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# BMJ Open

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

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4 **1 LAMC2 as a prognostic biomarker in human cancer: a systematic review and meta-analysis**  
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45 17 Word count: 2269 words.  
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51 **19 ABSTRACT**  
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53 20 **Objectives** Accumulating evidence suggested that the laminin  $\gamma$ 2 (LAMC2) expression level was  
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56 21 upregulated in various cancers. However, the potential prognostic value of LAMC2 in cancers  
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59 22 remains unclear. We conducted a meta-analysis to clarify the association of LAMC2 expression  
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4 23 with prognosis.

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6 24 **Method** We searched Embase, Web of Science, and PubMed through 25 November 2021 to  
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9 25 collect all eligible studies, and meta-analysis was performed to interpret the association of  
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12 26 LAMC2 expression with clinicopathological parameters, overall survival (OS) disease-specific  
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15 27 survival (DSS), and progression-free survival (PFS).

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17 28 **Results** Seven studies were included finally. We found that increased LAMC2 expression was  
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20 29 significantly associated with lymph node metastasis (Log odds ratio [OR]: 0.88, 95% confidence  
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22 30 interval [CI]: 0.38-1.38,  $p = 0.00$ ), tumor-node-metastasis stages (Log OR: 0.95, 95% CI:  
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24 31 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  
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26  
27 32 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,  
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30 33  $p = 0.75$ ). In addition, higher LAMC2 expression was found to be significantly associated with  
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33 34 OS/PFS/DSS (HR: 1.85, 95% CI: 1.31-2.40,  $p = 0.00$ ). A similar result was found from The  
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36 35 Cancer Genome Atlas (TCGA) database.

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38 36 **Conclusion** Our results suggested that higher LAMC2 expression was correlated with worse  
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41 37 survival. This study was subject to inherent limitations, but the results presented here provided  
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44 38 insights regarding the potential use of LAMC2 as a biomarker for human cancer.

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46 39 **Study registration** [researchregistry.com](http://researchregistry.com) (researchregistry1319).

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#### 50 51 41 **Strengths and limitations of this study**

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54 42 This systematic review and meta-analysis provides a comprehensive literature published up to  
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57 43 November 2020 was performed in Embase, Web of Science, and PubMed.

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59 44 This study adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide  
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4 45 lines.

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6 46 Additional data sources such as grey literature were not searched.

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11 48 **KEY WORDS**

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14 49 Cancer, Laminin  $\gamma$ 2 (LAMC2), Meta-analysis, Prognosis

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19 51 **INTRODUCTION**

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22 52 Laminins are trimeric proteins composed of  $\alpha$ ,  $\beta$ , and  $\gamma$  chains which are the main component of  
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24 53 basement membranes.<sup>1</sup> Mammalian genomes encode five  $\alpha$  chains, four  $\beta$  chains, and three  $\gamma$   
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26 54 chains.<sup>2</sup> Loss-of-function studies show that most laminin mutants are embryonic lethal.<sup>3</sup> Laminins  
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28 55 are involved in various biological processes, including cellular phenotype maintenance, adhesion,  
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30 56 migration, growth, and differentiation *in vivo* and *in vitro*.<sup>4,5</sup>

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38 58 In recent years, laminin  $\gamma$ 2 (LAMC2) has attracted increasingly attractive because of the  
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40 59 aberrant expression of LAMC2 in various cancer. The LAMC2 expression was significantly  
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42 60 upregulated in colorectal cancer tissues compared with adjacent normal tissues and high LAMC2  
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44 61 expression is known to be associated with poor patient prognosis.<sup>6</sup> Furthermore, overexpression of  
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46 62 LAMC2 has been reported in pancreatic ductal adenocarcinoma,<sup>7-10</sup> non-small cell lung cancer,<sup>11</sup>  
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48 63 penile squamous cell carcinoma,<sup>12</sup> ovarian cancer,<sup>13</sup> Oral tongue squamous cell carcinoma,<sup>14</sup>  
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50 64 Cholangiocarcinoma,<sup>15</sup> esophageal squamous cell carcinoma,<sup>16</sup> leading to poor clinicopathological  
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56 65 features and short survival time.

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4 67 However, individual studies may be inadequate and inaccurate due to their small sample and  
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6 68 study design. To date, there was no meta-analysis has been performed to investigate the  
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9 69 relationship between LAMC2 and the prognostic value. Therefore, we performed a comprehensive  
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11 70 meta-analysis to assess the correlation between LAMC2 and survival outcomes and  
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14 71 clinicopathological features in human cancers.  
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## 19 73 **METHODS**

22 74 This study was followed the Preferred Reporting Items for Systematic Reviews and  
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24 75 Meta-Analyses guidelines<sup>17</sup> (online supplemental table S1). and the protocol was published on  
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27 76 Research Registry (researchregistry1319).  
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### 32 78 **Search strategy**

35 79 A literature search was conducted in Embase, Web of Science, and PubMed through 25 November  
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37 80 2021. The keywords were (laminin C2 OR LAMC2 OR laminin subunit gamma 2) AND  
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40 81 (prognosis OR prognostic OR survival). The reference lists and citation sections of relevant  
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43 82 studies were also screened for additional eligible studies.  
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### 48 84 **Study selection**

51 85 Studies that met the following criteria were included in the meta-analysis: (1) study of the  
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53 86 relationship between LAMC2 and prognosis of cancers, (2) patients were divided into two groups:  
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56 87 high LAMC2 expression and low LAM2 expression group, and (3) associations of LAMC2  
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59 88 expression with overall survival and clinicopathologic features were described. The exclusion  
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4 89 criteria in our meta-analysis were as follows: (1) case reports, letters, reviews, editorials, and  
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6 90 expert opinions, (2) studies published non-English language, (3) non-human studies, and (4)  
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9 91 studies without sufficient available data.  
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### 11 92 12 13 14 93 **Quality assessment**

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17 94 The Newcastle-Ottawa Quality Assessment Scale (NOS) criteria was used to assess the quality of  
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19 95 the eligible studies.<sup>18</sup> The NOS contains nine items that include selection, comparability, and  
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22 96 outcome for studies. When the NOS score was  $\geq 6$ , the study was considered high quality.  
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### 26 27 98 **Data extraction**

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30 99 Two authors (T.F. and Z.-S.Y.) performed the data extraction independently. Disagreements were  
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32 100 resolved by discussion and consensus with the third author (J.X.). The following information from  
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35 101 the included studies was collected: the first author's name, publication year, country, number of  
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38 102 cases, cancer type, the detection method of LAMC2, clinicopathological features, and survival  
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41 103 outcome. When multivariate and univariate analyses were simultaneously reported, only the  
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43 104 former was extracted. If studies only provided Kaplan-Meier curves, the survival data were  
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46 105 extracted from the graphical curve and calculated HR and 95% CI were reckoned using the  
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48 106 published method.<sup>19</sup>  
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### 50 51 107 52 53 108 **Public data and tools**

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56 109 The web-based tool named Gene Expression Profiling Interactive Analysis (GEPIA) was used to  
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58 110 analyze associations between LAMC2 and clinical outcomes.<sup>20</sup>  
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6 112 **Statistical analysis**

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9 113 We used Stata MP 16 software (Stata, College Station, TX) to perform statistical analysis. Log  
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11 114 odds ratio (OR) and 95% confidence interval (CI) were calculated for the association LAMC2  
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13 115 expression and clinicopathological characteristics. The prognostic role of LAMC2 expression in  
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15 116 overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) was  
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17 117 evaluated through HR with 95% CI. The statistical heterogeneity among the studies was analyzed  
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19 118 by using  $I^2$  test and Q test. When significant heterogeneity ( $I^2 \geq 50\%$ ,  $p < 0.05$ ) was observed,  
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21 119 the random-effects model was chosen. Otherwise, the fixed-effects model was used. The Egger's  
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23 120 test and Begg's test were used to assessing the potential publication bias. We conducted a  
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25 121 sensitivity analysis to explore the stability of the overall meta-analysis results.  $p < 0.05$  was  
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27 122 considered as statistically significant.  
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37 124 **RESULTS**38  
39 125 **Study identification and characteristics**

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42 126 As is shown in Figure 1, a total of seven studies with 1,056 patients with cancer were included in  
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44 127 this meta-analysis satisfied the inclusion criteria.<sup>6, 7, 15, 16, 21-23</sup> The publication period ranged from  
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46 128 2017-2021. All of our included studies had high quality with Newcastle-Ottawa Quality  
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48 129 Assessment Scale scores  $\geq 6$ . The included studies addressed six different cancer types:  
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50 130 esophageal squamous cell carcinoma (n = 1), pancreatic ductal adenocarcinoma (n = 2),  
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52 131 cholangiocarcinoma (n = 1), papillary thyroid cancer (n = 1), colorectal cancer (n = 1), and penile  
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54 132 squamous cell carcinoma (n = 1). The main characteristics of the seven studies are summarized in  
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4 133 Table 1.

