Clinicopathological and prognostic significance of sialyl Lewis X overexpression in patients with cancer: a meta-analysis

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Abstract: Many studies have shown that sialyl Lewis X (sLeX) is related to cancer prognosis and clinicopathology, but failed to provide conclusive results. We conducted the present meta-analysis to identify the association between sLeX overexpression and cancer prognosis. We searched studies in PubMed and Embase databases. Relative risk or hazard ratio with 95% confidence intervals were estimated with the Mantel–Haenszel random-effect method and 29 studies were included. Our meta-analysis showed that sLeX overexpression is significantly related to lymphatic invasion, venous invasion, T stage, N stage, M stage, tumor stage, recurrence, and overall survival. In subgroup analysis, we found that cancer type and ethnicity might be two major contributing factors to the possible presence of heterogeneity among the studies. In conclusion, sLeX overexpression is associated with tumor metastasis, recurrence, and overall survival in cancer patients, it plays an important role in cancer prognosis.

Keywords: sialyl Lewis X, cancer, prognosis, meta-analysis

Introduction

As is known to all, cancer is a common life-threatening disease. According to recent studies, the incidence of cancer increases 1% per year in Europe.¹ Among the adult population, a rising trend is reported for soft tissue sarcoma.² Breast, colorectal, prostate, and lung cancers are the most common oncological cause for death among the European population.³ Cancer cannot be cured, as expected, due to the limited knowledge of iatrotechnique. So, exploration of more precise bio-indicators is valuable for early diagnosis of cancer and improving prognosis of patients.

Cell surface carbohydrates are involved in various biological processes such as cellular differentiation, maturation, proliferation, and malignant transformation.⁴ Dramatic changes of cell surface carbohydrates are associated with cancer occurrence, tumor invasiveness, and metastatic behavior.⁵ Sialyl Lewis X (sLeX) (NeuNAcα1,4[Galβ1,4(Fucα1,3)] GlcNAc), a carbohydrate antigen, is related to cell adhesion and our previous study showed that inhibition of sLeX synthesis leads to decreased adhesion of trophoblast cells to endometrial epithelial cells.⁶ Also, sLeX is frequently expressed in human cancer cells and primary tumors.⁷ ⁸ As a ligand for E-selectin and L-selectin, sLeX is related to cell adhesion.⁹ It has been demonstrated that sLeX was involved in the adhesion of tumor cells to vascular endothelium.¹⁰ The potential role of sLeX in the tumor metastatic process has been supported by several clinical studies.¹¹–¹⁴

Many studies have identified the relationship between sLeX and cancer prognosis, but individual studies of the influence of sLeX expression in cancer have failed to...
provide conclusive results. The present meta-analysis was
carried out to further explore the relationship between sLeX
expression and cancer prognosis and clinicopathology.

Materials and methods

Publication search

We searched published studies in the PubMed and Embase
databases up to May 2014 with the following search terms:
(slex OR sialyl lewis x) AND (cancer OR neoplasms
OR carcinoma OR tumor) AND prognosis. Furthermore,
reference lists of main reports and review articles were also
reviewed to identify additional relevant publications. The
study was conducted and reported following the PRISMA
(Preferred Reporting Items for Systematic Reviews and
Meta-Analyses) guidelines.

Selection criteria

Two authors (YL and JXL) reviewed the retrieved titles and
abstracts to discriminate the eligible studies for inclusion in
our meta-analysis independently. Published studies were
included based on the following criteria: 1) written and
published in English; 2) patients with cancer diagnosis by
pathology; 3) studies about sLeX expression in cancer tissues;
4) sLeX expression was measured by immunohistochemistry
(IHC) method; 5) full length paper with sufficient data on
sLeX expression and prognosis and prognosis-related factors;
6) we could find the full text. We excluded studies with the
following criteria: 1) written and published in a language
other than English; 2) studies about cell lines and animals;
3) studies about sLeX expression in serum; 4) review articles
without original data; 5) a commentary, letter to the editor,
or monograph.

