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LAMC2 as a prognostic biomarker in human cancer: a systematic review and meta-analysis

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ABSTRACT

Objectives Accumulating evidence suggested that the laminin γ2 (LAMC2) expression level was upregulated in various cancers. However, the potential prognostic value of LAMC2 in cancers remains unclear. We conducted a meta-analysis to clarify the association of LAMC2 expression

with prognosis.

Method We searched Embase, Web of Science, and PubMed through 25 November 2021 to collect all eligible studies, and meta-analysis was performed to interpret the association of LAMC2 expression with clinicopathological parameters, overall survival (OS) disease-specific survival (DSS), and progression-free survival (PFS).

Results Seven studies were included finally. We found that increased LAMC2 expression was significantly associated with lymph node metastasis (Log odds ratio [OR]: 0.88, 95% confidence interval [CI]: 0.38-1.38, p = 0.00), tumor-node-metastasis stages (Log OR: 0.95, 95% CI: 0.39-1.50, P = 0.00), and tumor status (Log OR: 1.26, 95% CI: 0.84-1.68, p = 0.00), but not with age (Log OR: -0.05, 95% CI: -0.37-0.27, p = 0.75) or gender (Log OR: -0.07, 95% CI: -0.52-0.38, p = 0.75). In addition, higher LAMC2 expression was found to be significantly associated with OS/PFS/DSS (HR: 1.85, 95% CI: 1.31-2.40, p = 0.00). A similar result was found from The Cancer Genome Atlas (TCGA) database.

Conclusion Our results suggested that higher LAMC2 expression was correlated with worse survival. This study was subject to inherent limitations, but the results presented here provided insights regarding the potential use of LAMC2 as a biomarker for human cancer.

Study registration researchregistry.com (researchregistry1319).

Strengths and limitations of this study

This systematic review and meta-analysis provides a comprehensive literature published up to November 2020 was performed in Embase, Web of Science, and PubMed.

This study adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide

lines.

Additional data sources such as grey literature were not searched.

KEY WORDS

Cancer, Laminin γ2 (LAMC2), Meta-analysis, Prognosis

INTRODUCTION

Laminins are trimeric proteins composed of α, β, and γ chains which are the main component of basement membranes.[1] Mammalian genomes encode five α chains, four β chains, and three γ chains.[2] Loss-of-function studies show that most laminin mutants are embryonic lethal.[3] Laminins are involved in various biological processes, including cellular phenotype maintenance, adhesion, migration, growth, and differentiation *in vivo* and *in vitro*.[4, 5]

In recent years, laminin γ2 (LAMC2) has attracted increasingly attractive because of the aberrant expression of LAMC2 in various cancer. The LAMC2 expression was significantly upregulated in colorectal cancer tissues compared with adjacent normal tissues and high LAMC2 expression is known to be associated with poor patient prognosis.[6] Furthermore, overexpression of LAMC2 has been reported in pancreatic ductal adenocarcinoma,[7-10] non-small cell lung cancer,[11] penile squamous cell carcinoma,[12] ovarian cancer,[13] Oral tongue squamous cell carcinoma,[14] Cholangiocarcinoma,[15] esophageal squamous cell carcinoma,[16] leading to poor clinicopathological features and short survival time.

However, individual studies may be inadequate and inaccurate due to their small sample and study design. To date, there was no meta-analysis has been performed to investigate the relationship between LAMC2 and the prognostic value. Therefore, we performed a comprehensive meta-analysis to assess the correlation between LAMC2 and survival outcomes and clinicopathological features in human cancers.

METHODS

This study was followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[17] (online supplemental table S1). and the protocol was published on Research Registry (researchregistry1319).

Search strategy

A literature search was conducted in Embase, Web of Science, and PubMed through 25 November 2021. The keywords were (laminin C2 OR LAMC2 OR laminin subunit gamma 2) AND (prognosis OR prognostic OR survival). The reference lists and citation sections of relevant studies were also screened for additional eligible studies.

Study selection

Studies that met the following criteria were included in the meta-analysis: (1) study of the relationship between LAMC2 and prognosis of cancers, (2) patients were divided into two groups: high LAMC2 expression and low LAM2 expression group, and (3) associations of LAMC2 expression with overall survival and clinicopathologic features were described. The exclusion

criteria in our meta-analysis were as follows: (1) case reports, letters, reviews, editorials, and expert opinions, (2) studies published non-English language, (3) non-human studies, and (4) studies without sufficient available data.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) criteria was used to assess the quality of the eligible studies.[18] The NOS contains nine items that include selection, comparability, and outcome for studies. When the NOS score was ≥ 6, the study was considered high quality.

Data extraction

Two authors (T.F. and Z.-S.Y.) performed the data extraction independently. Disagreements were resolved by discussion and consensus with the third author (J.X.). The following information from the included studies was collected: the first author's name, publication year, country, number of cases, cancer type, the detection method of LAMC2, clinicopathological features, and survival outcome. When multivariate and univariate analyses were simultaneously reported, only the former was extracted. If studies only provided Kaplan-Meier curves, the survival data were extracted from the graphical curve and calculated HR and 95% CI were reckoned using the published method.[19]

Public data and tools

The web-based tool named Gene Expression Profiling Interactive Analysis (GEPIA) was used to analyze associations between LAMC2 and clinical outcomes.[20]

Statistical analysis

We used Stata MP 16 software (Stata, College Station, TX) to perform statistical analysis. Log odds ratio (OR) and 95% confidence interval (CI) were calculated for the association LAMC2 expression and clinicopathological characteristics. The prognostic role of LAMC2 expression in overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) was evaluated through HR with 95% CI. The statistical heterogeneity among the studies was analyzed by using I^2 test and Q test. When significant heterogeneity ($I^2 \geq 50\%$, $p < 0.05$) was observed, the random-effects model was chosen. Otherwise, the fixed-effects model was used. The Egger's test and Begg's test were used to assessing the potential publication bias. We conducted a sensitivity analysis to explore the stability of the overall meta-analysis results. $p < 0.05$ was considered as statistically significant.

RESULTS

Study identification and characteristics

As is shown in Figure 1, a total of seven studies with 1,056 patients with cancer were included in this meta-analysis satisfied the inclusion criteria.[6, 7, 15, 16, 21-23] The publication period ranged from 2017-2021. All of our included studies had high quality with Newcastle-Ottawa Quality Assessment Scale scores $\geqslant$ 6. The included studies addressed six different cancer types: esophageal squamous cell carcinoma (n = 1), pancreatic ductal adenocarcinoma (n = 2), cholangiocarcinoma (n = 1), papillary thyroid cancer (n = 1), colorectal cancer (n = 1), and penile squamous cell carcinoma (n = 1). The main characteristics of the seven studies are summarized in

Table 1.

Table 1 Characteristics of studies included in this meta-analysis

Study	Year	Region	Sample	Cancer	Method	Outcome	NOS score
Okada et al.	2021	Japan	114	pancreatic ductal adenocarcinoma	qRT-PCR	OS	8
Okada et al.	2021	Japan	121	pancreatic ductal adenocarcinoma	qRT-PCR	OS	8
Pei et al.	2019	China	121	cholangiocarcinoma	IHC	-	7
Liang et al.	2018	China	64	esophageal squamous cell carcinoma	qRT-PCR	OS	7
Zhan et al.	2019	China	473	papillary Thyroid Cancer	RNA-seq	PFS	6
Zhou et al.	2018	China	114	penile squamous cell carcinoma	IHC	DSS	7
Huang et al.	2017	China	49	colorectal cancer	IHC	-	6

Abbreviations: DSS, disease-specific survival; IHC, immunocytochemistry; NOS, Newcastle-Ottawa scale; OS, overall survival; PFS, progression-free survival; qRT-PCR, quantitative real-time polymerase chain reaction.

