Comparisons of different lymph node staging systems for predicting overall survival of node-positive patients with renal cell carcinoma: a retrospective cohort study using the Surveillance, Epidemiology and End Results database

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ABSTRACT

Objectives To compare the prognostic values of three lymph node staging systems in renal cell carcinoma (RCC), including the number of positive lymph nodes (NPLN), lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS).

Design A retrospective cohort study using data from the Surveillance, Epidemiology and End Results (SEER) database.

Setting and participants 1904 patients with pathological N1 RCC, diagnosed from 2004 to 2015 and underwent nephrectomy combined with lymph node dissection, were identified from the SEER database.

Primary outcome measure The primary outcome of this study was overall survival (OS). Restricted cubic spline functions and multivariable Cox regression analyses were employed to characterise the associations of OS with NPLN, LNR and LODDS, respectively.

Results Data of 1904 eligible RCC patients were extracted from the SEER database. The mortality risks of RCC patients increased with the increasing of NPLN, LNR and LODDS. NPLN (NPLN3 vs NPLN1, HR 1.22, 95% CI 1.05 to 1.43, p=0.001), LNR (LNR3 vs LNR1, HR 1.46, 95% CI 1.28 to 1.67, p<0.001; LNR2 vs LNR1, HR 1.28, 95% CI 1.09 to 1.50, p=0.002) and LODDS (LODDS3 vs LODDS1, HR 1.48, 95% CI 1.28 to 1.72, p<0.001; LODDS2 vs LODDS1, HR 1.34, 95% CI 1.17 to 1.53, p<0.001) were all independent prognostic factors of OS. The predictive abilities of LNR (Akaike information criterion, AIC: 19576.3, optimism-corrected C-index: 0.673) and LODDS (AIC: 19579.2, optimism-corrected C-index: 0.676) were comparable, superior to NPLN (AIC: 19603.7, optimism-corrected C-index: 0.673). In subgroup analyses, the LODDS classification could better stratify survival of RCC patients, in particular for those with the number of dissected lymph nodes <13 or NPLN≤2.

Conclusions NPLN, LNR and LODDS were all independent predictors of OS in RCC. When compared with NPLN and LNR, LODDS had a better performance in survival prediction and risk stratification. The three metrics all had the potential to be integrated into future versions of the American Joint Committee on Cancer staging manual.

INTRODUCTION

Kidney and renal pelvis malignancies are the sixth most common cancers in men and the ninth most common cancers in women in the world, which account for 2.2% of new cancer cases and 1.8% of cancer deaths in 2020. In the USA alone, it is expected that 76080 new cases and 13780 deaths due to kidney and renal pelvis cancer will occur in 2021. Among all kidney neoplasms, renal cell carcinoma (RCC) is the most common histological subtype.

The therapeutic value of lymph node dissection (LND) in the management of RCC has been controversial. Some retrospective studies revealed survival benefits of LND whereas some did not. The only randomised controlled trial failed to exhibit
the association of LND with improved survival in low-risk patients.9 Though its impact on oncological outcomes has been questioned, LND can provide pathological assessment of node status which is also vitally important.10

According to the latest version of the American Joint Committee on Cancer (AJCC) manual, RCC patients with lymph node involvement were classified into N1 stages. Nevertheless, a small subcategory of node-positive patients had durable long-term survival, indicating the heterogeneity of these patients.11 In recent years, some lymph node staging systems including lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS) had been proved to be independent prognostic factors for several types of cancers.12–16 However, their data on RCC was rare. Liao et al17 reported node-positive RCC was rare. Liao et al17 reported node-positive RCC could be further stratified by LNR. The patients with LNR>35% were associated with worse cancer-specific survival than those with LNR<35% (HR 1.41, 95% CI 1.20 to 1.65, p<0.001). LODDS was incorporated into nomograms to predict overall and cancer-specific survival combined with other significant predictors for RCC. The nomograms were superior to the AJCC staging system in survival prediction.18 However, the prognostic roles of these metrics were not exhaustively investigated in these studies. Their thresholds for prognostication were not well explored either. Therefore, we constructed a contemporary cohort using the Surveillance, Epidemiology and End Results (SEER) database and aimed to comprehensively compare the abilities of these lymph-node metrics with respect to survival prediction and risk stratification. In addition, sensitivity analyses were performed to verify the robustness of the findings.

