

Comorbidities and mortality risk among extensive-stage small-cell lung cancer patients in mainland China: impacts of hypertension, type 2 diabetes mellitus, and chronic hepatitis B virus infection

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The present study investigated the impact of major comorbidities, including hypertension, type 2 diabetes mellitus (T2DM), and chronic hepatitis B virus (HBV) infection, on the progression-free survival (PFS) and overall survival (OS) of extensive-stage small-cell lung cancer (ES-SCLC) patients in China. Patients having a pathologic diagnosis of ES-SCLC between 2009 and 2017 were enrolled and grouped according to their specific comorbidities. The PFS and OS for each group were evaluated using the Kaplan–Meier method and Cox proportional hazard models. In total, 632 patients were analyzed. The median PFS (mPFS) of these patients was 9 months [95% confidence interval (CI), 6–12 months]. The mPFS of patients without hypertension or T2DM was 9 months; conversely, it was significantly reduced for patients with hypertension [7 months ($P < 0.0001$)] or T2DM [5 months ($P < 0.0001$)]. However, mPFS was not significantly different between patients with and without HBV infection ($P = 0.2936$). A similar trend was observed for OS as well. Further multivariate analyses showed that the OS of patients with hypertension [hazard ratio (HR), 1.344; 95% CI, 1.073–1.683; $P = 0.010$] or T2DM (HR,

1.455; 95% CI, 1.134–1.868; $P = 0.003$) was significantly shorter than that of patients without these comorbidities. Accordingly, mortality risk was the highest in patients with concurrent hypertension and T2DM (HR, 1.665; 95% CI, 1.037–2.672; $P = 0.00058$). Our study found that hypertension and T2DM may be associated with a worse prognosis in ES-SCLC patients. Considerable attention should be paid to the accompanying anti-comorbidity therapies available for patients with ES-SCLC. *Anti-Cancer Drugs* 33: 80–90 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

Anti-Cancer Drugs 2022, 33:80–90

Keywords: extensive-stage small-cell lung cancer, hepatitis B virus infection, hypertension, mortality risk, type 2 diabetes

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Received 8 June 2021 Revised form accepted 8 June 2021

Introduction

Small-cell lung cancer (SCLC) is among the most malignant cancers and affects approximately 180 000 individuals annually worldwide. Despite promising initial responses to first-line chemoradiotherapy, almost all patients with extensive-stage SCLC (ES-SCLC) virtually experience tumor progression [1]. In these patients, the median overall survival (OS) is 10–12 months, and the 5-year OS rate is <10% [2,3]. This poor prognosis of patients with ES-SCLC is mainly attributed to frequent relapses and metastasis [4]. Moreover, patients with SCLC are often diagnosed as having other chronic diseases. The presence of comorbidities in such patients is associated with not only old age but also sex and lifestyle habits. However, whether comorbidities can affect the prognosis of patients with ES-SCLC still remains unclear [5–7].

Numerous different associations between comorbidities and cancer have been reported. Although conclusive evidence is lacking, preexisting comorbidities have been associated with higher mortality risk in different cancer types, including lung cancer [8]. Preexisting comorbidities in patients with cancer are associated with age, sex, and socioeconomic status [9,10]. Hypertension extensively contributes to the global disease burden and global mortality and accounts for approximately 9.4 million deaths each year; furthermore, the number of diagnosed cases of hypertension in China was approximately 244.5 million in 2010 [11]. Type 2 diabetes mellitus (T2DM) is a major global health problem. It is associated with significant mortality and morbidity. The number of T2DM patients was 240 million in 2007 and is estimated to increase to 380 million by 2025 and 423 million by 2030 [12]. Additionally, China has a relatively high rate of hepatitis B virus (HBV) infections, with the prevalence of hepatitis B surface antigen (HBsAg) in the entire estimated population being 6.1%, and there were approximately 90 million chronic HBV infections nationwide in 2017 [13–15]. Furthermore,

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the prevalence of comorbidities is expected to increase over time because of lifestyle changes and a greater proportion of elderly patients having the disease owing to increased life expectancy. Monitoring for comorbidities will make both clinicians and researchers better aware of the effects of these diseases.

To our knowledge, few studies have reported the effects of hypertension, T2DM, and chronic HBV infections on the mortality risk of patients with ES-SCLC [16–18]. Herein, we have assessed the possible impacts of major comorbidities (hypertension, T2DM, and chronic HBV infection) on the prognoses of Chinese patients having ES-SCLC.

Materials and methods

Patient and study design

Herein, we reviewed patients from West China Hospital, Sichuan University, identified as having histologically confirmed SCLC between January 2009 and December 2018. The inclusion criteria were the following: (1) patients with ES-SCLC who were diagnosed with hypertension or T2DM; (2) patients with ES-SCLC who tested positive for serum HBsAg; and (3) patients with ES-SCLC with complete clinical data and follow-up information. Patients who met the following criteria were

Table 1. Baseline characteristics of the present study (n = 632)

Baseline characteristics	Number of patients (%)
Age	
≤60 years	324 (51.3%)
>60 years	308 (48.7%)
Sex	
Females	131 (20.7%)
Males	501 (79.3%)
Smoking status	
No	184 (29.1%)
Yes	448 (70.9%)
Performance status	
ECOG 0–2	614 (97.2%)
ECOG ≥ 3	18 (2.8%)
Brain metastases	
No	511 (80.9%)
Yes	121 (19.1%)
Hepatic metastasis	
No	510 (80.7%)
Yes	122 (19.3%)
Hypertension	
No	537 (85.0%)
Yes	95 (15.0%)
T2DM	
No	556 (88.0%)
Yes	76 (12.0%)
Anti-diabetic medication	
Insulin	539 (85.3%)
Other ADDs	93 (14.7%)
HBV infection	
No	589 (93.2%)
Yes	43 (6.8%)
Pretreatment HBV DNA copy number	
Normal	38 (among 43 patients, 88.4%)
Abnormal	5 (among 43 patients, 11.6%)
Consolidative thoracic radiotherapy	
No	175 (27.7%)
Yes	457 (72.3%)

ADD, anti-diabetic drug; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; T2DM, type 2 diabetes mellitus.

excluded: (1) patients with a history of other types of cancer and (2) those with acute serious and potentially fatal diseases. This retrospective study received approval from the West China Hospital Research Ethics Board.

