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*Original Article*

# Associations of miR-605 rs2043556 polymorphism with the susceptibility and overall survival of lung cancer in Chinese non-smoking females

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**Abstract:** The effects of miR-605 rs2043556 single nucleotide polymorphism (SNP) on the risk and prognosis of lung cancer are unclear. This study investigated the relationships between miR-605 rs2043556 and the susceptibility and overall survival (OS) of lung cancer in Chinese non-smoking females. This hospital-based case-control study included 450 cases and 450 controls. Also, a prospective cohort study was carried out, and the patients were followed up until February 29th, 2016. There were 334 patients with prognostic information. Odds ratio and hazard ratio (HR) and their 95% confidence intervals (CIs) were calculated, respectively. In squamous cell carcinomas (SqCC) patients, homozygous GG genotype carriers had a 2.157-fold elevated risk of lung cancer compared with homozygous AA genotype carriers after adjusting age (95% CI = 1.029-4.524, *P* = 0.042). After adjusting age, pathological type, clinical stage, chemotherapy and surgery, only a marginal significance was observed among the patients with GG genotype, who had a longer OS than those with AA genotype (HR = 0.632, 95% CI = 0.398-1.003, *P* = 0.051). For patients younger than 60 years, those containing GG genotype was independently associated with OS (HR = 0.511, 95% CI = 0.268-0.977, *P* = 0.042). Patients with adenocarcinomas containing GG genotype was independently associated with OS (HR = 0.530, 95% CI = 0.312-0.898, *P* = 0.018). MiR-605 rs2043556 polymorphism could be associated with the susceptibility of SqCC in northeast Chinese non-smoking females. Age and pathological type might have the potential to modify the association between miR-605 rs2043556 and the OS of non-smoking female lung cancer patients.

**Keywords:** Lung cancer, microRNA, single nucleotide polymorphism, susceptibility, overall survival

## Introduction

Among females, lung cancer is the third commonly diagnosed cancer worldwide, and the leading cause of cancer death in developed countries, and the second leading cause of cancer death in developing countries [1]. In China, lung cancer is the second commonly diagnosed cancer in women, and there could be about 224,000 newly diagnosed lung cancer cases in 2015, accounting for nearly 12.6% of all cancer cases [2]. More severely, lung cancer is the leading cause of cancer death among women in China, and 177,800 Chinese women could die from lung cancer in 2015, accounting for nearly 17.7% of all cancer deaths [2]. The interaction of environmental factors and genetic alteration is involved in the occurrence and development of lung cancer. Smoking is an established environmental risk factor for this disease, but there are still 53% of female lung cancer cases are not attributed to smoking [3]. In China, the prevalence of cigarette smoking in women was as low as 2.7% displayed by Adult Tobacco Survey data in 2015 [4]. Despite a lower prevalence of smoking, the incidence rate of lung cancer in Chinese women was higher than rates among women in some European countries [1]. However, its underlying mechanism has not been fully clarified. In addition to other known environmental risk factors, some previous studies have suggested that microRNA (miRNA) related genetic variations especially play an indispensable role in the lung can-

cer of Chinese non-smoking females [5-9]. Therefore, it is necessary to find the genetic miRNA targets of lung cancer in order to take precise treatment and improve the prognosis of Chinese non-smoking female patients.

MiRNAs, a subset of highly conserved small non-coding regulatory RNAs, are canonically 20-24 nucleotides in length [10]. MiRNAs can lead to the degradation or translation repression of the message RNAs (mRNAs) of targeted genes through completely or partially pairing in the 3'UTR of them [11]. Thus, miRNA is involved in almost all important cellular biological processes, including proliferation, differentiation and apoptosis. Abnormalities in these cellular biological processes may be associated with the susceptibility and prognosis of human cancer. In fact, dysregulation of miRNAs has been recognized in almost all human cancer types, and miRNAs can act as tumor suppressors or oncogenes [12].