Relationship between LAMC2 expression and clinicopathological parameters

We evaluated the relationship between LAMC2 expression and clinicopathological parameters in various cancers. As shown in Figures 2A and B, there were three and six studies describing patients of age and gender, respectively. The pooled analysis demonstrated that there was no significant association between LAMC2 expression and age or gender. High expression of LAMC2 was significantly associated with lymph node metastasis (LNM) (Log OR: 0.88, 95% CI:

0.38-1.38, p = 0.00, Figure 2C) and tumor-node-metastasis (TNM) stage (Log OR: 0.95, 95% CI: 0.39-1.50, p = 0.00, Figure 2D). There was significant heterogeneity among these studies (I^2 = 59.61%, P = 0.02; I^2 = 60.16%, p = 0.03), and thus the random-effects DerSimonian-Laird model was adopted. A total of four studies evaluated tumor status according to LAMC2 expression. No statistically significant heterogeneity was found among the studies (I^2 = 36.00%, p = 0.20); thus, the fixed-effect Mantel-Haenszel model was adopted. As shown in Figure 2E, high expression of LAMC2 was significantly associated with tumor status (Log OR: 1.26, 95% CI: 0.84-1.68, p = 0.00). This finding suggests that high LAMC2 expression is associated with clinicopathological features.

Relationship between LAMC2 expression and OS/PFS/DSS

There were five studies including 872 patients presenting the relationship between LAMC2 and OS/PFS/DSS. Due to no significant heterogeneity being found among studies (I^2 = 0.00%, p = 0.83), the fixed-effect inverse-variance model was adopted to estimate the pooled HR and 95% CI. The pooled HR indicated that the expression of LAMC2 was negatively associated with OS/PFS/DSS (HR: 1.85, 95% CI: 1.31-2.40, p = 0.00, Figure 3A), which demonstrated that LAMC2 was a risk factor for the prognosis of cancer patients. In addition, sensitivity analysis was performed to determine the effect of individual studies on the OS/PFS/DSS. It revealed that no single study altered the pooled LAMC2 HR result significantly (Figure 3B). This suggested that the result of the meta-analysis was stable.

Analysis of publication bias

Funnel pot (Figure 3C), Begg's test, and Egger's linear regression test (Figure 3D) were used to assess publication bias. The results showed that the funnel plots scatter symmetrically. The statistical tests showed *P* values were greater than 0.05 (Begg's test: $p = 0.4624$; Egger's test: $p = 0.329$). Thus, there was no obvious publication bias in prognostic meta-analysis.

Validation of TCGA data set results

To validate our result, we retrieved LAMC2 expression data and clinical data from the TCGA dataset. As shown in Figure 4A, LAMC2 was increased in colon adenocarcinoma (COAD), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), lung adenocarcinoma (LUAD), and lung squamous cell carcinoma (LUSC), determined using a log2FC cutoff of 1 and a p-value cutoff of 0.01. A total of 9502 patients with urinary, digestive, female reproductive, respiratory, and blood systems cancers were included in the survival analysis from the TCGA database. According to the expression of LAMC2, the patients were divided into high and low groups using the median score as the cutoff by GEPIA [20]. The results showed that higher LAMC2 expression was correlated with worse survival (Figure 4B). We also explored the prognostic role of LAMC2 in different cancer types. As shown in Figure 5, LAMC2 expression was significantly associated with OS in LUAD (Figure 5A), mesothelioma (MESO, Figure 5C), skin cutaneous melanoma (SKCM, Figure 5D), HNSC (Figure 5E), and brain lower grade glioma (LGG, Figure 5F). However, LAMC2 expression was not related to OS in LUSC (Figure 5B).

DISCUSSION

Laminins are involved in various cancer development and prognosis.[24, 25] Increasing evidence suggests that the various laminin isoforms could be useful biomarkers of cancer diagnosis and might be potential therapeutic targets for cancers treatment, such as LAMA5,[26] LAMB1,[27] and LAMC1,[28] LAMC2 is encoding by Laminin γ2 and has been confirmed as a therapeutic target for cancers. Here we performed a meta-analysis of seven studies to achieve a comprehensive evaluation between higher LAMC2 expression and clinicopathological characteristics in various cancer types. Our results showed that higher LAMC2 expression was significantly associated with LNM, TNM stage, and tumor status. However, there was no significant association between LAMC2 expression and age or gender. Simultaneously, we also found that OS/PFS/DSS was higher in patients with low LAMC2 expression. Publication bias analysis demonstrated that no publication bias was observed among the included studies. These results suggested that LAMC2 might be a valuable biomarker for predicting prognosis in cancer patients.

Several kinds of research have shown that LAMC2 promotes cancer cells proliferation, motility, and invasion. However, the specific mechanism remained uncertain. ZNF750 inhibited the migration of esophageal squamous cancer cells by inhibiting the LAMC2 transactivation.[29] In hepatocellular carcinoma (HCC), LAMC2 has been found regulated by miR-548c-3p and inhibited the epithelial-mesenchymal transition in HCC.[30] In pancreatic cancer cells, LAMC2 promoted Akt-Ser473 phosphorylation and increased expression and cell membrane accumulation of NHE1, promoting cells migration and invasion.[31] A study by Wu et al. showed that the LAMP3-LAMC2-TNC signal regulated the efficacy of radiation exposure in laryngeal squamous cell carcinoma.[32] High-throughput sequencing results showed that miR-338-5p/3p target LAMC2

to suppress invasion in salivary adenoid cystic carcinoma cells.[33] LAMC2 was found to promote tumor progression by EGFR signaling.[34, 35] These findings suggested that LAMC2 might play as an oncogene and predict prognosis in cancer patients.

Recent researches have also investigated LAMC2 as a valuable biomarker of cancer diagnosis.[36, 37] Due to a limitation of a small sample size, we explored the expression of LAMC2 in various cancer types using the TCGA database. The results showed that LAMC2 was upregulated in tumors and might be used as a biomarker for a variety of tumor types. Moreover, we explore the survival analysis from the TCGA database. The results demonstrated that higher LAMC2 expression was associated with poor OS in 9502 patients. We also explored the prognostic role of LAMC2 in different types of cancer. LAMC2 expression was significantly associated with OS in LUAD, MESO, SKCM, HNSC, and LGG, but not in LUSC. This deserves further investigation.

Some potential limitations of our study should be noted. First, only seven articles were included in our meta-analysis, the limited number of studies might influence the reliability of the results. Of the seven included studies, five were from China, and two were from Japan. So, our results may only be applicable to the Asian population. Although we determined data from the TCGA database, future studies from non-Asian populations are needed to confirm our findings. Second, there was no consensus on a cutoff value for higher LAMC2 expression. Third, in some researches, the data for HR and 95% CI value was not provided. Although we tried our best to extract the HR and 95% CI value from the Kaplan-Meier curve, some errors are inevitable. Fourth,

the numbers of patients and tumor types included in this meta-analysis were still limited. So, our results may exaggerate the prognostic value of LAMC2.

CONCLUSIONS

In conclusion, LAMC2 may be a valuable biomarker for cancer diagnosis, and upregulation of LAMC2 is associated with a poor prognosis in cancer patients. For future clinical application, more high-quality studies with large sample sizes are needed to confirm the role of LAMC2 in various cancers and regions.

Acknowledgments

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Contributors

T.F and Z.-S.Y designed the study; F.T and J.X searched the literature and extracted data; Z.-S.Y and T.F analyzed data; Z.-S.Y prepared the figures; Z.-S.Y, J.X.-L and Z.G. wrote the manuscript. All authors gave the final approval of the paper to be published.

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Competing interests

The authors declare that they have no conflict of interest.

Patient and Public Involvement

No patient involved.

Patient consent for publication

Not applicable.

Ethics approval

This study does not involve human participants.

Data availability statement

All data relevant to the study are included in the article.

