# Metformin Use and Survival after Non-Small Cell Lung Cancer: A Cohort Study in the U.S. Military Health System

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**Impact Statement** This is a major lung cancer study that demonstrated the association between improved survival and prolonged duration of metformin use among diabetic patients after NSCLC diagnosis. The survival benefits were more evident in early stage patients.

**Abstract**

Research suggests that metformin may be associated with improved survival in cancer patients with type II diabetes. This study assessed whether metformin use after non-small cell lung cancer (NSCLC) diagnosis is associated with overall survival among type II diabetic patients with NSCLC in the U.S. military health system (MHS). The study included 636 diabetic patients with histologically confirmed NSCLC diagnosed between 2002 and 2007, identified from the linked database from the Department of Defense's Central Cancer Registry (CCR) and the Military Health System Data Repository (MDR). Time-dependent multivariate Cox proportional hazards models were used to assess the association between metformin use and overall survival during follow up. Among the 636 patients, 411 died during the follow up. The median follow up time was 14.6 months. Increased post-diagnosis cumulative use (per one-year of use) conferred a significant reduction in mortality (adjusted hazard ratio (HR)=0.76; 95% CI=0.65 to 0.88). Further analysis by duration of use revealed that compared to non-users, the lowest risk reduction occurred among patients with the longest duration of use (i.e. use for more than 2 years) (HR=0.19; 95% CI=0.09 to 0.40). Finally, the reduced mortality was particularly observed only among patients who also used metformin before lung cancer diagnosis and among patients at early stage of diagnosis. Prolonged duration of metformin use in the study population was associated with improved survival, especially among early stage patients. Future research with a larger number of patients is warranted.

## Introduction

Diabetes is a common chronic disease that affects approximately 8.3% of the U.S. population, with type II diabetes accounting for 95% of the disease[1] . As one of the most prevalent chronic diseases in US, type II diabetes coexists with cancer in nearly 20% of cancer patients [2]. Type II diabetes is characterized by insulin resistance and compensatory hyperinsulinemia. Elevated insulin levels due to insulin resistance have been shown to promote tumor proliferation, increase cancer progression, and worsen clinical outcome[3]. Metformin is a glucose-lowering oral medication commonly prescribed as the first-line treatment of non-insulin dependent type II diabetes [4]. Metformin increases insulin sensitivity and lowers circulating insulin levels by activating AMP-activated protein kinase (AMK), leading to decreased hepatic gluconeogenesis [5]. Metformin has multiple anticancer mechanisms[6], including the induction of apoptosis [7], a direct down-regulation of tumor proliferating kinases[8] and an indirect benefit of reducing circulating glucose and insulin levels[9]. There is epidemiologic evidence that metformin may be associated with decreased cancer incidence[10]. A recent review and meta-analysis reported a 31% reduction in cancer incidence among metformin users, while some methodological issues remained [11].

The potential role of metformin in regulation of cellular energy metabolism, apoptosis and tumor proliferation has attracted much attention to its effects on cancer outcomes after diagnosis [11, 12]. The association between metformin use and survival among cancer patients has been studied but the results are not as consistent as those on cancer incidence. While favorable survival outcomes associated with metformin use have been found in patients with breast cancer[13, 14], colon cancer[15, 16], prostate cancer[17], and other cancers [18, 19] meta-analyses have

suggested interpretation with caution due to methodological bias (e.g. immortal time bias) and inadequate control for confounding in some studies [11, 12].

Lung cancer is the leading cause of cancer-related deaths worldwide[20]. Non-small cell lung cancer (NSCLC) comprises about 85% to 90% of all lung cancers [20]. Type II diabetes is a common comorbidity among lung cancer patients, which has been shown to increase the mortality among lung cancer patients[21, 22]. Based on research on other cancers [13-15, 17] and biological plausibility [23, 24] , we hypothesize that metformin use may also be associated with better survival among lung cancer patients with type II diabetes. There are few studies on the relationship between metformin use and survival among NSCLC patients with Type II diabetes [25-30] and the results showed survival benefit[25, 27, 28, 30], no association [29] or worse survival [26]. Among observational investigations, a recent study based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-Medicare database reported 20% mortality reduction associated with metformin use among stage IV NSCLC patients[28], while an earlier study based on medical records from the Cleveland Clinic Health System found increased risk of mortality among users[26]. Results from clinical trials are also inconsistent, supporting either a survival benefit[27] or no effects[29]. A recent lung cancer study, which did not differentiate NSCLC or small cell lung cancer, reported a weak non-significant reduction in lung-cancer specific mortality[31]. The differences in study design, timing of metformin use, characteristics of patient population, and variations in cancer treatment and data sources may have influenced the study results.

