.6 (0.14–2.48) | IHC | Tissue | 6 |
| Tsai et al. [19] | Taiwan | DDR2 | ≥65 (89/85) <65 (58/63) | UC | NR | 295 | 106/110 41/38 | NR | 147 | – | – | 148 | – | – | OS | 1.43 (0.67–3.02) | IHC/qRT-PCR | Tissue | 6 |
| Fan et al. [5] | China | DDR2 | >55 (43/24) ≤55 (20/16) | OvaC | >5 cm (39/18) ≤5 cm (33/22) | 103 | NR | NR | 63 | 16 | – | 40 | 4 | – | OS | 3.463 (0.375–7.602) | IHC | Tissue | 6 |
| Xie et al. [20] | China | DDR2 | >45 (46/37) ≤45 (10/19) | HCC | >5 cm (42/33) ≤5 cm (14/23) | 112 | 41/46 15/10 | I/II (25/42) III/IV (31/14) | 56 | – | – | 56 | – | – | OS | 2.169 (1.198–3.927) | IHC | Tissue | 6 |
| Huo et al. [11] | China | DDR1 | ≥65 (61/37) <65 (65/42) | PDAC | >2 cm (108/70) ≤2 cm (18/9) | 205 | 74/43 52/36 | I/II (80/93) III/IV (17/18) | 126 | – | – | 79 | – | – | OS | 1.02 (0.78–1.33) | IHC | Tissue | 6 |
| Toy et al. [12] | USA | DDR2 | NR | BC | >2 cm (45/32) ≤2 cm (52/48) | 198 | NR | NR | 110 | 49 | – | 87 | 27 | – | OS | 1.73 (1.13–2.63) | IHC | Tissue | 6 |
| Ren et al. [13] | USA | DDR2 | NR | BC | NR | 122 | NR | NR | 93 | – | – | 29 | – | – | OS | 0.47 (0.32–0.93) | IHC | Tissue | 6 |
| Miao et al. [6] | USA | DDR1 | ≥60 (24/20) <60 (26/11) | LC | >3 cm (38/24) ≤3 cm (12/8) | 82 | 26/21 24/11 | NR | 50 | – | – | 32 | – | – | OS | 1.51 (0.72–3.17) | qRT-PCR | Tissue | 6 |
| Quan et al. [8] | Japan | DDR1 | NR | OvaC | NR | 67 | NR | I/II (13/15) III/IV (32/7) | 46 | – | – | 21 | – | – | OS | 1.32 (0.49–3.53) | IHC | Tissue | 6 |
| Yang et al. [9] | Korea | DDR1 | ≥69 (46/38) <69 (49/22) | LC | >2 cm (77/47) ≤2 cm (18/13) | 171 | 50/39 45/21 | NR | 95 | 52 | – | 60 | 17 | – | OS | 0.600 (0.313–1.149) | IHC | Tissue | 6 |
| Ford et al. [10] | Canada | DDR1 | NR | LC | NR | 146 | 32/31 41/41 | I/II (66/63) III (7/10) | 73 | – | – | 73 | – | – | OS | 0.43 (0.22–0.83) | qRT-PCR | Tissue | 6 |

DDR, discoidin domain receptor; BC, breast cancer; EsoC, esophageal cancer; CRC, colorectal cancer; DM, distance metastasis; HCC, hepatocellular carcinoma; GC, gastric cancer; GBC, gallbladder cancer; IHC, immunohistochemistry; LC, lung cancer; LNM, lymph node metastasis; NR, not report; NOS, Newcastle-Ottawa Scale; OSCC, oral squamous cell carcinoma; OsteoC, osteosarcoma; OvaC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; RC, renal cancer; UC, urothelial carcinoma; HR, hazard ratio; CI, confidence interval; OS, overall survival.

quate data to evaluate the HR for quantitative analysis. Ultimately, 20 appropriate studies with the inclusion criteria were selected showing agreement for inclusion in the meta-analysis. The process of study selection is abstracted in Figure 1. The general characteristics of the research studies involved in the analysis from 2007 to 2020 are summarized in Table 1.

