Original Paper

The Clinicopathological and Prognostic Significance of IDO1 Expression in Human Solid Tumors: Evidence from a Systematic Review and Meta-Analysis

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Key Words

Ido1 • Carcinoma • Prognosis • Meta-analysis

Abstract

Background/Aims: Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme catalyzing the initial and rate-limiting steps in the kynurenine pathway, which converts tryptophan into kynurenine. Upregulation of IDO1 decreases tryptophan levels and increases the accumulation of kynurenine and its metabolites. These metabolites can affect the proliferation of T cells. Increasing evidence has shown that IDO1 is highly expressed in various cancer types and associated with poor prognosis of cancer patients. However, the results were inconsistent. **Methods:** We searched the Web of Science, PubMed, Embase and Cochrane library databases to identify studies evaluating the prognostic value of IDO1 in cancer patients. Pooled hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by using fixed-effects/random-effects models. **Results:** This systematic review and meta-analysis included 2706 patients from 24 articles. The results indicated a shorter overall survival in patients with high expression of IDO1 (hazard ratio [HR] = 2.03, 95% confidence interval [CI]: 1.56-2.63). Furthermore, disease-free survival was worse in patients with high expression of IDO1 (HR = 2.47, 95% CI: 1.46-4.20). Additionally, the pooled odds ratios (ORs) showed that increased IDO1 was significantly associated with tumor differentiation (OR = 1.81, 95% CI: 1.05-3.12), distant metastasis (OR = 1.45, 95% CI: 1.02-2.06), and poor clinical stage (OR = 1.89, 95% CI: 1.13-3.17). However, no significant correlation was observed of increased IDO1 expression with age, sex, lymph node metastasis, and tumor size. **Conclusion:** High expression of IDO1 is associated with poor clinical outcomes. IDO1 could serve as a biomarker

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of prognosis and a potential predictive factor of clinicopathology in various cancers. Further studies should be performed to verify the clinical utility of IDO1 in human solid tumors.

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Introduction

Indoleamine 2, 3-dioxygenase 1 (IDO1) is a heme-containing enzyme catalyzing the initial and rate-limiting steps in the kynurenine pathway, which catalyzes tryptophan into kynurenine. Overactivation of the kynurenine pathway results in a tryptophan decrease and kynurenine accumulation [1-3]. The former can result in the cell cycle arrest of immune cells, such as CD8⁺ T lymphocytes, natural killer (NK) cells, and invariant NK-T cells, via the general control non-depressible 2 stress kinase pathway and the mammalian target of rapamycin pathway [4-6]. The latter can cause the death of effector T cells due to the toxicity of its downstream product. Moreover, kynurenine can bind to aryl hydrocarbon receptor, which is involved in the regulation of Treg and inhibits TH17 cell differentiation, suppressing the immune system [7-10].

In 2003, Uyttenhove et al. found that IDO1 was expressed in various human cancer tissues and that tumors expressing IDO1 could resist immune rejection [2]. The following year, it was reported that IDO1 was also expressed by dendritic cells in tumor-draining lymph nodes and that melanoma patients with IDO-positive cells in lymph nodes had a poor clinical outcome [11]. A relationship has been found between clinical outcome and the expression of IDO1 in many human solid tumors, such as breast cancer, cervical cancer, colorectal cancer, endometrial cancer, and adrenal cell carcinoma [12-16]. However, the role of IDO1 in malignant tumors is controversial. Patients with multiple tumor types, such as nasopharyngeal carcinoma, colorectal cancer, endometrial cancer, and ovarian carcinoma, have poorer prognosis if they have high IDO1 levels [17-20]. In contrast, patients with high IDO1 expression in some tumors, such as renal cell carcinoma (RCC), have a longer survival [12]. This systematic review and meta-analysis investigated the role of IDO1 in human solid tumors.

Materials and Methods

Literature search

To identify potentially eligible studies, a comprehensive literature retrieval was conducted in PubMed, Web of Science, Embase, and Cochrane library databases with a cutoff date of December 15th, 2017. The keywords for the search were “indoleamine 2, 3-dioxygenase 1”, “IDO1”, “cancer”, “carcinoma”, “neoplasm”, and “tumor”. In addition, other relevant articles were also manually reviewed from the reference lists.