The U.S. Military Health System provides universal care to its beneficiaries and therefore, the potential effects of different levels of access to care, which are related to racial disparity in diabetes care [32, 33], the use of treatment and cancer outcomes, may be minimized for a

study on metformin and survival. Using the linked data from the Department of Defense (DoD) Central Cancer Registry (CCR) and the Military Health System (MHS) Data Repository (MDR), we assessed whether metformin use after NSCLC diagnosis is associated with overall survival in NSCLC patients with type II diabetes.

## Materials and Methods

*Data source*

This study was based on the MHS, which provides health care to active duty members, retirees, National Guard and Reserve members, and their dependents. The linked database from the CCR and MDR, described previously[34], served as the data source of this study. The CCR contains data on demographics, cancer diagnosis, tumor characteristics, cancer treatment, and vital status from the records of cancer patients diagnosed and/or treated at military treatment facilities (MTFs). Cancer site and histology codes are based on the International Classification of Diseases for Oncology, third edition (ICD-O-3)[35], in the CCR data. The registry staff conduct lifetime follow-up on patients. The CCR registrars follow up with patients and review medical records to identify vital status. The Defense Manpower Data Center (DMDC) data and obituary listings are also used for this purpose. Both CCR and MDR data in the linked database cover the period from 1998 to 2007. The MDR contains administrative and medical claims data from in-patient and out-patient services provided directly at MTFs (direct care) or paid for by the DoD at civilian facilities (indirect care). The MDR database includes information on clinical diagnoses of all medical conditions, which are coded using the International Classification of Disease, 9$^{th}$ Revision (ICD-9), and diagnostic and treatment procedures, which are coded using ICD-9 or Current Procedural Terminology (CPT) codes. The MDR pharmacy dataset contains pharmacy

records for all sources of care provided by military treatment facility, mail order, or retail. The pharmacy data are available from year 2002 and on.

The data linkage project was reviewed and approved by the institutional review boards of the Walter Reed National Military Medical Center, Tricare Management Activity, and the National Institutes of Health Office of Human Subjects Research.

*Study subjects*

Study subjects were patients with histologically-confirmed- primary malignant NSCLC diagnosed between 2002 (the year when MDR pharmacy data became available) and 2007 and identified from CCR that includes cancer patients diagnosed and/or treated at MTFs. Patients also had type II diabetes diagnosed before or at the time of NSCLC diagnosis. The study subjects were identified from the linked CCR and MDR database. Cancer site and histology were classified using the topography (C34.0 to C34.3, C34.8, C34.9) and morphology codes (8050-8078, 8083, 8084, 8250-8260, 8480-8490, 8570-8574, 8140, 8211, 8230, 8231, 8323, 8550, 8551, 8576, 8010-8012, 8014-8031, 8035, 8310) of the ICD-O-3[35]. Type II diabetes was ascertained from the MDR using ICD-9 diagnostic codes (250.x0, 250.x2, 357.2, 362.00-362.02, and 366.41), with the requirement that patients had the diagnosis in at least one inpatient record or three outpatient records[36]. Three outpatient records were used to reduce false diagnosis.

*Metformin use and survival*

The baseline was defined as the date of NSCLC diagnosis. The study outcome was all-cause death during follow up. The study end point was date of death, date of last contact, or the study end date, i.e. December 31, 2009. Survival times for subjects who did not die during

follow-up were censored at the study end date. We used proprietary and non-proprietary names recorded in the MDR's pharmacy database to identify prescriptions for metformin. We used two variables to measure post-diagnostic metformin use: ever use (yes or no) and cumulative duration of use. Ever use was defined as "yes" if there was at least one record indicating that the medication was prescribed after diagnosis. Cumulative duration of use was the sum of the mandatory days of supply of each prescription over time during follow up. Considering the potential impact of immortal time bias[37], in which exposure (metformin use) occurs after baseline and only those who survive to the point of exposure could have the chance to be exposed, therefore biasing the results towards a beneficial drug effect time, we analyzed the exposure variables as time-dependent variables (see statistical analysis below). Metformin use before NSCLC diagnosis was analyzed as a conventional time-fixed variable in the analysis.