Diagnostic criteria of hypertension, type 2 diabetes mellitus, and hepatitis B virus infection

Hypertension

The diagnostic criteria for hypertension were as follows: SBP ≥140 mmHg, DBP ≥90 mmHg, or both [19].

Type 2 diabetes mellitus

T2DM is characterized by hyperglycemia, insulin deficiency, and insulin resistance. A patient is said to have a confirmed diagnosis of T2DM based on one of the following findings which must be confirmed on the subsequent day by repeated measurements and performing the same tests: (1) fasting plasma glucose level, ≥7.0 mmol/L; (2) glycosylated hemoglobin level, ≥6.5%; (3) 2-hour postprandial plasma glucose level on an oral glucose tolerance test, ≥11.1 mmol/L; and (4) random plasma glucose level in the presence of symptoms, ≥11.1 mmol/L [20]. Patients on medication for T2DM and those with a similar medication history were also assessed for having T2DM.

Hepatitis B virus infection

Enzyme-linked immunosorbent assays for serological HBsAg, hepatitis B e-antigen, hepatitis B core antibody (anti-HBc), hepatitis B e-antibody, and hepatitis B surface antibody were performed for each patient before administering any anti-tumor treatment. Chronic HBV infection was defined by HBsAg seropositivity [21]. Patients were excluded if a hepatitis A, C, D, or E infection was confirmed by a serum test.

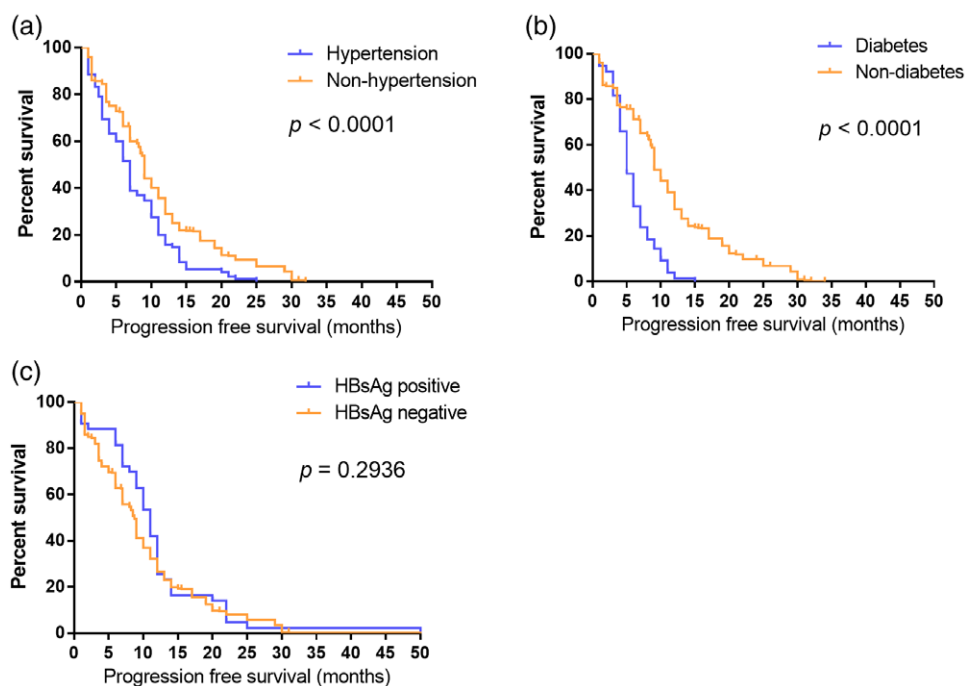
Treatments

According to the recommendations of the National Comprehensive Cancer Network (NCCN) guidelines for SCLC [22], all patients with ES-SCLC received first-line standard treatment, including etoposide/carboplatin or etoposide/cisplatin. The second-line treatment in such patients included docetaxel or irinotecan for preventing tumor progression.

Palliative thoracic radiotherapy (30 Gy/10 fractions) was performed if patients exhibited symptoms like hemoptysis, polypnea, and chest pain. Consolidative thoracic radiotherapy (30 Gy/10 fractions or 50 Gy/25 fractions) was performed if patients had reached at least partial response [23]. Prophylactic cranial irradiation (25 Gy/10 fractions) was considered when patients had at least complete remission at the distant level.

For this study, none of the patients received durvalumab, atezolizumab, nivolumab, or pembrolizumab because the Chinese Food and Drug Administration had not approved these immunotherapy drugs for SCLC at the time of this study.

Fig. 1



Progression-free survival (PFS) of extensive-stage small-cell lung cancer (ES-SCLC) patients with or without hypertension, T2DM, and HBV infection. (a) The median PFS was significantly longer in patients without hypertension than in those with hypertension (9 vs. 7 months; $P < 0.0001$). (b) The median PFS was significantly longer in patients without T2DM than in those with T2DM (9 vs. 5 months; $P < 0.0001$). (c) There was no significant difference in PFS between patients with or without HBV infection ($P = 0.2936$). HBV, hepatitis B virus; T2DM, type 2 diabetes mellitus.

According to the comorbidities that were confirmed before anti-tumor therapy initiation, all patients were divided into hypertension and non-hypertension, T2DM and non-T2DM, and HBV infection and non-HBV infection groups. We obtained data on clinicopathological parameters of the patients, including sex, age, smoking history, performance status, brain metastases, and hepatic metastases.

Follow-up

Herein, OS was defined as the survival time between the initial diagnosis and the last follow-up or cancer-related death. It was recorded via a clinical follow-up visit or a telephone interview. All patients were followed up until death or December 2017.

