Original Article

# The nomograms to predict early death among metastatic small-cell lung cancer patients: a retrospective study based on SEER database

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**Background:** This study aims to discriminate risk factors associated with early death (died within 3 months) in metastatic small-cell lung cancer (SCLC) patients, and construct predictive nomograms to help physicians in guiding individual treatment.

**Methods:** Surveillance, Epidemiology, and End Results (SEER) database was used to obtain records of deceased metastatic SCLC patients. The univariate and multivariate logistic regression methods were managed to identify risk factors for early death in overall patients and chemotherapy recipients. Predictive nomograms were developed and then validated by receiver operating characteristics curve (ROC) and calibration plots to verify its' precision.

**Results:** A total of 13,229 patients were collected of which 5,832 of them encountered early death. The univariate and multivariate logistic regression analysis identified variables that were negatively associated with early death include sex, age, race, sequence, T stage, N stage, organ metastasis. Chemotherapy and radiotherapy implementation significantly decreased the odds of early death. For the chemotherapy recipients, white male patients with advanced age (over 80 years old), T4 stage, multiple organ metastasis, and without radiotherapy most likely died within 3 months. The area under the curve (AUC) of the nomograms for overall population and chemotherapy recipients' early death prediction was 0.839 and 0.653.

**Conclusions:** Early death among metastatic SCLC patients was extremely common in clinical practice. The nomograms constructed were able to assist clinical physicians in discriminating high-risk SCLC patients for targeted intervention, and elderly white male patients diagnosed with advanced T stage and multiple organ metastasis might be exempted from systemic treatment to receive palliative care.

**Keywords:** Early death; small-cell lung cancer (SCLC); nomogram

Submitted Feb 23, 2022. Accepted for publication May 16, 2022.
doi: 10.21037/tcr-22-462
**View this article at:** https://dx.doi.org/10.21037/tcr-22-462

## Introduction

According to the latest published *Cancer Statistic 2020*, malignancies originated from lung and bronchus occupied the second position of all estimated new cases, and the trend incidence rate of lung cancer patients continued to decline steadily. Despite that, the estimated deaths among lung cancer patients still outnumbered any other malignancies in both genders (1). Small-cell lung cancer (SCLC), which accounts for 13% of all newly diagnosed lung cancer patients worldwide, presented with a poor prognosis and has limited treatment choices (2). SCLC was reported to be heavily related to elderly patients with smoking history and diagnosed with advanced stage, which is initially sensitive to standard first-line platinum-based cytotoxic therapy but soon experience disease relapse and resistance to further treatment (3).

With the rapid development of immunotherapy and radiation technology, de novo metastatic SCLC patients' survival has been prolonged over the past decades (4). However, SCLC patients with terminal stage often underwent aggressive disease progression and resulted in death in a very short amount of time. Early death (survival time ≤3 months) of cancer patients is an extremely objective and perceivable clinical characteristic in revealing advanced cancers' aggressive nature. Researchers have reported predictive factors related to early death among colorectal, ovarian, and gastric cancer patients, yet the risk factors of early death in metastatic SCLC remain unreported (5-7).

This study aims to learn the incidence of early death among metastatic SCLC patients based on a large population database in order to identify the risk factors attributing to early death, and determining which patients could be exempted from systemic treatment. After that, clinical oncologists could be more informed to make the medical decision with the aid of predictive nomograms with good validation. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-462/rc).

## Methods

### *Population*

The National Cancer Institutes' open public Surveillance, Epidemiology, End Results (SEER) database was constituted by 18 established cancer registries across the US. The data use agreement was submitted to the SEER database for Research Plus Data. After the approval of SEER data access, the latest updated SEER*Stat software version 8.9.3 (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc., Calverton, MD, USA) was used to initially generate an SCLC case list for further exclusion. The primary site codes C34.0-C34.3 were applied, and the diagnosis of SCLC was identified based on World Health Organization (WHO) International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology codes: small cell carcinoma (8041/3-8044/3). The data regarding metastatic to a remote organ include bone, brain, liver, lung was not recorded before the year 2010, thus SCLC patients diagnosed between 2010 to 2018 were collected in this study. The demographic characteristics extracted from SEER included sex, age at diagnosis, race, and marital status. Clinical variables available included sequence, primary site, AJCC staging record, metastasis at diagnosis, chemotherapy, radiation, cause of death, and survival. The exclusion criteria were presented as follows: demographics with unknown information, sequence number ≥2, unknown AJCC staging, unknown metastatic information, death attributable to causes other than this cancer diagnosis, diagnosis via death certificate or autopsy. Primary site surgical intervention isn't a standard treatment for extensive SCLC patients, thus excluded. The remaining SCLC patients obtained consistent demographics as well as clinical variables, then they were classified into five age groups: ≤50, 50–60, 60–70, 70–80, >80. Based on the previous studies, early death in SCLC patients was defined as survival less than 3 months following initial diagnosis (1,2). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Statistical analysis*

Categorical data were described by the number and the percentage (N, %) as demonstrated in *Table 1*. The univariate and multivariate logistic regression methods were taken to identify factors that were significantly associated with the early death of metastatic SCLC patients along with its odds ratio (OR), and corresponding 95% confidence interval (CI) based on the SEER database. Since chemotherapy was deemed standard treatment for metastatic or extensive SCLC in clinical practice, we used the same statistical method to identify patients who have received chemotherapy but eventually encountered early death, thus claimed them unsuitable for systemic treatment. And then, predictive nomograms were constructed

 