Abbreviations

CI, confidence interval; COAD, colon adenocarcinoma; DLBS, lymphoid neoplasm diffuse large B-cell lymphoma; DSS, disease-specific survival; ESCA, esophageal carcinoma; GEPIA, gene expression profiling interactive analysis; HCC, hepatocellular carcinoma; HNSC, head and neck squamous cell carcinoma; HR, hazard ratio; IHC, immunocytochemistry; LAMC2, laminin subunit gamma 2; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; NOS, Newcastle-Ottawa Quality Assessment Scale; OR, odds ratio; OS, overall survival; PFS, progression-free survival; qRT-PCR, quantitative real-time polymerase chain reaction; RNA-seq, RNA sequencing; SKCM, skin

cutaneous melanoma; TCGA, The Cancer Genome Atlas; TNM, tumor-node-metastasis.

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Figure legends

Figure 1 Flow diagram of the literature search and selection

Figure 2 Forest plots of studies evaluating the relationship between LAMC2 expression and clinicopathological features

(**A**) LNM, (**B**) TNM stage, (**C**) tumor status, (**D**) gender, (**E**) age.

Figure 3 The relationship between LAMC2 expression and OS/PFS/DSS

(**A**) Forest plot for the meta-analysis of OS/PFS/DSS. (**B**) Sensitivity analysis for LAMC2 expression with OS/PFS/DSS. (**C**) Funnel plot for the meta-analysis of OS/PFS/DSS. (**D**) Egger's graph for analyzing publication bias.

Figure 4 The expression of LAMC2 in the TCGA database

(**A**) LAMC2 expression in COAD, DLBC, ESCA, HNSC, LUAD, and LUSC. * = p value < 0.01. (**B**) OS rate of LAMC2 expression in TCGA database (n = 9502). Gray boxes indicate normal, and red boxes indicate tumor. T, tumor; N, normal.

Figure 5 Kaplan-Meier curves showing the prognostic value of LAMC2 in the TCGA database

(**A**) LUAD, (**B**) LUSC, (**C**) MESO, (**D**) SKCM, (**E**) HNSC, (**F**) LGG. *p* values were calculated using the log-rank test.

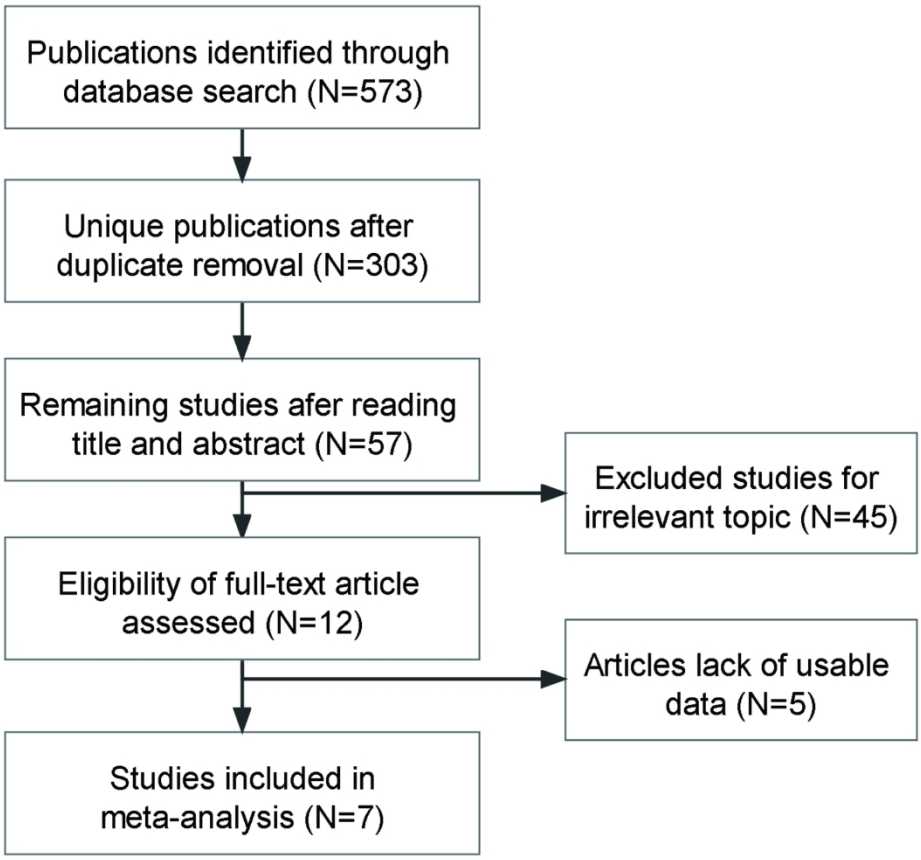

Figure1

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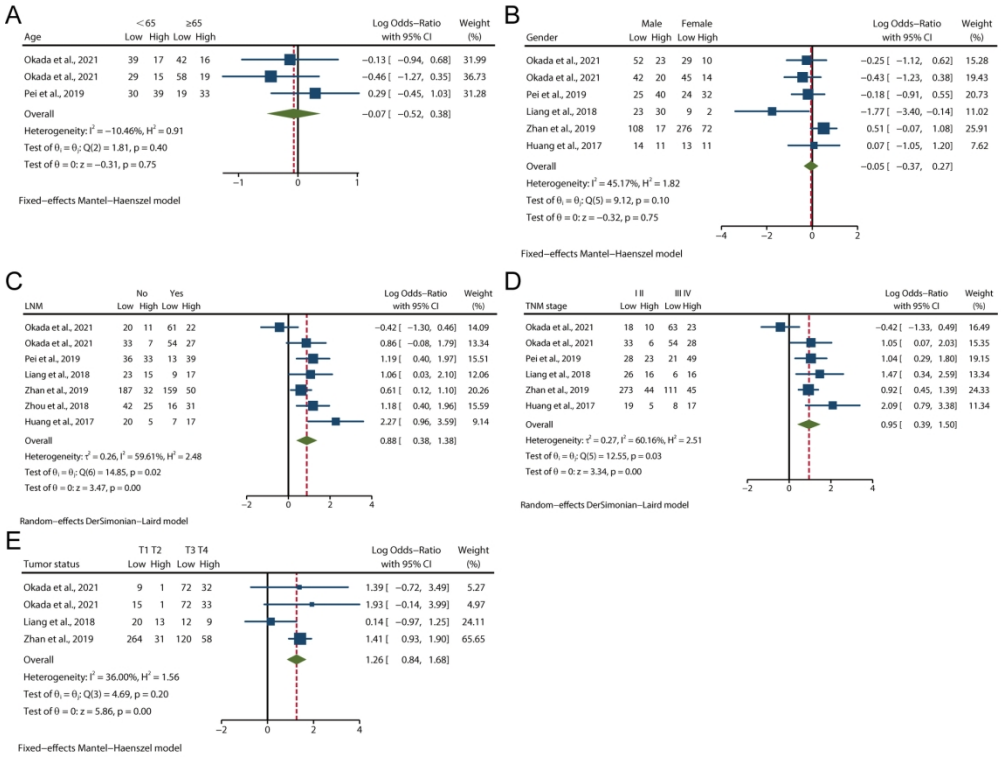