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9 135 **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

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36 136 Abbreviations: DSS, disease-specific survival; IHC, immunocytochemistry; NOS,

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38 137 Newcastle-Ottawa scale; OS, overall survival; PFS, progression-free survival; qRT-PCR,

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41 138 quantitative real-time polymerase chain reaction.

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47 140 **Relationship between LAMC2 expression and clinicopathological parameters**

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49 141 We evaluated the relationship between LAMC2 expression and clinicopathological parameters

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51 142 in various cancers. As shown in Figures 2A and B, there were three and six studies describing

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53 143 patients of age and gender, respectively. The pooled analysis demonstrated that there was no

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55 144 significant association between LAMC2 expression and age or gender. High expression of

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59 145 LAMC2 was significantly associated with lymph node metastasis (LNM) (Log OR: 0.88, 95% CI:

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4 146 0.38-1.38,  $p = 0.00$ , Figure 2C) and tumor-node-metastasis (TNM) stage (Log OR: 0.95, 95% CI:  
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6 147 0.39-1.50,  $p = 0.00$ , Figure 2D). There was significant heterogeneity among these studies ( $I^2 =$   
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9 148 59.61%,  $P = 0.02$ ;  $I^2 = 60.16%$ ,  $p = 0.03$ ), and thus the random-effects DerSimonian-Laird model  
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12 149 was adopted. A total of four studies evaluated tumor status according to LAMC2 expression. No  
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15 150 statistically significant heterogeneity was found among the studies ( $I^2 = 36.00%$ ,  $p = 0.20$ ); thus,  
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17 151 the fixed-effect Mantel-Haenszel model was adopted. As shown in Figure 2E, high expression of  
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20 152 LAMC2 was significantly associated with tumor status (Log OR: 1.26, 95% CI: 0.84-1.68,  $p =$   
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22 153 0.00). This finding suggests that high LAMC2 expression is associated with clinicopathological  
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25 154 features.  
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### 30 156 **Relationship between LAMC2 expression and OS/PFS/DSS**

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33 157 There were five studies including 872 patients presenting the relationship between LAMC2 and  
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35 158 OS/PFS/DSS. Due to no significant heterogeneity being found among studies ( $I^2 = 0.00%$ ,  $p =$   
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38 159 0.83), the fixed-effect inverse-variance model was adopted to estimate the pooled HR and 95% CI.  
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41 160 The pooled HR indicated that the expression of LAMC2 was negatively associated with  
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43 161 OS/PFS/DSS (HR: 1.85, 95% CI: 1.31-2.40,  $p = 0.00$ , Figure 3A), which demonstrated that  
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45 162 LAMC2 was a risk factor for the prognosis of cancer patients. In addition, sensitivity analysis was  
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48 163 performed to determine the effect of individual studies on the OS/PFS/DSS. It revealed that no  
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51 164 single study altered the pooled LAMC2 HR result significantly (Figure 3B). This suggested that  
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53 165 the result of the meta-analysis was stable.  
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### 56 166 57 58 167 **Analysis of publication bias**

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4 168 Funnel plot (Figure 3C), Begg's test, and Egger's linear regression test (Figure 3D) were used to  
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6 169 assess publication bias. The results showed that the funnel plots scatter symmetrically. The  
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9 170 statistical tests showed  $P$  values were greater than 0.05 (Begg's test:  $p = 0.4624$ ; Egger's test:  $p =$   
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11 171 0.329). Thus, there was no obvious publication bias in prognostic meta-analysis.  
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### 17 173 **Validation of TCGA data set results**

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19 174 To validate our result, we retrieved LAMC2 expression data and clinical data from the TCGA  
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22 175 dataset. As shown in Figure 4A, LAMC2 was increased in colon adenocarcinoma (COAD),  
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25 176 lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), head  
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28 177 and neck squamous cell carcinoma (HNSC), lung adenocarcinoma (LUAD), and lung squamous  
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30 178 cell carcinoma (LUSC), determined using a log<sub>2</sub>FC cutoff of 1 and a p-value cutoff of 0.01. A  
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33 179 total of 9502 patients with urinary, digestive, female reproductive, respiratory, and blood systems  
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36 180 cancers were included in the survival analysis from the TCGA database. According to the  
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38 181 expression of LAMC2, the patients were divided into high and low groups using the median score  
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40 182 as the cutoff by GEPIA<sup>20</sup>. The results showed that higher LAMC2 expression was correlated with  
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43 183 worse survival (Figure 4B). We also explored the prognostic role of LAMC2 in different cancer  
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46 184 types. As shown in Figure 5, LAMC2 expression was significantly associated with OS in LUAD  
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48 185 (Figure 5A), mesothelioma (MESO, Figure 5C), skin cutaneous melanoma (SKCM, Figure 5D),  
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51 186 HNSC (Figure 5E), and brain lower grade glioma (LGG, Figure 5F). However, LAMC2  
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53 187 expression was not related to OS in LUSC (Figure 5B).  
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### 58 189 **DISCUSSION**

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4 190 Laminins are involved in various cancer development and prognosis.<sup>24, 25</sup> Increasing evidence  
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6 191 suggests that the various laminin isoforms could be useful biomarkers of cancer diagnosis and  
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9 192 might be potential therapeutic targets for cancers treatment, such as LAMA5,<sup>26</sup> LAMB1,<sup>27</sup> and  
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11 193 LAMC1,<sup>28</sup> LAMC2 is encoding by Laminin  $\gamma$ 2 and has been confirmed as a therapeutic target for  
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14 194 cancers. Here we performed a meta-analysis of seven studies to achieve a comprehensive  
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17 195 evaluation between higher LAMC2 expression and clinicopathological characteristics in various  
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20 196 cancer types. Our results showed that higher LAMC2 expression was significantly associated with  
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22 197 LNM, TNM stage, and tumor status. However, there was no significant association between  
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25 198 LAMC2 expression and age or gender. Simultaneously, we also found that OS/PFS/DSS was  
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27 199 higher in patients with low LAMC2 expression. Publication bias analysis demonstrated that no  
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30 200 publication bias was observed among the included studies. These results suggested that LAMC2  
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32 201 might be a valuable biomarker for predicting prognosis in cancer patients.  
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37 203 Several kinds of research have shown that LAMC2 promotes cancer cells proliferation, motility,  
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39 204 and invasion. However, the specific mechanism remained uncertain. ZNF750 inhibited the  
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42 205 migration of esophageal squamous cancer cells by inhibiting the LAMC2 transactivation.<sup>29</sup> In  
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45 206 hepatocellular carcinoma (HCC), LAMC2 has been found regulated by miR-548c-3p and inhibited  
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48 207 the epithelial-mesenchymal transition in HCC.<sup>30</sup> In pancreatic cancer cells, LAMC2 promoted  
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51 208 Akt-Ser473 phosphorylation and increased expression and cell membrane accumulation of NHE1,  
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53 209 promoting cells migration and invasion.<sup>31</sup> A study by Wu et al. showed that the  
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56 210 LAMP3-LAMC2-TNC signal regulated the efficacy of radiation exposure in laryngeal squamous  
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58 211 cell carcinoma.<sup>32</sup> High-throughput sequencing results showed that miR-338-5p/3p target LAMC2  
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4 212 to suppress invasion in salivary adenoid cystic carcinoma cells.<sup>33</sup> LAMC2 was found to promote  
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6 213 tumor progression by EGFR signaling.<sup>34, 35</sup> These findings suggested that LAMC2 might play as  
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9 214 an oncogene and predict prognosis in cancer patients.  
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13  
14 216 Recent researches have also investigated LAMC2 as a valuable biomarker of cancer  
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17 217 diagnosis.<sup>36, 37</sup> Due to a limitation of a small sample size, we explored the expression of LAMC2  
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19 218 in various cancer types using the TCGA database. The results showed that LAMC2 was  
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22 219 upregulated in tumors and might be used as a biomarker for a variety of tumor types. Moreover,  
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25 220 we explore the survival analysis from the TCGA database. The results demonstrated that higher  
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27 221 LAMC2 expression was associated with poor OS in 9502 patients. We also explored the  
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30 222 prognostic role of LAMC2 in different types of cancer. LAMC2 expression was significantly  
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32 223 associated with OS in LUAD, MESO, SKCM, HNSC, and LGG, but not in LUSC. This deserves  
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35 224 further investigation.  
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40 226 Some potential limitations of our study should be noted. First, only seven articles were included  
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43 227 in our meta-analysis, the limited number of studies might influence the reliability of the results. Of  
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46 228 the seven included studies, five were from China, and two were from Japan. So, our results may  
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49 229 only be applicable to the Asian population. Although we determined data from the TCGA  
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52 230 database, future studies from non-Asian populations are needed to confirm our findings. Second,  
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54 231 there was no consensus on a cutoff value for higher LAMC2 expression. Third, in some  
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56 232 researches, the data for HR and 95% CI value was not provided. Although we tried our best to  
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59 233 extract the HR and 95% CI value from the Kaplan-Meier curve, some errors are inevitable. Fourth,  
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234 the numbers of patients and tumor types included in this meta-analysis were still limited. So, our  
235 results may exaggerate the prognostic value of LAMC2.

