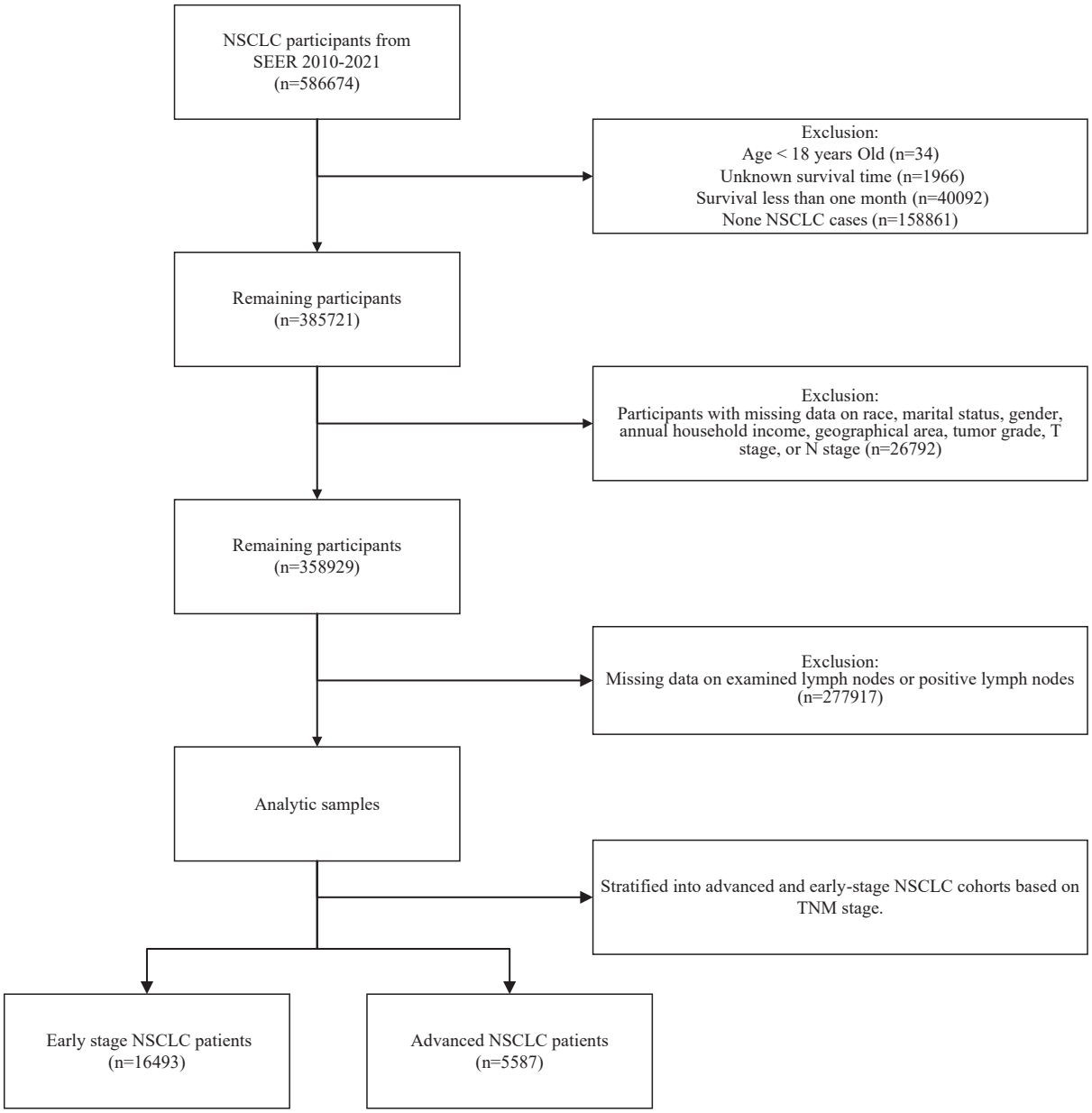

Figure S1 Flow diagrams for selection.

