Factors leading to the risk of stroke mortality: a cross-sectional study with lung cancer patient-based large sample
Lei Chen¹,*, Xinmin Zhao² and Sheng Wang³,*

To identify the risk factors for stroke mortality among lung cancer patients on the basis of the Surveillance, Epidemiology, and End Results (SEER) database. The clinical data of lung cancer patients diagnosed between 2004 and 2016 were collected in the SEER database. The stroke mortality rate in lung cancer patients was compared with the general population using standardized mortality ratios (SMRs). Cox proportional hazard model was applied to analyze the risk factors for stroke mortality among lung cancer patients. Among 82 454 patients, 4821 (5.85%) died of stroke. The stroke mortality rate in lung cancer patients significantly increased compared with the general population (SMR: 1.73, 95% confidence interval (CI), 1.69–1.78). Differences were pronounced between the patients with stroke death and those without regarding all the basic characteristics (P<0.001). Multivariate COX analysis showed that the risk factors for stroke mortality among lung cancer patients included increasing age, males, the black, grade II–III, distant metastasis and higher American Joint Committee on Cancer (AJCC) TNM stage, whereas adenocarcinoma was found to be a protective factor compared with squamous cell carcinoma. Increasing age, males, the black, grade II–III, distant metastasis and higher TNM stage are associated with an increased risk of stroke mortality among lung cancer patients, but adenocarcinoma with a lowered risk. European Journal of Cancer Prevention 31: 14–18 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: lung cancer, risk factor, SEER database, standardized mortality ratio, stroke

Introduction
Over the past decade, the development of lung cancer in epidemiology and its prevention have proceeded to some extent due to changes in cancer control, treatment options and understanding of the genetics. Despite these advances, lung cancer continues to be the leading cause of cancer death worldwide (Bade and Dela Cruz 2020). In 2018, 2.09 million new cases of lung cancer and 1.76 million deaths were estimated by GLOBOCAN, higher than that reported in 2012, 1.8 million new cases and 1.6 million deaths (Torre et al. 2015; Bray et al. 2018). Epidemiologic data show that various factors, such as tobacco use, radiation exposure, indoor and outdoor air pollution, hereditary susceptibility and unhealthy diet, contribute to increasing lung cancer incidence (Mao et al. 2016). Although treatment options, outcomes and disease understanding for lung cancer are improving, the survival remains low.

Cerebrovascular disease is thought to be the second most common central nervous system complication in cancer patients (Chen et al. 2011). Once stroke occurs in cancer patients, the patients’ neurological outcomes will deteriorate significantly, and the prognosis tends to be poor (Zhang et al. 2006; Stefan et al. 2009). The study showed that cancer patients were prone to develop stroke, particularly within 1 year of cancer proliferation (Selvik et al. 2015). Cancer induces stroke possibly through several mechanisms, including nonbacterial thrombotic endocarditis, hypercoagulability, direct tumor compression of blood vessels and therapies (Dearborn et al. 2014). By evaluating the incidence of stroke in cancer patients, Cestari et al. (2004) found that lung cancer was the most common primary tumor, accounting for 30% of cases. There is another study showing an association of lung cancer with a higher risk of subsequent stroke, especially within 6 months after cancer diagnosis (Chen et al. 2011).

Until now, the studies on the risk factors for stroke mortality in cancer patients are rare. This study was performed to identify the risk factors for stroke mortality among lung cancer patients based on the Surveillance, Epidemiology, and End Results (SEER) database, aiming at early prevention and treatment of patients at high risk of stroke to improve the prognosis.
Methods

Data sources
Patients were collected from the SEER program, a network of population-based cancer registries in the United States. It provides information on cancer statistics, including incidence, survival and surgical treatment, aiming at decreasing the cancer burden among the US population (National Cancer Institute XXXX). The data accessed from the SEER database include patients' demographic characteristics, primary tumor site, stage at diagnosis, tumor morphology, first cancer treatment and follow-up for vital status. The SEER 18 registry system that covers approximately 27.8% of all American population consists of 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG). Information was recorded including age at diagnosis, sex, race, laterality, histology, year of diagnosis, grade, SEER stage, American Joint Committee on Cancer (AJCC) T, N, M, as well as tumor size.

The approval from the Institutional Review Board of Ningbo First Hospital was not required because the data obtained from the SEER database were freely available.

Study population and study parameters

All patients with lung cancer diagnosis were involved. The diagnosis of lung cancer was confirmed through the International Classification of Diseases-Oncology 3 (ICD-O-3) site codes C34.0-C34.9. Inclusion criteria: (1) lung cancer diagnosed between 2004 and 2016; (2) age ≥40 years and (3) primary site codes C34.0-C34.9. Exclusion criteria: (1) ICD-O-3 histological codes 9050–9055, 9140 and 9590–9992; (2) patients only diagnosed by autopsy or death certificates and (3) incomplete information. Cases aged <40 years were excluded due to the low incidence of lung cancer in this age group (available at http://ghdx.healthdata.org/ghd-results-tool).