In total, there were 2,602 patients. Also, the majority of involved studies were reported by authors in Asia (China, Japan, Taiwan, and South Korea), and the other studies were 1 from Canada, 3 from the USA, and 1 from Brazil. Moreover, 12 types of cancers including 3 ovarian cancers [5, 7, 9], 2 breast cancers [12, 13], 1 osteosarcoma [16], 3 lung cancers [6, 9, 10], urological cancers (UC) which include 2 gallbladder carcinomas [17], 1 renal cancer [18], and 1 urothelial carcinoma [19], and gastrointestinal (GI) malignancies which include 1 gastric cancer [4], 2 HCCs [20, 21], 1 esophageal cancer [22], 1 colorectal cancer [23], 1 pancreatic carcinoma [11], and 1 oral cell carcinoma [24] were evaluated in this meta-analysis. The total subjects registered were divided into high and low DDR groups based on the DDR measurement results.

According to the HR estimations, the HR values were directly described from 12 studies, while for 8 studies, the HRs were calculated through data reading from Kaplan-Meier survival curves. In relation to clinicopathologic parameters, 9 articles provided data according to the association between DDR expression and LNM, 12 articles reported TNM stage, 11 articles reported tumor size, and 10 articles evaluated age.

*Association between DDR Expression and Survival in Cancer*

As for survival analysis, a total of 20 studies (a total number of patients = 2,602) had calculated the relation of DDR expression with OS. A random-effects framework was applied because of the significant heterogeneity among these studies ($I^2$ = 70.6%, $p$ = <0.001). The pooled HR showed that high expression levels of DDRs ($DDR_1$ and $DDR_2$) were significantly correlated with poor OS compared with the low DDR expression (pooled HR = 1.304, 95% CI 1.007–1.69, $p$ = 0.04) (Fig. 2). In addition, subgroup analyses were done according to cancer type (GI cancers, UC, and other malignancies), sample size, ethnicity, and DDR isoform (Table 2). The classification analysis by cancer types showed a significant link between a high DDR expression level and poor OS both in UC (pooled HR = 1.42, 95% CI 1.062–1.82, $p$ = 0.018) and GI cancers (pooled HR = 1.78, 95% CI 1.214–2.624, $p$ = 0.003) but not significant in other cancers (pooled HR = 1.002, 95% CI 0.631–1.59, $p$ = 0.99) (Fig. 3). In subgroup analysis according to sample size, a significant association was observed between DDR upregulation and OS in sample sizes <100 (pooled HR = 1.676, 95% CI 1.250–2.24, $p$ = 0.001). However, there was no significant association between DDR overexpression and sample size ≥100 (pooled HR = 1.119, 95% CI 0.798–1.570, $p$ = 0.51) (Table 2). In addition, high DDR expression was significantly related to poor OS in the Asian population based on ethnicity (pooled HR = 1.358, 95% CI 1.051–1.754, $p$ = 0.019) (Table 2). Finally, subgroup analysis based on the DDR isoform showed that just there was a significant association between DDR2 and poor OS (pooled HR = 1.55 95% CI 1.035–2.330, $p$ = 0.034) against DDR1 expression (pooled HR = 1.84 95% CI 0.788–1.491, $p$ = 0.62).

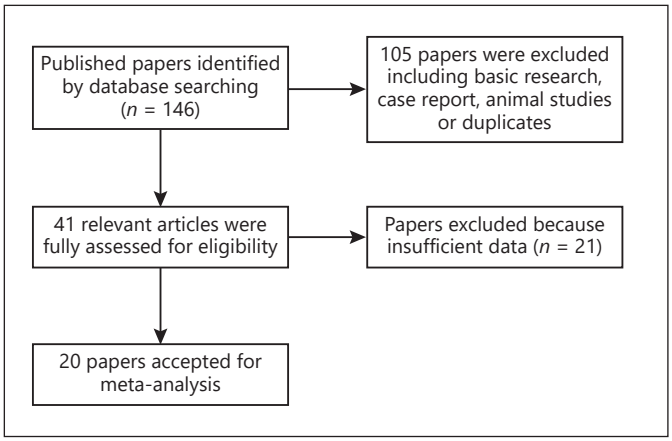


**Fig. 1.** Flow diagram of the study selection.

*Correlation between DDRs and Clinicopathologic Characteristics*

A meta-analysis was performed to evaluate the association between the DDR expression level and clinicopathologic features. The pooled OR and 95% CI of all outcomes including gender, age, LNM, DM, tumor size, and TNM stage are presented in Table 3. Reports from a collection of 11 studies found that the association of DDRs with gender in different tumors (pooled OR = 2.86, 95% CI 1.637–5.01, $p$ < 0.001, $I^2$ = 85.02% $p$ < 0.001, random-effects model) (Fig. 4) (Table 3). Nevertheless, no significance association was observed between overexpression of DDRs with TNM stage (pooled OR = 1.642, 95% CI 0.508–5.309, $p$ = 0.4, $I^2$ = 95.6% $p$ < 0.001, random-effects model), tumor size (pooled OR = 0.395, 95% CI 0.128–1.218, $p$ = 0.1, $I^2$ = 95.6% $p$ < 0.001, random-effects model), LNM (pooled OR = 0.989, 95% CI 0.263–3.718, $p$ =