Data extraction

Two authors (YL and WG) performed the data evaluation
independently. The following data were extracted from
each study: the first author’s last name; publication year;
country; cancer source; number of patients; number of sLeX
expressions (positive/negative); clinicopathological factors
(age, sex, tumor size, histological differentiation, lymphatic
invasion, venous invasion, T/N/M stage, tumor stage, and
recurrence); survival analysis.

Data synthesis and statistical analysis

Expression of sLeX was analyzed as dichotomous variables,
as positive expression versus negative expression. The clin-
icopathological factors were also conducted as dichotomous
variables, as older age versus younger age for age; male
versus female for sex; large versus small for tumor size;
high versus low for histological differentiation; I and II
versus III and IV for tumor stage; pT2 versus more than
pT3 for depth of invasion (T stage); with versus without for
lymphatic invasion, venous invasion, lymph node metastasis
(N stage), distant metastasis (M stage), recurrence. Survival
of sLeX expression was analyzed by Cox’s regression analysis
conducted as hazard ratio (HR) and 95% confidence interval
(95% CI). The data of expression of sLeX and clinicopatho-
logical factors or survival rate were extracted and calculated
by initial data of studies. These data were analyzed with
random-effect method, and were measured in relative risk
(RR) with 95% CI. Statistical heterogeneity was estimated
by means of Cochran’s Q test and I² test. The I² test repre-
sents the percentage of variation to heterogeneity, which
is categorized as low (0%–40%), moderate (40%–60%),
high (60%–90%), very high (>90%). Subgroup analyses
were carried out based on cancer or country of the included
studies if a significant heterogeneity was found in overall
meta-analysis. To identify any potential publication bias,
we used Begg’s test. All statistical analyses were performed
with Review Manager 5.2 and STATA 12.0.

Results

Systematic review

We identified 178 studies that fit our search strategy,
41 studies were identified in our primary search (Figure 1).
Finally, 29 studies published between 1993 and 2013 were
included in our meta-analysis. Detailed characteristics
of these studies are provided in Table 1.

Association of sLeX expression with
cancer prognosis and clinicopathology

sLeX expression correlated with prognostic factors, includ-
ing lymphatic invasion (lymphatic invasion versus non-
lymphatic invasion) (pooled RR = 1.36, 95% CI: 1.15–1.61,
I² = 62.3%), venous invasion (venous invasion versus non-
venous invasion) (pooled RR = 1.41, 95% CI: 1.18–1.67,
I² = 52.9%), T stage (pT3–4 stage versus pT2 stage) (pooled
RR = 1.14, 95% CI: 1.04–1.27, I² = 59.6%), N stage (lymph
node metastasis versus non-lymph node metastasis)
(pooled RR = 1.46, 95% CI: 1.29–1.66, I² = 55.1%), M stage
(distant metastasis versus non-distant metastasis) (pooled
RR = 1.76, 95% CI: 1.34–2.31, I² = 42.1%), tumor stage
(stage III/IV versus stage I/II) (pooled RR = 1.42, 95% CI:
1.19–1.68, I² = 69.9%), tumor recurrence (recurrence versus
non-recurrence) (pooled RR = 2.92, 95% CI: 2.02–4.23,
I² = 0%) (Figure 2A).
128 studies were identified in the PubMed search
123 studies were identified in the Embase search
73 studies were duplicates
178 potential relevant studies
136 records excluded after reviewing titles and abstracts
41 full-text articles reviewed for relevance to key question
1 study was excluded because of ineligible study object
11 studies were excluded because they lacked sufficient information to calculate effect estimates
29 studies were included in qualitative synthesis
29 studies were included in meta-analysis

Figure 1 The flow diagram of included/excluded studies.