*Other variables*

This study also included variables of NSCLC tumor stage, grade, cancer treatments, comorbidity index, tobacco use, and demographic characteristics. Tumor stage and grade were obtained from CCR. Tumor stage was in accordance of the American Joint Committee on Cancer (AJCC) staging system[38]. Stage was further grouped into early stage (stages I and II)[39], and late stage (stages III and IV) [40]. Data on the receipt of cancer surgery, chemotherapy, and radiation therapy were from both MDR and CCR and consolidated. Comorbidities were obtained from the MDR. A comorbid condition was considered to be present if at least one inpatient record or three outpatient records [41, 42] showed the diagnosis prior to the NSCLC diagnosis. The level of comorbidity was categorized according to the Charlson comorbidity index [43] with lung cancer diagnosis and type II diabetes diagnosis excluded. The index score

was further grouped into three groups with index score of 0, 1 and 2 or more, respectively. Tobacco use (never, former and current use) and demographic characteristics were available in CCR. Similar to metformin use, use of other anti-diabetic medications, such as insulin, insulin secretagogues (i.e. a group of drugs including sulfonylureas) and aspirin, was extracted from the MDR pharmacy database.

*Statistical analysis*

As mentioned, the study end point was death, date of last contact, or the study end date, i.e. December 31, 2009. Differences in characteristics by post-diagnostic user status were compared and tested using Chi-square test. The effect of post-diagnosis use (yes vs. no) and risk of all-cause mortality was analyzed in time-dependent Cox regression model. Post-diagnosis cumulative duration of use in relation to the risk of all-cause mortality was also modeled as a time-dependent variable in Cox proportional hazard models. This variable was a continuous variable with unit in days. Since the clinical effect of single day use is negligible, we assessed the effects of post-diagnostic cumulative use based on year of use. We then categorized cumulative use into three groups (>0 to ≤12 months, > 12 to ≤24 months and > 24 months) and investigated the effects of each duration group compared to no use as the reference group.

In all models, hazard ratios (HRs) and 95% confidence interval (95% CI) were estimated, adjusting for confounding variables that were related to both metformin use and survival, including tumor stage (stages I, II, III and IV); cancer treatments (yes or no); tobacco use (no use, previous use, current use and unknown); comorbidity index groups (0, 1, 2 or more); age, sex (male, female), race (White, Black, Asian, Other and unknown); baseline use of metformin (yes, no), insulin and insulin secretogogues (yes, no), baseline aspirin use (yes, no) and years in

cohort . Baseline use of anti-diabetic drugs was defined as the use before NSCLC diagnosis. The effect of cumulative post-diagnostic duration on all-cause mortality was also stratified by metformin use at baseline and tumor stage.

Statistical Analysis System (SAS) software, Version 9.3 for Windows (SAS Institute, Inc., Cary, North Carolina) was used to perform statistical analyses. All tests of significance were two-tailed and performed at an alpha of 0.05.

**Results**

The study included a cohort of 636 NSCLC patients with type II diabetes. The median time from diagnosis of Type II diabetes to NSCLC diagnosis was 72 months. As this is a cohort of diabetic patients with NSCLC, some patients had already taken metformin and/or other diabetic medications at baseline. The median time of metformin use at baseline was 20.65 months. During follow up, among the 636 patients, 259 patients used metformin, while 377 patients did not use.

Table 1 showed characteristics of the study population by post-diagnostic metformin user groups. Due to the low number of subjects who used more than 24 months, this group was combined with the group of >12 and ≤ 24 months in this table. Overall, non-users, short-term users (use 12 months or shorter) and long-term users (use more than 12 months) were significantly different by age (P=0.016), sponsor service branch (P=0.019), comorbidity index group (P=0.002), tumor stage (P<0.001), baseline metformin use (P<0.001), insulin secretogogues use (P<0.001) and aspirin use (P<0.001). Short-term and long-term users were similar in the distribution of age, comorbidity, baseline metformin use, baseline insulin

secretogogues use, and baseline aspirin use, but both groups were different from non-users by these variables. For example, compared to non-users, both short term users and long term users were younger, had less comorbidity, more likely to use metformin, insulin secretogogues and aspirin at baseline. However, compared to long-term users, short term users were more likely to be diagnosed at advanced stage.

During the follow up period (median follow up time of 14.6 months), 411 patients died. The time-dependent Cox model using post-diagnostic metformin use (yes vs. no) as the exposure variable did not show significant association between the use and all-cause mortality after adjusting for age, sex, race, tobacco use, comorbidity, cancer stage, histology, receipt of treatments, baseline use of metformin, insulin, insulin secretogogue, aspirin and years in the cohort (HR=1.27, 95% CI=0.94 to 1.72) (Data not shown). However, post-diagnostic cumulative metformin use, modeled as per one-year of use during follow up, was associated with a 24% reduction in all-cause mortality (HR=0.76, 95% CI=0.65 to 0.88) in time-dependent Cox model, after adjusting for the same set of covariates (Table 2).

