International Journal of Clinical Oncology (2019) 24:476–484
https://doi.org/10.1007/s10147-018-01386-7

STAT3 rs4796793 contributes to lung cancer risk and clinical outcomes of platinum-based chemotherapy

Wei-Jing Gong[1] · Li-Yun Ma[1] · Lei Hu[2] · Yong-Ning Lv[1] · Hong Huang[3] · Jia-Qiang Xu[1] · Dan-Dan Huang[4] · Rui-Jie Liu[5] · Yong Han[1] · Yu Zhang[1] · Shao-Jun Shi[1] · San-Lan Wu[1]

Received: 13 September 2018 / Accepted: 19 December 2018 / Published online: 28 January 2019

Abstract

Background Signal transducer and activator of transcription (STAT) 3 plays a vital role in carcinogenesis and drug response. Platinum-based chemotherapy is the first-line treatment for lung cancer patients, especially those in advanced stages. In the present study, we investigated the association of *STAT3* polymorphism rs4796793 with lung cancer susceptibility, platinum-based chemotherapy response, and toxicity.

Methods A total of 498 lung cancer patients and 213 healthy controls were enrolled in the study. 467 of them received at least 2-cycle platinum-based chemotherapy. Unconditional logistical regression analysis was used to assess the associations.

Results *STAT3* rs4769793 G allele carriers had an increased susceptibility of lung cancer [additive model: adjusted OR (95% CI) 1.376 (1.058–1.789), $P=0.017$; recessive model: adjusted OR (95% CI) 1.734 (1.007–2.985), $P=0.047$]. Rs4796793 was not significantly associated with platinum-based chemotherapy response in lung cancer patients. *STAT3* rs4796793 was associated with an increased risk of severe overall toxicity [additive model: adjusted OR (95% CI) 1.410 (1.076–1.850), $P=0.013$; dominant model: adjusted OR (95% CI) 1.638 (1.091–2.459), $P=0.017$], especially hematological toxicity [additive model: adjusted OR (95% CI) 1.352 (1.001–1.826), $P=0.049$].

Conclusions *STAT3* rs4796793 may be considered as a potential candidate biomarker for the prediction of susceptibility and prognosis in Chinese lung cancer patients. However, well-designed studies with larger sample sizes are required to verify the results.

Keywords *STAT3* rs4769793 · Lung cancer · Susceptibility · Platinum-based chemotherapy · Prognosis

Introduction

Lung cancer is a great public health burden in China with the most common incidence and the leading cause of cancer death [1]. Though significant progress in diagnosis has been achieved, most lung cancer patients are in advanced stages and metastatic when diagnosed [2]. Platinum-based chemotherapy regimens remain to be the standard care for lung cancer cases, especially for those in late stages. The 5-year overall survival rate for lung cancer is still approximately 18%. The major obstacles in lung cancer treatment are the late diagnosis, fast onset of chemoresistance, and unpredictable severe side effects.

Signal transducer and activator of transcription (STAT) 3, a member of cytoplasmic transcription factors, mediates various biological responses induced by cytokines and growth factors [3]. STAT3 is recognized as an oncogene that promotes tumor cell proliferation, survival, tumor invasion,

Wei-Jing Gong, Li-Yun Ma and Lei Hu have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-018-01386-7) contains supplementary material, which is available to authorized users.

✉ San-Lan Wu
sanlan2000@163.com

[1] Department of Pharmacy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[2] Department of Pharmacy, Peking University People's Hospital, 100044 Beijing, China

[3] Wuhan Highway Management Office, Wuhan 430000, China

[4] Department of Nursing, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[5] Department of Pathology, Xiangya Hospital, Central South University, Changsha 410008, China

angiogenesis, and immunosuppression [4]. Constitutive activation of STAT3 has been routinely reported in a plethora of cancers, including lung cancer, gastric cancer, ovarian cancer, and breast cancer [5]. STAT3 prevents cell-cycle arrest and cell death through upregulation of survival proteins and downregulation of tumor suppressors, which may counteract the effect of chemotherapeutic agents [6]. It is reported that STAT3-expressing tumors are likely to be resistant to chemotherapy [7]. Inhibition of activated STAT3 could reverse resistance to chemotherapy agents in human gastric cancer cells [8]. However, tumor STAT3 tyrosine phosphorylation status was a marker of favorable outcome in breast cancer patients treated with adjuvant chemotherapy [9]. Cervical carcinoma patients with tumor positive for phospho-STAT3 had a longer disease-free survival [10]. The role of STAT3 in clinical outcomes in lung cancer patients with platinum-based chemotherapy still needs to be elucidated.

Single nucleotide polymorphisms (SNPs), the most common type of genetic variation, can affect gene expression and function [11]. Rs4796793 is located in the 5′ region of STAT3. It is reported that rs4796793 was associated with the expression of STAT3 expression [12]. However, few studies focused on the association of *STAT3* rs4796793 with lung cancer risk, and prognosis in lung cancer patients with platinum-based chemotherapy.

In the present study, we performed the genotype analysis for *STAT3* rs4796793 in a hospital-based case–control study and investigated the association of rs4796793 with lung cancer susceptibility, and clinical outcomes in lung cancer patients treated with platinum-based chemotherapy.

