Acupuncture Reduced Incidence of Insomnia in Patients with Lung Cancer: A Retrospective Cohort Study

Handbook of Researchers

Guangdong Provincial Hospital of Chinese Medicine

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Dear Researcher,

Welcome to the “Acupuncture Reduced Incidence of Insomnia in Patients with Lung Cancer: A Retrospective Cohort Study”. Please strictly follow the standard operating procedure outlined in the handbook of researchers. Thank you in advance for your dedicated participation!

Guangdong Provincial Hospital of Chinese Medicine

Contents

1. Research Protocol

1.1. Background

Insomnia, a sleep disorder characterized by difficulties initiating or maintaining sleep and dissatisfaction with sleep duration or quality [1], is a common and disturbing symptom in lung cancer survivors. About 30%-50% of lung cancer survivors report having the condition[2-4], which is around twice to three times that of the general population[5-7]. Current main treatments include medication and cognitive-behavioral therapy for insomnia. Acupuncture, a traditional Chinese therapy with minimal side effects and good efficacy, is widely used among cancer patients. Due to its safety, accessibility, and potential preventive effects, acupuncture may be a good option for preventing insomnia in lung cancer patients. However clinical evidence is limited. Therefore, we aimed to examine the association between acupuncture and incidence of insomnia in lung cancer survivors through a retrospective propensity-score matched cohort study.

1.2. Objective

To investigate whether acupuncture could reduce the risk of developing insomnia.

1.3. Study design

A single-center retrospective propensity score-matched cohort study

1.4. Participants

1.4.1. Inclusion criteria

1) Patients newly diagnosed with lung cancer (ICD-10 C34.900) in the Electronic Medical Records Database (EMRD) of Guangdong Hospital of Chinese Medicine between 2012 and 2021. "Newly diagnosed" specifically refers to individuals for whom the first diagnosis of lung cancer was made at Guangdong Provincial Hospital of Chinese Medicine.

2) Patients aged 18 years or older.

1.4.2. Exclusion criteria

1) Patients who had insomnia at the time of lung cancer diagnosis or before.

2) Patients who had coma, drowsiness, or delirium at the time of lung cancer diagnosis. (information from medical records)

3) Patients with a follow-up period of less than 14 days

4) Patients whose data sources lack important information such as age, sex, and past medical history.

1.5. Exposures group and non-exposures group

Exposures were defined as receiving two or more sessions of acupuncture treatment (information from medical records) after being diagnosed with lung cancer.

1.6. Endpoint events

The primary endpoint was the occurrence of insomnia. Insomnia patients in this study were defined as those who were diagnosed with insomnia (ICD-10 G47.001) or prescribed sleeping pills for more than or equal to 2 consecutive days, including benzodiazepines (zolpidem, zopiclone, etc.), non-benzodiazepines (alprazolam, estazolam, diazepam, lorazepam, etc.), antidepressants (sertraline, amitriptyline, etc.), atypical antipsychotics (olanzapine, quetiapine, etc.).

The use of hypnotics was obtained by consulting the patients' consultation records and medication order information in the EMRD. For antidepressant drugs and atypical antipsychotic drugs, which are sometimes used to treat insomnia, we confirmed the occurrence of insomnia by checking the electronic medical records of patients.

1.7. Outcomes

1.7.1. Primary outcome

The hazard ratio for the association between acupuncture use and insomnia incidence in lung cancer patients, as determined by Cox proportional hazards regression models.

1.7.2. Secondary outcome

1) The cumulative incidence of insomnia in acupuncture and non-acupuncture groups (analyzed by Kaplan-Meier curves and log-rank test).

2) The association between the incidence of insomnia and the age in the propensity score matched sample (analyzed by restricted cubic splines).

3) The association between the incidence of insomnia and days (days from diagnosis of lung cancer to acupuncture) in the acupuncture cohort (analyzed by restricted cubic splines).

