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External validation of prognostic indices for overall survival of malignant pleural mesothelioma

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ABSTRACT

Objective: There are several prognostic indices (PIs) to predict overall survival (OS) in malignant pleural mesothelioma (MPM) patients. Before using a clinical prediction model in the actual clinical setting, empiric evaluation of its performance based on datasets that were not used to develop the model (i.e., external validation) is essential. The purpose of this study was to conduct an external validation of the PIs for MPM.

Materials and methods: A retrospective cohort study was performed on MPM patients treated at 2 tertiary hospitals in Japan between 2007 and 2015. The primary outcome was OS. Harrell's c-index, and was calculated to examine the discrimination of three models. The bootstrapping technique was used to evaluate optimism.

Results: The participants comprised 183 patients who underwent surgical treatment (n = 61), chemotherapy (n = 101), and best supportive care (BSC, n = 21). The median OS rates were 1014 days for surgery, 690 days for chemotherapy, and 545 days for best supportive care (BSC). The respective discriminations (95% confidence interval) of the Eastern Cooperative Oncology Group Performance Status, the European Organisation for Research and Treatment of Cancer index, regimen, PS, histology or stage (rPHS) index, and Tagawa index for the OS of MPM patients were 0.532 (0.444–0.620), 0.560 (0.472–0.648), 0.584 (0.452–0.716), and 0.525 (0.453–0.596) for surgery; 0.632 (0.539-0.724), 0.622 (0.548–0.696), 0.677 (0.587–0.766), and 0.545 (0.436–0.653) for chemotherapy; and 0.504 (0.365–0.644), 0.583 (0.456-–0.710), 0.704 (0.508–0.899), and 0.583 (0.436–0.730) for BSC.

Conclusions: Each PI showed poor discrimination for MPM patients who underwent surgical treatment. The rPHS index showed moderate discrimination for patients given chemotherapy and BSC.

1. Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare cancer [1], a great majority of which are due to asbestos exposure [2]. Although the use of asbestos has been banned, the global incidence of MPM has been increasing because of its long latency [3]. Moreover, MPM remains a fatal disease despite recent advances in treatment [4–6]. Majority of patients receive palliative chemotherapy or best supportive care (BSC) [7].

In palliative care, estimation and discussion of prognosis is important [8]. For that purpose, we previously developed a prognostic index (PI) based on variables in usual care for overall survival (OS) of MPM patients treated with chemotherapy or BSC [9]. Before using a clinical prediction model in the actual clinical setting, empiric evaluation of its performance based on datasets that were not used to develop the model (i.e. external validation) is essential [10]. The limited sample size in the past study did not allow us to conduct external validation [9].

Abbreviations: BSC, best supportive care; EORTC, European Organisation for Research and Treatment of Cancer; EPP, extrapleural pneumonectomy; IMIG, International Mesothelioma Interest Group; MPM, malignant pleural mesothelioma; PEM, pemetrexed; PD, pleurectomy decortication; PI, prognostic index; PS, the Eastern Cooperative Oncology Group Performance Status; OS, overall survival; rPHS, regimen performance status histology or stage

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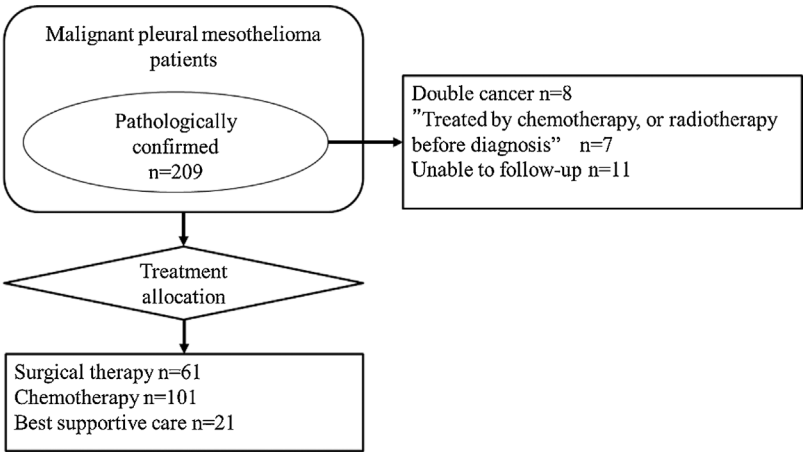

Fig. 1. Study flow chart.