**Table 1** Characteristics of deceased metastatic SCLC patients extracted from SEER database

| Variables | Total death, N=13,229 (%) | Died within 0–3 m, N=5,832 (%) | Died within 4–6 m, N=1,978 (%) | Died within 7–12 m, N=3,437 (%) | Died >1 year, N=1,982 (%) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 6,962 (52.6) | 3,172 (54.4) | 1,088 (55.0) | 1,741 (50.7) | 961 (48.5) |
| Female | 6,267 (47.4) | 2,660 (45.6) | 890 (45.0) | 1,696 (49.3) | 1,021 (51.5) |
| Age (years) | | | | | |
| <50 | 526 (4.0) | 137 (2.3) | 101 (5.1) | 182 (5.3) | 106 (5.3) |
| 50–60 | 2,748 (20.8) | 876 (15.0) | 444 (22.4) | 854 (24.8) | 574 (29.0) |
| 60–70 | 4,903 (37.1) | 2,023 (34.7) | 713 (36.0) | 1,373 (39.9) | 794 (40.1) |
| 70–80 | 3,780 (28.5) | 1,951 (33.5) | 546 (27.6) | 848 (24.7) | 435 (21.9) |
| >80 | 1,272 (13.2) | 845 (14.5) | 174 (8.9) | 180 (5.3) | 73 (3.7) |
| Race | | | | | |
| White | 11,650 (88.1) | 5,197 (89.1) | 1,729 (87.4) | 3,027 (88.1) | 1,697 (85.6) |
| Black | 1,113 (8.4) | 442 (7.6) | 181 (9.2) | 287 (8.4) | 203 (10.2) |
| Others | 466 (3.5) | 193 (3.3) | 68 (3.4) | 123 (3.5) | 82 (4.2) |
| Marital status | | | | | |
| Married | 6,911 (52.2) | 2,788 (47.8) | 1,047 (52.9) | 1,915 (55.7) | 1,161 (58.6) |
| Widowed | 2,280 (17.2) | 1,231 (21.1) | 327 (16.5) | 494 (14.4) | 228 (11.5) |
| Divorced | 2,097 (15.9) | 928 (15.9) | 309 (15.6) | 543 (15.8) | 317 (16.0) |
| Single | 1,941 (14.7) | 885 (15.2) | 295 (15.0) | 485 (14.1) | 276 (13.9) |
| Sequence | | | | | |
| First primary | 11,342 (85.7) | 4,983 (85.4) | 1,681 (85.0) | 2,967 (86.3) | 1,711 (86.3) |
| Second primary | 1,887 (14.3) | 849 (14.6) | 297 (15.0) | 470 (13.7) | 271 (13.7) |
| Laterality | | | | | |
| Right | 7,356 (55.6) | 3,256 (55.8) | 1,080 (54.6) | 1,910 (55.6) | 1,110 (56.0) |
| Left | 5,873 (44.4) | 2,576 (44.2) | 898 (45.4) | 1,527 (44.4) | 872 (44.0) |
| Primary site | | | | | |
| Upper lobe | 7,497 (56.7) | 3,224 (55.3) | 1,117 (56.5) | 1,981 (57.6) | 1,175 (59.3) |
| Middle lobe | 562 (4.2) | 226 (3.9) | 77 (3.9) | 166 (4.8) | 93 (4.7) |
| Lower lobe | 3,362 (25.4) | 1,557 (26.7) | 522 (26.4) | 839 (24.4) | 444 (22.4) |
| Main bronchus | 1,808 (12.7) | 825 (14.1) | 262 (13.2) | 451 (13.2) | 270 (13.6) |
| T stage | | | | | |
| T1 | 1,471 (11.1) | 620 (10.6) | 226 (11.4) | 389 (11.3) | 236 (11.9) |
| T2 | 3,491 (26.4) | 1,556 (26.7) | 504 (25.5) | 879 (25.6) | 552 (27.9) |
| T3 | 3,012 (22.8) | 1,337 (22.9) | 462 (23.4) | 789 (23.0) | 424 (21.4) |
| T4 | 5,255 (39.7) | 2,319 (39.8) | 786 (39.7) | 1,380 (40.1) | 770 (38.8) |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Variables | Total death, N=13,229 (%) | Died within 0–3 m, N=5,832 (%) | Died within 4–6 m, N=1,978 (%) | Died within 7–12 m, N=3,437 (%) | Died >1 year, N=1,982 (%) |
|---|---|---|---|---|---|
| N stage | | | | | |
| N0 | 1,522 (11.5) | 730 (12.5) | 242 (12.2) | 289 (8.4) | 261 (13.2) |
| N1 | 799 (6.0) | 346 (5.9) | 110 (5.6) | 199 (5.8) | 144 (7.3) |
| N2 | 7,607 (57.5) | 3,420 (58.6) | 1,130 (57.1) | 1,984 (57.7) | 1,073 (54.1) |
| N3 | 3,301 (25.0) | 1,336 (23.0) | 496 (25.1) | 965 (28.1) | 504 (25.4) |
| Met-bone | | | | | |
| Yes | 5,815 (44.0) | 2,396 (41.1) | 894 (45.2) | 1,700 (49.5) | 825 (41.6) |
| No | 7,414 (56.0) | 3,436 (58.9) | 1,084 (54.8) | 1,737 (50.5) | 1,157 (58.4) |
| Met-brain | | | | | |
| Yes | 4,047 (30.6) | 1,746 (29.9) | 693 (35.0) | 995 (28.9) | 613 (30.9) |
| No | 9,812 (69.4) | 4,086 (70.1) | 1,285 (65.0) | 2,442 (71.1) | 1,369 (69.1) |
| Met-liver | | | | | |
| Yes | 7,592 (57.4) | 3,711 (63.6) | 1,080 (54.6) | 1,947 (56.6) | 854 (43.1) |
| No | 5,637 (42.6) | 2,121 (36.4) | 898 (45.4) | 1,490 (43.4) | 1,128 (56.9) |
| Met-lung | | | | | |
| Yes | 3,233 (24.4) | 1,491 (25.6) | 459 (23.2) | 806 (23.5) | 477 (24.1) |
| No | 9,996 (75.6) | 4,341 (74.4) | 1,519 (76.8) | 2,631 (76.5) | 1,505 (75.9) |
| Chemotherapy | | | | | |
| Yes | 9,095 (68.8) | 2,258 (38.7) | 1,690 (85.4) | 3,253 (94.6) | 1,894 (95.6) |
| No | 4,134 (31.2) | 3,574 (61.3) | 288 (14.6) | 184 (5.4) | 88 (4.4) |
| Radiation | | | | | |
| Yes | 5,421 (41.0) | 1,547 (26.5) | 916 (46.3) | 1,747 (50.8) | 1,211 (61.1) |
| No | 7,808 (59.0) | 4,285 (73.5) | 1,062 (53.7) | 1,690 (49.2) | 771 (38.9) |