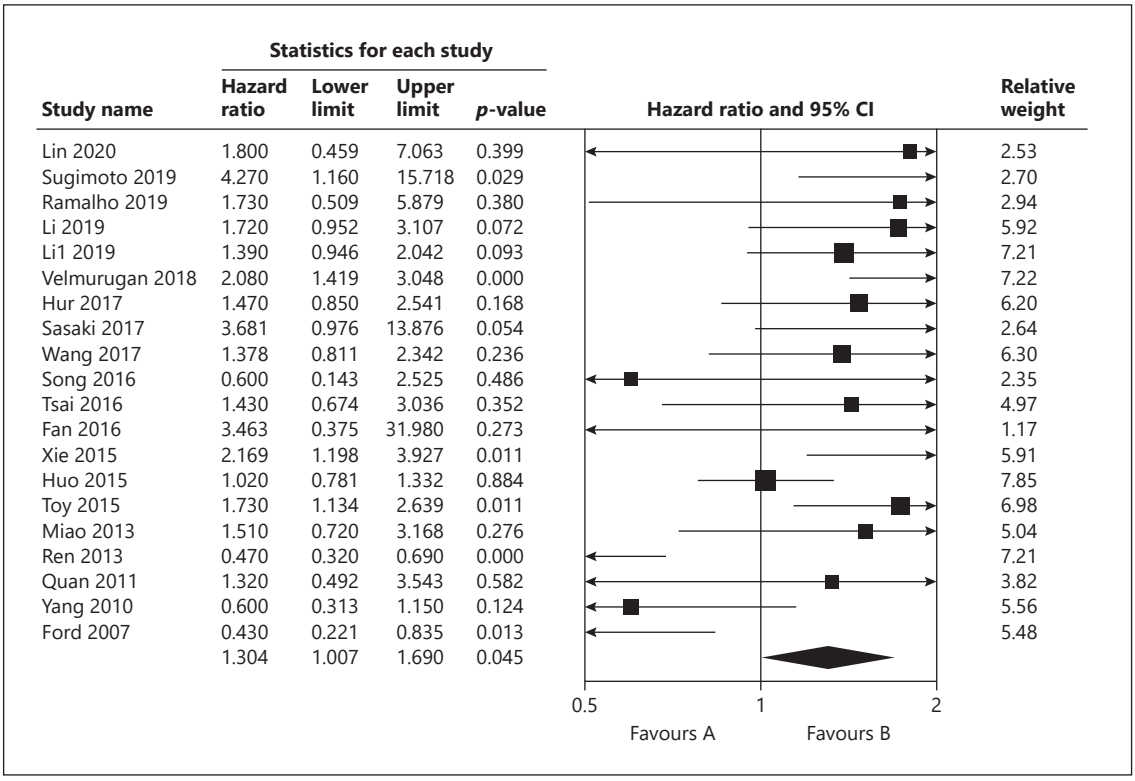


**Fig. 2.** Forest plots for the association between SNHG20 expression and OS; HR with 95% CI. Pooled HR shows the association between OS and DDR expression on various cancers. OS, overall survival; HR, hazard ratio; CI, confidence interval; DDR, discoidin domain receptor.