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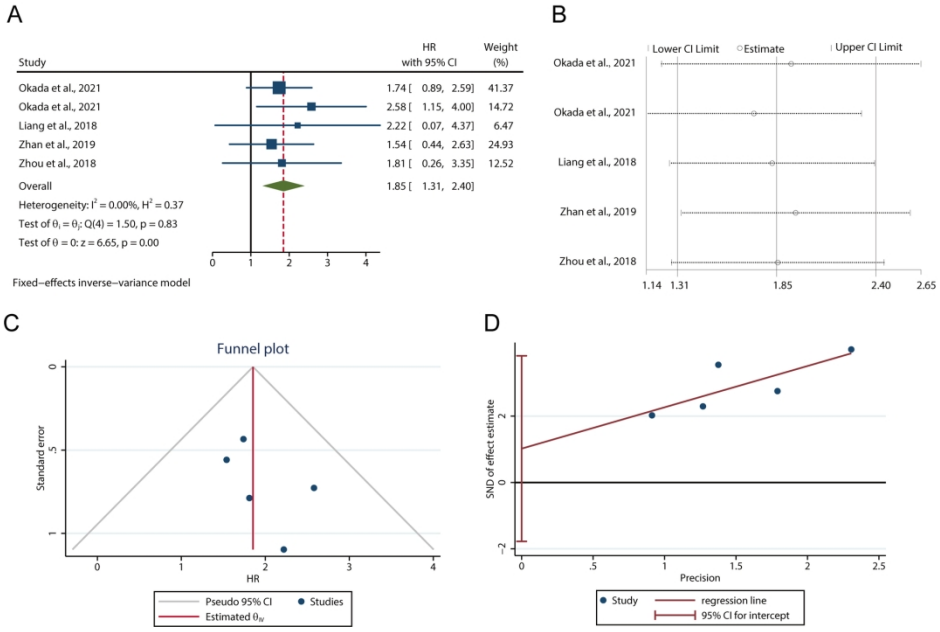

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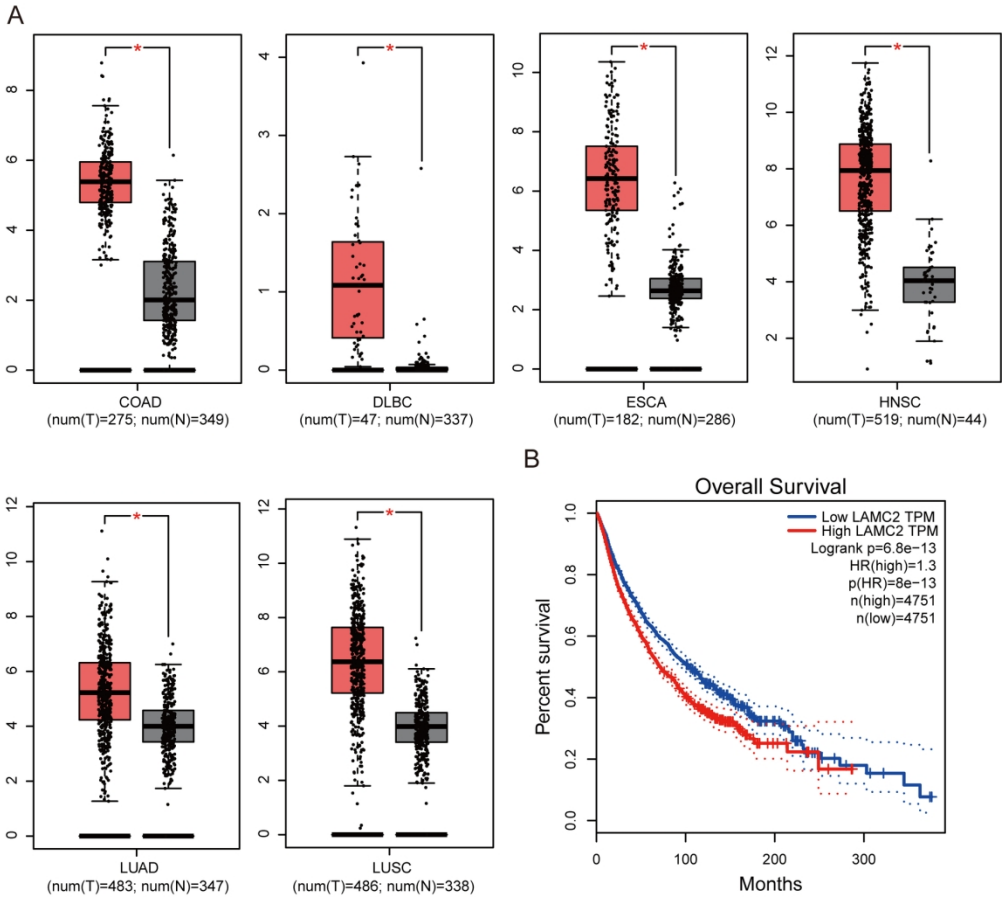

Figure4

166x148mm (300 x 300 DPI)

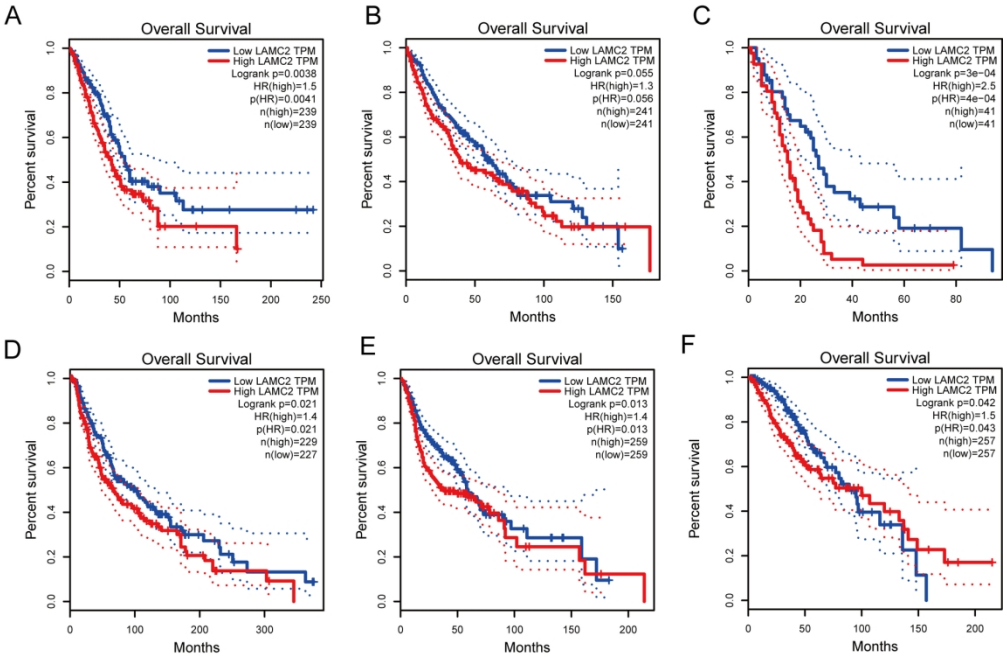

Figure5

162x106mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Page 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9
	23b	Discuss any limitations of the evidence included in the review.	Page 11
	23c	Discuss any limitations of the review processes used.	Page 11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 12
Competing interests	26	Declare any competing interests of review authors.	Page 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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LAMC2 as a prognostic biomarker in human cancer: a systematic review and meta-analysis

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ABSTRACT

Objectives Accumulating evidence suggested that the laminin γ2 (LAMC2) expression level was

upregulated in various cancers. However, the potential prognostic value of LAMC2 in cancers remains unclear. We conducted a meta-analysis to clarify the association of LAMC2 expression with prognosis.

Design We searched Embase, Web of Science, and PubMed (up to 25 November 2021) to collect all eligible studies, and meta-analysis was performed to interpret the association of LAMC2 expression with clinicopathological parameters, overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS).

Eligibility criteria for including studies We included studies that investigate the relationship between LAMC2 and prognosis of cancers, patients were divided into two groups, and associations of LAMC2 expression with clinicopathologic features were described.

Results Seven studies were finally included. We found that increased LAMC2 expression was significantly associated with lymph node metastasis (Log odds ratio [OR]: 0.88, 95% confidence interval [CI]: 0.38-1.38, p <0.001), tumor-node-metastasis stages (Log OR: 0.95, 95% CI: 0.39-1.50, p <0.001), and tumor status (Log OR: 1.26, 95% CI: 0.84-1.68, p <0.001), but not with age (Log OR: -0.05, 95% CI: -0.37-0.27, p =0.75) or gender (Log OR: -0.07, 95% CI: -0.52-0.38, p =0.75). In addition, higher LAMC2 expression was found to be significantly associated with OS/PFS/DSS (Hazard ratio [HR]: 1.85, 95% CI: 1.31-2.40, p <0.001). A similar result was found in The Cancer Genome Atlas database. High LAMC2 expression was significantly associated with OS in lung adenocarcinoma, mesothelioma, skin cutaneous melanoma, neck squamous cell carcinoma, and brain lower grade glioma.