1.8. Statistical analysis

1.8.1. Data cleaning and description

Microsoft Excel for Mac (16.57) software was used for preliminary data cleaning,

including validating problematic data, removing duplicate values, and then importing them into RStudio software for further statistical analysis. Categorical variables such as sex, pathological diagnosis, and comorbidities are expressed as numbers and percentages of samples. Mean values and SDs are presented for continuous variables.

1.8.2. Propensity scores match

To account for the nonrandomized treatment administration of acupuncture, 1:1 greedy nearest neighbors matching was performed using matching without replacement and a maximum caliper width of 0.02 times the pooled SD of the logit of the propensity scores for the cohort[8]. Standardized mean difference (SMD) was used to evaluate the covariate balance between the acupuncture and control groups for which a difference of less than 0.10 was considered to indicate good balance[9].

1.8.3. Directed acyclic graph

To reduce bias in treatment effect estimates, the covariates were determined in advance. Combined with literature and clinicians' recommendations[4, 10], potential covariates were identified by a directed acyclic graph. The minimally sufficient adjustment set was determined using the DAGitty v3.1. The minimally sufficient adjustment set represents covariates such that the adjustment for this set of variables will minimize confounding bias when estimating the association between the exposure and the outcome.

1.8.4. Cox proportional hazards models

Survival analyses were conducted for outcome using Cox proportional hazards regression models. All the Cox proportional hazards models tested satisfied the proportional hazards assumption. Hazard ratios (HRs), adjusted hazard ratios (aHRs), and 95% confidence intervals (Cis) were reported.

In this study，the "index date" is defined as follows: For the acupuncture cohort, the index date is the specific date when a patient first undergoes acupuncture treatment after a new diagnosis of lung cancer. For the non-acupuncture cohort, their index date is randomly generated within the same year as the matched acupuncture case's index date. It must satisfy two conditions: it cannot be earlier than the patient's enrollment date in the study or later than the end of the follow-up period.

By aligning the follow-up start time (index date) in this way, the researchers aim to make the index dates of the two groups as comparable as possible. This approach helps to more accurately evaluate the effect of acupuncture and mitigates the impact of immortal time bias on the study results.

1.8.5. Kaplan-Meier method and log-rank test

The Kaplan-Meier method was used to estimate the cumulative incidence of insomnia

in acupuncture and control groups, and the log-rank test was used to test the difference.

1.8.6. Sensitivity analysis

For the unmatched samples, univariate and multivariate Cox proportional hazards regression analyses were performed as a sensitivity analysis. Furthermore, the E-value for the statistically significant primary outcome was calculated to assess the robustness of observed associations to potential unmeasured confounding[11]. All statistical analyses were performed using RStudio software and differences with a two-sided p value of less than 0.05 was considered statistically significant.

2. Organization and Management Responsibilities

2.1. Principal investigator

The principal investigator is responsible for designing the research protocol, securing funding, and assembling a qualified research team. They must ensure the study adheres to ethical guidelines and that all team members understand the research objectives and procedures. This includes overseeing the data collection process to ensure it aligns with the study design and that relevant data from the electronic medical record system of Guangdong Hospital of Chinese Medicine is accurately retrieved and analyzed. The principal investigator addresses any major issues during data collection and analysis and is ultimately responsible for the quality and integrity of the research findings.

2.2. Data collectors

Data collectors must rigorously adhere to the SOP outlined to guarantee the precision and comprehensiveness of the collected data. Within this study, they are responsible for extracting in-depth information from the electronic medical records of lung cancer patients. This involves employing a thorough data collection methodology with a high level of diligence to maintain data accuracy and timeliness, and ensuring no pertinent details are omitted. Should they encounter any discrepancies or incomplete data entries, they are obligated to promptly notify either the principal investigator or the quality control team.

2.3. Quality controllers

Quality controllers are responsible for maintaining the high standard of the research data. After each data collection, they conduct thorough verification to ensure data accuracy, completeness, and alignment with the research objectives. They also identify and address deviations from SOP, including proposing and monitoring corrective actions to guarantee data quality meets the required standards.

