Oncology and Translational Medicine
DOI 10.1007/s10330-020-0403-3

April 2020, Vol. 6, No. 2, P57–P63

ORIGINAL ARTICLE

Prognostic factors for pN2 non-small cell lung cancer: a comprehensive evidence from 73 studies involving 23,772 patients*

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Abstract

Obobjective Non-small-cell lung cancer (NSCLC) is a common malignancy. pN2 NSCLC, with pathologically confirmed ipsilateral mediastinal/subcarinal nodes metastasis, has been known as a very heterogeneous subgroup in terms of its anatomical, biological and patient characteristics. Prognostic factors based on patient characteristics were not well determined yet in this subgroup, and there is currently no standard treatment recommendation for these heterogeneous pN2 subjects. Apparent disagreements and inconsistency exist in study reports concerning the prognostic significance of certain factors in pN2 NSCLC, especially regarding to the issue about whether skip N2 metastasis benefit from surgery.

Methods We therefore performed this comprehensive summary of the published literatures to draw a more precise and less uncertain conclusion. After a comprehensive literature search, a total of 73 studies involving 23,773 subjects were included according to eligibility criteria.

Results As expected, most of the investigated factors, such as old age, male, advanced pathological T stage, advanced clinical N stage, multiple N2 stations, extended surgical resection (pneumonectomy), and incomplete resection, but not post-operation treatment (eg. chemotherapy and radiotherapy) were significantly associated with poor survival. However, skip N2 metastasis was favourable prognostic factors in operable pN2 NSCLC subjects. Other factors (histological type and primary tumour side) were neutral in terms of association with overall survival. We highlighted a number of important prognostic factors for pN2 NSCLC patients. Particularly, patients with skip N2 disease benefit from surgery.

Conclusion Our findings could be used as reference information for decision-making in clinical practice and future study design.

Received: 16 January 2020
Revised: 19 March 2020
Accepted: 9 April 2020

Key words: non-small cell lung cancer; meta-analysis; prognostic factors; overall survival

Annually, more than one million deaths are attributed to lung cancer, the most common malignancy worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer cases. pN2 NSCLC, with pathologically confirmed ipsilateral mediastinal/subcarinal node metastases, is a heterogeneous subgroup in terms of its anatomical, biological, and patient characteristics [2]. Prognostic factors based on patient characteristics are not yet well-characterized in this subgroup. Furthermore, there was no major improvement regarding N descriptors in the lung cancer tumor node metastasis (TNM) stage classification system until 2017 in the 8th edition by AJCC/UICC [3], where not only metastatic lymph node location but also the numbers of involved nodes were considered. Treatment options have varied from surgery alone to surgery in combination with adjuvant and/or neo-adjuvant therapies [4–6]; however, there is currently no standard treatment recommendation for these heterogeneous pN2 subjects. Consequently, pN2 patient survival outcomes vary to a large extent and the reported 5-year overall survival rate ranges from 10 to 40% [3, 7].

To improve the prognosis of patients with pN2 disease, several clinical trials have evaluated the effectiveness of different treatment modalities, such

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* Supported by grants from the National Basic Research Program of China (973 Program; No. 2012CB720605) and the Zhongnan Hospital of Wuhan University Science, Technology and Innovation Seed Fund (No. znpy2016046).

surgery and with or without pre-/post-operative adjuvant therapies. However, the results achieved limited success [8–10]. Although recently developed techniques, including video-assisted thoracoscopic surgery for lobectomy and lymphadenectomy, have been used and assessed in clinical practice, their actual impacts on prognosis, especially long-term outcomes, remain controversial [11–12]. Therefore, determining prognostic factors continues to be of utmost importance for the clinical management of pN2 NSCLC.

To address this point, numerous retrospective or prospective studies have repeatedly reported certain clinicopathological features as independent prognostic factors, such as age, gender, histology type, primary tumor side/location/size, N2 stations, and skip N2 metastasis. In addition, several studies revealed that the surgery and degree of resection, as well as post-operative adjuvant therapy, were associated with long-term outcomes (see our included studies). However, apparent disagreements and inconsistencies concerning the prognostic significance of certain factors in pN2 NSCLC exist in these reports. For example, although many studies indicated that multiple N2 station involvement independently predicted worse prognosis compared with a single N2 station, others reported that no significant difference was found between them.