Conclusion Our results suggested that higher LAMC2 expression was correlated with worse survival, lymph node metastasis, tumor-node-metastasis stages, and tumor status. This study was

subject to inherent limitations, but the results presented here provide insights regarding the potential use of LAMC2 as a biomarker for human cancer.

Study registration researchregistry.com (researchregistry1319).

Strengths and limitations of this study

This systematic review and meta-analysis provide comprehensive literature published up to November 2020 was performed in Embase, Web of Science, and PubMed.

This study adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Additional data sources, such as grey literature, were not searched.

KEY WORDS

Cancer, Laminin γ2 (LAMC2), Meta-analysis, Prognosis

INTRODUCTION

Laminins are trimeric proteins composed of α, β, and γ chains which are the main component of basement membranes.[1] Mammalian genome encodes five α chains, four β chains, and three γ chains.[2] Loss-of-function studies show that most laminin mutants are embryonic lethal.[3] Laminins are involved in various biological processes, including cellular phenotype maintenance, adhesion, migration, growth, and differentiation *in vivo* and *in vitro*.[4, 5]

In recent years, laminin γ2 (LAMC2) has attracted increasingly attractive because of the

aberrant expression of LAMC2 in various cancer. The LAMC2 expression was significantly upregulated in colorectal cancer tissues compared with adjacent normal tissues, and high LAMC2 expression is known to be associated with poor patient prognosis.[6] Furthermore, overexpression of LAMC2 has been reported in pancreatic ductal adenocarcinoma,[7-11] non-small cell lung cancer,[12] penile squamous cell carcinoma,[13] ovarian cancer,[14] Oral tongue squamous cell carcinoma,[15] Cholangiocarcinoma,[16] and esophageal squamous cell carcinoma,[17] leading to poor clinicopathological features and short survival time.

However, individual studies may be inadequate and inaccurate due to their small sample and study design. To date, there was no meta-analysis has been performed to investigate the relationship between LAMC2 and the prognostic value. Therefore, we performed a comprehensive meta-analysis to assess the correlation between LAMC2 and survival outcomes and clinicopathological features in human cancers.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[18] (online supplemental table S1). and the protocol was published on Research Registry (researchregistry1319).

Patient and Public Involvement

No patient was involved.

Search strategy

A literature search was conducted in Embase, Web of Science, and PubMed (up to 25 November 2021). The keywords were (laminin C2 OR LAMC2 OR laminin subunit gamma 2) AND (prognosis OR prognostic OR survival). The detailed search strategy is in supplemental file 1. The reference lists and citation sections of relevant studies were also screened for additional eligible studies.

Study selection

Studies that met the following criteria were included in the meta-analysis: (1) study of the relationship between LAMC2 and prognosis of cancers, (2) patients were divided into two groups: high LAMC2 expression and low LAM2 expression group, and (3) associations of LAMC2 expression with overall survival and clinicopathologic features were described. The exclusion criteria in our meta-analysis were as follows: (1) case reports, letters, reviews, editorials, and expert opinions, (2) studies published non-English language, (3) non-human studies, and (4) studies without sufficient available data.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) criteria was used to assess the quality of the eligible studies.[19] The NOS contains nine items that include selection, comparability, and outcome for studies. When the NOS score was ≥ 6, the study was considered high quality.

Data extraction

Two authors (T.F. and Z.-S.Y.) performed the data extraction independently. Disagreements were resolved by discussion and consensus with the third author (J.X.). The following information from the included studies was collected: the first author's name, publication year, country, number of cases, cancer type, the detection method of LAMC2, clinicopathological features, and survival outcome. When multivariate and univariate analyses were simultaneously reported, only the former was extracted. If studies only provided Kaplan-Meier curves, the survival data were extracted from the graphical curve and calculated HR and 95% CI were reckoned using the published method.[20]

Public data and tools

The web-based tool named Gene Expression Profiling Interactive Analysis (GEPIA) was used to analyze associations between LAMC2 and clinical outcomes.[21]

Statistical analysis

We used Stata MP 16 software (Stata, College Station, TX) to perform statistical analysis. Log odds ratio (OR) and 95% confidence interval (CI) were calculated for the association of LAMC2 expression and clinicopathological characteristics. The prognostic role of LAMC2 expression in overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) was evaluated through Hazard ratio [HR] with 95% CI. The statistical heterogeneity among the studies was analyzed by using I^2 test and Q test. When significant heterogeneity ($I^2 \geq 50\%$, $p < 0.05$) was observed, the random-effects model was chosen. Otherwise, the fixed-effects model was used. The Egger's test and Begg's test were used to assess the potential publication bias. We conducted

a sensitivity analysis to explore the stability of the overall meta-analysis results. $p < 0.05$ was considered as statistically significant.

RESULTS

Study identification and characteristics

As is shown in Figure 1, a total of seven studies with 1,056 patients with cancer were included in this meta-analysis satisfied the inclusion criteria.[6, 7, 16, 17, 22-24] The publication period ranged from 2017-2021. All of our included studies had high quality with Newcastle-Ottawa Quality Assessment Scale scores $\geqslant$ 6. The included studies addressed six different cancer types: esophageal squamous cell carcinoma (n = 1), pancreatic ductal adenocarcinoma (n = 2), cholangiocarcinoma (n = 1), papillary thyroid cancer (n = 1), colorectal cancer (n = 1), and penile squamous cell carcinoma (n = 1). The main characteristics of the seven studies are summarized in Table 1.

Table 1 Characteristics of studies included in this meta-analysis

Study	Year	Region	Sample	Cancer	Method	Outcome	NOS score
Okada et al.	2021	Japan	114	pancreatic ductal adenocarcinoma	qRT-PCR	OS	8
Okada et al.	2021	Japan	121	pancreatic ductal adenocarcinoma	qRT-PCR	OS	8
Pei et al.	2019	China	121	cholangiocarcinoma	IHC	-	7
Liang et al.	2018	China	64	esophageal squamous cell carcinoma	qRT-PCR	OS	7
Zhan et al.	2019	China	473	papillary Thyroid Cancer	RNA-seq	PFS	6

Zhou et al.	2018	China	114	penile squamous cell carcinoma	IHC	DSS	7
Huang et al.	2017	China	49	colorectal cancer	IHC	-	6

Abbreviations: DSS, disease-specific survival; IHC, immunocytochemistry; NOS, Newcastle-Ottawa scale; OS, overall survival; PFS, progression-free survival; qRT-PCR, quantitative real-time polymerase chain reaction.

Relationship between LAMC2 expression and clinicopathological parameters

We evaluated the relationship between LAMC2 expression and clinicopathological parameters in various cancers. As shown in Figures 2A and B, there were three and six studies describing patients of age and gender, respectively. The pooled analysis demonstrated that there was no significant association between LAMC2 expression and age or gender. High expression of LAMC2 was significantly associated with lymph node metastasis (LNM) (Log OR: 0.88, 95% CI: 0.38-1.38, $p < 0.001$, Figure 2C) and tumor-node-metastasis (TNM) stage (Log OR: 0.95, 95% CI: 0.39-1.50, $p < 0.001$, Figure 2D). There was significant heterogeneity among these studies (I^2 = 59.61%, $P = 0.02$; $I^2 = 60.16\%$, $p = 0.03$), and thus the random-effects DerSimonian-Laird model was adopted. A total of four studies evaluated tumor status according to LAMC2 expression. No statistically significant heterogeneity was found among the studies ($I^2 = 36.00\%$, $p = 0.20$); thus, the fixed-effect Mantel-Haenszel model was adopted. As shown in Figure 2E, high expression of LAMC2 was significantly associated with tumor status (Log OR: 1.26, 95% CI: 0.84-1.68, $p <$ 0.001). This finding suggests that high LAMC2 expression is associated with clinicopathological features.