2.4. Data manager

The data manager is responsible for overseeing all aspects of data management. This

includes designing and maintaining the database, ensuring data security and confidentiality, and implementing data backup. Additionally, the data manager works closely with data collectors and quality controllers to resolve any data-related issues and ensures that data is available in the required format for analysis.

2.5. External Consultant

The external consultant provides expert advice and guidance on specific aspects of the study. They may be consulted on matters related to acupuncture, sleep disorder management, or statistical analysis. They reviews the study design and protocol to ensure scientific rigor and relevance. They also provide input on the interpretation of the study results and help disseminate the findings to the broader research community.

3. Standard Operating Procedure of Data Collection

3.1. Purpose

This SOP is formulated to ensure that the electronic medical record system data collection in this study meets the requirements for accurate clinical research data reporting.

3.2. Data collector qualifications

Data collectors need to have a medical background in oncology treatment, be familiar with standard lung cancer treatment protocols, and proficient in operating electronic medical record systems. They need to complete a comprehensive 4-hour training program in data collection and management, gain proficiency in data collection methods, and demonstrate competency through a evaluation.

3.3. Data collection process

3.3.1. Collection tool

Using the structured questionnaire that have been tested and validated, designed on the WJX (Wenjuanxing) platform. WJX offers diverse question types and logic settings that skip irrelevant questions based on prior answers, enhancing the survey experience. Using advanced security measures like encryption, access controls, and firewalls, along with internal protocols, it ensures data safety. The strictest restrictions on survey access and visibility are applied to protect data security when collecting information.

The questionnaire consists of 23 questions of various types, including single-choice, multiple-choice, date-selection, and fill-in-the-blank questions. It can only be submitted after all the required questions are completed. Question two, concerning inclusion and exclusion criteria, allows respondents to continue with subsequent questions if they select "Yes" and terminates the questionnaire immediately if "No" is selected. The questionnaire items are presented in Table 1, which also provides for explanations the questions.

3.3.2. Collection Process

Data collectors will receive a preliminarily filtered list of medical records and are

required to use the structured questionnaire on Wenjuanxing to collect the required study data from the electronic medical record system.

Data collectors first need to determine whether participants meet the inclusion/exclusion criteria for study enrollment. Then they gather information on demographics, diagnosis, ECOG PS score, treatment, medical history, acupuncture details (including type, points, and purpose), and track insomnia endpoint events, including medication use and timing. Detailed explanations for data collection of each item are provided in Table 1.

Uncertain parts were double-checked. When encountering unconfirmable information (e.g., diagnostic details), data collectors must report it to the data manager and PI. The PI then submits the issue to oncology clinical experts, relays the solution back to the data collectors, while the data manager documents the process.

All key information is set as required fields in the collection questionnaire. The questionnaire can only be submitted after all required fields are completed. Therefore, during data collection, if a medical record with missing key information is encountered, this case is excluded and recorded. This approach largely ensures that the collected information has no missing data.

Key information includes: ID number, Inclusion date, Gender, age, the date of lung cancer diagnosis, Clinical stage, Pathological diagnosis, ECOG PS score, Treatment, Comorbidities, the endpoint event of insomnia, Medications, the date of insomnia occurrence and the end date of the follow-up

If a patient received acupuncture, additional information includes: First acupuncture date, Acupuncture type, Purpose of acupuncture, and Acupoints.

Observation was discontinued if any of the following occurred:

1.A endpoint event (a diagnosis of insomnia disorder, or insomnia symptoms in progress notes, plus $\geqslant$2 consecutive days of sleep pills).

2.Patient death.

3.Onset of coma, drowsiness, or delirium in patients.