Considering the aforementioned discrepancies among prior studies, a comprehensive summary of the published literature is essential to reach a more precise and certain conclusion. A meta-analysis based on pooled data from single studies is one of the best methods to provide high level evidence to be integrated into clinical guidelines [13]. Herein, with a quantitative synopsis of studies published in the last few decades, we performed a meta-analysis to examine the prognostic significance of reported factors in pN2 NSCLC patients. Our report may provide clues and references for optimal clinical management of this specific subgroup, as well as guidance for future research designs.

Materials and methods

Literature search and study selection

A systematic literature search of the PubMed, EMBASE, and Cochrane Library databases up to March 2019 was conducted. For each database, all possible combinations of the following search terms were used: “non-small cell lung cancer”, “NSCLC”, “N2 disease”, “lymph node”, and “survival”. The publication language was limited to English. Reference lists of the included studies, as well as relevant systematic reviews, were checked manually to identify additional related studies. We collected published studies assessing the prognostic value of clinicopathological features and treatment elements in patients with pN2 NSCLC. All of the included subjects were pathologically proven to have N2 metastases by means of preoperative mediastinoscopy, lymph node biopsy, or mediastinal lymph node dissection at the time of resection. Overall survival (OS) was the only endpoint considered. Prognostic factors of interest could be any of those reported in prior studies; however, we only included those factors with reported or calculable hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) obtained by multivariate analysis. Definitions of these factors were in accordance with those described in the original studies. Studies containing relevant data with the following exclusion criteria were considered eligible: (1) Letters, reviews, case-reports, conference abstracts; (2) Studies that discussed the relationship between clinicopathological features or treatment strategies and OS in patients with NSCLC not proven to be pN2 disease; and (3) Articles in which multivariate HR values for OS were not reported and could not be calculated using other information. A systematic literature search of the PubMed, EMBASE, and Cochrane Library databases up to March 2019 was conducted. For each database, all possible combinations of the following search terms were used: “non-small cell lung cancer”, “NSCLC”, “N2 disease”, “lymph node”, and “survival”. The publication language was limited to English. Reference lists of the included studies, as well as relevant systematic reviews, were checked manually to identify additional related studies. We collected published studies assessing the prognostic value of clinicopathological features and treatment elements in patients with pN2 NSCLC. All of the included subjects were pathologically proven to have N2 metastases by means of preoperative mediastinoscopy, lymph node biopsy, or mediastinal lymph node dissection at the time of resection. Overall survival (OS) was the only endpoint considered. Prognostic factors of interest could be any of those reported in prior studies; however, we only included those factors with reported or calculable hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) obtained by multivariate analysis. Definitions of these factors were in accordance with those described in the original studies. Studies containing relevant data with the following exclusion criteria were considered eligible: (1) Letters, reviews, case-reports, conference abstracts; (2) Studies that discussed the relationship between clinicopathological features or treatment strategies and OS in patients with NSCLC not proven to be pN2 disease; and (3) Articles in which multivariate HR values for OS were not reported and could not be calculated using other information.

Statistical analyses

For prognostic factors, HR point estimates and 95% CIs were extracted. The Cochran Q test and I2 statistic were used to evaluate between-study heterogeneity

and as guidance for model selection for meta-analytic pooling. Statistical heterogeneity was defined as a Cochran Q test $P < 0.05$ or I2 statistic > 50% [14]. In the presence of statistical heterogeneity, a random-effects model was used; otherwise, we used a fixed-effects model for meta-analysis [15]. For pooled analysis with statistical heterogeneity, we either performed a sensitivity analysis by removal of individual studies to test stability of the results with newly recalculated pooled HRs, or conducted a meta-regression with publication year, sample size, and country (non-Asian or Asian, represented in the model by 0 and 1, respectively) as covariates to investigate possible explanations for heterogeneity. Egger's linear regression test and funnel plots were used for evaluating publication bias[16]. When publication bias was suspected (an asymmetry funnel plot or Egger's test $P < 0.05$), a trim-and-fill analysis was performed to further investigate publication bias and result stability [17]. Pooled estimates with 95% CIs not covering "1" were considered statistically significant. All meta-analyses were performed using R version 3.4.3, which was also used for result visualization. Reporting was according to the PRISMA guidelines.