Meantime, we found that sLe\textsuperscript{X} overexpression was not significantly related to cancer prognosis and clinicopathology factors, including age (older versus younger) (pooled RR =1.08, 95% CI: 0.97–1.21, \(I^2=0.0\%\)), sex (male versus female) (pooled RR =0.97, 95% CI: 0.88–1.07, \(I^2=47.0\%\)), tumor size (larger versus smaller) (pooled RR =1.23, 95% CI: 0.94–1.62, \(I^2=51.1\%\)), tumor differentiation (lower differentiation versus higher differentiation) (pooled RR =0.94, 95% CI: 0.72–1.21, \(I^2=75.1\%\)) (Figure 2B).

sLe\textsuperscript{X} overexpression on cancer survival
Eight studies analyzed the overall survival (OS) of human cancer with positive/negative sLe\textsuperscript{X} overexpression, the HRs ranged from 2.42 to 9.10.\textsuperscript{18,30,32,34–36,38,39} The summarized HR of negative versus positive was 3.11 (95% CI: 2.25–4.32) with low heterogeneity (\(I^2=0.0\%\)) (Figure 3).

Subgroup analyses
We chose subgroup analyses in meta-analysis with relative high heterogeneity (\(I^2>40\%\)). In subgroup analyses, studies were stratified by cancer category (colorectal cancer, gastric cancer, lung cancer, breast cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, oral squamous cell carcinoma, gallbladder cancer, pancreatic ductal adenocarcinoma, prostate cancer, and extrahepatic bile duct carcinoma) or ethnicity (Asia, America, and Europe). In addition, most of these analyses showed low heterogeneity after stratification (Tables 2 and 3).

Publication bias
Begg’s test was created for assessment of possible publication bias. It suggested that publication bias had little influence on these meta-analysis results (\(P>0.05\)) (Figure 4).