https://dx.doi.org/10.21037/tlcr-2025-447

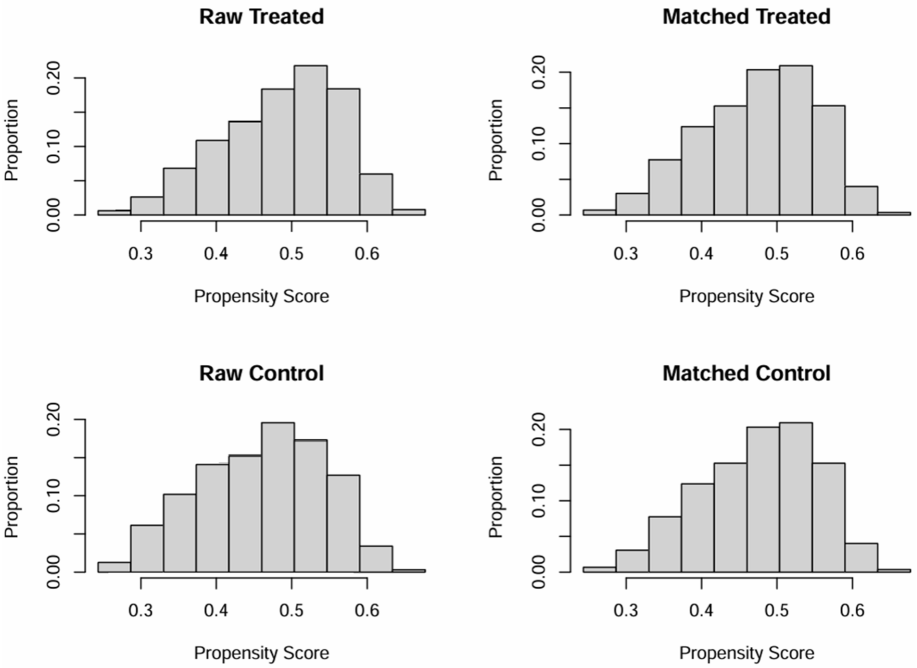

Figure S2 Results of 1:1 propensity score matching analysis for non-small cell lung cancer (NSCLC) patients.

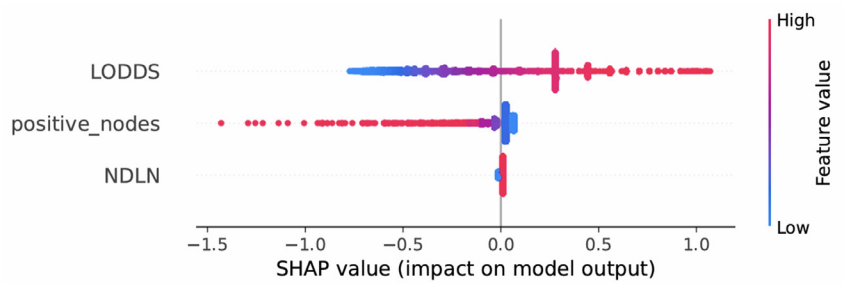

Figure S3 SHapley Additive exPlanations (SHAP) summary plot demonstrating the impact of lymph node burden indicators on mortality risk prediction.

