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ORIGINAL ARTICLE

Association between Serum Angiotensin-converting Enzyme 2 Level with Postoperative Morbidity and Mortality after Major Pulmonary Resection in Non-small Cell Lung Cancer Patients

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Background To explore the association between serum angiotensin-converting enzyme 2 (ACE2) levels and postoperative morbidity and mortality after major pulmonary resection in non-small cell lung cancer (NSCLC) patients.

Methods Preoperative and postoperative serum ACE2 levels in 320 NSCLC patients who underwent major pulmonary resection were measured. The serum ACE2 levels on postoperative day 1 were divided into quartile categories.

Results After adjustment for age, sex, body mass index, current smoking status, forced expiratory volume in 1 second, coronary heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and tumour clinical stages, the risk of developing postoperative morbidities was significantly higher in the lowest serum ACE2 level quartile than in the highest quartile (hazard ratio, 2.12; 95% CI, 1.57-6.23; p=0.008). NSCLC patients with a serum ACE2 level $\leq$3.21 ng/mL had significantly higher rates of pneumonia, pleural effusion, atrial fibrillation as well as higher in-hospital mortality after major pulmonary resection, compared with those with a serum ACE2 level >3.21ng/mL.

Conclusions The serum ACE2 level one day post surgery is an independent risk factor for postoperative morbidities after major pulmonary resection in NSCLC patients. Thus, it could be used as a prognostic factor for postoperative morbidities after major pulmonary resection in NSCLC patients.

Keywords Angiotensin-converting enzyme 2 • Pulmonary resection • Non-small cell lung cancer • Morbidity • Mortality

Introduction

The major comorbidity in patients with non-small cell lung cancer (NSCLC) is of cardiovascular nature and is reported to be up to 23% [1]. The incidence of cardiovascular disease has been described to be a major risk factor for morbidity and mortality following surgery for NSCLC [1–5].

The renin-angiotensin system (RAS) plays a crucial role in cardiovascular regulation [6]. In the RAS, angiotensin-converting enzyme (ACE) metabolises angiotensin I

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(Ang I) to form angiotensin II (Ang II), which exerts direct trophic actions on cardiovascular cells [6]. Local Ang II production is of key importance in the pathophysiology of the RAS in cardiovascular system [7]. Recently, ACE2, a new member of the RAS, was found to function as a negative regulator of the Ang system by metabolising Ang II to a putatively protective peptide Ang-(1-7) with high efficiency [8–10]. ACE2 is expressed and active in most tissues. The highest expression of ACE2 is observed in the endothelium, the lungs, and the heart [11]. It has been widely accepted that ACE2 is critical in balancing the activity of the ACE-Ang II axis and thus plays a pivotal role in the body as an endogenous regulator of the RAS [10]. In the present study, we for the first time explored the association between serum ACE2 levels and postoperative morbidity and mortality after major pulmonary resection in NSCLC patients.

Materials and methods

Patients

From January 2008 to March 2013, 320 Han Chinese NSCLC patients who underwent major pulmonary resection were enrolled in this study. The inclusion criteria included: (1) Definitely diagnosed with NSCLC; (2) Underwent major pulmonary resection including lobectomy, bilobectomy, and pneumonectomy, but not segmentectomy and wedge resection; (3) Had not received any treatment for NSCLC before pulmonary resection. Patients with other concurrent malignancies, congenital heart diseases, or a previous cardiovascular surgical history were excluded. This study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. Before the start of the study, all participants provided written informed consent.

Data collection

Operations were performed under general anaesthesia through lateral thoracotomy completed with radical systematic lymphadenectomy. Staging was reevaluated according to the seventh edition of the TNM classification [12]. Histologic typing was carried out according to the World Health Organization histologic classification [13]. Morbidity was defined as any postoperative event, such as pneumonia, prolonged air leak with postoperative chest tube drainage >7 days, atrial fibrillation, or pleural effusion requiring renewed drainage. Operative mortality was defined as in-hospital mortality. Blood samples were drawn on preoperative day 3, preoperative day 1, postoperative day 1, and postoperative 3, respectively. All blood samples were subject to ELISA assays for serum ACE2 levels using an ACE2 (human) ELISA Kit (K4918-100) purchased from BioVision (Milpitas, CA, USA).

Statistical analysis

Serum ACE2 levels were divided into quartile categories: ≤3.21, 3.22-3.86, 3.87-4.52, and ≥4.53 ng/mL. The adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using the Cox proportional hazard model. All continuous variable values were expressed as Mean ± SD. Comparisons of means between two groups was performed with student t tests. Categorical variables were expressed as n(%) and analysed with Chi-square tests or Fisher's exact tests where appropriate. All statistical analyses were performed with SAS 9.1.3. The statistical significance level of this study was set at a two-tailed α=0.05.

Results

Serum ACE2 levels were measured in blood samples collected on preoperative day 3, preoperative day 1, postoperative day 1 and postoperative day 3. As shown in Fig. 1, the serum ACE2 level in NSCLC patients was at baseline level preoperatively, peaked 24 hours after major pulmonary resection, and returned to baseline level three days after the surgery. We divided the serum ACE2 levels on postoperative day 1 into quartile categories: ≤3.21, 3.22-3.86, 3.87-4.42, and ≥4.43 ng/mL. As shown in Table 1, there were no significant differences among the quartile categories in age, sex, body mass index (BMI), current smoking status, forced expiratory volume in 1 second (FEV1), and prevalence of coronary heart disease, hypertension, diabetes mellitus and chronic obstructive pulmonary disease (COPD). There were also no significant differences among the quartile categories in distribution of NSCLC histology and clinical stages (Table 2).

As shown in Table 3, postoperative morbidities increased with descending quartiles of serum ACE2 levels, and the risk was significantly higher in the first quartile than in the second, third, and fourth quartiles (Model 1). After adjustment for age, sex, BMI, current smoking status, FEV1, coronary heart disease, hypertension, diabetes mellitus, COPD, and tumour clinical stages (model 2), the risk of developing postoperative morbidities was significantly higher in the lowest serum ACE2 level quartile than in the highest quartile (hazard ration, 2.12; 95% CI, 1.57-6.23; p = 0.008).

We then examined the association between the lowest serum ACE2 level quartile (≤3.21 ng/mL) and the incidence

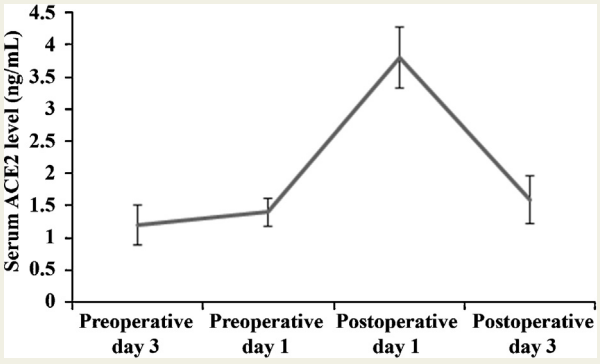

Figure 1 Preoperative and postoperative serum angiotensin-converting enzyme 2 (ACE2) levels in non-small cell lung cancer patients undergoing major pulmonary resection.