In particular, some miRNAs are identified as important components of the signaling cascades that mediate and regulate tumor suppression exerted by p53 [13]. In 2011, Xiao et al. demonstrated that miR-605 was a new component in the p53 gene network, being transcriptionally activated by p53 and post-transcriptionally repressing Mdm2 [14]. MiR-605 could interrupt the p53:Mdm2 interaction to create a positive feedback loop aiding rapid accumulation of p53 to facilitate its function in response to cellular stresses including DNA damage, hypoxia and oncogene activation [14]. In addition to Mdm2, there are a lot of candidate target genes of miR-605, such as PSMD10, PDCD2, TGFBR1, RABL5, P21 and CADM1 [15], which play important roles in the process of tumor biology.

In recent years, the relationships between the deregulation and genetic variants of miR-605 and the occurrence and progression of different cancer types have been studied. For lung cancer, Ye et al. demonstrated that miR-650 was highly expressed in non-small cell lung cancers (NSCLC) tissue samples and cell lines [16]. The expression inhibition of miR-650 suppressed NSCLC cell proliferation, migration and invasion in vitro. Additionally, large tumor suppressor kinase 2 (LATS2) was identified as a direct target gene of miR-650 in NSCLC. LATS2 was negatively correlated with the level of miR-650 in NSCLC tissues. Therefore, miR-650 may serve as an oncogene by direct targeting LATS2 in NSCLC formation and progression. Nymark et al. stated miRNA-605 was under-expressed in asbestos-related lung cancer [17]. Further, single nucleotide polymorphism (SNP) in miRNA (miRNA-SNP) has been recognized for its role in cancer incidence and prognosis [18] . MiRNA-SNP influences the maturation of miRNA or the affinity of miRNA binding to its target mRNAs, and then may modify the expression levels of cancer-related target genes [19]. Thus, they may prognosticate the development of cancer susceptibility and prognosis as genetic detection markers. In 2011, Zhang et al. reported that only a marginal significance was observed among the males with at least one G allele of miR-605 rs2043556 had higher risk of lung cancer than those with AA genotype, but not in women [20]. Recently, Yin et al. showed that miR-605 rs2043556 polymorphism was not associated with the incidence of lung cancer in Chinese non-smoking females [8]. However, the sample size of the two studies mentioned above should be enlarged in a further study. In addition to susceptibility, miRNA-SNPs can also affect the prognostic outcomes of cancer, such as treatment effects, recurrence and overall survival (OS). Fang et al. found that miR-605 rs2043556 was significantly related to the severe hepatotoxicity of lung cancer, which revealed that the miR-605 SNP may serve as a predictive tool for toxicity evaluation of platinum-based chemotherapy in lung cancer patients [21]. To our best knowledge, the study on exploring the relationship between miR-605 rs2043556 and the OS of lung cancer has not been found yet. Therefore, the roles of the deregulation and genetic variants of miR-605 needs to be confirmed in lung cancer.

In view of the inconsistency of the existing research results and the gaps of research in this filed, the present study aimed to investigate the relationship between miR-605 rs2043556 and the susceptibility and overall survival (OS) of lung cancer in a Chinese non-smoking female population.

## Materials and methods

### *Study design and sample*

An ongoing molecular epidemiologic study of lung cancer in non-smoking females was conducted in Shenyang, located in the northeast of China. There were 450 cases and 450 controls

**Table 1.** Genotype frequencies of miR-605 rs2043556 and the susceptibility of lung cancer

| Genotypes | Controls (%) | Lung cancer cases (%) | OR[a] (95% CI) | *P*-value |
|---|---|---|---|---|
| miR-605 rs2043556 | | | | |
| AA | 250 (55.6) | 252 (56.0) | 1.000 (ref) | |
| AG | 171 (38.0) | 154 (34.2) | 0.895 (0.677-1.184) | 0.437 |
| GG | 29 (6.4) | 44 (9.8) | 1.505 (0.912-2.483) | 0.110 |
| Dominant model | | | | |
| AG+GG vs. AA | | | 0.984 (0.756-1.280) | 0.902 |
| Recessive model | | | | |
| GG vs. AA+AG | | | 1.572 (0.964-2.563) | 0.070 |

OR = odds ratio, CI = confidence interval. [a]OR was adjusted by age.