METHODS

Data source

The SEER programme (http://www.seer.cancer.gov), covering approximately 28% of the US population, was used to identify eligible patients in this study. The cancer-related data in this database were gathered from 1973 and could be freely provided to registered researchers. We used SEER*Stat software (V.8.3.6) to extract the relevant data.

Study population

The SEER database was queried for all cases who were diagnosed with kidney cancer between 2004 and 2015. The cases were further identified using the morphology codes 8050/3, 8260/3, 8310/3, 8312/3, 8317/3, 8318/3 and 8319/3 for RCC based on the International Classification of Disease for Oncology, third edition. RCC was the first and only primary cancer diagnosis subjected to histological confirmation. In this study, the eligible patients underwent either partial or radical nephrectomy (surgery code: 30, 40, 50 or 70) combined with LND, and only those with at least 1 positive lymph node were included. However, the patients with age at diagnosis <18 were excluded, as well as those with missing data on tumour stage, nephrectomy, the number of positive lymph nodes (NPLN), the number of dissected lymph nodes (NDLN) or follow-up time. Finally, the study cohort was composed of 1904 RCC patients who fulfilled the aforementioned inclusion criteria. The flow chart for patient selection was presented in online supplemental figure S1.

Measurements of variables

Demographic and clinical variables such as age at diagnosis, sex, race, marital status, histological subtype, tumour grade, tumour size, T classification, M classification, NDLN, NPLN, follow-up time and vital status were retrospectively extracted from the SEER database. LNR was defined as the ratio of metastatic lymph nodes count to the total number of lymph nodes harvested.15 LODDS, defined as the ratio between the NPLN and negative lymph nodes, was calculated through the formula: loge[(NPLN+0.5)/(NDLN–NPLN+0.5)].14 The aim of adding 0.5 to numerator and denominator was to avoid singularity.

Ascertainment of the outcome

The primary outcome of this study was overall survival (OS) which was defined as survival time from RCC diagnosis to death, attributed to any cause. The OS was ascertained through the code ‘vital status’ in the SEER database.

Statistical analysis

In baseline specification, continuous variables were presented as median (IQR) and categorical variables as frequency (percentage). The optimal cut-off values of NPLN, LNR and LODDS were determined via X-tile software (V.3.6.1, Yale University, New Haven, Connecticut, USA) based on the lowest p values and the maximum χ² of log-rank tests. We used the reversed Kaplan-Meier method to calculate the median follow-up time of the entire cohort.

The Spearman bivariate correlation analysis was used to evaluate the correlations between NDLN, NPLN, LNR and LODDS. Additionally, we used scatterplots to graphically exhibit the relationships between these metrics. Kaplan-Meier survival analyses were then employed to calculate the cumulative survival rates and the log-rank test was used to compare survival differences.

The restricted cubic splines with four knots at the 0.05, 0.35, 0.65 and 0.95 centiles were applied to model the associations of three lymph node staging systems (NPLN, LNR and LODDS) with OS flexibly. Subsequently, multiple variable Cox regression analyses were performed to identify the independent prognostic factors of OS for RCC.

In this study, we employed several statistical indices to evaluate the predictive abilities of NPLN, LNR and LODDS. The Akaike information criterion (AIC) was used to estimate the model fit, with a lower AIC indicating a better fitted model. We used the Harrell’s concordance index (C-index) to compare the discriminative ability of NPLN, LNR and LODDS. The C-index represented a
probability that the predicted risk for a random patient with an event was always higher than for a random patient without an event.19 Here, we also used the bootstrap method (n=500) to obtain optimism-corrected C-indices which were more reliable than the original ones. The integrated discrimination improvement (IDI) could reflect the improvement of a model in respect of sensitivity and specificity.20 It was calculated by adding the increased probability predicted by the new model relative to the old one for patients having events to the decreased probability predicted by the new model relative to the old one for those not having events. The index of prediction accuracy (IPA), a promising measure that could simultaneously reflect discrimination and calibration, was reported in this study as well.21 Model 1 was regarded as the null model.

All statistical analyses were performed using R software (V.3.5.3, http://www.r-project.org/). All tests were two sided and the statistical significance was set at p<0.05.

**Patient and public involvement**

None.

