Genetic variants in cytokine signaling pathways and clinical outcomes in early-stage lung cancer patients

Boris Sepesi, MD,^a Yuanqing Ye, PhD,^b Kyle G. Mitchell, MD,^a Liren Zhang, PhD,^b Jianchun Gu, PhD,^b Lin Ji, PhD,^a Mara B. Antonoff, MD,^a Wayne L. Hofstetter, MD,^a David C. Rice, MD,^a Reza J. Mehran, MD,^a Garrett L. Walsh, MD,^a Ara A. Vaporciyan, MD,^a Stephen G. Swisher, MD,^a Jack A. Roth, MD,^a and Xifeng Wu, MD, PhD^b

ABSTRACT

Objectives: The purpose of this study was to explore the role of single nucleotide polymorphisms (SNPs) in cytokine signaling genes and to compare them with clinical outcomes in surgical patients with non-small cell lung cancer (NSCLC).

Methods: SNPs of the cytokine signaling pathway were analyzed using peripheral blood of 722 patients who underwent resection of stage I to III NSCLC between 1995 and 2009. Cox proportional hazard analyses were performed to identify SNPs associated with overall survival (OS) and risk of recurrence. Internal validation using bootstrap analysis selected SNPs for unfavorable genotype and survival tree analysis.

Results: Seventeen and 9 SNPs were independently associated with OS and recurrence, respectively. Patients with ≥ 9 unfavorable genotypes experienced worse OS (median, 41 months) than patients with 7 to 8 (89 months) and ≤ 6 (153 months) after median follow-up of 71 months ($P = 2.86 \times 10^{-23}$). Patients with ≤ 3 unfavorable genotypes had greater time to recurrence (median not reached) than those with 4 to 6 (114 months) and ≥ 7 (44 months; $P = 1.3 \times 10^{-5}$). Survival tree analysis classified patients into 3 risk groups. Patients in the intermediate- (median OS, 82 months) and high-risk groups (43 months) had worse survival than the low-risk group (176 months; $P = 5.51 \times 10^{-20}$). Median time to recurrence was worse in the intermediate- (114 months) and high-risk groups (58 months) than the low-risk group (median not reached; $P = 2.52 \times 10^{-9}$).

Conclusions: Genetic variants in cytokine signaling pathways were associated with clinical outcomes in NSCLC patients treated with surgery individually and cumulatively. Further studies are necessary to elucidate our findings and translate them into the clinical setting. (J Thorac Cardiovasc Surg 2018;155:2635-45)

Overall survival on the basis of unfavorable genotype.

Central Message

Select single nucleotide polymorphisms that code for cytokine pathways are associated with prognosis in non-small cell lung cancer patients who undergo surgical resection.

Perspective

Survival in lung cancer patients depends not only on tumor characteristics, but might also depend on patients' genetics. In this study we show that survival of lung cancer patients after surgery could be prognosticated on the basis of the number of unfavorable single nucleotide polymorphisms coding for cytokine pathways when controlling for stage and other variables.

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in men as well as women in the United States.¹ Complete resection of lung cancer along with removal of parenchymal (N1) and ipsilateral mediastinal (N2) lymph nodes represents the current standard of

care for early stages of lung cancer, and offers potential for cure or prolonged survival. Despite complete resection, up to 30% of patients with stage I disease and 50% of patients with stage II disease recur at local, regional, or distant sites and eventually die of their disease.² This high recurrence

From the ^aDepartment of Thoracic and Cardiovascular Surgery, and ^bDepartment of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Tex.

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Address for reprints: Boris Sepesi, MD, Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (E-mail: bsepesi@mdanderson.org), or Xifeng Wu, MD, PhD, Department of Epidemiology, The University of Texas MD Anderson Cancer Center, 1155 Pressler, Houston, TX 77030 (E-mail: xwu@mdanderson.org).

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Abbreviations and Acronyms

ADD	= additive
BMP	= bone morphogenic protein
CEBPB	= CCATT (nucleotide sequence) enhancer binding protein beta
CI	= confidence interval
CSF2RB	= colony stimulating factor 2 receptor beta
DLCO	= diffusing capacity of the lungs for carbon monoxide
DOM	= dominant
FDR	= false discovery rate
FEV1	= forced expiratory volume in 1 second
GH2	= growth hormone 2
HR	= hazard ratio
IFNK	= interferon kappa
IL	= interleukin
ILF2	= interleukin enhancer binding factor 2
IL1R	= interleukin 1 receptor
IL31RA	= interleukin 31 receptor A
IL17RB	= interleukin 17 receptor B
IL1RL2	= interleukin 1 receptor like 2
ILR1RL2	= interleukin receptor 1 receptor like 2
IRF2	= interferon regulatory factor 2
LTB	= lymphotoxin beta
MRFT	= median recurrence-free time
MST	= median survival time
NSCLC	= non-small cell lung cancer
OS	= overall survival
OSMR	= oncostatin M receptor
REC	= recessive
S100A9	= S100 calcium binding protein A9
SNP	= single nucleotide polymorphism
STAT1	= signal transducer and activator of transcription 1
TGFR2	= transforming growth factor beta receptor 2
TPO	= thyroid peroxidase
TYK2	= tyrosine kinase 2

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rate highlights the prognostic limitations of pathologic staging. Even among patients with the same disease stage there is a significant variability in cancer recurrence, suggesting that

other tumor-, patient-, or treatment-related factors influence the prognosis. Therefore, discovery of novel prognostic and/or predictive biomarkers creates an opportunity to further stratify patients for more personalized treatment.

The personalized approach is already available in patients with metastatic lung adenocarcinoma harboring targetable mutations of either epidermal growth factor receptors or anaplastic lymphoma kinase receptor.^{3,4} Over the past 2 years, exciting developments in the treatment of lung cancer have occurred with immunotherapy. Checkpoint inhibitor therapy targets the interaction between programmed cell death protein 1 and programmed death ligand 1 pathway, which blocks the T-cell immune response against tumors. However, even with immunotherapy the search for reliable biomarkers that would predict therapy response is ongoing.⁵

The complexities of each lung cancer on the genetic, epigenetic, or cell signaling level juxtaposed with the intricacies of each individual's immune system and its antitumor response are vast; hence the variable effectiveness and durability of lung cancer responses and prognosis to the previously mentioned surgical or drug therapies.⁶ Many of these complex interactions between the tumor, normal tissue, and immune system are regulated by cytokine-mediated pathways. Depending on the milieu, cytokines can promote tumor growth or angiogenesis, attenuate apoptosis, facilitate tumor invasiveness and development of metastases, or conversely play a role in tumor suppression.⁷ Cytokines have pleiotropic effects and sometimes redundant actions, which complicates the full understanding of the complex associations between cytokines and tumors. However, assessment of the biomarker potential of cytokines or inherent cytokine signaling pathways is appealing and might provide further insight into long-term prognosis of surgically resectable lung cancers or help generate novel hypotheses about therapy resistance.⁷

With these concepts in mind, we explored the utility of germline single nucleotide polymorphisms (SNPs), variations in single nucleotides occurring at specific positions in the genome, and their potential as candidate biomarkers in NSCLC. First, we tested a hypothesis of whether SNP genetic variants in cytokine signaling pathways are associated with clinical oncologic outcomes (survival and recurrence) in early stages of surgically treated NSCLC patients. Second, after identification of SNPs associated with outcome, we further explored combinations of cytokine signaling pathways coding SNPs and their association with high, moderate, or low incidence of recurrence and survival.

METHODS**Patient Population**

In this study, we included a total of 722 NSCLC patients with clinical stage I to III disease who were enrolled in an ongoing epidemiologic lung cancer study at The University of Texas MD Anderson Cancer Center

between 1995 and 2009. All patients had histologically confirmed NSCLC with no recruitment restrictions on age, sex, and ethnicity. All patients were treated with surgery; patients who underwent neoadjuvant or adjuvant chemotherapy combined with surgery were also included in the study. Surveillance consisted of a clinical examination as well as serial computed tomography scans with or without positron emission tomography imaging every 3 to 6 months for a minimum of 2 years and annually thereafter. More frequent surveillance imaging, bronchoscopy, and biopsy of any suspected sites of recurrence were pursued when clinically appropriate. Unfortunately, the adherence rate was not available.

Collection of Epidemiological and Clinical Data

The patients were interviewed by trained MD Anderson staff, who used a structured questionnaire to collect information on demographic characteristics (age, sex, ethnicity, etc), work history, smoking status, medical history, and family history of cancer. Performance status was defined according to the Eastern Cooperative Oncology Group scale at diagnosis. Peripheral blood samples were collected from patients at the end of each interview before initiation of any lung cancer treatment. Clinical and follow-up data were abstracted from medical records and included tumor size, clinical stage, pathologic stage, histological type, tumor grade, treatment type, chemotherapy regimen, tumor recurrence, progression, date of recurrence or progression, vital status, and date of last follow-up or death. To differentiate between metastatic recurrence versus second primary lung cancer, subsequent malignancy was categorized as a second primary tumor if found to meet the following criteria: (1) different histology; (2) same histology, diagnosed at least 2 years after resection of the primary tumor; (3) same histology, diagnosed within 2 years of resection of the primary, and arising from carcinoma in situ; or (4) same histology, diagnosed within 2 years of the primary, with no evidence of lymphatic involvement.⁸ Written informed consent was signed by all participants and the study was approved by MD Anderson Cancer Center's institutional review board. Median follow-up time was 66 (range, 63.1-72.3) months.

SNP Selection and Genotyping

We selected 266 cytokine signaling pathway genes on the basis of a published panel of inflammation-associated genes⁹ and a database of diabetes and inflammation genes (T1DBase/ImmunoBase; <http://www.t1dbase.org>; University of Cambridge, Cambridge, United Kingdom). For each gene, we selected tagging SNPs and potentially functional SNPs located 10 kb before the transcription start site and 10 kb after the transcription end site using the International HapMap Project (<http://www.hapmap.org>) and dbSNP (<http://www.ncbi.nlm.nih.gov/SNP>). Tagger algorithm (<https://www.broadinstitute.org/tagger>) was used to select the tagging SNPs with an r^2 threshold of 0.80 and a minor allele frequency of at least 0.05 in the Caucasian population. Potentially functional SNPs included synonymous SNPs, nonsynonymous SNPs, and SNPs in promoter, splicing site, 5' untranslated region, and 3' untranslated regions. A total of 3098 SNPs from 266 genes were included in the final analysis. High-quality genomic DNA was extracted from peripheral blood using a QIAamp DNA Mini Kit (Qiagen, Valencia, Calif). Genotyping experiments were performed using iSelect Custom Genotyping BeadChips according to Illumina Infinium II assay (Illumina, San Diego, Calif) protocol.

Statistical Analysis

The primary end point of the study was overall survival (OS) and secondary end point was recurrence. OS time was calculated from the date of diagnosis to the date of death or last follow-up. Patients who were alive at the end of the study or who were lost to follow-up were censored. Time to recurrence was calculated from the date of diagnosis to the date of first documented recurrence or last follow-up. Patients who were alive at the end of the study without developing recurrence, who were lost to follow-up, or who died were censored.

The associations of each SNP with risk of recurrence or death were estimated as hazard ratios (HRs) and 95% confidence intervals (CIs) using the multivariate Cox proportional hazards model, while adjusting for age, sex, smoking status, clinical stage, chemotherapy (yes/no), radiation (yes/no), and chemoradiation (yes/no). We considered 3 genetic models (dominant, recessive, and additive) and chose the model with the smallest P value as the best-fitting model. False discovery rate adjusted Q value (ie, P value adjusted to account for the proportion of rejected null hypotheses that are false positive results) was used to control for multiple comparisons.¹⁰ To internally validate the SNPs associated with recurrence and survival, we performed bootstrap resampling 100 times, estimated the HRs, 95% CIs, and P values for each bootstrap run, and counted the number of times the P value from bootstrap $< .01$. In each bootstrap run, data were randomly drawn from the observed data set with replacement. We selected SNPs with $>90\%$ of bootstrap P values $< .01$ for the further cumulative effect analysis and survival tree analysis. In the cumulative effect analysis, we counted the number of unfavorable genotypes. Tertile distribution was used to determine cutoffs for categorizing the number of unfavorable genotypes into low-, medium-, and high-risk groups.

Survival tree analysis, which allows for identification and division of the cohort into groups with similar risk profile, was performed using the STREE program (<http://c2s2.yale.edu/software/stree>). High-order gene-gene interactions were identified and used to classify patients into subgroups with differential risk of recurrence and death. Kaplan-Meier curves and log-rank tests were also used to evaluate the effect of the SNPs on survival time. The statistical analyses described previously were completed using STATA software (version 10; StataCorp, College Station, Tex) and $P < .05$ was considered statistically significant.

RESULTS

Demographic, clinical, and pathologic variables of the study population are described in Table 1. The mean age was 65 years (SD, 39.1) and 52% ($n = 373$) were female. Most patients were former or current smokers (84%); patients with a history of smoking had accumulated a mean of 53 pack-years (SD, 34.5). Nearly 60% of patients ($n = 423$) had clinical stage I, 23% ($n = 166$) had stage II, and 18% ($n = 133$) stage IIIA NSCLC. Most (64%; $n = 459$) patients had adenocarcinoma, and 24% ($n = 172$) had squamous cell carcinoma; poor (42%; $n = 301$) and moderate (39%; $n = 281$) differentiation were most prevalent. Sixty-two percent ($n = 450$) were treated with surgery alone and 38% ($n = 272$) received chemotherapy in addition to surgery. Of patients receiving chemotherapy, 175 patients received adjuvant chemotherapy, 71 received neoadjuvant chemotherapy, and 26 received neoadjuvant as well as adjuvant chemotherapy. Recurrence occurred in 274 patients, of whom 51 had local recurrence, 177 had distant metastasis, and 46 local as well as distant metastasis. At the time of last follow-up, 44% of the patients ($n = 317$) had died.

On the basis of the bootstrap analysis we identified 17 of 3098 SNPs to be significantly associated with OS. The SNPs and genes are presented in Table 2 and Tables E1-E3. Six SNPs coding for cytokine pathways were associated with favorable HR < 1 whereas 11 SNPs were independently associated with high risk of death. The most significant association was observed for a SNP in

TABLE 1. Demographic characteristics of the population

Variable	Value
Total, n	722
Median follow-up time, mo	66.4 (63.1-72.3)
Mean age (SD)	65.5 (39.1)
Mean pack-years smoked (SD)	52.7 (34.5)
Sex	
Male	349 (48.3)
Female	373 (51.7)
Smoking status	
Never	127 (17.6)
Former	338 (46.8)
Current and RQ	257 (35.6)
Clinical stage	
1	423 (58.6)
2	166 (23.0)
3A	133 (18.4)
Pathology	
Adenocarcinoma	459 (63.6)
Squamous cell carcinoma	172 (23.8)
Other	91 (12.6)
Grade	
Well differentiated	80 (11.1)
Moderately differentiated	281 (38.9)
Poorly differentiated/undifferentiated	301 (41.7)
Unknown	60 (8.3)
Chemotherapy	
No	467 (64.7)
Yes	255 (35.3)
Radiation therapy	
No	664 (92.0)
Yes	58 (8.0)
Chemoradiation therapy	
No	694 (96.1)
Yes	28 (3.9)
Pathology stage	
0	7 (1.0)
1	395 (54.7)
2	186 (25.8)
3	132 (18.3)
4	2 (0.3)
Pathology T stage	
1A	178 (24.7)
1B	176 (24.4)
2A	204 (28.3)
2B	64 (8.9)
3	76 (10.5)
4	14 (1.9)
IS	2 (0.3)
X	7 (1.0)
Pathology N stage	
0	488 (67.6)
1	131 (18.1)
2	103 (14.3)

(Continued)

TABLE 1. Continued

Variable	Value
Recurrence	
No	448 (62.0)
Yes	274 (38.0)
Death	
No	405 (56.1)
Yes	317 (43.9)

Data are presented as n (%) except where otherwise stated. *SD*, Standard deviation; *RQ*, recently quit.

the interleukin (IL) enhancer binding factor 2 gene with a HR of 1.78 (95% CI, 1.39-2.27; $P = 4.56 \times 10^{-6}$). Interestingly, a separate set of 9 SNPs coding for cytokine pathways were independently associated with disease recurrence (Table 3 and Tables E4-E6). The most significant association was observed for an SNP in the interleukin 1 receptor like 2 (*IL1RL2*) gene with a HR of 1.44 (95% CI, 1.18-1.76; $P = 3.70 \times 10^{-4}$). A competing risk analysis of the 9 SNPs independently associated with recurrence showed similar results (Table E7).

