A Prognostic Model to Predict Mortality among Non–Small-Cell Lung Cancer Patients in the U.S. Military Health System

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Introduction: Accurate prognosis assessment after non–small-cell lung cancer (NSCLC) diagnosis is an essential step for making effective clinical decisions. This study is aimed to develop a prediction model with routinely available variables to assess prognosis in patients with NSCLC in the U.S. Military Health System.

Methods: We used the linked database from the Department of Defense's Central Cancer Registry and the Military Health System Data Repository. The data set was randomly and equally split into a training set to guide model development and a testing set to validate the model prediction. Stepwise Cox regression was used to identify predictors of survival. Model performance was assessed by calculating area under the receiver operating curves and construction of calibration plots. A simple risk scoring system was developed to aid quick risk score calculation and risk estimation for NSCLC clinical management.

Results: The study subjects were 5054 patients diagnosed with NSCLC between 1998 and 2007. Age, sex, tobacco use, tumor stage, histology, surgery, chemotherapy, peripheral vascular disease, cerebrovascular disease, and diabetes mellitus were identified as significant predictors of survival. Calibration showed high agreement between predicted and observed event rates. The area under the receiver operating curves reached 0.841, 0.849, 0.848, and 0.838 during 1, 2, 3, and 5 years, respectively.

Conclusions: This is the first NSCLC prognosis model for quick risk assessment within the Military Health System. After external validation, the model can be translated into clinical use both as a web-based tool and through mobile applications easily accessible to physicians, patients, and researchers.

Key Words: Model, Military health system, Mortality, Non–small-cell lung cancer, Risk prediction.

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Non–small-cell lung cancer (NSCLC) comprises more than 85% of lung cancers.[1] The 5-year survival rates for NSCLC range from 58.2% for early-stage disease to a dismal 4.5% for advanced disease.[2] Prognosis assessment upon NSCLC diagnosis is the first essential step toward making informed medical care decisions. Currently, cancer stage remains the most widely used prognostic factor in risk assessment for NSCLC.[3] However, the heterogeneity of the disease coupled with comorbidities results in substantial variability in survival among patients diagnosed at the same stage.[4] A more accurate risk stratification tool will likely aid in shared clinical decision making, designs of clinical trials, and a better allocation of health-care resources.[5]

To date, most models are derived from patient populations of clinical trials with small numbers of patients, confinement to specific tumor stages, and homogeneous patient characteristics.[6–12] These models are often aimed at patients with advanced stage NSCLC and lack applicability to nonclinical trial patients.[13–16] Some models have variables that are not readily available in routine clinical practice. In regard to population-based models, Blanchon et al.[13] have developed one using medical records and questionnaire data from study participants diagnosed with NSCLC in French general hospitals. This model demonstrated good discrimination accuracy and calibration by internal validation. However, the application of the model to U.S. populations has not been conducted with

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an external validation. A recent U.S. based model[14] derived from the Surveillance, Epidemiology and End Results (SEER) database identified age, sex, tumor grade, tumor stage, and race as prognostic factors. However, the clinical application of this model is limited by the lack of chemotherapy data. An updated version was based on SEER-Medicare population and incorporated chronic obstructive pulmonary disease as an additional predictor.[15] However, the model applies only to patients 65 year of age or older.

The U.S. Military Health System (MHS) is an equal access health-care system that provides universal health care to its beneficiaries including military service members, retirees, and their dependents. The Department of Defense (DoD) has a Central Cancer Registry (CCR) that collects detailed diagnosis, treatment, and follow-up information for patients diagnosed with cancer. The DoD also maintains a MHS Data Repository (MDR) that contains administrative and medical care information for MHS beneficiaries. The linked CCR and MDR database contains comprehensive data on demographics, tumor characteristics, medical history, and treatment information for MHS beneficiaries,[17–21] which offers a unique resource to comprehensively study cancer prognosis. So far, there is no NSCLC prognosis prediction tool for MHS beneficiaries and their physicians. The major independent risk factors for predicting survival among NSCLC patients receiving care from the MHS have not been identified. It is not clear whether risk factors identified from the general population apply to patients in the MHS system. Therefore, this study aimed to develop a prognostic assessment tool, which can be applied upon the diagnosis of NSCLC to the MHS beneficiaries, using the data in the MHS system.

MATERIALS AND METHODS

Sources of data

Linked data from the DoD's CCR and the MDR were used in this study, as previously described.[20,21] Currently, the linked database contains the data with cancer diagnosis from 1998 to 2007. The CCR contains information for cancer patients diagnosed or treated at military treatment facilities, including active duty military personnel, retirees, and their dependents. The CCR data included demographic variables, tumor characteristics, cancer diagnosis, treatment, recurrence, and vital status. The registry staff conduct lifetime follow-up on patients. Quality assurance was conducted following the guidelines established by the North America Association of Central Cancer Registries. The MDR contains administrative and medical care information that includes both inpatient and outpatient care provided at military treatment facilities and civilian facilities paid for by the DoD. The MDR database includes information on clinical diagnoses of all medical conditions, which are coded using the diagnostic and treatment procedures or Current Procedural Terminology of the International Classification of Disease, 9th Revision (ICD-9). 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 approved the data linkage project.

Study Subjects and Variables

A total of 5054 patients diagnosed with histologically confirmed primary NSCLC between 1998 and 2007 were identified from the linked 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, and any NSCLC codes between 8010 and 8576) of the International Classification of Diseases for Oncology, third edition (ICD-O-3).[22]

Demographic variables, tobacco use history, and tumor characteristics were obtained from the CCR. Demographic variables included age, sex, race, marital status, active duty status, and military service branch of patient or sponsor at the time of diagnosis. Tumor characteristics included tumor stage, histology, and tumor recurrence. Comorbidity data were obtained from the MDR. Comorbidities were considered as present if a diagnosis was recorded in at least one inpatient record or three or more outpatient records. Comorbidities were included if diagnosed at or before the diagnosis of NSCLC. Vital status and date of death were obtained from CCR. Both CCR and MDR data were used to determine the receipt of surgery, chemotherapy, and radiation therapy. Missing values in a variable were coded as a separate missing/unknown category.

Statistical Analyses

The survival time was calculated as the difference between date of diagnosis and date of death or censored at the date of last contact or the end of the study, December 31, 2009. The data set was randomly and equally split into a training set (50% of the data) to guide the building of the risk model and a testing set (the remaining 50% of the data) to validate the model prediction. Model development was performed in both the training and further repeated using the full data set. As the results were similar, only results from the full data set are presented in the final model. The assessment of model discriminatory accuracy and calibration was performed in training, testing, and the full datasets.

We first performed univariate Cox regression to assess the association between individual variables and death. Variables with statistical significance ($p < 0.05$) and clinical relevance were considered as candidates for stepwise Cox regression analysis. Stepwise Cox regression was performed to choose the final subset of predictors. The model's discriminatory accuracy for predicting mortality was assessed by constructing the time-dependent receiver operating characteristic curves for censored survival data[23] and calculated area under curve (AUC). We assessed model calibration capability by assessing the agreement between predicted and observed death rates.[24]

To facilitate the utility of the models in the clinical setting, we derived risk scores based on regression coefficients in the Cox proportional hazards model following standard procedures.[25] The risk score was calculated by dividing each regression coefficient by the smallest coefficient significantly

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