https://dx.doi.org/10.21037/tlcr-2025-447

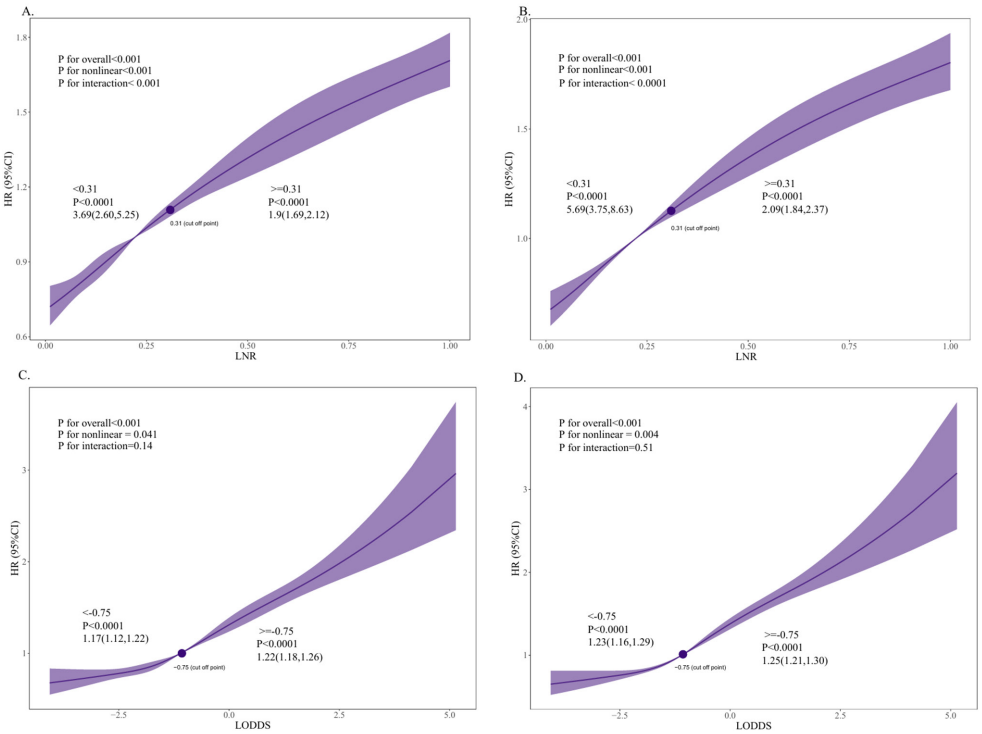

Figure S4 RCS analysis of the dose-response relationship between LNR or LODDS and mortality risk: (A) LNR and all-cause mortality risk; (B) LNR and cancer-specific mortality risk; (C) LODDS and all-cause mortality risk; (D) LODDS and cancer-specific mortality risk.

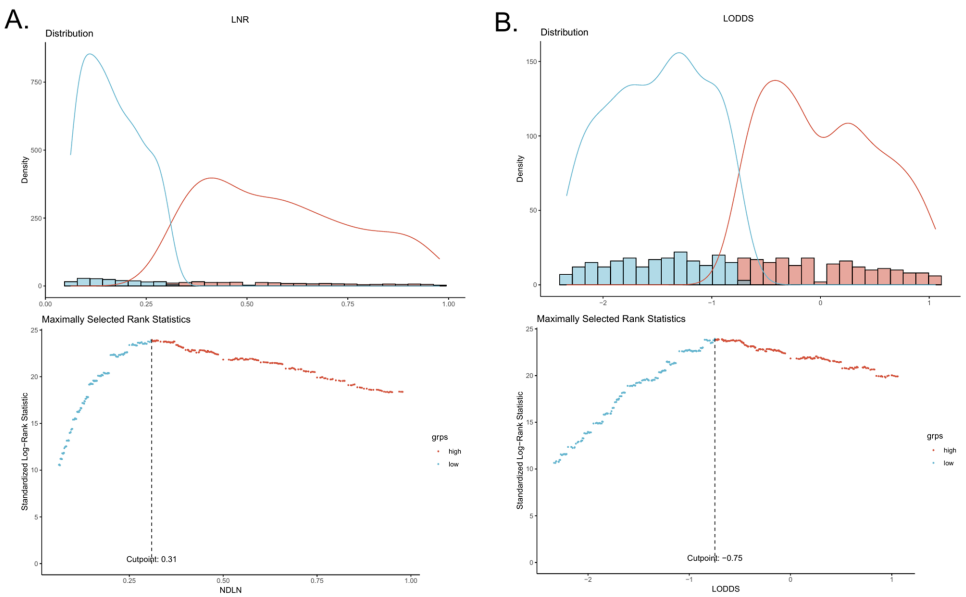

Figure S5 Determination of optimal cut-off points for LNR and LODDS through the maximal selected rank method: (A) optimal cut-off point for LNR; (B) optimal cut-off point for LODDS.