We stratified patients on the basis of the favorable or unfavorable genotypes and performed Kaplan–Meier analysis for OS and recurrence. For OS, we observed that patients with ≥ 9 unfavorable genotypes experienced the worst survival with median of 41 (95% CI, 31-46) months (HR, 4.3; 95% CI, 3.24-5.8) compared with patients with 7 to 8 unfavorable genotypes (median OS, 90 months; 95% CI, 71-118 months; HR 1.9; 95% CI, 1.43-2.6), and ≤ 6 unfavorable genotypes (median OS, 153 months; 95% CI, 118-191 months; HR, 1.0; log-rank $P = 2.86 \times 10^{-23}$; Figure 1). Survival tree analysis was subsequently performed and classified patients in 3 groups. Table E8 shows the characteristics of the 3 risk groups identified using survival tree analysis. A comparison of survival of patients in the low-risk group (median OS, 176 months; 95% CI, 133 to not reached; HR, 1), patients in the medium-risk group (median OS, 82 months; 95% CI, 70-106 months; HR, 2.26; 95% CI, 1.66-3.07), and patients in the high-risk group (median OS, 43 months; 95% CI, 38-54 months; HR, 4.01; 95% CI, 2.98-5.40) showed that medium- and high-risk groups were associated with a 2.3 and 4.0-fold increased risk of death, respectively (log rank $P = 5.51 \times 10^{-20}$; Figure 2).

Similarly, we performed the Kaplan–Meier analysis to evaluate recurrence. The best recurrence was observed in patients with ≤ 3 unfavorable genotypes where median survival was not reached (HR, 1.0). In the group with 4 to 6 unfavorable genotypes median recurrence-free time was 114 (95% CI, 67 to not reached) months (HR, 1.98; 95% CI, 1.43-2.75), and in patients with ≥ 7 unfavorable genotypes 45 (95% CI, 29 to not reached) months (HR, 2.84; 95% CI, 1.90-4.22; log rank $P = 1.3 \times 10^{-5}$;

TABLE 2. SNPs independently associated with risk of death

SNP	Gene	Dead, n*	Alive, n*	Model†	HR (95% CI)	P	Q‡	Times with P < .01 in 100 bootstrap runs, n
rs4845563	ILF2	80/140/97	138/196/71	REC	1.78 (1.39-2.27)	4.56E-06	0.00652	100
rs173107	BMP2	138/132/47	131/208/66	DOM	0.65 (0.52-0.82)	1.95E-04	0.14	100
rs235757	BMP2	133/141/43	125/219/60	DOM	0.66 (0.53-0.83)	2.83E-04	0.14	100
rs2310047	IRF2	99/152/65	160/186/59	ADD	1.32 (1.13-1.55)	5.78E-04	0.16	96
rs814030	IFNK	162/129/26	228/159/18	ADD	1.36 (1.14-1.63)	6.91E-04	0.16	98
rs1800630	LTB	199/108/10	295/98/12	DOM	1.48 (1.18-1.87)	8.67E-04	0.16	98
rs4351684	ILF2	114/142/61	99/205/101	DOM	0.67 (0.53-0.85)	9.45E-04	0.16	98
rs4865998	IL31RA	166/122/27	246/148/11	REC	1.97 (1.32-2.95)	9.68E-04	0.16	99
rs6445608	IL17RB	139/134/44	136/220/49	DOM	0.70 (0.56-0.87)	1.54E-03	0.16	99
rs6020348	CEBPB	88/169/59	159/177/69	DOM	1.49 (1.16-1.91)	1.73E-03	0.16	90
rs3917335	IL1R	280/37/0	377/28/0	DOM	1.74 (1.23-2.46)	1.75E-03	0.16	96
rs9867701	TGFBR2	99/175/43	176/175/54	DOM	1.47 (1.15-1.87)	1.85E-03	0.16	90
rs2072707	CSF2RB	136/135/46	192/178/35	REC	1.65 (1.20-2.27)	1.85E-03	0.16	95
rs357291	OSMR	73/163/81	121/208/76	ADD	1.29 (1.10-1.52)	2.04E-03	0.16	94
rs692890	IL12A	162/116/39	175/187/43	DOM	0.70 (0.56-0.88)	2.12E-03	0.16	93
rs883844	STAT1	110/169/38	180/171/54	DOM	1.43 (1.13-1.82)	2.72E-03	0.16	92
rs2706399	IL5	88/171/58	106/192/107	REC	0.64 (0.48-0.86)	2.74E-03	0.16	95

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval; ILF2, interleukin enhancer binding factor 2; REC, recessive; BMP2, bone morphogenic protein 2; DOM, dominant; IRF2, interferon regulatory factor 2; ADD, additive; IFNK, interferon kappa; LTB, lymphotoxin beta; IL31RA, interleukin 31 receptor A; IL17RB, interleukin 17 receptor B; CEBPB, CCAAT (nucleotide sequence) enhancer binding protein beta; IL1R, interleukin 1 receptor; TGFBR2, transforming growth factor beta receptor 2; CSF2RB, colony stimulating factor 2 receptor beta; OSMR, oncostatin M receptor; IL12A, interleukin 12 A; STAT1, signal transducer and activator of transcription 1; IL, interleukin. *Genotype counts in the order of common homozygous/heterozygous/rare homozygous. †The genetic model used for the SNP (REC, DOM, and ADD). ‡Q value is the FDR adjusted P value, where FDR is a measure to control for multiple hypothesis testing, which is the expected proportion of false positive findings among all of the rejected hypotheses.

Figure 3). In the survival tree analysis, which again compared patients in the low-risk group (median not reached), with patients in the medium-risk group (median recurrence-free time, 114 months; 95% CI, 51 to not reached; HR, 2.47; 95% CI, 1.68-3.62) and patients in the high-risk group (median recurrence-free time 58 months; 95% CI, 33-111 months; HR, 3.44; 95% CI,

2.39-4.97), we observed a 2.5-fold and 3.4-fold increased association with recurrence in the medium- and high-risk groups, respectively (log rank $P = 2.52 \times 10^{-9}$; Figure 4). Statistically significant differences in OS and risk of recurrence were identified between medium- and high-risk groups defined using survival tree as well as unfavorable genotype analyses (Table E9 and Video 1).

TABLE 3. SNPs independently associated with risk of recurrence

SNP	Gene	Recurrence, n*	No recurrence, n*	Model†	HR (95% CI)	P	Q‡	Times with P < .01 in 100 bootstrap runs, n
rs2287040	IL1RL2	101/135/38	205/197/46	ADD	1.44 (1.18-1.76)	3.70E-04	0.19	100
rs11211654	TPO	239/34/1	412/36/0	DOM	2.00 (1.35-2.96)	4.99E-04	0.19	98
rs2008018	GH2	117/127/29	233/171/42	DOM	1.63 (1.24-2.15)	5.17E-04	0.19	100
rs3917239	IL1R1	74/141/59	162/214/72	ADD	1.39 (1.15-1.67)	6.26E-04	0.19	99
rs280523	TYK2	221/53/0	399/46/3	DOM	1.82 (1.28-2.57)	7.58E-04	0.19	92
rs17026782	IL1RL2	131/122/21	262/168/18	ADD	1.46 (1.17-1.81)	7.97E-04	0.19	98
rs3014866	S100A9	70/130/74	152/198/98	DOM	1.67 (1.23-2.28)	1.20E-03	0.21	96
rs4927632	TPO	95/135/44	195/209/44	ADD	1.39 (1.14-1.70)	1.26E-03	0.21	90
rs2110726	IL1RL2	93/140/41	198/193/57	DOM	1.58 (1.19-2.10)	1.74E-03	0.21	91

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval; IL1RL2, interleukin 1 receptor like 2; ADD, additive; TPO, thyroid peroxidase; DOM, dominant; GH2, growth hormone 2; IL1R1, interleukin 1 receptor 1; TYK2, tyrosine kinase 2; S100A9, S100 calcium binding protein A9; IL1RL2, interleukin receptor 1 receptor like 2. *Genotype counts in the order of common homozygous, heterozygous, and rare homozygous. †The genetic model used for the SNP (REC/DOM/ADD). ‡Q value is the FDR adjusted P value, where FDR is a measure to control for multiple hypothesis testing, which is the expected proportion of false positive findings among all of the rejected hypotheses.

FIGURE 1. Kaplan–Meier analysis for unfavorable genotype, overall survival time; analysis time in months and 95% confidence intervals are provided in parentheses. *MST*, Median survival time; *HR*, hazard ratio.

DISCUSSION

In addition to tumor stage and the effect of locoregional and systemic therapies, long-term survival and oncologic recurrence outcomes after curative-intent resection of NSCLC might also be dependent on patients' genomic characteristics that regulate immune surveillance and inflammatory pathways. Our exploratory discovery biomarker study shows that SNPs coding for cytokine signaling pathways were associated with survival and recurrence outcomes in NSCLC patients treated with definitive

surgical therapy. Specific SNP cytokine pathways that were associated with favorable survival included IL-12, which is naturally produced by dendritic cells, macrophages, neutrophils, and B cells in response to antigenic stimulation, IL-5, which is produced by T-helper cells and mast cells, IL-17, a strong inducer of inflammation produced by T-helper cells, bone morphogenic protein, a growth factor belonging to transforming growth factor β family, and IL enhancer binding factor 2, a transcription nuclear factor of activated T cells required for T-cell

FIGURE 2. Kaplan–Meier analysis for survival tree, overall survival time; analysis time in months and 95% confidence intervals are provided in parentheses. *MST*, Median survival time; *HR*, hazard ratio.

FIGURE 3. Kaplan–Meier analysis for unfavorable genotype, risk of recurrence; analysis time in months. *MRFT*, Median recurrence-free time; *HR*, hazard ratio.

expression of the IL-2 gene. Sensitivity analysis with inclusion of additional clinical factors also showed similar estimates and results for the top SNPs (Tables E10 and E11). We have also identified a number of unfavorable SNPs and were able to show distinct and ordered survival curves of lung cancer patients associated with the high-, intermediate-, and low-risk genotype groups.

Cytokines are known to be involved in the inflammatory processes and potentially in carcinogenesis, tumor invasion, and metastases development.⁷ Although their function is pleiotropic, some cytokines have been proposed to function as cancer biomarkers, and several cytokines have been identified as either pro-oncogenic, antitumor, or context-dependent cytokines.⁷ Cytokines can be measured either

in the blood, tumor tissue, sputum, pleural, or other bodily fluids. In lung cancer, several blood cytokines have been identified as potential biomarkers. Pro-oncogenic cytokines include IL-6, IL-8, vascular endothelial growth factor, tumor necrosis factor α , IL-10, IL-22, and IL-32, and anti-tumor cytokines include IL-7, and IL-10, depending on the context, and IL-37, which has been shown in some studies to have a protective role against cancer progression.⁷ Interestingly, our results did not identify any of these previously known cytokines to be associated with either favorable or unfavorable outcome. We have, however, studied germline SNPs coding for cytokine pathways, rather than measured the quantity or the function of cytokines themselves.

FIGURE 4. Kaplan–Meier analysis for survival tree, risk of recurrence; analysis time in months. *MRFT*, Median recurrence-free time; *HR*, hazard ratio; NA, not applicable.

Genetic Variants in Cytokine Signaling Pathways and Clinical Outcomes in Early Stage Lung Cancer Patients

Boris Sepesi MD*, Yuanqing Ye PhD*, Kyle G Mitchell MD*, Liren Zhang PhD, Jianchun Gu PhD, Lin Ji PhD, Mara Antonoff MD, Wayne Hofstetter MD, David Rice MD, Reza Mehran MD, Garrett Walsh MD, Ara Vaporciyan MD, Stephen Swisher MD, Jack A Roth MD*, Xifeng Wu MD PhD*

Narration: Kyle G Mitchell, MD

VIDEO 1. A summary of the key findings of the study and their relevance. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(18\)30372-6/fulltext](http://www.jtcvsonline.org/article/S0022-5223(18)30372-6/fulltext).

There have been a few genome-wide association studies to date, which used SNPs to prognosticate outcomes in NSCLC.¹¹⁻¹⁵ In 2009, Huang et al investigated SNPs in tumors and their association with prognosis in early-stage NSCLC. They analyzed extracted DNA from lung tissue with at least 70% tumor cellularity from 100 patients for the discovery set and 89 patients as a validation set.¹² They identified 5 SNPs, located on genes serine/threonine kinase 39, ataxin 2 binding protein 1, protocadherin 7, and eyes absent transcriptional coactivator and phosphatase 2, that might be prognostic of OS in early stage NSCLC, and that survival decreased with the number of the risk alleles. The authors concluded that larger studies are needed along with the functional assessment to confirm the role of tumor SNPs in NSCLC behavior.¹² In another study, Wu et al conducted a genome-wide association study of genetic predictors of OS in never-smokers.¹³ This study included the discovery set and 2 validation data sets for a total of 1876 patients using tumor and matched normal parenchymal tissue. The authors identified 94 loci to be significant for OS in 2 data sets from the United States, with 2 variants of the top 25 loci being also significant in the Taiwanese population. Identified loci were associated with decreased survival by 5 to 8 months.¹³ SNPs have also been shown to be predictive of platinum chemotherapy response^{14,15} in NSCLC. In a genome-wide scan of 307,260 germline SNPs in 327 advanced NSCLCs, SNP rs1878022 coding for chemokine-like receptor 1 was significantly associated with poor OS (HR, 1.59).¹⁵ The authors concluded that these results have a potential to contribute to the future development of personalized chemotherapy treatments for patients with NSCLC.¹⁵

The pathway-based approach to identifying SNPs predictive of survival was also studied by Pang et al.¹⁶ In their study they used a machine learning algorithm to correlate SNPs with survival outcomes, and applied this methodology to a data set of plasma cells of 192 multiple myeloma

patients genotyped for 500,000 SNPs. They were able to stratify patients' OS on the basis of high- and low-risk SNPs coding for cytokine pathways, as well as according to high- and low-risk of stress induction of the heat shock protein regulation pathway. For the cytokine network, they identified *IL-15*, *IL-18*, and *IL-12A* to be the most important.¹⁶ Whereas *IL-12A* SNPs have been shown to be associated with elevated risk of multiple myeloma in women in a population-based study, in our study *IL-12A* was associated with a favorable HR of 0.7 for OS in lung cancer. In one study, which measured serum cytokine concentration, a higher IL-12 serum concentration was associated with worse (HR, 1.98; 95% CI, 1.14-3.44) survival in lung cancer patients, as was IL-6. Surprisingly, higher IL-10 levels were associated with worse survival initially, but better survival beyond 18 months after diagnosis.¹⁷

In our study, SNP coding for IL-1 was associated with worse OS as well as recurrence. Solid tumors (breast, colon, lung, head and neck cancers, and melanoma) in which IL-1 has been shown to be upregulated have generally a bad prognosis. IL-1 is a pluripotent cytokine, with roles in vascular permeability, fever, release of prostaglandins, pituitary hormones, and collagenases. The ability of IL-1 to promote tumor proliferation and metastases via neoangiogenesis by inducing other factors such as vascular endothelial growth factor and IL-8 has been previously documented, as was the ability of the IL-1 receptor antagonist to decrease tumor growth, angiogenesis, and metastases in murine xenograft models.¹⁸ Therefore, SNPs coding for IL-1, its protein product, and associated downstream protein-protein interactions encourage further study.