Patients and methods

Patients and clinical information

The study was approved by the Ethics Committee of Xiangya School of Medicine, Central South University (registration number: CTXY-110008-2) [13]. All subjects signed informed consent prior to inclusion in the study. 498 lung cancer patients and 213 healthy controls were consecutively recruited from November 2011 to May 2013 at the Xiangya Hospital and the Affiliated Cancer Hospital of Central South University. All healthy individuals who were enrolled from an annual health check-up at physical examination center of Xiangya Hospital during the same period were used as controls. The healthy controls did not have any disease at physical examination.

All the cases were cytologically or histologically diagnosed with primary lung cancer. Among them, 467 patients received at least 2 cycles of platinum-based chemotherapy. Those 467 patients were not given radiotherapy and/or biological therapy before and during chemotherapy and underwent full follow-up. Platinum-based chemotherapy regimens included pemetrexed + platinum (PP), gemcitabine + platinum (GP), paclitaxel + platinum (TP), docetaxel + platinum (DP), etoposide + platinum (EP), and other platinum-based chemotherapy (irinotecan + platinum, navelbine + platinum). The responses to chemotherapy were assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [14], which were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Those CR and PR were considered as responders, while SD and PD were regarded as non-responders. Platinum-based chemotherapy toxicity mainly included gastrointestinal toxicity and hematological toxicity, including nausea, vomiting, hypochromia, leukopenia, neutropenia, and thrombocytopenia. The severity of toxicity was evaluated with the National Cancer Institute Common Toxicity Criteria version 3.0 [15]. Grade 3 or 4 toxicity was considered as severe toxicity. Patients who experienced any type of severe toxicities described above were considered as suffering severe overall toxicity. The demographic and clinical information was collected according to medical records and follow-up data.

DNA extraction and genotyping analysis

Genomic DNA was isolated from 5 ml venous blood using the Genomic DNA Purification Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. The DNA was stored at − 20 °C before usage. *STAT3* polymorphism rs4796793 was genotyped using the Sequenom MassARRAY System (Sequenom, San Diego, CA, USA).

Publication search and inclusion criteria

We searched for original studies investigating the associations between *STAT3* rs4796793 and cancer susceptibility using Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www.embase.com/) and Cochrane (http://www.cochranelibrary.com/) up to July 26th, 2018. The following terms were used in combination to retrieve the relevant literature: "signal transducer and activator or transcription 3 or STAT3" AND "genetic polymorphism or polymorphisms or variant or rs4796793" AND "cancer or carcinoma or tumor". The study was planned and conducted in accordance with the standards of quality for reporting meta-analysis.

The inclusion study must be an original case–control study and had detailed genotype frequency of cases and controls or data to calculate them. Studies that did not provide the raw data of the *STAT3* rs4796793 genotype or deviated from the Hardy–Weinberg equilibrium (HWE) in controls were excluded. Two investigators reviewed all studies independently to identify and determine the inclusion studies.

Data extraction

Data extracted from the eligible studies included first author's last name, year of publication, nation, the number of cases and controls, genotypes or allele frequency, genotyping method, source of controls, and HWE in controls.

Statistical analysis

In our genotyping study, the chi-square and Student's *t* test were used to assess differences in proportions between groups for the categorical variables. The goodness-of-fit chi-squared test was used to determine the Hardy–Weinberg equilibrium (HWE). Unconditional logistic regression was conducted to estimate the association of *STAT3* rs4796793 with lung cancer susceptibility, chemotherapy response and toxicity by calculating the odds ratio (OR) and 95% confidence interval (CI) with adjustments. All tests were 2 sided, and $P < 0.05$ was statistically significant. These statistical analyses were performed by PLINK 1.9 and PASW statistics v18.0 (IBM Co., Armonk, NY, USA).

In the meta-analysis, the risk of cancer associated with *STAT3* rs4796793 was estimated by calculating pooled OR and 95% CI. The Cochrane's Q test and I^2 test were used to assess the heterogeneity of effect size among studies. If $P < 0.05$ or $I^2 > 50\%$, the random effect model was selected. Otherwise, the fixed effect model was used. Sensitivity analysis was used to assess the stability of the results. The inverted funnel plots were performed to estimate publication bias. These statistical analyses were performed by STATA 12.0 (STAT Corp, College Station, TX, USA), and tests were 2 sided with the criterion of statistical significance at $P < 0.05$.

Table 1 Demographics of lung cancer patients and healthy controls

Characteristics	Patients, *n* (%) (*n* = 498)	Controls, *n* (%) (*n* = 213)	*P*
Sex			
Male	394 (79.1)	80 (37.6)	< 0.001
Female	104 (20.9)	133 (62.4)	
Age (years)			
< 50	124 (24.9)	95 (44.6)	< 0.001
≥ 50	374 (75.1)	118 (55.4)	
Histology			
SCC	189 (37.9)		
ADC	217 (43.6)		
SCLC	69 (13.9)		
Other	23 (4.6)		
Stage(NSCLC)	429		
I, II	13 (3.0)		
III, IV	416 (97.0)		
Stage (SCLC)	69		
Limited	36 (52.2)		
Extensive	33 (47.8)		
Chemotherapy response	467		
Responder	283 (60.6)		
Non-responder	184 (39.4)		
Overall toxicity			
Grade 0–2	286 (61.2)		
Grade 3–4	181 (38.8)		
Gastrointestinal toxicity			
Grade 0–2	366 (78.4)		
Grade 3–4	101 (21.6)		
Hematological toxicity			
Grade 0–2	353 (75.6)		
Grade 3–4	114 (24.4)		

n number, *SCC* squamous cell carcinoma, *ADC* adenocarcinoma, *SCLC* small cell lung cancer, *Other* mixed-cell or undifferentiated carcinoma, *NSCLC* non-small cell lung cancer

Results

Association of *STAT3* rs4796793 with lung cancer susceptibility

498 lung cancer patients and 213 healthy controls were enrolled in our genotyping study and their clinical characteristics are presented in Table 1. The genotype distribution of rs4796793 in healthy controls was consistent with HWE ($P = 0.999$). And the call rate of rs4796793 was 99.4%.