Results

Characteristics of included studies

The scheme used for the literature search and study selection is shown in Fig. 1. Two authors selected full-text articles independently after a comprehensive review of potentially relevant citations. Finally, 73 studies with 23,772 patients were considered eligible for subsequent analyses (Table 1). Except for three very large studies (two based on the National Cancer database [18–19] and one based on the SEER database [20]) that included thousands of

Table 1 Basic information of included studies

Authors	Year	Country	pN2 patients	Male	Mean or Median Age (y)
Nakanishi	1997	Japan	53	33	66
Tanaka	1997	Japan	155	111	60.8
Suzuki	1999	Japan	242	140	63
Andre	2000	France	686	606	61
Bueno	2000	USA	103	59	59
Fukuse	2000	Japan	76	52	62.3
Ichinose	2001	Japan	406	291	62.4
Tomita	2003	Japan	60	42	63.9
Ueda	2003	Japan	147	102	NA
Inoue	2004	Japan	154	99	62
Tanaka	2004	Japan	99	64	62.2
Casali	2005	Italy	183	153	64
Martin	2005	USA	353	208	63
Port	2005	USA	78	39	64
Takenaka	2005	Japan	118	80	62
Benoit	2006	France	142	NA	NA
Iwasaki	2006	Japan	142	94	NA
Ohta	2006	Japan	94	52	65.5
Sakao	2006	Japan	53	38	63
Cerfolio	2008	USA	148	89	66
Lee	2008	Korea	358	283	61
Matsuguma	2008	Japan	91	50	NA
Misthos	2008	Greece	302	240	62
Decaluwe	2009	Belgium	92	68	64
Mohamed	2009	Egypt	78	58	NA
Ratto	2009	Italy	277	229	NA
Zou	2009	China	183	129	NA
Kim	2010	Korea	217	170	60.5
Ma	2010	China	173	130	NA
Sakao	2010	Japan	106	57	61
Scotti	2010	Italy	175	145	NA
Dai	2011	China	221	160	60
Fontaine	2011	UK	146	69	66
Meacci	2011	Italy	40	36	58.7
Nakagiri	2011	Japan	121	79	65
Sakao	2011	Japan	45	22	61
Zheng	2011	China	720	515	57
Amini	2012	USA	61	27	61
Baba	2012	Japan	46	35	68
Funakoshi	2012	Japan	103	55	62.7
Ito	2012	Japan	40	12	65
Hishida	2013	Japan	97	74	66
Shah	2013	USA	55	35	62
Sonobe	2013	Japan	496	325	NA
Yan	2013	China	115	81	62
Zheng	2013	China	180	124	57.7
Askoxylakis	2014	Germany	71	48	59
Ichinose	2014	Japan	67	43	65
Kim	2014	Korea	129	88	62.1
Lee	2014	Korea	355	275	60
Legras	2014	France	871	712	61.2
Lim	2014	Korea	104	86	61
Tsitsias	2014	UK	68	33	66
Wang	2014	China	263	168	NA
Cao	2015	China	208	129	59.4
Fu	2015	China	204	143	58
Hsieh	2015	Taiwan	108	56	60.2
Kawasaki	2015	Japan	121	81	66.6
Lee	2015	Korea	105	79	62
Mikell	2015	USA	2115	991	64
Robinson	2015	USA	4483	2094	NA
Uehara	2015	Japan	287	169	62
Feng	2015	China	357	209	NA
Yang	2015	USA	111	70	62
Yoo	2015	Korea	250	145	59
Garelli	2016	France	982	706	61
Kim	2016	Korea	574	444	58.8
Spaggiari	2016	Italy	141	104	63
Tamura	2016	Japan	182	127	64.6
Guerrera	2017	Italy	279	168	63
Wang	2017	China	112	77	NA
Kou	2018	China	2949	1457	NA
Xu	2018	China	246	175	59