SCLC, small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results.

according to independent factors originated from above.

### *Nomogram validation*

The discrimination and calibration of the nomograms were measured to evaluate the predicted probabilities of the nomograms. For calibration, the nomogram predicted probabilities were contrasted with the actual probabilities by bootstrapping with 1,000 resamples. The receiver operating characteristic (ROC) curve was used to judge discrimination. The area under the curve (AUC) of between 0.5 to 1.0 indicated good discrimination, and the higher the AUC was, the better the accuracy would be. Statistically significant levels were two-tailed and set at $P<0.05$. All statistical analyses were conducted by the R software (version 4.0.4).

## Results

### *Demographics and clinical characteristics*

A total of 13,229 deceased metastatic SCLC patients were extracted from SEER database after data exclusion and integration. The demographics and clinical characteristics

 

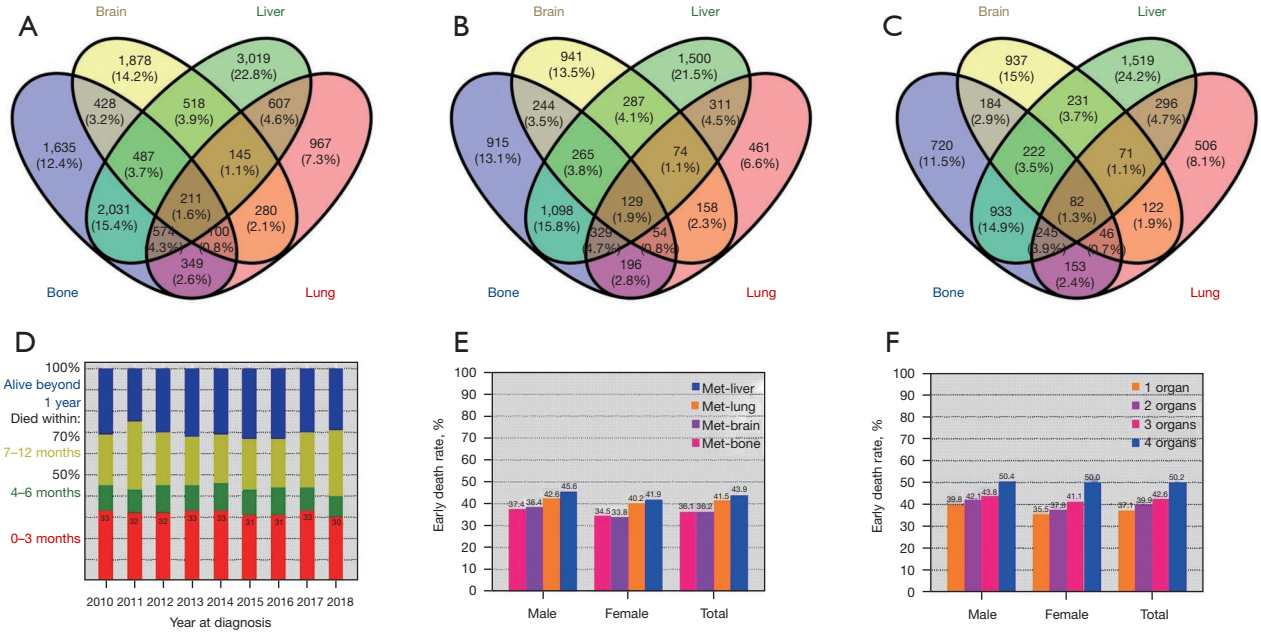


**Figure 1** Variate configuration to present multiple organ metastasis. (A) The venn diagram of organ metastasis in overall population; (B) The venn diagram of organ metastasis in male population; (C) The venn diagram of organ metastasis in female population; (D) The trend and distribution of early death stratified by year of diagnosis; (E) The trend and distribution of early death stratified by different organs; (F) The trend and distribution of early death stratified by numbers of organs.

of them were listed in *Table 1*. Among all the patients, the percentage of male was slightly higher than female with an median age of 67 (range, 27–100) in overall population, but the incidence of female patients died over 1 year were a lot bit higher than male. Most of them were White while black and other races were less than 20% combined, and over half of them were married. The distribution of variables such as sequence, laterality, TNM stages stratified by death duration intervals was not significantly different from one another.

Liver was the most frequent metastatic sites (57.4%, N=7,592) while lung metastasis were least common sites of all patients (24.4%, N=3,233). Venn diagrams of distant metastasis (*Figure 1A-1C*) showed that synchronous or multiple organ metastasis occurred in over 40% of patients. Among them, bone and liver (15.4%, N=2,031) were the most common multiple metastatic organs while 1.6% (N=211) patients had all four organs metastasis. Patients who received chemotherapy accounted for 68.8% (N=9,095), and 41.0% (N=5,421) of them had radiotherapy. Patients' survivals were classified into 4 death duration intervals: died within 3 months, died within 3–6 months, died within 7–12 months, and died >1 year, and results of these groups were 5,832 (44.1%), 1,978 (15.0%), 3,437 (25.9%), 1,982 (15.0%), respectively.