Inclusion and exclusion criteria

Inclusion criteria for the articles were as follows: (1) investigation of the role of IDO1 in the development of human cancer; (2) description of the associations of IDO1 expression with prognosis or clinicopathological features; (3) determination of the expression level of IDO1 in primary cancerous tissue by immunohistochemistry, immunofluorescence, or quantitative real-time polymerase chain reaction (qPCR); (4) division of patients into high and low expression groups according to the expression level of IDO1; and (5) no patients with HIV or active Epstein-Barr virus infection. Exclusion criteria were as follows: (1) duplicate publications; (2) studies without valuable data; and (3) reviews, letters, case reports, and expert opinions.

Date extraction and quality assessment

The data and information from all included studies were independently extracted by two investigators (FSF and CX). The following information was collected from each study: first author's name, publication year, study country, cancer type, total number of patients, tumor stage, follow-up period, outcome measures, criteria for high IDO1 expression, determination method, hazard ratios (HRs), and corresponding 95%

confidence intervals (CIs). In addition, data on clinicopathological parameters were also extracted from the eligible studies. For all included studies, only multivariate analysis was selected because of its increased precision in interpreting confounding factors. Any studies reporting only Kaplan-Meier curves and not providing multivariate data were excluded. In the event of a disagreement, a consensus was reached by a third investigator (YJ). The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of all included studies. The NOS scores ranged from 0 to 9, with an NOS score ≥ 6 considered to indicate high quality. The quality of all studies included in this meta-analysis varied from 4 to 9, with a mean value of 6.5.

Statistical methods

The current meta-analysis was performed with RevMan5.3 software and Stata SE12.0. Heterogeneity between studies was determined with the chi-square-based Q test and I^2 statistic. A P value less than 0.05 for the Q test and an I^2 value greater than 50% were considered to indicate significant heterogeneity. The fixed-effects model was applied for studies with no obvious heterogeneity ($P > 0.05$, $I^2 < 50\%$); otherwise, the random-effects model was adopted ($P \leq 0.05$, $I^2 \geq 50\%$). Potential publication bias was assessed with Begg's Test and Egger's test. Sensitivity analysis was also performed to assess the stability of the results. A P value less than 0.05 was considered statistically significant.

Results

Study characteristics

The literature retrieval process is detailed in Fig. 1. A total of 24 eligible articles were ultimately identified [12-34] and 2,706 cancer patients were included in the present meta-analysis; the mean patient sample size was 113 (range, 28-362). The 24 included studies were from the United States, Africa, Asia, and Europe. Eighteen different solid tumor types were evaluated in our study: 2 Hodgkin's lymphomas, 2 breast cancers, 2 cervical cancers, 2 endometrial carcinomas, 2 esophageal squamous cell carcinomas, 2 gastric cancers, and 1 each of colorectal cancer, glioma, hepatocarcinoma, lung cancer, laryngeal squamous cell carcinoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, ovarian cancer, osteosarcoma, oral squamous cell carcinoma, RCC, and vulvar squamous cell carcinoma. All cancerous specimens were well preserved before experiments were performed. Diagnoses were all made based on pathology. The main characteristics are summarized in Table 1.

Increased IDO1 expression and overall survival

Among the 24 eligible articles, the overall survival (OS) according to IDO1 expression was reported in 18 articles. The random-effects model was adopted to estimate the pooled HRs and corresponding 95% CIs. The results showed a small heterogeneity across studies ($I^2 = 46.0\%$, $P = 0.020$). The HR for the high IDO1 expression group versus the low IDO1 expression group was 2.03 (95% CI: 1.56-2.63) (Fig. 2A). After stratification by study type, the HRs for the high IDO1 expression group versus the low IDO1 expression group were 3.62 (95% CI: 2.19-5.97) in prospective studies and 1.74 (95% CI: 1.33-2.29) in retrospective studies (Fig. 2B). After

Fig. 1. Flowchart showing the literature search and selection process.

