■ ORIGINAL ARTICLE ■

Prognostic Role of Claudin-1 Immunohistochemistry in Malignant Solid Tumors: A Meta-Analysis

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Background: Although the correlation between low claudin-1 expression and worse prognosis has been reported, details on the prognostic implications of claudin-1 expression in various malignant tumors remain unclear. The present study aimed to elucidate the prognostic roles of claudin-1 immunohistochemistry (IHC) in various malignant tumors through a meta-analysis. **Methods:** The study included 2,792 patients from 22 eligible studies for assessment of the correlation between claudin-1 expression and survival rate in various malignant tumors. A subgroup analysis based on the specific tumor and evaluation criteria of claudin-1 IHC was conducted. **Results:** Low claudin-1 expression was significantly correlated with worse overall survival (OS) (hazard ratio [HR], 1.851; 95% confidence interval [CI], 1.506 to 2.274) and disease-free survival (DFS) (HR, 2.028; 95% CI, 1.313 to 3.134) compared to high claudin-1 expression. Breast, colorectal, esophageal, gallbladder, head and neck, and lung cancers, but not cervical, liver or stomach cancers, were significantly correlated with worse OS. Breast, colorectal, esophageal, and thyroid cancers with low claudin-1 expression were associated with poorer DFS. In the lower cut-off subgroup (<25.0%) with respect to claudin-1 IHC, low claudin-1 expression was significantly correlated with worse OS and DFS. **Conclusions:** Taken together, low claudin-1 IHC expression is significantly correlated with worse survival in various malignant tumors. More detailed criteria for claudin-1 IHC expression in various malignant tumors are needed for application in daily practice.

Key Words: Claudin-1; Immunohistochemistry; Prognosis; Malignancy; Meta-analysis

Claudins comprise a large family of tetraspan trans-membrane proteins and are required for tight junction formation.[1] Claudin-1 expression is regulated by the β-catenin–T-cell factor/lymphoid enhancing factor signaling pathway.[2,3] Claudins have potentially different functions driven by the formation of homotypic or heterotypic interactions across the junction in various tissues.[4-8] The epithelial-to-mesenchymal transition, which is correlated with tumor invasiveness, is affected by the change of expression and the redistribution of tight junction proteins including claudin.[9] Expression patterns of claudins can differ by tumor or tissue type, which can affect tumor behavior and prognosis.[10] The prognostic roles of claudin-1 have been diverse in several studies involving various tumor types.[9,11-31] However, in stomach cancer, increased claudin-1 expression in tumor cells has been significantly correlated with worse prognosis in the intestinal type, but not in the diffuse type. In kidney and lung cancers, high claudin-1 expression has likewise been correlated with worse prognosis.[12,14] Although a correlation between low claudin-1

expression and worse prognosis has been reported, details on the prognostic implications of claudin-1 expression in various malignant tumors remain unclear.

To elucidate the prognostic role of claudin-1 immunohistochemistry (IHC), the correlation between claudin-1 IHC expression and survival rates was investigated in various malignant tumors. A subgroup analysis based on the evaluation criteria of claudin-1 IHC was conducted.

MATERIALS AND METHODS

Literature search and selection criteria

Relevant articles were obtained by searching the PubMed and MEDLINE databases through February 28, 2018. The search was performed using 'claudin-1' and 'survival' as search terms. The titles and abstracts of all returned articles were screened for exclusion. Review articles were also screened to find additional eligible studies. English language studies addressing claudin-1

IHC expression in human malignant tumors and the correlation between claudin-1 IHC expression and survival rate were included. Case reports were excluded. This meta-analysis did not require the approval of an institutional review board.

Data extraction

The following information was collected and verified from the full texts of eligible studies:[9,11-31] first author's name, publication date, study location, number of patients analyzed, antibody manufacturer, dilution ratio, cut-offs for assessing high claudin-1 IHC expression, tumor type, and data allowing estimation of the impact of claudin-1 IHC expression on overall survival (OS) and disease-free survival (DFS). We did not define a minimum number of patients to be included in a study. Any disagreements were resolved by consensus.