The information below was acquired from the SEER database, including age at diagnosis (40–49, 50–59, 60–69, 70–79 and ≥80 years), sex, race (white, black and others), laterality (unilateral and bilateral), histological types (squamous cell, small cell, adenocarcinoma and other nonsmall cell lung cancer), year of diagnosis (2004–2006, 2007–2009, 2010–2012 and 2013–2015), SEER stage (local, regional and distant), AJCC T, N and M as well as tumor size (<5 and ≥5 cm).

According to death certificates, mortality codes in the SEER database were assigned. Generally, the diagnosis of stroke was made as central nervous system infarction due to ischemia on the basis of clinical evidence of permanent injury or neuroimaging and neuropathological evidence. In our study, however, patients were thought to die of stroke when the following death certificates existed, including cerebrovascular accident, ICD-9 code 434.11, or ICD-10 code I63.9. SEER data for stroke as the cause of death were collected as the primary endpoint.

Statistical analysis

Data were analyzed using R software (The R Foundation for Statistical Computing, Vienna, Austria). Enumeration data were compared by the χ² test or Fisher’s exact test and manifested with N (%). The stroke mortality of lung cancer patients in the SEER database was compared with that of the US general population using standardized mortality ratios (SMRs). SMRs were defined as the ratio of total number of the observed death cases/total number of the expected death cases (The source of calculation was available at https://seer.cancer.gov/stdpopulations/stdpop.singleages.html). COX proportional hazard model was used to analyze the risk factors for stroke mortality among lung cancer patients. P<0.05 was considered statistically significant.

Results

Characteristics of study population

There were 147,256 lung cancer patients aged ≥40 years and diagnosed between 2004 and 2016. Their ICD-O-3 site codes were C34.0-C34.9. After ICD-O-3 histological codes 9050–9055, 9140 and 9590–9992 were excluded, 132,793 cases were left. Finally, 82,454 cases were included into the study when autopsy or death certificate cases and those with incomplete information, such as survival months, SEER stage, tumor size, AJCC T, N and M, were excluded. Among these patients included, 4821 cases (5.85%) died of stroke, whereas 77,633 did not. The characteristics of included patients were shown in Table 1.

As shown in Table 1, the stroke mortality rate in lung cancer patients significantly increased compared with the US general population [SMR: 1.73; 95% confidential interval (95% CI), 1.69–1.78]. All subgroup analyses exhibited the stroke mortality rate in lung cancer patients was higher than that in the general population. The stroke mortality rates were different among different age groups. The SMR was up to 3.58 in patients aged 40–49 years (95% CI, 3.03–4.20). Between the patients who died of stroke and those without, the differences were pronounced in all basic characteristics (P<0.001), including age, sex, laterality, race, histological types, year of diagnosis, SEER stage, AJCC T, N and M, as well as tumor size.

Analysis of the risk factors for stroke mortality among lung cancer patients

The influencing factors for stroke mortality among lung cancer patients were analyzed using the COX proportional hazard model, as shown in Table 2. The results showed that compared with those aged 40–49 years, the patients aged 50–59 years (hazard ratio, 1.809; 95% CI, 1.209–2.707), 60–69 years (hazard ratio, 3.534; 95% CI, 2.410–5.181), 70–79 years (hazard ratio, 9.96; 95% CI, 6.826–14.534) and ≥80 years (hazard ratio, 27.196; 95%
CI, 18.579–39.811) had a significantly increased risk of stroke mortality; the risk of stroke mortality in males was higher than that in females (hazard ratio, 1.177; 95% CI, 1.082–1.282); the black people had an increased risk of stroke mortality than the white people (hazard ratio, 1.37; 95% CI, 1.198–1.567); the risk of stroke mortality in patients with adenocarcinoma was lower than those with squamous cell carcinoma (hazard ratio, 0.843; 95% CI, 0.754–0.942); patients with grade II (hazard ratio, 1.237; 95% CI, 1.046–1.461) and III (hazard ratio, 1.494; 95% CI, 1.260–1.772) had a higher risk of stroke mortality by comparison to grade I; the risk of stroke mortality in patient with distant metastasis was greater than those with local metastasis (hazard ratio, 1.422; 95% CI, 1.13–1.789). Additionally, compared with T1, N0 and M0 patients, those with T2-T4, N2-NX and D M1-MX, had a higher risk of stroke mortality; see Table 2.

### Discussion

In this population-based cohort study, 82454 out of 147 256 lung cancer patients were eligible, among whom 4821 cases died of stroke. It can be observed that the risk of stroke mortality in lung cancer patients significantly increased compared with the general population. Multivariate analysis exhibited that increasing age, males, the black, grade II–III, distant metastasis and higher TNM stage were associated with a greater risk of stroke mortality among lung cancer patients, but adenocarcinoma was related to a reduced risk of stroke mortality.