Unconditional logistic regression analysis with adjustments of age and sex revealed that rs4796793 was significantly associated with lung cancer risk in both additive (adjusted OR = 1.376, 95% CI = 1.058–1.789, $P = 0.017$) and recessive (adjusted OR = 1.734, 95% CI = 1.007–2.985, $P = 0.047$) models (Table 2). Stratified analysis showed that those age < 50 with rs4796793 CC genotype had lower incidence of lung cancer (adjusted OR = 2.581, 95% CI = 1.006–6.624, $P = 0.049$) compared with those with GG and GC genotypes. Rs4796793 was significantly associated with lung cancer susceptibility in female (additive model: adjusted OR = 1.677, 95% CI = 1.140–2.468, $P = 0.009$; dominant model: adjusted OR = 2.014, 95% CI = 1.173–3.457, $P = 0.011$), NSCLC (additive model: adjusted OR = 1.460, 95% CI = 1.117–1.908, $P = 0.006$; dominant model: adjusted OR = 1.542, 95% CI = 1.061–2.239, $P = 0.023$; recessive model: adjusted OR = 1.910, 95% CI = 1.105–3.302, $P = 0.021$), ADC (additive model: adjusted OR = 1.436, 95% CI = 1.067–1.931, $P = 0.017$; dominant model: adjusted OR = 1.579, 95% CI = 1.048–2.380, $P = 0.029$), SCC (additive model: adjusted OR = 1.418, 95% CI = 1.007–1.996, $P = 0.045$; recessive model: adjusted OR = 2.291, 95% CI = 1.145–4.580, $P = 0.019$) (Fig. 1).

Table 2 Association of STAT3 rs4796793 with lung cancer susceptibility and clinical outcomes in lung cancer patients with platinum-based chemotherapy

Type	Genotype	*n* (%)	*n* (%)	Additive model		Dominant model		Recessive model	
				OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Susceptibility[a]		Case	Control	1.376 (1.058–1.789)	0.017	1.434 (0.998–2.061)	0.052	1.734 (1.007–2.985)	0.047
	GG	87 (17.5)	22 (10.4)						
	GC	226 (45.6)	93 (44.1)						
	CC	183 (36.9)	96 (45.5)						
Chemotherapy response[b]		Responder	Non-responder	1.085 (0.829–1.421)	0.551	1.200 (0.808–1.782)	0.367	0.994 (0.601–1.641)	0.980
	GG	50 (17.7)	33 (18.0)						
	GC	133 (47.2)	78 (42.6)						
	CC	99 (35.1)	72 (39.3)						
Overall toxicity[b]		Grade 3–4	Grade 0–2	1.410 (1.076–1.850)	0.013	1.638 (1.091–2.459)	0.017*	1.516 (0.923–2.489)	0.100
	GG	38 (21.0)	45 (15.8)						
	GC	88 (48.6)	123 (43.3)						
	CC	55 (30.4)	116 (40.8)						
Gastrointestinal toxicity[b]		Grade 3–4	Grade 0–2	1.254 (0.910–1.727)	0.166	1.403 (0.863–2.280)	0.172	1.287 (0.718–2.305)	0.396
	GG	20 (19.8)	63 (17.3)						
	GC	50 (49.5)	161 (44.2)						
	CC	31 (30.7)	140 (38.5)						
Hematological toxicity[b]		Grade 3–4	Grade 0–2	1.352 (1.001–1.826)	0.049	1.404 (0.887–2.222)	0.148	1.651 (0.971–2.806)	0.064
	GG	27 (23.7)	56 (16.0)						
	GC	51 (44.7)	160 (45.6)						
	CC	36 (31.6)	135 (38.5)						

n number, *OR* odds ratio, *CI* confidence interval

[a]Adjustments for age and sex

[b]Adjustments for age, sex, stage, histological type, smoking status, and chemotherapy regimens

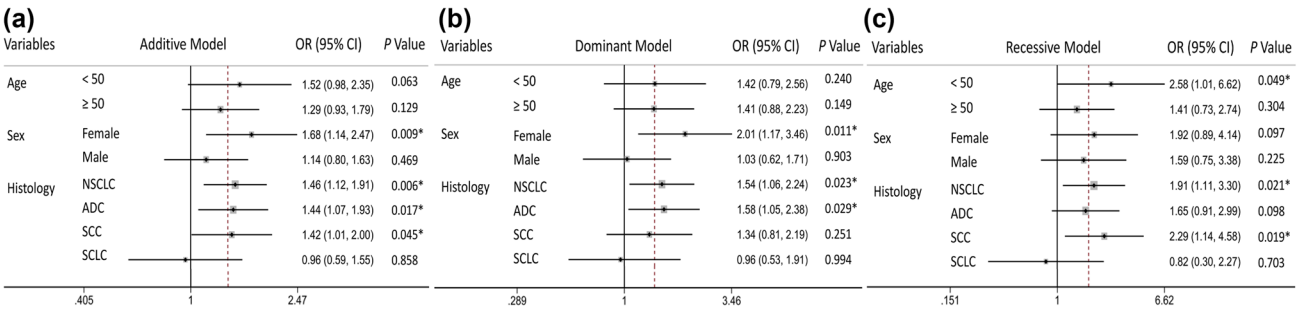

Fig. 1 Stratification analyses of the association of *STAT3* rs4796793 and lung cancer susceptibility in additive (**a**), dominant (**b**), and recessive (**c**) models with adjustments of age and sex. Each box and horizontal line represents the odds ratio (OR) and 95% confidence interval (CI). *NSCLC* non-small cell lung carcinoma, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *SCLC* small cell lung cancer. *$P < 0.05$