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**RESULTS**

**Patient baseline characteristics**

The study cohort was composed of 1904 RCC patients undergoing partial or radical nephrectomy together with LND, of whom 70.0% were males. The median age of the participants was 59 (IQR: 51–67) years old. The majority of these patients were white (79.6%) and married (63.1%). The predominant histological subtype was clear cell RCC (65.8%), with grade III (41.4%) being the most common tumour grade. T classification was T1–T4 in 156 (8.2%), 227 (11.9%), 1346 (70.7%) and 175 (9.2%), respectively. For M classification, 48.1% of the patients presented distant metastases. The median values of NDLN, NPLN, LNR and LODDS were 3 (IQR: 1–9), 2 (IQR: 1–4), 0.92 (IQR: 0.36–1.00) and 1.10 (IQR: 0.51 to 1.61), respectively. To comprehensively investigate the associations of lymph node staging systems with mortality, we also used X-tile software to determine the optimal cut-off values of continuous NPLN, LNR and LODDS.

The median follow-up time of the cohort was 70 months (95% CI 64 to 77 months), whereas the median OS time was 17 months (95% CI 16 to 18 months). By the end of the survey, 1469 participants died, of which 1361 from RCC and 108 from other causes. The detailed demographic and clinical characteristics of the selected patients were summarised in table 1.

**Correlations between lymph node staging systems**

We used the Spearman bivariate correlation analysis to evaluate the correlations between NDLN, NPLN, LNR and LODDS. The results were presented in the form of a correlation coefficient matrix in figure 1. Blue denoted a positive correlation, while red denoted a negative correlation. LODDS positively correlated with NPLN (r=0.30,
Associations of lymph node staging systems with mortality

Restricted cubic spline functions were employed to explore the associations of NPLN, LNR and LODDS as continuous variables with mortality. As shown in figure 3, NPLN, LNR and LODDS were approximately linearly correlated with the HR of mortality. An increased risk of death along with increased NPLN was observed, as well as LNR and LODDS. Additionally, we constructed four Cox regression models in which lymph node staging systems were incorporated as categorical variables. In model 1, we adjusted for age, race, marital status, histological subtype, grade, tumour size, T classification and M classification. For these variables, we simultaneously adjusted for NPLN in model 2, LNR in model 3 and LODDS in model 4, respectively. On multivariable analyses, NPLN, LNR and LODDS were all significantly associated with OS. As depicted in online supplemental table S1), the patients in LODDS1 had survival benefits relative to those in LODDS2 and 3 (LODDS3 vs LODDS1, HR 1.48, 95% CI 1.28 to 1.72, p<0.001; LODDS2 vs LODDS1, HR 1.34, 95% CI 1.17 to 1.53, p<0.001). Likewise, the patients in LNR 3 had worse OS than those in LNR 1 and 2 (LNR 3 vs LNR 1, HR 1.46, 95% CI 1.28 to 1.67, p<0.001; LNR 2 vs LNR 1, HR 1.28, 95% CI 1.09 to 1.50, p=0.002). For NPLN classification, only the patients in NPLN 3 were more likely to succumb to death compared with those in NPLN 1 (NPLN 3 vs NPLN 1, HR 1.22, 95% CI 1.05 to 1.43, p=0.001). However, statistical significance was not achieved for NPLN 2 vs NPLN 1 (p=0.498). A tendency was also demonstrated that the risk of death increased with the increasing of NPLN, LNR or LODDS classifications in each model (p for trend of NPLN=0.010, p for trend of LNR<0.001, p for trend of LODDS<0.001).

Prognostic performance of lymph node staging systems

To comprehensively compare model performance, we constructed another three Cox regression models, models 5–7, in which NPLN, LNR and LODDS as continuous variables were incorporated, respectively. The prognostic performance of models 1–7 was evaluated and summarised in table 2. The LNR classification had a lower AIC (19576.3) compared with the NPLN (19603.7) and LODDS (19579.2) classifications. The original and optimism-corrected C-indices of LNR classification (0.681 and 0.677) were higher than those of NPLN (0.676 and 0.673) and LODDS (0.680 and 0.676) classifications. The IDI of LNR classification for 1-year, 3-year and 5-year follow-up were 0.010 (p<0.001), 0.013 (p<0.001) and 0.013 (p<0.001), which were higher than those of NPLN. Likewise, the IPA estimates for LNR classification were greater than NPLN classification estimates (15.2% vs 14.3%, 18.8% vs 18.4%, 16.9% vs 16.7%, for 1-year, 3-year and 5-year IPA). When analysed as a continuous variable,