in the hospital-based case-control section of this study. The patients were recruited at Shenyang Northern Hospital, The First Affiliated Hospital of China Medical University, Liaoning Cancer Hospital & Institute during February 2010 to December 2012. The inclusion criteria of patients were: (1) non-smoking females, (2) newly diagnosed with histologically confirmed lung cancer, (3) without chemotherapy or radiotherapy, (4) without other endocrine or metabolic comorbidities. Patients with previous cancer or metastasized cancer from other cancers were excluded. Meanwhile, non-smoking healthy women were collected from general population with frequency matching method according to age ± 5 years as controls. All participants were from unrelated ethnic Han Chinese. Demographic information was collected by face-to-face interviews. Clinical data were obtained from clinical records. Individual with a total of 100 cigarettes in her life-time was defined as a smoker, otherwise as a non-smoker. Ten ml venous blood was drawn for each participant.

The cases in the case-control section of this study were followed up until February 29th, 2016 in order to ensure a sufficient follow-up time. Death from lung cancer was defined as the outcome event. Death cause was collected based on data from Shenyang Center for Disease Control and Prevention (CDC) registry system for each participant. The date of death was confirmed based on Death Registry System of Shenyang Public Security Bureau. In final, there were 334 non-smoking female lung cancer patients with prognostic information.

The protocol of this study was approved by the institutional review board of China Medical University. This study was conducted in accordance with the amended Declaration of Helsinki. Informed consent was obtained from each participant or each participant's representative if direct consent could not be obtained.

*SNP identification and genotyping*

Genomic DNA samples were isolated from venous blood using the Phenol-chloroform method. SNP genotyping using Taqman1 allelic discrimination (Applied Biosystems, Foster City, CA) with primer probe set was performed by the Applied Biosystems 7500 FAST Real-Time PCR System (Foster City, CA, USA). In this study, the SNP genotyping of 10% random samples were performed a second time by two investigators separately. Genotyping results were checked to be concordant by different investigators for quality control. Moreover, negative control was included in each run of SNP genotyping.

*Statistical analysis*

Student's *t*-test was used to examine differences in age between cases and controls. Hardy-Weinberg's equilibrium (HWE) was tested by Pearson's goodness-of fit test in the control group. The odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by logistic regression to assess the relationship between SNP and lung cancer risk. Median survival time (MST) was compared by log-rank test between groups with different demographic and clinical characteristics. Kaplan-Meier method and log-rank test were performed to evaluate the relationships of OS with miRNA-SNP genotypes. Hazard ratios (HRs) and their 95% CIs for OS were estimated by univariate and multivariate Cox proportional hazards regression models. All data were analyzed by SPSS 22.0 (IBM, New York, NY, USA). A $P < 0.05$ (two-tailed) was considered statistically significant.

## Results

*Subjects characteristics*

There was no significant difference in the distribution of the age ($t = 1.220$, $P = 0.223$) between

**Table 2.** Genotype frequencies of miR-605 rs2043556 and the susceptibility of ADC and SqCC

| Genotypes | Controls | Lung ADC | | | Lung SqCC | | |
|---|---|---|---|---|---|---|---|
| | n (%) | n (%) | OR[a] (95% CI) | *P*-value | n (%) | OR[a] (95% CI) | *P*-value |
| miR-605 rs2043556 | | | | | | | |
| AA | 250 (55.6) | 170 (57.0) | 1.000 (ref) | | 48 (49.0) | 1.000 (ref) | |
| AG | 171 (38.0) | 101 (33.9) | 0.871 (0.637-1.193) | 0.390 | 38 (38.8) | 1.158 (0.725-1.849) | 0.539 |
| GG | 29 (6.4) | 27 (9.1) | 1.379 (0.788-2.414) | 0.260 | 12 (12.2) | 2.157 (1.029-4.524) | 0.042 |
| Dominant model | | | | | | | |
| AG+GG vs. AA | | | 0.945 (0.703-1.270) | 0.706 | | 1.303 (0.841-2.018) | 0.236 |
| Recessive model | | | | | | | |
| GG vs. AA+AG | | | 1.455 (0.843-2.513) | 0.178 | | 2.027 (0.995-4.131) | 0.052 |

ADC = adenocarcinomas, SqCC = squamous cell carcinomas, OR = odds ratio, CI = confidence interval. [a]OR was adjusted by age.