### *Incidence of early death*

As stated above, 5832 patients succumbed to early death (died within 3 months) caused by metastatic SCLC. Over the study period, the number of patients died in the first 3 months, 4–6 months, 7–12 months and alive beyond 1 year each year were slightly fluctuated, thus no significance founded between year at diagnosis (P>0.05) (*Figure 1D*). Incidence of early death in different organ metastasis was highest for liver (43.9%), followed by lung (41.5%), brain (36.2%) and bone (36.1%) (*Figure 1E*). Although female patients presented with slightly lower incidence rate in each one of these organs metastasis compared with male patients, there were no statistically significance between gender groups (P=0.267). The number of metastatic organs increased, the higher incidence of early death would achieve (*Figure 1F*).

### *Independent factors and nomograms construction*

As depicted in *Table 2*, the application of the univariate logistic regression modeling resulted in several statistically

**Table 2** Univariate and multivariate logistic regression for analyzing the risk factors for early death among overall population

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Sex | | | | | | |
| Male | Ref | | | Ref | | |
| Female | 0.878 | 0.819–0.942 | <0.001 | 0.753 | 0.686–0.827 | <0.001 |
| Age (years) | | | | | | |
| <50 | Ref | | | Ref | | |
| 50–60 | 1.234 | 1.017–1.497 | 0.033 | 1.212 | 0.998–1.471 | 0.052 |
| 60–70 | 1.770 | 1.470–2.131 | <0.001 | 1.523 | 1.264–1.835 | <0.001 |
| 70–80 | 2.379 | 1.976–2,865 | <0.001 | 1.572 | 1.303–1.897 | <0.001 |
| >80 | 3,567 | 2.940–4.327 | <0.001 | 1.711 | 1.407–2.083 | <0.001 |
| Race | | | | | | |
| White | Ref | | | Ref | | |
| Black | 0.811 | 0.712–0.923 | <0.001 | 0.807 | 0.682–0.953 | 0.012 |
| Others | 0.855 | 0.705–1.037 | 0.645 | 0.782 | 0.612–1.001 | 0.837 |
| Marital status | | | | | | |
| Married | Ref | | | Ref | | |
| Widowed | 1.671 | 1.519–1.839 | <0.001 | 1.112 | 0.976–1.268 | 0.856 |
| Divorced | 1.130 | 1.021–1.250 | <0.001 | 1.096 | 0.963–1.247 | 0.164 |
| Single | 1.260 | 1.137–1.397 | 0.091 | 1.134 | 0.989–1.301 | 0.678 |
| Sequence | | | | | | |
| First primary | Ref | | | Ref | | |
| Second primary | 1.029 | 0.931–1.137 | 0.581 | 0.866 | 0.761–0.984 | 0.027 |
| Laterality | | | | | | |
| Right | Ref | | | Ref | | |
| Left | 0.980 | 0.913–1.052 | 0.573 | 0.955 | 0.8731.044 | 0.310 |
| Primary site | | | | | | |
| Pulmonary lobe | Ref | | | Ref | | |
| Main bronchus | 1.076 | 0.973–1.191 | 0.154 | 1.110 | 0.975–1.264 | 0.116 |
| T stage | | | | | | |
| T1 | Ref | | | Ref | | |
| T2 | 1.115 | 1.009–1.233 | 0.032 | 1.190 | 1.076–1.316 | <0.001 |
| T3 | 1.081 | 0.976–1.198 | 0.135 | 1.165 | 1.050–1.292 | 0.004 |
| T4 | 1.099 | 0.999–1.208 | 0.053 | 1.243 | 1.127–1.371 | <0.001 |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| N stage | | | | | | |
| N0 | Ref | | | Ref | | |
| N1 | 0.828 | 0.721–0.950 | 0.007 | 0.912 | 0.794–1.048 | 0.193 |
| N2 | 0.912 | 0.837–0.993 | 0.033 | 1.101 | 1.013–1.205 | 0.024 |
| N3 | 0.804 | 0.730–0.885 | <0.001 | 1.123 | 1.018–1.238 | 0.021 |
| Met-bone | | | | | | |
| No | Ref | | | Ref | | |
| Yes | 0.818 | 0.762–0.878 | <0.001 | 1.069 | 0.975–1.173 | 0.155 |
| Met-brain | | | | | | |
| No | Ref | | | Ref | | |
| Yes | 0.858 | 0.795–0.927 | <0.001 | 1.859 | 1.653–2.091 | <0.001 |
| Met-liver | | | | | | |
| No | 0.598 | 0.557–0.643 | <0.001 | 0.611 | 0.553–0.674 | <0.001 |
| Yes | Ref | | | Ref | | |
| Met-lung | | | | | | |
| No | Ref | | | Ref | | |
| Yes | 1.163 | 1.072–1.261 | <0.001 | 1.114 | 1.000–1.241 | 0.0503 |
| Chemotherapy | | | | | | |
| No | 17.410 | 15.860–19.112 | <0.001 | 15.182 | 13.744–16.770 | <0.001 |
| Yes | Ref | | | Ref | | |
| Radiation | | | | | | |
| No | Ref | | | Ref | | |
| Yes | 0.296 | 0.274–0.320 | <0.001 | 0.367 | 0.329–0.409 | <0.001 |

OR, odds ratio; CI, confidence internal; Ref, reference.

significant variables (P<0.05): sex, age, race, marital status, T stage, N stage, Met-bone, Met-brain, Met-liver, Met-lung, chemotherapy and radiation. Additionally, multivariate logistic regression modeling concluded with meaningful variables that were similar to results mentioned above, with the exception of marital status and Met-bone (P>0.01), adding sequence (P=0.027) that deeply associated with early death of metastatic SCLC patients.

