INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Radiomics for predicting tumor microenvironment phenotypes in non-small cell lung cance: A systematic review and meta-analysis

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Review question / Objective: **Tumor microenvironment (TIME) phenotype is an important factor to affect the response and prognosis of immunotherapy in non-small cell lung cancer (NSCLC). Recently, accumulating studies have noninvasivly perdited the TIME phenotypes of NSCLC by using CT or PET/CT based radiomics. We will conduct this study by means of meta-analysis to eveluate the power and value of CT or PET/CT based radiomics for predicting TIME phenotypes in NSCLC patients.**
Condition being studied: **At present, several recent prospective or retrospective cohort studies and randomized controlled studies have confirmed that CT or PET/CT-based radiomics were the potential tools to predict TIME phenotypes in NSCLC. However, this conclusion is controversial because of the difference of prediction profermance of different studies. The published and unpublished investigations will be included in this study. We will comprehensively evaluate the heterogeneity of these investigations, and the power and value of radiomics for predicting TIME phenotypes.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 September 2022 and was last updated on 14 September 2022 (registration number INPLASY202290060).

INTRODUCTION

Review question / Objective: **Tumor microenvironment (TIME) phenotype is an important factor to affect the response and prognosis of immunotherapy in non-small cell lung cancer (NSCLC). Recently, accumulating studies have noninvasivly perdited the TIME phenotypes of NSCLC by using CT or PET/CT based radiomics. We will conduct this study by means of meta-analysis to eveluate the power and value of CT or PET/CT based radiomics for predicting TIME phenotypes in NSCLC patients.**

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METHODS

Search strategy: A systematic search in 4 international databases (PubMed, Embase, Web of Science and Cochrane Library) was performed up to August 31th, 2022. Search terms include: (lung cancer OR non-small cell lung cancer OR non-small cell lung carcinoma OR NSCLC OR lung adenocarcinoma OR lung squamous cell carcinoma OR lung SCC) AND (tumor immune microenvironment OR TIME OR immune microenvironment OR immune phenotype OR immune profile) AND (radiomics OR radiomic OR machine learning OR artificial intelligence OR AI OR deep learning OR convolutional neural network).

Participant or population: Patients - who were diagnosed with NSCLC and had TIME phenotype analysis results.

Intervention: Intervention - preoperative CT or PET/CT scan.

Comparator: Comparator - hot TIME versus cold TIME in tumors of NSCLC patients before immunotherapy.

Study designs to be included: Study design - systematic review and meta-analysis of relevant prospective or retrospective cohort studies and randomized controlled studies.

Eligibility criteria: Studies were excluded if they: (1)Non-treatise: case studies, editorials, letters, review articles, and conference abstracts;(2)Studies not in the field of interest;(3)Using MRI-based radiomics to predict TIME phenotypes; (4)Overlaps in study populations.

Information sources: A systematic literature search will be conducted in four electronic databases including PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials for articles with terms related to "non-small cell lung cancer", "tumor microenvironment" and "radiomics" from the establishment date of databases to August 31th, 2022. Besides, potentially eligible studies which with no restriction on publication language, publication year and nationality were also manually checked through the reference lists of included studies.

Main outcome(s): Main outcome: the phenotypes of umor microenvironment (TIME) : hot TIME or cold TIME.

Additional outcome(s): Additional outcomes: sensitivity, specificity, positive and negative likelihood ratio, and area under ROC curve (AUC).

Data management: For each study, the main metrics to evaluate model performance will be collected: sensitivity, specificity, positive and negative likelihood ratio, and AUC. Studies that meet the criteria will be to estimate the overall performance of predictive models according to those metrics as expained above.

Quality assessment / Risk of bias analysis: The risk of bias (quality) assessment will be eveluated at study level by two reviewers (Ou ZQ and Li Q) using quality assessment of diagnostic accuracy studies-2 (QUADAS-2) method. Liao, CD will resolve any possible disagreement and calculate the Cohen's Kappa coefficient of above two reviewers. Through QUADAS-2, the following aspects will be evaluated: (1) sample size: whether it is sufficient to build a predictive model; (2) validation: the type of validation (split sample, cross-validation, external vs. internal validation); (3) methodology: machine learning or deep

learning models (type of models and their suitability for the objective proposed); (4) performance metrics: whether all required metrics to assess model performance are provided. Any potential publication bias will be assessed via funnel plot asymmetry and Egger's test.

Strategy of data synthesis: For each study, the main metrics to evaluate model performance will be collected: sensitivity, specificity, positive and negative likelihood ratio, and AUC. Studies that meet the criteria will be to estimate the overall performance of predictive models according to those metrics as expained above. Thus, a meta-analysis will be performed for each effect of interest. A fixed or random effects model will be fitted, depending on the empirical value of the Tau variability. The overall effect will be estimated with its 95% confidence interval, and the presence of heterogeneity will be analysed using the Q test and the I^2 index. If there is little heterogeneity in the data, it will be pooled and reported using forest plots.

Subgroup analysis: The type of imaging modality used CT or PET/CT in the included studies may determine the 'subgroups'.

Sensitivity analysis: The sensitivity analysis was conducted by excluding each study from the meta-analysis at each time.

Language restriction: None.

Country(ies) involved: China.

Keywords: Non-small cell lung cancer; Tumor immune microenvironment; Computer tomography; Positron emission tomography; Radiomics.

Dissemination plans: Anticipated start date 20 September 2022. Anticipated completion date 20 NovemberOctober 2022.

Contributions of each author:

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