

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	<p>Indicate the study’s design with a commonly used term in the title or the abstract</p> <p>This retrospectively study 259 cases of oesophageal signet ring cell carcinoma after oesophagectomy were obtained from the Surveillance, Epidemiology, and End Results database between 2006 and 2016.</p> <hr/> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found. LODDS is a superior prognostic factor for patients with oesophageal signet ring cell carcinoma after oesophagectomy than N stage.</p>
Introduction		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p>Signet ring cell carcinoma is a rare type of oesophageal cancer. Log odds of positive lymph nodes (LODDS) is a novel prognostic factor associated with lymph nodes. It is reported that LODDS is a better prognostic factor for many other type of cancer.</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p>As the study is based on Seer database, the population of 18 registries in the USA enrolled in the study. The purpose of this research was to explore a novel prognostic factor for oesophageal signet ring cell carcinoma by comparing two lymph node-related prognostic factors, log odds of positive lymph nodes (LODDS) and N stage. We hypothesized that LODDS is a better prognostic factor for oesophageal signet ring cell carcinoma.</p>
Methods		
Study design	4	<p>Present key elements of study design early in the paper</p> <p>A total of 259 cases of oesophageal signet ring cell carcinoma after oesophagectomy were obtained from the Surveillance, Epidemiology, and End Results database between 2006 and 2016. The prognostic values of LODDS and N stage for oesophageal signet ring cell carcinoma were evaluated by univariate and multivariate analyses. The Akaike information criterion (AIC) and the Harrell’s C-index were used to assess the value of two prediction models based on lymph nodes.</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. (1)</p> <p>All the cases in the study cohort were from the Surveillance,</p>

Epidemiology, and End Results (SEER) database (SEER 18 registries database with the additional treatment field, released in April 2019, www.seer.cancer.gov), SEER*Stat 8.3.6 software was installed to extract the information of patients with oesophageal SRC carcinoma diagnosed between 2006 and 2016 with surgical resection (Site recode is oesophagus, histology code is 8490/3 signet ring cell carcinoma; Year of diagnosis is 2006-2016; Surgery Primary Site codes is 30,40,50-55,80,90).

Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p>
		<p>(b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case</p> <p><i>A total of 17 variables were obtained from the SEER (18 registries custom database with additional treatment fields) database: age, insurance, marital status, sex, race, pathology grade, T stage, N stage, M stage, AJCC TNM stage, radiation sequence with surgery, chemotherapy, the number of total lymph nodes dissected, the number of positive lymph nodes, cause of death, survival time, and vital status. Patient deaths from all causes were regarded as uncensored cases for the overall survival analysis, while the cancer-specific survival analysis only involved deaths caused by oesophageal SRC cancer. The exclusion criteria were (1) cases with unknown TNM stage and (2) cases without accurate lymph node dissection information. Ultimately, 259 cases were enrolled in our study cohort.</i></p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</p> <p>All cases were restaged to the latest TNM staging system according to the AJCC Cancer Staging Manual(8th edition) [9]. Age as the continuous variable was divided into three groups (≤ 60, 61-70, > 70). The variable of marital status was classified into three category variables: married, single (divorced, separated, unmarried or domestic partner, never married, widowed) and unknown. The variable insurance was divided into three groups: insured (any Medicaid, insured, insured/no specifics), uninsured and unknown.</p>
Data sources/ measurement	8*	<p>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</p> <p>LODDS was calculated by $\log_e \left[\frac{(\text{PLN}+0.5)}{(\text{NLN}+0.5)} \right]$ [21]. PLN is the number of positive lymph nodes, and NLN is the number of negative lymph nodes. The numerator and denominator were increased by 0.5 to avoid</p>

singularity.

Bias	9	Describe any efforts to address potential sources of bias Choose as many cases as possible to study
Study size	10	Explain how the study size was arrived at SEER*Stat 8.3.6 software was installed to extract the information of patients with oesophageal SRC carcinoma diagnosed between 2006 and 2016 with surgical resection (Site recode is oesophagus, histology code is 8490/3 signet ring cell carcinoma; Year of diagnosis is 2006-2016; Surgery Primary Site codes is 30,40,50-55,80,90). The exclusion criteria were (1) cases with unknown TNM stage and (2) cases without accurate lymph node dissection information. Ultimately, 259 cases were enrolled in our study cohort
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 17 variables were obtained from the SEER (18 registries custom database with additional treatment fields) database: age, insurance, marital status, sex, race, pathology grade, T stage, N stage, M stage, AJCC TNM stage, radiation sequence with surgery, chemotherapy, the number of total lymph nodes dissected, the number of positive lymph nodes, cause of death, survival time, and vital status.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy . (e) Describe any sensitivity analyses X-Tile software version 3.6.1 (Yale University, USA) was used to establish the optimal cut-off values for OS analysis of LODDS. The LODDS was converted to three categorical variables: LODDS1 ($4.55 \leq \text{LODDS} \leq 1.90$), LODDS2 ($1.89 \leq \text{LODDS} \leq 0.15$), and LODDS3 ($0.16 \leq \text{LODDS} \leq 4.27$). Overall survival (OS) and cancer-specific survival (CSS) were estimated by the Kaplan - Meier method. Univariate and multivariate analyses were performed using a Cox proportional hazard regression model. Variables with statistical significance ($P < 0.1$) in univariate analysis were included in the multivariate analysis. The Akaike information criterion (AIC) and the Harrell's C-index were used to estimate the discriminative power of the Cox multivariate regression model (lower AIC indicates better model fit, higher Harrell's C-index indicates better degree of discrimination). All the statistical analyses were performed using SPSS version 25.0 (IBM, USA) and R software version 4.0.0 (R Foundation, Vienna, Austria). The statistical significance level was set at a P value less than 0.05.