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## 237 **CONCLUSIONS**

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

242

## 243 **Acknowledgments**

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## 246 **Contributors**

247 T.F and Z.-S.Y designed the study; F.T and J.X searched the literature and extracted data; Z.-S.Y  
248 and T.F analyzed data; Z.-S.Y prepared the figures; Z.-S.Y, J.X.-L and Z.G. wrote the manuscript.

249 All authors gave the final approval of the paper to be published.

250

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253

## 254 **Competing interests**

255 The authors declare that they have no conflict of interest.

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6 257 **Patient and Public Involvement**

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9 258 No patient involved.  
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14 260 **Patient consent for publication**

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17 261 Not applicable.  
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22 263 **Ethics approval**

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24 264 This study does not involve human participants.  
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30 266 **Data availability statement**

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32 267 All data relevant to the study are included in the article.  
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37 269 **Abbreviations**

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39 270 CI, confidence interval; COAD, colon adenocarcinoma; DLBS, lymphoid neoplasm diffuse large

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41 271 B-cell lymphoma; DSS, disease-specific survival; ESCA, esophageal carcinoma; GEPIA, gene

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43 272 expression profiling interactive analysis; HCC, hepatocellular carcinoma; HNSC, head and neck

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45 273 squamous cell carcinoma; HR, hazard ratio; IHC, immunocytochemistry; LAMC2, laminin

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47 274 subunit gamma 2; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; LUSC, lung

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49 275 squamous cell carcinoma; MESO, mesothelioma; NOS, Newcastle-Ottawa Quality Assessment

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51 276 Scale; OR, odds ratio; OS, overall survival; PFS, progression-free survival; qRT-PCR,

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53 277 quantitative real-time polymerase chain reaction; RNA-seq, RNA sequencing; SKCM, skin  
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4 278 cutaneous melanoma; TCGA, The Cancer Genome Atlas; TNM, tumor-node-metastasis.  
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## 15 16 17 371 **Figure legends**

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19 372 **Figure 1 Flow diagram of the literature search and selection**

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24 374 **Figure 2 Forest plots of studies evaluating the relationship between LAMC2 expression and**  
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27 375 **clinicopathological features**

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29 376 (A) LNM, (B) TNM stage, (C) tumor status, (D) gender, (E) age.

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34 378 **Figure 3 The relationship between LAMC2 expression and OS/PFS/DSS**

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37 379 (A) Forest plot for the meta-analysis of OS/PFS/DSS. (B) Sensitivity analysis for LAMC2  
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39 380 expression with OS/PFS/DSS. (C) Funnel plot for the meta-analysis of OS/PFS/DSS. (D) Egger's  
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41 381 graph for analyzing publication bias.

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46 383 **Figure 4 The expression of LAMC2 in the TCGA database**

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48 384 (A) LAMC2 expression in COAD, DLBC, ESCA, HNSC, LUAD, and LUSC. \* =  $p$  value < 0.01.

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50 385 (B) OS rate of LAMC2 expression in TCGA database (n = 9502). Gray boxes indicate normal,  
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53 386 and red boxes indicate tumor. T, tumor; N, normal.

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4 388 **Figure 5 Kaplan-Meier curves showing the prognostic value of LAMC2 in the TCGA**  
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6 389 **database**  
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9 390 **(A) LUAD, (B) LUSC, (C) MESO, (D) SKCM, (E) HNSC, (F) LGG.** *p* values were calculated  
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11 391 using the log-rank test.  
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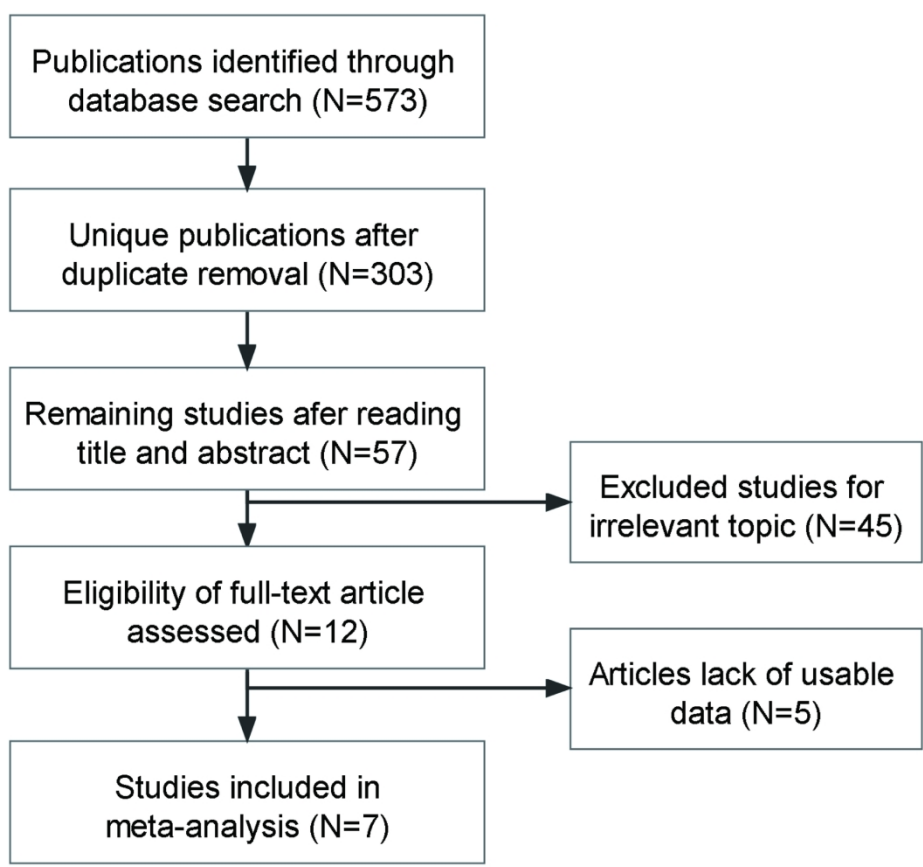


Figure1

170x158mm (300 x 300 DPI)

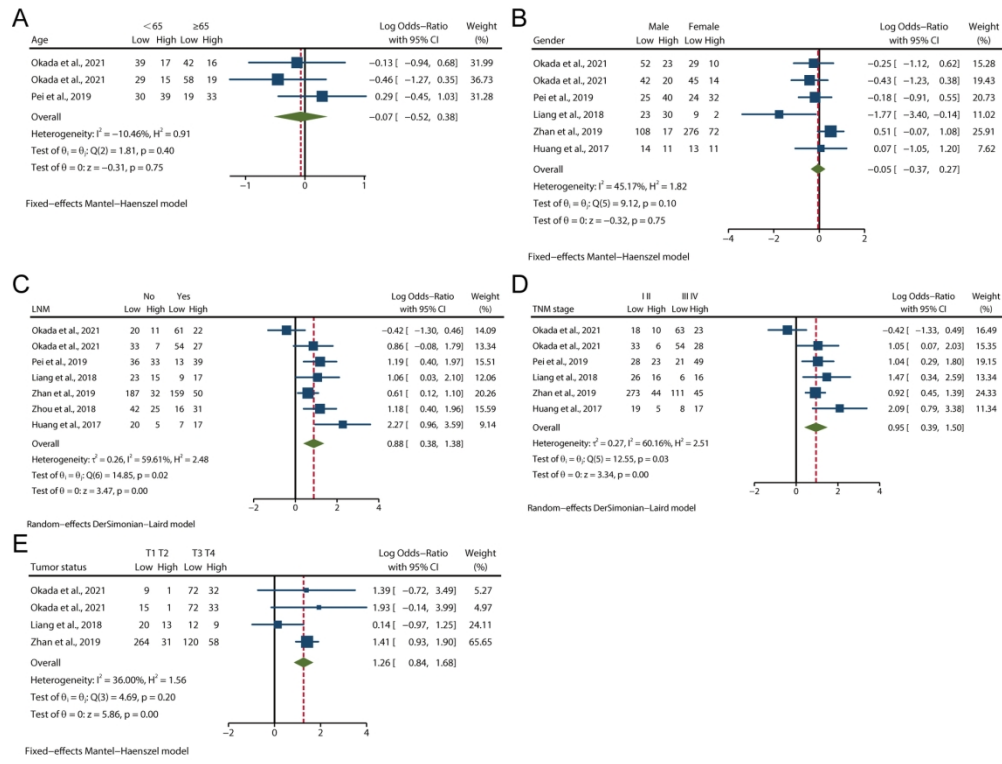


Figure2

168x126mm (300 x 300 DPI)