Discussion
The cancer statistics of the USA, in 2013,\textsuperscript{41} clearly indicated that the methods of treatment for cancer need to be improved. Exploring new molecular biological prognostic and predictive markers is a hot topic in modern medicine. Nakagoe et al first reported that sLe\textsuperscript{X} was expressed in serum
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Cancer source</th>
<th>Number of patients</th>
<th>sLeX expression (positive/negative)</th>
<th>Clinicopathological factors</th>
<th>Survival analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamori et al^1^ (1993)</td>
<td>Japan</td>
<td>Colorectal cancer</td>
<td>132</td>
<td>50/82</td>
<td>Sex, differentiation, T stage, N stage, lymphatic invasion, venous invasion, tumor stage, recurrence</td>
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</tr>
<tr>
<td>Yamaguchi et al^2^ (1994)</td>
<td>Japan</td>
<td>Colorectal cancer</td>
<td>170</td>
<td>56/114</td>
<td>Differentiation, T stage, N stage, lymphatic invasion, venous invasion, tumor stage, recurrence</td>
<td>NA</td>
</tr>
<tr>
<td>Idikio^3^ (1997)</td>
<td>Canada</td>
<td>Prostate cancer</td>
<td>38</td>
<td>30/8</td>
<td>Age, sex, differentiation, T stage, N stage, lymphatic invasion, venous invasion, tumor stage</td>
<td>NA</td>
</tr>
<tr>
<td>Nakamori et al^4^ (1997)</td>
<td>Japan</td>
<td>Colorectal cancer</td>
<td>159</td>
<td>58/101</td>
<td>N stage, M stage, lymphatic invasion, venous invasion, tumor stage</td>
<td>NA</td>
</tr>
<tr>
<td>Shimodaira et al^5^ (1997)</td>
<td>Japan</td>
<td>Colorectal cancer</td>
<td>43</td>
<td>28/15</td>
<td>Tumor size, differentiation, T stage, N stage, lymphatic invasion, venous invasion, tumor stage</td>
<td>NA</td>
</tr>
<tr>
<td>Ura et al^6^ (1997)</td>
<td>Japan</td>
<td>Gastric cancer</td>
<td>110</td>
<td>91/19</td>
<td>T stage, N stage</td>
<td>NA</td>
</tr>
<tr>
<td>Baldus et al^7^ (1998)</td>
<td>Germany</td>
<td>Gastric cancer</td>
<td>127</td>
<td>85/42</td>
<td>Sex, tumor stage</td>
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</tr>
<tr>
<td>Farmer et al^8^ (1998)</td>
<td>United States</td>
<td>HNSCC</td>
<td>82</td>
<td>51/31</td>
<td>Age, sex, M stage, tumor stage</td>
<td>NA</td>
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<td>Fukuoka et al^9^ (1998)</td>
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<td>52</td>
<td>34/18</td>
<td>N stage, M stage</td>
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</tr>
<tr>
<td>Tatsumi et al^10^ (2000)</td>
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<td>Gastric cancer</td>
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<td>41/46</td>
<td>Differentiation, T stage, N stage, M stage, lymphatic invasion, venous invasion, tumor stage</td>
<td>NA</td>
</tr>
<tr>
<td>Kurahara et al^12^ (1999)</td>
<td>Japan</td>
<td>OSCC</td>
<td>70</td>
<td>24/46</td>
<td>M stage</td>
<td>NA</td>
</tr>
<tr>
<td>Takao et al^13^ (1999)</td>
<td>Japan</td>
<td>EBDC</td>
<td>73</td>
<td>45/28</td>
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<tr>