4.The follow-up end date of January 31, 2022

Item	**Question**	**Question Type/** **Field Attributes**	**Explanation**
1	ID number	Fill-in/Numeric	You will receive a preliminary list of patients diagnosed with lung cancer from the electronic medical record system between 2012 and 2021. Use this questionnaire to collect information on the IDs listed.
2	**Inclusion criteria：** 1. Patients newly diagnosed with lung cancer between 2012 and 2021. ☐YES ☐NO 2. Patients aged 18 years or older. ☐YES ☐NO **Exclusion criteria：** 1. Patients who had insomnia at the time of lung cancer diagnosis or before. ☐YES ☐NO 2. Patients who had coma, drowsiness, or delirium at the time of lung cancer diagnosis. ☐YES ☐NO 3. Patients with a follow-up period of less than 14 days. ☐YES ☐NO 4. Patients whose data sources lack important information such as age, sex, and past medical history. ☐YES ☐NO **Whether inclusion and exclusion criteria are**	Single-select/ Dichotomous variable	Inclusion criteria： 1. "Newly diagnosed" refers to patients who were first diagnosed with lung cancer (C34.900) at our hospital. Patient diagnosis information was determined based on the patient's diagnoses and ICD -10 codes in the EMRD. 2. Age is obtained from the inpatient record when the patient was first diagnosed with lung cancer. Exclusion criteria： 1. Locate the inpatient record from when the patient was diagnosed with lung cancer. Review the current medical history, past medical history, admission diagnosis, and progress notes to determine if there's a diagnosis of insomnia disorder or insomnia symptoms like difficulty falling asleep, early awakening, or poor sleep quality. 2. Locate the inpatient record from when the patient was diagnosed with lung cancer. Review the current medical history and progress notes to check if the patient's mental status is described as coma, drowsiness, or delirium. 3. Exclude patients whose length of hospital stay in the medical record system is less than 14 days (follow-up period is less than 14 days). Only when all inclusion criteria are satisfied and none of the exclusion criteria apply can "YES" be selected. Choosing YES allows you to continue to the next questions, while selecting NO will terminate the

	met. ☐YES ☐NO		questionnaire.
3	Inclusion date yyyy/mm/dd	Date selection (2012-2021)	The date of lung cancer diagnosis, which can be obtained from the diagnostic information.
4	Gender ☐male ☐female	Single-select/ Dichotomous variable	
5	Age (years)	Fill-in/Numeric (18-99)	Age is obtained from the inpatient record when the patient was first diagnosed with lung cancer.
6	The date of lung cancer diagnosis yyyy/mm/dd	Date selection (2012-2021)	The date of lung cancer diagnosis, which can be obtained from the diagnostic records.
7	Clinical stage ☐Stage I ☐Stage II ☐Stage III ☐Stage IVA ☐Stage IVB	Single-select/ Categorical variable	The staging criteria are based on the 8th edition of the International Association for the Study of Lung Cancer (IASLC) TNM staging for lung cancer, which can be obtained from the diagnostic records.
8	Pathological diagnosis ☐Adenocarcinoma ☐Squamous cell carcinoma	Single-select/ Categorical variable	This information can be obtained from the diagnostic records.

	☐Large cell carcinoma ☐Other non-small cell carcinoma ☐Small cell carcinoma ☐Pathology not specified		
9	ECOG PS score ☐0 ☐1 ☐2 ☐3 ☐4	Single-select/ Categorical variable	This information can be obtained from the specialty examination in the initial progress notes.
10	Treatment ☐Chemotherapy ☐Radiotherapy ☐Target ☐Immunotherapy ☐Surgery (during the follow-up period) ☐Opioids	Multi-select/ Categorical variable	Compile information on the treatments the patient received during the follow-up period (from enrollment to the endpoint event or January 31, 2022). This info can be found in the current medical history of the patient's last hospitalization during follow-up. (Per our hospital's requirements, medical records must document all anticancer treatments the patient has received.)
11	Comorbidities ☐Infection ☐Hypertension ☐Diabetes ☐Mental disorder	Multi-select/ Categorical variable	Patient diagnosis information was determined based on the patient's diagnoses and ICD-10 codes in the EMRD. Determine whether the patient was diagnosed with any of the following conditions during the follow-up period (from inclusion to the time of a positive event or until the end of follow-up on January 31, 2022): Infection： Acute upper respiratory infections (ICD-10 J00-J06)