At present, the death of most cancer patients results from noncancer causes (Zaorsky et al. 2017). Our results suggested that the stroke mortality rate of lung cancer patients was significantly higher than that in the general population, which might be attributed to the fact that
cancer increased the risk of stroke (Wei et al. 2019). There are different mechanisms of stroke between cancer and noncancer patients. A multicenter study in Korea indicated that conventional mechanisms, such as atherosclerotic and cardioembolic causes, may be related to 60% of stroke events in cancer patients; cryptogenic mechanisms, such as cancer-related causes, were associated with the remaining 40%, but only with 18% of stroke events in noncancer patients (Kim et al. 2010; Chen et al. 2011).

In most studies, the association of stroke with cancer is highlighted by tumor-related causes, including coagulation disorders, embolism, brain infection and metastasis, as well as treatment-induced adverse reactions (Seok et al. 2010; Bang et al. 2011; Dardiotis et al. 2019). All these have been clearly embodied in lung cancer patients (Selvik et al. 2015; Xie et al. 2016; Yoon et al. 2019).

In this study, it was found that the increased age was a significant risk factor for stroke mortality, supported by a previous study that the prevalence of any kinds of vascular diseases increased distinctly with advanced age (Savji et al. 2013). Compared with women, men showed a greater risk of stroke mortality. A nationwide population-based survey reported that the age-specific mortality rate of stroke in males aged ≥60 years was markedly higher than that in females (Wang et al. 2017). Females are seemingly protected from cerebrovascular diseases even after menopause, probably through hormone-independent and hormone-dependent mechanisms (Herson and Hurn 2010). Studies have affirmed that estrogens are not only conducive to improving the vasculature by ameliorating endothelial dysfunction, reinforcing vasodilatation and promoting blood flow after vascular occlusion, but also have neuroprotective effects in several brain cell types, such as microglia, neurons, oligodendrocytes and astrocytes, thus accelerating the recovery from brain injury (Liu et al. 2009; Katsiki et al. 2011). Our results also indicated that lung adenocarcinoma was a protective factor for stroke mortality relative to squamous cell lung carcinoma. Previous studies have suggested that among lung cancer patients, adenocarcinoma was more common in women than men, and squamous cell carcinoma often occurs in men (Wisnivesky and Halm 2007; Sereno et al. 2012; Welcker 2015). Additionally, in our study, the black participants showed an increased risk of stroke mortality than the white participants, supported by the results of the study made by Marron et al. (2018). This racial difference in mortality may be explained by pervasive and longstanding socioeconomic and health disadvantages in the black people (Pathak 2018).

There were findings in our study showing that higher TNM stage and distant metastasis were associated with a higher risk of stroke mortality in lung cancer patients, which might be ascribed to malignant degrees of the tumor and use of chemotherapy and radiation therapy. The higher the malignant degree, the poorer the patient’s prognosis. Although chemotherapy only appears in the setting of advanced malignancies, it is usually considered as the cause of cerebral venous or arterial thrombosis. It can result in stroke through endothelial toxicity, coagulation and hemostasis disorders, and can also induce the stroke manifestation (Saynak et al. 2008; Zembower et al. 2010). Studies have affirmed that estrogens are not only conducive to improving the vasculature by ameliorating endothelial dysfunction, reinforcing vasodilatation and promoting blood flow after vascular occlusion, but also have neuroprotective effects in several brain cell types, such as microglia, neurons, oligodendrocytes and astrocytes, thus accelerating the recovery from brain injury (Liu et al. 2009; Katsiki et al. 2011). Our results also indicated that lung adenocarcinoma was a protective factor for stroke mortality relative to squamous cell lung carcinoma. Previous studies have suggested that among lung cancer patients, adenocarcinoma was more common in women than men, and squamous cell carcinoma often occurs in men (Wisnivesky and Halm 2007; Sereno et al. 2012; Welcker 2015). Additionally, in our study, the black participants showed an increased risk of stroke mortality than the white participants, supported by the results of the study made by Marron et al. (2018). This racial difference in mortality may be explained by pervasive and longstanding socioeconomic and health disadvantages in the black people (Pathak 2018).

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after radiation, and the subsequent occlusion or stenosis was more extensive in the radiation portal (Rogers 2003, Dardiotis et al. 2019).

This was the first population-based, large-scale study to determine the risk factors for stroke mortality among lung cancer patients. The death-related information was credible because the follow-up data from the SEER database were relatively complete. Moreover, compared with single-center studies, our results might be more generalizable. However, some limitations remained to be concerned. First, the SEER database had lack of information on behavioral factors, such as smoking and commodities, that may increase the risk of stroke, such as hypertension and diabetes mellitus. Second, information on stroke subtypes, biomarkers (e.g., D-dimer levels and prothrombin time) and treatment methods was absent. Notably, there are no nationally representative databases to data involving the above-mentioned covariates. Despite these limitations, our findings were valuable in better understating the risk of stroke mortality among lung cancer patients.

Conclusions
Our study suggests that lung cancer patients are at a high risk of stroke mortality; increasing age, males, the black, grade II–III, distant metastasis and higher TNM stage are associated with an increased risk of stroke mortality among lung cancer patients, but adenocarcinoma is related to a reduced risk.

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Conflicts of interest
There are no conflicts of interest.

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