<td>Futamura et al^14^ (2000)</td>
<td>Japan</td>
<td>Gastric cancer</td>
<td>245</td>
<td>135/110</td>
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<td>NA</td>
</tr>
<tr>
<td>Grabowski et al^15^ (2000)</td>
<td>Germany</td>
<td>Colorectal cancer</td>
<td>182</td>
<td>103/79</td>
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<td>Multi</td>
</tr>
<tr>
<td>Nakagoe et al^16^ (2000)</td>
<td>Japan</td>
<td>Colorectal cancer</td>
<td>101</td>
<td>76/25</td>
<td>Tumor stage</td>
<td>Uni</td>
</tr>
<tr>
<td>Machida et al^17^ (2001)</td>
<td>Japan</td>
<td>Lung cancer</td>
<td>25</td>
<td>19/6</td>
<td>Tumor size, N stage, M stage, lymphatic invasion, venous invasion, tumor stage</td>
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<tr>
<td>Takahashi et al^18^ (2001)</td>
<td>Japan</td>
<td>PDAC</td>
<td>23</td>
<td>15/8</td>
<td>Differentiation, N stage, M stage, tumor stage</td>
<td>Multi</td>
</tr>
<tr>
<td>Baldus et al^19^ (2002)</td>
<td>Germany</td>
<td>Colorectal cancer</td>
<td>243</td>
<td>165/78</td>
<td>N stage, M stage, venous invasion</td>
<td>NA</td>
</tr>
<tr>
<td>Nakagoe et al^21^ (2002)</td>
<td>Japan</td>
<td>Breast cancer</td>
<td>87</td>
<td>37/50</td>
<td>Age, differentiation, T stage, N stage, M stage, tumor stage</td>
<td>Multi</td>
</tr>
<tr>
<td>Nakagoe et al^22,23^ (2002)</td>
<td>Japan</td>
<td>Gastric cancer</td>
<td>101</td>
<td>31/70</td>
<td>Age, sex, tumor size, differentiation, T stage, N stage, lymphatic invasion, venous invasion</td>
<td>Multi</td>
</tr>
<tr>
<td>Yu et al^25^ (2005)</td>
<td>People’s Republic of China</td>
<td>Lung cancer</td>
<td>61</td>
<td>40/21</td>
<td>Age, sex, T stage, N stage, recurrence</td>
<td>Uni</td>
</tr>
<tr>
<td>Faried et al^26^ (2007)</td>
<td>Japan</td>
<td>ESCC</td>
<td>130</td>
<td>40/90</td>
<td>Sex, differentiation, T stage, N stage, M stage, lymphatic invasion, venous invasion, tumor stage</td>
<td>Multi</td>
</tr>
<tr>
<td>Croce et al^27^ (2008)</td>
<td>Argentina</td>
<td>HNSCC</td>
<td>125</td>
<td>29/96</td>
<td>Age, sex, differentiation, T stage, N stage, M stage, tumor stage</td>
<td>NA</td>
</tr>
<tr>
<td>Sozzani et al^28^ (2008)</td>
<td>Italy</td>
<td>Breast cancer</td>
<td>127</td>
<td>37/90</td>
<td>Differentiation, T stage, N stage, venous invasion</td>
<td>NA</td>
</tr>
<tr>
<td>Portela et al^29^ (2011)</td>
<td>Spain</td>
<td>Colorectal cancer</td>
<td>155</td>
<td>67/88</td>
<td>Age, sex, tumor size, differentiation, T stage, N stage, M stage, tumor stage</td>
<td>NA</td>
</tr>
<tr>
<td>Schiffmann et al^30^ (2012)</td>
<td>Germany</td>
<td>Colorectal cancer</td>
<td>215</td>
<td>102/113</td>
<td>Sex, differentiation, T stage, N stage, M stage</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; OSCC, oral squamous cell carcinoma; EBDC, extrahepatic bile duct carcinoma; PDAC, pancreatic ductal adenocarcinoma; Multi, Multivariate; Uni, Univariate; sLeX, sialyl Lewis X; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma.
Figure 2 (Continued)
Figure 2 The association between sLe\textsuperscript{X} and cancer prognostic factors.