**Table 3.** Characteristics of the follow-up patients and OS

| Characteristics | n (%) | MST (months) | Log-rank $\chi^2$ | *P*-value |
|---|---|---|---|---|
| Age (years) | | | | |
| < 60 | 180 (53.9) | 32 | 24.314 | < 0.001 |
| ≥ 60 | 154 (46.1) | 25 | | |
| Histological type | | | | |
| ADC | 249 (74.6) | 29 | 7.939 | 0.019 |
| SqCC | 56 (16.8) | 25 | | |
| Others | 29 (8.7) | 18 | | |
| Clinical stage | | | | |
| I-II | 92 (27.5) | 31 | 2.951 | 0.086 |
| III-IV | 199 (59.6) | 28 | | |
| Chemotherapy | | | | |
| No | 19 (5.7) | 31 | 1.173 | 0.279 |
| Yes | 276 (82.6) | 28 | | |
| Surgery | | | | |
| No | 74 (22.2) | 32 | 0.936 | 0.333 |
| Yes | 221 (66.2) | 28 | | |

OS = overall survival, MST = median survival time, ADC = adenocarcinomas, SqCC = squamous cell carcinomas.

cases (56.99 ± 11.83 years) and controls (56.01 ± 12.34 years). Cases included 298 adenocarcinomas (ADC) and 98 squamous cell carcinomas (SqCC).

*SNP frequencies and the susceptibility of lung cancer*

SNP frequencies and their relationships with lung cancer susceptibility are presented in **Table 1**. The genotype frequencies of miR-605 rs2043556 in controls were conformed to HWE ($\chi^2$ = 0.001, *P* = 0.973). The minor allele frequency (MAF) of miR-605 rs2043556 was 0.254. For the distribution of miR-605 rs2043556, no significant association was observed between the SNP and the risk of lung cancer in genotype comparisons or allele comparisons after adjusting age.

To further investigate the association between miR-605 rs2043556 and lung cancer risk, stratification analysis was conducted in lung ADC and lung SqCC patients, respectively. The results are displayed in **Table 2**. After adjusting age in ADC patients, no significant association was observed between miR-605 rs2043556 and the susceptibility of lung cancer in genotype comparisons or allele comparisons. In SqCC patients, homozygous GG genotype carriers had a 2.157-fold elevated risk of lung cancer compared with homozygous AA genotype carriers (95% CI = 1.029-4.524, *P* = 0.042). The distribution of miR-605 rs2043556 was marginally different between cases and controls in recessive model. Individuals with GG genotype had a 2.027-fold increased risk of lung cancer than those carrying AA or AG genotype (95% CI = 0.995-4.131, *P* = 0.052).

*Follow-up patients' characteristics and the OS of lung cancer*

Of the patients in this study, there were 334 patients with prognostic information. The demographic and clinical characteristics of these follow-up patients as well as their effects on OS are displayed in **Table 3**. The median age of the follow-up patients was 58 years, ranging from 22 to 83 years, and median MST was 28 months. The significant differences of MST were observed in patients with different age ($\chi^2$ = 24.314, *P* < 0.001) and pathological type ($\chi^2$

**Table 4.** Genotype distributions of miR-605 rs2043556 and the OS of lung cancer

| Genotypes | n (%) | MST (months) | HR[a] (95% CI) | *P*-value |
|---|---|---|---|---|
| miR-605 rs2043556 | | | | |
| AA | 190 (56.9) | 27 | 1.000 (ref) | |
| AG | 115 (34.4) | 29 | 0.843 (0.645-1.101) | 0.210 |
| GG | 29 (8.7) | 35 | 0.632 (0.398-1.003) | 0.051 |
| Dominant model | | | | |
| AG+GG vs. AA | | | 0.806 (0.627-1.035) | 0.091 |
| Recessive model | | | | |
| GG vs. AA+AG | | | 0.675 (0.430-1.060) | 0.088 |

OS = overall survival, MST = median survival time, HR = hazard ratio, CI = confidence interval. [a]HR was adjusted by age, histological type, clinical stage, chemotherapy and surgery.