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=1904)</th>
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<tr>
<td>LODDS1 (&lt;−0.48)</td>
<td>481 (25.3%)</td>
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<tr>
<td>LODDS2 (−0.48 to 1.22)</td>
<td>916 (48.1%)</td>
</tr>
<tr>
<td>LODDS3 (&gt;1.22)</td>
<td>507 (26.6%)</td>
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<tr>
<td>Follow-up, month Median (95% CI)</td>
<td>70 (64 to 77)</td>
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LODDS, log odds of positive lymph nodes; NDLN, the number of dissected lymph nodes; NPLN, the number of positive lymph nodes; RCC, renal cell carcinoma.
Figure 2  Kaplan-Meier curves for overall survival based on the AJCC lymph node staging system (A), the number of positive lymph nodes (NPLN) (B), lymph node ratio (LNR) (C) and log odds of positive lymph nodes (LODDS) (D) in node-positive RCC patients. AJCC, American Joint Committee on Cancer; OS, overall survival; RCC, renal cell carcinoma.

Figure 3  Restricted spline curves for the associations of mortality risk with the number of positive lymph nodes (NPLN) (A), lymph node ratio (LNR) (B) and log odds of positive lymph nodes (LODDS) (C). The three models were adjusted for age, race, marital status, histological subtype, grade, tumour size, T classification and M classification.
LODDS had a lower AIC (19572.9) relative to NPLN (19596.6) and LNR (19576.6). Measured by C-index, LODDS was superior to NPLN and LNR in discriminative capability. LODDS also had higher IDI (1-year, 3-year and 5-year: 0.009, 0.013 and 0.013, all p<0.001) and IPA (1-year, 3-year and 5-year: 15.1%, 18.8% and 16.8%) values in comparison with NPLN (1-year, 3-year and 5-year IDI: 0.005, 0.004 and 0.010, all p<0.001; 1-year, 3-year and 5-year IPA: 14.5%, 18.6% and 16.9%) and LNR (1-year, 3-year and 5-year IDI: 0.010, 0.013 and 0.012, all p<0.001; 1-year, 3-year and 5-year IPA: 15.1%, 18.7% and 16.8%). The models with NPLN, LNR or LODDS (models 2–7) had better predictive power than the model with no lymph node staging system included (model 1) for node-positive RCC patients. Either in continuous or categorical scales, the predictive performance of LODDS was similar to that of LNR regarding OS prediction for the entire cohort.

**Subgroup analysis for OS**

Since NPLN was significantly associated with clinical outcomes of patients with cancer, subgroup analyses were initially performed based on it. 1904 RCC patients were divided into two subgroups, 1248 with NDLN≤2 and 656 with NDLN>2. As presented in online supplemental table S2), for NPLN>2, LODDS and LNR classifications all could further stratify RCC patients into different risk groups, except NPLN classification. However, only the LODDS classification could better differentiate RCC patients in comparison with LNR and NPLN classifications when NPLN was at most 2. Considering inadequate lymph node harvested might influence the prognostic performance of lymph node staging systems, we also carried out subgroup analyses according to whether the patients underwent extended LND (NDLN≥3). The results showed only LODDS classification could effectively stratify RCC patients based on mortality risk regardless of the number of lymph nodes harvested.

In addition, subgroup analyses were performed according to M classification. Of 1904 node-positive patients with RCC, 915 were diagnosed with distant metastases. As could be seen from the results in online supplemental table S3i, LNR and LODDS classifications could better stratify the survival of RCC patients with M0 or M1 diseases compared with NPLN classification.

**DISCUSSION**

The prognostic capabilities of three lymph node staging systems were comprehensively compared in terms of OS prediction and risk stratification for RCC. The results showed NPLN, LNR and LODDS were all independent predictors of OS for node-positive RCC. The prognostic performances of LNR and LODDS for the entire cohort were similar, superior to NPLN. In subgroup analyses, only the LODDS classification could effectively stratify