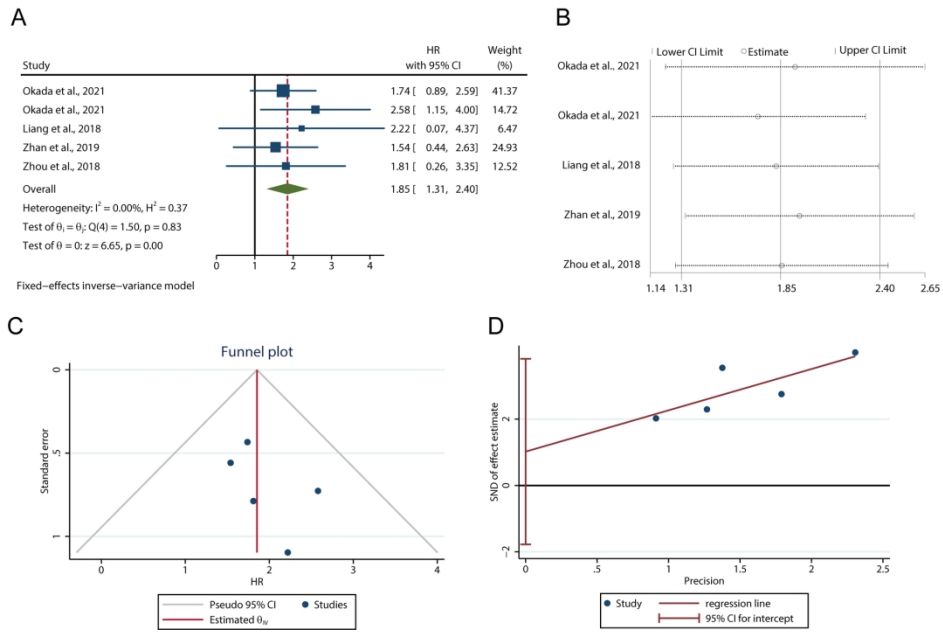


Figure 3

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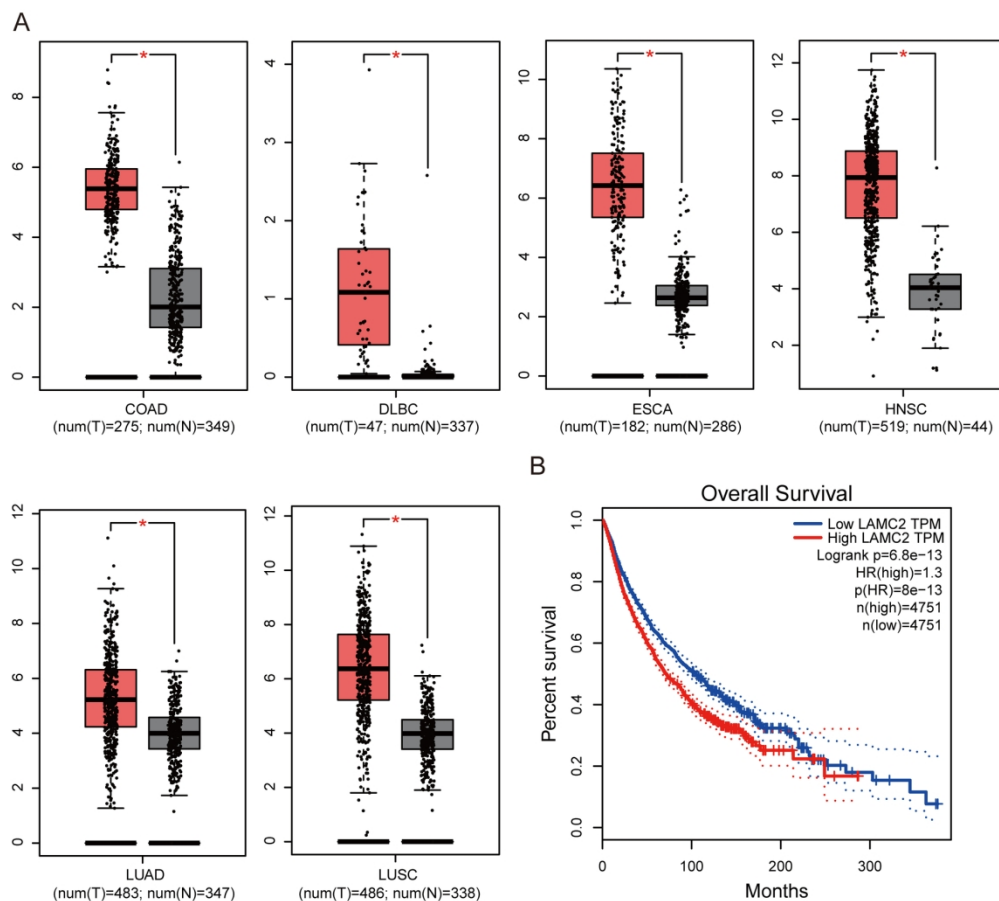


Figure4

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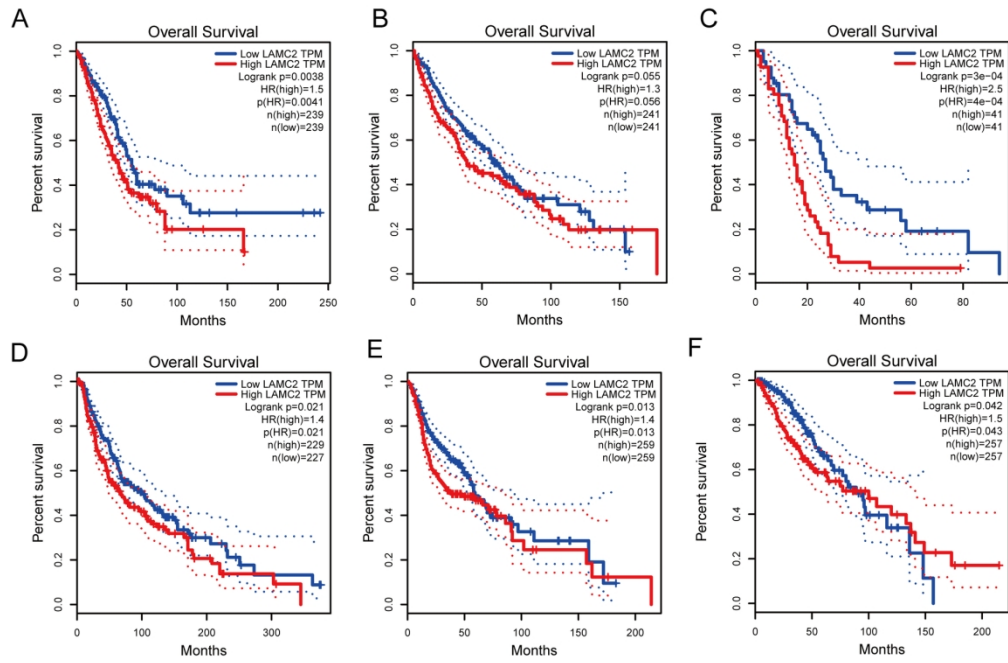


Figure5

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## PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Page 1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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. For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	Page 6



## PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>OTHER INFORMATION</b>			
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

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-063682.R1
Article Type:	Original research
Date Submitted by the Author:	30-Sep-2022
Complete List of Authors:	Fu, Tao; Chongqing Key Laboratory of Human Engineering, Center for Reproductive Medicine, Women and Children's Hospital of Chongqing Medical University; Chongqing Clinical Research Center for Reproductive Medicine, Chongqing Health Center for Women and Children Liu, Jun-Xia; Chongqing Key Laboratory of Human Engineering, Center for Reproductive Medicine, Women and Children's Hospital of Chongqing Medical University; Chongqing Clinical Research Center for Reproductive Medicine, Chongqing Health Center for Women and Children Xie, Juan; Chongqing Key Laboratory of Human Engineering, Center for Reproductive Medicine, Women and Children's Hospital of Chongqing Medical University; Chongqing Clinical Research Center for Reproductive Medicine, Chongqing Health Center for Women and Children Gao, Zhen; College of Animal Veterinary Medicine, Northwest A & F University Yang, Zhenshan; College of Veterinary Medicine, South China Agricultural University
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	ONCOLOGY, Adult oncology < ONCOLOGY, Oncogenes < ONCOLOGY

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Word count: 4031 words.