Statistical analyses

To perform the meta-analysis, all data were analyzed using the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA). Correlations between claudin-1 IHC expression and survival were measured by hazard ratios (HR) obtained from the eligible study data. We aggregated the estimated HR and its standard error using given parameters, which were the HR point estimate, log-rank statistic or its p-value, O–E statistic (difference between numbers of observed and expected events), or its variance.[32] If the extractable data only included the survival curve, two persons independently extracted survival rates to reduce reading variability, according to Parmar's recommendation.[32] Meta-analysis was performed using fixed-effects and random-effects models. The values pooled using the random effects model were utilized for interpretation. Subsequently, a study showing results of an estimated HR > 1, with a 95% confidence interval (CI) that does not include 1, implied poor survival with a low or a loss of claudin-1 expression. Because eligible studies used various antibodies and evaluation criteria, a random-effects model was more suitable than a fixed-effects model. Subgroup analyses based on specific organs and cut-off value for high expression of claudin-1 IHC were performed. In addition, heterogeneous and sensitivity analyses were conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect, respectively. Heterogeneity between studies was checked by the Q and I^2 statistics and demonstrated p-values. For assessment of publication bias, Begg's funnel plot and Egger's test were performed. The results were considered statistically significant when p < 0.05.

RESULTS

Selection and characteristics of studies

One hundred seventy reports were identified in the database search. Of these, 44 were excluded due to lack of sufficient information. Other studies were excluded because they reported the results of other diseases (n = 38), used animals or cell lines (n = 57), were not written in English (n = 5), or were non-original articles (n = 3) (Fig. 1). In addition, one article was excluded due to duplication. After applying the inclusion and exclusion criteria, 22 reports were finally included in the meta-analysis (Table 1). Eligible studies used various manufacturers' antibodies and variable dilution ratios, as shown in Table 1. The cut-off values to distinguish between low or high claudin-1 IHC expressions varied between 1% and 50%.

The correlation between claudin-1 IHC expression and survival

The correlation between low expression of claudin-1 IHC and survival was investigated by subdividing data according to OS in 15 studies and according to DFS in 15 studies. Low expression of claudin-1 IHC was significantly correlated with worse OS (HR, 1.851; 95% CI, 1.506 to 2.274) (Fig. 2A) and DFS (HR, 2.028; 95% CI, 1.313 to 3.134) (Fig. 2B). Eligible studies showed significant heterogeneity in OS and DFS. Sensitivity analysis showed that eligible studies had no effect on the pooled HR. In sensitivity analysis, the ranges of HRs were 1.745–1.917 and
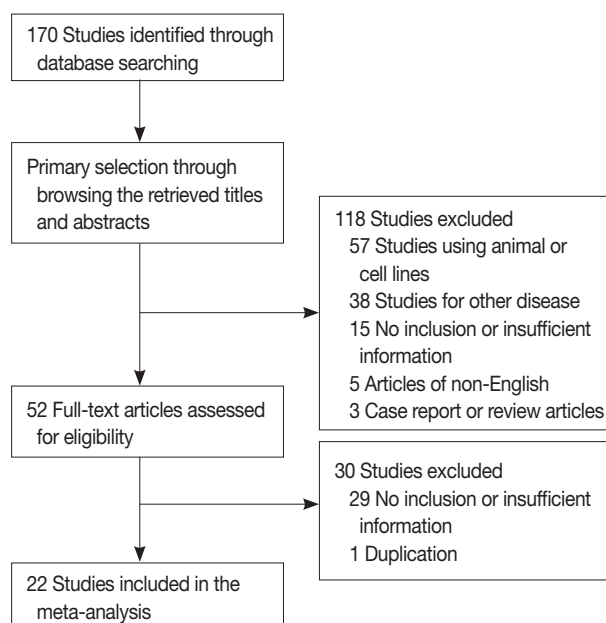
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│ 170 Studies identified through  │
│ database searching              │
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│ Primary selection through       │      │ 118 Studies excluded               │
│ browsing the retrieved titles   │─────▶│   57 Studies using animal or       │
│ and abstracts                   │      │      cell lines                    │
└─────────────────────────────────┘      │   38 Studies for other disease     │
              │                           │   15 No inclusion or insufficient  │
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              │                           │   5 Articles of non-English        │
              │                           │   3 Case report or review articles │
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│ 52 Full-text articles assessed  │      │ 30 Studies excluded                │
│ for eligibility                 │─────▶│   29 No inclusion or insufficient  │
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│ 22 Studies included in the      │
│ meta-analysis                   │
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Fig. 1. Flow chart for study search and selection methods.