These studies as well as our current study draw attention to the potential prognostic value of SNPs detected in the peripheral blood of patients with early stages of NSCLC. Despite the fact that each study contained either an external or internal validation set, the results among these studies are inconsistent in terms of the specific SNPs, and their value in prognosticating outcome in NSCLC because of the difference in study populations (early stage NSCLC patients vs never smoking NSCLC patients vs platinum-based chemotherapy in late stage NSCLC patients). In our study, we explored the association of germline SNPs coding for cytokine pathways and were able to identify several SNPs associated with OS and several SNPs associated with recurrence; however, many of them seem to be inconsistent with the more commonly referenced cytokines that have been reported to influence outcome in NSCLC. Whether this represents chance or is a more uniform finding remains to be determined in other studies. Cytokines are dynamic molecules that can regulate cellular function and homeostasis in several types of tissues. Although cytokines are believed to be major biomarker candidates, the measurement of their dynamic function likely requires longitudinal surveillance to improve our understanding of their

pleiotropic function. Rather than measuring cytokine levels, we studied SNP cytokine pathways from the peripheral blood drawn before any therapy. Although these were germline SNPs, and should therefore be consistent, the influence of all potential external factors (treatment, diet, stress, environment) on these and other cytokine pathways as well as on OS cannot be quantified. Because of the poor prognosis of lung cancer, it is, however, important to continue to study the biology of this disease as well as the heterogeneous interaction of human and cancer biology.

Limitation

There are limitations to our study, mainly in the lack of a validation set. A bootstrap internal validation technique was used, but this is not ideal. Larger data sets are necessary to validate our findings, and additional studies are needed to dive deeper into the mechanisms of germline cytokine pathways and their influence on oncologic outcomes. Another limitation includes the lack of knowledge about the functional product (or lack thereof) generated or influenced by the SNP pathways that were associated with survival and recurrence. Determination of the effect of these SNPs on host gene expression and function, as well as their interaction with tumor biology, would require additional extensive studies to fully understand the translational value of our results. Therefore, the results of our study should be considered exploratory.

CONCLUSIONS

Our discovery biomarker study shows that germline SNPs coding for cytokine signaling pathways were associated with survival and recurrence outcomes in NSCLC patients treated with definitive surgical therapy, when controlling for stage and other variables. This suggests that not only tumor or treatment characteristics, but also patients' genetic characteristics are important in determining long-term outcomes in NSCLC. Further studies are needed to validate our findings and to understand the role of cytokine pathways and whether they can serve as potential novel biomarkers in NSCLC patients treated with definitive surgical therapy.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/17AM/2017-05-01/RM302-304/05-01-17_Room302-304_1631_Sepesi.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: single nucleotide polymorphism, lung cancer, survival, surgical therapy

Discussion

Dr Bryan M. Burt (*Houston, Tex*). Boris, I very much enjoyed listening to your talk and reading your paper. In brief summary, your group retrospectively evaluated these tagging and potentially functional SNPs in 266 cytokine signaling pathway genes in the peripheral blood, which I will emphasize are germline SNPs, and this is among a robust cohort of 722 patients who were treated surgically for non-small cell lung cancer at your institution. You have shown to us that a handful of these SNPs were independently associated with recurrence-free survival, either better survival and another handful with worse survival, and the same thing for overall survival, and you have implied that these data might have potentially prognostic importance for patients with non-small cell lung cancer who are treated surgically. I will ask you 3 questions.

Now, we have all, unfortunately, seen cases like the one you have presented where a patient with clinical stage I non-small cell lung cancer will undergo a thoughtful and complete oncologic operation and then in what seems like no time demonstrates widely metastatic disease. So we as surgeons have the ability to affect locoregional control. However, as you have noted in your data and as we have heard in the Memorial data earlier in this session, most patients will recur systematically. Does your panel of germline cytokine signaling SNPs have the ability to predict distant recurrence compared with locoregional recurrence? Certainly this would move us forward in selecting patients appropriate for lung cancer resection.

Dr Boris Sepesi (*Houston, Tex*). Thank you very much for the question. We did not specifically look at locoregional versus distant recurrence, but everything being equal, 90% of patients with lung cancer develop distant recurrence. So just by that statistic alone, I would be making that assumption.

But we can go back into our data and more specifically look at locoregional versus distant recurrence, although some patients experienced both.

I think that this study really highlights the fact that as much as we have been looking for tumor-related factors and outcomes in lung cancer patients, there are probably treatment-related factors, and specifically patient-related factors, that might ultimately influence outcome. And we see that now, for example, with immune responses to checkpoint inhibitors and basically learning more about the immunology and how a patient's immune system actually is reacting to it. Interestingly enough, those 5 SNPs are coding for cytokines that are very much used

in T-cell-mediated pathways, so are these patients who just have sort of a better T-cell milieu that is protected against their cancer. This all will be part of more ongoing research.

Dr Burt. That is a great prelude to my second question. I was simply going to ask you to comment further on the translational relevance and potential importance of these findings; a blood-based biomarker test has obvious advantage compared with tissue-based biomarker tests that we currently have available. Should we use a test like this in the clinic, or how do you see this evolving?

Dr Sepesi. There have been only 4 or so genome-wide studies that use SNPs to prognosticate survival in lung cancer, and this is one of them. So there are not enough data in the literature, and interestingly enough, as I reviewed the literature for this study, most of the results are not really concordant; each study seems to find some sort of a different SNP.

Part of the reason that we looked into this is because we are currently undergoing an immunogenomic profiling project where we deeply are profiling all of our tumors, not only from the genomic standpoint but we also are drawing peripheral blood and extracting T cells. All that comprehensive data will then give us an opportunity to look at these patient tumor- and perhaps treatment-related factors of inflammation. This was a retrospective attempt to look at some of the data that we have from this genomic level that we can later on compare with some of our new results from this comprehensive peripheral blood profiling.

But as I mentioned in the Limitation section, these are genomic traits, essentially, and I cannot really comment about the values or functionality of different cytokines that are produced by these pathways and their influence on outcome.

Dr Burt. That is great. That is my third question for those of us interested in immunology, if you could comment on the function relevance. Is there any reason to think that these genes related to cytokine signaling, these polymorphisms, that there is a functional implication of it? You showed IL-1 and IL-1 receptor polymorphisms have an effect on recurrence-free survival and overall survival. There are a number of reports now that people are measuring circulating cytokines like IL-6, IL-8, and a number of other things that show also an effect on prognosis.

In your data set, would it be worth it to try figure out if these SNPs have any functional relevance in terms of—you have all the serum—in circulating cytokines, and if so, is that easy to measure or less expensive to measure than a genomic-based SNP array?

Dr Sepesi. I am not sure how to comment on the cost of whether it is less expensive or not. Certainly these SNP arrays are done on automated machines. But, as you

mentioned, the cytokines are very pleiotropic molecules, and they could be influenced, for example, by thoracotomy versus VATS, they could be influenced by postoperative pneumonia, they could be influenced by perhaps a patient having some traits to have collagen vascular diseases or some of the other things. So it is very difficult to sort out this pleiotropic effect.

But one of the things that we do in our immunogenomic profiling is that we are drawing these bloods at different time points, every 3 months at least up to a year, to look at trends, and then we should be able to sort out patients who had, for example, good perioperative outcomes and then correlate the levels of these peripheral cytokines with long-term outcome, survival, recurrence, and other data. But it is not mature yet. I think we have to do more research into this to find the translational value.

Dr Burt. Excellent. Thank you very much.

Dr Sai Yendamuri (*Buffalo, NY*). That was a great talk. I have 3 methods questions. The first one is, it has now become standard practice when you have a large number of variables and a relatively small number of samples relative to the variables to do some sort of adjustment for false discovery

rates, and I didn't see that adjustment done in this. Did you do it?

Dr Sepesi. Yes, it was. I didn't include it in my talk, but the adjustment was done for false discovery according to standard protocols.

Dr Yendamuri. Bonferroni or something like that?

Dr Sepesi. Yes. We collaborated with our epidemiologists and statisticians on that.

Dr Yendamuri. The second question I have is that, you have a fairly large number of samples, like 700 plus.

Dr Sepesi. Correct.

Dr Yendamuri. Why did you not take the strategy of having a test set and then a validation set, because that's a fair number of tumors that you have there. So I was just curious why you chose to do internal bootstrapping versus another model.

Dr Sepesi. We would have essentially just divided the set in half rather than using this bootstrap technique, which I sort of learned about. Performing the substitution 100 times, it is not a perfect validation set. The perfect validation set would be from another institution, from another patient data set. Splitting the data in half and saying one of this is

a validation and one of this is the original set, we didn't feel like that would have changed things very much.

Some of these markers, as you can see, some of the SNPs had a hazard ratio of 0.6, for example. That is pretty protective, and some of them remained in a bootstrap analysis 100% of the time, so 90% or a 100% of the time. So these have come up over and over and over again. Again, it is the same set, so you would assume they are going to come up over and over again. There is no way to overcome it.

Dr Yendamuri. Last question. When you use this as a clinical tool, often instead of having survival curves it is useful to look at, say, the accuracy of recurrence prediction. Say if it is a high-risk sort of profile, you would say the chance of recurrence is 60% versus 40%. That is another way of making it clinically useful, because if the difference between a high-risk profile and low-risk profile is 55% versus 45%, then there is nothing else we would do differently in terms of intervention, versus if it is a 75% and 25% risk of recurrence at 3 years, then you can actually intervene and it makes it more clinically useful.

Have you done that or are you planning on doing that?

Dr Sepesi. We could go back and take a look. This was really just sort of a discovery kind of data set.

Dr Ayman Abdul-Ghani (*Honolulu, Hawaii*). Maybe I missed it on your slides, but you did this study on surgically resectable lung cancer. Did you correlate it with the stage of the tumor?

Dr Sepesi. Correct. Everything was adjusted for tumor stage, grade, age, all the other variables, all the hazard ratios.

Dr Abdul-ghani. So did you have a relationship between the stage of the tumor and the higher-dose genomes or those cytokines that correlate with poor prognosis?

Dr Sepesi. We did not specifically look at that. Just so we all understand, these are patient-related factors; these are SNPs that are taken from patients' leukocytes. They should be essentially independent from whatever the tumor is. So we can look at that correlation, but it doesn't necessarily make sense to me to compare the stage of disease with these patient-related variables. This is patients' DNA, specifically patients' DNA that was analyzed from leukocytes. So there is no cross-reactivity with tumor-related DNA in this.

TABLE E1. Detailed results for SNPs independently associated with risk of death

Variable	Adjusted HR (95% CI)	P
rs4845563	1.78 (1.39-2.27)	4.56E-06
Sex (female vs male)	0.75 (0.60-0.95)	1.58E-02
Age	1.01 (1.00-1.01)	3.81E-09
Smoking status (former vs never)	0.99 (0.72-1.37)	9.72E-01
Smoking status (current vs never)	1.18 (0.85-1.64)	3.18E-01
Clinical stage (stage II vs stage I)	1.57 (1.19-2.07)	1.37E-03
Clinical stage (stage III vs stage I)	2.19 (1.57-3.06)	3.65E-06
Radiation (yes vs no)	1.36 (0.88-2.09)	1.66E-01
Chemotherapy (yes vs no)	0.77 (0.58-1.01)	5.71E-02
Chemoradiation (yes vs no)	0.95 (0.54-1.66)	8.59E-01
rs173107	0.65 (0.52-0.82)	1.95E-04
Sex (female vs male)	0.74 (0.59-0.93)	9.29E-03
Age	1.01 (1.00-1.01)	3.24E-09
Smoking status (former vs never)	1.03 (0.74-1.42)	8.70E-01
Smoking status (current vs never)	1.23 (0.88-1.70)	2.21E-01
Clinical stage (stage II vs stage I)	1.62 (1.23-2.14)	6.44E-04
Clinical stage (stage III vs stage I)	2.02 (1.46-2.79)	2.15E-05
Radiation (yes vs no)	1.40 (0.91-2.15)	1.24E-01
Chemotherapy (yes vs no)	0.78 (0.60-1.03)	8.20E-02
Chemoradiation (yes vs no)	0.88 (0.51-1.53)	6.57E-01
rs235757	0.66 (0.53-0.83)	2.83E-04
Sex (female vs male)	0.74 (0.59-0.93)	9.61E-03
Age	1.01 (1.00-1.01)	3.66E-09
Smoking status (former vs never)	1.03 (0.74-1.42)	8.70E-01
Smoking status (current vs never)	1.23 (0.89-1.71)	2.08E-01
Clinical stage (stage II vs stage I)	1.60 (1.21-2.11)	9.51E-04
Clinical stage (stage III vs stage I)	1.97 (1.42-2.73)	4.29E-05
Radiation (yes vs no)	1.44 (0.93-2.21)	9.89E-02
Chemotherapy (yes vs no)	0.79 (0.60-1.04)	9.29E-02
Chemoradiation (yes vs no)	0.89 (0.51-1.55)	6.88E-01
rs2310047	1.32 (1.13-1.55)	5.78E-04
Sex (female vs male)	0.75 (0.60-0.95)	1.48E-02
Age	1.00 (1.00-1.01)	7.33E-08
Smoking status (former vs never)	1.05 (0.76-1.45)	7.80E-01
Smoking status (current vs never)	1.28 (0.92-1.79)	1.38E-01
Clinical stage (stage II vs stage I)	1.56 (1.18-2.05)	1.71E-03
Clinical stage (stage III vs stage I)	1.99 (1.44-2.76)	3.17E-05
Radiation (yes vs no)	1.42 (0.92-2.19)	1.09E-01
Chemotherapy (yes vs no)	0.79 (0.60-1.04)	9.92E-02
Chemoradiation (yes vs no)	0.96 (0.55-1.67)	8.81E-01
rs814030	1.36 (1.14-1.63)	6.91E-04
Sex (female vs male)	0.73 (0.58-0.91)	6.09E-03
Age	1.01 (1.00-1.01)	2.50E-09
Smoking status (former vs never)	1.01 (0.73-1.39)	9.57E-01
Smoking status (current vs never)	1.20 (0.86-1.66)	2.86E-01
Clinical stage (stage II vs stage I)	1.66 (1.25-2.19)	3.86E-04
Clinical stage (stage III vs stage I)	2.07 (1.49-2.86)	1.32E-05
Radiation (yes vs no)	1.48 (0.96-2.28)	7.60E-02
Chemotherapy (yes vs no)	0.77 (0.58-1.01)	5.69E-02
Chemoradiation (yes vs no)	0.94 (0.54-1.65)	8.39E-01
rs1800630	1.48 (1.18-1.87)	8.67E-04
Sex (female vs male)	0.77 (0.61-0.97)	2.80E-02

(Continued)