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21 **ABSTRACT**

22 **Objectives** Accumulating evidence suggested that the laminin  $\gamma$ 2 (LAMC2) expression level was



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4 23 upregulated in various cancers. However, the potential prognostic value of LAMC2 in cancers  
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6 24 remains unclear. We conducted a meta-analysis to clarify the association of LAMC2 expression  
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9 25 with prognosis.

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11 26 **Design** We searched Embase, Web of Science, and PubMed (up to 25 November 2021) to collect  
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14 27 all eligible studies, and meta-analysis was performed to interpret the association of LAMC2  
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17 28 expression with clinicopathological parameters, overall survival (OS), disease-specific survival  
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20 29 (DSS), and progression-free survival (PFS).

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22 30 **Eligibility criteria for including studies** We included studies that investigate the relationship  
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25 31 between LAMC2 and prognosis of cancers, patients were divided into two groups, and  
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28 32 associations of LAMC2 expression with clinicopathologic features were described.

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30 33 **Results** Seven studies were finally included. We found that increased LAMC2 expression was  
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33 34 significantly associated with lymph node metastasis (Log odds ratio [OR]: 0.88, 95% confidence  
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36 35 interval [CI]: 0.38-1.38,  $p < 0.001$ ), tumor-node-metastasis stages (Log OR: 0.95, 95% CI:  
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38 36 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  
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41 37 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,  
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44 38  $p = 0.75$ ). In addition, higher LAMC2 expression was found to be significantly associated with  
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47 39 OS/PFS/DSS (Hazard ratio [HR]: 1.85, 95% CI: 1.31-2.40,  $p < 0.001$ ). A similar result was found  
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50 40 in The Cancer Genome Atlas database. High LAMC2 expression was significantly associated with  
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53 41 OS in lung adenocarcinoma, mesothelioma, skin cutaneous melanoma, neck squamous cell  
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55 42 carcinoma, and brain lower grade glioma.

56 43 **Conclusion** Our results suggested that higher LAMC2 expression was correlated with worse  
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59 44 survival, lymph node metastasis, tumor-node-metastasis stages, and tumor status. This study was  
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4 45 subject to inherent limitations, but the results presented here provide insights regarding the  
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7 46 potential use of LAMC2 as a biomarker for human cancer.

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9 47 **Study registration** researchregistry.com (researchregistry1319).  
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#### 13 14 49 **Strengths and limitations of this study**

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17 50 This systematic review and meta-analysis provide comprehensive literature published up to  
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19 51 November 2020 was performed in Embase, Web of Science, and PubMed.

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22 52 This study adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
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24 53 guidelines.

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27 54 Additional data sources, such as grey literature, were not searched.  
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#### 31 32 56 **KEY WORDS**

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35 57 Cancer, Laminin  $\gamma$ 2 (LAMC2), Meta-analysis, Prognosis  
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#### 39 40 59 **INTRODUCTION**

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43 60 Laminins are trimeric proteins composed of  $\alpha$ ,  $\beta$ , and  $\gamma$  chains which are the main component of  
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45 61 basement membranes.<sup>1</sup> Mammalian genome encodes five  $\alpha$  chains, four  $\beta$  chains, and three  $\gamma$   
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47 62 chains.<sup>2</sup> Loss-of-function studies show that most laminin mutants are embryonic lethal.<sup>3</sup> Laminins  
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49 63 are involved in various biological processes, including cellular phenotype maintenance, adhesion,  
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51 64 migration, growth, and differentiation *in vivo* and *in vitro*.<sup>4,5</sup>  
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59 66 In recent years, laminin  $\gamma$ 2 (LAMC2) has attracted increasingly attractive because of the  
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4 67 aberrant expression of LAMC2 in various cancer. The LAMC2 expression was significantly  
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6 68 upregulated in colorectal cancer tissues compared with adjacent normal tissues, and high LAMC2  
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9 69 expression is known to be associated with poor patient prognosis.<sup>6</sup> Furthermore, overexpression of  
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11 70 LAMC2 has been reported in pancreatic ductal adenocarcinoma,<sup>7-11</sup> non-small cell lung cancer,<sup>12</sup>  
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14 71 penile squamous cell carcinoma,<sup>13</sup> ovarian cancer,<sup>14</sup> Oral tongue squamous cell carcinoma,<sup>15</sup>  
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17 72 Cholangiocarcinoma,<sup>16</sup> and esophageal squamous cell carcinoma,<sup>17</sup> leading to poor  
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19 73 clinicopathological features and short survival time.  
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25 75 However, individual studies may be inadequate and inaccurate due to their small sample and  
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27 76 study design. To date, there was no meta-analysis has been performed to investigate the  
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30 77 relationship between LAMC2 and the prognostic value. Therefore, we performed a comprehensive  
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32 78 meta-analysis to assess the correlation between LAMC2 and survival outcomes and  
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35 79 clinicopathological features in human cancers.  
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## 40 81 **METHODS**

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43 82 This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
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45 83 guidelines<sup>18</sup> (online supplemental table S1). and the protocol was published on Research Registry  
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48 84 (researchregistry1319).  
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### 53 86 **Patient and Public Involvement**

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56 87 No patient was involved.  
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## 89 **Search strategy**

90 A literature search was conducted in Embase, Web of Science, and PubMed (up to 25 November  
91 2021). The keywords were (laminin C2 OR LAMC2 OR laminin subunit gamma 2) AND  
92 (prognosis OR prognostic OR survival). The detailed search strategy is in supplemental file 1. The  
93 reference lists and citation sections of relevant studies were also screened for additional eligible  
94 studies.

## 96 **Study selection**

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

## 105 **Quality assessment**

106 The Newcastle-Ottawa Quality Assessment Scale (NOS) criteria was used to assess the quality of  
107 the eligible studies.<sup>19</sup> The NOS contains nine items that include selection, comparability, and  
108 outcome for studies. When the NOS score was  $\geq 6$ , the study was considered high quality.

## 110 **Data extraction**

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4 111 Two authors (T.F. and Z.-S.Y.) performed the data extraction independently. Disagreements were  
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6 112 resolved by discussion and consensus with the third author (J.X.). The following information from  
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9 113 the included studies was collected: the first author's name, publication year, country, number of  
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11 114 cases, cancer type, the detection method of LAMC2, clinicopathological features, and survival  
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14 115 outcome. When multivariate and univariate analyses were simultaneously reported, only the  
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17 116 former was extracted. If studies only provided Kaplan-Meier curves, the survival data were  
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20 117 extracted from the graphical curve and calculated HR and 95% CI were reckoned using the  
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22 118 published method.<sup>20</sup>  
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#### 27 120 **Public data and tools**

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30 121 The web-based tool named Gene Expression Profiling Interactive Analysis (GEPIA) was used to  
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32 122 analyze associations between LAMC2 and clinical outcomes.<sup>21</sup>  
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#### 38 124 **Statistical analysis**

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40 125 We used Stata MP 16 software (Stata, College Station, TX) to perform statistical analysis. Log  
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42 126 odds ratio (OR) and 95% confidence interval (CI) were calculated for the association of LAMC2  
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45 127 expression and clinicopathological characteristics. The prognostic role of LAMC2 expression in  
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48 128 overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) was  
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51 129 evaluated through Hazard ratio [HR] with 95% CI. The statistical heterogeneity among the studies  
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53 130 was analyzed by using  $I^2$  test and Q test. When significant heterogeneity ( $I^2 \geq 50\%$ ,  $p < 0.05$ )  
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56 131 was observed, the random-effects model was chosen. Otherwise, the fixed-effects model was used.  
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59 132 The Egger's test and Begg's test were used to assess the potential publication bias. We conducted  
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133 a sensitivity analysis to explore the stability of the overall meta-analysis results.  $p < 0.05$  was  
 134 considered as statistically significant.