Table 1. Main characteristics of eligible studies

Study	Location	Antibody company	Dilution	Cut-off value (%)	Organ	Tumor type	Claudin-1 expression, n (%)	
							Low	High
Ma et al. (2014)[19]	China	Zymed	1:50	10	Breast	-	96 (55.5)	77 (44.5)
Morohashi et al. (2007)[23]	Japan	Zymed	1:50	10	Breast	-	104 (52.0)	96 (48.0)
Matsuoka et al. (2011)[20]	Japan	Spring Bioscience	ND	33.3	Colorectum	-	124 (79.5)	32 (20.5)
Resnick et al. (2005)[24]	USA	Zymed	1:125	ND[a]	Colorectum	-	32 (25.0)	96 (75.0)
Shibutani et al. (2013)[26]	Japan	Zymed	1:100	25	Colorectum	-	110 (32.0)	234 (68.0)
Yoshida et al. (2011)[30]	Japan	Zymed	1:400	30	Colorectum	-	92 (49.7)	93 (50.3)
Miyamoto et al. (2008)[22]	Japan	Zymed	1:100	10	Esophagus	SCC	11 (20.4)	43 (79.6)
Xiong et al. (2011)[29]	China	Fuzhou Maixin Biotech	ND	25	Gallbladder	-	37 (55.2)	30 (44.8)
Li et al. (2015)[18]	China	Beijing ZSGB-BIO	ND	40	H&N	SCC	26 (26.8)	71 (73.2)
Sappayatosok and Phattarataratip (2015)[25]	Thailand	Invitrogen	1:200	50	H&N	SCC	33 (73.3)	12 (26.7)
Fritzsche et al. (2008)[14]	Switzerland	Zymed	1:50	10	Kidney	Clear cell RCC	210 (75.5)	68 (24.5)
						Papillary RCC	6 (15.8)	32 (84.2)
Shin et al. (2011)[27]	Korea	Abcam	1:200	5	Kidney	Clear cell RCC	101 (84.9)	18 (15.1)
Bouchagier et al. (2014)[11]	Greece	Zymed	1:40	1[a]	Liver	HCC	9 (13.4)	58 (86.6)
Higashi et al. (2007)[15]	USA	Zymed	1:50	ND	Liver	HCC	28 (50.9)	27 (49.1)
Chae et al. (2014)[12]	Korea	Abcam	1:500	50	Lung	AdCa	ND	ND
Chao et al. (2009)[13]	Taiwan	Zymed	ND	ND	Lung	AdCa	34 (50.7)	33 (49.3)
Merikallio et al. (2011)[21]	Finland	Zymed	1:50	25	Lung	SCC	15 (12.1)	109 (87.9)
						AdCa	2 (20.0)	8 (80.0)
Zhang et al. (2013)[31]	China	Zymed	ND	10	Lung	AdCa	33 (40.7)	48 (59.3)
Huang et al. (2014)[9]	China	Zymed	1:100	5	Stomach	-	63 (36.4)	110 (63.6)
Jung et al. (2011)[17]	Korea	Lab Vision	1:200	25	Stomach	-	31 (43.1)	41 (56.9)
Tzelepi et al. (2008)[28]	Greece	Zymed	1:100	5	Thyroid	-	24 (26.4)	67 (73.6)
Hoellen et al. (2017)[16]	Germany	Thermo Fisher Scientific Inc.	ND	>0	Uterine cervix	SCC	14 (13.2)	92 (86.8)

ND, non-description; SCC, squamous cell carcinoma; H&N, head and neck; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; AdCa, adenocarcinoma.
[a]Using criteria for intensity.

1.869–2.324 in OS and DFS, respectively. There was no evidence of publication bias in Egger's test (p = .505 in OS and p = .956 in DFS) and no asymmetry in Begg's funnel plot.

We conducted subgroup analysis based on specific tumors. In OS, low expression of claudin-1 IHC was significantly correlated with a lower survival rate in breast, colorectal, esophageal, gallbladder, head and neck, and lung cancers, but not in cervical, liver, or stomach cancers (Table 2). In addition, there was significant correlation between low expression of claudin-1 IHC and worse DFS in breast, colorectal, esophageal, and thyroid cancers, but not in liver, lung, kidney, or stomach cancers (Table 2). However, in DFS of head and neck cancer, low claudin-1 IHC expression showed a reverse correlation (HR, 0.396; 95% CI, 0.160 to 0.765). The cancer with the highest HR was breast cancer in both OS (HR, 3.364; 95% CI, 1.898 to 5.961) and DFS (HR, 5.182; 95% CI, 3.749 to 7.162).