**Table 2.** Stratified analyses of pooled HRs for OS

| Category | Studies, *n* | Patients, *n* | Test of association | | Test of heterogeneity | | |
|---|---|---|---|---|---|---|---|
| | | | pooled HR (95% CI) | *p* value | $I^2$, % | *p* value | Model |
| Cancer type | | | | | | | |
| GI | 7 | 924 | 1.78 (1.214–2.624) | 0.003 | 63.6 | 0.011 | R |
| UC | 4 | 629 | 1.42 (1.062–1.82) | 0.0018 | 76.3 | <0.001 | R |
| Others | 8 | 1,049 | 1.002 (0.631–1.59) | 0.99 | 0 | 0.6 | R |
| Sample size | | | | | | | |
| ≥100 | 12 | 2.087 | 1.119 (0.798–1.570) | 0.51 | 79.9 | <0.001 | R |
| <100 | 8 | 515 | 1.676 (1.250–2.24) | 0.001 | 0 | 0.76 | F |
| Ethnicity | | | | | | | |
| Asian | 16 | 2,122 | 1.358 (1.051–1.754) | 0.019 | 86.9 | <0.001 | R |
| American | 4 | 480 | 1.149 (0.51–2.58) | 0.73 | 59.2 | 0.001 | R |
| DDR isoform | | | | | | | |
| DDR1 | 10 | 1,148 | 1.84 (0.788–1.491) | 0.62 | 52.77 | 0.025 | R |
| DDR2 | 10 | 1,454 | 1.55 (1.035–2.330) | 0.034 | 78.2 | <0.001 | R |

DDR, discoidin domain receptor; UC, urological cancer; GI, gastrointestinal; OS, overall survival; HR, hazard ratio; CI, confidence interval.

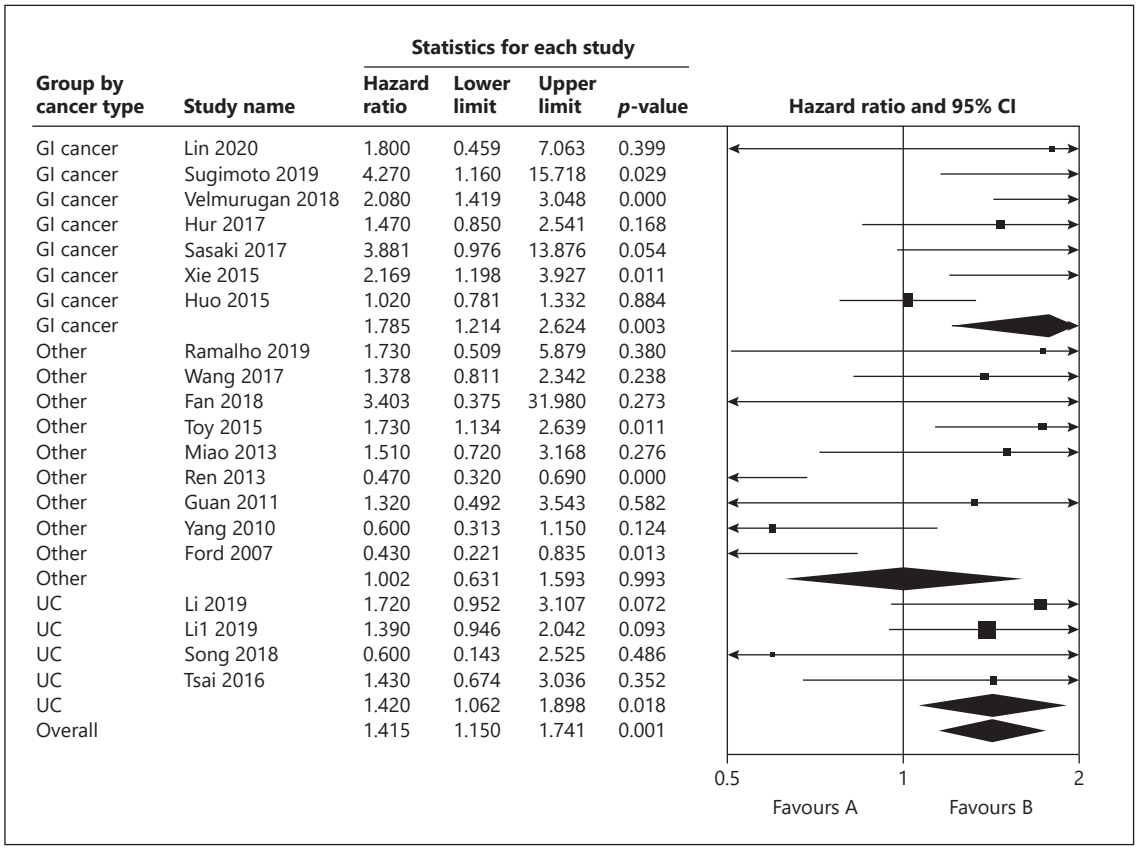


**Fig. 3.** Forest plot based on subgroup analysis showed a significant association between high DDR expression and poor OS in UC and GI cancers. UC, urological cancer; GI, gastrointestinal; OS, overall survival; DDR, discoidin domain receptor.