Further analysis by duration groups showed that compared to non-users, there was an initial increased mortality risk during the first year of use (HR=2.05, 95% CI=1.51 to 2.78), and then the risk declined as the duration of use increased, with the most risk reduction observed in the patients who used metformin for the longest period of time (more than 24 months) (HR=0.19, 95% CI=0.09 to 0.40), respectively (Table 3).

We further stratified the analysis of cumulative duration of post-diagnostic use by metformin use before NSCLC diagnosis. As shown in Table 4, cumulative use (per one-year of use) during follow up was associated with a significant reduction in mortality (HR=0.68, 95% CI=0.57 to 0.82) only among those who used metformin before NSCLC diagnosis, while there

was no association among those who did not use metformin before diagnosis (HR=0.99, 95% CI=0.78 to 1.25) (Table 4). Similarly, in cumulative group analysis, significant risk reduction conferred by the longest duration of use (more than 24 months) was only observed among patients who used metformin before cancer diagnosis (HR=0.13, 95% CI=0.06 to 0.29), but not in those who did not use metformin before cancer diagnosis (HR=0.80, 95% CI=0.31 to 2.10) (Table 4).

We finally stratified the analysis by tumor stage groups. As shown in Table 5, cumulative use (per one-year of use) during follow up conferred a non-significant reduction in mortality (HR=0.84, 95% CI=0.66 to 1.06) among early stage patients, but not among late stage patients (HR=0.92, 95% CI=0.78 to 1.10) (Table 5). Among early stage patients, HR first increased for ≤12 month and then reduced with the most reduction in mortality occurred among those who used for the longest period of time (HR=0.26, 95% CI=0.09 to 0.73) (Table 5).

**Discussion**

Our study in the U.S. military health system showed that ever use of metformin (yes vs. no) after NSCLC diagnosis was not associated with all-cause mortality during follow up in the study population. However, cumulative use (modeled as per one-year of use) after diagnosis was associated with an overall significant reduction in mortality. When analyzed by specific duration of use, there was an initial increase of mortality associated with the first twelve months of use, followed by continued risk reduction with the highest reduction occurred among patients with the longest duration of use (i.e. use for more than 2 years). Finally, the reduced mortality conferred by a long cumulative duration was only observed among patients who also used

metformin before cancer diagnosis, suggesting that the beneficial effect was apparent with prolonged use, and it may be particularly true for those with early-stage tumors.

There have been a few studies examining metformin use and survival among lung cancer patients [25-31]. However, the results have been inconsistent. A close examination of these studies revealed that these studies differed by timing of metformin exposure, population characteristics (cancer stage and histology), reference group, and adjustment for confounders. A study on small cell lung cancer reported improved survival [30], but the time window of metformin use was unclear. In a study of 750 Stage IV NSCLC patients based on the SEER-Medicare data, pre-diagnostic metformin use was associated with significantly improved overall survival, after adjustment for tumor characteristics and chemotherapy [28]. However, in another study of lung cancer patients (NSCLC and small cell lung cancer were not differentiated), pre-diagnostic use of metformin increased risk of death after adjustment for age and tumor stage [26]. Among studies that evaluated post-diagnostic metformin use [25-27, 29, 31], a recent retrospective cohort study reported a non-significant HR of 0.86 (95% CI, 0.68 to 1.09) for lung cancer-specific mortality [31], after adjustment for multiple variables, although cancer stage was not adjusted and NSCLC and small cell lung cancer were not differentiated. A small clinical trial reported improved overall survival with metformin use compared to those on other anti-diabetic drugs among advanced stage NSCLC patients [27], while another small study found similar overall survival between patients with and without metformin use among locally advanced NSCLC patients[29]. No adjustment was made for confounders in both studies [27, 29]. Another report found borderline survival benefit associated with metformin mono-therapy after lung cancer diagnosis [25], but the survival was compared to non-diabetic patients rather than diabetics not on metformin, and

tumor characteristics such as stage, grade or histology were not controlled in the multivariate analysis.

Compared to these studies, we were able to adjust for key confounders with available data on demographics, tumor characteristics, treatments, comorbidity, and other anti-diabetic medication use. Further, our study was based on the data from the MHS, an equal access system. Since use of medication and cancer outcomes are related to accessibility to medical care, including diabetes care and treatment, a study in an equal access system can minimize the potential effects of unequal access to health care and cancer outcome.