https://dx.doi.org/10.21037/tlcr-2025-447

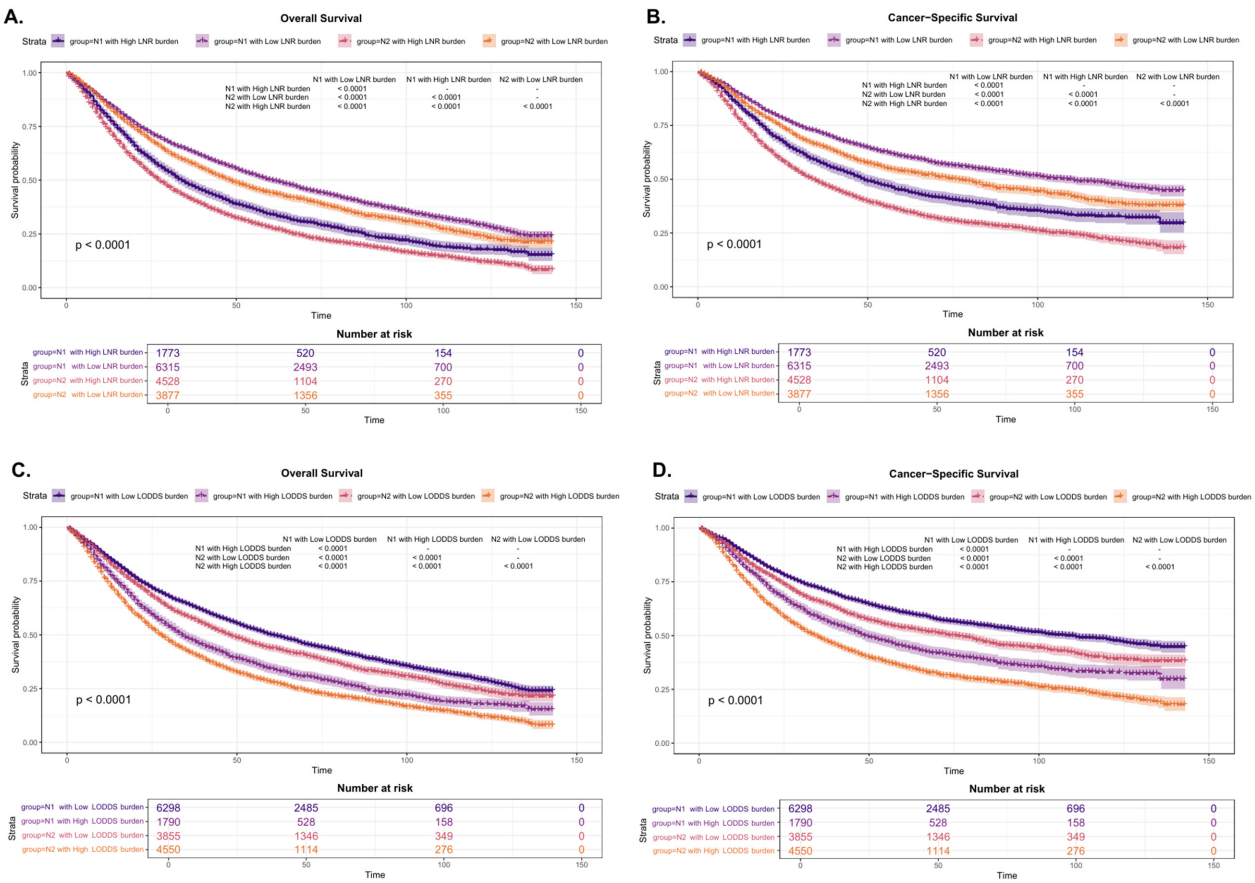

Figure S6 KM survival curves for LNR or LODDS burden combined with N staging: (A) LNR burden and OS; (B) LNR burden and CSS; (C) LODDS burden and OS; (D) LODDS burden and CSS.