TABLE E1. Continued

Variable	Adjusted HR (95% CI)	P
Age	1.01 (1.00-1.01)	5.61E-09
Smoking status (former vs never)	1.03 (0.74-1.41)	8.79E-01
Smoking status (current vs never)	1.20 (0.86-1.66)	2.86E-01
Clinical stage (stage II vs stage I)	1.58 (1.20-2.09)	1.22E-03
Clinical stage (stage III vs stage I)	1.99 (1.43-2.75)	3.65E-05
Radiation (yes vs no)	1.39 (0.90-2.13)	1.38E-01
Chemotherapy (yes vs no)	0.80 (0.61-1.06)	1.22E-01
Chemoradiation (yes vs no)	0.90 (0.52-1.57)	7.06E-01
rs4351684	0.67 (0.53-0.85)	9.45E-04
Sex (female vs male)	0.76 (0.60-0.95)	1.75E-02
Age	1.01 (1.00-1.01)	4.49E-08
Smoking status (former vs never)	1.01 (0.73-1.39)	9.71E-01
Smoking status (current vs never)	1.21 (0.87-1.67)	2.65E-01
Clinical stage (stage II vs stage I)	1.56 (1.18-2.06)	1.65E-03
Clinical stage (stage III vs stage I)	2.14 (1.54-2.98)	6.60E-06
Radiation (yes vs no)	1.38 (0.90-2.12)	1.43E-01
Chemotherapy (yes vs no)	0.76 (0.58-1.01)	5.68E-02
Chemoradiation (yes vs no)	0.94 (0.54-1.64)	8.23E-01
rs4865998	1.97 (1.32-2.95)	9.68E-04
Sex (female vs male)	0.76 (0.61-0.96)	2.13E-02
Age	1.01 (1.00-1.01)	5.67E-09
Smoking status (former vs never)	1.05 (0.76-1.45)	7.76E-01
Smoking status (current vs never)	1.17 (0.84-1.63)	3.51E-01
Clinical stage (stage II vs stage I)	1.61 (1.22-2.12)	7.76E-04
Clinical stage (stage III vs stage I)	1.96 (1.42-2.71)	4.97E-05
Radiation (yes vs no)	1.42 (0.92-2.18)	1.15E-01
Chemotherapy (yes vs no)	0.80 (0.61-1.06)	1.20E-01
Chemoradiation (yes vs no)	0.89 (0.51-1.54)	6.66E-01
rs6445608	0.70 (0.56-0.87)	1.54E-03
Sex (female vs male)	0.75 (0.60-0.95)	1.45E-02
Age	1.01 (1.00-1.01)	3.68E-09
Smoking status (former vs never)	1.05 (0.76-1.45)	7.48E-01
Smoking status (current vs never)	1.24 (0.90-1.73)	1.92E-01
Clinical stage (stage II vs stage I)	1.63 (1.23-2.15)	5.85E-04
Clinical stage (stage III vs stage I)	2.04 (1.47-2.83)	1.99E-05
Radiation (yes vs no)	1.41 (0.91-2.18)	1.20E-01
Chemotherapy (yes vs no)	0.79 (0.60-1.04)	8.90E-02
Chemoradiation (yes vs no)	0.89 (0.51-1.55)	6.74E-01
rs6020348	1.49 (1.16-1.91)	1.73E-03
Sex (female vs male)	0.75 (0.60-0.94)	1.41E-02
Age	1.01 (1.00-1.01)	1.31E-09
Smoking status (former vs never)	1.03 (0.74-1.42)	8.72E-01
Smoking status (current vs never)	1.23 (0.88-1.70)	2.25E-01
Clinical stage (stage II vs stage I)	1.62 (1.23-2.14)	6.14E-04
Clinical stage (stage III vs stage I)	2.00 (1.45-2.76)	2.57E-05
Radiation (yes vs no)	1.51 (0.98-2.32)	6.17E-02
Chemotherapy (yes vs no)	0.78 (0.59-1.03)	7.43E-02
Chemoradiation (yes vs no)	0.98 (0.56-1.70)	9.39E-01
rs3917335	1.74 (1.23-2.46)	1.75E-03
Sex (female vs male)	0.75 (0.60-0.95)	1.48E-02
Age	1.01 (1.00-1.01)	3.33E-09
Smoking status (former vs never)	1.05 (0.76-1.45)	7.51E-01
Smoking status (current vs never)	1.25 (0.90-1.74)	1.78E-01

(Continued)

TABLE E1. Continued

Variable	Adjusted HR (95% CI)	P
Clinical stage (stage II vs stage I)	1.63 (1.23-2.15)	5.75E-04
Clinical stage (stage III vs stage I)	1.97 (1.43-2.73)	3.92E-05
Radiation (yes vs no)	1.43 (0.93-2.20)	1.03E-01
Chemotherapy (yes vs no)	0.78 (0.60-1.03)	8.40E-02
Chemoradiation (yes vs no)	0.95 (0.54-1.65)	8.55E-01
rs9867701	1.47 (1.15-1.87)	1.85E-03
Sex (female vs male)	0.75 (0.60-0.94)	1.31E-02
Age	1.01 (1.00-1.01)	2.68E-08
Smoking status (former vs never)	1.07 (0.77-1.47)	6.87E-01
Smoking status (current vs never)	1.26 (0.91-1.76)	1.62E-01
Clinical stage (stage II vs stage I)	1.63 (1.23-2.15)	6.11E-04
Clinical stage (stage III vs stage I)	1.96 (1.41-2.72)	5.61E-05
Radiation (yes vs no)	1.52 (0.99-2.34)	5.74E-02
Chemotherapy (yes vs no)	0.76 (0.58-1.01)	5.71E-02
Chemoradiation (yes vs no)	0.93 (0.53-1.62)	7.96E-01
rs2072707	1.65 (1.20-2.27)	1.85E-03
Sex (female vs male)	0.74 (0.59-0.92)	8.54E-03
Age	1.01 (1.00-1.01)	6.80E-09
Smoking status (former vs never)	1.02 (0.74-1.41)	9.01E-01
Smoking status (current vs never)	1.20 (0.87-1.67)	2.66E-01
Clinical stage (stage II vs stage I)	1.60 (1.21-2.11)	9.49E-04
Clinical stage (stage III vs stage I)	2.03 (1.46-2.81)	2.23E-05
Radiation (yes vs no)	1.38 (0.89-2.12)	1.48E-01
Chemotherapy (yes vs no)	0.79 (0.60-1.04)	9.37E-02
Chemoradiation (yes vs no)	0.93 (0.53-1.61)	7.89E-01
rs357291	1.29 (1.10-1.52)	2.04E-03
Sex (female vs male)	0.75 (0.60-0.94)	1.33E-02
Age	1.00 (1.00-1.01)	8.42E-08
Smoking status (former vs never)	1.03 (0.74-1.42)	8.71E-01
Smoking status (current vs never)	1.21 (0.87-1.68)	2.57E-01
Clinical stage (stage II vs stage I)	1.63 (1.23-2.15)	5.63E-04
Clinical stage (stage III vs stage I)	2.02 (1.46-2.79)	2.30E-05
Radiation (yes vs no)	1.40 (0.91-2.15)	1.23E-01
Chemotherapy (yes vs no)	0.80 (0.61-1.05)	1.02E-01
Chemoradiation (yes vs no)	0.97 (0.55-1.69)	9.04E-01
rs692890	0.70 (0.56-0.88)	2.12E-03
Sex (female vs male)	0.75 (0.60-0.94)	1.39E-02
Age	1.01 (1.00-1.01)	2.75E-09
Smoking status (former vs never)	1.05 (0.77-1.45)	7.45E-01
Smoking status (current vs never)	1.23 (0.89-1.71)	2.13E-01
Clinical stage (stage II vs stage I)	1.63 (1.23-2.14)	5.91E-04
Clinical stage (stage III vs stage I)	2.01 (1.46-2.76)	2.08E-05
Radiation (yes vs no)	1.46 (0.95-2.24)	8.11E-02
Chemotherapy (yes vs no)	0.78 (0.60-1.03)	8.19E-02
Chemoradiation (yes vs no)	0.84 (0.48-1.47)	5.44E-01
rs883844	1.43 (1.13-1.82)	2.72E-03
Sex (female vs male)	0.75 (0.60-0.94)	1.31E-02
Age	1.01 (1.00-1.01)	1.88E-08
Smoking status (former vs never)	1.07 (0.77-1.48)	6.85E-01
Smoking status (current vs never)	1.27 (0.92-1.77)	1.50E-01
Clinical stage (stage II vs stage I)	1.64 (1.24-2.17)	4.60E-04
Clinical stage (stage III vs stage I)	2.08 (1.50-2.89)	1.25E-05
Radiation (yes vs no)	1.48 (0.96-2.28)	7.37E-02

(Continued)

TABLE E1. Continued

Variable	Adjusted HR (95% CI)	P
Chemotherapy (yes vs no)	0.79 (0.60-1.04)	8.83E-02
Chemoradiation (yes vs no)	0.92 (0.53-1.60)	7.64E-01
rs2706399	0.64 (0.48-0.86)	2.74E-03
Sex (female vs male)	0.74 (0.59-0.93)	8.77E-03
Age	1.01 (1.00-1.01)	1.75E-08
Smoking status (former vs never)	1.02 (0.74-1.40)	9.19E-01
Smoking status (current vs never)	1.21 (0.87-1.69)	2.46E-01
Clinical stage (stage II vs stage I)	1.56 (1.19-2.06)	1.48E-03
Clinical stage (stage III vs stage I)	1.99 (1.44-2.75)	3.11E-05
Radiation (yes vs no)	1.53 (1.00-2.36)	5.21E-02
Chemotherapy (yes vs no)	0.79 (0.60-1.05)	1.02E-01
Chemoradiation (yes vs no)	0.94 (0.54-1.64)	8.38E-01

HR, Hazard ratio; CI, confidence interval.

TABLE E2. Stage-adjusted analysis of overall survival

SNP	Overall survival					
	Adjusting for clinical stage		Adjusting pathology T, N stage		Adjusting for pathology stage	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
rs4845563	1.78 (1.39-2.27)	4.56E-06	1.69 (1.32-2.16)	2.77E-05	1.66 (1.3-2.12)	4.28E-05
rs173107	0.65 (0.52-0.82)	1.95E-04	0.66 (0.52-0.83)	3.28E-04	0.62 (0.49-0.78)	3.06E-05
rs235757	0.66 (0.53-0.83)	2.83E-04	0.66 (0.53-0.83)	3.66E-04	0.63 (0.5-0.79)	5.17E-05
rs2310047	1.32 (1.13-1.55)	5.78E-04	1.26 (1.08-1.48)	4.12E-03	1.29 (1.1-1.51)	1.46E-03
rs814030	1.36 (1.14-1.63)	6.91E-04	1.35 (1.13-1.61)	9.56E-04	1.35 (1.13-1.61)	7.71E-04
rs1800630	1.48 (1.18-1.87)	8.67E-04	1.47 (1.16-1.86)	1.52E-03	1.46 (1.16-1.85)	1.30E-03
rs4351684	0.67 (0.53-0.85)	9.45E-04	0.74 (0.58-0.94)	1.21E-02	0.73 (0.58-0.93)	1.01E-02
rs4865998	1.97 (1.32-2.95)	9.68E-04	1.79 (1.19-2.7)	5.05E-03	1.89 (1.27-2.83)	1.86E-03
rs6445608	0.7 (0.56-0.87)	1.54E-03	0.68 (0.54-0.86)	1.06E-03	0.69 (0.55-0.86)	1.28E-03
rs6020348	1.49 (1.16-1.91)	1.73E-03	1.56 (1.21-2.01)	5.92E-04	1.52 (1.18-1.95)	1.05E-03
rs3917335	1.74 (1.23-2.46)	1.75E-03	1.88 (1.33-2.66)	3.57E-04	1.78 (1.26-2.51)	1.00E-03
rs9867701	1.47 (1.15-1.87)	1.85E-03	1.5 (1.18-1.91)	1.13E-03	1.49 (1.17-1.89)	1.27E-03
rs2072707	1.65 (1.2-2.27)	1.85E-03	1.74 (1.27-2.4)	6.10E-04	1.7 (1.24-2.33)	1.03E-03
rs357291	1.29 (1.1-1.52)	2.04E-03	1.27 (1.08-1.5)	3.98E-03	1.27 (1.08-1.5)	3.33E-03
rs692890	0.7 (0.56-0.88)	2.12E-03	0.7 (0.56-0.88)	2.08E-03	0.69 (0.55-0.86)	1.18E-03
rs883844	1.43 (1.13-1.82)	2.72E-03	1.38 (1.09-1.76)	7.31E-03	1.43 (1.13-1.8)	3.16E-03
rs2706399	0.64 (0.48-0.86)	2.74E-03	0.7 (0.52-0.93)	1.53E-02	0.66 (0.49-0.88)	4.24E-03

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval.

TABLE E3. Analysis of overall survival adjusting for performance status

SNP	Overall survival			
	Without adjusting performance status		Adjusting performance status	
	HR (95% CI)	P	HR (95% CI)	P
rs4845563	1.78 (1.39-2.27)	4.56E-06	1.79 (1.40-2.29)	3.90E-06
rs173107	0.65 (0.52-0.82)	1.95E-04	0.64 (0.51-0.80)	8.74E-05
rs235757	0.66 (0.53-0.83)	2.83E-04	0.64 (0.51-0.81)	1.30E-04
rs2310047	1.32 (1.13-1.55)	5.78E-04	1.30 (1.11-1.53)	1.09E-03
rs814030	1.36 (1.14-1.63)	6.91E-04	1.34 (1.12-1.60)	1.19E-03
rs1800630	1.48 (1.18-1.87)	8.67E-04	1.49 (1.18-1.88)	7.51E-04
rs4351684	0.67 (0.53-0.85)	9.45E-04	0.67 (0.53-0.85)	8.81E-04
rs4865998	1.97 (1.32-2.95)	9.68E-04	2.02 (1.35-3.03)	6.13E-04
rs6445608	0.7 (0.56-0.87)	1.54E-03	0.69 (0.55-0.87)	1.39E-03
rs6020348	1.49 (1.16-1.91)	1.73E-03	1.47 (1.14-1.88)	2.79E-03
rs3917335	1.74 (1.23-2.46)	1.75E-03	1.78 (1.26-2.53)	1.22E-03
rs9867701	1.47 (1.15-1.87)	1.85E-03	1.42 (1.11-1.81)	4.62E-03
rs2072707	1.65 (1.2-2.27)	1.85E-03	1.70 (1.24-2.34)	1.07E-03
rs357291	1.29 (1.1-1.52)	2.04E-03	1.28 (1.09-1.50)	3.03E-03
rs692890	0.7 (0.56-0.88)	2.12E-03	0.71 (0.57-0.89)	3.24E-03
rs883844	1.43 (1.13-1.82)	2.72E-03	1.44 (1.14-1.82)	2.44E-03
rs2706399	0.64 (0.48-0.86)	2.74E-03	0.64 (0.48-0.86)	2.76E-03

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval.