Relationship between LAMC2 expression and OS/PFS/DSS

There were five studies including 872 patients presenting the relationship between LAMC2 and OS/PFS/DSS. Due to no significant heterogeneity being found among studies (I^2 = 0.00%, p = 0.83), the fixed-effect inverse-variance model was adopted to estimate the pooled HR and 95% CI. The pooled HR indicated that the expression of LAMC2 was negatively associated with OS/PFS/DSS (HR: 1.85, 95% CI: 1.31-2.40, $p < 0.001$, Figure 3A), which demonstrated that LAMC2 was a risk factor for the prognosis of cancer patients. In addition, sensitivity analysis was performed to determine the effect of individual studies on the OS/PFS/DSS. It revealed that no single study altered the pooled LAMC2 HR result significantly (Figure 3B). This suggested that the result of the meta-analysis was stable.

Analysis of publication bias

Funnel plot (Figure 3C), Begg's test, and Egger's linear regression test (Figure 3D) were used to assess publication bias. The results showed that the funnel plots scatter symmetrically. The statistical tests showed *P* values were greater than 0.05 (Begg's test: p = 0.4624; Egger's test: p = 0.329). Thus, there was no obvious publication bias in the prognostic meta-analysis.

Validation of TCGA data set results

To validate our result, we retrieved LAMC2 expression data and clinical data from the TCGA dataset. As shown in Figure 4A, LAMC2 was increased in colon adenocarcinoma (COAD), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), lung adenocarcinoma (LUAD), and lung squamous

cell carcinoma (LUSC), determined using a log2FC cutoff of 1 and a *p*-value cutoff of 0.01. A total of 9502 patients with urinary, digestive, female reproductive, respiratory, and blood systems cancers were included in the survival analysis from the TCGA database. According to the expression of LAMC2, the patients were divided into high and low groups using the median score as the cutoff by GEPIA.[21] The results showed that higher LAMC2 expression was correlated with worse survival (Figure 4B). We also explored the prognostic role of LAMC2 in different cancer types. As shown in Figure 5, LAMC2 expression was significantly associated with OS in LUAD (Figure 5A), mesothelioma (MESO, Figure 5B), skin cutaneous melanoma (SKCM, Figure 5C), HNSC (Figure 5D), and brain lower grade glioma (LGG, Figure 5E). However, LAMC2 expression was not related to OS in LUSC (Figure 5F).

DISCUSSION

Laminins are involved in various cancer development and prognosis.[25, 26] Increasing evidence suggests that the various laminin isoforms could be useful biomarkers of cancer diagnosis and might be potential therapeutic targets for cancers treatment, such as LAMA5,[27] LAMB1,[28] and LAMC1,[29] LAMC2 is encoding by Laminin γ2 and has been confirmed as a therapeutic target for cancers. Here we performed a meta-analysis of seven studies to achieve a comprehensive evaluation between higher LAMC2 expression and clinicopathological characteristics in various cancer types. Our results showed that higher LAMC2 expression was significantly associated with LNM, TNM stage, and tumor status. However, there was no significant association between LAMC2 expression and age or gender. Simultaneously, we also found that OS/PFS/DSS was higher in patients with low LAMC2 expression. Publication bias analysis demonstrated that no

publication bias was observed among the included studies. These results suggested that LAMC2 might be a valuable biomarker for predicting prognosis in cancer patients. Steyerberg et al. provide the prognostic model that can provide effective solving discrimination and predictiveness measures.[30] We will plan to investigate this in a later study.

Several kinds of research have shown that LAMC2 promotes cancer cells proliferation, motility, and invasion.[29-35] However, the specific mechanism are not particularly well understood. There is a study indicating that ZNF750 inhibited the migration of esophageal squamous cancer cells by inhibiting the LAMC2 transactivation.[31] In hepatocellular carcinoma (HCC), LAMC2 has been found to be regulated by miR-548c-3p and inhibited the epithelial-mesenchymal transition in HCC.[32] In pancreatic cancer cells, LAMC2 promoted Akt-Ser473 phosphorylation and increased expression and cell membrane accumulation of NHE1, promoting cell migration and invasion.[33] A study by Wu et al. showed that the LAMP3-LAMC2-TNC signal regulated the efficacy of radiation exposure in laryngeal squamous cell carcinoma.[34] High-throughput sequencing results showed that miR-338-5p/3p targets LAMC2 to suppress invasion in salivary adenoid cystic carcinoma cells.[35] LAMC2 was found to promote tumor progression by EGFR signaling.[36, 37] The latest research showed that overexpression of LAMC2 enhances pancreatic ductal adenocarcinoma metastasis and tumorigenesis through the EGFR/ERK1/2/AKT/mTOR signaling pathway.[11] These findings suggested that LAMC2 might play as an oncogene and predict prognosis in cancer patients.

Recent researches have also investigated LAMC2 as a valuable biomarker of cancer

diagnosis.[38, 39] Due to a limitation of the small sample size, we explored the expression of LAMC2 in various cancer types using the TCGA database. The results showed that LAMC2 was upregulated in tumors and might be used as a biomarker for a variety of tumor types. Moreover, we explore the survival analysis from the TCGA database. The results demonstrated that higher LAMC2 expression was associated with poor OS in 9502 patients. We also explored the prognostic role of LAMC2 in different types of cancer. LAMC2 expression was significantly associated with OS in LUAD, MESO, SKCM, HNSC, and LGG, but not in LUSC. This deserves further investigation.

Some potential limitations of our study should be noted. First, only seven articles were included in our meta-analysis, the limited number of studies might influence the reliability of the results. Of the seven included studies, five were from China, and two were from Japan. So, our results may only be applicable to the Asian population. Although we determined data from the TCGA database, future studies from non-Asian populations are needed to confirm our findings. Second, there was no consensus on a cutoff value for higher LAMC2 expression. Third, in some researches, the data for HR and 95% CI value was not provided. Although we tried our best to extract the HR and 95% CI value from the Kaplan-Meier curve, some errors are inevitable. Fourth, the numbers of patients and tumor types included in this meta-analysis were still limited. So, our results may exaggerate the prognostic value of LAMC2.

CONCLUSIONS

In conclusion, LAMC2 may be a valuable biomarker for cancer diagnosis, and upregulation of

LAMC2 is associated with a poor prognosis in cancer patients. And increased LAMC2 expression was significantly associated with bad tumor status, tumor-node-metastasis stages, and lymph node metastasis. For future clinical applications, more high-quality studies with large sample sizes are needed to confirm the role of LAMC2 in various cancers and regions.

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Contributors

T.F and Z.-S.Y designed the study; T.F, Z.-S.Y, and J.X searched the literature and extracted data; Z.-S.Y and T.F analyzed data; Z.-S.Y prepared the figures; Z.-S.Y, J.-X.L, and Z.G. wrote the manuscript. All authors gave the final approval for the paper to be published.

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Competing interests

The authors declare that they have no conflict of interest

Patient consent for publication

Not applicable.

Ethics approval

This study does not involve human participants.

Data availability statement

All data relevant to the study are included in the article.

Abbreviations

CI, confidence interval; COAD, colon adenocarcinoma; DLBS, lymphoid neoplasm diffuse large B-cell lymphoma; DSS, disease-specific survival; ESCA, esophageal carcinoma; GEPIA, gene expression profiling interactive analysis; HCC, hepatocellular carcinoma; HNSC, head and neck squamous cell carcinoma; HR, hazard ratio; IHC, immunocytochemistry; LAMC2, laminin subunit gamma 2; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; NOS, Newcastle-Ottawa Quality Assessment Scale; OR, odds ratio; OS, overall survival; PFS, progression-free survival; qRT-PCR, quantitative real-time polymerase chain reaction; RNA-seq, RNA sequencing; SKCM, skin cutaneous melanoma; TCGA, The Cancer Genome Atlas; TNM, tumor-node-metastasis.