**Table 3.** Meta-analysis of the association between DDR expression and clinicopathologic characteristics

| Stratified analysis | Studies, *n* | Patients, *n* | Test of association | | Test of heterogeneity | | |
|---|---|---|---|---|---|---|---|
| | | | pooled OR (95% CI) | *p* value | $I^2$, % | *p* value | Model |
| Gender (male vs. female) | 11 | 1,241 | 2.86 (1.637–5.01) | <0.001 | 82.02 | <0.001 | R |
| Age (≥55 vs. <55 years) | 10 | 1,433 | 1.34 (0.52–3.46) | 0.54 | 94.5 | <0.001 | R |
| Tumor size (large vs. small) | 11 | 1,349 | 0.395 (0.128–1.218) | 0.1 | 95.6 | <0.001 | R |
| LNM (yes vs. no) | 9 | 1,197 | 0.989 (0.263–3.718) | 0.98 | 96.3 | <0.001 | R |
| Tumor stage (III + IV vs. I + II) | 12 | 1,414 | 1.642 (0.508–5.309) | 0.4 | 95.6 | <0.001 | R |

DDR, discoidin domain receptor; OR, odds ratio; CI, confidence interval; LNM, lymph node metastasis.

0.98, $I^2 = 96.3\%$ $p < 0.001$, random-effects model), and age (pooled OR = 1.34, 95% CI 0.52–3.46, $p = 0.54$, $I^2 = 94.5\%$ $p < 0.001$, random-effects model) on patients (Table 3).

*Sensitivity Analysis*

Sensitivity analysis was conducted to evaluate the effect of each study on the robustness of the analysis. In our meta-analysis, the pooled HR was not significantly influenced by any single study (Fig. 5).

*Publication Bias*

Begg's test and Egger's test were also carried out to evaluate the publication bias for the present meta-analysis. The outcome of Begg's test ($p = 0.97$) and Egger's test

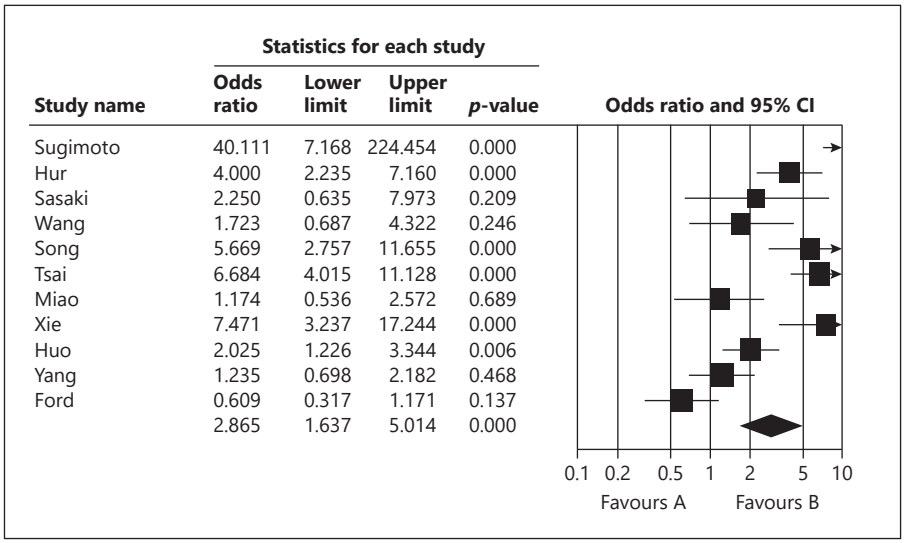


**Fig. 4.** Forests plots for the association between DDR expression and gender; OR with 95% CI. DDR, discoidin domain receptor; OR, odds ratio; CI, confidence interval.