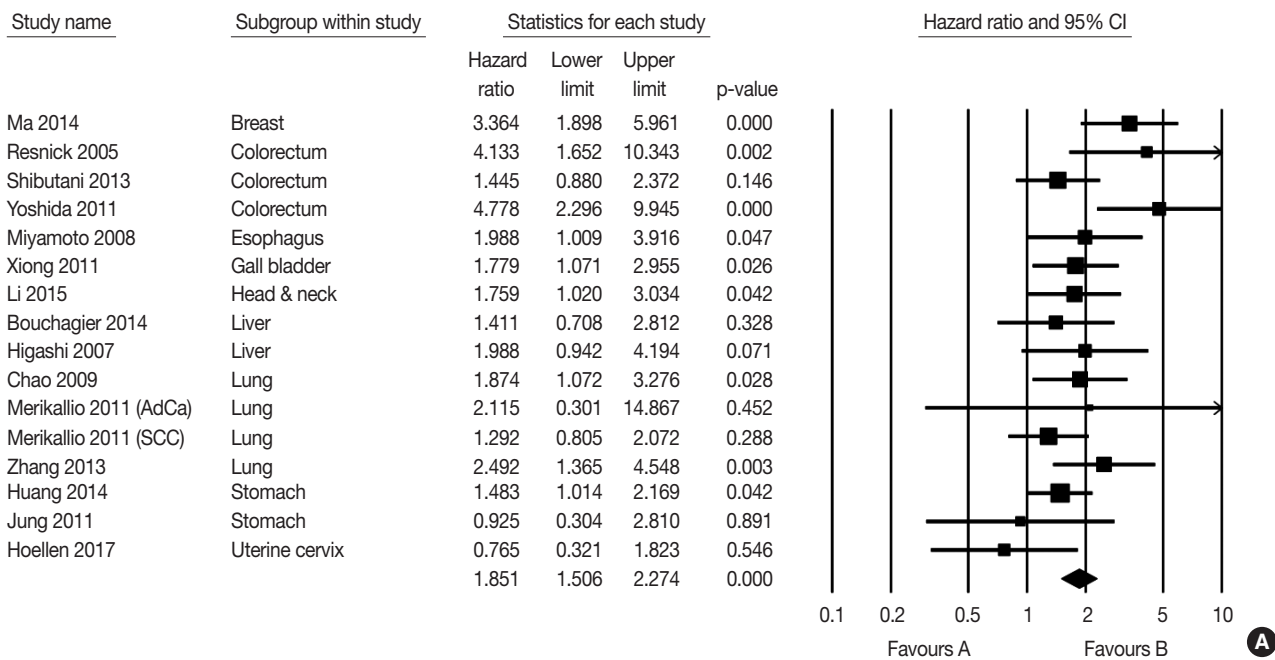Next, to evaluate the optimal criteria of low claudin-1 IHC expression, we created subgroups using the median value of cut-offs from eligible studies (25.0%). The results of subgroup analysis based on the evaluation criteria are shown in Fig. 3. In OS, HRs were 1.738 (95% CI, 1.251 to 2.415) and 1.805 (95% CI, 1.252 to 2.602) in the ≥ 25.0% and < 25.0% cut-off subgroups, respectively. In DFS, HRs were 1.492 (95% CI, 0.808 to 2.753) and 2.611 (95% CI, 1.218 to 5.597) in subgroups with the ≥ 25.0% and < 25.0% cut-offs, respectively.

DISCUSSION

While claudin-1 has been studied in various malignant tumors, the prognostic role of claudin-1 IHC has not been fully elucidated and may vary.[9,11-31] The current study is the first meta-analysis of published studies on the prognostic role of claudin-1 IHC in various malignant tumors.

