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The impact of clinical parameters on progression-free survival of non-small cell lung cancer patients harboring EGFR-mutations receiving first-line EGFR-tyrosine kinase inhibitors

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ABSTRACT

Objectives: In daily practice, some patients with certain clinical characteristics may have better responses to the administration of epidermal growth factor receptor (EGFR)—tyrosine kinase inhibitors (TKIs). It is therefore reasonable to stratify and weigh the importance of these clinical parameters which may not only affect patients' responses to TKIs but also progression-free survival (PFS) other than the impact of EGFR mutation status per se.

Materials and methods: This retrospective study evaluated *EGFR*-mutant, non-small cell lung cancer patients who received EGFR-TKIs as a first-line therapy between January 2011 and December 2013. Several potential prognostic factors were analyzed with respect to PFS, and the results of this analysis were validated in another time cohort.

Results: A total of 262 patients were included in the study. Age $\leq$ 40 years, uncommon *EGFR* mutations, poor performance status, more sites of distal metastasis, and blood lymphocyte to monocyte ratio $\leq$ 3 were independently associated with poor PFS. These five factors were included in a scoring system and three prognostic groups A, B, and C, were formed based on total scores of 0–1, 2, and $\geq$3, respectively.

In the test group, the PFS was 15.7 month, 9.3 month, and 4.0 month in groups A, B, and C, respectively ($p < 0.001$). Between the test and validation groups, no significant differences were found in each one of the three prognostic groups.

Conclusions: The scoring system appears valid and reproducible for PFS prognosis in *EGFR*-mutant patients who received first-line EGFR-TKIs.

1. Introduction

Lung cancer is the leading cause of cancer-related death in Taiwan and worldwide [1,2]. NSCLC patients harboring *EGFR* mutations exhibit longer progression-free survival (PFS), experience less toxicity, and a better quality of life when treated with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) compared to those treated with platinum-based doublet chemotherapy [3,4].

A patient's ethnicity and sex (Asian and female, respectively), smoking status (non-smoker), and cancer histology (adenocarcinoma) were good clinical predictors of positive *EGFR* mutation status in previous studies [5–8] and *EGFR* mutations were found to be a strong predictor of PFS for patients receiving EGFR-TKIs [9,10].

However, approximately 17–29% of TKI-naïve patients with *EGFR* mutations do not respond to treatment with first line TKIs [11–13]. Wide ranges of PFS among these patients suggest that clinical, genetic, or epigenetic heterogeneity may exist among *EGFR*-mutant NSCLC populations that influence the patient's response to TKIs.

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Several factors have been shown to affect PFS in response to EGFR-TKIs, including major mutation type, adenocarcinoma histology, tumor burden, and Eastern Cooperative Oncology Group (ECOG) performance status (PS), but only a few studies focus on clinical factors [14–16]. Recent studies focusing on the correlation between the clinical presentation of *EGFR*-mutant NSCLC patients and patient response to EGFR-TKIs resulted in conflicting results [17,18]. One study suggested that the major *EGFR* mutation and adenocarcinoma histology were independent prognostic factors for patient response to drug, whereas another study revealed no clinical predictors for patient response. In both studies, the majority of patients received EGFR-TKIs as a second or later line of therapy. Thus, to decrease possible confounding factors, the current study focuses on patients receiving first-line EGFR-TKIs.

Other clinical factors including blood lymphocyte-to-monocyte ratio (LMR) and obesity/overweight have been shown to affect survival in NSCLC patients. Specifically, LMR was found recently to be an independent prognostic marker in patients with NSCLC after complete resection and in patients treated with TKIs [19,20]. Obese/overweight has been shown to have a time dependence protective effect in lung cancer patients receiving first line systemic chemotherapy [21]. However, these clinical factors have not been well studied in patients receiving TKIs.

We speculated that several clinical parameters might differentially affect treatment response in patients receiving EGFR-TKIs. We therefore retrospectively analyzed the prognostic role of several clinical parameters in *EGFR*-mutant, NSCLC patients who received EGFR-TKIs as a first-line therapy and created a scoring system in one cohort of patient population. A validation test was conducted in another cohort of patients to verify the usefulness of the scoring system.