	☐No complication		Influenza and pneumonia (ICD-10 J09-J18) Other acute lower respiratory infections (ICD-10 J20-J22) Urinary tract infection, site not specified (ICD-10 N39) Intestinal infectious diseases (ICD-10 N39A00-A09) Bacterial, viral and other infectious agents (ICD-10 B95-B98) Diabetes mellitus (ICD-10 E10-E14) Hypertensive diseases (ICD-10 I10-I15) Mental disorders： Schizophrenia, schizotypal and delusional disorders (ICD-10 F20-F29) Mood [affective] disorders (ICD-10 F30-F39) Neurotic, stress-related and somatoform disorders (ICD-10 F40-F48) Mental disorder, not otherwise specified (ICD-10 F99)
12	Did the patient receive acupuncture? ☐YES ☐NO	Single-select/ Dichotomous variable	Determine whether the patient received acupuncture during the follow-up period (from inclusion to the time of a positive event or until the end of follow-up on January 31, 2022). The criteria are met if any of the following conditions are satisfied: 1. The patient had two or more acupuncture department consultations during the follow-up, with acupuncture treatment recorded. 2. Acupuncture orders (e.g., manual/electro/scalp acupuncture) were issued during ≥2 hospitalizations in follow-up.
13	First acupuncture date	Date selection	The date of acupuncture consultation and treatment, or the date when acupuncture treatment orders were

	yyyy/mm/dd	(2012-2022)	issued.
14	Acupuncture type ☐Body acupuncture (BA) ☐Electroacupuncture(EA) ☐Scalp acupuncture(SA) ☐BA+EA ☐BA+SA ☐BA+EA+SA	Single-select/ Categorical variable	Select based on acupuncture consultation records or orders.
15	Purpose of acupuncture ☐Cancer pain ☐Cancer-related symptoms ☐Neurological symptoms ☐Digestive symptoms ☐Respiratory symptoms ☐Circulatory symptoms ☐Urinary symptoms ☐Endocrine and nutritional metabolism symptoms ☐Psychiatric symptoms	Multi-select/ Categorical variable	The purpose of acupuncture is primarily determined by reviewing the consultation purpose of the acupuncture department consultation (obtained from the consultation record) and the acupuncture-related records in the medical record. Classify symptoms based on their system. "Cancer-related symptoms" refer to general or systemic symptoms caused directly or indirectly by the cancer itself or its treatment, including: Fatigue: A persistent feeling of tiredness or lack of energy, often disproportionate to activity level. Weight loss: Unexplained loss of weight, which may be significant.

	☐Others		
16	Acupoints	Fill-in/ Character (Chinese)	Obtain specific acupoints from consultation records or medical orders.
17	Did the patient experience the endpoint event of insomnia? ☐YES ☐NO	Single-select/ Dichotomous variable	Patient diagnosis information was determined based on the patient's diagnoses and ICD-10 codes in the EMRD. Definition of Insomnia in this Study: 1. Diagnosed with insomnia (ICD-10 G47.0) after consultation with a psychiatric department. 2. Insomnia symptoms noted in progress notes, plus prescription of sleeping pills for ≥2 consecutive days. Sleeping pills include: - Benzodiazepines (e.g., zolpidem, zopiclone) - Non-benzodiazepines (e.g., alprazolam, estazolam, diazepam, lorazepam) - Antidepressants (e.g., sertraline, amitriptyline) - Atypical antipsychotics (e.g., olanzapine, quetiapine) If the answer is "No," the questionnaire will jump to the observation end time.
18	Medications ☐Nonbenzodiazepine ☐Benzodiazepine ☐Antidepressants ☐Atypical antipsychotics	Multi-select/ Categorical variable	Obtain medications used to treat insomnia from medical orders and verify them through progress notes.