Notes: (A) The cancer prognostic factors which were significantly related to sLe\textsuperscript{X} overexpression. (a) Lymphatic invasion; (b) venous invasion; (c) T stage; (d) N stage; (e) M stage; (f) tumor stage; (g) recurrence. (B) The cancer prognostic factors which were not significantly related to sLe\textsuperscript{X} overexpression. (a) Age; (b) sex; (c) tumor size; (d) differentiation. Weights are from random effects analysis.

Abbreviations: RR, relative risk; CI, confidence interval; sLe\textsuperscript{X}, sialyl Lewis X.
Figure 3 Meta-analysis with a random-effect model for the association of sLe\textsuperscript{X} overexpression with overall survival.

Note: Weights are from random effects analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; sLe\textsuperscript{X}, sialyl Lewis X.

Table 2 Subgroup analyses of country

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Summary RR (95% CIs)</th>
<th>I\textsuperscript{2} value</th>
<th>p\textsubscript{h}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>12</td>
<td>0.97 (0.88, 1.07)</td>
<td>47.0%</td>
</tr>
<tr>
<td>Asia</td>
<td>7</td>
<td>0.92 (0.80, 1.06)</td>
<td>56.5%</td>
</tr>
<tr>
<td>Europe</td>
<td>3</td>
<td>0.99 (0.83, 1.18)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Americas</td>
<td>2</td>
<td>1.13 (0.95, 1.34)</td>
<td>24.2%</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5</td>
<td>1.23 (0.94, 1.62)</td>
<td>51.1%</td>
</tr>
<tr>
<td>Asia</td>
<td>4</td>
<td>1.43 (1.16, 1.77)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
<td>0.85 (0.62, 1.16)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17</td>
<td>0.94 (0.72, 1.21)</td>
<td>75.1%</td>
</tr>
<tr>
<td>Asia</td>
<td>11</td>
<td>1.11 (0.80, 1.55)</td>
<td>82.3%</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>0.66 (0.46, 0.93)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Americas</td>
<td>2</td>
<td>0.63 (0.25, 1.57)</td>
<td>67.8%</td>
</tr>
<tr>
<td><strong>Venous invasion</strong></td>
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<td></td>
</tr>
<tr>
<td>Overall</td>
<td>13</td>
<td>1.41 (1.18, 1.67)</td>
<td>52.9%</td>
</tr>
<tr>
<td>Asia</td>
<td>12</td>
<td>1.49 (1.29, 1.72)</td>
<td>31.0%</td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
<td>0.69 (0.42, 1.11)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>18</td>
<td>1.14 (1.04, 1.27)</td>
<td>59.6%</td>
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<tr>
<td>Asia</td>
<td>13</td>
<td>1.23 (1.03, 1.47)</td>
<td>67.5%</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1.11 (1.05, 1.19)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Americas</td>
<td>1</td>
<td>0.91 (0.71, 1.17)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>23</td>
<td>1.46 (1.29, 1.66)</td>
<td>55.1%</td>
</tr>
<tr>
<td>Asia</td>
<td>17</td>
<td>1.53 (1.28, 1.82)</td>
<td>65.7%</td>
</tr>
<tr>
<td>Europe</td>
<td>5</td>
<td>1.40 (1.21, 1.61)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Americas</td>
<td>1</td>
<td>1.23 (0.83, 1.83)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>M stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>14</td>
<td>1.76 (1.34, 2.31)</td>
<td>42.1%</td>
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<tr>
<td>Asia</td>
<td>9</td>
<td>2.20 (1.47, 3.30)</td>
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</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1.37 (1.09, 1.72)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Americas</td>
<td>1</td>
<td>0.89 (0.39, 2.05)</td>
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<tr>
<td><strong>Tumor stage</strong></td>
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<td></td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>1.42 (1.19, 1.68)</td>
<td>69.9%</td>
</tr>
<tr>
<td>Asia</td>
<td>9</td>
<td>1.62 (1.24, 2.10)</td>
<td>69.4%</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1.32 (1.10, 1.59)</td>
<td>22.3%</td>
</tr>
<tr>
<td>Americas</td>
<td>2</td>
<td>1.08 (0.79, 1.49)</td>
<td>58.7%</td>
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</tbody>
</table>

Note: p\textsubscript{h}: P-value for heterogeneity within each subgroup.