A meta-analysis was conducted to investigate the association between *STAT3* rs4796793 and cancer risk. The search strategy retrieved 45 potentially relevant studies. According to the inclusion criteria, a total of 7 studies with 4667 cases and 4282 controls were included finally (Supplementary Table 1) [9, 16–20]. All patients are from Asian populations. Because of high heterogeneity across the studies, a random-effects model was used. There was no significant

association between *STAT3* rs4796793 and cancer risk in dominant, recessive, and allele models (Fig. 2). Sensitivity analysis was conducted to test the robustness of the results of meta-analysis by omitting one study each time. No single study was found to significantly affect the summary results (Supplementary Fig. 1). Publication bias was examined by visual inspection of funnel plots. Results indicated that there was no significant publication bias (Supplementary Fig. 2).

Association of *STAT3* rs4796793 with platinum-based chemotherapy response in lung cancer patients

467 lung cancer patients received at least 2 cycles of platinum-based chemotherapy treatment. 184 of them showed a good response while 283 had a poor response to the chemotherapy treatment. After adjustments for age, sex, stage, histological type, smoking status, and chemotherapy regimens, *STAT3* rs4796793 failed to be significantly associated with short-term platinum-based chemotherapy response in lung cancer patients (Table 2). By subgroup analysis, we still did not found any significant association (Fig. 3).

Association of *STAT3* rs4796793 with platinum-based chemotherapy toxicity in lung cancer patients

Of 467 lung cancer patients with at least two cycles of platinum-based chemotherapy, 101 and 114 patients suffered severe gastrointestinal and hematological toxicities, respectively. 181 patients experienced at least one type of severe toxicity. Unconditional logistic regression analysis was used to explore the association between *STAT3* rs4796367 and overall toxicity with the adjustments of age, sex, stage, histological type, smoking status, and chemotherapy regimens. *STAT3* rs4796793 was significantly associated with an increased incidence of severe overall toxicity in both additive (adjusted OR = 1.410, 95% CI = 1.076–1.850, $P = 0.013$) and dominant (adjusted OR = 1.638, 95% CI = 1.091–2.459, $P = 0.017$) models (Table 2). Subsequently, stratification analysis showed that *STAT3* rs4796793 was associated with

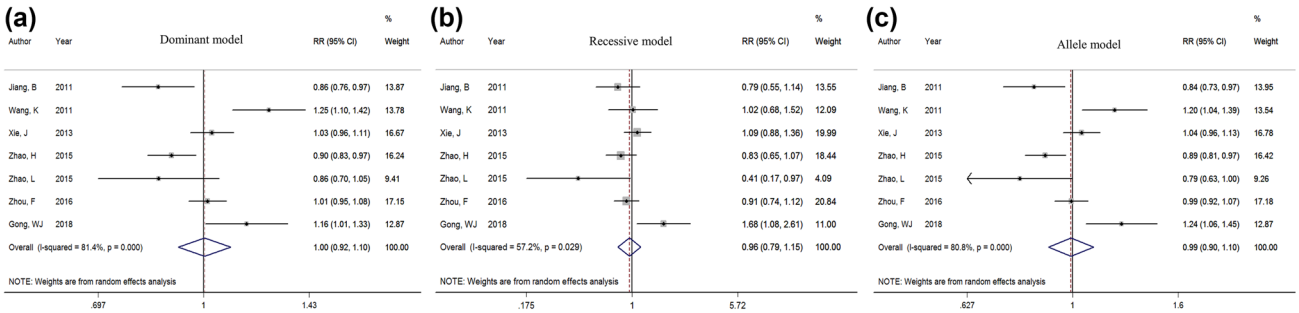

Fig. 2 Meta-analysis of the association between *STAT3* rs4796793 and cancer risk in dominant (**a**), recessive (**b**) and allele (**c**) models. Each box and horizontal line represents the risk ratio (RR) and 95% confidence interval (CI)