2. Materials and methods

2.1. Patients and clinical characteristics

This study was conducted at Kaohsiung Chang Gung Memorial Hospital, a university-affiliated medical center. More than 400 new NSCLC patients each year were documented and received treatment in this hospital. Patients were included if they were 18 years or older, had histologically or cytologically confirmed stage IIIB or IV NSCLC with a positive *EGFR* mutation test, were tak-

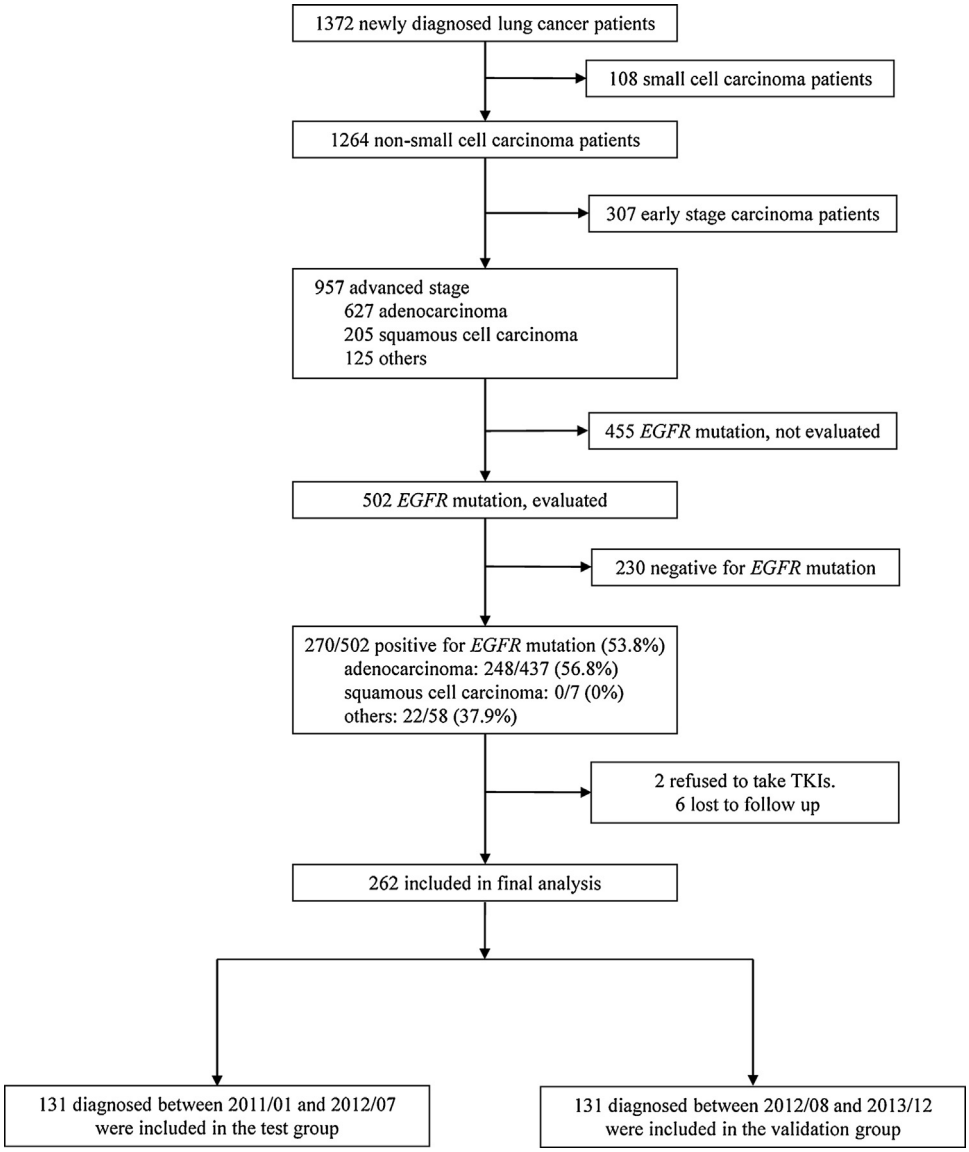

Fig. 1. Inclusion, screening, and group assignment of patients.