Abbreviations: RR, relative risk; CI, confidence interval; NA, not available.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of studies</th>
<th>Summary RR (95% CIs)</th>
<th>P value</th>
<th>Pw</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>12</td>
<td>0.97 (0.88, 1.07)</td>
<td>47.0%</td>
<td>0.036</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4</td>
<td>0.92 (0.80, 1.06)</td>
<td>0.0%</td>
<td>0.978</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3</td>
<td>1.12 (0.97, 1.29)</td>
<td>0.0%</td>
<td>0.981</td>
</tr>
<tr>
<td>HNSCC</td>
<td>2</td>
<td>1.13 (0.95, 1.34)</td>
<td>24.2%</td>
<td>0.251</td>
</tr>
<tr>
<td>EBDC</td>
<td>1</td>
<td>0.79 (0.59, 1.07)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>0.61 (0.44, 0.83)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESCC</td>
<td>1</td>
<td>0.96 (0.82, 1.11)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>5</td>
<td>1.23 (0.94, 1.62)</td>
<td>51.1%</td>
<td>0.085</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>2</td>
<td>0.99 (0.68, 1.44)</td>
<td>46.7%</td>
<td>0.171</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1</td>
<td>1.38 (0.98, 1.93)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>1.42 (0.42, 4.85)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1</td>
<td>1.60 (1.13, 2.27)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17</td>
<td>0.94 (0.72, 1.21)</td>
<td>75.1%</td>
<td>0.000</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>8</td>
<td>1.06 (0.74, 1.52)</td>
<td>69.6%</td>
<td>0.022</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3</td>
<td>0.63 (0.53, 0.73)</td>
<td>0.0%</td>
<td>0.978</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>1.07 (0.72, 1.60)</td>
<td>0.0%</td>
<td>0.548</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1</td>
<td>0.87 (0.53, 1.41)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EBDC</td>
<td>1</td>
<td>2.70 (0.84, 8.63)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESCC</td>
<td>1</td>
<td>1.46 (0.81, 2.64)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HNSCC</td>
<td>1</td>
<td>0.39 (0.15, 1.01)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Lymphatic invasion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>1.36 (1.15, 1.61)</td>
<td>62.3%</td>
<td>0.005</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4</td>
<td>1.36 (1.09, 1.68)</td>
<td>56.7%</td>
<td>0.074</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2</td>
<td>1.23 (0.55, 2.73)</td>
<td>85.4%</td>
<td>0.009</td>
</tr>
<tr>
<td>EBDC</td>
<td>1</td>
<td>1.31 (0.97, 1.78)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>2.53 (0.39, 16.31)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>1</td>
<td>1.39 (0.92, 2.11)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESCC</td>
<td>1</td>
<td>1.71 (1.40, 2.08)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Venous invasion</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>13</td>
<td>1.41 (1.18, 1.67)</td>
<td>52.9%</td>
<td>0.013</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5</td>
<td>1.57 (1.33, 1.84)</td>
<td>0.0%</td>
<td>0.746</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3</td>
<td>1.48 (1.04, 2.12)</td>
<td>35.6%</td>
<td>0.212</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1</td>
<td>0.69 (0.42, 1.11)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EBDC</td>
<td>1</td>
<td>0.95 (0.61, 1.49)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>3.16 (0.50, 19.87)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>1</td>
<td>1.05 (0.68, 1.64)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESCC</td>
<td>1</td>
<td>2.05 (1.48, 2.83)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>18</td>
<td>1.14 (1.04, 1.27)</td>
<td>59.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>7</td>
<td>1.22 (1.08, 1.38)</td>
<td>65.6%</td>
<td>0.008</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>4</td>
<td>1.04 (0.85, 1.28)</td>
<td>29.7%</td>
<td>0.234</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>0.66 (0.31, 1.40)</td>
<td>0.0%</td>
<td>0.895</td>
</tr>
<tr>
<td>EBDC</td>
<td>1</td>
<td>1.13 (0.79, 1.62)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>0.83 (0.66, 1.04)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>1</td>
<td>1.00 (0.47, 2.14)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ESCC</td>
<td>1</td>
<td>2.09 (1.43, 3.06)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HNSCC</td>
<td>1</td>
<td>0.91 (0.71, 1.17)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>23</td>
<td>1.46 (1.29, 1.66)</td>
<td>55.1%</td>
<td>0.001</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>9</td>
<td>1.54 (1.34, 1.75)</td>
<td>24.5%</td>
<td>0.226</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>4</td>
<td>1.28 (1.11, 1.47)</td>
<td>0.0%</td>
<td>0.393</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3</td>
<td>1.46 (1.04, 2.04)</td>
<td>41.6%</td>
<td>0.180</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3</td>
<td>2.00 (0.44, 8.97)</td>
<td>80.2%</td>
<td>0.006</td>
</tr>
<tr>
<td>EBDC</td>
<td>1</td>
<td>1.06 (0.57, 1.97)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

(Continued)
of patients with gastric and colorectal cancer as a tumor-associated carbohydrate antigen, which was also proven by clinicopathological and immunohistochemical studies. The relationship between sLe^X expression and cancer prognosis was identified by a number of studies, which did not show conformable results. To our knowledge, this is the first meta-analysis that systematically evaluates the relationship between sLe^X expression and cancer prognosis and clinicopathology.

In the present study, a combined analysis of 29 articles (3,253 cancer patients) which showed the detection of high sLe^X expression in tumor tissues with poor prognosis outcome in cancer patients was conducted. Our results indicated that sLe^X expression was significantly correlated with lymphatic invasion, venous invasion, deep invasion (T stage), lymph node metastasis (N stage), distant metastasis (M stage), tumor stage, tumor recurrence, and OS. On the other hand, although a high level of sLe^X expression was found in patients like the elderly, females, or patients with large size tumor and high differentiation, these results did not show any significance.