In this current study, we aimed to evaluate the predictive performance of our index, the Eastern Cooperative Oncology Group Performance Status (PS), and 3 other PIs that use variables in usual care in an independent cohort [9,11–13].

2. Materials and methods

2.1. Study design and patients

We followed the statement of the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis [14] during all stages of study design, implementation, and reporting. This was a retrospective cohort study on all patients who received chemotherapy or BSC from April 2013 to March 2015 and surgical treatment from April 2007 to March 2015 for histologically proven MPM at either one of 2 tertiary hospitals in the South Hanshin medical region, which was an area with high MPM incidence in Japan [15,16]. Patients who had more than one cancer, those who were diagnosed by autopsy, and those who received chemotherapy or radiotherapy before a definite diagnosis of MPM were excluded. Demographic data and prognostic factors were obtained from chart review.

2.2. Prognostic indices

The Eastern Cooperative Oncology Group Performance Status (PS) is well known prognostic factor for MPM [11,17]. PS is categorical variable defined as follows: zero means fully active, one means restricted in physically strenuous activity, two means ambulatory and capable of all selfcare but unable to carry out any work activities, three means capable of only limited selfcare, four means completely disabled, and five means dead respectively [11].

The European Organization for Research and Treatment of Cancer (EORTC) index was developed based on populations from five prospective phase II clinical trials that were designed to assess the efficacy of various anticancer drugs for MPM [12]. The index used 5 variables to predict OS: white blood cell count, PS, probable or possible histologic diagnosis, histologic subtype, and gender. Patients were divided into 2 groups according to the total score.

The regimen, PS, histology, or stage (rPHS) index was developed based on populations of 2 hospitals that covered one medical region, but excluded patients who received surgical therapy [9]. To predict OS, the index used 4 variables, including regimen [e.g., platinum derivative, pemetrexed (PEM), or others]; PS; histologic subtype; and the International Mesothelioma Interest Group (IMIG) stage. Patients were divided into 5 groups according to the total counts of the variables.

The Tagawa score was developed from a population of patients who underwent extrapleural pneumonectomy (EPP) for MPM at 3 hospitals [13]. The index used the variables sex and platelet-to-lymphocyte ratio. Patients were divided into 3 groups according to the total score.

2.3. Primary outcomes measurement

The primary outcome was OS, which was previously defined as the time interval between diagnosis and death. Patients who did not die or who were lost to follow-up were censored on the date that they were last known to be alive before September 30, 2015 [9].

2.4. Statistical analyses

OS was estimated using the Kaplan–Meier method. Calibration curves showing agreement between observed and predicted outcomes were drawn. Harrell's c-index was used to assess discrimination of the model [18]. The bootstrapping technique was used to obtain the 95% confidence interval (for 500 replications [19]). We used Stata® ver. 13.1 (Stata Corp., College Station, TX, US). P values of less than 0.05 were considered to indicate statistical significance.

2.5. Ethical considerations

This study was performed according to the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Japanese Ministry of Health, Labour and Welfare. The protocol for the study was approved by the ethics committees of two hospitals, which granted a waiver for consent. The protocol was registered in the University Hospital Medical Information Network Clinical Trials Registry with the number: UMIN000018143.

3. Results

3.1. Validation cohorts

This study included 183 MPM patients. The details of the recruitment are shown in Fig. 1. Among patients under 75 years of age, 100% underwent surgery, 81.2% received chemotherapy, and 52.4% were given BSC. Among patients with PS 0, 55.7% underwent surgery, 29.7% received chemotherapy, and 14.3% were given BSC (Table 1). The survival curves for each treatment group are shown in Fig. 2. The median OS after surgery, chemotherapy, and BSC were 1014 days, 690 days, and 545 days, respectively.

3.2. External validation

3.2.1. Calibration

The survival curves according to the PI for each treatment group are shown in Fig. 3. Each curve showed good agreement between observed and predicted survival. PS showed separate observation curves for