TABLE E4. Detailed results for SNPs independently associated with risk of recurrence

Variable	Adjusted HR (95% CI)	P
rs2287040	1.44 (1.18-1.76)	3.70E-04
Sex (female vs male)	1.02 (0.77-1.34)	9.06E-01
Age	1.00 (0.98-1.01)	6.41E-01
Smoking status (former vs never)	0.92 (0.62-1.37)	6.89E-01
Smoking status (current vs never)	1.03 (0.69-1.54)	8.83E-01
Clinical stage (stage II vs stage I)	2.13 (1.50-3.02)	2.14E-05
Clinical stage (stage III vs stage I)	3.14 (2.14-4.61)	5.08E-09
Radiation (yes vs no)	1.17 (0.75-1.82)	4.94E-01
Chemotherapy (yes vs no)	1.02 (0.74-1.41)	8.86E-01
Chemoradiation (yes vs no)	1.17 (0.65-2.12)	6.05E-01
rs11211654	2.00 (1.35-2.96)	4.99E-04
Sex (female vs male)	1.02 (0.77-1.34)	9.09E-01
Age	1.00 (0.99-1.01)	8.38E-01
Smoking status (former vs never)	0.99 (0.66-1.48)	9.62E-01
Smoking status (current vs never)	1.12 (0.75-1.68)	5.83E-01
Clinical stage (stage II vs stage I)	2.14 (1.51-3.04)	2.15E-05
Clinical stage (stage III vs stage I)	3.06 (2.07-4.52)	1.82E-08
Radiation (yes vs no)	1.29 (0.83-2.02)	2.61E-01
Chemotherapy (yes vs no)	1.00 (0.73-1.38)	9.90E-01
Chemoradiation (yes vs no)	1.01 (0.55-1.84)	9.83E-01
rs2008018	1.63 (1.24-2.15)	5.17E-04
Sex (female vs male)	0.98 (0.74-1.29)	8.70E-01
Age	1.00 (0.99-1.01)	6.95E-01
Smoking status (former vs never)	0.93 (0.62-1.38)	7.11E-01
Smoking status (current vs never)	1.09 (0.73-1.63)	6.80E-01
Clinical stage (stage II vs stage I)	2.00 (1.41-2.83)	9.97E-05
Clinical stage (stage III vs stage I)	2.91 (1.99-4.25)	3.57E-08
Radiation (yes vs no)	1.27 (0.82-1.96)	2.94E-01
Chemotherapy (yes vs no)	1.06 (0.77-1.46)	7.03E-01
Chemoradiation (yes vs no)	1.04 (0.57-1.89)	8.99E-01
rs3917239	1.39 (1.15-1.67)	6.26E-04
Sex (female vs male)	1.00 (0.76-1.33)	9.79E-01
Age	1.00 (0.99-1.01)	6.74E-01
Smoking status (former vs never)	0.89 (0.60-1.32)	5.66E-01
Smoking status (current vs never)	0.99 (0.66-1.48)	9.68E-01
Clinical stage (stage II vs stage I)	2.05 (1.45-2.90)	5.41E-05
Clinical stage (stage III vs stage I)	3.01 (2.05-4.42)	1.68E-08
Radiation (yes vs no)	1.23 (0.78-1.92)	3.72E-01
Chemotherapy (yes vs no)	1.03 (0.75-1.42)	8.40E-01
Chemoradiation (yes vs no)	1.18 (0.65-2.14)	5.89E-01
rs280523	1.82 (1.28-2.57)	7.58E-04
Sex (female vs male)	1.02 (0.77-1.34)	9.16E-01
Age	1.00 (0.99-1.01)	7.29E-01
Smoking status (former vs never)	0.96 (0.65-1.43)	8.45E-01
Smoking status (current vs never)	1.02 (0.68-1.52)	9.17E-01
Clinical stage (stage II vs stage I)	2.05 (1.45-2.90)	5.31E-05
Clinical stage (stage III vs stage I)	2.97 (2.03-4.35)	2.22E-08
Radiation (yes vs no)	1.16 (0.74-1.81)	5.17E-01
Chemotherapy (yes vs no)	1.07 (0.78-1.48)	6.60E-01
Chemoradiation (yes vs no)	0.95 (0.52-1.73)	8.56E-01
rs17026782	1.46 (1.17-1.81)	7.97E-04
Sex (female vs male)	1.01 (0.76-1.33)	9.67E-01

(Continued)

TABLE E4. Continued

Variable	Adjusted HR (95% CI)	P
Age	1.00 (0.99-1.01)	6.97E-01
Smoking status (former vs never)	0.95 (0.64-1.42)	8.17E-01
Smoking status (current vs never)	1.05 (0.71-1.57)	8.01E-01
Clinical stage (stage II vs stage I)	2.06 (1.45-2.91)	4.71E-05
Clinical stage (stage III vs stage I)	2.99 (2.04-4.38)	2.04E-08
Radiation (yes vs no)	1.20 (0.77-1.87)	4.18E-01
Chemotherapy (yes vs no)	1.02 (0.74-1.40)	9.09E-01
Chemoradiation (yes vs no)	1.18 (0.65-2.15)	5.82E-01
rs3014866	1.67 (1.23-2.28)	1.20E-03
Sex (female vs male)	0.99 (0.75-1.30)	9.31E-01
Age	1.00 (0.99-1.01)	7.97E-01
Smoking status (former vs never)	0.95 (0.64-1.42)	8.12E-01
Smoking status (current vs never)	1.08 (0.73-1.62)	6.93E-01
Clinical stage (stage II vs stage I)	2.10 (1.48-2.97)	2.93E-05
Clinical stage (stage III vs stage I)	2.91 (1.98-4.28)	4.85E-08
Radiation (yes vs no)	1.30 (0.83-2.03)	2.46E-01
Chemotherapy (yes vs no)	1.04 (0.76-1.44)	8.00E-01
Chemoradiation (yes vs no)	1.04 (0.58-1.89)	8.88E-01
rs4927632	1.39 (1.14-1.70)	1.26E-03
Sex (female vs male)	1.00 (0.75-1.32)	9.77E-01
Age	1.00 (0.98-1.01)	5.63E-01
Smoking status (former vs never)	0.91 (0.61-1.36)	6.52E-01
Smoking status (current vs never)	0.99 (0.66-1.48)	9.58E-01
Clinical stage (stage II vs stage I)	2.18 (1.54-3.09)	1.30E-05
Clinical stage (stage III vs stage I)	2.97 (2.02-4.39)	3.92E-08
Radiation (yes vs no)	1.25 (0.80-1.95)	3.29E-01
Chemotherapy (yes vs no)	0.98 (0.71-1.34)	8.80E-01
Chemoradiation (yes vs no)	1.02 (0.56-1.86)	9.50E-01
rs2110726	1.58 (1.19-2.10)	1.74E-03
Sex (female vs male)	0.99 (0.75-1.31)	9.54E-01
Age	1.00 (0.98-1.01)	5.84E-01
Smoking status (former vs never)	0.90 (0.61-1.34)	6.13E-01
Smoking status (current vs never)	1.03 (0.69-1.54)	8.74E-01
Clinical stage (stage II vs stage I)	2.07 (1.46-2.93)	4.11E-05
Clinical stage (stage III vs stage I)	3.00 (2.04-4.40)	2.05E-08
Radiation (yes vs no)	1.20 (0.77-1.87)	4.24E-01
Chemotherapy (yes vs no)	1.03 (0.75-1.42)	8.58E-01
Chemoradiation (yes vs no)	1.15 (0.63-2.09)	6.45E-01

HR, Hazard ratio; CI, confidence interval.

TABLE E5. Stage-adjusted analysis of risk of recurrence

SNP	Risk of recurrence					
	Adjusting for clinical stage		Adjusting pathology T, N stage		Adjusting for pathology stage	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
rs2287040	1.44 (1.18-1.76)	3.70E-04	1.39 (1.14-1.7)	1.42E-03	1.34 (1.1-1.64)	4.10E-03
rs11211654	2 (1.35-2.96)	4.99E-04	1.9 (1.28-2.81)	1.32E-03	1.8 (1.22-2.65)	2.97E-03
rs2008018	1.63 (1.24-2.15)	5.17E-04	1.63 (1.23-2.15)	5.71E-04	1.59 (1.2-2.09)	1.02E-03
rs3917239	1.39 (1.15-1.67)	6.26E-04	1.39 (1.15-1.68)	6.28E-04	1.37 (1.13-1.66)	1.08E-03
rs280523	1.82 (1.28-2.57)	7.58E-04	1.9 (1.34-2.68)	2.80E-04	1.89 (1.34-2.67)	2.75E-04
rs17026782	1.46 (1.17-1.81)	7.97E-04	1.44 (1.15-1.8)	1.35E-03	1.4 (1.12-1.76)	3.06E-03
rs3014866	1.67 (1.23-2.28)	1.20E-03	1.69 (1.23-2.32)	1.33E-03	1.69 (1.23-2.31)	1.07E-03
rs4927632	1.39 (1.14-1.7)	1.26E-03	1.4 (1.14-1.71)	1.17E-03	1.34 (1.09-1.64)	4.83E-03
rs2110726	1.58 (1.19-2.1)	1.74E-03	1.59 (1.19-2.12)	1.77E-03	1.49 (1.12-1.98)	5.91E-03

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval.

TABLE E6. Analysis of risk of recurrence adjusting for performance status

SNP	Risk of recurrence			
	Without adjusting performance status		Adjusting performance status	
	HR (95% CI)	P	HR (95% CI)	P
rs2287040	1.44 (1.18-1.76)	3.70E-04	1.46 (1.19-1.79)	2.78E-04
rs11211654	2 (1.35-2.96)	4.99E-04	2.00 (1.35-2.96)	5.01E-04
rs2008018	1.63 (1.24-2.15)	5.17E-04	1.63 (1.24-2.16)	5.35E-04
rs3917239	1.39 (1.15-1.67)	6.26E-04	1.38 (1.15-1.67)	7.45E-04
rs280523	1.82 (1.28-2.57)	7.58E-04	1.81 (1.28-2.57)	7.88E-04
rs17026782	1.46 (1.17-1.81)	7.97E-04	1.46 (1.17-1.82)	7.20E-04
rs3014866	1.67 (1.23-2.28)	1.20E-03	1.67 (1.22-2.28)	1.28E-03
rs4927632	1.39 (1.14-1.7)	1.26E-03	1.39 (1.13-1.70)	1.44E-03
rs2110726	1.58 (1.19-2.1)	1.74E-03	1.58 (1.19-2.11)	1.83E-03

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval.

TABLE E7. Competing risk analysis of SNPs independently associated with recurrence

SNP	Risk of recurrence			
	Cox		Competing risk	
	HR (95% CI)	P	HR (95% CI)	P
rs2287040	1.44 (1.18-1.76)	3.70E-04	1.23 (1.03-1.46)	2.13E-02
rs11211654	2 (1.35-2.96)	4.99E-04	1.64 (1.13-2.38)	8.90E-03
rs2008018	1.63 (1.24-2.15)	5.17E-04	1.42 (1.11-1.82)	5.71E-03
rs3917239	1.39 (1.15-1.67)	6.26E-04	1.28 (1.08-1.51)	3.62E-03
rs280523	1.82 (1.28-2.57)	7.58E-04	1.62 (1.17-2.23)	3.37E-03
rs17026782	1.46 (1.17-1.81)	7.97E-04	1.32 (1.09-1.60)	3.88E-03
rs3014866	1.67 (1.23-2.28)	1.20E-03	1.40 (1.06-1.86)	1.82E-02
rs4927632	1.39 (1.14-1.7)	1.26E-03	1.29 (1.07-1.54)	6.32E-03
rs2110726	1.58 (1.19-2.1)	1.74E-03	1.39 (1.07-1.80)	1.21E-02

SNP, Single nucleotide polymorphism; HR, hazard ratio; CI, confidence interval.

TABLE E8. Host table according to risk groups defined according to survival tree

Variable	Overall survival				Risk of recurrence			
	Low risk	Medium risk	High risk	P	Low risk	Medium risk	High risk	P
Mean age (SD)	66.95 (61.33)	64.53 (10.78)	64.70 (14.03)	3.09E-02	63.61 (12.67)	64.66 (11.43)	68.33 (65.68)	6.66E-01
Mean pack-years (SD)	51.53 (33.62)	55.06 (36.77)	51.75 (33.40)	7.42E-01	48.31 (30.81)	51.69 (35.35)	58.57 (36.91)	2.87E-03
Sex								
Male	131 (47.6)	107 (45.9)	109 (51.4)		126 (50.2)	106 (46.1)	115 (48.1)	
Female	144 (52.4)	126 (54.1)	103 (48.6)	4.97E-01	125 (49.8)	124 (53.9)	124 (51.9)	6.66E-01
Smoking status								
Never	50 (18.2)	45 (19.3)	32 (15.1)		42 (16.7)	39 (17.0)	46 (19.2)	
Former	125 (45.5)	115 (49.4)	97 (45.8)		124 (49.4)	107 (46.5)	106 (44.4)	
Current and RQ	100 (36.4)	73 (31.3)	83 (39.2)	4.53E-01	85 (33.9)	84 (36.5)	87 (36.4)	8.25E-01
Clinical stage								
1	160 (58.2)	137 (58.8)	125 (59.0)		142 (56.6)	139 (60.4)	141 (59.0)	
2	65 (23.6)	50 (21.5)	51 (24.1)		64 (25.5)	48 (20.9)	53 (22.2)	
3a	50 (18.2)	46 (19.7)	36 (17.0)	9.29E-01	45 (17.9)	43 (18.7)	45 (18.8)	8.12E-01
Pathology								
Adenocarcinoma	178 (64.7)	147 (63.1)	133 (62.7)		160 (63.7)	152 (66.1)	146 (61.1)	
Squamous cell carcinoma	64 (23.3)	51 (21.9)	56 (26.4)		62 (24.7)	56 (24.3)	54 (22.6)	
Other	33 (12.0)	35 (15.0)	23 (10.8)	5.98E-01	29 (11.6)	22 (9.6)	39 (16.3)	2.61E-01
Grade								
Well differentiated	28 (10.2)	34 (14.6)	18 (8.5)		32 (12.7)	21 (9.1)	26 (10.9)	
Moderately differentiated	112 (40.7)	84 (36.1)	85 (40.1)		98 (39.0)	101 (43.9)	82 (34.3)	
Poorly differentiated/ undifferentiated	121 (44.0)	90 (38.6)	89 (42.0)		100 (39.8)	87 (37.8)	113 (47.3)	
Unknown	14 (5.1)	25 (10.7)	20 (9.4)	8.24E-02	21 (8.4)	21 (9.1)	18 (7.5)	2.86E-01
Chemotherapy								
Yes	183 (66.5)	145 (62.2)	138 (65.1)		153 (61.0)	155 (67.4)	158 (66.1)	
No	92 (33.5)	88 (37.8)	74 (34.9)	5.93E-01	98 (39.0)	75 (32.6)	81 (33.9)	2.90E-01
Radiation therapy								
Yes	252 (91.6)	218 (93.6)	192 (90.6)		232 (92.4)	210 (91.3)	220 (92.1)	
No	23 (8.4)	15 (6.4)	20 (9.4)	4.96E-01	19 (7.6)	20 (8.7)	19 (7.9)	9.00E-01
Chemoradiation therapy								
Yes	261 (94.9)	226 (97.0)	205 (96.7)		241 (96.0)	224 (97.4)	227 (95.0)	
No	14 (5.1)	7 (3.0)	7 (3.3)	4.18E-01	10 (4.0)	6 (2.6)	12 (5.0)	4.00E-01
Pathological stage								
0	2 (0.7)	3 (1.3)	2 (0.9)		3 (1.2)	2 (0.9)	2 (0.8)	
1	153 (55.6)	136 (58.4)	106 (50.0)		138 (55.0)	126 (54.8)	130 (54.4)	
2	68 (24.7)	56 (24.0)	60 (28.3)		66 (26.3)	60 (26.1)	59 (24.7)	
3	52 (18.9)	36 (15.5)	44 (20.8)		44 (17.5)	41 (17.8)	47 (19.7)	
4	0 (0.0)	2 (0.9)	0 (0.0)	3.64E-01	0 (0.0)	1 (0.4)	1 (0.4)	9.87E-01
Pathological T stage								
1a	76 (27.6)	53 (22.7)	49 (23.2)		61 (24.3)	64 (27.8)	52 (21.8)	
1b	63 (22.9)	59 (25.3)	54 (25.6)		57 (22.7)	53 (23.0)	66 (27.7)	
2a	76 (27.6)	69 (29.6)	58 (27.5)		75 (29.9)	65 (28.3)	64 (26.9)	
2b	25 (9.1)	19 (8.2)	19 (9.0)		25 (10.0)	14 (6.1)	24 (10.1)	
3	26 (9.5)	24 (10.3)	26 (12.3)		23 (9.2)	27 (11.7)	26 (10.9)	
4	6 (2.2)	6 (2.6)	2 (0.9)		5 (2.0)	5 (2.2)	4 (1.7)	
IS	0 (0.0)	1 (0.4)	1 (0.5)		1 (0.4)	1 (0.4)	0 (0.0)	
X	3 (1.1)	2 (0.9)	2 (0.9)	9.60E-01	4 (1.6)	1 (0.4)	2 (0.8)	7.57E-01
Pathological N stage								
0	188 (68.4)	167 (71.7)	132 (62.3)		171 (68.1)	154 (67.0)	162 (67.8)	
1	46 (16.7)	39 (16.7)	45 (21.2)		45 (17.9)	44 (19.1)	41 (17.2)	
2	41 (14.9)	27 (11.6)	35 (16.5)	2.72E-01	35 (13.9)	32 (13.9)	36 (15.1)	9.80E-01

(Continued)

TABLE E8. Continued

Variable	Overall survival				Risk of recurrence			
	Low risk	Medium risk	High risk	P	Low risk	Medium risk	High risk	P
Recurrence								
No	192 (69.8)	140 (60.1)	115 (54.2)	1.57E-03	193 (76.9)	134 (58.3)	119 (49.8)	1.97E-09
Yes	83 (30.2)	93 (39.9)	97 (45.8)		58 (23.1)	96 (41.7)	120 (50.2)	
Death								
No	206 (74.9)	125 (53.6)	74 (34.9)	7.77E-18	163 (64.9)	126 (54.8)	114 (47.7)	5.64E-04
Yes	69 (25.1)	108 (46.4)	138 (65.1)		88 (35.1)	104 (45.2)	125 (52.3)	

Data are presented as n (%) except where otherwise noted. RQ, Recently quit.