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>C-index (Optimism corrected)</th>
<th>IDI</th>
<th>IPA</th>
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<tr>
<td>Model 1*</td>
<td>19606.3</td>
<td>0.675 (0.660–0.690)</td>
<td>0.672</td>
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<tr>
<td>Model 2</td>
<td>19603.7</td>
<td>0.676 (0.661–0.691)</td>
<td>0.673</td>
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<td>3-year: 0.003</td>
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<td>5-year: 0.003</td>
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<td>Model 3</td>
<td>19576.3</td>
<td>0.681 (0.666–0.696)</td>
<td>0.677</td>
<td>1-year: 0.010</td>
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<tr>
<td>(Model 1+LNR classification)</td>
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<td></td>
<td>3-year: 0.013</td>
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<td>5-year: 0.013</td>
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<td>Model 4</td>
<td>19579.2</td>
<td>0.680 (0.666–0.695)</td>
<td>0.676</td>
<td>1-year: 0.009</td>
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<tr>
<td>(Model 1+LODDS classification)</td>
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<td>3-year: 0.013</td>
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<td>5-year: 0.013</td>
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<tr>
<td>Model 5</td>
<td>19596.6</td>
<td>0.677 (0.662–0.691)</td>
<td>0.673</td>
<td>1-year: 0.004</td>
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<td>3-year: 0.005</td>
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<td>5-year: 0.004</td>
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<td>Model 6</td>
<td>19576.6</td>
<td>0.681 (0.666–0.696)</td>
<td>0.677</td>
<td>1-year: 0.010</td>
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<td>3-year: 0.013</td>
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<td></td>
<td></td>
<td>5-year: 0.012</td>
</tr>
<tr>
<td>Model 7</td>
<td>19572.9</td>
<td>0.682 (0.667–0.697)</td>
<td>0.678</td>
<td>1-year: 0.011</td>
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<td>3-year: 0.014</td>
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<td></td>
<td></td>
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<td>5-year: 0.013</td>
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</tbody>
</table>

*Model 1 was adjusted for age, sex, race, marital status, histological subtype, grade, tumour size, T classification and M classification. AIC, Akaike information criterion; IDI, integrated discrimination improvement; IPA, Index of Prediction Accuracy; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; NPLN, the number of positive lymph nodes.
RCC patients based on mortality risk, in particular for those with NDLN<13 or NPLN≤2.

Lymph node involvement in RCC portended poor oncological outcomes.25 LND could accurately provide pathological staging information, though its therapeutic value remained controversial.26 The NCCN guideline recommended that LND should be performed only in cases where there was resectable adenopathy detected by preoperative imagining or palpable enlarged lymph nodes at the time of surgery.27 The latest AJCC cancer staging manual (eighth edition) did not further differentiate RCC patients with regional lymph node involvement which were all classified as N1 stages.28 However, the clinical outcomes of these patients were not homogeneous. Currently, only limited studies revealed that the lymph node staging systems, such as NPLN, LNR and LODDS, could further stratify node-positive RCC patients based on mortality risk.17 18 22 Additionally, there was a lack of a thorough comparison of these metrics with respect to prognostic capacity.

Generally, more positive lymph nodes harvested predicted worse survival,22–24 which was also confirmed in our study. Besides an apparent increasing trend of mortality risk with increased NPLN, NPLN3 classification was associated with a 22% higher risk of mortality relative to NPLN1 classification. However, there was no statistical survival difference between NPLN2 and NPLN1, indicating the imperfect discriminative ability of NPLN. Canfield et al29 investigated 40 RCC patients with positive lymph nodes who underwent nephrectomy together with extent lymphadenectomy. The patients with >1 positive lymph node were associated with decreased recurrence-free survival and OS. Zhuang et al24 retrospectively analysed 4917 RCC patients undergoing radical nephrectomy and reported that localised high-risk RCC patients with NPLN<5 had survival benefits relative to those with NPLN≥5. Chipollini et al24 studied 293 metastatic RCC patients treated with cytoreductive nephrectomy and LND. On multivariable analyses, NPLN was revealed to be a significant predictor of cancer-specific survival.

LNR and LODDS, as novel indices of lymph node staging, were proved to be independent prognostic factors in many malignancies.13–15 The previous studies manifested LNR and LODDS were preferable to pathological N stage in survival predication for lung cancer,12 breast cancer,29 gastric cancer16 and penile cancer.30 In our study, increased NPLN, NPLN3 classification was associated with a 22% higher risk of mortality relative to NPLN1 classification. However, the clinical outcomes of these patients were not homogeneous. Currently, only limited studies revealed that the lymph node staging systems, such as NPLN, LNR and LODDS, could further stratify node-positive RCC patients based on mortality risk.17 18 22 Additionally, there was a lack of a thorough comparison of these metrics with respect to prognostic capacity.