Table 1. Main characteristics of all included studies

First author	Publication year	Cancer type	Total number	Tumor stage	Follow-up (years)	Detection method	Outcome measure	Multivariate analysis	Treatment received	Study type
Mitsuka	2013	GLI	68	15/60 (I-II/III-IV)	Over 13	IHC	OS	Yes	Surgical resection	Retrospective study
Gao	2009	CRC	71	16/55 (I-II/III-IV)	Over 6	IHC	OS	Yes	Radical resection	Retrospective study
Inaba	2010	CC	112	67/45 (IIB/IIA-B)	10	IHC	OS DFS	Yes	Radical resection	Retrospective study
Ino	2006	EC	80	64/16 (I-II/III-IV)	Over 10	IHC	OS PFS	Yes	Surgical treatment	Retrospective study
Masaki	2017	HL	52	26/26 (I-II/III-IV)	10	IHC	OS PFS	Yes	Chemotherapy	Prospective study
Pan	2008	HCC	138	NR	Over 6	IHC	OS	Yes	Surgical treatment	Retrospective study
Soliman	2013	BC	203	92/92 (I-II/III-IV)	Over 15	IHC	OS	Yes	Surgical treatment	Retrospective study
Urakawa	2009	OSC	47	29/18 (IIA/IIIB)	Over 15	IHC	OS	Yes	Chemotherapy	Prospective study
Ye	2013	LSCC	187	78/109 (I-II/III-IV)	Over 5	IHC	OS DFS	Yes	Surgical treatment	Prospective study
Ben-Haj-Ayed	2016	NPC	71	10/53 (I-II/III-IV)	Over 6	IHC	OS DFS	Yes	No report	Prospective study
Brandacher	2006	CC	143	53/90 (I-II/III-IV)	Over 8	IHC	OS	Yes	Surgical resection	Retrospective study
Carvajal-Hausdorf	2017	BC	362	278/63 (I-II/III-IV)	Over 20	IF	OS	Yes	No report	Retrospective study
Inaba	2009	OC	60	38/22 (I-II/III-IV)	14	IHC	OS PFS	No	Surgical treatment	Retrospective study
Ino	2008	EC	65	50/15 (I-II/III-IV)	Over 10	IHC	PFS	Yes	Surgical treatment	Retrospective study
Jia	2015	ESCC	196	113/83 (I-II/III-IV)	5	IHC	OS	No	Surgical treatment	Retrospective study
Karanikas	2007	LC	28	19/9 (I-II/III-IV)	Over 10	qPCR	NR	NR	Surgical treatment	Retrospective study
Kim	2016	GC	243	161/82 (I-II/III-IV)	Over 10	IHC	DFS OS	NR	Surgical treatment	Retrospective study
Lamier	2011	OSCC	88	16/72 (I-II/III-IV)	Over 10	IHC	OS	Yes	Chemotherapy radiation therapy	Retrospective study
Liu	2017	NHL	57	28/29 (I-II/III-IV)	Over 7	IHC	OS	Yes	Chemotherapy	Prospective study
Ninomiyama	2011	HL	119	42/77 (I-II/III-IV)	Over 5	IHC	OS	Yes	Chemotherapy	Retrospective study
Riesenberg	2007	RCC	55	22/33 (I-II/III-IV)	Over 6	IHC	OS	Yes	Surgical treatment	Retrospective study
Sznurkowski	2011	vSCC	76	NR	Over 10	IHC	OS	Yes	Surgical treatment and radiotherapy	Retrospective study
Zhang	2011	ESCC	135	74/61 (I-II/III-IV)	Over 6	IHC	OS	No	Surgical treatment	Prospective study
Zhang	2013	GC	50	16/34	NR	IHC	NR	NR	Surgical treatment	Prospective study

Fig. 2. Forest plot of the HR for the relationship between high IDO1 expression and OS: (A) overall, (B) stratified by study type, (C) stratified by detection method, and (D) after exclusion of Riesenberg et al.

stratification by detection method, the HR for the high IDO1 expression group versus the low IDO1 expression group was 2.14 (95% CI: 1.58-2.90) in the immunohistochemistry subgroup (Fig. 2C). The results indicated that there was a significant difference in OS between the two groups. A significantly shorter OS was observed in patients with high IDO1 expression versus those with low IDO1 expression. Thus, we concluded that high expression of IDO1 was associated with poor OS.