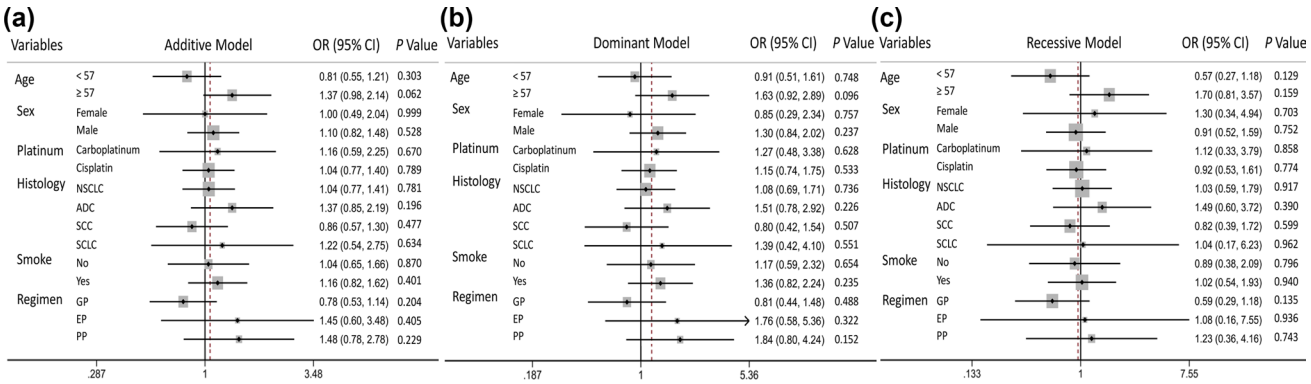

Fig. 3 Stratification analyses of the association of *STAT3* rs4796793 and platinum-based chemotherapy response in lung cancer patients in additive (**a**), dominant (**b**), and recessive (**c**) models with adjustments of age, sex, stage, histological type, smoking status, and chemotherapy regimens. Each box and horizontal line represent the odds ratio (OR) and 95% confidence interval (CI). *NSCLC* non-small cell lung carcinoma, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *SCLC* small cell lung cancer, *GP* platinum + gemcitabine, *EP* platinum + etoposide, *PP* platinum + pemetrexed. $^{*}P < 0.05$

an increased risk of overall toxicity in those male (additive model: adjusted OR = 1.385, 95% CI = 1.023–1.876, $P = 0.035$), age < 57 (additive model: adjusted OR = 1.532, 95% CI = 1.031–2.278, $P = 0.035$; dominant model: adjusted OR = 1.846, 95% CI = 1.035–3.293, $P = 0.038$), NSCLC (additive model: adjusted OR = 1.399, 95% CI = 1.036–1.891, $P = 0.029$; dominant model: adjusted OR = 1.630, 95% CI = 1.022–2.601, $P = 0.040$) patients (Fig. 4).

Logistic regression analysis revealed that *STAT3* rs4796793 was not associated with severe gastrointestinal toxicity induced by platinum-based chemotherapy in lung cancer patients (Table 2). Further stratification analysis also did not find any significant association (Fig. 5).

We further evaluated the association of *STAT3* rs4796793 with severe hematological toxicity. *STAT3* rs4796793 was significantly associated with an increased risk of severe hematological toxicity in an additive model (adjusted OR = 1.352, 95% CI = 1.001–1.826, $P = 0.049$) (Table 2). By subgroup analysis, *STAT3* rs4796793 was associated with severe hematological analysis in those age < 57 (additive model: adjusted OR = 1.803, 95% CI = 1.143–2.844, $P = 0.011$; dominant model: adjusted OR = 2.301, 95% CI = 1.120–4.278, $P = 0.023$), and SCC (recessive model: adjusted OR = 2.458, 95% CI = 1.104–5.472, $P = 0.028$) patients (Fig. 6).

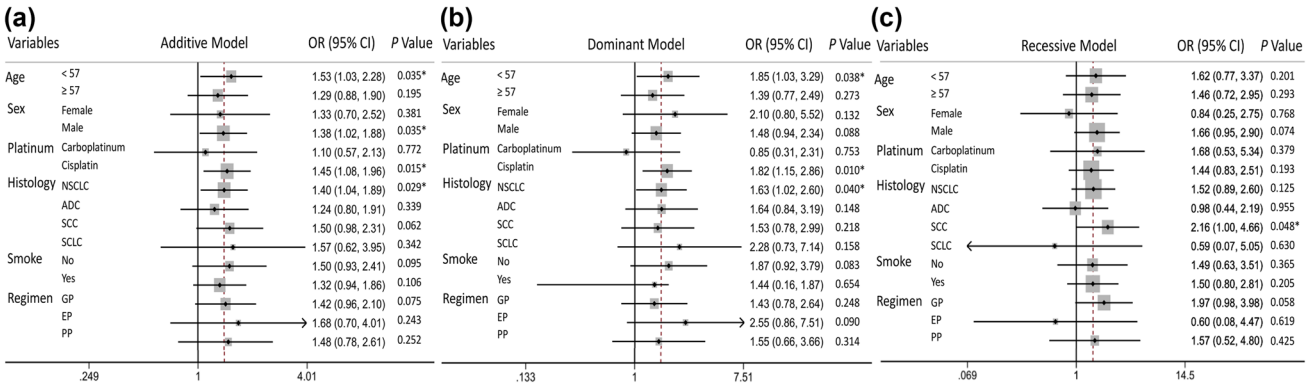

Fig. 4 Stratification analyses of the association of *STAT3* rs4796793 and overall toxicity in lung cancer patients treated with platinum-based chemotherapy in additive (**a**), dominant (**b**), and recessive (**c**) models with adjustments of age, sex, stage, histological type, smoking status, and chemotherapy regimens. Each box and horizontal line represent the odds ratio (OR) and 95% confidence interval (CI). *NSCLC* non-small cell lung carcinoma, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *SCLC* small cell lung cancer, *GP* platinum + gemcitabine, *EP* platinum + etoposide, *PP* platinum + pemetrexed. $^{*}P < 0.05$