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Table S1 FDA-approved targeted and immunotherapy agents for advanced NSCLC: approval timeline and representative clinical trials

Drug name	Approval/ development time	Clinical trials (Name/NCT/Phase)	Notes (source)	Group
Osimertinib (Tagrisso)	2015	AURA3 (NCT02151981, Phase III), FLAURA (NCT02296125, Phase III)	FDA approved for EGFR-mutant NSCLC first-line treatment	Targeted Drug Therapy
Afatinib (Gilotrif)	2013	LUX-Lung 3 (NCT00949650, Phase III), LUX-Lung 6 (NCT01121393, Phase III)	FDA approved for EGFR-mutant NSCLC	Targeted Drug Therapy
Crizotinib (Xalkori)	2011	PROFILE 1007 (NCT00932893, Phase III), PROFILE 1014 (NCT01154140, Phase III)	FDA approved for ALK-positive NSCLC	Targeted Drug Therapy
Alectinib (Alecensa)	2015	ALEX (NCT02075840, Phase III)	FDA approved for ALK-positive NSCLC	Targeted Drug Therapy
Brigatinib (Alunbrig)	2017	ALTA-1L (NCT02737501, Phase III)	FDA approved for ALK-positive NSCLC	Targeted Drug Therapy
Lorlatinib (Lorbrena)	2018	CROWN (NCT03052608, Phase III)	FDA approved for ALK-positive NSCLC	Targeted Drug Therapy
Dacomitinib (Vizimpro)	2018	ARCHER 1050 (NCT01774721, Phase III)	FDA approved for EGFR-mutant NSCLC	Targeted Drug Therapy
Amivantamab (Rybrevant)	2021	CHRYSALIS (NCT02609776, Phase I)	FDA approved for EGFR exon20 insertion NSCLC	Targeted Drug Therapy
Mobocertinib (Exkivity)	2021	EXCLAIM (NCT02716116, Phase I/II)	FDA approved for EGFR exon20 insertion NSCLC	Targeted Drug Therapy
Sotorasib (Lumakras)	2021	CodeBreaK 100 (NCT03600883, Phase II)	FDA approved for KRAS G12C-mutant NSCLC	Targeted Drug Therapy
Adagrasib (Krazati)	2022	KRYSTAL-1 (NCT03785249, Phase I/II)	FDA approved for KRAS G12C-mutant NSCLC	Targeted Drug Therapy
Capmatinib (Tabrecta)	2020	GEOMETRY mono-1 (NCT02414139, Phase II)	FDA approved for MET exon14 skipping NSCLC	Targeted Drug Therapy
Tepotinib (Tepmetko)	2021	VISION (NCT02864992, Phase II)	FDA approved for MET exon14 skipping NSCLC	Targeted Drug Therapy
Pralsetinib (Gavreto)	2020	ARROW (NCT03037385, Phase I/II)	FDA approved for RET fusion-positive NSCLC	Targeted Drug Therapy
Selpercatinib (Retevmo)	2020	LIBRETTO-001 (NCT03157128, Phase I/II)	FDA approved for RET fusion-positive NSCLC	Targeted Drug Therapy
Ensartinib	2024	eXalt3 (NCT02767804, Phase III)	FDA approved for ALK positive NSCLC	Targeted Drug Therapy
Entrectinib	2019	LKA-372-001 (NCT02097810, Phase I)	FDA approved for ROS1 positive NSCLC	Targeted Drug Therapy
Dabrafenib	2017	BRF113928 (NCT01336634, Phase II)	FDA approved for BRAF V600E+ NSCLC	Targeted Drug Therapy
Trametinib	2017	BRF113928 (NCT01336634, Phase II) used in combination with Dabrafenib	FDA approved for BRAF V600E+ NSCLC	Targeted Drug Therapy
Encorafenib	2023	BEACON (NCT02928224, Phase III)	FDA approved for BRAF V600E+ NSCLC	Targeted Drug Therapy
Larotrectinib	2018	LOXO-TRK-14001 (NCT02122913, Phase I)	FDA approved for NTRK + NSCLC	Targeted Drug Therapy
Nivolumab (Opdivo)	2015	CheckMate 017 (NCT01642004, Phase III), CheckMate 057 (NCT01673867, Phase III)	FDA	Immunotherapy
Pembrolizumab (Keytruda)	2015	KEYNOTE-024 (NCT02142738, Phase III), KEYNOTE-042 (NCT02220894, Phase III)	FDA	Immunotherapy
Atezolizumab (Tecentriq)	2021	POPLAR (NCT01903993, Phase II), BIRCH (NCT02031458, Phase II)	FDA	Immunotherapy
Durvalumab (Imfinzi)	2018	PACIFIC (NCT02125461, Phase III)	FDA	Immunotherapy
Tremelimumab	2022	POSEIDON (Phase III)	FDA approved, Tremelimumab + Durvalumab for metastatic NSCLC	Immunotherapy
Cemiplimab	2022	EMPOWER-Lung 3 (Phase III)	FDA approved, Cemiplimab in combination with platinum-based chemotherapy for NSCLC	Immunotherapy
Ipilimumab	2020	CHECKMATE-227 (Phase III)	FDA approved, nivolumab + Ipilimumab for advanced NSCLC without EGFR/ALK mutation	Immunotherapy
Serplulimab	2022 FDA For SCLC; 2024 NMPA For NSCLC	ASTRUM-005 (Phase III, SCLC); ASTRUM-004 (Phase III, NSCLC)	FDA approved for SCLC; NMPA approved for NSCLC	Immunotherapy