TABLE E9. Analysis of overall survival and risk of recurrence for medium- and high-risk groups

	Alive, n (%)	Dead, n (%)	Adjusted HR	Lower (95% CI)	Upper (95% CI)	P
Unfavorable genotype analysis						
Medium risk	146 (58.87)	102 (41.13)	1 (reference)			
High risk	58 (30.85)	130 (69.15)	2.24	1.72	2.91	1.78E-09
Survival tree						
Medium risk	125 (53.65)	108 (46.35)	1 (reference)			
High risk	74 (34.91)	138 (65.09)	1.74	1.34	2.25	3.12E-05
	No recurrence, n (%)	Recurrence, n (%)				
Unfavorable genotype analysis						
Medium risk	217 (60.28)	143 (39.72)	1 (reference)			
High risk	45 (45.00)	55 (55.00)	1.43	1.00	2.04	4.75E-02
Survival Tree						
Medium risk	134 (58.26)	96 (41.74)	1 (reference)			
High risk	119 (49.79)	120 (50.21)	1.41	1.04	1.93	2.80E-02

HR, Hazard ratio; CI, confidence interval.

TABLE E10. Sensitivity analysis for SNPs independently associated with risk of death with inclusion of additional clinical factors

Variable	Adjusted HR (95% CI)	P
rs4845563	1.75 (1.37-2.24)	8.11E-06
Sex (female vs male)	0.77 (0.61-0.97)	2.72E-02
Age	1.01 (1.00-1.01)	2.28E-09
Smoking status (former vs never)	1.08 (0.78-1.50)	6.43E-01
Smoking status (current vs never)	1.26 (0.89-1.77)	1.88E-01
Performance status (1 vs 0)	1.41 (1.00-1.97)	4.76E-02
Performance status (2-4 vs 0)	1.36 (0.71-2.61)	3.59E-01
Performance status (unknown vs 0)	1.54 (1.12-2.12)	8.00E-03
FEV1 ≤ 50% predicted (yes vs no)	0.90 (0.42-1.96)	8.00E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.53 (0.67-3.51)	3.15E-01
DLCO ≤ 50% predicted (yes vs no)	1.17 (0.61-2.25)	6.31E-01
DLCO ≤ 50% predicted (unknown vs no)	0.79 (0.45-1.39)	4.14E-01
Postoperative pulmonary complications (yes vs no)	1.40 (1.04-1.87)	2.43E-02
Postoperative pulmonary complications (unknown vs no)	1.28 (0.63-2.61)	4.96E-01
Clinical stage (stage II vs stage I)	1.56 (1.18-2.06)	1.94E-03
Clinical stage (stage III vs stage I)	2.25 (1.60-3.17)	3.58E-06
Radiation (yes vs no)	1.38 (0.89-2.13)	1.50E-01
Chemotherapy (yes vs no)	0.81 (0.61-1.07)	1.36E-01
Chemoradiation (yes vs no)	0.87 (0.49-1.54)	6.34E-01
rs173107	0.64 (0.51-0.80)	1.27E-04
Sex (female vs male)	0.76 (0.60-0.96)	1.99E-02
Age	1.01 (1.00-1.01)	2.18E-09
Smoking status (former vs never)	1.17 (0.84-1.62)	3.63E-01
Smoking status (current vs never)	1.33 (0.95-1.87)	9.82E-02
Performance status (1 vs 0)	1.37 (0.98-1.91)	6.87E-02
Performance status (2-4 vs 0)	1.27 (0.66-2.44)	4.81E-01
Performance status (unknown vs 0)	1.58 (1.15-2.17)	4.77E-03
FEV1 ≤ 50% predicted (yes vs no)	0.93 (0.43-2.02)	8.52E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.49 (0.68-3.30)	3.20E-01
DLCO ≤ 50% predicted (yes vs no)	1.04 (0.54-2.01)	9.01E-01
DLCO ≤ 50% predicted (unknown vs no)	0.86 (0.49-1.53)	6.10E-01
Postoperative pulmonary complications (yes vs no)	1.44 (1.07-1.92)	1.47E-02
Postoperative pulmonary complications (unknown vs no)	1.23 (0.63-2.42)	5.39E-01
Clinical stage (stage II vs stage I)	1.63 (1.23-2.16)	6.69E-04
Clinical stage (stage III vs stage I)	2.10 (1.50-2.93)	1.31E-05
Radiation (yes vs no)	1.42 (0.92-2.18)	1.11E-01
Chemotherapy (yes vs no)	0.82 (0.62-1.09)	1.68E-01
Chemoradiation (yes vs no)	0.83 (0.47-1.47)	5.26E-01
rs235757	0.65 (0.52-0.82)	2.05E-04
Sex (female vs male)	0.77 (0.61-0.97)	2.56E-02
Age	1.01 (1.00-1.01)	2.25E-09
Smoking status (former vs never)	1.17 (0.84-1.63)	3.48E-01

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
Smoking status (current vs never)	1.35 (0.96-1.89)	8.44E-02
Performance status (1 vs 0)	1.40 (1.00-1.97)	4.84E-02
Performance status (2-4 vs 0)	1.30 (0.67-2.50)	4.36E-01
Performance status (unknown vs 0)	1.57 (1.15-2.16)	5.09E-03
FEV1 ≤ 50% predicted (yes vs no)	0.91 (0.42-1.98)	8.14E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.51 (0.68-3.34)	3.07E-01
DLCO ≤ 50% predicted (yes vs no)	1.11 (0.58-2.14)	7.45E-01
DLCO ≤ 50% predicted (unknown vs no)	0.86 (0.48-1.51)	5.91E-01
Postoperative pulmonary complications (yes vs no)	1.43 (1.07-1.91)	1.58E-02
Postoperative pulmonary complications (unknown vs no)	1.24 (0.63-2.43)	5.35E-01
Clinical stage (stage II vs stage I)	1.59 (1.20-2.11)	1.22E-03
Clinical stage (stage III vs stage I)	2.04 (1.46-2.85)	2.91E-05
Radiation (yes vs no)	1.46 (0.95-2.25)	8.57E-02
Chemotherapy (yes vs no)	0.82 (0.62-1.09)	1.77E-01
Chemoradiation (yes vs no)	0.84 (0.48-1.49)	5.56E-01
rs2310047	1.35 (1.15-1.59)	3.17E-04
Sex (female vs male)	0.78 (0.61-0.98)	3.39E-02
Age	1.01 (1.00-1.01)	3.87E-08
Smoking status (former vs never)	1.17 (0.84-1.63)	3.53E-01
Smoking status (current vs never)	1.41 (1.00-1.99)	4.77E-02
Performance status (1 vs 0)	1.31 (0.93-1.83)	1.21E-01
Performance status (2-4 vs 0)	1.38 (0.72-2.67)	3.31E-01
Performance status (unknown vs 0)	1.46 (1.06-2.01)	1.95E-02
FEV1 ≤ 50% predicted (yes vs no)	0.93 (0.43-2.02)	8.55E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.73 (0.75-4.01)	1.98E-01
DLCO ≤ 50% predicted (yes vs no)	1.28 (0.67-2.46)	4.55E-01
DLCO ≤ 50% predicted (unknown vs no)	0.78 (0.44-1.37)	3.84E-01
Postoperative pulmonary complications (yes vs no)	1.36 (1.01-1.82)	4.11E-02
Postoperative pulmonary complications (unknown vs no)	1.25 (0.61-2.59)	5.40E-01
Clinical stage (stage II vs stage I)	1.54 (1.17-2.05)	2.43E-03
Clinical stage (stage III vs stage I)	2.04 (1.46-2.86)	2.94E-05
Radiation (yes vs no)	1.43 (0.93-2.20)	1.07E-01
Chemotherapy (yes vs no)	0.83 (0.63-1.09)	1.83E-01
Chemoradiation (yes vs no)	0.86 (0.49-1.51)	6.03E-01
rs814030	1.34 (1.12-1.60)	1.33E-03
Sex (female vs male)	0.75 (0.59-0.95)	1.59E-02
Age	1.01 (1.00-1.01)	1.79E-09
Smoking status (former vs never)	1.13 (0.81-1.57)	4.85E-01
Smoking status (current vs never)	1.30 (0.92-1.83)	1.32E-01
Performance status (1 vs 0)	1.35 (0.97-1.90)	7.75E-02
Performance status (2-4 vs 0)	1.29 (0.67-2.48)	4.45E-01
Performance status (unknown vs 0)	1.49 (1.08-2.05)	1.41E-02
FEV1 ≤ 50% predicted (yes vs no)	0.92 (0.42-1.99)	8.24E-01

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
FEV1 ≤ 50% predicted (unknown vs no)	1.57 (0.68-3.64)	2.92E-01
DLCO ≤ 50% predicted (yes vs no)	1.09 (0.57-2.09)	7.94E-01
DLCO ≤ 50% predicted (unknown vs no)	0.76 (0.43-1.35)	3.52E-01
Postoperative pulmonary complications (yes vs no)	1.40 (1.05-1.87)	2.27E-02
Postoperative pulmonary complications (unknown vs no)	1.32 (0.63-2.75)	4.64E-01
Clinical stage (stage II vs stage I)	1.64 (1.24-2.17)	6.03E-04
Clinical stage (stage III vs stage I)	2.07 (1.48-2.90)	1.99E-05
Radiation (yes vs no)	1.50 (0.97-2.32)	6.76E-02
Chemotherapy (yes vs no)	0.80 (0.61-1.06)	1.28E-01
Chemoradiation (yes vs no)	0.87 (0.50-1.53)	6.31E-01
rs1800630	1.52 (1.20-1.92)	4.35E-04
Sex (female vs male)	0.79 (0.63-1.00)	5.39E-02
Age	1.01 (1.00-1.01)	3.52E-09
Smoking status (former vs never)	1.15 (0.83-1.59)	4.11E-01
Smoking status (current vs never)	1.30 (0.93-1.82)	1.31E-01
Performance status (1 vs 0)	1.37 (0.98-1.92)	6.44E-02
Performance status (2-4 vs 0)	1.44 (0.75-2.79)	2.73E-01
Performance status (unknown vs 0)	1.54 (1.12-2.12)	7.78E-03
FEV1 ≤ 50% predicted (yes vs no)	0.86 (0.40-1.87)	7.04E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.67 (0.73-3.82)	2.20E-01
DLCO ≤ 50% predicted (yes vs no)	1.21 (0.63-2.32)	5.66E-01
DLCO ≤ 50% predicted (unknown vs no)	0.80 (0.45-1.41)	4.32E-01
Postoperative pulmonary complications (yes vs no)	1.42 (1.06-1.90)	1.84E-02
Postoperative pulmonary complications (unknown vs no)	1.21 (0.59-2.46)	6.07E-01
Clinical stage (stage II vs stage I)	1.55 (1.17-2.06)	2.20E-03
Clinical stage (stage III vs stage I)	2.01 (1.44-2.82)	4.56E-05
Radiation (yes vs no)	1.40 (0.91-2.16)	1.30E-01
Chemotherapy (yes vs no)	0.85 (0.64-1.12)	2.49E-01
Chemoradiation (yes vs no)	0.85 (0.48-1.49)	5.65E-01
rs4351684	0.68 (0.54-0.87)	1.68E-03
Sex (female vs male)	0.77 (0.61-0.97)	2.89E-02
Age	1.01 (1.00-1.01)	2.25E-08
Smoking status (former vs never)	1.11 (0.80-1.54)	5.43E-01
Smoking status (current vs never)	1.29 (0.92-1.81)	1.42E-01
Performance status (1 vs 0)	1.38 (0.99-1.94)	5.86E-02
Performance status (2-4 vs 0)	1.29 (0.67-2.48)	4.48E-01
Performance status (unknown vs 0)	1.54 (1.12-2.12)	7.90E-03
FEV1 ≤ 50% predicted (yes vs no)	0.89 (0.41-1.93)	7.65E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.55 (0.69-3.49)	2.92E-01
DLCO ≤ 50% predicted (yes vs no)	1.20 (0.63-2.31)	5.76E-01