= 7.939, *P* = 0.019). However, significant MST difference was not observed in patients with other clinical characteristics.

*SNP frequencies and the OS of lung cancer*

The distribution of genotypes and their relationships with OS are summarized in **Table 4**. After adjusting age, pathological type, clinical stage, chemotherapy and surgery, only a marginal significance was observed among the patients with the GG genotype of miR-605 rs2043556, who had a longer OS of lung cancer than those with AA genotype (HR = 0.632, 95% CI = 0.398-1.003, *P* = 0.051). In stratification analyses, for patients younger than 60 years (**Table 5**), those containing the GG genotype was independently associated with lung cancer survival (HR = 0.511, 95% CI = 0.268-0.977, *P* = 0.042), who may have a longer MST. The survival curves for those patients with different genotypes of miR-605 rs2043556 are shown in **Figure 1**. Moreover, the recessive model (HR = 0.552, 95% CI = 0.302-1.010, *P* = 0.054) was marginally significant. As shown in **Table 6**, patients with ADC containing GG genotype of miR-605 rs2043556 was independently associated with lung cancer survival (HR = 0.530, 95% CI = 0.312-0.898, *P* = 0.018), who may have a longer MST. The survival curves for ADC patients with different genotypes of miR-605 rs2043556 are shown in **Figure 2**. Moreover, the recessive model of miR-605 rs2043556 (HR = 0.541, 95% CI = 0.323-0.908 *P* = 0.020) was statistically significant.

## Discussion

Alterations in miRNAs are of biological importance in the pathophysiology of cancers, including lung cancer. The present study indicated that polymorphism of miR-605 rs2043556 could be associated with the risk of lung SqCC, but not lung ADC among Chinese nonsmoking females. In addition, age and pathological type might have the potential to modify the association between miR-605 polymorphism and the OS of these patients. Specifically, for age < 60 years and ADC patients, the individuals who carried GG genotype had less death risk than those who carried AA genotype.

Human miR-605 gene is located on chromosome 10q21.1. MiR-605 is a direct transcriptional target of p53 and in turn enhances its tumor suppressor function by acting upstream and downstream of it. As a multifunctional transcription factor, p53 is encoded by a tumor suppressor gene, which is presumably the most commonly modulated gene in human cancer [22]. The protein-coding genes regulated by p53 elicit various essential roles in regulating cellular processes including induction of cell senescence and apoptosis, and inhibition of metastasis [23]. Zhou et al. developed a four-module model of the p53 network to investigate the effect of miR-605 on the cell-fate decision after ionizing radiation [24]. The amplitude of p53 pulses rises to various extents depending on miR-605 expression, and miR-605 accelerates the switching behavior of p53 levels to trigger apoptosis. In addition, miR-605 and PTEN complement each other to elevate p53 levels. Therefore, these results indicated that miR-605 can mediate the timing of apoptosis.

SNPs can change the sequence of gene products to affect the function of genes, or regulate the expression of genes. As a result, SNPs often play a crucial role in the process of tumor biology. Based on the results of a previous study, individuals carrying at least one G allele

**Table 5.** Genotype distributions of miR-605 rs2043556 and the OS of age < 60 and ≥ 60 years lung cancer patients

| Genotypes | < 60 years | | | | ≥ 60 years | | | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | MST (months) | HR[a] (95% CI) | *P*-value | n (%) | MST (months) | HR[a] (95% CI) | *P*-value |
| miR-605 rs2043556 | | | | | | | | |
| AA | 104 (57.8) | 32 | 1.000 (ref) | | 86 (55.8) | 23 | 1.000 (ref) | |
| AG | 61 (33.9) | 32 | 0.822 (0.569-1.187) | 0.296 | 54 (35.1) | 26 | 0.756 (0.505-1.132) | 0.174 |
| GG | 15 (8.3) | 37 | 0.511 (0.268-0.977) | 0.042 | 14 (9.1) | 26 | 0.613 (0.305-1.231) | 0.169 |
| Dominant model | | | | | | | | |
| AG+GG vs. AA | | | 0.783 (0.555-1.105) | 0.165 | | | 0.714 (0.486-1.047) | 0.085 |
| Recessive model | | | | | | | | |
| GG vs. AA+AG | | | 0.551 (0.292-1.037) | 0.065 | | | 0.704 (0.360-1.377) | 0.305 |