Increased IDO1 expression and disease-free survival

Only 3 studies, comprising a total of 338 patients, provided appropriate data for analysis of disease-free survival (DFS). No severe statistical heterogeneity was observed across studies ($I^2 = 0\%$; $P_h = 0.784$). The fixed-effects model was applied to analyze the pooled HRs with their corresponding 95% CIs. The overall result indicated a significantly positive association between high expression of IDO1 and poor DFS (HR = 2.47, 95% CI: 1.46-4.20) (Fig. 3).

Associations between IDO1 expression and clinicopathological parameters

From the pooled results (Table 2), it was found that increased IDO1 was significantly associated with tumor differentiation (OR = 1.81, 95% CI: 1.05-3.12) (Fig. 4), distant metastasis (OR = 1.45, 95% CI: 1.02-2.06) (Fig. 5), and poor clinical stage (OR = 1.89, 95% CI: 1.13-3.17) (Fig. 6). However, no significant correlation was observed between increased IDO1 expression and age, sex, lymph node metastasis, and tumor size (data not shown). Because of the insufficient data, we failed to detect a relationship between overexpression of IDO1 and some other clinicopathological parameters.

Fig. 3. Forest plot of HR for the relationship between high IDO1 expression and DFS.

Table 2. Meta-analysis results of the associations of increased IDO1 expression with clinicopathological parameters

Clinicopathological parameter	Studies (n)	Number of patients	OR (95% CI)	P value (95% CI)	I ² (%)	P _h	Model
Age (<60 vs. >60 years)	8	850	1.15 (0.86-1.55)	0.352	25.3	0.227	Fixed-effects
Sex (male vs. female)	12	1191	1.27 (0.98-1.64)	0.071	26.5	0.184	Fixed-effects
TNM stage (III-IV vs. I-II)	14	1629	1.89 (1.13-3.17)	0.015	76.5	0.000	Random-effects
Lymph node metastasis (yes vs. no)	12	1475	1.56 (0.84-2.89)	0.157	78.9	0.000	Random-effects
Tumor differentiation (moderate/poor vs. well)	9	1014	1.81 (1.05-3.12)	0.033	66.6	0.002	Random-effects
Tumor size (>5 vs. <5 cm)	4	376	1.43 (0.57-3.57)	0.446	74.6	0.008	Random-effects
Distant metastasis (yes vs. no)	7	738	1.45 (1.02-2.06)	0.039	14.6	0.318	Fixed-effects

Fig. 4. Forest plot of OR for the relationship between high IDO1 expression and TNM: (A) stratified by study type, and (B) stratified by detection method.

Fig. 5. Forest plot of OR for the relationship between high IDO1 expression and tumor differentiation: (A) stratified by study type, and (B) stratified by detection method.

Fig. 6. Forest plot of OR for the relationship between high IDO1 expression and distant metastasis: (A) overall, and (B) stratified by study type.

Sensitivity analysis

For meta-analysis of the association between the IDO1 expression level and OS, sensitivity analysis was performed by removing each study in turn from the pooled analysis. This process aimed to assess the influence of the removed data set on the overall HRs. The result was not significantly influenced by the exclusion of any study, indicating the robustness of the results.

Publication bias

For meta-analysis of the association between IDO1 expression levels and OS, Begg's Test and Egger's test were adopted to test for publication bias. The results showed no publication bias among the included studies (Fig. 7).

Fig. 7. Publication bias results for OS.