Statistical analysis

The SPSS 18.0 statistical software (SPSS, Chicago, Illinois, USA) was used for analyses. The Kaplan-Meier method was used to assess clinical outcomes and the log-rank test to determine statistical significance. Cox proportional hazards regression models were used to elucidate the relationship between progression-free survival (PFS)/OS and ES-SCLC patients with comorbidities. First, univariate Cox regression analysis was performed to estimate the relationship between each potential confounding factor and clinical outcomes (e.g. age, sex, smoking index,

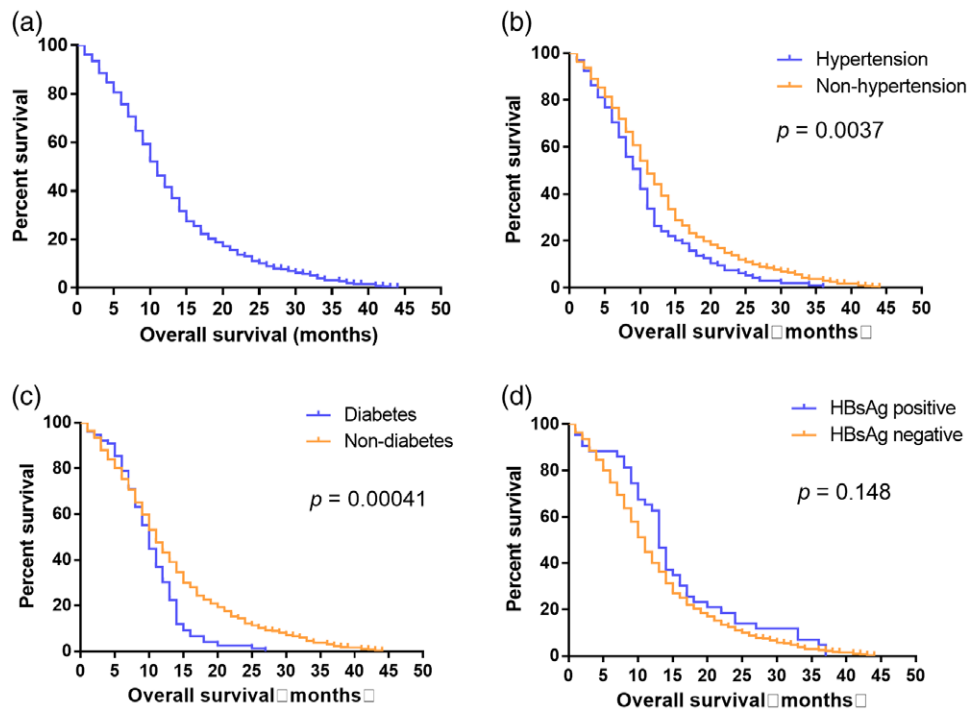
performance status, brain metastases, and hepatic metastasis). Then, separate univariate Cox regression models were used to assess the impact of each covariate on the strength of the association between ES-SCLC patients with comorbidities and clinical outcomes. Findings of the Cox regression models were presented as hazard ratios (HRs) with a 95% confidence interval (CI). Next, multivariate analysis was used to elucidate significant independent prognostic factors associated with OS. Statistically significant difference was defined as p values (two-sided) < 0.05 .

Results

Patient characteristics

We performed a retrospective observational study of 1345 patients with a pathological diagnosis of SCLC between January 2009 and December 2017 at West China Hospital, Sichuan University. Overall, we excluded 713 patients who had limited-stage SCLC and enrolled 632 patients with ES-SCLC in the present study. Clinicopathologic characteristics of the enrolled patients are summarized in Table 1. The enrolled patients (age, 23–74 years) comprised 501 men (79.3%) and 131 women (20.7%). Most patients ($n = 614$; 97.2%) had low-grade performance statuses [Eastern Cooperative Oncology Group (ECOG) 0–2]. The electronic records confirmed that 95 patients (15.0%) had hypertension, 76 patients (12.0%) had

Fig. 2



Overall survival (OS) of ES-SCLC patients with or without hypertension, T2DM, and HBV infection. (a) The median OS of 632 ES-SCLC patients was 12.9 months (95% CI, 12.2–13.6 months). (b) The median OS was significantly longer in patients without hypertension than in those with hypertension (13.3 vs. 10.8 months; $P = 0.0037$). (c) The median OS was significantly longer in patients without T2DM than in patients with T2DM (13.2 vs. 10.2 months; $P = 0.00041$). (d) There was no significant difference in OS between patients with or without HBV infection ($P = 0.148$). CI, confidence interval; ES-SCLC, extensive-stage small-cell lung cancer; HBV, hepatitis B virus; T2DM, type 2 diabetes mellitus.

T2DM, and 43 patients (6.8%) had chronic HBV infection. The median follow-up duration was 36.0 months (range, 22.0–50.0 months).

As shown in Fig. 1, the median PFS was 9 months (95% CI, 6–12 months) in all patients. The PFS was significantly shorter in patients with hypertension (median PFS, 7 months; 95% CI, 6–8 months) or T2DM (median PFS, 5 months; 95% CI, 3–7 months) than in patients without hypertension (median PFS, 9 months; 95% CI, 7–11 months; $P < 0.0001$; Fig. 1a) or T2DM (median PFS, 9 months; 95% CI 5–13 months; $P < 0.0001$; Fig. 1b). No significant difference ($P = 0.2936$) between the PFS of ES-SCLC patients with chronic HBV infection (median PFS, 8.7 months; 95% CI, 6.5–10.9 months) and without chronic HBV infection (median PFS, 11 months; 95% CI, 8–14 months) was noted (Fig. 1c).

As shown in Fig. 2a, the median OS of the whole population was 12.9 months (95% CI, 12.2–13.6 months). The OS of patients with hypertension (median OS, 10.8 months; 95% CI, 9.3–12.2 months) or T2DM (median OS, 10.2 months; 95% CI, 9.1–11.3 months) was significantly shorter than that of patients without hypertension (median OS, 13.3 months; 95% CI, 12.5–14.1 months; $P = 0.0037$; Fig. 2b) or T2DM

(median OS, 13.2 months; 95% CI, 12.5–14.0 months; $P = 0.0004$; Fig. 2c). However, the OS of ES-SCLC patients with chronic HBV infection (median OS, 15.1 months; 95% CI, 12.3–18.0 months) and without chronic HBV infection (median OS, 12.7 months; 95% CI, 12.0–13.5 months) did not significantly differ ($P = 0.148$; Fig. 2d).