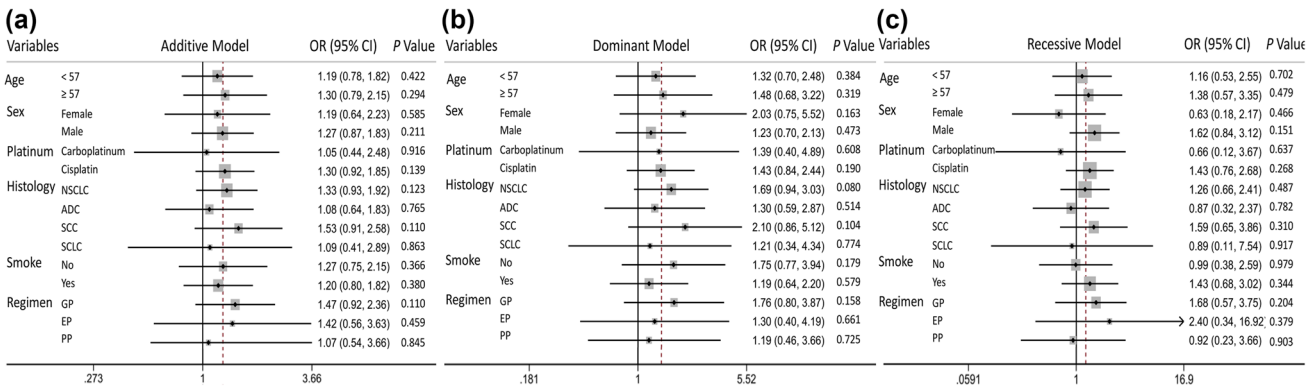

Fig. 5 Stratification analyses of the association of *STAT3* rs4796793 and gastrointestinal toxicity in lung cancer patients treated with platinum-based chemotherapy in additive (**a**), dominant (**b**), and recessive (**c**) models with adjustments of age, sex, stage, histological type, smoking status, and chemotherapy regimens. Each box and horizontal line represent the odds ratio (OR) and 95% confidence interval (CI). *NSCLC* non-small cell lung carcinoma, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *SCLC* small cell lung cancer, *GP* platinum + gemcitabine, *EP* platinum + etoposide, *PP* platinum + pemetrexed. $^{*}P < 0.05$

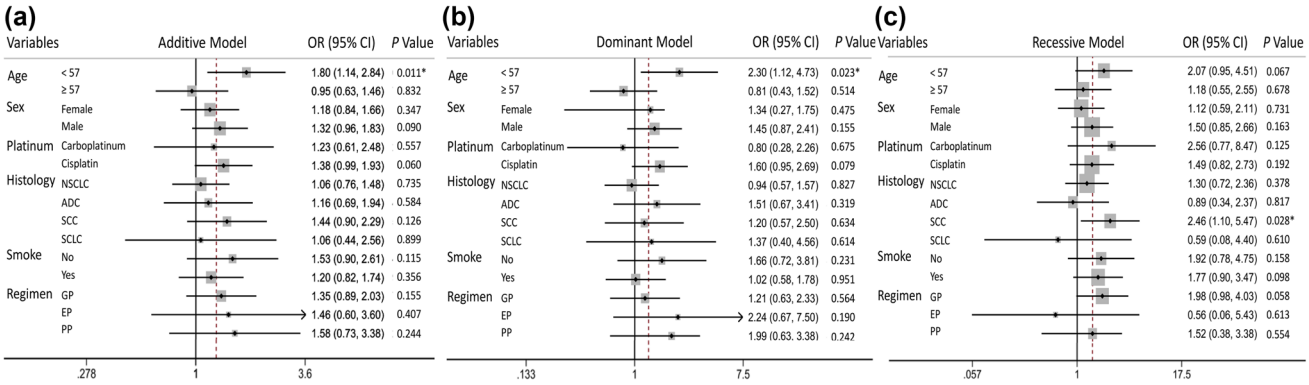

Fig. 6 Stratification analyses of the association of *STAT3* rs4796793 and hematological toxicity in lung cancer patients treated with platinum-based chemotherapy in additive (**a**), dominant (**b**), and recessive (**c**) models with adjustments of age, sex, stage, histological type, smoking status, and chemotherapy regimens. Each box and horizontal line represent the odds ratio (OR) and 95% confidence interval (CI). *NSCLC* non-small cell lung carcinoma, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *SCLC* small cell lung cancer, *GP* platinum + gemcitabine, *EP* platinum + etoposide, *PP* platinum + pemetrexed. $^{*}P < 0.05$

Discussion

STAT3 is a point of convergence for numerous oncogenic signaling pathways. STAT3 is constitutively activated in various cancers including lung cancer, and associated with progression, metastasis, and poor prognosis. However, few studies focused on the association of *STAT3* rs4796793 with lung cancer susceptibility and platinum-based chemotherapy clinical outcomes. In the study, we analyzed *STAT3* polymorphism rs4796793 in 498 lung cancer patients and 213 healthy controls. We found *STAT3* rs4796793 was significantly associated with the prevalence of lung cancer, the incidence of overall toxicity and hematological toxicity. But it was not associated with platinum-based chemotherapy response. Our findings suggest that *STAT3* rs4796793 may be a potential pharmacogenomic factor to assess susceptibility and prognosis in lung cancer patients with platinum-based chemotherapy.