As the insignificance of bone metastasis, multiple organ metastasis with at least one of these organs: liver, brain, and lung metastasis was thought to be much more meaningful for the analysis of chemotherapy recipients, then variables associated with organ metastasis were converted into Metastatic numbers. After the statistical procedure, sex, age, race, T stage, metastatic numbers, and radiation were independently correlated with early death in patients initially treated with chemotherapy (*Table 3*).

All the independent risk factors identified from multivariate logistic analysis were applied into the construction of predictive nomograms (*Figure 2*). After total scoring of these variables combine, the probability of a certain individual encounter early death after diagnosis of metastatic SCLC can be clearly visualized. The areas under the curve were 0.839 and 0.653 means a satisfactory

 

**Table 3** Univariate and multivariate logistic regression for analyzing the risk factors for early death among chemotherapy recipients

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Sex | | | | | | |
| Male | Ref | | | Ref | | |
| Female | 0.762 | 0.686 | <0.001 | 0.761 | 0.680–0.851 | <0.001 |
| Age (years) | | | | | | |
| <50 | Ref | | | Ref | | |
| 50–60 | 1.234 | 1.017–1.497 | 0.033 | 1.212 | 0.998–1.471 | 0.052 |
| 60–70 | 1.770 | 1.470–2.131 | <0.001 | 1.523 | 1.254–1.835 | <0.001 |
| 70–80 | 2.379 | 1.976–2.865 | <0.001 | 1.572 | 1.303–1.897 | <0.001 |
| >80 | 3.567 | 2.940–4.327 | <0.001 | 1.712 | 1.407–2.083 | <0.001 |
| Race | | | | | | |
| White | Ref | | | Ref | | |
| Black | 0.731 | 0.598–0.895 | <0.001 | 0.769 | 0.623–0.948 | 0.014 |
| Others | 0.816 | 0.609–1.094 | 0.535 | 0.762 | 0.564–1.028 | 0.959 |
| Marital status | | | | | | |
| Married | Ref | | | Ref | | |
| Widowed | 1.155 | 0.994–1.341 | 0.308 | 1.093 | 0.928–1.2286 | 0.637 |
| Divorced | 1.049 | 0.906–1.214 | 0.524 | 1.146 | 0.984–1.334 | 0.663 |
| Single | 1.002 | 0.856–1.172 | 0.637 | 1.197 | 1.013–1.414 | 0.080 |
| Primary sequence | | | | | | |
| First primary | Ref | | | Ref | | |
| Second primary | 1.029 | 0.931–1.137 | 0.581 | 0.880 | 0.753–1.030 | 0.110 |
| T stage | | | | | | |
| T1 | Ref | | | Ref | | |
| T2 | 1.115 | 1.009–1.233 | 0.032 | 1.190 | 1.076–1.316 | <0.001 |
| T3 | 1.081 | 0.976–1.198 | 0.135 | 1.165 | 1.050–1.292 | 0.004 |
| T4 | 1.099 | 0.999–1.208 | 0.053 | 1.242 | 1.127–1.371 | <0.001 |
| N stage | | | | | | |
| N0 | Red | | | Ref | | |
| N1 | 0.827 | 0.721–0.950 | 0.007 | 0.912 | 0.794–1.048 | 0.193 |
| N2 | 0.912 | 0.837–0.993 | 0.033 | 1.105 | 1.013–1.205 | 0.024 |
| N3 | 0.804 | 0.730–0.885 | <0.001 | 1.123 | 1.018–1.238 | 0.021 |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Metastatic numbers | | | | | | |
| 1 | Ref | | | Ref | | |
| 2 | 1.243 | 1.109–1.393 | <0.001 | 1.212 | 1.078–1.362 | 0.001 |
| 3 | 1.385 | 1.168–1.642 | <0.001 | 1.431 | 1.200–1.707 | <0.001 |
| 4 | 2.349 | 1.665–3.314 | <0.001 | 2.802 | 1.958–4.010 | <0.001 |
| Radiation | | | | | | |
| No | Ref | | | Ref | | |
| Yes | 0.408 | 0.366–0.455 | <0.001 | 0.419 | 0.375–0.469 | <0.001 |

OR, odds ratio; CI, confidence internal; Ref, reference.

discrimination strength were made (*Figure 3A*,*3B*). Additionally, the calibration curves were close to the 45-degree line with the predicted and observed probabilities fitted well (*Figure 3C*,*3D*).

## Discussion

Lung cancer is the deadliest cancer around the world, and the main reason for cancer-specific death (8). The advanced stage of SCLC has been widely known as an incurable calamity because of the high rate of remote metastasis and resistance to prior treatment with a median survival of 2–4 months for those who didn't receive any treatment. A vast stretch of therapeutic advances has prolonged the SCLC patients' survival, such as the application of immune-checkpoint- inhibitor which has been written in the guideline of extensive SCLC as first-line treatment (9-11). Despite that, a lot of patients died shortly after metastatic SCLC diagnosis, therefore has no chance of getting further appropriate anti-cancer treatment and consultation. Prior studies focusing on the early death of gastric, colorectal, and ovarian cancer based on a large population have identified related risk factors (5-7). In this study, we were trying to describe the demographics and clinical characteristics associated with short-term survival for patients after diagnosis of de novo metastatic SCLC.