	☐Other medicine		
19	The date of insomnia occurrence. yyyy/mm/dd	Date selection (2012-2022)	The date of insomnia diagnosis or when sleeping pills were prescribed.
20	The ECOG Ps score at the time of endpoint event or end of follow-up. ☐0 ☐1 ☐2 ☐3 ☐4	Single-select/ Categorical variable	Obtain the ECOG PS score from the specialty examination in the admission record at the time of insomnia occurrence, or from the admission record at the end of follow-up.
21	end date of the follow-up. yyyy/mm/dd	Date selection (2012-2022)	1. No insomnia during follow-up: End date of follow-up (last discharge date or project follow-up end date) 2. Insomnia occurred during follow-up: Date of insomnia occurrence
22	Did the patient die during the follow-up period? ☐YES ☐NO	Single-select/Dichotomous variable	
23	Date of death yyyy/mm/dd	Date selection (2012-2022)	

4. Standard Operating Procedure of Quality Control

4.1. Purpose

Ensure the scientific and standardized internal quality control of this study.

4.2. Responsibility assignment

4.2.1. Principal Investigator

Responsible for designing the quality control plan and appointing quality controllers. Must appoint 1-2 clinical physicians as quality controllers before the study starts.

4.2.2. Quality Controller

Thoroughly study the research protocol. After each data collection, conduct quality control as required by the protocol, including verifying data accuracy, completeness, and alignment with research objectives.

4.3. Quality control process

4.3.1. Checklist for quality control

Design a checklist for data collection questionnaires based on the clinical research protocol, covering:

1) Verification of basic information (gender, age, diagnosis date, comorbidities) collected from the electronic medical record database for accuracy.
2) Check for data logical consistency, time accuracy at observation points, and logical relationships.
3) Despite mandatory fields, still need to check for filling errors (wrong entries, missing key information).
4) Verify the accuracy of lung cancer diagnosis, oncological treatment, and medication information in the questionnaires.
5) Check the accuracy of endpoint event determination.
6) Check whether patients received acupuncture and verify the accuracy of recorded acupuncture points (no typos, omissions, or ambiguities).

4.3.2. Feedback procedure

Design a data issue feedback form by data managers to document problems during verification. It should include:

1) Participant ID

2) Issues found

3) Inspection date

4) Corrections and explanations

5) Submission date

6) Feedback date

7) Feedback and improvement results

8) QC officer and researcher signatures.

5. Standard Operating Procedure of data management

5.1. Purpose

To attain effective data management, upon verification of the accuracy of data by quality controllers, the data collected via the WenJuanXing platform should be promptly secured, locked, exported, and backed up on separate computers or hard drives.

5.2. Responsibility assignment

A specifically assigned researcher is responsible for overseeing all aspects of data management, including designing and maintaining the database, monitoring the progress of data collection, ensuring data security and confidentiality, performing data backup, assisting data collectors and quality controllers to resolve any data-related issues, and ensuring that data is available in the required format for analysis. Additionally, this also involves data database cleaning and submitting the locking database.

5.3. Data management process

5.3.1. Database Establishment

1) Name variables and establish a variable dictionary

After exporting data from the WenJuanXing platform, name variables based on question content and create a variable dictionary (including variable meanings, Field Attributes, and filling requirements).

2) Variable Value Coding Rules

① For continuous variables, the variable values are actual measured values, and their minimum and maximum values should be indicated.

② For ordinal/categorical variables, code "No" or "Not present" as 0, and other values as 1, 2, 3, 4, etc., in their order.

③ Date variables are presented in the format of yyyy/mm/dd.

④ The counting unit of time intervals can be days, weeks (7 days), or months (30 days), and are coded with the letters d, w, and m respectively.

⑤ -3 indicates that the question was skipped.

5.3.2. Database Closure and locking

1) Checklist for Database Closure

① All participants' data collection is complete.

② All quality control feedback forms are properly handled.

③ Data consistency, coding, and logical checks are accurate.

④ Outliers and missing data are verified.

⑤ Data quality assessments and audits are finished.

The database manager must confirm that the checklist meets lock requirements before closing the database.

2) Database Locking

Set the database file to read-only and store it securely (Note the database name, research number, research date, lock date, and operator.). If errors are found post-locking, follow approval steps to unlock, correct, and re-lock the database.

5.3.3. Data Storage

Store research archives securely with fire, theft, and damage prevention. Protect databases from unauthorized access via encryption, save them as read-only, and maintain multiple backups on different media. Ensure all storage media are properly preserved.

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