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
DLCO ≤ 50% predicted (unknown vs no)	0.76 (0.43-1.35)	3.55E-01
Postoperative pulmonary complications (yes vs no)	1.36 (1.02-1.82)	3.66E-02
Postoperative pulmonary complications (unknown vs no)	1.31 (0.66-2.61)	4.41E-01
Clinical stage (stage II vs stage I)	1.55 (1.17-2.05)	2.30E-03
Clinical stage (stage III vs stage I)	2.21 (1.57-3.11)	5.44E-06
Radiation (yes vs no)	1.39 (0.90-2.15)	1.34E-01
Chemotherapy (yes vs no)	0.80 (0.61-1.07)	1.28E-01
Chemoradiation (yes vs no)	0.86 (0.49-1.51)	6.00E-01
rs4865998	2.15 (1.42-3.26)	2.81E-04
Sex (female vs male)	0.78 (0.61-0.98)	3.55E-02
Age	1.01 (1.00-1.01)	3.87E-09
Smoking status (former vs never)	1.18 (0.85-1.64)	3.32E-01
Smoking status (current vs never)	1.29 (0.92-1.81)	1.44E-01
Performance status (1 vs 0)	1.40 (1.00-1.97)	5.10E-02
Performance status (2-4 vs 0)	1.34 (0.69-2.57)	3.86E-01
Performance status (unknown vs 0)	1.53 (1.11-2.10)	8.69E-03
FEV1 ≤ 50% predicted (yes vs no)	0.74 (0.33-1.63)	4.54E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.67 (0.74-3.78)	2.15E-01
DLCO ≤ 50% predicted (yes vs no)	1.09 (0.57-2.10)	7.93E-01
DLCO ≤ 50% predicted (unknown vs no)	0.84 (0.47-1.47)	5.35E-01
Postoperative pulmonary complications (yes vs no)	1.40 (1.05-1.87)	2.34E-02
Postoperative pulmonary complications (unknown vs no)	1.16 (0.58-2.33)	6.76E-01
Clinical stage (stage II vs stage I)	1.58 (1.19-2.09)	1.43E-03
Clinical stage (stage III vs stage I)	1.98 (1.41-2.77)	7.29E-05
Radiation (yes vs no)	1.45 (0.94-2.24)	9.64E-02
Chemotherapy (yes vs no)	0.84 (0.64-1.12)	2.34E-01
Chemoradiation (yes vs no)	0.84 (0.48-1.48)	5.56E-01
rs6445608	0.70 (0.56-0.88)	2.13E-03
Sex (female vs male)	0.77 (0.61-0.97)	2.66E-02
Age	1.01 (1.00-1.01)	2.48E-09
Smoking status (former vs never)	1.17 (0.84-1.62)	3.54E-01
Smoking status (current vs never)	1.35 (0.96-1.90)	8.50E-02
Performance status (1 vs 0)	1.38 (0.99-1.94)	5.98E-02
Performance status (2-4 vs 0)	1.25 (0.65-2.41)	4.98E-01
Performance status (unknown vs 0)	1.53 (1.11-2.11)	8.84E-03
FEV1 ≤ 50% predicted (yes vs no)	0.87 (0.40-1.89)	7.27E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.45 (0.65-3.21)	3.62E-01
DLCO ≤ 50% predicted (yes vs no)	1.15 (0.60-2.21)	6.70E-01
DLCO ≤ 50% predicted (unknown vs no)	0.84 (0.47-1.49)	5.47E-01
Postoperative pulmonary complications (yes vs no)	1.42 (1.07-1.91)	1.70E-02

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
Postoperative pulmonary complications (unknown vs no)	1.29 (0.65-2.56)	4.64E-01
Clinical stage (stage II vs stage I)	1.61 (1.22-2.13)	9.01E-04
Clinical stage (stage III vs stage I)	2.10 (1.50-2.94)	1.51E-05
Radiation (yes vs no)	1.42 (0.92-2.20)	1.13E-01
Chemotherapy (yes vs no)	0.83 (0.63-1.10)	1.89E-01
Chemoradiation (yes vs no)	0.84 (0.48-1.48)	5.45E-01
rs6020348	1.49 (1.15-1.91)	2.09E-03
Sex (female vs male)	0.77 (0.61-0.97)	2.81E-02
Age	1.01 (1.00-1.01)	9.03E-10
Smoking status (former vs never)	1.15 (0.83-1.60)	4.00E-01
Smoking status (current vs never)	1.34 (0.95-1.88)	9.24E-02
Performance status (1 vs 0)	1.34 (0.95-1.87)	9.24E-02
Performance status (2-4 vs 0)	1.29 (0.65-2.55)	4.65E-01
Performance status (unknown vs 0)	1.50 (1.09-2.06)	1.28E-02
FEV1 $\leq$ 50% predicted (yes vs no)	0.92 (0.43-2.01)	8.43E-01
FEV1 $\leq$ 50% predicted (unknown vs no)	1.67 (0.75-3.72)	2.09E-01
DLCO $\leq$ 50% predicted (yes vs no)	1.15 (0.60-2.21)	6.74E-01
DLCO $\leq$ 50% predicted (unknown vs no)	0.83 (0.47-1.47)	5.29E-01
Postoperative pulmonary complications (yes vs no)	1.41 (1.05-1.88)	2.08E-02
Postoperative pulmonary complications (unknown vs no)	1.16 (0.58-2.29)	6.77E-01
Clinical stage (stage II vs stage I)	1.61 (1.22-2.13)	8.77E-04
Clinical stage (stage III vs stage I)	2.05 (1.47-2.86)	2.58E-05
Radiation (yes vs no)	1.51 (0.98-2.33)	6.12E-02
Chemotherapy (yes vs no)	0.82 (0.62-1.09)	1.82E-01
Chemoradiation (yes vs no)	0.92 (0.52-1.61)	7.61E-01
rs3917335	1.70 (1.20-2.42)	3.13E-03
Sex (female vs male)	0.77 (0.61-0.97)	2.81E-02
Age	1.01 (1.00-1.01)	1.94E-09
Smoking status (former vs never)	1.17 (0.84-1.63)	3.44E-01
Smoking status (current vs never)	1.35 (0.96-1.89)	8.51E-02
Performance status (1 vs 0)	1.37 (0.98-1.92)	6.87E-02
Performance status (2-4 vs 0)	1.19 (0.61-2.29)	6.13E-01
Performance status (unknown vs 0)	1.55 (1.13-2.13)	7.15E-03
FEV1 $\leq$ 50% predicted (yes vs no)	0.93 (0.43-2.03)	8.64E-01
FEV1 $\leq$ 50% predicted (unknown vs no)	1.52 (0.68-3.41)	3.06E-01
DLCO $\leq$ 50% predicted (yes vs no)	1.20 (0.62-2.29)	5.92E-01
DLCO $\leq$ 50% predicted (unknown vs no)	0.82 (0.47-1.46)	5.04E-01
Postoperative pulmonary complications (yes vs no)	1.40 (1.04-1.87)	2.43E-02
Postoperative pulmonary complications (unknown vs no)	1.24 (0.62-2.46)	5.40E-01
Clinical stage (stage II vs stage I)	1.61 (1.22-2.13)	8.72E-04
Clinical stage (stage III vs stage I)	2.03 (1.45-2.83)	3.26E-05
Radiation (yes vs no)	1.46 (0.94-2.24)	8.86E-02

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
Chemotherapy (yes vs no)	0.82 (0.62-1.09)	1.76E-01
Chemoradiation (yes vs no)	0.89 (0.50-1.56)	6.79E-01
rs9867701	1.42 (1.11-1.81)	5.39E-03
Sex (female vs male)	0.76 (0.60-0.96)	2.37E-02
Age	1.01 (1.00-1.01)	1.79E-08
Smoking status (former vs never)	1.18 (0.85-1.64)	3.27E-01
Smoking status (current vs never)	1.36 (0.96-1.91)	7.99E-02
Performance status (1 vs 0)	1.32 (0.94-1.85)	1.05E-01
Performance status (2-4 vs 0)	1.20 (0.62-2.32)	5.83E-01
Performance status (unknown vs 0)	1.46 (1.06-2.01)	2.18E-02
FEV1 $\leq$ 50% predicted (yes vs no)	0.98 (0.45-2.14)	9.67E-01
FEV1 $\leq$ 50% predicted (unknown vs no)	1.77 (0.78-4.04)	1.73E-01
DLCO $\leq$ 50% predicted (yes vs no)	1.20 (0.63-2.31)	5.79E-01
DLCO $\leq$ 50% predicted (unknown vs no)	0.80 (0.45-1.41)	4.39E-01
Postoperative pulmonary complications (yes vs no)	1.37 (1.03-1.83)	3.35E-02
Postoperative pulmonary complications (unknown vs no)	1.12 (0.55-2.28)	7.50E-01
Clinical stage (stage II vs stage I)	1.60 (1.21-2.13)	1.07E-03
Clinical stage (stage III vs stage I)	2.01 (1.43-2.81)	5.16E-05
Radiation (yes vs no)	1.51 (0.98-2.34)	6.19E-02
Chemotherapy (yes vs no)	0.81 (0.61-1.08)	1.48E-01
Chemoradiation (yes vs no)	0.83 (0.47-1.47)	5.32E-01
rs2072707	1.74 (1.26-2.40)	7.98E-04
Sex (female vs male)	0.75 (0.59-0.94)	1.42E-02
Age	1.01 (1.00-1.01)	3.95E-09
Smoking status (former vs never)	1.14 (0.82-1.59)	4.33E-01
Smoking status (current vs never)	1.32 (0.94-1.85)	1.13E-01
Performance status (1 vs 0)	1.41 (1.00-1.97)	4.76E-02
Performance status (2-4 vs 0)	1.35 (0.70-2.59)	3.73E-01
Performance status (unknown vs 0)	1.55 (1.13-2.13)	7.10E-03
FEV1 $\leq$ 50% predicted (yes vs no)	0.96 (0.44-2.09)	9.17E-01
FEV1 $\leq$ 50% predicted (unknown vs no)	1.70 (0.75-3.85)	2.00E-01
DLCO $\leq$ 50% predicted (yes vs no)	1.22 (0.64-2.35)	5.45E-01
DLCO $\leq$ 50% predicted (unknown vs no)	0.87 (0.49-1.54)	6.40E-01
Postoperative pulmonary complications (yes vs no)	1.41 (1.05-1.88)	2.09E-02
Postoperative pulmonary complications (unknown vs no)	1.09 (0.54-2.19)	8.03E-01
Clinical stage (stage II vs stage I)	1.57 (1.18-2.08)	1.82E-03
Clinical stage (stage III vs stage I)	2.07 (1.48-2.90)	2.23E-05
Radiation (yes vs no)	1.39 (0.90-2.15)	1.38E-01
Chemotherapy (yes vs no)	0.83 (0.63-1.10)	2.02E-01
Chemoradiation (yes vs no)	0.86 (0.49-1.52)	6.07E-01
rs357291	1.30 (1.10-1.53)	1.84E-03
Sex (female vs male)	0.76 (0.60-0.96)	2.19E-02
Age	1.01 (1.00-1.01)	4.29E-08

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
Smoking status (former vs never)	1.14 (0.82-1.59)	4.35E-01
Smoking status (current vs never)	1.33 (0.95-1.87)	1.02E-01
Performance status (1 vs 0)	1.34 (0.95-1.87)	9.13E-02
Performance status (2-4 vs 0)	1.27 (0.66-2.45)	4.69E-01
Performance status (unknown vs 0)	1.48 (1.08-2.04)	1.49E-02
FEV1 ≤ 50% predicted (yes vs no)	0.84 (0.39-1.83)	6.57E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.47 (0.65-3.36)	3.57E-01
DLCO ≤ 50% predicted (yes vs no)	1.30 (0.68-2.51)	4.26E-01
DLCO ≤ 50% predicted (unknown vs no)	0.88 (0.49-1.55)	6.51E-01
Postoperative pulmonary complications (yes vs no)	1.36 (1.02-1.82)	3.73E-02
Postoperative pulmonary complications (unknown vs no)	1.28 (0.63-2.63)	4.96E-01
Clinical stage (stage II vs stage I)	1.61 (1.22-2.14)	8.98E-04
Clinical stage (stage III vs stage I)	2.05 (1.47-2.87)	2.35E-05
Radiation (yes vs no)	1.41 (0.92-2.17)	1.19E-01
Chemotherapy (yes vs no)	0.83 (0.63-1.10)	2.04E-01
Chemoradiation (yes vs no)	0.88 (0.50-1.55)	6.54E-01
rs692890	0.73 (0.58-0.92)	6.34E-03
Sex (female vs male)	0.77 (0.61-0.97)	2.64E-02
Age	1.01 (1.00-1.01)	1.81E-09
Smoking status (former vs never)	1.18 (0.85-1.64)	3.26E-01
Smoking status (current vs never)	1.34 (0.95-1.88)	9.12E-02
Performance status (1 vs 0)	1.31 (0.93-1.84)	1.17E-01
Performance status (2-4 vs 0)	1.26 (0.66-2.43)	4.81E-01
Performance status (unknown vs 0)	1.49 (1.09-2.05)	1.34E-02
FEV1 ≤ 50% predicted (yes vs no)	0.90 (0.41-1.95)	7.87E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.61 (0.72-3.62)	2.47E-01
DLCO ≤ 50% predicted (yes vs no)	1.20 (0.63-2.31)	5.76E-01
DLCO ≤ 50% predicted (unknown vs no)	0.84 (0.47-1.48)	5.46E-01
Postoperative pulmonary complications (yes vs no)	1.36 (1.02-1.82)	3.77E-02
Postoperative pulmonary complications (unknown vs no)	1.17 (0.58-2.34)	6.61E-01
Clinical stage (stage II vs stage I)	1.61 (1.21-2.13)	9.09E-04
Clinical stage (stage III vs stage I)	2.05 (1.48-2.85)	1.96E-05
Radiation (yes vs no)	1.47 (0.96-2.25)	8.01E-02
Chemotherapy (yes vs no)	0.82 (0.62-1.09)	1.73E-01
Chemoradiation (yes vs no)	0.80 (0.45-1.40)	4.30E-01
rs883844	1.39 (1.10-1.76)	6.42E-03
Sex (female vs male)	0.76 (0.60-0.96)	2.20E-02
Age	1.01 (1.00-1.01)	1.02E-08
Smoking status (former vs never)	1.18 (0.85-1.64)	3.26E-01
Smoking status (current vs never)	1.36 (0.97-1.92)	7.49E-02
Performance status (1 vs 0)	1.37 (0.98-1.92)	6.89E-02
Performance status (2-4 vs 0)	1.35 (0.70-2.59)	3.71E-01
Performance status (unknown vs 0)	1.54 (1.12-2.11)	8.25E-03

(Continued)

TABLE E10. Continued

Variable	Adjusted HR (95% CI)	P
FEV1 ≤ 50% predicted (yes vs no)	0.88 (0.41-1.93)	7.57E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.48 (0.64-3.38)	3.57E-01
DLCO ≤ 50% predicted (yes vs no)	1.19 (0.62-2.28)	5.93E-01
DLCO ≤ 50% predicted (unknown vs no)	0.83 (0.47-1.47)	5.32E-01
Postoperative pulmonary complications (yes vs no)	1.39 (1.04-1.85)	2.75E-02
Postoperative pulmonary complications (unknown vs no)	1.26 (0.62-2.55)	5.29E-01
Clinical stage (stage II vs stage I)	1.61 (1.22-2.14)	8.41E-04
Clinical stage (stage III vs stage I)	2.12 (1.51-2.98)	1.25E-05
Radiation (yes vs no)	1.51 (0.98-2.34)	6.14E-02
Chemotherapy (yes vs no)	0.83 (0.62-1.09)	1.83E-01
Chemoradiation (yes vs no)	0.86 (0.49-1.52)	6.14E-01
rs2706399	0.63 (0.47-0.84)	1.87E-03
Sex (female vs male)	0.76 (0.60-0.95)	1.88E-02
Age	1.01 (1.00-1.01)	9.05E-09
Smoking status (former vs never)	1.15 (0.82-1.60)	4.16E-01
Smoking status (current vs never)	1.34 (0.96-1.89)	8.92E-02
Performance status (1 vs 0)	1.37 (0.98-1.92)	6.62E-02
Performance status (2-4 vs 0)	1.35 (0.70-2.61)	3.64E-01
Performance status (unknown vs 0)	1.54 (1.12-2.11)	8.15E-03
FEV1 ≤ 50% predicted (yes vs no)	0.85 (0.39-1.84)	6.78E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.60 (0.71-3.63)	2.58E-01
DLCO ≤ 50% predicted (yes vs no)	1.08 (0.56-2.06)	8.25E-01
DLCO ≤ 50% predicted (unknown vs no)	0.79 (0.45-1.40)	4.18E-01
Postoperative pulmonary complications (yes vs no)	1.39 (1.04-1.86)	2.61E-02
Postoperative pulmonary complications (unknown vs no)	1.28 (0.63-2.58)	4.91E-01
Clinical stage (stage II vs stage I)	1.52 (1.15-2.02)	3.42E-03
Clinical stage (stage III vs stage I)	2.04 (1.46-2.84)	2.93E-05
Radiation (yes vs no)	1.54 (1.00-2.38)	5.03E-02
Chemotherapy (yes vs no)	0.84 (0.63-1.11)	2.20E-01
Chemoradiation (yes vs no)	0.87 (0.49-1.53)	6.23E-01

HR, Hazard ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lungs for carbon monoxide.