A study by Liao et al25 reported that for node-positive patients diagnosed with RCC, every 10% increase of NNR was associated with a 5% increase of cancer-specific mortality (HR 1.05, 95% CI 1.02 to 1.05, p<0.001). When assessed as a categorical variable, NNR≥35% portended a 41% increase of cancer-specific mortality (HR 1.41, 95% CI 1.20 to 1.65, p<0.001). Although LNR could stratify survival differences, its prognostic performance was not systematically assessed. Up to now, the corresponding study on LODDS in RCC was rare. The only study focused on this issue was implemented by Zhou et al.18 The LODDS with an optimal cut-off value of −0.23 was incorporated into nomograms to predict 1-year, 3-year and 5-year overall and cancer-specific survival. Likewise, this study did not further evaluate the prognostic performance of these lymph node staging systems. Herein, though NPLN, LNR and LODDS were all independent prognostic factors of OS, the predictive abilities of LNR and LODDS were superior to NPLN. Meanwhile, LNR and LODDS could effectively stratify node-positive RCC patients into three distinct risk groups, whereas NPLN could not.

Adequate lymph node harvested indicated a high-quality surgery, which was a guarantee of accurate lymph node staging.14 Moreover, it also implied better survival.13 According to subgroup analyses were performed to verify whether these lymph node staging systems could further discriminate the patients with adequate or inadequate lymph nodes harvested. Based on the published literature,11 the patients who underwent extended LND, defined as removal of at least 13 lymph nodes, were regarded as those with adequate lymph nodes harvested. The results illustrated LNR and LODDS classifications could further stratify the patients undergoing extended LND. For those with NPLN<13, only LODDS classification could achieve the goal of risk stratification, whereas LNR classification could not. LODDS has its advantage in survival predication especially when NDLN was insufficient.15 30 Patel et al30 evaluated the role of LNR and LODDS as prognostic factors in penile cancer. They found LODDS had better power of discrimination relative to LNR when NDLN was less than 15. Wang et al36 assessed the impact of NDLN on the prognostic performance of LNR and LODDS in gastric cancer. When NDLN≤9, the C-index of LNR was lower than that of LODDS. Whereas, the predictive capability of LNR was comparable to LODDS among patients with the removal of >9 lymph nodes. Additionally, considering the prognostic value of NPLN, we also implemented the subgroup analyses based on NPLN. Likewise, only
LODDS classification could discriminate the patients with low (NPLN≤2) and high (NPLN>2) mortality risks. This study had its strengths. We comprehensively compared the prognostic capabilities of three lymph node staging systems in RCC by using a population-based dataset. Multiple statistical measures were employed to evaluate the associations of these metrics with mortality risks and characterise the prognostic performances of these models. Moreover, sensitivity analyses were performed to verify the robustness of the findings. Nonetheless, there were still some limitations in our study. First, due to the retrospective nature of our study, inherent bias was unavoidable. The lack of central pathology review in the SEER database might induce measurement bias. Second, we adjusted many known confounders through Cox regression analyses. However, there still existed some potential confounders which were not recognised or recorded in the SEER database. The incomplete LND would lead to misclassification on the extent of lymph nodes involvement, and furtherly affect the prognosis of RCC patients. However, the information about anatomic templates and the extent of lymphadenectomy was not captured in the SEER database, which might impact the accuracy of the results. Third, considering the approval of more and more new drugs in recent years, the cohort composed of patients diagnosed with RCC between 2004 and 2015 could not completely represent the contemporary population with RCC. The SEER database did not record the medication regimen in detail and the prognostic data could not realise live updates. The findings, therefore, need to be interpreted and extrapolated with caution and validations were still needed before their clinical application.

CONCLUSIONS

In conclusion, NPLN, LNR and LODDS were demonstrated to be independent prognostic factors of OS in RCC. The predictive abilities of LNR and LODDS were comparable, superior to NPLN. LODDS classification could better stratify survival of RCC patients relative to NPLN and LNR classifications, in particular for those with NDNLN<13 or NPLN≤2. These metrics had the potential to be powerful additions to the current AJCC staging system, and their clinical application might be beneficial to patient counselling, disease management and rationalising therapeutic modalities.

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