Univariate and multivariate analyses

Univariate analysis indicated that hypertension was statistically significantly associated with increased mortality risk in patients with ES-SCLC (HR, 1.363; 95% CI, 1.094–1.698; $P = 0.006$; Table 2). Furthermore, T2DM was identified as a negative predictor for the survival of patients with ES-SCLC (HR, 1.522; 95% CI, 1.192–1.943; $P = 0.001$). There was no significant association between chronic HBV infection and other analyzed clinical characteristics in terms of the OS of the studied cohort (all $P > 0.05$). A multivariate analysis of OS revealed that the mortality risk of ES-SCLC patients with hypertension was higher than that of patients without hypertension by 34.4% (HR, 1.344; 95% CI, 1.073–1.683; $P = 0.010$). Notably, in the studied samples, T2DM was another unfavorable prognostic factor for OS (HR, 1.455; 95% CI, 1.134–1.868; $P = 0.003$).

Table 2. Univariate analysis of overall survival in extensive-stage small-cell lung cancer patients with or without type 2 diabetes mellitus, hypertension, and hepatitis B virus infection

Variable	Median OS (95% CI)	Univariate analysis		Multivariate analysis	
		<i>P</i> value	HR (95% CI)	<i>P</i> value	
Age		0.370			
≤60 years	13.219 (12.219–14.219)		1.014 (0.862–1.192)		0.867
>60 years	12.555 (11.588–13.522)				
Sex		0.451		1.036 (0.765–1.404)	0.819
Females	13.427 (11.771–15.084)				
Males	12.756 (11.992–13.521)				
Smoking history		0.547		1.033 (0.788–1.355)	0.812
No	13.125 (11.755–14.495)				
Yes	12.801 (11.995–13.607)				
Performance status		0.786		1.069 (0.663–1.722)	0.784
ECOG 0–2	12.902 (12.192–13.612)				
ECOG ≥ 3	12.667 (9.228–16.106)				
Brain metastases		0.629		1.088 (0.888–1.332)	0.417
No	12.963 (12.180–13.746)				
Yes	12.612 (11.091–14.132)				
Hepatic metastasis		0.751		0.940 (0.767–1.153)	0.554
No	12.882 (12.145–13.620)				
Yes	12.951 (11.069–14.832)				
Hypertension		0.006		1.344(1.073–1.683)	0.010
No	13.276 (12.502–14.049)				
Yes	10.747 (9.286–12.208)				
T2DM		0.001		1.455(1.134–1.868)	0.003
No	13.264 (12.492–14.037)				
Yes	10.197 (9.104–11.291)				
HBsAg		0.169		0.804(0.586–1.103)	0.177
No	12.732 (12.015–13.449)				
Yes	15.140 (12.322–17.957)				

95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HR, hazard ratio; OS, overall survival; T2DM, type 2 diabetes mellitus.

In this study, 2.8% of patients (18/632) were confirmed as having both hypertension and T2DM simultaneously. The median OS of these patients was 9.3 months (95% CI, 6.4–12.2 months) and that of patients without any comorbidities was 11 months (95% CI, 8–14 months; Fig. 3). Furthermore, patients with concurrent hypertension and T2DM showed a high HR of 1.665 (95% CI, 1.037–2.672; $P = 0.00058$) in multivariate analyses.

As shown in Fig. 4, the mortality risk in ES-SCLC patients with hypertension increased significantly in the presence of brain metastasis (HR, 1.310; 95% CI, 1.019–1.683; $P = 0.03$). In addition, a higher mortality risk was noted in ES-SCLC patients with T2DM, particularly in (1) patients older than 60 years (HR, 1.520; 95% CI, 1.113–2.076; $P = 0.04$), (2) female patients (HR, 1.947; 95% CI, 1.032–3.670; $P = 0.03$), and (3) patients with brain metastasis (HR, 1.455; 95% CI, 1.119–1.891; $P = 0.003$; Fig. 5). Chronic HBV infection did not increase the mortality risk in ES-SCLC patients (all $P > 0.05$; Fig. 6).