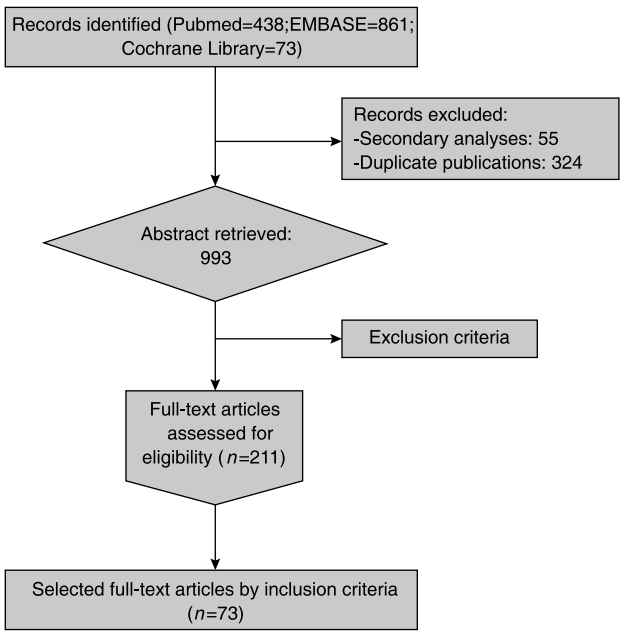

Fig. 1 Flow diagram of the meta-analysis

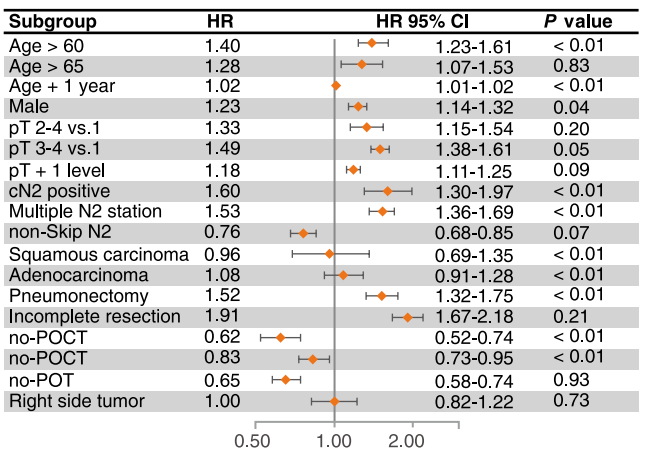

Fig. 2 Meta-analytical pooled results of investigated factors and their prognostic value. The vertical line with a value of "1" represents the risk boundary. For each factor, a black dot equals the HR value and the length of the colored line equals the 95% CI. A poor prognosis factor was defined as its HR value together with the corresponding 95% CI located outside of the risk boundary. pT, pathological T stage; cN, clinical N stage; POCT, postoperative chemotherapy; PORT, postoperative radiotherapy; POT, postoperative treatment; HR, hazard ratio; CI, confidence interval

patients, all other eligible studies were retrospective cohort studies with sample sizes less than 1000. Basic information of these included studies is provided in Table 1.

Pooled analysis

Results of the meta-analytical pooled analysis are summarized in Fig. 2.

Among demographic factors, age ≥ 60 (HR = 1.40, 95% CI = 1.23–1.61), age ≥ 65 (HR = 1.28, 95% CI = 1.07–1.53), 1 year increment in age (HR = 1.02, 95% CI = 1.01–1.02), and male (HR = 1.23, 95% CI = 1.14–1.32) were all negative prognostic factors for OS.

Among clinicopathologic factors, advanced pathologic T stage (pT2-4 *vs.* 1: HR = 1.33, 95% CI = 1.15–1.54; pT3–4 *vs.* 1–2: HR = 1.49, 95% CI = 1.38–1.61; and 1 level increment: HR = 1.18, 95% CI = 1.11–1.25), positive clinical N2 disease (cN2 vs. cN0–1: HR = 1.60, 95% CI = 1.30–1.97), and multiple N2 station involvement (HR = 1.53, 95% CI = 1.36–1.69) were prognostic factors significantly associated with poor survival. Interestingly, the presence of skip N2 metastasis was a significant protective prognostic factor in the operable pN2 NSCLC group (HR = 0.76, 95% CI = 0.68–0.85). In contrast, there was no significance regarding histological type of tumor (squamous vs. non-squamous carcinoma: HR = 0.96, 95% CI = 0.69–1.35; and adenocarcinoma vs. non-adenocarcinoma: HR = 1.08, 95% CI = 0.91–1.28).

For surgical treatment, both, extended operation type and incomplete resection, were negatively associated with OS (pneumonectomy vs. lobectomy: HR = 1.52, 95% CI = 1.32–1.75; R1 + R2 vs. R0: HR = 1.91, 95% CI = 1.67–2.18, respectively).