OS = overall survival, MST = median survival time, HR = hazard ratio, CI = confidence interval. [a]HR was adjusted by histological type, clinical stage, chemotherapy and surgery.

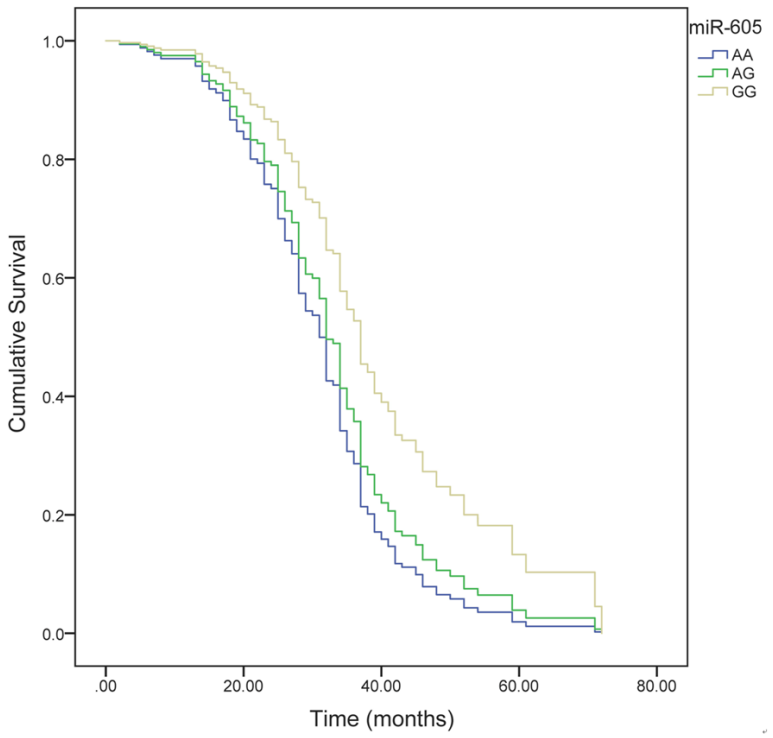


**Figure 1.** Survival curves for age < 60 years patients with different genotypes of miR-605 rs2043556. Histological type, clinical stage, chemotherapy and surgery were adjusted.

of miR-605 rs2043556 had a marginally significant higher risk of lung cancer than those carrying AA genotype in males [20]. A possible reason is that the miR-605 rs2043556 gene mutation reduces its transcriptional activity, leading to the down-regulation of miR-605 expression. For females, a consistent result was reported by Yin et al. in a Chinese nonsmoking female population that miR-605 rs2043556 had no statistically significant associations with the risk of lung cancer [8]. Consistent with the results of the two studies, the association between the miRNA-SNP and lung cancer risk was not found in this study. However, we found that in lung SqCC patients, GG genotype carriers had an elevated risk of lung cancer compared with AA genotype carriers. Also, Yin et al. showed that there were no significant association between miR-605 rs2043556 polymorphism and lung ADC, and the association in lung SqCC was not examined due to inadequate sample size [8]. As one of the major histological types of lung cancer, NSCLC is mostly comprised of lung ADC and lung SqCC. Lung ADC and lung SqCC have both unique and shared clinical and histopathological characteristics [25, 26]. There may be a significant difference in the somatic drivers of carcinogenesis between lung ADC and lung SqCC. Only 6 genes, p53, RB1, ARID1A, CDKN2A, PIK3CA, and NF1, were significantly mutated in both lung ADC and lung SqCC, and 3 genes, p53, CDKN2A, and PIK3CA were mutated more frequently in lung SqCC [27]. As a result, as a member of the p53 regulatory network, miR-