135

## 136 RESULTS

### 137 Study identification and characteristics

138 As is shown in Figure 1, a total of seven studies with 1,056 patients with cancer were included in  
 139 this meta-analysis satisfied the inclusion criteria.<sup>6, 7, 16, 17, 22-24</sup> The publication period ranged from  
 140 2017-2021. All of our included studies had high quality with Newcastle-Ottawa Quality  
 141 Assessment Scale scores  $\geq 6$ . The included studies addressed six different cancer types:  
 142 esophageal squamous cell carcinoma (n = 1), pancreatic ductal adenocarcinoma (n = 2),  
 143 cholangiocarcinoma (n = 1), papillary thyroid cancer (n = 1), colorectal cancer (n = 1), and penile  
 144 squamous cell carcinoma (n = 1). The main characteristics of the seven studies are summarized in  
 145 Table 1.

147 **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

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4	Zhou et al.	2018	China	114	penile squamous cell carcinoma	IHC	DSS	7
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6	Huang et al.	2017	China	49	colorectal cancer	IHC	-	6
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148 Abbreviations: DSS, disease-specific survival; IHC, immunocytochemistry; NOS,  
 149 Newcastle-Ottawa scale; OS, overall survival; PFS, progression-free survival; qRT-PCR,  
 150 quantitative real-time polymerase chain reaction.

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### 152 Relationship between LAMC2 expression and clinicopathological parameters

153 We evaluated the relationship between LAMC2 expression and clinicopathological parameters  
 154 in various cancers. As shown in Figures 2A and B, there were three and six studies describing  
 155 patients of age and gender, respectively. The pooled analysis demonstrated that there was no  
 156 significant association between LAMC2 expression and age or gender. High expression of  
 157 LAMC2 was significantly associated with lymph node metastasis (LNM) (Log OR: 0.88, 95% CI:  
 158 0.38-1.38,  $p < 0.001$ , Figure 2C) and tumor-node-metastasis (TNM) stage (Log OR: 0.95, 95% CI:  
 159 0.39-1.50,  $p < 0.001$ , Figure 2D). There was significant heterogeneity among these studies ( $I^2 =$   
 160 59.61%,  $P = 0.02$ ;  $I^2 = 60.16%$ ,  $p = 0.03$ ), and thus the random-effects DerSimonian-Laird model  
 161 was adopted. A total of four studies evaluated tumor status according to LAMC2 expression. No  
 162 statistically significant heterogeneity was found among the studies ( $I^2 = 36.00%$ ,  $p = 0.20$ ); thus,  
 163 the fixed-effect Mantel-Haenszel model was adopted. As shown in Figure 2E, high expression of  
 164 LAMC2 was significantly associated with tumor status (Log OR: 1.26, 95% CI: 0.84-1.68,  $p <$   
 165 0.001). This finding suggests that high LAMC2 expression is associated with clinicopathological  
 166 features.

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## 168 **Relationship between LAMC2 expression and OS/PFS/DSS**

169 There were five studies including 872 patients presenting the relationship between LAMC2 and  
170 OS/PFS/DSS. Due to no significant heterogeneity being found among studies ( $I^2 = 0.00\%$ ,  $p =$   
171  $0.83$ ), the fixed-effect inverse-variance model was adopted to estimate the pooled HR and 95% CI.  
172 The pooled HR indicated that the expression of LAMC2 was negatively associated with  
173 OS/PFS/DSS (HR: 1.85, 95% CI: 1.31-2.40,  $p < 0.001$ , Figure 3A), which demonstrated that  
174 LAMC2 was a risk factor for the prognosis of cancer patients. In addition, sensitivity analysis was  
175 performed to determine the effect of individual studies on the OS/PFS/DSS. It revealed that no  
176 single study altered the pooled LAMC2 HR result significantly (Figure 3B). This suggested that  
177 the result of the meta-analysis was stable.

## 179 **Analysis of publication bias**

180 Funnel plot (Figure 3C), Begg's test, and Egger's linear regression test (Figure 3D) were used to  
181 assess publication bias. The results showed that the funnel plots scatter symmetrically. The  
182 statistical tests showed  $P$  values were greater than 0.05 (Begg's test:  $p = 0.4624$ ; Egger's test:  $p =$   
183  $0.329$ ). Thus, there was no obvious publication bias in the prognostic meta-analysis.

## 185 **Validation of TCGA data set results**

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



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4 190 cell carcinoma (LUSC), determined using a log<sub>2</sub>FC cutoff of 1 and a *p*-value cutoff of 0.01. A  
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6 191 total of 9502 patients with urinary, digestive, female reproductive, respiratory, and blood systems  
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9 192 cancers were included in the survival analysis from the TCGA database. According to the  
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11 193 expression of LAMC2, the patients were divided into high and low groups using the median score  
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14 194 as the cutoff by GEPIA.<sup>21</sup> The results showed that higher LAMC2 expression was correlated with  
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17 195 worse survival (Figure 4B). We also explored the prognostic role of LAMC2 in different cancer  
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19 196 types. As shown in Figure 5, LAMC2 expression was significantly associated with OS in LUAD  
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22 197 (Figure 5A), mesothelioma (MESO, Figure 5B), skin cutaneous melanoma (SKCM, Figure 5C),  
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25 198 HNSC (Figure 5D), and brain lower grade glioma (LGG, Figure 5E). However, LAMC2  
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27 199 expression was not related to OS in LUSC (Figure 5F).  
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## 32 201 **DISCUSSION**

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35 202 Laminins are involved in various cancer development and prognosis.<sup>25, 26</sup> Increasing evidence  
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37 203 suggests that the various laminin isoforms could be useful biomarkers of cancer diagnosis and  
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40 204 might be potential therapeutic targets for cancers treatment, such as LAMA5,<sup>27</sup> LAMB1,<sup>28</sup> and  
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43 205 LAMC1,<sup>29</sup> LAMC2 is encoding by Laminin  $\gamma$ 2 and has been confirmed as a therapeutic target for  
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46 206 cancers. Here we performed a meta-analysis of seven studies to achieve a comprehensive  
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49 207 evaluation between higher LAMC2 expression and clinicopathological characteristics in various  
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52 208 cancer types. Our results showed that higher LAMC2 expression was significantly associated with  
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55 209 LNM, TNM stage, and tumor status. However, there was no significant association between  
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58 210 LAMC2 expression and age or gender. Simultaneously, we also found that OS/PFS/DSS was  
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60 211 higher in patients with low LAMC2 expression. Publication bias analysis demonstrated that no

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4 212 publication bias was observed among the included studies. These results suggested that LAMC2  
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6 213 might be a valuable biomarker for predicting prognosis in cancer patients. Steyerberg et al.  
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9 214 provide the prognostic model that can provide effective solving discrimination and predictiveness  
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11 215 measures.<sup>30</sup> We will plan to investigate this in a later study.  
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17 217 Several kinds of research have shown that LAMC2 promotes cancer cells proliferation, motility,  
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19 218 and invasion.<sup>29-35</sup> However, the specific mechanism are not particularly well understood. There is  
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21 219 a study indicating that ZNF750 inhibited the migration of esophageal squamous cancer cells by  
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23 220 inhibiting the LAMC2 transactivation.<sup>31</sup> In hepatocellular carcinoma (HCC), LAMC2 has been  
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25 221 found to be regulated by miR-548c-3p and inhibited the epithelial-mesenchymal transition in  
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27 222 HCC.<sup>32</sup> In pancreatic cancer cells, LAMC2 promoted Akt-Ser473 phosphorylation and increased  
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29 223 expression and cell membrane accumulation of NHE1, promoting cell migration and invasion.<sup>33</sup> A  
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31 224 study by Wu et al. showed that the LAMP3-LAMC2-TNC signal regulated the efficacy of  
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33 225 radiation exposure in laryngeal squamous cell carcinoma.<sup>34</sup> High-throughput sequencing results  
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35 226 showed that miR-338-5p/3p targets LAMC2 to suppress invasion in salivary adenoid cystic  
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37 227 carcinoma cells.<sup>35</sup> LAMC2 was found to promote tumor progression by EGFR signaling.<sup>36, 37</sup> The  
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39 228 latest research showed that overexpression of LAMC2 enhances pancreatic ductal adenocarcinoma  
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41 229 metastasis and tumorigenesis through the EGFR/ERK1/2/AKT/mTOR signaling pathway.<sup>11</sup> These  
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43 230 findings suggested that LAMC2 might play as an oncogene and predict prognosis in cancer  
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45 231 patients.  
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49 233 Recent researches have also investigated LAMC2 as a valuable biomarker of cancer  
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4 234 diagnosis.<sup>38, 39</sup> Due to a limitation of the small sample size, we explored the expression of LAMC2  
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6 235 in various cancer types using the TCGA database. The results showed that LAMC2 was  
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9 236 upregulated in tumors and might be used as a biomarker for a variety of tumor types. Moreover,  
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11 237 we explore the survival analysis from the TCGA database. The results demonstrated that higher  
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14 238 LAMC2 expression was associated with poor OS in 9502 patients. We also explored the  
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17 239 prognostic role of LAMC2 in different types of cancer. LAMC2 expression was significantly  
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20 240 associated with OS in LUAD, MESO, SKCM, HNSC, and LGG, but not in LUSC. This deserves  
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22 241 further investigation.  
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27 243 Some potential limitations of our study should be noted. First, only seven articles were included  
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30 244 in our meta-analysis, the limited number of studies might influence the reliability of the results. Of  
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33 245 the seven included studies, five were from China, and two were from Japan. So, our results may  
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36 246 only be applicable to the Asian population. Although we determined data from the TCGA  
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38 247 database, future studies from non-Asian populations are needed to confirm our findings. Second,  
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41 248 there was no consensus on a cutoff value for higher LAMC2 expression. Third, in some  
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43 249 researches, the data for HR and 95% CI value was not provided. Although we tried our best to  
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46 250 extract the HR and 95% CI value from the Kaplan-Meier curve, some errors are inevitable. Fourth,  
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49 251 the numbers of patients and tumor types included in this meta-analysis were still limited. So, our  
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51 252 results may exaggerate the prognostic value of LAMC2.  
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## 55 254 **CONCLUSIONS**