Post-operative treatment was associated with improved OS (post-operative radiotherapy (PORT) vs. no-PORT: HR = 0.83, 95% CI = 0.73–0.95; post-operative chemotherapy (POCT) vs. no-POCT: HR = 0.62, 95% CI = 0.52–0.74; and post-operative adjuvant treatment (POT) vs. no-POT: HR = 0.65, 95% CI = 0.58–0.74).

Heterogeneity

Statistical heterogeneity was detected in the meta-analyses for comparisons concerning age (cut-off line 60 and 1 year increment), gender, clinical N2 disease, operation type, single/multiple N2 stations, histological type, and post-operative treatment (PORT and POCT). As shown in Fig. 3, none of the pooled effects changed significantly after adjustment for influential studies. According to results of the meta-regression with country (Asian or non-Asian), sample size, and year of publication as covariates, country was a possible source of heterogeneity for analysis on age ≥ 60 vs. age < 60 (P = 0.01). Varying sample sizes might have contributed to the heterogeneity found for the analysis concerning clinical N2 disease (P = 0.042), and country and sample size could be sources of heterogeneity for analyses on single vs. multiple N2 stations (P = 0.007 and 0.0002, respectively). Furthermore, year of publication was a possible explanation for the heterogeneity found in meta-analyses on POCT vs. non-POCT (P = 0.005) and PORT vs. non-PORT (P = 0.02). The meta-regression results for other analyses were all non-significant.

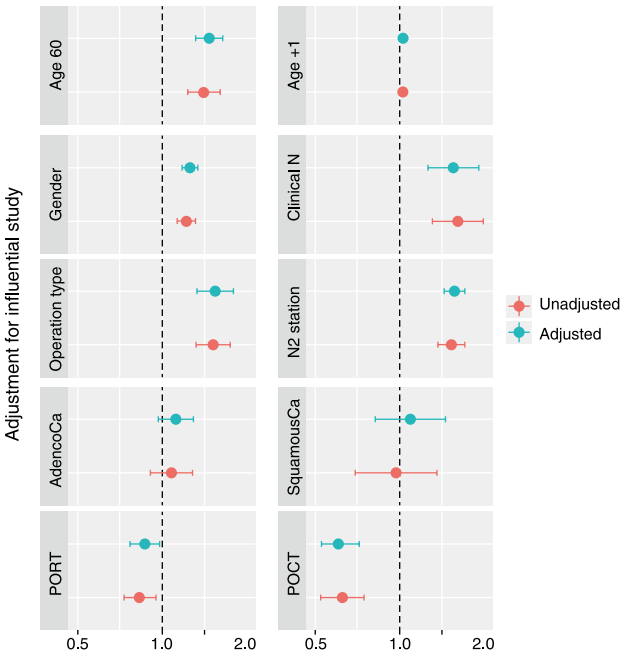

Fig. 3 Pooled effects after adjusting for influential individual studies. POCT, postoperative chemotherapy; PORT, postoperative radiotherapy; POT, postoperative treatment

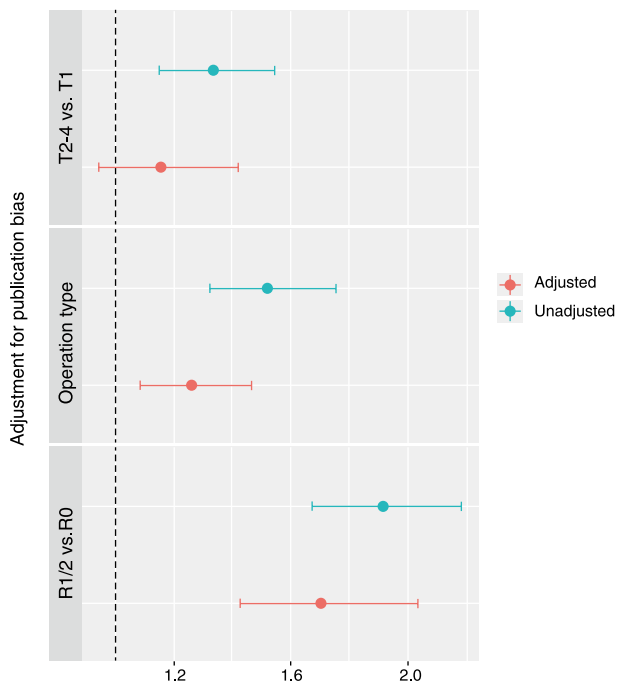

Fig. 4 Adjusted publication bias with the trim-and-fill method regarding several prognosis factors. T, pathological T stage; R, resection completeness