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Table S2 Causal mediation analysis of lymph node metastatic burden in the relationship between ICI introduction and all-cause and cancer-specific mortality in advanced NSCLC patients

Group	All-cause mortality		Cancer-specific mortality	
	ICI-introduction era cohort	Pre-ICI era cohort	ICI-introduction era cohort	Pre-ICI era cohort
LNR				
Model 1	Ref	1.25 (1.18, 1.33)	Ref	1.32 (1.23, 1.41)
Model 2	Ref	1.24 (1.16, 1.32)	Ref	1.30 (1.22, 1.39)
Mediation proportion (%)		10.7 (3.6, 21.7)		9.0 (3.0, 17.4)
P value		0.002		0.002
LODDS				
Model 1	Ref	1.25 (1.18, 1.33)	Ref	1.32 (1.23, 1.41)
Model 2	Ref	1.24 (1.17, 1.32)	Ref	1.31 (1.22, 1.40)
Mediation proportion (%)		9.0 (1.3, 19.4)		7.6 (1.1, 15.9)
P value		0.02		0.022
NPLN				
Model 1	Ref	1.25 (1.18, 1.33)	Ref	1.32 (1.23, 1.41)
Model 2	Ref	1.25 (1.18, 1.33)	Ref	1.31 (1.23, 1.40)
Mediation proportion (%)		0.5 (-0.8, 2.5)		0.3 (-0.5, 1.9)
P value		0.33		0.39

Model 1: adjusted for age, sex, race/ethnicity, chemotherapy, radiation, annual household income, marital status, geographical area, T stage, and N stage. Model 2: Model 1 + mediation variables (NPLN, LNR, LODDS).

Table S3 Association of LODDS and LNR with all-cause and cancer-specific mortality risk in advanced NSCLC patients

Group	LNR	P value	LODDS	P value
All-cause mortality				
Model 1	2.28 (2.14, 2.44)	<0.0001	1.23 (1.21, 1.25)	<0.0001
Model 2	1.87 (1.69, 2.06)	<0.0001	1.19 (1.16, 1.22)	<0.0001
Cancer-specific mortality				
Model 1	2.46 (2.29, 2.65)	<0.0001	1.26 (1.23, 1.28)	<0.0001
Model 2	1.94 (1.74, 2.15)	<0.0001	1.20 (1.17, 1.23)	<0.0001

Model 1: crude model. Model 2: adjusted for age, sex, race/ethnicity, chemotherapy, radiation, annual household income, marital status, geographical area, T stage, and N stage.

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Table S4 Baseline characteristics of the validation cohort (n=16493)

Variable	N (%)
Age (years)	
<60	3439 (20.85)
60–74	9142 (55.43)
>74	3912 (23.72)
Sex	
Female	7904 (47.92)
Male	8589 (52.08)
Race/ethnicity	
White	13615 (82.55)
Black	1491 (9.04)
Other	1387 (8.41)
Chemotherapy	
No/Unknown	4618 (28.00)
Yes	11875 (72.00)
Radiation	
None/Unknown	10931 (66.28)
Yes	5562 (33.72)
Annual household income ($)	
<70K	6154 (37.31)
≥70K	10339 (62.69)
Marital status	
Married	9786 (59.33)
Unmarried	6707 (40.67)
Geographical area	
Metropolitan counties	14077 (85.35)
Nonmetropolitan counties	2416 (14.65)
T stage	
T1	4548 (27.58)
T2	7352 (44.58)
T3	3110 (18.86)
T4	1483 (8.99)
N stage	
N1	8088 (49.04)
N2	8405 (50.96)