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58 255 In conclusion, LAMC2 may be a valuable biomarker for cancer diagnosis, and upregulation of  
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4 256 LAMC2 is associated with a poor prognosis in cancer patients. And increased LAMC2 expression  
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6 257 was significantly associated with bad tumor status, tumor-node-metastasis stages, and lymph node  
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9 258 metastasis. For future clinical applications, more high-quality studies with large sample sizes are  
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11 259 needed to confirm the role of LAMC2 in various cancers and regions.  
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#### 17 261 **Acknowledgments**

18  
19 262 We sincerely thank Dr. Yang Wu for her support in this study.  
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22 263

#### 25 264 **Contributors**

26  
27 265 T.F and Z.-S.Y designed the study; T.F, Z.-S.Y, and J.X searched the literature and extracted data;  
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29 266 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  
30  
31 267 manuscript. All authors gave the final approval for the paper to be published.  
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38  
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42 271

#### 45 272 **Competing interests**

46  
47 273 The authors declare that they have no conflict of interest  
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#### 50 274 **Patient consent for publication**

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52 275 Not applicable.  
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#### 58 277 **Ethics approval**

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278 This study does not involve human participants.

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#### 280 **Data availability statement**

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

282

#### 283 **Abbreviations**

284 CI, confidence interval; COAD, colon adenocarcinoma; DLBS, lymphoid neoplasm diffuse large

285 B-cell lymphoma; DSS, disease-specific survival; ESCA, esophageal carcinoma; GEPIA, gene

286 expression profiling interactive analysis; HCC, hepatocellular carcinoma; HNSC, head and neck

287 squamous cell carcinoma; HR, hazard ratio; IHC, immunocytochemistry; LAMC2, laminin

288 subunit gamma 2; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; LUSC, lung

289 squamous cell carcinoma; MESO, mesothelioma; NOS, Newcastle-Ottawa Quality Assessment

290 Scale; OR, odds ratio; OS, overall survival; PFS, progression-free survival; qRT-PCR,

291 quantitative real-time polymerase chain reaction; RNA-seq, RNA sequencing; SKCM, skin

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

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9 390 **Figure legends**

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11 391 **Figure 1 Flow diagram of the literature search and selection**

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17 393 **Figure 2 Forest plots of studies evaluating the relationship between LAMC2 expression and**  
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19 394 **clinicopathological features**

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22 395 (A) LNM, (B) TNM stage, (C) tumor status, (D) gender, (E) age.  
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27 397 **Figure 3 The relationship between LAMC2 expression and OS/PFS/DSS**

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30 398 (A) Forest plot for the meta-analysis of OS/PFS/DSS. (B) Sensitivity analysis for LAMC2  
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32 399 expression with OS/PFS/DSS. (C) Funnel plot for the meta-analysis of OS/PFS/DSS. (D) Egger's  
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34 400 graph for analyzing publication bias.  
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40 402 **Figure 4 The expression of LAMC2 in the TCGA database**

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43 403 (A) LAMC2 expression in COAD, DLBC, ESCA, HNSC, LUAD, and LUSC. \* =  $p$  value < 0.01.  
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45 404 (B) OS rate of LAMC2 expression in TCGA database (n = 9502). Gray boxes indicate normal,  
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47 405 and red boxes indicate tumor. T, tumor; N, normal.  
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53 407 **Figure 5 Kaplan-Meier curves showing the prognostic value of LAMC2 in the TCGA**  
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55 408 **database**

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58 409 (A) LUAD, (B) MESO, (C) SKCM, (D) HNSC, (E) LGG, (F) LUSC.  $p$  values were calculated  
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410 using the log-rank test.

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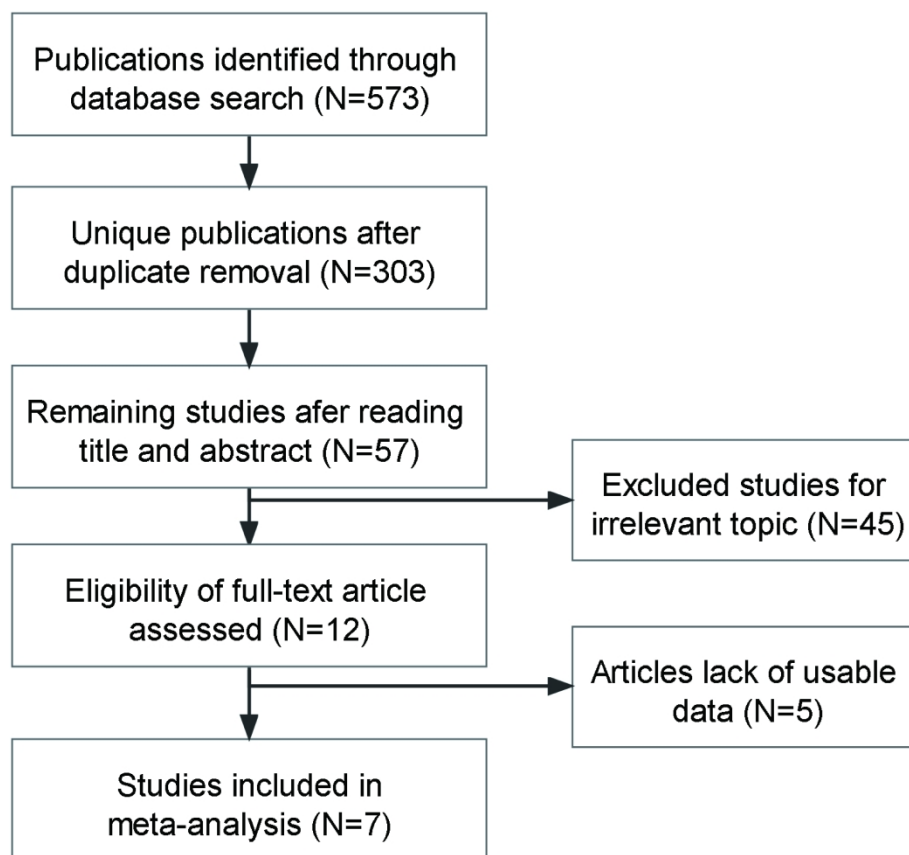