Although 27 subtypes of claudin are currently known in human tissues,[33] the expressions and functions of claudins in malignant tumors are not fully understood. In tumor cells, claudin-1 partic-

Overall survival

Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	p-value	Hazard ratio and 95% CI
Ma 2014	Breast	3.364	1.898	5.961	0.000	
Resnick 2005	Colorectum	4.133	1.652	10.343	0.002	
Shibutani 2013	Colorectum	1.445	0.880	2.372	0.146	
Yoshida 2011	Colorectum	4.778	2.296	9.945	0.000	
Miyamoto 2008	Esophagus	1.988	1.009	3.916	0.047	
Xiong 2011	Gall bladder	1.779	1.071	2.955	0.026	
Li 2015	Head & neck	1.759	1.020	3.034	0.042	
Bouchagier 2014	Liver	1.411	0.708	2.812	0.328	
Higashi 2007	Liver	1.988	0.942	4.194	0.071	
Chao 2009	Lung	1.874	1.072	3.276	0.028	
Merikallio 2011 (AdCa)	Lung	2.115	0.301	14.867	0.452	
Merikallio 2011 (SCC)	Lung	1.292	0.805	2.072	0.288	
Zhang 2013	Lung	2.492	1.365	4.548	0.003	
Huang 2014	Stomach	1.483	1.014	2.169	0.042	
Jung 2011	Stomach	0.925	0.304	2.810	0.891	
Hoellen 2017	Uterine cervix	0.765	0.321	1.823	0.546	
		1.851	1.506	2.274	0.000	

0.1 0.2 0.5 1 2 5 10

Favours A   Favours B   (A)

Disease-free survival

Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	p-value	Hazard ratio and 95% CI
Ma 2014	Breast	4.354	2.667	7.106	0.000	
Morohashi 2007	Breast	5.930	3.853	9.127	0.000	
Matsuoka 2011	Colorectum	6.074	3.049	12.101	0.000	
Resnick 2005	Colorectum	3.979	1.663	9.518	0.002	
Shibutani 2013	Colorectum	1.881	1.259	2.812	0.002	
Yoshida 2011	Colorectum	2.323	1.313	4.110	0.004	
Miyamoto 2008	Esophagus	2.375	1.177	4.791	0.016	
Sappayatosok 2015	Head & neck	0.396	0.161	0.975	0.044	
Fritzsche 2008 (cRCC)	Kidney	0.607	0.373	0.987	0.044	
Fritzsche 2008 (cRCC)	Kidney	1.972	0.671	5.795	0.217	
Shin 2011	Kidney	1.412	0.645	3.093	0.388	
Higashi 2007	Liver	1.394	0.800	2.427	0.241	
Chae 2014	Lung	1.014	0.634	1.623	0.953	
Jung 2011	Stomach	0.838	0.395	1.778	0.645	
Tzelepi 2008	Thyroid	8.697	3.120	24.241	0.000	
		2.028	1.313	3.134	0.001	

0.1 0.2 0.5 1 2 5 10
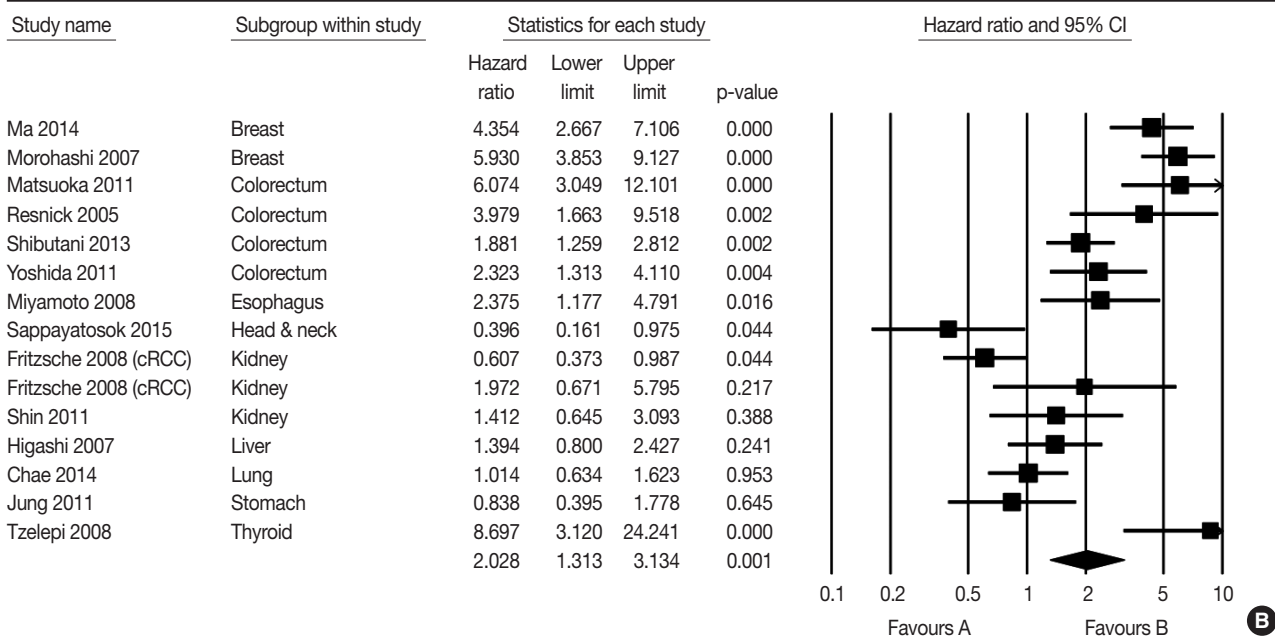
Favours A   Favours B   (B)