Publication bias

Publication bias was suspected for comparisons regarding pathological T stage (T2-4 *vs.* T1, $P = 0.037$), operation type ($P = 0.025$), and surgical completeness ($P = 0.018$). Results before and after adjustment by the trim-and-fill method are shown in Fig. 4. Funnel plots for each comparison are provided in Supplementary Data 4.

Discussion

Abundant literature focusing on the prognosis factors of pN2 NSCLC have been published; however, there has been a lack of definitive consensus among these researchers. pN2 NSCLC remains a contested issue due to apparent heterogeneity regarding its anatomical, biological, and patient characteristics. This has resulted in problematic prognosis and difficult treatment decisions. In addition to studies indicating a possible correlation between demographic characteristics (such as age, gender, and smoking history) and outcomes, certain studies showed that the outcomes of patients with pN2 NSCLC could be further influenced by tumor parameters (*e.g.*, size, side, location, and histology type) and N2 patterns (single/multiple N2 station involvement, skip N2 metastasis, and lymphadenopathy). However, in terms of the prognostic significance of these clinicopathological factors, varying opinions are held by different investigators, based on their own experience and study results. Thus, to end this chaos and find new clues for further investigation, a comprehensive synopsis of currently available data is one of the best methods to reach a relatively decisive conclusion. To the best of our knowledge, this meta-analysis, which comprehensively summarized all potential prognosis factors reported previously by applying standardized statistical methods, is the first contribution focusing on the pN2 NSCLC subgroup.

In the present study, dozens of important clinical, pathological, and treatment factors were included in the meta-analysis to assess the pN2 NSCLC patients. Notably, we applied a stringent filter for including eligible studies; only those factors with reported HRs and corresponding 95% CIs obtained from multivariate analyses were considered. According to our results, old age, male gender, advanced pathological T stage, positive clinical N2 disease, multiple positive N2 stations, extended surgery, and incomplete resection were negative prognostic factors, while post-operative treatments, including radiotherapy, chemotherapy, or bimodality therapy, improved the overall survival.

Skip N2 metastasis accounts for one third of overall cases of pN2 NSCLC [21], and is the most debated factor regarding whether skip N2 metastasis benefit from surgery. Our pooled evidence indicated that skip N2 metastasis was a favourable prognostic factor in operable pN2 NSCLC subjects, though the reasons for that remain unknown. Li *et al* reported that there was no difference

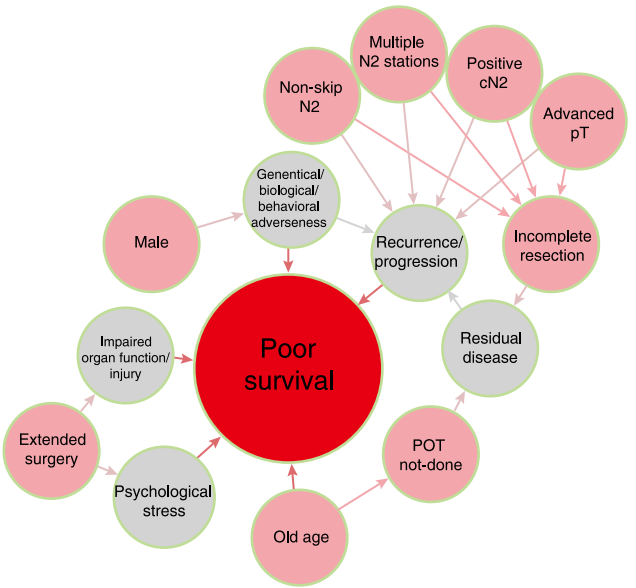

Fig. 5 Hypothetical prognostic model of investigated and latent factors, and their plausible associations with survival outcome

in terms of well-identified genetic alterations, but a significantly lower incidence of lymphovascular invasion was observed in pN2 NSCLC tumors with skip N2 compared to non-skip N2 cases [21].