STAT3 was a latent cytosolic transcription factor, and routinely activated or overexpressed in a number of cancers including lung cancer. SNP rs4769793 or a combination of SNPs in LD with rs4769793 might affect STAT3 expression. It was reported that G allele carriers had a tendency for higher STAT3 expression [12]. Our study found *STAT3* rs4769793 G allele carriers had an increased susceptibility of lung cancer, especially NSCLC. Similar to our findings, Zhao et al. [9] reported that the GG genotype of *STAT3* rs4769793 had a significantly increased risk of breast cancer. Xie et al. [18] found that *STAT3* rs4769793 polymorphism significantly increased hepatocellular carcinoma risk after adjusting for covariates including hepatitis B virus mutations in the preS region. Wang et al. [17] revealed that *STAT3* rs4769793 was associated with an increased risk of cervical cancer and poor tumor differentiation. However, Jiang et al. [16] found *STAT3* rs4769793 polymorphism decreased the risk of NSCLC, which was contrasted with our results. We performed a meta-analysis to assess the association between *STAT3* rs4769793 and cancer risk. However, we did not find any significant association. We compared the allele frequency among the controls among the studies. We did not found significant difference between our study and other studies. However, compare with the allele frequency between Chinese populations in 1000 Genomes Project (http://grch37.ensembl.org/index.html) with the studies, there were significant differences in several studies [16, 18–20] (Supplementary Table 2). Those may partly explain the inconsistence of cancer risk.

Because of its dual function as a signal transduction factor and transcription activity, STAT3 was involved in the regulation of cellular differentiation, survival, and proliferation [5]. STAT3 was considered as a potential therapeutic target and predictor factor of cancer treatment [21]. The role of STAT3 in cancer treatment was controversial. Berre et al. [7] proposed that STAT3 was involved in intrinsic drug resistance and STAT3-expressing tumors were resistant to chemotherapeutic agents. Huang et al. [8] reported that interruption of STAT3 signaling could reverse resistance to chemotherapy agents in human gastric cancer cells. However, Sonnenblick et al. [10] found tumor STAT3 tyrosine phosphorylation status was a predictor of favorable outcome in breast cancer patients treated with adjuvant chemotherapy. Walch-Ruckheim et al. [22] revealed that STAT3 activation rendered cervical cancer cells significantly more susceptible to chemotherapeutic drugs, such as cisplatin or etoposide. So far, few studies paid attention to the effect of STAT3 on clinical outcomes in lung cancer patients treated with platinum-based chemotherapy. We explored the association of *STAT3* rs4769793 polymorphism in lung cancer patients with platinum-based chemotherapy. We did not find the association between *STAT3*

rs4796793 and chemotherapy response. Yamamoto et al. [23] reported STAT3 polymorphism rs4796793 might be a predictor of tumor response to multiple tyrosine kinase inhibitors in metastatic renal cell carcinoma in Japanese population. Zhao et al. found that *STAT3* rs4796793 was associated with increased progression-free survival in breast cancer patients treated with anthracycline-based chemotherapy.

We also explored the association of STAT3 polymorphism rs4796793 with platinum-based chemotherapy toxicity in lung cancer patients. We found *STAT3* rs4796793 was associated with severe overall toxicity, especially hematological toxicity. We did not find a significant association between *STAT3* rs4796793 and severe gastrointestinal toxicity. STAT3 played a vital role in hematopoietic homeostasis [24]. It was commonly activated by thrombopoietic cytokines including thrombopoietin, and vital for the early stage of megakaryopoiesis. The platelet recovery from myelosuppression after 5-fluorouracil treatment was delayed when STAT3 was overexpressed [25]. So the G allele carriers might have an increased risk of severe hematological toxicity.

It must be admitted that the present study had some limitations. First, we conducted the case–control study in a single ethnicity and relatively small population retrospectively. The results need to be verified in a large-scale prospective study. Second, the combination of chemotherapy drugs may be a confounding factor for chemotherapy response and severe toxicity evaluation. Additionally, carcinogenesis, chemotherapy resistance, and toxicity may result from multiple genetic factors. More studies on different levels are needed.

In conclusion, we investigated the association between *STAT3* polymorphism rs4796793 and susceptibility, and chemotherapeutic outcomes in a case–control study of 498 lung cancer patients and 213 healthy controls. *STAT3* rs4796793 G allele was associated with an increased susceptibility of lung cancer, especially NSCLC. In addition, we found that *STAT3* rs4796793 G allele lung cancer patients with platinum-based chemotherapy had more chance to suffer severe hematological toxicity. Our findings suggest that *STAT3* rs4796793 may be considered as a candidate biomarker for the prediction of susceptibility and prognosis in Chinese lung cancer patients. However, more randomized and large-scale clinical trials are needed to confirm the association in the future.

Acknowledgements The authors thank all the subjects who volunteered to take part in the study.

Funding The work was supported by the National Key R&D Program of China (No. 2017YFC0909900) and Hubei Province health and family planning scientific research project (WJ2017M118).