What makes sLe^X overexpression account for the poor prognosis in cancer? By chemical analyses, it was shown that sLe^X oligosaccharide was the minimal structure binding to E-, L-, and P-selectin, which was closely involved in the interaction between the endothelium and cancer cells. sLe^X is most commonly found in malignant tumors and plays a key role in cancer stem cell metastasis, hypoxia, and TNF-α, and promotes tumor adhesion, invasion, and metastasis by upregulating the sLe^X expression in the tumor microenvironment. In the present meta-analysis study, we also found that sLe^X expression was correlated with tumor recurrence. On the other hand, it is widely accepted that expression of cell surface carbohydrates is altered during malignant transformation and tumor progression, and may influence determination of metastatic behavior of tumor cells. It has been identified that sLe^X was a terminal tetrasaccharide moiety present on numerous membrane glycoproteins and glycolipids of epithelial and lymphatic cells. With such characters, a high level of sLe^X contributes to cell adhesion, metastasis, and invasion because the cell surface antigens can combine with other cells directly. sLe^X in conjunction with mucins, promotes cellular motility, thus contributing to tumor cell spreading and metastasis. Furthermore, sLe^X is expressed on granulocytes and monocytes which mediates inflammatory extravasation. However, the molecular biological mechanisms of how sLe^X overexpression affects the cancer prognosis are complicated and still need further exploration. For the first time, our meta-analysis study revealed that sLe^X could be a potential biomarker for poor cancer prognosis.
Figure 4 Begg’s test results of sLe-X overexpression and prognostic factors.

Notes: (A) Age; (B) sex; (C) tumor size; (D) differentiation; (E) lymphatic invasion; (F) venous invasion; (G) T stage; (H) N stage; (I) M stage; (J) tumor stage; (K) recurrence; (L) overall survival.

Abbreviations: sLe-X, sialyl Lewis X; SE, standard error.
Due to the differences in nationality and cancer types which could cause heterogeneity among the studies, we conducted a subgroup analysis. In the subgroup analysis, the sLe^x overexpression may play different roles caused by differentiation, venous invasion, T stage, M stage, tumor stage, and sex factors among different types of cancers. These factors contribute to the possible presence of heterogeneity between the studies. The difference might be owing to the molecular biological mechanisms of interactions between sLe^x overexpression, and the occurrence and development of different types of cancers. Otherwise, ethnicity may be another factor that contributes to heterogeneity in sex, tumor size, differentiation, venous invasion, T stage, and M stage. It might be owing to the differences in genetic backgrounds and the environment among different races. We also found high heterogeneity in some subgroups, because biological behavior of cancer might be affected by many possible factors during the complicated process of tumor development.

Some limitations of this meta-analysis need to be acknowledged. First, all published studies and papers were written in English, some related published or unpublished studies that met the inclusion criteria were missed. Most of the studies reported positive results, while studies of negative results were all rejected. Second, some cancers such as oral squamous cell carcinoma, gallbladder cancer, pancreatic ductal adenocarcinoma, prostate cancer, and extrahepatic bile duct carcinoma were included in only one article respectively, so we could not evaluate pooled data in subgroup analyses. Third, all of the included studies had data of the sLe^x expression which was detected by IHC methods. It might have some bias because of different antibodies and different standards of positive/negative sLe^x expression. However, it was not available for us to do a subgroup analysis to analyze the underlying bias of IHC on the pooled odds ratios or HRs. Finally, multivariate analyses were not performed on OS data in most included studies, we calculated the pooled HR only from available HRs.

In conclusion, our meta-analysis showed that a high level of sLe^x expression was significantly associated with lymphatic invasion, venous invasion, deep invasion, lymph node metastasis, distant metastasis, tumor stage, tumor recurrence, and OS in cancer. sLe^x might be a new prognostic biomarker, and it might become a new diagnostic and therapeutic target for cancer. Further studies are required to explore the molecular biological mechanisms of sLe^x and factors that caused significant heterogeneity in the present meta-analysis study.

Acknowledgments
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Disclosure
The authors declare no conflict of interest.

References