Fig. 2. Forest plot diagram showing the correlation between low claudin-1 immunohistochemical expression and overall survival (A) and disease-free survival (B).[9,11-31] CI, confidence interval.

ipates in the up-regulation of ZEB-1, which induces reduction of E-cadherin expression and leads to invasive activity.[34] Loss of claudin-1 expression might induce loosening of tight junctions, which would alter the cohesion and invasiveness of tumor cells.[1,7,8,35] Furthermore, by loosening tight junctions, diffusion

of nutrients and other growth factors may be increased in tumor cells, which could induce proliferation of tumor cells. Claudin-1 overexpression inhibits the dissociation of cancer cells and suppresses migration, invasion, and metastasis.[13,36] Claudin-1 can also be expressed in normal cells, but the function and expression

Table 2. Meta-analysis for the correlation between low claudin-1 expression and overall and disease-free survival

	No. of subset	Fixed effect (95% CI)	Heterogeneity test p-value	Random effect (95% CI)	Egger's test p-value
Overall survival					
Breast*	1	3.364 (1.898–5.961)	>.99	3.364 (1.898–5.961)	-
Cervix	1	0.765 (0.321–1.823)	>.99	0.765 (0.321–1.823)	-
Colorectum*	3	2.354 (1.618–3.425)	.013	2.906 (1.244–6.786)	.286
Esophagus*	1	1.988 (1.009–3.916)	>.99	1.988 (1.009–3.916)	-
Gallbladder*	1	1.779 (1.071–2.955)	>.99	1.779 (1.071–2.955)	-
Head and neck*	1	1.759 (1.020–3.034)	>.99	1.759 (1.020–3.034)	-
Liver	2	1.652 (0.995–2.742)	.508	1.652 (0.995–2.742)	-
Lung*	4	1.731 (1.275–2.350)	.391	1.731 (1.275–2.350)	.648
Stomach	2	1.411 (0.985–2.022)	.431	1.411 (0.985–2.022)	-
Disease-free survival					
Breast*	2	5.182 (3.749–7.162)	.353	5.182 (3.749–7.162)	-
Colorectum*	4	2.599 (1.963–3.441)	.025	3.012 (1.763–5.146)	.178
Esophagus*	1	2.375 (1.177–4.791)	>.99	2.375 (1.177–4.791)	-
Head and neck*	1	0.396 (0.160–0.765)	>.99	0.396 (0.160–0.765)	-
Liver	1	1.394 (0.800–2.427)	>.99	1.394 (0.800–2.427)	-
Lung	1	1.014 (0.634–1.623)	>.99	1.014 (0.634–1.623)	-
Kidney	3	0.866 (0.589–1.274)	.056	1.072 (0.510–2.254)	.133
Stomach	1	0.838 (0.395–1.778)	>.99	0.838 (0.395–1.778)	-
Thyroid*	1	8.697 (3.120–24.241)	>.99	8.697 (3.120–24.241)	-

CI, confidence interval.
*p<.05.
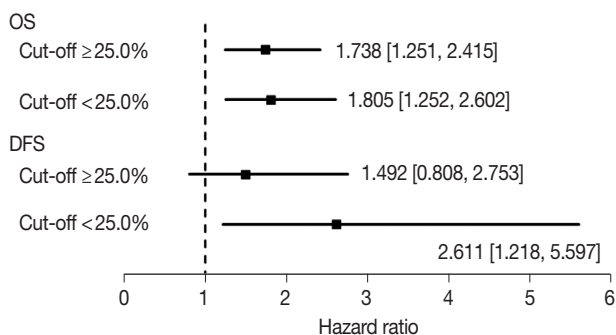
Fig. 3. Forest plot diagram for subgroup analysis based on cut-off value of low claudin-1 immunohistochemical expression. OS, overall survival; DFS, disease-free survival.

pattern of claudin-1 might vary in different organs. More studies are needed to clarify the potential gamut of functions.