**Table 6.** Genotype distributions of miR-605 rs2043556 and the OS of ADC and SqCC

| Genotypes | ADC | | | | SqCC | | | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | MST (months) | HR[a] (95% CI) | *P*-value | n (%) | MST (months) | HR[a] (95% CI) | *P*-value |
| miR-605 rs2043556 | | | | | | | | |
| AA | 139 (55.8) | 28 | 1.000 (ref) | | 31 (55.4) | 23 | 1.000 (ref) | |
| AG | 87 (34.9) | 29 | 0.944 (0.702-1.268) | 0.701 | 19 (33.9) | 26 | 0.718 (0.340-1.518) | 0.386 |
| GG | 23 (9.2) | 37 | 0.530 (0.312-0.898) | 0.018 | 6 (10.7) | 25 | 0.908 (0.315-2.619) | 0.859 |
| Dominant model | | | | | | | | |
| AG+GG vs. AA | | | 0.841 (0.637-1.112) | 0.225 | | | 0.759 (0.378-1.522) | 0.437 |
| Recessive model | | | | | | | | |
| GG vs. AA+AG | | | 0.541 (0.323-0.908) | 0.020 | | | 1.077 (0.401-2.893) | 0.882 |

OS = overall survival, ADC = adenocarcinomas, SqCC = squamous cell carcinomas, MST = median survival time, HR = hazard ratio, CI = confidence interval. [a]HR was adjusted by age, clinical stage, chemotherapy and surgery.

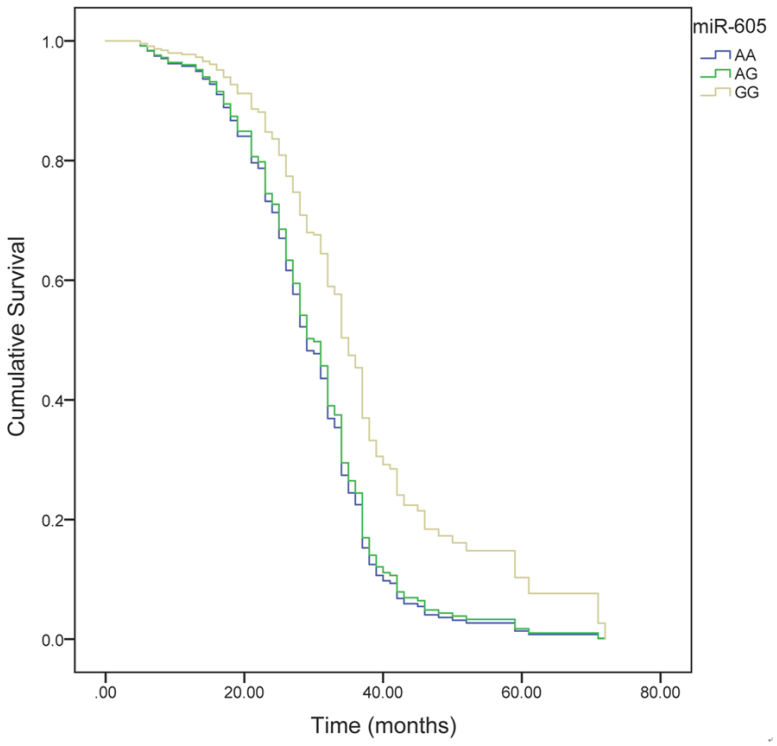


**Figure 2.** Survival curves for ADC patients with different genotypes of miR-605 rs2043556. Age, clinical stage, chemotherapy and surgery were adjusted.