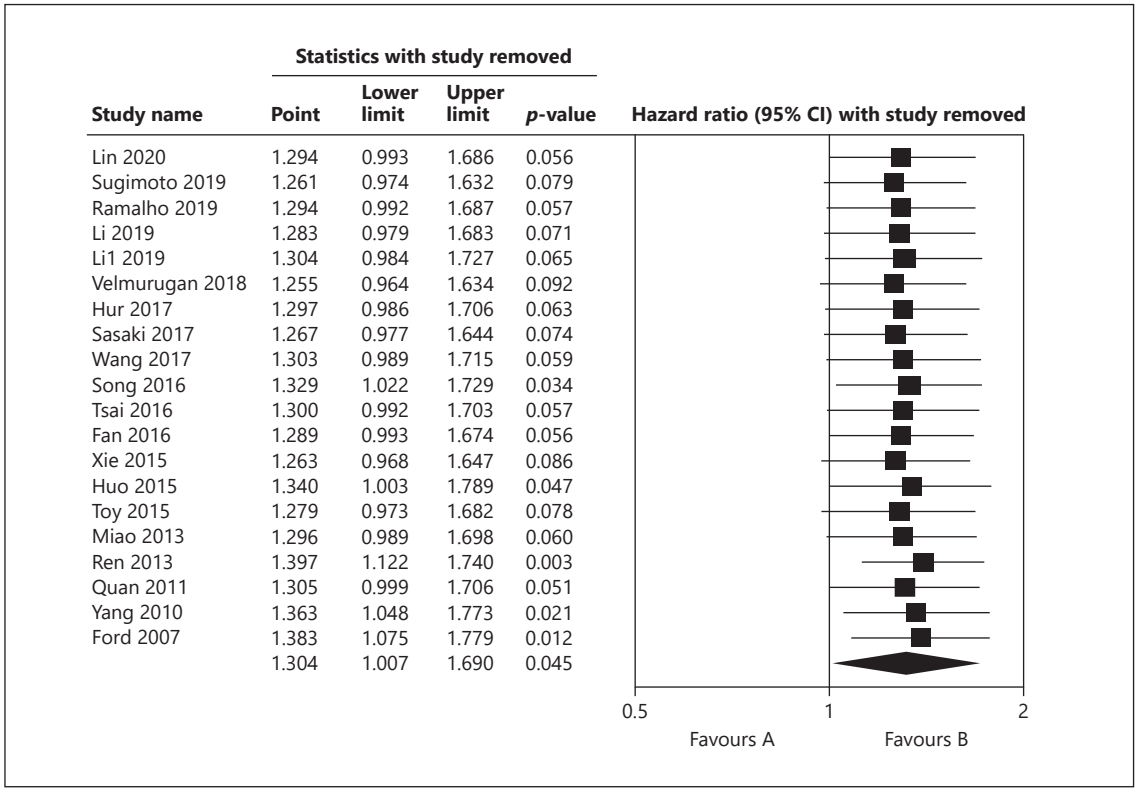


**Fig. 5.** Sensitivity analysis for the correlation between DDR expression with OS. DDR, discoidin domain receptor; OS, overall survival.

($p = 0.31$) results for OS conducted that there was no significant publication bias across the included studies. Furthermore, there was no publication bias based on Egger's test results for ORs of DDR overexpression on gender, age, tumor size, TNM stage, and LNM.

## Discussion

Although there have been advances in cancer prediction and treatment during the past decades, many cancers cannot currently be adequately treated because of

the lack of efficient biomarkers for early detection and subsequent useful treatment at the terminal stages. Currently, many investigations have concentrated on finding tumor markers to predict cancer prognosis. Now, increasing evidence supports the association between DDRs and collagen overexpression and cancer risk. In this way, several investigations have described altered DDRs expression in different types of cancer [4, 6, 19]. In the current study, we showed the correlation between DDR expression and worse overall prognosis in malignant tumors in patients.