In this study of metastatic SCLC with a slightly higher rate of male patients diagnosis (52.6%), there were approximately 70% of patients died within 12 months, and over one-third of patients died within 90 days. A staggering sum, but the actual survival rate in recent years was assumed to have gone up due to new therapies and sophisticated screening strategies emerging such as Low-Dose Computerized Tomography before disease occurrence (12,13). Researches focusing on the molecular level has determined that factors including tumor mutational burden, the expression level of PD-L1, circulating tumor DNA, and so forth have a deep connection to the efficacy of implemented immunotherapy, and therefore impact the survival of SCLC patients (14-16). However, these factors were generally incompetent for patients who were facing imminent life threat, and patients experienced early death usually lack of the chance of getting additional treatment. Factors associated with early death have been initially studied in hematological disease or infectious disease, most of these presented factors were symptomatic and severe such as febrile neutropenia, hemorrhage, and septic shock (17-19). Clinical presentations stated above were indeed very noticeable situations to draw clinical physicians' much attention and handle accordingly, but the incidence rate of situations like this usually depends on the initial status of the disease, and in this study, baseline characteristics of patients and later intervention methods.

To be sure, the definition of early death varied from one malignancy to another. For example, died within 3 months was most commonly applied, but died within 1 year as early death was also widely used in breast cancer, bladder cancer, and stage I lung cancer patients which were, to a large extent, the result of relatively longer survival time among these cancer survivors (20-22). Due to the considerably

 

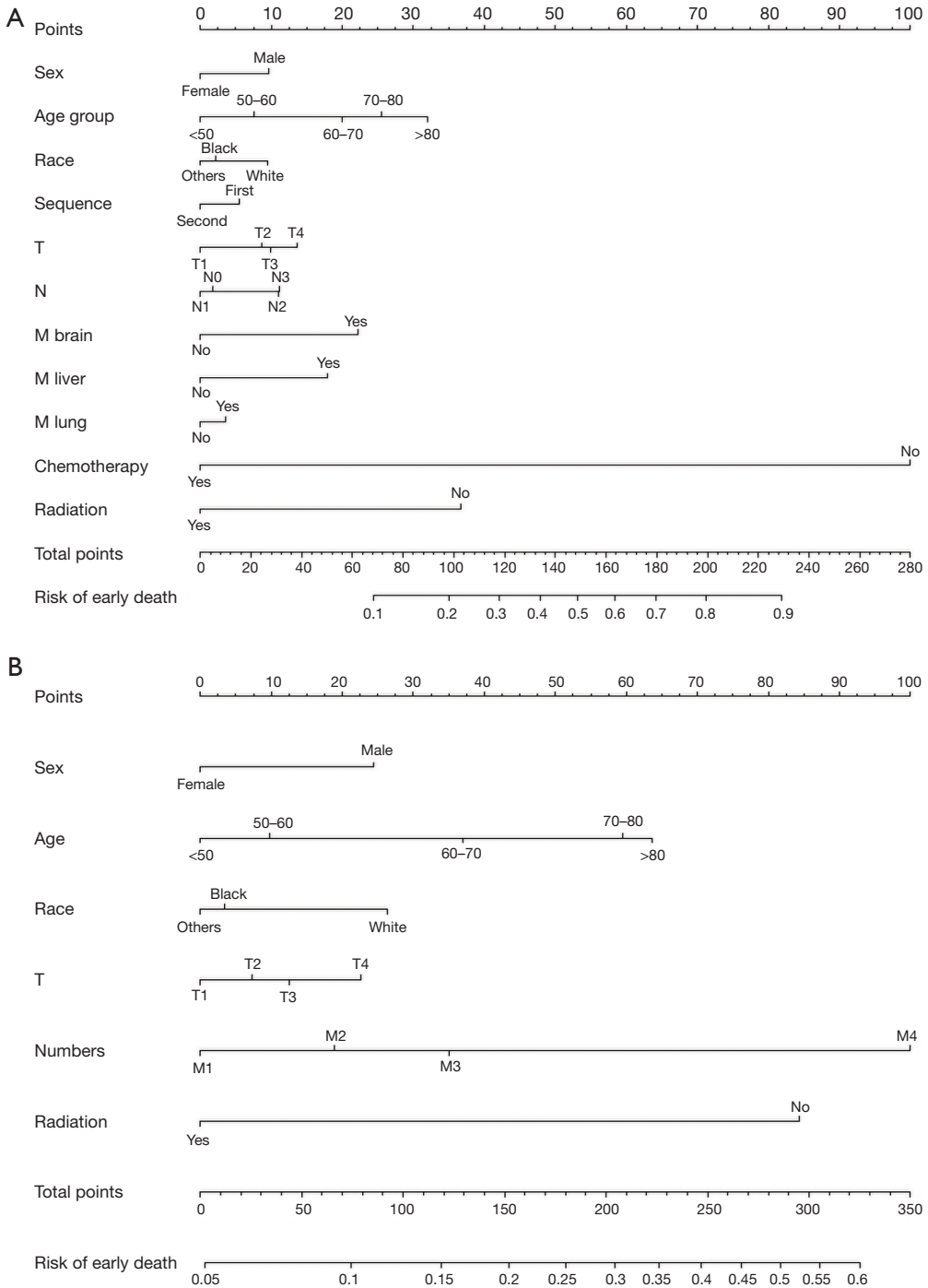


**Figure 2** The predictive nomograms for the early death of metastatic small-cell lung cancer. (A) Early death in overall population. (B) Early death in chemotherapy recipients.

short survival of metastatic SCLC and the method attained from prior studies, early death was defined as died within 3 months after the initial diagnosis of the target disease in this study (5-7).