Towards better interpretation of our results, we propose a hypothetical prognosis model (Fig. 5). Several latent factors are included in this model. Each directed edge between two factor nodes indicates a hypothetical causal relationship, which can be translated as "the source factor cause, or increase the possibility of the target factor". For example, according to this model, older people naturally have a shorter remaining life-span, and old age also precludes post-operative treatments, increasing the possibility of residual disease, that is a causal factor of disease recurrence or progression and results in poor survival. This model provides an overview of the potential causal relationships among the factors and the outcome. However, because data from observational studies form the basis of our study, our findings and hypotheses embedded in the prognostic model should be treated with caution and be further verified in well-designed clinical trials. Nevertheless, we suggest that prognostic factors determined as significant in the present study should be taken into consideration in further relevant studies, especially for research design and data analysis. In addition, the hypothetical relations proposed in our prognostic model incorporating latent factors may be a good starting points for subsequent confirmatory studies.

There are several limitations of the present study. Firstly, except for the prognostic factors investigated above, the biological and genetic backgrounds of individuals with pN2 NSCLC will largely affect outcomes and should be taken into account. Consistent with this, several studies found that lower PD-L1 expression and increased tumor-infiltrating lymphocytes predicted good prognosis in pN2 NSCLC[22–24], while mutation of the epidermal growth factor receptor gene and p16 gene deletion shortened OS in this group[25–26].

Secondly, statistically significant heterogeneity was detected in the meta-analysis of certain comparisons. Adjustment for influential individual studies, which were identified by a sensitivity analysis, did not change many of the pooled effects, indicating these studies were not important sources of heterogeneity. In contrast, meta-regression analyses indicated that country, year of publication, and sample size were possible sources of heterogeneity. In addition, we should be aware that, in each study, different combinations of factors were adopted for the Cox model (i.e., the statistical model used to calculate multivariate HRs and 95% CIs) and this difference may be an important source of heterogeneity. For example, whether including a certain factor into the Cox model for a given dataset will influence, to some degree, the final results. Nevertheless, the use of heterogeneous Cox models in different studies is quite common, and may inevitably introduce heterogeneity into meta-analyses.

Lastly, another important limitation of our study is publication bias. Although we cannot exclude the possibility that the detected publication bias is a consequence of selective reporting, we think it might be better to treat this publication bias as a reflection of the true effect. Unlike a meta-analysis of interventions, the present study focused on the association between certain factors and OS, and these factors were not involved with any artificial interests (i.e., the main cause of intended selective reporting). Therefore, the risk that our results were influenced by artificial selective reporting is relatively low. On the other hand, if true associations do exist, it is possible that a large proportion of studies reported results consistent enough to cause asymmetry of the funnel plot. Whether the suspected publication bias in our study is a genuine or false finding needs to be confirmed in further studies.

To summarize, our results support that the following factors are important prognostic factors for pN2 NSCLC: age, gender, pathological T stage, clinical N2 disease, number of involved N2 stations, skip N2 disease, operation type, completeness of surgery, and postoperative treatments. Our findings could be used as reference information for clinical decision-making and as guidance for the design of future studies.

Acknowledgments

We thank the DSC (Wuhan) Scientific Co.Ltd. for consulting services on data management, statistical