Although there are limited data on the role of DDRs and their molecular targets, they have been suggested to be essential to control cell behavior. DDRs and tyrosine kinases have been shown to be included in a wide range of cell functions such as cellular proliferation, differentiation, migration, cytokines secretion, and extracellular matrix (ECM) hemostasis and remodeling [25]. Triple-helical conformations of collagens are the main ligands for both receptors of DDR. Different types of collagen (mainly type 1) can active DDRs [26, 27]. While activation of DDRs is needed for normal cell function, studies have demonstrated the upregulation and mutations of $DDR_1$ and $DDR_2$ in different cancers [25]. The emerging role of DDRs in the proliferation and survival of tumor cells and their association with oncogenic signaling are shown in in vitro and in vivo studies [28, 29]. Investigation in human colon carcinoma cell lines (HCT116) indicated that $DDR_1$, in response to collagen-induced activation, stimulates cell survival through activation of Notch signaling [30]. Another study showed that overexpression of $DDR_2$ is the result of mutations and promotes cell growth and proliferation in NIH3T3 mouse fibroblast cells [31]. Han et al. [32] have reported that $DDR_2$ has the potential to upregulate cell growth and proliferation of human osteosarcoma cell lines by overexpression of cyclooxygenase 2. Epithelial-mesenchymal transition (EMT) contributes to fibrosis and tumor progression through different mechanisms. Tumor cells by expression of epithelial and mesenchymal markers promote tumor migration to other organs. In relation to this, $DDR_1$ is an epithelial marker, and $DDR_2$ is a mesenchymal marker besides well-known EMT markers such as vimentin and N-cadherin. Therefore, overexpression of $DDR_1$ and $DDR_2$ reflects a result of the EMT process toward the majority of malignant tumor cells [12, 33]. DDR1 and DDR2 can support EMT and so have the potential to contribute to tumor cell migration. Herein, various studies reported the role of $DDR_1$ in the regulation of cell migration in different malignant cell lines such as HCC, pancreas, breast, colorectal cancer, and lung [9, 29, 34, 35]. In addition, tumor cell invasion is a complicated process performed by cancer cells to attack to other organs. Cell invasion requires ECM degradation and tissue remodeling. Some reports indicated that $DDR_1$ can induce the matrix metalloproteinase 2 (MMP2) and MMP9, which play an important role in ECM degradation [6, 36]. Hu et al. [37] reported that overexpression of $DDR_1$ promotes invasion in colon carcinoma by the upregulation of MMP-2. Also, $DDR_2$ overexpression has been found to stimulate invasion in different cancer cell lines like metastatic melanoma [38], breast [39], and prostate [40]. Given the above molecular mechanisms of DDRs among different carcinomas, the hypothesis is that DDR overexpression has the potential to connect with an unfavorable prognosis in cancer patients, which provides support for the clinical value of DDRs.

We aimed to explore the association between DDR expression levels and the prognosis of human malignant tumors in the present comprehensive meta-analysis. We pooled a total of 20 independent studies with 2,602 malignant patients. Our meta-data indicated that high DDR expression was an indicator for progressive disease and poor prognosis with statistical significance for OS (HR = 1.304, 95% CI 1.007–1.69, $p = 0.04$). This result shows the role of DDRs overexpression as a prognostic biomarker in cancers. In subgroup analysis based on cancer types, high DDR expression was correlated with poor OS in GI cancers and UC. The reasons for this link may be existing high fibrotic conditions with high expression and cross-linking of collagens and increased interactions between collagens and DDRs in tumor stroma. Herein, different studies have shown that DDRs can promote tissue fibrosis [41–43]. More research studies are required to confirm this relationship between DDR expression and GI and UC. Also in subgroup analysis, high expression of DDRs was associated with poor survival in the Asian population. Moreover, subgroup analysis according to the DDR isoform showed that $DDR_2$, but not $DDR_1$, was correlated with poor OS in patients. This result demonstrated that $DDR_2$ is a better prognostic marker for malignant tumors. Likewise, the clinicopathologic analyses revealed that high expression of DDRs was associated with gender; however, no prominent correlation was observed between DDR expression and TNM stage, tumor size, LNM, and age.

Our meta-analysis has some limitations that need to be pointed out. First, the majority of clinical studies carried

out in China develop the risk of geographic bias. Second, all involved studies were only published in English, which increases selection bias. Third, existing heterogeneity among studies affects the results of the study; however, we make subgroup analyses to explore the potential sources of heterogeneity. Fourth, no appropriate and standard cutoff value was reported to make an accurate evaluation of the association between DDR expression and the survival outcome.

## Conclusion

In conclusion, the present meta-analysis indicates a significant association of DDR overexpression with poor OS in several different cancers. Our findings provide further supportive evidence that DDR overexpression may be a promising potential biomarker to predict poor prognosis in cancer patients. More clinical studies are needed to clarify this association.


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## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.


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## Author Contributions

M.-H.A. and M.S.S.A. researched the literature and conceived the study, A.F. consulted us about the field, S.S. researched the literature and collected data as the third author, and G.A.F. reviewed and edited the manuscript. M.-H.A. designed the study, wrote the first draft, and approved the final version of the manuscript.

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