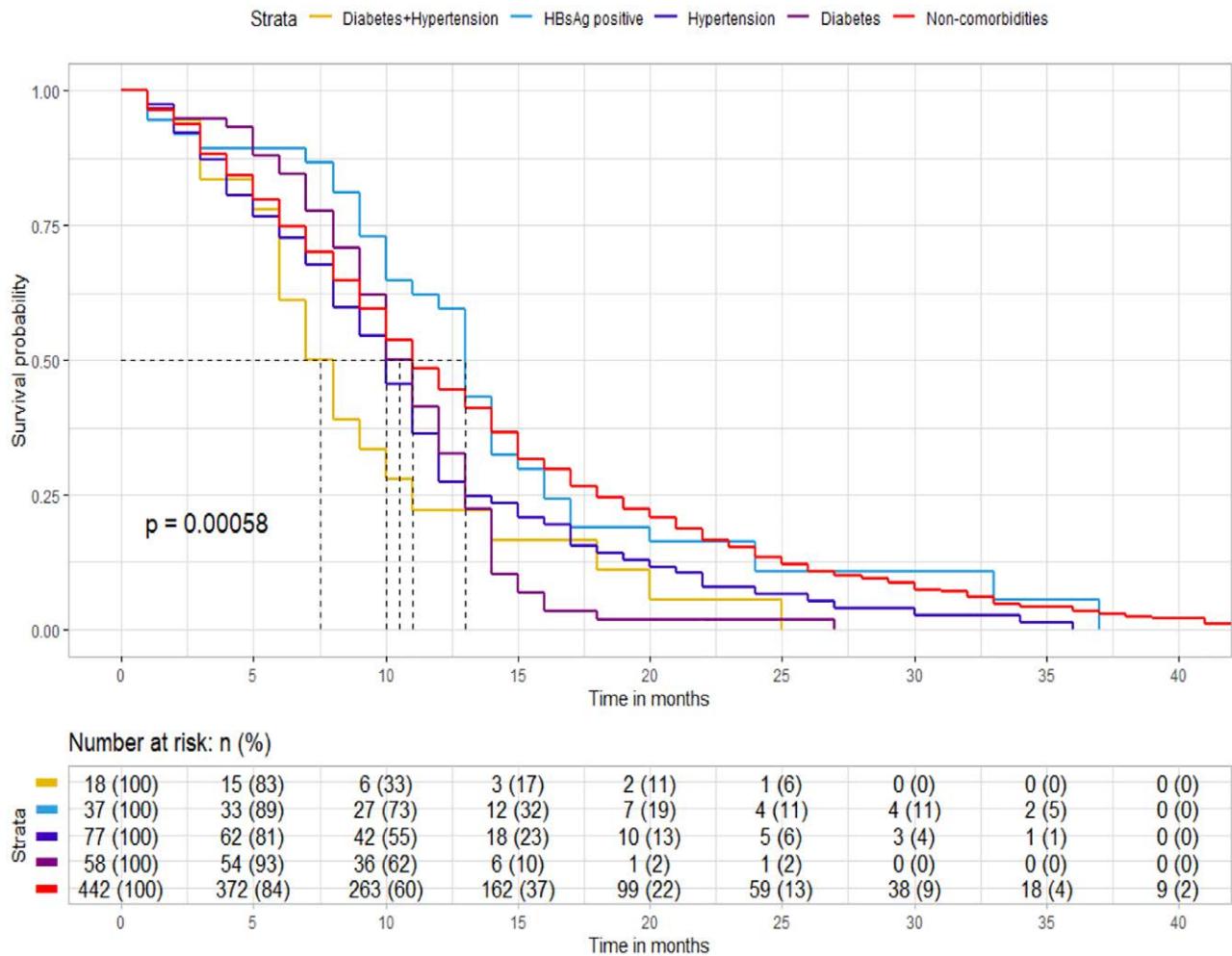
Discussion

Regarding patients with malignant tumors, the potential impact of comorbidities on their OS remains unclear. To our knowledge, this is the largest study thus far aimed at elucidating the impact of several comorbidities, such as hypertension, T2DM, and chronic HBV infections, on the prognosis of patients with ES-SCLC. Kaplan–Meier and multivariate analyses indicated that a confirmed diagnosis

of hypertension or T2DM significantly decreased the OS in patients with ES-SCLC.

Associations were found between anti-tumor treatments for cancer and the development or exacerbation of hypertension. Almost every chemotherapy regimen for lung cancer causes myocardial dysfunction, including ischemic disease, valvular disease, and arrhythmia [24]. Studies with a long-term follow-up reveal that thoracic irradiation is also related to an increased risk of heart failure [25]. Although ejection fraction is often normal, systolic dysfunction has been more widely reported with modern techniques [25]. In 1953, Dyer *et al.* [26] found that after adjusting for age, serum cholesterol level, and smoking history, blood pressure was strongly related to subsequent cancer-related mortality in men. Since the 1960s, beta-blockers have been used for treating hypertension and anxiety disorders [27]. Owing to their preclinical protective mechanisms against cancer progression, several epidemiological studies have investigated the association of hypertension and beta-blocker use with the OS of lung cancer patients; however, the findings were inconclusive. Aydiner *et al.* [28] identified beta-blockers as having a protective effect during chemotherapy in a univariate analysis; however, this finding could not be replicated in a multivariate analysis. A recent meta-analysis has suggested an association between nonselective beta-blocker use and reduced the OS of lung cancer patients [29]. The findings of a prospective cohort study

Fig. 3

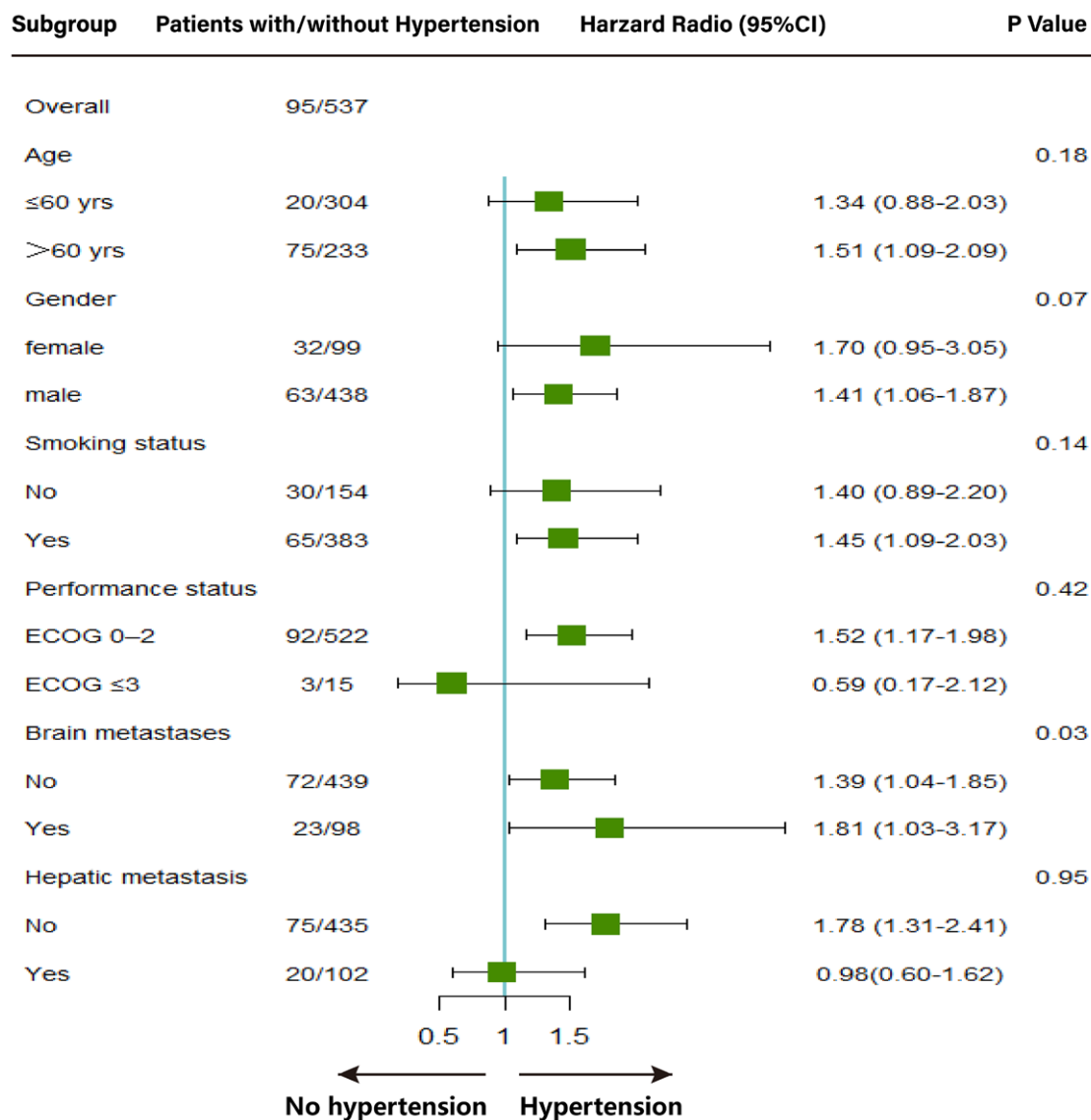


Kaplan–Meier curves for OS in patients with concurrent hypertension and T2DM, patients with either hypertension or T2DM, and the patients without these two comorbidities. OS, overall survival; T2DM, type 2 diabetes mellitus.