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Table S5 Association of LODDS and LNR with mortality risk in early-stage NSCLC patients

Group	Model 1	P value	Model 2	P value
All-cause mortality				
LNR				
Low	ref		ref	
High	1.64 (1.58, 1.71)	<0.0001	1.56 (1.50, 1.63)	<0.0001
Per point increase in LNR	2.43 (2.29, 2.59)	<0.0001	2.25 (2.10, 2.40)	<0.0001
LODDS				
Low	ref		ref	
High	1.63 (1.57, 1.70)	<0.0001	1.56 (1.49, 1.62)	<0.0001
Per point increase in LODDS	1.24 (1.22, 1.26)	<0.0001	1.22 (1.20, 1.24)	<0.0001
Cancer-specific mortality				
LNR				
Low	ref		ref	
High	1.79 (1.71, 1.87)	<0.0001	1.65 (1.57, 1.74)	<0.0001
Per point increase in LNR	2.81 (2.62, 3.02)	<0.0001	2.46 (2.28, 2.65)	<0.0001
LODDS				
Low	ref		ref	
High	1.78 (1.70, 1.86)	<0.0001	1.64 (1.57, 1.73)	<0.0001
Per point increase in LODDS	1.29 (1.27, 1.31)	<0.0001	1.25 (1.23, 1.28)	<0.0001

Model 1, crude model. Model 2: adjusted for age, sex, race/ethnicity, chemotherapy, radiation, annual household income, marital status, geographical area, T stage, and N stage.

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Table S6 Cox regression analysis of the association between LNR or LODDS burden combined with N staging and mortality risk in NSCLC patients

Group	Model 1	P value	Model 2	P value
All-cause mortality				
LNR				
N1 with Low LNR burden	ref		ref	
N1 with High LNR burden	1.51 (1.41, 1.61)	<0.0001	1.55 (1.45, 1.65)	<0.0001
N2 with Low LNR burden	1.16 (1.10, 1.22)	<0.0001	1.26 (1.19, 1.33)	<0.0001
N2 with High LNR burden	1.84 (1.75, 1.93)	<0.0001	1.98 (1.88, 2.09)	<0.0001
LODDS				
N1 with Low LODDS burden	ref		ref	
N1 with High LODDS burden	1.50 (1.41, 1.61)	<0.0001	1.54 (1.44, 1.65)	<0.0001
N2 with Low LODDS burden	1.16 (1.10, 1.22)	<0.0001	1.26 (1.19, 1.33)	<0.0001
N2 with High LODDS burden	1.83 (1.74, 1.92)	<0.0001	1.98 (1.87, 2.09)	<0.0001
Cancer-specific mortality				
LNR				
N1 with Low LNR burden	ref		ref	
N1 with High LNR burden	1.58 (1.46, 1.71)	<0.0001	1.61 (1.49, 1.74)	<0.0001
N2 with Low LNR burden	1.24 (1.16, 1.32)	<0.0001	1.31 (1.23, 1.41)	<0.0001
N2 with High LNR burden	2.11 (1.99, 2.23)	<0.0001	2.21 (2.08, 2.35)	<0.0001
LODDS				
N1 with Low LODDS burden	ref		ref	
N1 with High LODDS burden	1.57 (1.45, 1.70)	<0.0001	1.60 (1.48, 1.73)	<0.0001
N2 with Low LODDS burden	1.24 (1.16, 1.32)	<0.0001	1.31 (1.23, 1.41)	<0.0001
N2 with High LODDS burden	2.10 (1.98, 2.22)	<0.0001	2.20 (2.07, 2.34)	<0.0001

Model 1, crude model. Model 2: adjusted for age, sex, race/ethnicity, chemotherapy, radiation, annual household income, marital status, geographical area, T stage, and N stage.

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