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Chen W, Zheng R, Baade PD et al. (2016) Cancer statistics in China, 2015. CA Cancer J Clin 66(2):115–132. https://doi.org/10.3322/caac.21338
2. Gong WJ, Yin JY, Li XP et al. (2016) Association of well-characterized lung cancer lncRNA polymorphisms with lung cancer susceptibility and platinum-based chemotherapy response. Tumour Biol 37(6):8349–8358. https://doi.org/10.1007/s13277-015-4497-5
3. Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 9(11):798–809. https://doi.org/10.1038/nrc2734
4. Chai EZ, Shanmugam MK, Arfuso F et al. (2016) Targeting transcription factor STAT3 for cancer prevention and therapy. Pharmacol Ther 162:86–97. https://doi.org/10.1016/j.pharmthera.2015.10.004
5. Yu H, Lee H, Herrmann A et al. (2014) Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer 14(11):736–746. https://doi.org/10.1038/nrc3818
6. Lee HJ, Zhuang G, Cao Y et al. (2014) Drug resistance via feedback activation of Stat3 in oncogene-addicted cancer cells. Cancer Cell 26(2):207–221. https://doi.org/10.1016/j.ccr.2014.05.019
7. Barre B, Vigneron A, Perkins N et al. (2007) The STAT3 oncogene as a predictive marker of drug resistance. Trends Mol Med 13(1):4–11. https://doi.org/10.1016/j.molmed.2006.11.001
8. Huang S, Chen M, Shen Y et al. (2012) Inhibition of activated Stat3 reverses drug resistance to chemotherapeutic agents in gastric cancer cells. Cancer Lett 315(2):198–205. https://doi.org/10.1016/j.canlet.2011.10.011
9. Zhao L, Zhang Q, Luan X et al. (2015) STAT3 and STAT5b polymorphism contributes to breast cancer risk and clinical outcomes. Int J Clin Exp Pathol 8(2):2033–2038
10. Sonnenblick A, Uziely B, Nechushtan H et al. (2013) Tumor STAT3 tyrosine phosphorylation status, as a predictor of benefit from adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat 138(2):407–413. https://doi.org/10.1007/s10549-013-2453-x
11. Gong W, Xiao D, Ming G et al. (2014) Type 2 diabetes mellitus-related genetic polymorphisms in microRNAs and microRNA target sites. J Diabetes 6(4):279–289. https://doi.org/10.1111/1753-0407.12143
12. Ito N, Eto M, Nakamura E et al. (2007) STAT3 polymorphism predicts interferon-alfa response in patients with metastatic renal cell carcinoma. J Clin Oncol 25(19):2785–2791. https://doi.org/10.1200/jco.2006.09.8897
13. Gong WJ, Peng JB, Yin JY et al. (2017) Association between well-characterized lung cancer lncRNA polymorphisms and platinum-based chemotherapy toxicity in Chinese patients with lung cancer. Acta Pharmacol Sin 38(4):581–590. https://doi.org/10.1038/aps.2016.164

14. Duffaud F, Therasse P (2000) New guidelines to evaluate the response to treatment in solid tumors. Bull Cancer 87(12):881–886
15. Trotti A, Colevas AD, Setser A et al. (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13(3):176–181. https://doi.org/10.1016/s1053-4296(03)00031-6
16. Jiang B, Zhu ZZ, Liu F et al. (2011) STAT3 gene polymorphisms and susceptibility to non-small cell lung cancer. Genet Mol Res 10(3):1856–1865. https://doi.org/10.4238/vol10-3gmr1071
17. Wang KN, Zhou B, Zhang J et al. (2011) Association of signal transducer and activator of transcription 3 gene polymorphisms with cervical cancer in chinese women. DNA Cell Biol 30(11):931–936. https://doi.org/10.1089/dna.2010.1179
18. Xie J, Zhang Y, Zhang Q et al. (2013) Interaction of signal transducer and activator of transcription 3 polymorphisms with hepatitis B virus mutations in hepatocellular carcinoma. Hepatology 57(6):2369–2377. https://doi.org/10.1002/hep.26303
19. Zhao H, Wang Z, Wu H et al. (2015) STAT3 genetic variant, alone and in combination with STAT5b polymorphism, contributes to breast cancer risk and clinical outcomes. Med Oncol 32 (1). https://doi.org/10.1007/s12032-014-0375-z
20. Zhou F, Cheng L, Qiu LX et al. (2016) Associations of potentially functional variants in IL-6, JAKs and STAT3 with gastric cancer risk in an eastern Chinese population. Oncotarget 7(19):28112–28123. https://doi.org/10.18632/oncotarget.8492
21. Sellier H, Rebillard A, Guette C et al. (2013) How should we define STAT3 as an oncogene and as a potential target for therapy?. JAKSTAT 2 (3):e24716. https://doi.org/10.4161/jkst.24716
22. Walch-Ruckheim B, Pahne-Zeppenfeld J et al. (2016) STAT3/IRF1 pathway activation sensitizes cervical cancer cells to chemotherapeutic drugs. Cancer Res 76(13):3872–3883. https://doi.org/10.1158/0008-5472.can-14-1306
23. Yamamoto K, Ioroi T, Kanaya K et al. (2016) STAT3 polymorphism rs4796793 may be a predictive factor of tumor response to multiple tyrosine kinase inhibitors in metastatic renal cell carcinoma in Japanese population. Med Oncol 33 (3):24. https://doi.org/10.1007/s12032-016-0733-0. (Northwood, London, England)
24. Jenkins BJ, Roberts AW, Greenhill CJ et al. (2007) Pathologic consequences of STAT3 hyperactivation by IL-6 and IL-11 during hematopoiesis and lymphopoiesis. Blood 109(6):2380–2388. https://doi.org/10.1182/blood-2006-08-040352
25. Kirito K, Osawa M, Morita H et al. (2002) A functional role of Stat3 in in vivo megakaryopoiesis. Blood 99(9):3220–3227