In the present meta-analysis, low expression of claudin-1 IHC was significantly correlated with worse OS and DFS in human malignant tumors (HR, 1.851; 95% CI, 1.506 to 2.274 and HR, 2.028; 95% CI, 1.313 to 3.134, respectively). Unlike the results of most reports showing the correlation between low expression of claudin-1 IHC and a lower survival rate, inverse correlations or no correlations were found in stomach cancer, clear renal cell carcinoma, and lung adenocarcinoma. Among eligible studies with stomach cancers, Huang et al. reported that low claudin-1 expression was significantly correlated with better survival rate.[17]

The prognostic role of claudin-1 was different between intestinal and diffuse types of gastric cancer.[10] In addition, in meta-analysis for clear cell renal cell carcinoma, the estimated HR was 0.873 (95% CI, 0.385 to 1.981; p = .746).[14,27] However, the estimated HR of papillary renal cell carcinoma was 1.972 (95% CI, 0.671 to 5.795), but there was no statistical significance (p = .217). Although low claudin-1 IHC expression was significantly correlated with poor prognosis in lung cancer, significant correlation was found in adenocarcinoma, but not squamous cell carcinoma.[12,13,21,31] Cancers with an HR exceeding 1 in both OS and DFS were breast, colorectal, and esophageal cancers.

This meta-analysis included studies using IHC for the evaluation of claudin-1 expression. The rate of low claudin-1 IHC expression ranged from 15.8% to 84.9%, which varied according to specific tumor type. Various cut-off values (1%–50%) were used in eligible studies; therefore, the rates of low or high claudin-1 IHC expression could be largely affected by the cut-off value. Consequently, this discrepancy might affect the correlation between claudin-1 IHC expression and survival rate. In addition, discrepancies between investigators were possible concerning the rates of low claudin-1 IHC expression. Detailed evaluations, such as subgroup analysis based on median cut-off values, were required to elucidate the cause of the large difference between eligible studies. In OS, the HR of cases with low claudin-1 IHC expression was significantly higher in both cut-off subgroups (Fig. 3).

However, in the higher cut-off value subgroup, low claudin-1 IHC expression was not significantly correlated with worse DFS (HR, 1.492; 95% CI, 0.808 to 2.753). Our results suggest that a lower cut-off value might be more suitable for evaluation of low claudin-1 expression rather than a higher cut-off value. However, further studies based on specific tumor types will be needed to elucidate the effect of cut-off value on the correlation with survival.

There are a number of limitations in the current study. First, the study investigated the correlation between claudin-1 expression and prognosis in various malignant tumors. Although several studies have reported the prognostic roles of claudin-1, they were limited in their interpretive value because of the small number of studies for specific tumor types. Interestingly, in head and neck cancer, the prognostic roles of low claudin-1 IHC expression were different between OS and DFS.[18,25] The discrepancy between included studies could not be found due to the small number of studies. Second, the adequate antigenicity of included tissues in eligible studies could not be guaranteed due to the use of old specimens in some studies. Whether the low expression of claudin-1 reflected this problem could not be determined in the present study. Third, to avoid bias from follow-up periods, survival data were extracted at a 60-month follow-up. This follow-up period had no effect on the correlation between claudin-1 expression and survival in the present study, and the correlation between claudin-1 expression and survival could differ from those in previous reports.

In conclusion, low claudin-1 expression was significantly correlated with lower survival rates in various malignant tumors. Lower criteria for claudin-1 IHC expression could be suitable for prediction of a patient's prognosis. More detailed criteria for claudin-1 IHC expression in various malignant tumors is needed for application of claudin-1 IHC expression in daily practice.

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Funding acquisition: WJC.
Investigation: NYK.
Methodology: JSP, WJC.
Writing—original draft: JSP, NYK.
Writing—review & editing: JSP, WJC.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

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