605 may play a more important role in the development of lung SqCC than in lung ADC. In the studies focused on some other cancer types, a HuGE meta-analysis executed by Chen et al. showed that the miR-605 rs2043556 A allele predicted a decreased risk of breast cancer among Asians, while not Caucasians [28]. With a novel statistic, cross phenotype meta-analysis (CPMA), Hu et al. found that the allele C of miR-605 rs2043556 was associated with an increased risk of developing bladder cancer in Caucasians [29]. Id Said and Malkin found the variant G-allele of miR-605 was associated with a 10-year acceleration in the mean age of Li-Fraumeni syndrome onset and caused a 2.6-fold reduction in the processing levels of its host miRNA [30]. In Chinese cancer patients, Zhang et al. also found a marginally significant association between miR-605 rs2043556 and colorectal cancer risk in males [31], and no significant association between miR-605 rs2043556 genotypes and the risks of gastric cancer and breast cancer was detected [31, 32]. However, on the contrary, Miao et al. identified a significant linkage between the miR-605 rs2043556 G allele and the decreased risk of oral squamous cell carcinoma (OSCC) in a Chinese population [33].

Previous studies have shown that miR-605 can also affect the progression, treatment outcome, and prognosis of different types of cancer. Parasramka et al. showed that garcinol could induce PaCa cell growth arrest and apoptosis in vitro. In a subsequent study, they reported that garcinol treatment resulted in

approximately 1.81-fold increase in miR-605 expression [34]. Ramaiah et al. showed that treatment of neuroblastoma IMR-32 cells with anthranilamide-pyrazolo[1,5-a]pyrimidine conjugates caused 3.5-fold increase in the expression of miR-605 revealing a direct role of the miRNA in regulating p53 activity in MYCN positive cells in response to chemical treatment [35]. Sun et al. found that the level of miR-605 was considerably higher with neoadjuvant chemotherapy (NAC) relative to without NAC in patients with cervical cancer. As an anti-cancer drug, cisplatin was found to be the main component that caused increases in p53 protein levels and miR-605 miRNA levels, and decreases in Mdm2 and E2F1 protein levels [36]. Therefore, miR-605 is involved in the therapeutic effects of these anticancer drugs. In addition, Alhasan et al. suggested circulating miR-605 could be identified as a useful miRNA biomarker for differentiating indolent and aggressive forms of prostate cancer [37]. Fang et al. reported that miR-605 rs2043556 was significantly related to the severe hepatotoxicity of lung cancer in dominant model, which revealed that the miR-605 polymorphism may serve as a predictive tool for toxicity evaluation of platinum-based chemotherapy in lung cancer patients [21]. Huang et al. reported that miR605 rs2043556 was associated with biochemical recurrence after radical prostatectomy in localized prostate cancer [38]. Nevertheless, research on the relationship between miR-605 rs2043556 and lung cancer prognosis has not been found yet. In this study, we found that the GG genotype of miR-605 rs2043556 could improve the OS of age < 60 years and ADC patients in Chinese non-smoking females. Age and pathological type might have the potential to modify the association between miR-605 polymorphism and lung cancer prognosis. In addition to the effect of SNPs on miRNA level, the genome-wide assessment of miRNA expression revealed that the majority of miRNAs decreased in abundance with age. The finding suggests that miRNAs have the potential to be the diagnostic and prognostic indicators of age-related diseases, including cancer [39]. To our best knowledge, the study was the first to explore the relationship between miR-605 rs2043556 and the prognosis of lung cancer.

Several limitations in this study should be elucidated. Firstly, this is a hospital-based study, which may have resulted in selection bias for the overall population. This was a multi-center study, enhancing the reliability of the results. Secondly, the sample size was not large. Thus, the statistical power of this study could be limited, especially in stratification analysis. A large sample size should be need in a further study. Thirdly, the present study was only conducted in a province of northeast China. Thus, a more diversified population is required to verify the results in the future. In addition, functional assessment of the genetic variants identified in this study should be carried out through in vitro and in vivo experiment. It will provide a powerful answer to the relationships of the miRNA-SNP and cancer risk and prognosis.

## Conclusion

MiR-605 rs2043556 polymorphism could be associated with the risk of SqCC in northeast Chinese non-smoking females. Age and pathological type might have the potential to modify the association between miR-605 rs2043556 and the OS of non-smoking female lung cancer patients. The results are still necessary to be confirmed by larger prospective studies.

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## Disclosure of conflict of interest

None.

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