Figure1

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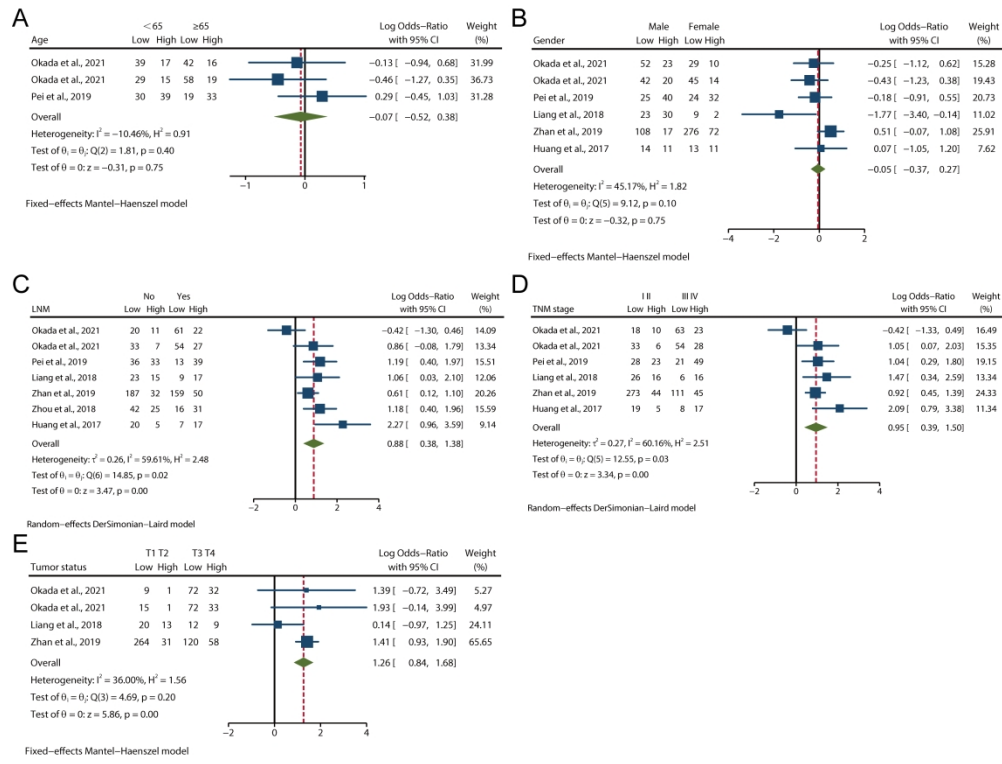


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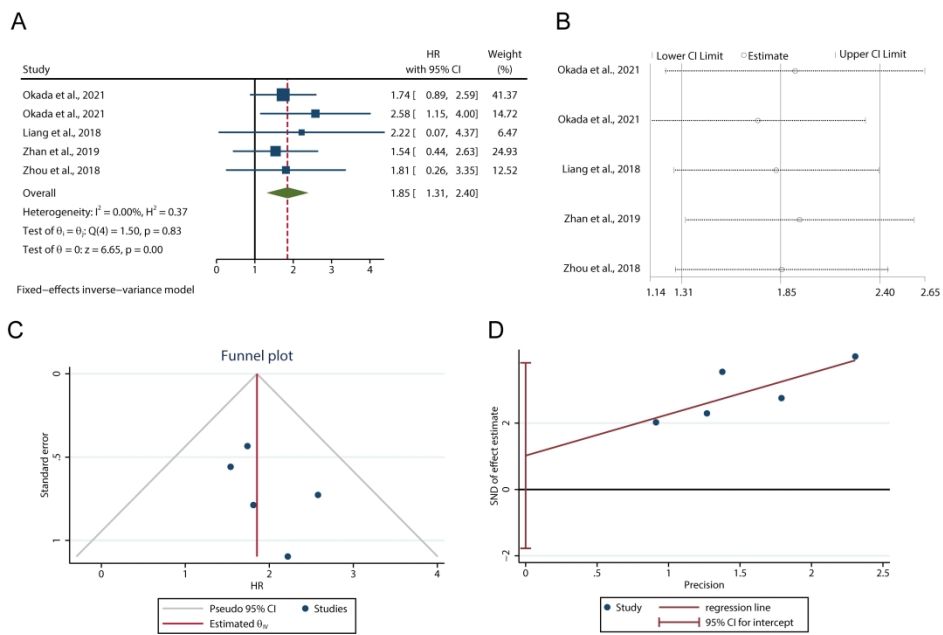


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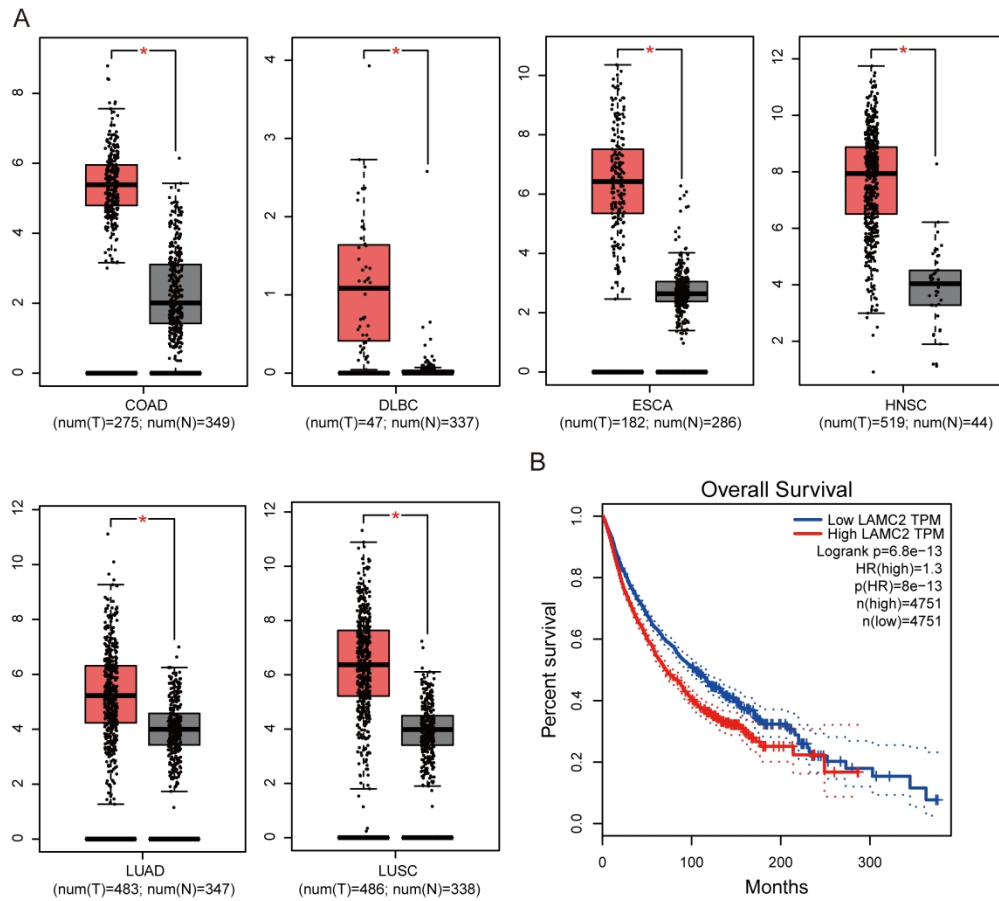


Figure4

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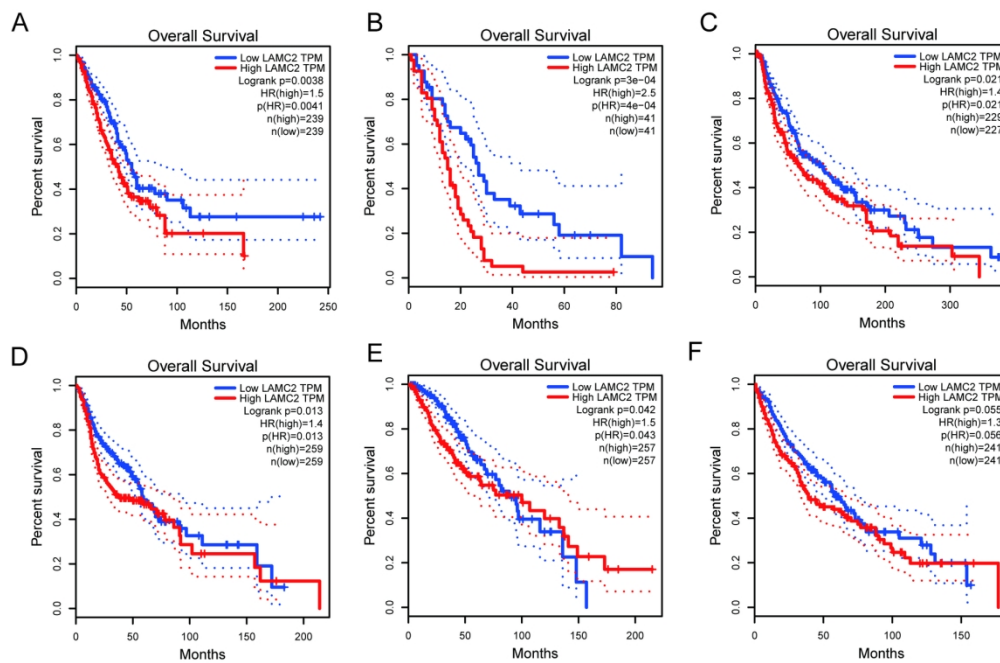


Figure5

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PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Page 1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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. For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	Page 6



## PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>OTHER INFORMATION</b>			
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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For more information, visit: <http://www.prisma-statement.org>

**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))