The univariate and multivariate regression analysis has identified several predictive factors for the early death of

 

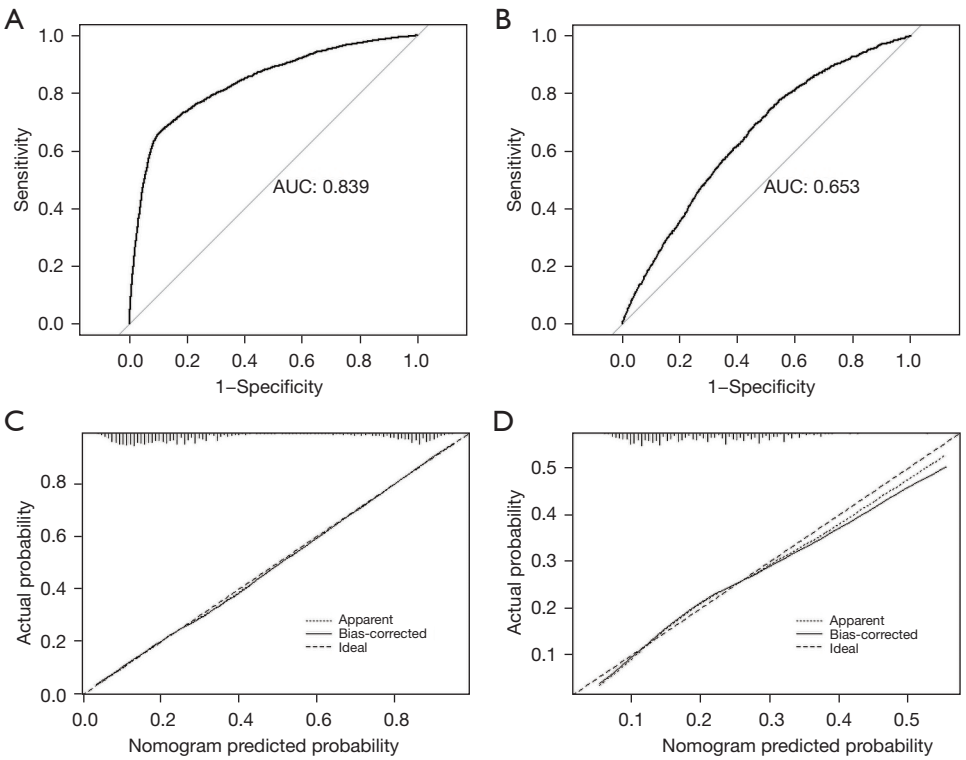


**Figure 3** ROC curves and calibration plots for the nomogram. (A) The ROC curve for the nomogram in overall population. (B) The ROC curve for the nomogram in chemotherapy recipients. (C) The calibration plots for the nomogram in overall population. (D) The calibration plots for the nomogram in chemotherapy recipients. AUC, area under the curve; ROC, receiver operating characteristic.

metastatic SCLC patients whether its' positive or negative including sex, age, race, sequence, T stage, N stage, remote organ metastasis (brain, liver, lung), chemotherapy and radiotherapy received. Although there were no studies exploring the different mechanism of survival pattern of SCLC between males and females, B. E. Johnson has first stated that female SCLC patients outlived male patients in 1988 (23). The higher rate of tobacco consumption among the male population not only resulted in a higher incidence of cancer but also increase the probability of developing other comorbidities which makes male patients much more likely to succumb to early death (24). Patients with advanced age were a negative predictor for survival can be explained by the substantial decline of physical performance that made individual patients unable to receive early involvement of palliative care, and also the high incidence of having chronic cardiovascular, pulmonary disease, and diabetes over 60 years old (25). While younger patients tend to have fewer complications and much tolerance to systemic therapy.

Liver metastasis, compared with other organs, demonstrated the highest incidence (57.4%) and risk of early death (total: 43.9%). However, in a large population-based study that covered 20,000 lung cancer patients in Sweden, liver metastasis comprised only 7% of all patients (26). Another study led by Japanese with nearly 2,000 patients also resulted in 7.1% of liver metastasis (27). The patients obtained in the present study were defined as de novo metastatic SCLC which has essential differences compared with previous studies. Despite that, patients with liver metastasis of SCLC had the lowest survival in these two studies as well. Patients with only one metastatic organ had a 37.1% risk of early death, as the number of metastatic organs increases, the risk of early death went up accordingly at a speed of 4.37% (male: 3.53%; female: 4.83%).

Chemotherapy and radiation were the only two variables significantly correlated with a good prognosis. Chemotherapy still remained the first-line option for unresectable SCLC while immunotherapy was flourishing mostly due to the chemosensitivity that SCLC patients initially presented. Severe symptoms such as superior vena

 

cava syndrome caused by SCLC itself were considered to be a possible candidate to receive emergency radiotherapy. Most importantly, patients that were deemed qualified for intensive treatment usually had lower performance status scores, younger age, relatively good liver and kidney function, and mild symptoms. Treatment-related death has been rarely seen in clinical practice because of the strictly censoring process (28).

Chemotherapy was the most significant variable, it has profoundly impacted the survival of metastatic SCLC as platinum-based chemotherapy remains the first-line treatment for these patients, and most of the patients in this study received chemotherapy (68.8%, N=9,095). However, a certain group of patients who had received systemic treatment yet died within 3 months. Statistical analysis showed that elderly white male patients diagnosed with advanced T stage and multiple organ metastasis were most vulnerable when facing the threat of early death even after chemotherapy was implemented. In clinical practice, patients with these characteristics must be carefully scrutinized to whether receive anti-cancer or palliative treatment.

Predictive nomograms for early death in metastatic SCLC patients and chemotherapy recipients were constructed based on risk factors unfolded and have demonstrated satisfactory predictive ability (AUC: 0.839 and 0.653). Patients with a higher incidence of early death can be screened from other patients to receive individualized palliative care, which is critical for further scheduled anti-cancer treatment.