Discussion

Tumor immune escape plays an important role in the development and metastasis of tumors [35]. Multiple immunosuppressive mechanisms in the tumor microenvironment can impair the functions of tumor-infiltrating lymphocytes. One of these immunosuppressive mechanisms is mediated by the IDO enzyme [27]. In 1998, Munn et al. found that IDO1 could prevent fetus rejection by allowing maternal-fetal immune tolerance in the mouse placenta [36]. Subsequent studies showed that a local depletion of tryptophan and the accumulation of toxic downstream products mediated by IDO1 could affect T-cell proliferation, metabolism, and functions [6, 37]. Moreover, IDO1 was also expressed in tumor cells as well as in various non-tumor cells in the tumor microenvironment, such as fibroblasts, endothelial cells, eosinophils, dendritic cells, and macrophages [2, 38, 39]. In addition, the expression of IDO by tumor cells can result in a decrease in the number of tumor-infiltrating lymphocytes in various tumors [40]. Many studies subsequently demonstrated that the expression of IDO1 in tumors was associated with patients' clinical outcome [12-34]. However, the results were inconsistent. The expression of IDO1 predicted a poor clinical outcome in many tumors, such as ovarian adenocarcinomas, colorectal adenocarcinomas, and endometrial and esophageal cancer [12-16]. In contrast, patients with high IDO1 expression in some tumors, such as RCC and hepatocellular carcinoma, have a longer survival [37]. The results of this meta-analysis showed a shorter OS in patients with high expression of IDO1 (HR = 2.03, 95% CI: 1.56-2.63). Furthermore, poorer DFS was observed in patients with high expression of IDO1 (HR = 2.47, 95% CI: 1.46-4.20), implying that the expression of IDO was a hazardous factor for the clinical outcome of cancer patients. Moreover, increased IDO1 was significantly associated with tumor differentiation (OR = 1.81, 95% CI: 1.05-3.12), distant metastasis (OR = 1.45, 95% CI: 1.02-2.06), and poor clinical stage (OR = 1.89, 95% CI: 1.13-3.17). This showed that more malignant tumor cells could express more IDO1, which promotes tumor development and metastasis.

However, there are some limitations to our meta-analysis. First, the total sample size was relatively small and we failed to detect a relationship between overexpression of IDO1 and some clinicopathological parameters. Second, there was some minor heterogeneity in our meta-analysis result. Subsequent regression analysis found that publication year and publication country were not associated with the heterogeneity (data not shown). Although the sensitivity analysis showing that the result was not significantly influenced by the exclusion of any study, we excluded a study by Riesenberger et al. [12] and found that the I^2 value fell from 46% to 11.9% (Fig. 2D), demonstrating that the heterogeneity is mainly due to this single study. This study was the only one of the included studies to show that the expression of IDO1 was associated with better OS in RCC patients, which may be why this study caused the heterogeneity. In Riesenberger et al. [12], the explanation for the association between IDO1 expression and improved survival in RCC is that IDO is nearly exclusively expressed in the endothelial cells of predominantly newly formed blood vessels, which limit the influx of tryptophan from the blood to the tumor or generate tumor-toxic metabolites, thus restricting tumor growth and contributing to survival. Thus, the location of IDO1 expression in different solid tumors may also result in the observed effects on patient survival. Third, many studies did not meet the inclusion criterion and were thus excluded, including some contradictory results, which may have caused a deviation of the result of this

meta-analysis. Fourth, the consistency of antibody staining and the cutoffs used to assign patients to high or low IDO1 expressions differed among studies, which may also influence the results of the meta-analysis. Fifth, prospective and retrospective studies are included together in this meta-analysis. A subgroup analysis of study types found that there was a slight difference between the results of the subgroup analysis and overall results, which may also cause a deviation of the result of this meta-analysis. Therefore, larger, multicenter, and higher-quality studies with a unified criterion for determining IDO1 expression are necessary to validate the results of this study.

Abbreviations

BC (breast cancer); CC (cervical cancer); CRC (colorectal cancer); EC (endometrial carcinoma); ESCC (esophageal squamous cell carcinoma); GC (gastric cancer); GLI (glioma); HCC (hepatocarcinoma); HL (Hodgkin's lymphoma); LC (lung cancer); LSCC (laryngeal squamous cell carcinoma); NLH (non-Hodgkin's lymphoma); OSC (osteosarcoma); NPC (nasopharyngeal carcinoma); OC (ovarian cancer); OSCC (oral squamous cell carcinoma); RCC (renal cell carcinoma); vSCC (vulvar squamous cell carcinoma); DFS (disease-free survival); PFS (progression-free survival); OS (overall survival); NR (not reported); IHC (immunohistochemistry); IF (immunofluorescence); qPCR (quantitative real-time polymerase chain reaction).

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Disclosure Statement

No conflicts of interest exist.

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