While post-diagnostic cumulative metformin use was associated with improved survival in our study, it is noteworthy that post-diagnostic users were younger, had less comorbidity and were more likely to be diagnosed at early stages, which may be related to better survival. However, these factors as well as baseline metformin, insulin and insulin secretogogues use were controlled for in the multivariate model and stratified analysis by tumor stage was conducted, suggesting that post-diagnostic cumulative metformin use was independently associated with improved survival. However, the residual confounding by these variables on survival outcome cannot be ruled out. In addition, we do not exclude the possible effects of diabetes complications on the results if their distributions varied between the comparison groups.

Improved survival associated with metformin use is biologically plausible. Metformin activates AMPK-mTOR pathways and inhibits downstream cellular growth and proliferation in cancer cells [23, 44]. The direct inhibition of cancer cell proliferation by metformin treatment has been demonstrated in *in vitro* studies of prostate and breast cancers [23, 45, 46]. In lung cancer, research has shown that metformin could induce apoptosis and inhibit lung cancer cell growth in vitro[7] and in xenograft models[47]. In addition to the direct involvement in cellular process,

metformin also indirectly contributes to anticancer actions by reducing insulin levels and improving insulin sensitivity [5]. Reductions in endogenous insulin levels have been shown to reduce tumor burden and growth [47] .

The finding that the protective effect of post-diagnostic metformin use was only observed among those who also used metformin before cancer diagnosis suggests that the impact of metformin may appear only when it has been used for a certain length of period. However, this may also result from the possibility that patients with pre-diagnostic use discontinued the use after diagnosis due to more severe lung cancer, disease progression, or treatment complications, for which metformin is not recommended[48]. Thus, longer duration of use could be the result of, rather than the cause of stable disease. For patients who used metformin only after lung cancer diagnosis, metformin use tended to have protective effects but the effects were not statistically significant probably because the duration of use might not be long enough to observe the significant effects. Furthermore, the protective effect of post-diagnostic metformin use was particularly significant among early-stage patients. The beneficial effects of metformin may be overwhelmed by disease severity among late stage patients.

While the survival benefit has molecular and biological relevance, there is a concern of healthy-user effect, in which metformin users may be at earlier stage of type II diabetes (because metformin is the first line treatment of type II diabetes) than non-users and thus may be healthier with better survival than non-users. However, in our study, there was higher percentage of insulin users among metformin users than metformin non-users (e.g. 23.75% vs. 8.31% at baseline, and 37.84% vs. 14.85% during follow up). As insulin is usually prescribed to patients with more advanced type II diabetes[49], the higher percentage of insulin users among metformin users in our study population suggested that metformin users in our study might not have a

milder form of diabetes than non-users and thus the healthy-user effect might not be likely. Despite the fact that insulin use and advanced type II diabetes could increase mortality among cancer patients[21, 22], we still observed a reduced mortality among metformin users with prolonged duration of use.

It is noteworthy that there was an increase in mortality within 12 months of use and especially among early stage patients. It is not clear what factors might be related to the increased mortality in this group and further research is warranted.

Our study has the limitation of small numbers of subjects in stratified analysis. The unavailability of pharmacy data before year 2002 may have resulted in misclassification of baseline exposure status (metformin use before cancer diagnosis). However, the baseline exposure in our study was only analyzed for effect modification but not for the main effect, which only involved use after lung cancer diagnosis. Similarly, due to the unavailability of MDR pharmacy data before 2002, misclassification in determining other anti-diabetic medications may have occurred. In addition, we do not exclude the possibility of residual confounding. For example, we used AJCC tumor stage, which is a general predictor of prognosis and does not contain more detailed information that may also affect prognosis (e.g. a single bone metastasis vs. metastases in multiple organs for stage IV tumors). Thus, residual confounding due to unmeasured tumor features might exist when overall tumor stage was used. Moreover, the length of follow up may not allow assessment of long-term use. However, the survival time is often short for lung cancer patients and thus lack of a long-term assessment due to a short follow-up time might be of less concern compared to cancers with long term survival. Finally, information in the current data was not sufficient to accurately estimate the cumulative doses, thus analysis by cumulative dose was not conducted.

In conclusion, among NSCLC diabetic patients in U.S. Military Health System, we observed survival benefit among patients with prolonged duration of metformin use and especially among early stage patients. Future research with a larger number of patients is warranted to confirm the findings.