in Korea suggested that hypertension exacerbated the lung cancer-associated mortality risk [risk ratio (RR), 1.3; 95% CI, 1.1–1.5], particularly in current smokers (RR, 1.4; 95% CI, 1.2–1.6) after stratification for the smoking status [30]. In another population-based cohort study in Taiwan, Dima *et al.* [31] found that patients with hypertension had the lowest OS among lung cancer patients with non-pulmonary comorbidities. In agreement with these results, the present study indicated significantly reduced survival in ES-SCLC patients with hypertension than in those without hypertension. After adjusting for age, sex, smoking status, ECOG performance, and metastatic sites, the mortality risk increased 1.34-fold in ES-SCLC patients with hypertension when compared with those without hypertension (HR, 1.344; 95% CI, 1.073–1.683; $P = 0.010$). Specifically, subgroup analysis indicated an increased mortality risk in patients who were older than 60 years, were male, had an ECOG 0–2, had a smoking history, or had a brain/liver metastasis (all $P < 0.05$).

In 2009, Vigneri *et al.* [32] reviewed a plethora of epidemiological studies indicating that the mortality risk of several cancer types (including cancers of the breast, liver, colorectum, urinary tract, and female reproductive organs) was moderately increased in patients with T2DM, with the RR in the range of 1.12–2.51; however, a study on long-term, all-cause mortality found that the mortality risk was not significantly higher in lung cancer patients with T2DM than in those without T2DM [33]. Recent retrospective studies on the association between survival outcomes of lung cancer patients and preexisting T2DM (or anti-T2DM drug use) have yielded inconsistent results [34–37]. In a state database study from the US, Islam *et al.* reported that comorbid conditions were associated with worse survival among lung cancer patients; furthermore, mortality risk was notably higher in patients with diagnosis of T2DM with complications (HR, 2.167; 95% CI, 1.122–4.185) [18]. In a pooled analysis of over 770 000 individuals in Asia, Chen *et al.* [38] reported a

Fig. 4

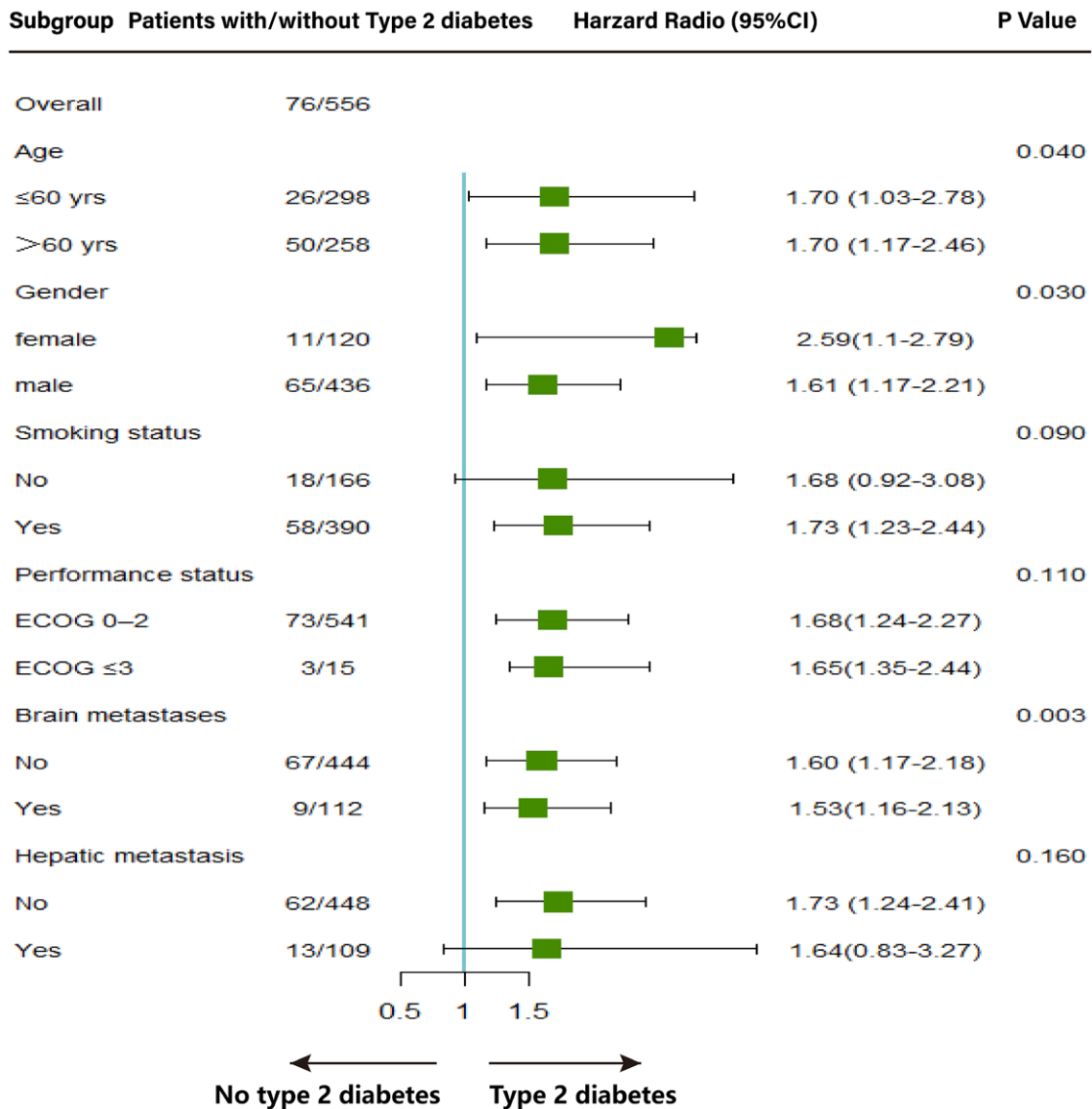


Mortality risk in ES-SCLC patients with or without hypertension. Forest map shows increased mortality risk in patients with hypertension. ES-SCLC, extensive-stage small-cell lung cancer.