analysis, and scientific writing. We thank Pr. Conghua Xie and Pr. Ye Tian for manuscript consulting and improving.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015, 136: E359–386.
2. Shien K, Toyooka S. Role of surgery in N2 NSCLC: pros. Jpn J Clin Oncol, 2016, 46: 1168–1173.
3. Detterbeck FC, Boffa DJ, Kim AW, *et al*. The Eighth Edition Lung Cancer Stage Classification. Chest, 2017, 151: 193–203.
4. Vansteenkiste J, Betticher D, Eberhardt W, *et al*. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Thorac Oncol, 2007, 2: 684–685.
5. Chen D, Wang H, Song X, *et al*. Preoperative radiation may improve the outcomes of resectable IIIA/N2 non-small-cell lung cancer patients: A propensity score matching-based analysis from surveillance, epidemiology, and end results database. Cancer Med, 2018, 7: 4354–4360.
6. Jeremić B, Casas F, Dubinsky P, *et al*. Surgery for stage IIIA non-small-cell lung cancer: lack of predictive and prognostic factors identifying any subgroup of patients benefiting from it. Clin Lung Cancer, 2016, 17: 107–112.
7. van Meerbeeck JP, Surmont VFM. Stage IIIA-N2 NSCLC: a review of its treatment approaches and future developments. Lung Cancer, 2009, 65: 257–267.
8. Glimelius B, Bergh J, Brandt L, *et al.* The Swedish Council on Technology Assessment in Health Care (SBU) systematic overview of chemotherapy effects in some major tumour types – Summary and conclusions. Acta Oncol, 2001, 40: 135–154.
9. Glimelius B, Grönberg H, Järhult J, *et al*. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol, 2003, 42: 476–492.
10. Eberhardt WE, Gauler TC, Lepechoux C, *et al.* 10-year long-term survival (LTS) of induction chemotherapy with three cycles cisplatin/paclitaxel followed by concurrent chemoradiation cisplatin/etoposide/45 Gy (1.5 Gy bid) plus surgery in locally advanced non-small-cell lung cancer (NSCLC)-a multicenter phase-II trial (CISTAXOL). Lung Cancer, 2013, 82: 83–89.
11. Zhou W, Chen X, Zhang H, *et al*. Video-assisted thoracic surgery lobectomy for unexpected pathologic N2 non-small cell lung cancer. Thorac Cancer, 2013, 4: 287–294.
12. Marty-Ané CH, Canaud L, Solovei L, *et al*. Video-assisted thoracoscopic lobectomy: An unavoidable trend? A retrospective single-institution series of 410 cases. Interact Cardiovasc Thorac Surg, 2013, 17: 36–43.
13. Atkins D, Eccles M, Flottorp S, *et al.* Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res, 2004, 4: 38.
14. Higgins JPT and Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med, 2002, 21: 1539–1558.
15. Fidler V and Nagelkerke N. The Mantel-Haenszel procedure revisited: models and generalizations. PLoS One, 2013, 8: 1–4.
16. Egger M, Smith GD, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997, 315: 629–634.
17. Carpenter CJ. A trim and fill examination of the extent of publication bias in communication research. Commun Methods Meas, 2012, 6: 41–55.
18. Mikell JL, Gillespie TW, Hall WA, *et al.* Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the national cancer data base. J Thorac Oncol, 2015, 10: 462–471.
19. Robinson CG, Patel AP, Bradley JD, *et al.* Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the national cancer data base. J Clin Oncol, 2015, 33: 870–876.
20. Kou P, Wang H, Lin J, *et al*. Male patients with resected IIIA-N2 non-small-cell lung cancer may benefit from postoperative radiotherapy: a population-based survival analysis. Futur Oncol, 2018, 14: 2371–2381.
21. Li H, Hu H, Wang R, *et al*. Lung adenocarcinoma. Are skip N2 metastases different from non-skip? J Thorac Cardiovasc Surg, 2015, 150: 790–795.
22. Ameratunga M, Asadi K, Lin X, *et al.* PD-L1 and Tumor infiltrating lymphocytes as prognostic markers in resected NSCLC. PLoS One, 2016, 11: e0153954.
23. Keller MD, Neppl C, Irmak Y, *et al*. Adverse prognostic value of PD-L1 expression in primary resected pulmonary squamous cell carcinomas and paired mediastinal lymph node metastases. Mod Pathol, 2018, 31: 101–110.
24. Feng W, Li Y, Shen L, *et al.* Prognostic value of tumor-infiltrating lymphocytes for patients with completely resected stage IIIA(N2) non-small cell lung cancer. Oncotarget, 2016, 7: 7227–7240.
25. Xiong L, Li R, Sun J, *et al.* Erlotinib as neoadjuvant therapy in stage IIIA (N2) EGFR mutation-positive non-small cell lung cancer: a prospective, single-arm, phase II Study. Oncologist, 2019, 24: 157–e64.
26. Schneider F, Derrick V, Davison JM, *et al*. Morphological and molecular approach to synchronous non-small cell lung carcinomas: Impact on staging. Mod Pathol, 2016, 29: 735–742.

DOI 10.1007/s10330-020-0403-3
Cite this article as: Li S, Feng YL, Liang CZ, *et al*. Prognostic factors for pN2 non-small cell lung cancer: a comprehensive evidence from 73 studies involving 23,772 patients. Oncol Transl Med, 2020, 6: 57–63.