TABLE E11. Sensitivity analysis for SNPs independently associated with risk of recurrence with inclusion of additional clinical factors

Variable	Adjusted HR (95% CI)	P
rs2287040	1.45 (1.18-1.78)	3.78E-04
Sex (female vs male)	1.10 (0.83-1.47)	5.12E-01
Age	1.00 (0.99-1.01)	7.90E-01
Smoking status (former vs never)	1.06 (0.70-1.58)	7.95E-01
Smoking status (current vs never)	1.17 (0.77-1.76)	4.61E-01
Performance status (1 vs 0)	1.19 (0.82-1.72)	3.73E-01
Performance status (2-4 vs 0)	0.83 (0.35-1.96)	6.72E-01
Performance status (unknown vs 0)	1.27 (0.88-1.82)	2.03E-01
FEV1 ≤ 50% predicted (yes vs no)	1.16 (0.46-2.94)	7.54E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.59 (0.47-5.38)	4.55E-01
DLCO ≤ 50% predicted (yes vs no)	0.95 (0.41-2.20)	9.03E-01
DLCO ≤ 50% predicted (unknown vs no)	0.72 (0.32-1.66)	4.47E-01
Postoperative pulmonary complications (yes vs no)	1.26 (0.88-1.79)	2.02E-01
Postoperative pulmonary complications (unknown vs no)	1.65 (0.65-4.21)	2.91E-01
Clinical stage (stage II vs stage I)	2.03 (1.43-2.89)	7.46E-05
Clinical stage (stage III vs stage I)	3.12 (2.10-4.62)	1.60E-08
Radiation (yes vs no)	1.17 (0.74-1.83)	5.05E-01
Chemotherapy (yes vs no)	1.04 (0.75-1.45)	7.93E-01
Chemoradiation (yes vs no)	1.08 (0.59-1.98)	7.96E-01
rs11211654	2.05 (1.38-3.04)	4.08E-04
Sex (female vs male)	1.10 (0.83-1.46)	5.14E-01
Age	1.00 (0.99-1.01)	9.08E-01
Smoking status (former vs never)	1.14 (0.76-1.71)	5.35E-01
Smoking status (current vs never)	1.27 (0.84-1.92)	2.52E-01
Performance status (1 vs 0)	1.15 (0.79-1.68)	4.60E-01
Performance status (2-4 vs 0)	0.78 (0.33-1.83)	5.64E-01
Performance status (unknown vs 0)	1.22 (0.85-1.76)	2.79E-01
FEV1 ≤ 50% predicted (yes vs no)	1.30 (0.51-3.30)	5.82E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.75 (0.52-5.86)	3.63E-01
DLCO ≤ 50% predicted (yes vs no)	0.82 (0.35-1.92)	6.53E-01
DLCO ≤ 50% predicted (unknown vs no)	0.73 (0.32-1.68)	4.62E-01
Postoperative pulmonary complications (yes vs no)	1.28 (0.90-1.83)	1.74E-01
Postoperative pulmonary complications (unknown vs no)	1.50 (0.60-3.78)	3.84E-01
Clinical stage (stage II vs stage I)	2.07 (1.45-2.95)	5.76E-05
Clinical stage (stage III vs stage I)	3.05 (2.04-4.55)	4.63E-08
Radiation (yes vs no)	1.30 (0.83-2.05)	2.55E-01

(Continued)

TABLE E11. Continued

Variable	Adjusted HR (95% CI)	P
Chemotherapy (yes vs no)	1.03 (0.74-1.42)	8.70E-01
Chemoradiation (yes vs no)	0.96 (0.52-1.76)	8.87E-01
rs2008018	1.63 (1.23-2.16)	6.10E-04
Sex (female vs male)	1.04 (0.78-1.38)	8.00E-01
Age	1.00 (0.99-1.01)	7.57E-01
Smoking status (former vs never)	1.06 (0.70-1.59)	7.92E-01
Smoking status (current vs never)	1.24 (0.82-1.88)	3.01E-01
Performance status (1 vs 0)	1.11 (0.76-1.61)	5.94E-01
Performance status (2-4 vs 0)	0.74 (0.31-1.75)	4.91E-01
Performance status (unknown vs 0)	1.21 (0.84-1.74)	3.00E-01
FEV1 ≤ 50% predicted (yes vs no)	1.20 (0.47-3.05)	6.99E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.90 (0.57-6.30)	2.97E-01
DLCO ≤ 50% predicted (yes vs no)	0.87 (0.37-2.02)	7.45E-01
DLCO ≤ 50% predicted (unknown vs no)	0.76 (0.33-1.76)	5.27E-01
Postoperative pulmonary complications (yes vs no)	1.25 (0.87-1.78)	2.24E-01
Postoperative pulmonary complications (unknown vs no)	1.34 (0.54-3.32)	5.29E-01
Clinical stage (stage II vs stage I)	1.94 (1.36-2.75)	2.22E-04
Clinical stage (stage III vs stage I)	2.85 (1.93-4.22)	1.39E-07
Radiation (yes vs no)	1.26 (0.81-1.98)	3.07E-01
Chemotherapy (yes vs no)	1.08 (0.78-1.49)	6.35E-01
Chemoradiation (yes vs no)	0.95 (0.52-1.73)	8.57E-01
rs3917239	1.36 (1.12-1.65)	1.57E-03
Sex (female vs male)	1.08 (0.81-1.44)	5.85E-01
Age	1.00 (0.99-1.01)	7.84E-01
Smoking status (former vs never)	1.02 (0.68-1.53)	9.30E-01
Smoking status (current vs never)	1.14 (0.75-1.72)	5.37E-01
Performance status (1 vs 0)	1.17 (0.80-1.70)	4.17E-01
Performance status (2-4 vs 0)	0.88 (0.37-2.08)	7.63E-01
Performance status (unknown vs 0)	1.21 (0.84-1.74)	2.97E-01
FEV1 ≤ 50% predicted (yes vs no)	1.12 (0.44-2.85)	8.19E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.67 (0.51-5.51)	3.96E-01
DLCO ≤ 50% predicted (yes vs no)	0.93 (0.40-2.17)	8.63E-01
DLCO ≤ 50% predicted (unknown vs no)	0.78 (0.34-1.80)	5.60E-01
Postoperative pulmonary complications (yes vs no)	1.19 (0.83-1.69)	3.45E-01
Postoperative pulmonary complications (unknown vs no)	1.45 (0.58-3.62)	4.23E-01
Clinical stage (stage II vs stage I)	1.95 (1.37-2.77)	2.04E-04

(Continued)

TABLE E11. Continued

Variable	Adjusted HR (95% CI)	P
Clinical stage (stage III vs stage I)	2.94 (1.99-4.35)	6.66E-08
Radiation (yes vs no)	1.23 (0.78-1.94)	3.66E-01
Chemotherapy (yes vs no)	1.04 (0.76-1.44)	7.92E-01
Chemoradiation (yes vs no)	1.09 (0.60-2.01)	7.71E-01
rs280523	1.82 (1.28-2.58)	7.65E-04
Sex (female vs male)	1.10 (0.83-1.47)	5.09E-01
Age	1.00 (0.99-1.01)	8.09E-01
Smoking status (former vs never)	1.12 (0.75-1.69)	5.72E-01
Smoking status (current vs never)	1.18 (0.78-1.78)	4.35E-01
Performance status (1 vs 0)	1.15 (0.79-1.68)	4.61E-01
Performance status (2-4 vs 0)	0.78 (0.33-1.84)	5.70E-01
Performance status (unknown vs 0)	1.25 (0.87-1.79)	2.31E-01
FEV1 ≤ 50% predicted (yes vs no)	1.28 (0.50-3.23)	6.06E-01
FEV1 ≤ 50% predicted (unknown vs no)	2.02 (0.61-6.68)	2.46E-01
DLCO ≤ 50% predicted (yes vs no)	0.84 (0.36-1.96)	6.92E-01
DLCO ≤ 50% predicted (unknown vs no)	0.70 (0.30-1.60)	3.92E-01
Postoperative pulmonary complications (yes vs no)	1.21 (0.85-1.72)	2.93E-01
Postoperative pulmonary complications (unknown vs no)	1.36 (0.55-3.36)	5.04E-01
Clinical stage (stage II vs stage I)	1.96 (1.38-2.78)	1.74E-04
Clinical stage (stage III vs stage I)	2.94 (1.99-4.34)	6.46E-08
Radiation (yes vs no)	1.18 (0.75-1.85)	4.67E-01
Chemotherapy (yes vs no)	1.09 (0.79-1.50)	6.13E-01
Chemoradiation (yes vs no)	0.88 (0.48-1.62)	6.75E-01
rs17026782	1.42 (1.14-1.76)	1.91E-03
Sex (female vs male)	1.08 (0.81-1.44)	5.96E-01
Age	1.00 (0.99-1.01)	8.45E-01
Smoking status (former vs never)	1.08 (0.72-1.61)	7.22E-01
Smoking status (current vs never)	1.18 (0.78-1.77)	4.34E-01
Performance status (1 vs 0)	1.15 (0.79-1.67)	4.60E-01
Performance status (2-4 vs 0)	0.80 (0.34-1.89)	6.12E-01
Performance status (unknown vs 0)	1.24 (0.87-1.78)	2.40E-01
FEV1 ≤ 50% predicted (yes vs no)	1.16 (0.46-2.94)	7.49E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.63 (0.49-5.44)	4.30E-01
DLCO ≤ 50% predicted (yes vs no)	0.92 (0.40-2.14)	8.50E-01
DLCO ≤ 50% predicted (unknown vs no)	0.72 (0.31-1.65)	4.37E-01
Postoperative pulmonary complications (yes vs no)	1.22 (0.86-1.74)	2.68E-01

(Continued)

TABLE E11. Continued

Variable	Adjusted HR (95% CI)	P
Postoperative pulmonary complications (unknown vs no)	1.59 (0.63-3.99)	3.27E-01
Clinical stage (stage II vs stage I)	1.98 (1.39-2.81)	1.33E-04
Clinical stage (stage III vs stage I)	2.95 (1.99-4.37)	6.30E-08
Radiation (yes vs no)	1.20 (0.77-1.89)	4.23E-01
Chemotherapy (yes vs no)	1.04 (0.75-1.43)	8.28E-01
Chemoradiation (yes vs no)	1.10 (0.60-2.01)	7.56E-01
rs3014866	1.73 (1.26-2.36)	6.65E-04
Sex (female vs male)	1.06 (0.79-1.40)	7.10E-01
Age	1.00 (0.99-1.01)	8.95E-01
Smoking status (former vs never)	1.10 (0.73-1.65)	6.47E-01
Smoking status (current vs never)	1.23 (0.81-1.85)	3.29E-01
Performance status (1 vs 0)	1.10 (0.76-1.60)	6.10E-01
Performance status (2-4 vs 0)	0.75 (0.32-1.77)	5.08E-01
Performance status (unknown vs 0)	1.22 (0.85-1.75)	2.83E-01
FEV1 ≤ 50% predicted (yes vs no)	1.13 (0.44-2.87)	7.99E-01
FEV1 ≤ 50% predicted (unknown vs no)	2.05 (0.62-6.82)	2.41E-01
DLCO ≤ 50% predicted (yes vs no)	1.01 (0.43-2.33)	9.90E-01
DLCO ≤ 50% predicted (unknown vs no)	0.60 (0.26-1.38)	2.31E-01
Postoperative pulmonary complications (yes vs no)	1.23 (0.86-1.74)	2.58E-01
Postoperative pulmonary complications (unknown vs no)	1.56 (0.63-3.90)	3.37E-01
Clinical stage (stage II vs stage I)	2.00 (1.41-2.84)	9.62E-05
Clinical stage (stage III vs stage I)	2.88 (1.94-4.28)	1.44E-07
Radiation (yes vs no)	1.32 (0.84-2.07)	2.24E-01
Chemotherapy (yes vs no)	1.07 (0.78-1.48)	6.79E-01
Chemoradiation (yes vs no)	0.96 (0.53-1.75)	8.89E-01
rs4927632	1.41 (1.15-1.72)	9.37E-04
Sex (female vs male)	1.07 (0.81-1.43)	6.27E-01
Age	1.00 (0.98-1.01)	6.22E-01
Smoking status (former vs never)	1.05 (0.70-1.57)	8.25E-01
Smoking status (current vs never)	1.13 (0.75-1.70)	5.69E-01
Performance status (1 vs 0)	1.19 (0.82-1.73)	3.64E-01
Performance status (2-4 vs 0)	0.84 (0.35-1.99)	6.91E-01
Performance status (unknown vs 0)	1.21 (0.84-1.75)	2.94E-01
FEV1 ≤ 50% predicted (yes vs no)	1.29 (0.51-3.28)	5.89E-01
FEV1 ≤ 50% predicted (unknown vs no)	1.81 (0.54-6.04)	3.33E-01
DLCO ≤ 50% predicted (yes vs no)	0.90 (0.39-2.11)	8.17E-01

(Continued)

TABLE E11. Continued

Variable	Adjusted HR (95% CI)	P
DLCO $\leq$ 50% predicted (unknown vs no)	0.72 (0.31-1.65)	4.34E-01
Postoperative pulmonary complications (yes vs no)	1.25 (0.88-1.78)	2.21E-01
Postoperative pulmonary complications (unknown vs no)	1.50 (0.60-3.78)	3.85E-01
Clinical stage (stage II vs stage I)	2.08 (1.46-2.96)	5.17E-05
Clinical stage (stage III vs stage I)	2.91 (1.95-4.34)	1.76E-07
Radiation (yes vs no)	1.25 (0.79-1.96)	3.37E-01
Chemotherapy (yes vs no)	1.00 (0.72-1.38)	9.98E-01
Chemoradiation (yes vs no)	0.93 (0.50-1.71)	8.13E-01
rs2110726	1.55 (1.16-2.08)	3.05E-03
Sex (female vs male)	1.07 (0.81-1.43)	6.32E-01
Age	1.00 (0.99-1.01)	7.21E-01
Smoking status (former vs never)	1.04 (0.69-1.56)	8.61E-01
Smoking status (current vs never)	1.17 (0.77-1.76)	4.59E-01
Performance status (1 vs 0)	1.21 (0.83-1.76)	3.29E-01
Performance status (2-4 vs 0)	0.81 (0.34-1.92)	6.39E-01
Performance status (unknown vs 0)	1.21 (0.84-1.74)	2.99E-01
FEV1 $\leq$ 50% predicted (yes vs no)	1.23 (0.49-3.11)	6.61E-01
FEV1 $\leq$ 50% predicted (unknown vs no)	1.71 (0.51-5.71)	3.87E-01
DLCO $\leq$ 50% predicted (yes vs no)	0.95 (0.41-2.20)	9.00E-01
DLCO $\leq$ 50% predicted (unknown vs no)	0.76 (0.33-1.75)	5.23E-01
Postoperative pulmonary complications (yes vs no)	1.27 (0.89-1.80)	1.93E-01
Postoperative pulmonary complications (unknown vs no)	1.47 (0.58-3.69)	4.14E-01
Clinical stage (stage II vs stage I)	1.95 (1.37-2.76)	1.96E-04
Clinical stage (stage III vs stage I)	2.91 (1.97-4.31)	8.62E-08
Radiation (yes vs no)	1.21 (0.77-1.91)	4.01E-01
Chemotherapy (yes vs no)	1.05 (0.76-1.44)	7.88E-01
Chemoradiation (yes vs no)	1.07 (0.58-1.95)	8.35E-01

HR, Hazard ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lungs for carbon monoxide.