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Table 1. Characteristics of non-small cell lung cancer patients by post-diagnostic metformin use in the Military Health System (2002-2007)

| Variables | Total | No Use | | Ever Use | | | | P-Value |
|---|---|---|---|---|---|---|---|---|
| | | | | ≤12 Months | | > 12 months | | |
| | N | N | % | N | % | N | % | |
| **Age** | | | | | | | | **0.016** |
| <60 | 80 | 40 | 10.61 | 16 | 12.70 | 24 | 18.05 | |
| 60-69 | 237 | 131 | 34.75 | 53 | 42.06 | 53 | 39.85 | |
| 70-79 | 256 | 157 | 41.64 | 49 | 38.89 | 50 | 37.59 | |
| 80 and older | 63 | 49 | 13.00 | 8 | 6.35 | 6 | 4.51 | |
| **Sex** | | | | | | | | 0.100 |
| Male | 469 | 288 | 76.39 | 92 | 73.02 | 89 | 66.92 | |
| Female | 167 | 89 | 23.61 | 34 | 26.98 | 44 | 33.08 | |
| **Race** | | | | | | | | 0.387 |
| White | 495 | 302 | 80.11 | 97 | 76.98 | 96 | 72.18 | |
| Black | 88 | 47 | 12.47 | 20 | 15.87 | 21 | 15.79 | |
| Asian | 32 | 15 | 3.98 | 7 | 5.56 | 10 | 7.52 | |
| Other or Unknown | 21 | 13 | 3.45 | 2 | 1.59 | 6 | 4.51 | |
| **Marital Status** | | | | | | | | 0.493 |
| Married | 484 | 286 | 75.86 | 91 | 72.22 | 107 | 80.45 | |
| Separated, Divorced or Widowed | 122 | 75 | 19.89 | 28 | 22.22 | 19 | 14.29 | |
| Other or Unknown | 30 | 16 | 4.24 | 7 | 5.56 | 7 | 5.26 | |
| **Sponsor Service Branch** | | | | | | | | **0.019** |
| Army | 242 | 137 | 36.34 | 52 | 41.27 | 53 | 39.85 | |
| Navy | 119 | 76 | 20.16 | 13 | 10.32 | 30 | 22.56 | |
| Air Force | 226 | 133 | 35.28 | 46 | 36.51 | 47 | 35.34 | |
| Other or Unknown | 49 | 31 | 8.22 | 15 | 11.90 | 3 | 2.26 | |
| **Tobacco Use** | | | | | | | | 0.167 |
| Never used | 40 | 19 | 5.04 | 10 | 7.94 | 11 | 8.27 | |
| Previous use | 379 | 227 | 60.21 | 66 | 52.38 | 86 | 64.66 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Current use | 180 | 105 | 27.85 | 44 | 34.92 | 31 | 23.31 | |
| Unknown | 37 | 26 | 6.90 | 6 | 4.76 | 5 | 3.76 | |
| **Comorbidity Index Group** | | | | | | | | **0.002** |
| 0 | 145 | 63 | 16.71 | 40 | 31.75 | 42 | 31.58 | |
| 1 | 135 | 81 | 21.49 | 23 | 18.25 | 31 | 23.31 | |
| 2 or more | 336 | 233 | 61.80 | 63 | 50.00 | 60 | 45.11 | |
| **Tumor Stage** | | | | | | | | **<0.001** |
| Stage I | 213 | 108 | 28.65 | 37 | 39.37 | 68 | 51.13 | |
| Stage II | 49 | 26 | 6.90 | 10 | 7.94 | 13 | 9.77 | |
| Stage III | 161 | 101 | 26.79 | 31 | 24.60 | 29 | 21.80 | |
| Stage IV | 190 | 127 | 33.69 | 43 | 34.13 | 20 | 15.04 | |
| Unknown | 23 | 15 | 3.98 | 5 | 3.97 | 3 | 2.26 | |
| **Histology** | | | | | | | | 0.189 |
| Squamous cell carcinoma | 167 | 94 | 24.93 | 44 | 34.82 | 29 | 21.80 | |
| Adenocarcinoma | 267 | 157 | 41.64 | 46 | 36.51 | 64 | 48.12 | |
| Large cell carcinoma | 26 | 15 | 3.98 | 4 | 3.17 | 7 | 5.26 | |
| Other or Unknown | 176 | 111 | 29.44 | 32 | 25.40 | 33 | 24.81 | |
| **Baseline Metformin use[#]** | | | | | | | | **<0.001** |
| No | 337 | 284 | 75.33 | 30 | 23.81 | 23 | 17.29 | |
| Yes | 299 | 93 | 24.67 | 96 | 76.19 | 110 | 82.71 | |
| **Baseline Insulin use[#]** | | | | | | | | 0.183 |
| No | 537 | 321 | 85.15 | 100 | 79.37 | 116 | 87.22 | |
| Yes | 99 | 56 | 14.85 | 26 | 20.63 | 17 | 12.78 | |
| **Baseline Insulin secretogogues use[#]** | | | | | | | | **<0.001** |
| No | 435 | 304 | 80.64 | 70 | 55.56 | 61 | 45.86 | |
| Yes | 201 | 73 | 19.36 | 56 | 44.44 | 72 | 54.14 | |
| **Baseline aspirin use[#]** | | | | | | | | **<0.001** |
| No | 472 | 306 | 81.17 | 80 | 63.49 | 86 | 64.66 | |
| Yes | 164 | 71 | 18.83 | 46 | 36.51 | 47 | 35.34 | |