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Figure legends

Figure 1 Flow diagram of the literature search and selection

Figure 2 Forest plots of studies evaluating the relationship between LAMC2 expression and clinicopathological features

(**A**) LNM, (**B**) TNM stage, (**C**) tumor status, (**D**) gender, (**E**) age.

Figure 3 The relationship between LAMC2 expression and OS/PFS/DSS

(**A**) Forest plot for the meta-analysis of OS/PFS/DSS. (**B**) Sensitivity analysis for LAMC2 expression with OS/PFS/DSS. (**C**) Funnel plot for the meta-analysis of OS/PFS/DSS. (**D**) Egger's graph for analyzing publication bias.

Figure 4 The expression of LAMC2 in the TCGA database

(**A**) LAMC2 expression in COAD, DLBC, ESCA, HNSC, LUAD, and LUSC. * = p value < 0.01. (**B**) OS rate of LAMC2 expression in TCGA database (n = 9502). Gray boxes indicate normal, and red boxes indicate tumor. T, tumor; N, normal.

Figure 5 Kaplan-Meier curves showing the prognostic value of LAMC2 in the TCGA database

(**A**) LUAD, (**B**) MESO, (**C**) SKCM, (**D**) HNSC, (**E**) LGG, (**F**) LUSC. p values were calculated

using the log-rank test.

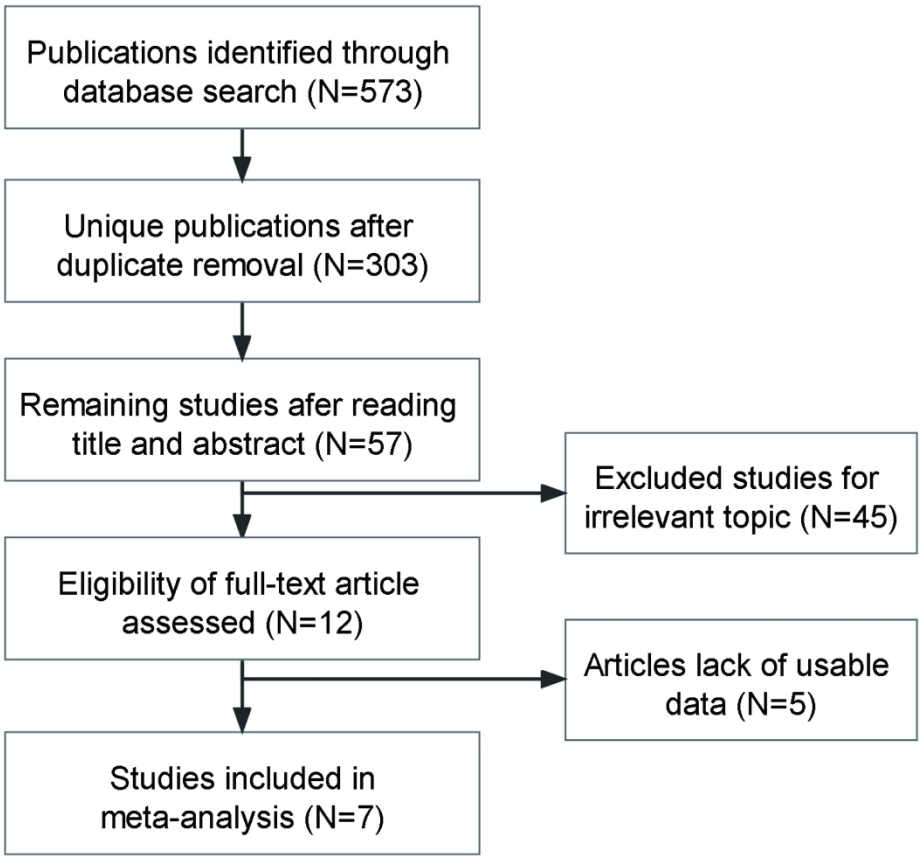

Figure1

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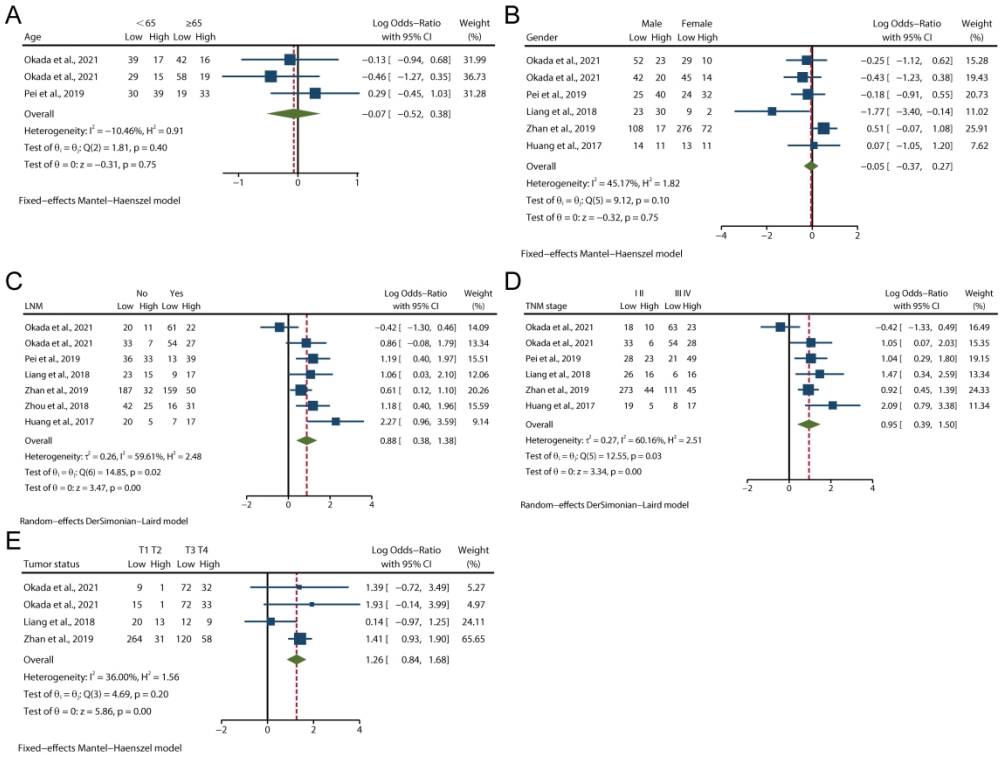

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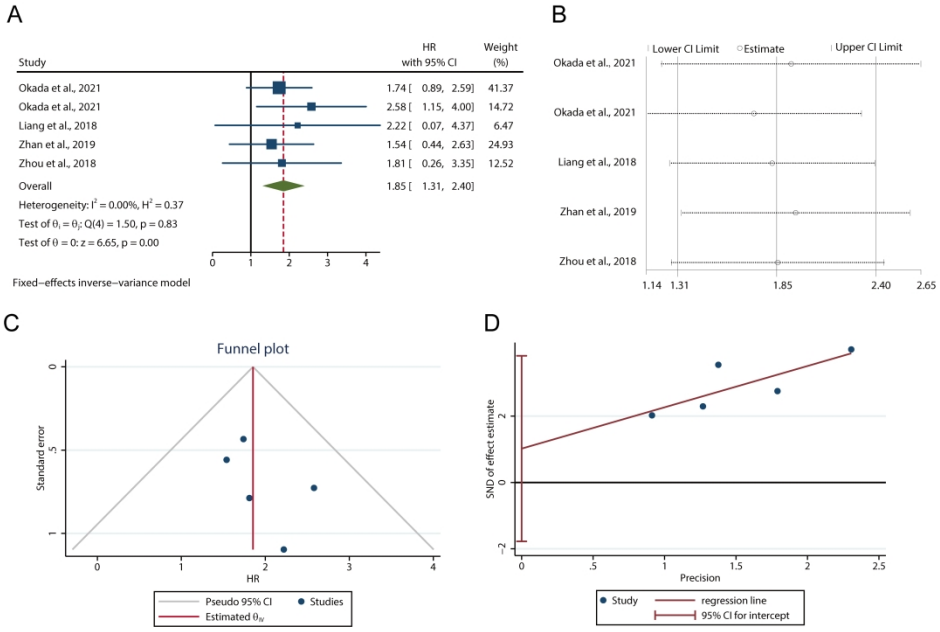