significant positive association of comorbid T2DM with increased mortality risk in several cancers, such as cancers of the colorectum, liver, breast, kidney, prostate, gallbladder, pancreas, and ovary, but not in lung cancer (HR, 0.98; 95% CI, 0.89–1.09). Conversely, a prospective population study showed that compared with female lung cancer patients without T2DM, those with T2DM showed a significantly increased risk of overall mortality (HR, 1.27; 95% CI, 1.07–1.50) [39]. Furthermore, a study in Japan reported that in SCLC patients who received chemotherapy (*n* = 284), OS was significantly prolonged for patients without T2DM compared with those with T2DM (*P* = 0.026) [33]. Significantly worse OS was

observed in the present study in patients with T2DM (median OS, 10.2 months; 95% CI, 9.1–11.3 months; *P* = 0.0004) as confirmed by multivariate analysis (HR, 1.455; 95% CI, 1.134–1.868; *P* = 0.003). Subgroup data suggest that patients with T2DM who are aged >60 years (both sexes included), have an ECOG 0–2, are current smokers, and have no brain or hepatic metastasis have significantly reduced OS compared with patients without T2DM who are aged >60 years (both sexes included), have an ECOG 0–2, are current smokers, and have no brain or hepatic metastasis (all *P* < 0.05). Several T2DM-related conditions could potentially contribute to the development of lung cancer, such as hyperinsulinemia, hyperglycemia,

Fig. 5



Mortality risk in ES-SCLC patients with or without T2DM. Forest map shows increased mortality risk in patients with T2DM. ES-SCLC, extensive-stage small-cell lung cancer; T2DM, type 2 diabetes mellitus.

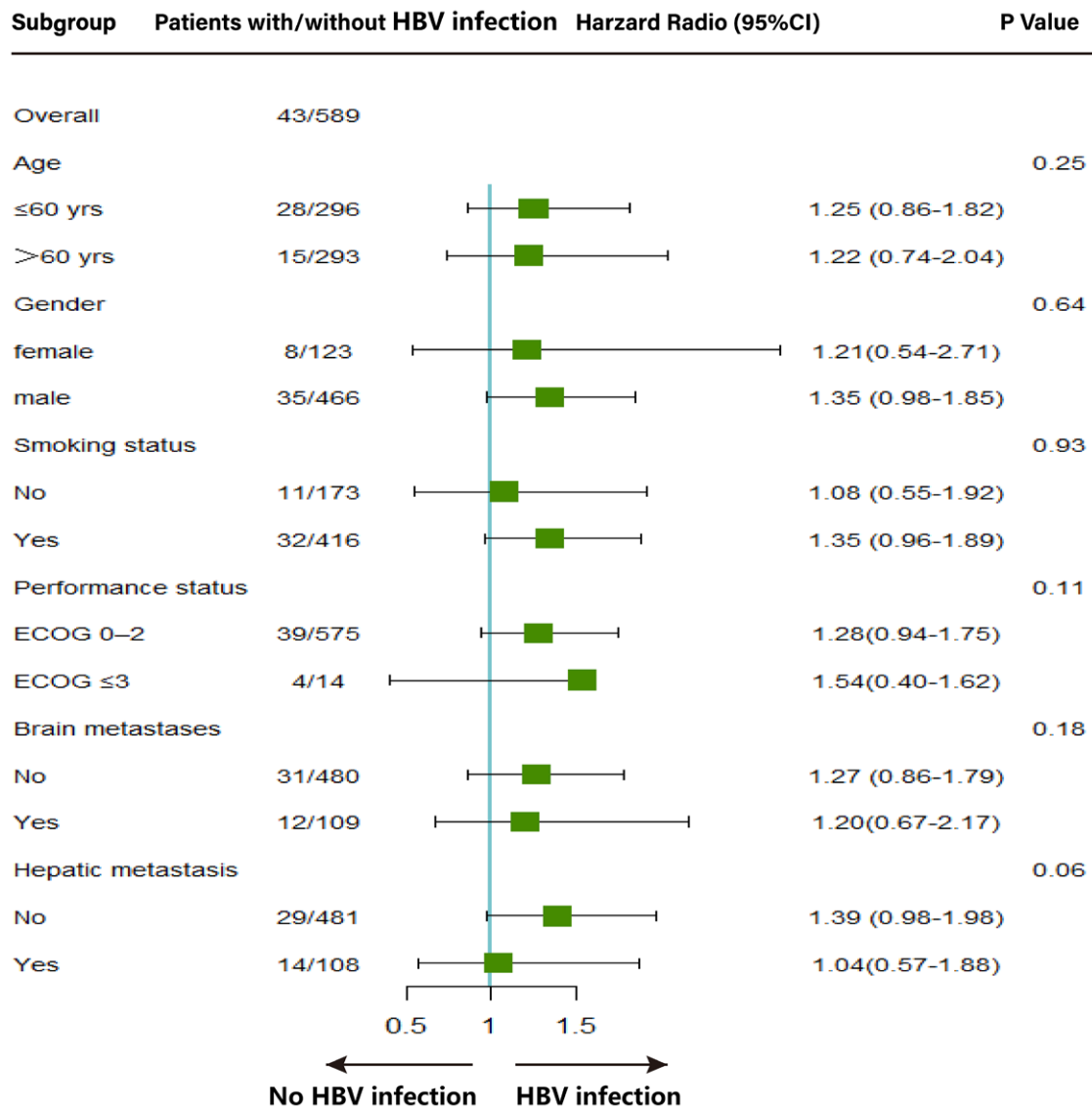
and metabolic disorder of cancer cells; from a molecular perspective, it can be hypothesized that these conditions are responsible for the negative effect of T2DM on the survival of patients with lung cancer [40,41]. In addition, the various complications induced by T2DM may decrease the tolerance of patients with cancer to chemo/radiotherapy, consequently leading to shorter survival.