[#] Baseline use means use before NSCL diagnosis

Table 2. Post-diagnostic cumulative metformin use in time-dependent multivariate Cox model for all-cause mortality

| Variables | No. Alive/Dead | HR[#] | 95% CI |
|---|---|---|---|
| **Metformin use*** | | | |
| No use | 104/273 | 1.00 (ref.) | 1.00 (ref.) |
| Cumulative use (per one-year of use) | 121/138 | 0.76 | 0.65 to 0.88 |
| **Age (yrs)** | 377/259 | 0.98 | 0.97 to 1.00 |
| **Sex** | | | |
| Female | 69/98 | 1.00 (ref.) | 1.00 (ref.) |
| Male | 156/313 | 1.12 | 0.87 to 1.45 |
| **Race** | | | |
| White | 162/333 | 1.00 (ref.) | 1.00 (ref.) |
| Black | 36/52 | 0.87 | 0.64 to 1.18 |
| Asian | 15/17 | 0.99 | 0.60 to 1.65 |
| Other and Unknown | 12/9 | 0.88 | 0.42 to 1.85 |
| **Tobacco use** | | | |
| No use | 19/21 | 1.00 (ref.) | 1.00 (ref.) |
| Previous use | 139/240 | 0.92 | 0.57 to 1.48 |
| Current use | 58/122 | 0.66 | 0.40 to 1.10 |
| Unknown | 9/28 | 1.51 | 0.84 to 2.73 |
| **Comorbidity index group** | | | |
| 0 | 54/91 | 1.00 (ref.) | 1.00 (ref.) |
| 1 | 57/78 | 0.78 | 0.56 to 1.08 |
| 2 or more | 114/242 | 0.82 | 0.63 to 1.08 |
| **Tumor Stage** | | | |
| I | 126/87 | 1.00 (ref.) | 1.00 (ref.) |
| II | 24/25 | 1.13 | 0.69 to 1.83 |
| III | 42/119 | 1.80 | 1.27 to 2.54 |
| IV | 25/165 | 2.03 | 1.44 to 2.86 |
| Unknown | 8/15 | 1.26 | 0.69 to 2.30 |
| **Histology** | | | |

| | | | |
|---|---|---|---|
| Squamous cell carcinoma | 55/112 | 1.00 (ref.) | 1.00 (ref.) |
| Adenocarcinoma | 113/154 | 1.15 | 0.88 to 1.52 |
| Large cell carcinoma | 10/16 | 0.83 | 0.45 to 1.51 |
| Other | 47/129 | 1.09 | 0.83 to 1.43 |
| **Surgery** | | | |
| No | 54/287 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 171/124 | 0.45 | 0.34 to 0.59 |
| **Chemotherapy** | | | |
| No | 110/197 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 113/208 | 0.49 | 0.38 to 0.62 |
| Unknown | 2/6 | 1.20 | 0.53 to 2.75 |
| **Radiation** | | | |
| No | 137/173 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 87/237 | 1.14 | 0.91 to 1.43 |
| Unknown | 1/1 | 4.41 | 0.58 to 33.38 |
| **Baseline metformin use** | | | |
| No | 113/224 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 112/187 | 1.24 | 0.94 to 1.63 |
| **Baseline insulin use** | | | |
| No | 190/347 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 35/64 | 1.12 | 0.76 to 1.67 |
| **Baseline insulin secretogogues use** | | | |
| No | 155/280 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 70/131 | 1.45 | 1.12 to 1.88 |
| **Baseline aspirin use** | | | |
| No | 162/310 | 1.00 (ref.) | 1.00 (ref.) |
| Yes | 63/101 | 0.95 | 0.67 to 1.33 |
| **Years in cohort (yrs)** | 377/259 | 0.29 | 0.25 to 0.33 |

* Modeled as a time-dependent variable; The unit modeled is the effect of use per year.