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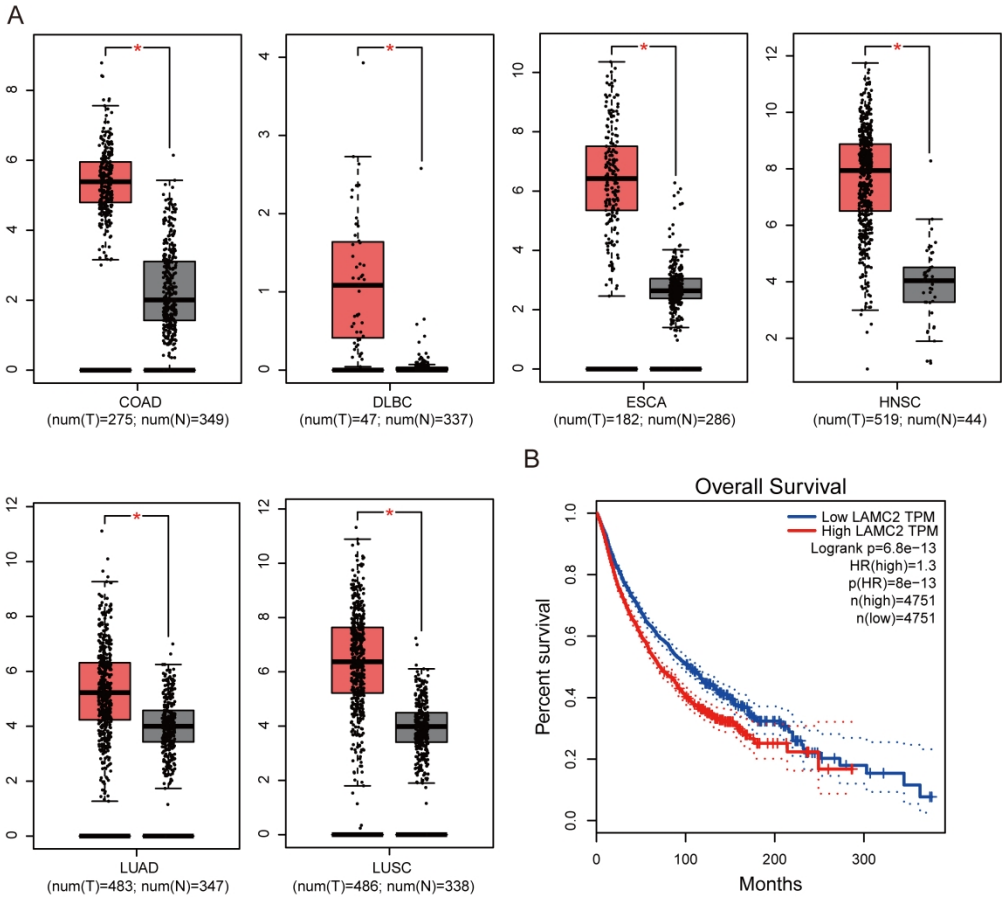

Figure4

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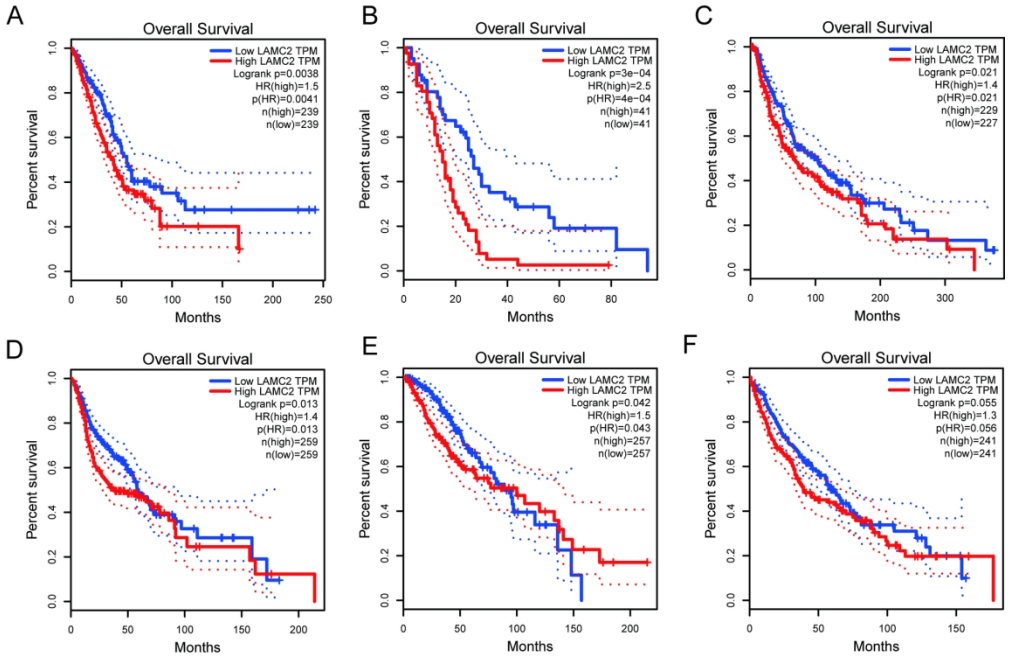

Figure5

162x106mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Page 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9
	23b	Discuss any limitations of the evidence included in the review.	Page 11
	23c	Discuss any limitations of the review processes used.	Page 11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 12
Competing interests	26	Declare any competing interests of review authors.	Page 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Search strategy for PubMed (search date: from inception to 25 November 2021).

((("laminin"[MeSH Terms] OR "laminin"[All Fields] OR "laminins"[All Fields] OR "laminine"[Supplementary Concept] OR "laminine"[All Fields]) AND "C2"[All Fields]) OR "LAMC2"[All Fields] OR (("laminin"[MeSH Terms] OR "laminin"[All Fields] OR "laminins"[All Fields] OR "laminine"[Supplementary Concept] OR "laminine"[All Fields]) AND ("protein subunits"[MeSH Terms] OR ("protein"[All Fields] AND "subunits"[All Fields]) OR "protein subunits"[All Fields] OR "subunit"[All Fields] OR "subunit s"[All Fields] OR "subunits"[All Fields]) AND ("gamma rays"[MeSH Terms] OR ("gamma"[All Fields] AND "rays"[All Fields]) OR "gamma rays"[All Fields] OR "gamma"[All Fields] OR "gamma s"[All Fields] OR "gammae"[All Fields] OR "gammas"[All Fields]) AND "2"[All Fields])) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields] OR ("prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields]) OR ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]))

Search strategy for the Embase (search date: from inception to 25 November 2021).

('laminin c2' OR (('laminin'/exp OR laminin) AND ('c2'/exp OR c2)) OR lamc2 OR 'laminin subunit gamma 2'/exp OR 'laminin subunit gamma 2' OR (('laminin'/exp OR laminin) AND subunit AND gamma AND ('2'/exp OR 2))) AND ('prognosis'/exp OR prognosis OR prognostic OR 'survival'/exp OR survival)

Search strategy for Web of Science (search date: from inception to 25 November 2021)

TS=((laminin C2 OR LAMC2 OR laminin subunit gamma 2) AND (prognosis OR prognostic OR survival))