There are several limitations to this study. Firstly, patients who developed remote organ metastasis later after initial SCLC diagnosis was not recorded in the SEER database; the medical history that profoundly associated with survival include smoking, alcohol consumption, comorbidity, and performance status were not investigated. Secondly, although chemotherapy and radiotherapy were discussed in the present study, detailed information concerning regimens, cycles, dosage, and radiation fields was absent in the SEER database. Finally, non-cancer-specific death patients were excluded in order to make this study mainly focus on death by metastatic SCLC itself, these patients were not uncommon in clinical practice, thus the predictive model was not practical for them. Findings in the present study should be further tested and verified by external data.

## Conclusions

In conclusion, this is the first study exploring variables correlated with early death in SCLC patients. More than one-third of metastatic SCLC patients died within 3 months after diagnosis. The liver was the most common metastatic organ, attributed to the highest number of the early death toll. Factors associated with early death were identified to construct predictive nomograms to assist clinical physicians in discriminating high-risk SCLC patients for targeted intervention. Elderly white male patients diagnosed with advanced T stage and multiple organ metastasis might be exempted from systemic treatment to receive palliative care.

## Acknowledgments

The authors would like to thank the SEER database for providing clinical information.
*Funding:* This study was supported by Sichuan Science and Technology Program (No. 2019YFS0323).

## Footnote

*Reporting Checklist*: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-462/rc

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-462/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020.

 

CA Cancer J Clin 2020;70:7-30.
2. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet 2011;378:1741-55.
3. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer 2017;17:725-37.
4. Pacheco J, Bunn PA. Advancements in Small-cell Lung Cancer: The Changing Landscape Following IMpower-133. Clin Lung Cancer 2019;20:148-60.e2.
5. Wang X, Mao M, Xu G, et al. The incidence, associated factors, and predictive nomogram for early death in stage IV colorectal cancer. Int J Colorectal Dis 2019;34:1189-201.
6. Urban RR, He H, Alfonso R, et al. Ovarian cancer outcomes: Predictors of early death. Gynecol Oncol 2016;140:474-80.
7. Zhu Y, Fang X, Wang L, et al. A Predictive Nomogram for Early Death of Metastatic Gastric Cancer: A Retrospective Study in the SEER Database and China. J Cancer 2020;11:5527-35.
8. Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med 2020;383:640-9.
9. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-39.
10. Yang S, Zhang Z, Wang Q. Emerging therapies for small cell lung cancer. J Hematol Oncol 2019;12:47.
11. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
12. Kang HR, Cho JY, Lee SH, et al. Role of Low-Dose Computerized Tomography in Lung Cancer Screening among Never-Smokers. J Thorac Oncol 2019;14:436-44.
13. Pinsky PF, Church TR, Izmirlian G, et al. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. Cancer 2013;119:3976-83.
14. Hellmann MD, Callahan MK, Awad MM, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. Cancer Cell 2018;33:853-861.e4.
15. Nong J, Gong Y, Guan Y, et al. Circulating tumor DNA analysis depicts subclonal architecture and genomic evolution of small cell lung cancer. Nat Commun 2018;9:3114.
16. Nabet BY, Esfahani MS, Moding EJ, et al. Noninvasive Early Identification of Therapeutic Benefit from Immune Checkpoint Inhibition. Cell 2020;183:363-376.e13.
17. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994;330:1639-44.
18. Guarana M, Nucci M, Nouér SA. Shock and Early Death in Hematologic Patients with Febrile Neutropenia. Antimicrob Agents Chemother 2019;63:e01250-19.
19. Golamari KR, Mikkilineni A, Chappidi S. Early death in acute promyelocytic leukemia: Evidence from a rural cancer center. Indian J Cancer 2020;57:451-6.
20. Zhao Y, Xu G, Guo X, et al. Early Death Incidence and Prediction in Stage IV Breast Cancer. Med Sci Monit 2020;26:e924858.
21. Zhu Z, Wang X, Wang J, et al. Preoperative predictors of early death risk in bladder cancer patients treated with robot-assisted radical cystectomy. Cancer Med 2019;8:3447-52.
22. Christensen NL, Rasmussen TR, Hansen KH, et al. Comorbidity and early death in Danish stage I lung cancer patients - an individualised approach. Acta Oncol 2020;59:994-1001.
23. Johnson BE, Steinberg SM, Phelps R, et al. Female patients with small cell lung cancer live longer than male patients. Am J Med 1988;85:194-6.
24. Christensen CH, Rostron B, Cosgrove C, et al. Association of Cigarette, Cigar, and Pipe Use With Mortality Risk in the US Population. JAMA Intern Med 2018;178:469-76.
25. Lamprea-Montealegre JA, Zelnick LR, Hall YN, et al. Prevalence of Hypertension and Cardiovascular Risk According to Blood Pressure Thresholds Used for Diagnosis. Hypertension 2018;72:602-9.
26. Riihimäki M, Hemminki A, Fallah M, et al. Metastatic sites and survival in lung cancer. Lung Cancer 2014;86:78-84.
27. Oikawa A, Takahashi H, Ishikawa H, et al. Application of conditional probability analysis to distant metastases from lung cancer. Oncol Lett 2012;3:629-34.
28. Ochi N, Hotta K, Takigawa N, et al. Treatment-related death in patients with small-cell lung cancer in phase III trials over the last two decades. PLoS One 2012;7:e42798.

**Cite this article as:** Hai T, Zhou L, Wang J, Wei H, Wang Y, Tian T, Wu W, Mei T. The nomograms to predict early death among metastatic small-cell lung cancer patients: a retrospective study based on SEER database. Transl Cancer Res 2022;11(7):2122-2134. doi: 10.21037/tcr-22-462

 