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Results

Participants	13*	<p>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</p> <hr/> <p>(b) Give reasons for non-participation at each stage</p> <hr/> <p>(c) Consider use of a flow diagram</p> <p>(c) Cohort study—Summarise follow-up time (eg, average and total amount) The baseline characteristics of this cohort are shown in Table 1. A total of 259 oesophageal SRC patients with surgical resection were retained. Most of them were male (89.2%), married (77.2%), insured (83.8%) and non-Hispanic white (86.1%). The age of majority cases were 61-70 (43.2%). Due to the high degree of malignancy and rapid progression of SRC, more patients were pathologically graded as grade III-IV (82.6%), and more patients were stage III (50.2%) in the TNM stage system (as stage IV patients were rarely treated by surgery, without accurate lymph node information, they were excluded from the cohort). The mean follow - up time of this study cohort was 30 months (range, 1 - 127 months).</p>
Descriptive data	14*	<p>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</p> <hr/> <p>(b) Indicate number of participants with missing data for each variable of interest</p> <hr/> <p>Calculated by Kaplan - Meier method, the 5 - year overall survival and 5 - year cancer - specific survival rates were 27.0% and 41.3%, as shown in Figure 2</p>
Outcome data	15*	<p><i>Cohort study</i>—Report numbers of outcome events or summary measures over time</p> <hr/> <p><i>Case-control study</i>—Report numbers in each exposure category, or summary measures of exposure</p> <hr/> <p><i>Cross-sectional study</i>—Report numbers of outcome events or summary measures The Kaplan-Meier survival curves drawn with the N stage and LODDS categories as univariates are shown in Figure 3 (Figure 3). The analysis showed that OS and CSS decreased with the increasing N stage (log rank chi-squared score: OS 36.215, P<0.001, CSS 31.583, P<0.001, Figure 3 a, b). For LODDS, we observed that the LODDS category increased with decreasing OS and CSS (log rank chi-squared score: OS 46.162, P<0.001, CSS 41.178, P<0.001, Figure 3 c, d). The log rank chi-squared score of LODDS category was higher (OS 46.162, CSS 41.178) than that of N stage (OS 36.215, CSS 31.583).</p>
Main results	16	<p>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.</p> <hr/> <p>(b) Report category boundaries when continuous variables were categorized</p> <hr/> <p>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</p> <p>The results of Cox regression univariate analysis for each variable are shown in Table 1. Univariate analyses showed that insurance, race, radiation therapy, T stage, N stage, M stage, TNM stage and LODDS were potential prognostic factors for overall survival (OS) (p<0.1). Afterwards, Cox multivariate analyses were conducted to estimate N stage (Model 1) and</p>

LODDS (Model 2). As shown in Table 2, LODDS in Model 2 was an independent prognostic factor for oesophageal signet ring carcinoma patients after surgical resection ($P < 0.05$). Conversely, the p value of N stage in Model 1 was 0.122; thus, N stage was not a statistically significant prognostic factor in Model 1.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives LODDS has a certain degree of differentiation for them, which is also theoretically better than N stage.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias This study is designed to compare the predictive value of LODDS with N stage in the prediction of overall survival (OS) for patients with oesophageal SRC carcinoma after surgery. The study also has its limitations. First, as a retrospective study, selection bias is inevitable. At the same time, due to the low incidence of SRC carcinoma, the number of cases that can be included in the analysis is small, and it is expected that in the future, prospective multi-centre, large-sample studies will further confirm the conclusion. Second, in the SEER database, the scheme of radiotherapy programs, chemotherapy regimens, detailed surgical approach, comorbidities and other meaningful information on prognosis are not given. These will have a certain impact on the research conclusion. Third, due to the low incidence of the disease, we do not collect enough cases in our hospital for further external validation, which should be performed to reinforce the conclusion.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. In many studies, LODDS has been shown to be advantageous as a novel prognostic factor in many other types of cancer[14-16, 18, 20, 28-31]. Few studies have found this to be controversial[32]. However, whether LODDS is also a better prognostic indicator for oesophageal SRC carcinoma has not been studied. In our research, after we performed Kaplan-Meier survival analyses of OS and CSS stratified by N stage and LODDS, the log rank chi-squared score of LODDS was higher (OS 46.162 vs 36.215, CSS 41.178 vs 31.583). After multivariate Cox regression analyses of LODDS and N stages, LODDS was still an independent prognostic factor, while N stage was not (Table 2). We also noted that the multivariate prediction model constructed by LODDS has better goodness of fit and discriminatory power than the model constructed by N stage, as shown in Table 3. Consequently, we conclude that LODDS may be a better prognostic factor than N stage in patients with oesophageal SRC carcinoma after surgical resection. Our study confirmed the predictive value of LODDS for the prognosis of oesophageal SRC carcinoma.
Generalisability	21	Discuss the generalisability (external validity) of the study results For patients with oesophageal SRC carcinoma who underwent surgery, LODDS had superior prognostic efficacy over the N stage for estimating OS. Therefore, LODDS could be a superior prognostic factor for patients

with SRC carcinoma after oesophagectomy compared with N stage.

Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is basedv

the Capital Health Development Research Project, No. 2014-1-4021.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.