# Adjusted for all variables shown in table.

HR=Hazard Ratio; CI=Confidence Interval

Table 3. Hazard ratios of post-diagnostic cumulative use of metformin groups in time-dependent Cox model for all-cause mortality

| Cumulative use groups* | No. (Alive/Dead) | HR[#] | 95% CI |
|---|---|---|---|
| No use | 104/273 | 1.00 (ref.) | 1.00 (ref.) |
| >0 to ≤12 months | 24/102 | 2.05 | 1.51 to 2.78 |
| >12 to≤24 months | 19/27 | 0.95 | 0.59 to 1.53 |
| >24 months | 78/9 | 0.19 | 0.09 to 0.40 |

* Modeled as a time-dependent variable

[#] Adjusted for the same variables in Table 2, including age, sex, race, tobacco use, comorbidity index, tumor stage, histology, surgery, chemotherapy, radiation therapy, baseline metformin use, baseline insulin use, baseline insulin secretogogues use, baseline aspirin use

HR=Hazard Ratio; CI=Confidence Interval

Table 4. Post-diagnostic cumulative use of metformin for all-cause mortality in time-dependent Cox model, stratified by baseline metformin use before cancer diagnosis

| Variables | Metformin use before diagnosis: Yes | | | Metformin use before diagnosis: No | | |
|---|---|---|---|---|---|---|
| | No. (Alive/Dead) | HR[#] | 95% CI | No. (Alive/Dead) | HR[#] | 95% CI |
| **Cumulative use*** | | | | | | |
| No use | 23/70 | 1.00 (ref.) | 1.00 (ref.) | 81/203 | 1.00 (ref.) | 1.00 (ref.) |
| Cumulative use (per one year of use) | 89/117 | 0.68 | 0.57 to 0.82 | 32/21 | 0.99 | 0.78 to 1.25 |
| **Cumulative use group*** | | | | | | |
| No use | 23/70 | 1.00 (ref.) | 1.00 (ref.) | 81/203 | 1.00 (ref.) | 1.00 (ref.) |
| >0 to ≤12 months | 12/84 | 1.70 | 1.18 to 2.45 | 12/18 | 1.84 | 0.99 to 3.40 |
| >12 to≤24 months | 16/25 | 0.75 | 0.43 to 1.31 | 3/2 | 0.96 | 0.24 to 3.91 |
| >24 months | 61/8 | 0.13 | 0.06 to 0.29 | 17/1 | 0.80 | 0.31 to 2.10 |

* Modeled as a time-dependent variable

[#] Adjusted for all variables shown in Table 2 except the stratifying variable

HR=Hazard Ratio; CI=Confidence Interval

Table 5. Post-diagnostic cumulative use of metformin for all-cause mortality in time-dependent Cox model, stratified by cancer stage group

| Variables | Early Stage (stages I and II) | | | Late Stage (stages III and IV) | | |
|---|---|---|---|---|---|---|
| | No. (Alive/Dead) | HR[#] | 95% CI | No. (Alive/Dead) | HR[#] | 95% CI |
| **Cumulative use*** | | | | | | |
| No use | 69/65 | 1.00 (ref.) | 1.00 (ref.) | 31/197 | 1.00 (ref.) | 1.00 (ref.) |
| Cumulative use (per one-year of use) | 81/47 | 0.84 | 0.66 to 1.06 | 36/87 | 0.92 | 0.78 to 1.10 |
| **Cumulative use group*** | | | | | | |
| No use | 69/65 | 1.00 (ref.) | 1.00 (ref.) | 31/197 | 1.00 (ref.) | 1.00 (ref.) |
| >0 to ≤12 months | 16/31 | 4.09 | 2.32 to 7.19 | 7/67 | 1.34 | 0.90 to 1.99 |
| >12 to≤24 months | 12/11 | 1.93 | 0.85 to 4.39 | 6/16 | 0.88 | 0.50 to 1.53 |
| >24 months | 53/5 | 0.26 | 0.09 to 0.73 | 23/4 | 0.75 | 0.43 to 1.31 |

* Modeled as a time-dependent variable

[#] Adjusted for all variables shown in Table 2 except the stratifying variable

HR=Hazard Ratio; CI=Confidence Interval