In the present population, patients with concurrent hypertension and T2DM showed the worst survival outcome (median OS, 9.1 months; 95% CI, 6.3–11.4 months). As per a review by Santos and Shah, numerous studies have demonstrated hypertension as an important risk factor for cardiovascular mortality and morbidity, including

heart failure, with both preserved and reduced ejection fraction [42]. Additionally, Braunwald [43] reported in a review that T2DM progressively causes macrovascular pathologic changes or microvascular pathologic changes or both and consequently increases the risk for the development of multi-organ dysfunction (e.g. myocardial and renal dysfunction). Furthermore, physiologic functions of patients with cancer who also have hypertension or T2DM may be too compromised to tolerate treatment-related toxicities [44–46], which may result in the reduced survival rate.

In-vivo and in-vitro, HBV could promote the production of a tumor necrosis factor through residual immune cells;

Fig. 6



Mortality risk in ES-SCLC patients with or without chronic HBV infection. Forest map shows chronic HBV infection did not increase the mortality risk. ES-SCLC, extensive-stage small-cell lung cancer; HBV, hepatitis B virus.

this factor exhibits anti-tumor effects on tumor cells [47]. A study on tumor and stroma interactions found that tumor cells have an inherent propensity for developing into metastatic liver cancer which is affected by the local environment of metastatic sites [48]. Theoretically, HBV infection may activate liver-associated immunity and consequently decrease the occurrence of liver metastasis among cancer patients. As HBV infection is a major health problem in China, several epidemiologic studies have been reported on its association with mortality risk. A study by Liu *et al.* [49] showed that chronic HBV infection (HBsAg positivity) is an independent adverse prognostic predictor for poor OS (HR, 1.73; $P = 0.004$)

in patients with stage III/IV nasopharyngeal carcinoma. In a similar study, Fu *et al.* [50] reported that high pre-treatment serum HBV DNA copy numbers could act as a negative prognostic marker for survival among NSCLC patients with chronic HBV infection. Conversely, Zou *et al.* [51] found that among esophageal cancer patients, those who were HBsAg-positive had a more favorable OS (HR, 0.80; 95% CI, 0.65–0.95; $P = 0.020$) than those who were HBsAg-negative. In the current study, we noted no significant difference between the survival of ES-SCLC patients with and without HBV infection (HR, 0.80; 95% CI, 0.59–1.10; $P = 0.068$); 88.4% of patients (38/43) had been treated with anti-HBV drugs (lamivudine,

entecavir, or adefovir) before the diagnosis of ES-SCLC, and their pretreatment HBV DNA copy numbers were normal. This may explain why HBV infection was not a prognostic factor among these patients.

Currently, in the era of precision medicine and multidisciplinary team efforts, treatment strategy may undoubtedly affect the survival of patients with cancer. We chose patients with ES-SCLC as the target population because the first-line and second-line treatments for ES-SCLC were relatively uniform worldwide at the beginning of this analysis. Based on the present NCCN panel recommendations, systematic chemotherapy is the standard first-line treatment for ES-SCLC. Most regimens used in practice were etoposide–cisplatin or etoposide–carboplatin regimens, resulting in a median OS of 12–13 months, even after maintenance therapy with atezolizumab or durvalumab [52,53]. Only topotecan was recommended as the preferred second-line treatment. Since the publication by Jeremic *et al.* [54] in 1999, thoracic radiotherapy has become a standard treatment for ES-SCLC patients with thoracic symptoms, and irradiation doses are usually 30 Gy/10 fractions (3 Gy/fraction) or 50 Gy/25 fractions (2 Gy/fraction) for residual thoracic tumors. Additionally, since the publication by Slotman *et al.* in 2015 [55], patients who responded to initial chemotherapy were also administered thoracic radiotherapy at our institution before or after prophylactic cranial irradiation (25 Gy/10 fractions). Considering the guidelines, reports, and our practice mentioned above, the impact of treatment strategies on the survival of patients with ES-SCLC has been balanced as equally as possible in the present study.

Our study has several limitations that need to be acknowledged. First, owing to the retrospective nature of the present study, there may have been some selection bias. Second, despite the relatively large sample size of our study, all data still came from a single institution, and thus, the results should be interpreted by oncologists with caution. Third, although the medical records of anti-comorbidity drugs were sufficient, the sample sizes for a single drug or specific combinations of different drugs were too small to obtain a definitive conclusion. For example, the anti-T2DM drugs prescribed in the present study included biguanides, sulfonylureas, thiazolidinediones, meglitinides, α -glucosidase inhibitors, and insulins. These drugs would be changed regularly by an endocrinologist depending on the different stage or status of T2DM. Therefore, this could have resulted in statistical bias as these patients were included in univariate/multivariate analyses. Finally, several clinical characteristics of the three comorbidities studied herein (hypertension, T2DM, and chronic HBV infection) were unknown, such as disease duration, varying levels of metabolic control, and complications. Other common risk factors (BMI, socioeconomic status, and alcohol intake) associated with cancer survival were not recorded or analyzed. In the future, an ideal study should

be carefully designed and conducted using the national database along with detailed medical records.

In conclusion, our study identified that comorbidities, such as hypertension and T2DM, may be independent negative prognostic factors for patients with ES-SCLC. As these two comorbidities are widely prevalent, specific attention should be paid to administering anti-hypertension/T2DM therapy concurrently during anti-tumor treatment for these patients.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (No. 2018YFC1311400/2018YFC1311402) and Sichuan Provincial Research Foundation for Basic Research (2018SZ0023). This work was technically supported by You Lu, MD, PhD; Lin Zhou, MD, PhD; Jianxin Xue, MD, PhD; Jiang Zhu, MD; Meijuan Huang, MD, PhD; Feng Peng, MD, PhD; Bingwen Zou, MD, Yongmei Liu, MD, PhD; Yong Xu, MD; Yan Zhang, MD, PhD; Xiaojuan Zhou, MD; Feifei Na, MD; Yang Yu, MD; Xuanwei Zhang, MD; and Yongsheng Wang, MD, PhD.

The authors (via the corresponding author) have full control of all primary data and agree to allow the journal to review this data if requested.

Ethical approval: This retrospective study was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Sichuan University approved this study.

Funding: This work was supported by the 1.3.5 Project for Disciplines of Excellence, West China Hospital, University (ZYJC21075 to GYL).

Conflicts of interest

There are no conflicts of interest.

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