The use of trastuzumab affected by health insurance policy in Jiangsu Province of China

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Background: Breast cancer recurrence and mortality have been shown to decrease after trastuzumab treatment in human epidermal growth factor 2 (HER2)-positive early-stage breast cancer (EBC) patients. In Jiangsu Province, trastuzumab has been subsidized for patients with HER2-positive EBC since 2013. Several studies showed that Jiangsu was one of the provinces with the highest rates of adjuvant trastuzumab therapy. To uncover the underlying reason, we designed the study to investigate trastuzumab use for HER2-positive breast cancer patients, and to examine the changes caused by medical insurance coverage for trastuzumab in Jiangsu province of China.

Methods: This was a retrospective, multicenter clinical study with follow-up data. HER2-positive EBC patients diagnosed in 7 representative hospitals in 2010, 2011, and 2013 were enrolled. Demographic and clinical data, and details of diagnosis, treatments, and prognosis, were collected. Data analysis included univariate analysis, multivariate logistic regression, survival analysis, and subgroup analysis.

Results: Of the 641 patients (mean age 51.01±10.79 years) included, 412 (64.27%) patients had medical insurance. Trastuzumab therapy was given to 214 (33.39%) patients. The multivariate logistic regression showed that medical insurance coverage, age, and radiotherapy were associated with trastuzumab use (P<0.05). The overall survival was significantly better in the trastuzumab group than in the non-trastuzumab group (HR: 1.607; 95% CI: 1.046–2.469; P=0.040). Subgroup analysis revealed that there was a trend towards more patients with medical insurance (P=0.073), and significantly more patients received trastuzumab therapy (P<0.001) in 2013 than in 2010–2011. Additionally, trastuzumab use in China was lower than in developed countries. Patients with medical insurance were more likely to use trastuzumab, and more patients could afford trastuzumab therapy with the development of China's health-care reform.

Conclusions: Our study suggested that the percentage of patients who received trastuzumab in China was lower than developed countries. Patients who had medical insurance were more likely to use trastuzumab than those without medical insurance. The health insurance policy in China has improved access for breast cancer patients who require trastuzumab therapy.

Keywords: Health insurance; breast cancer; trastuzumab
Introduction

Breast cancer is the most commonly diagnosed cancer (11.6%) and the leading cause of cancer death (6.6%) among females worldwide (1). Different subtypes of breast cancer have distinct risk profiles and prognosis (2). Approximately 20% of breast cancer patients are human epidermal growth factor 2 (HER2)-positive, which was known to have a poorer prognosis before the development of targeted therapies (3).

Trastuzumab (Herceptin, Roche), a monoclonal antibody targeting the extracellular domain of ERBB2, is a targeted therapy for HER2-positive breast cancer patients. Breast cancer recurrence and mortality have been shown to decrease after trastuzumab treatment in HER2-positive early-stage breast cancer (EBC) patients (4). Clinical guidelines recommend trastuzumab-based chemotherapy (along with pertuzumab in some cases) as the standard (neo) adjuvant therapy for HER2-positive EBC patients (5-7).

Trastuzumab was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an adjuvant therapy in 2006, and by the EMA as a neoadjuvant therapy in 2011 for patients with HER2-positive EBC (8). Trastuzumab was registered by the China Food and Drug Administration (now renamed State Administration for Market Regulation) in 2008 as the treatment for HER2-positive EBC patients. In 2009, China launched a major health-care reform (9). Under this new system, since January 2013, trastuzumab has been subsidized for patients with HER2-positive EBC under the Ministry of Human Resources and Social Security of the People’s Republic of China (MOHRSS). The policy has greatly reduced the out-of-pocket costs of patients with HER2-positive EBC. Jiangsu was one of the first provinces to reimburse trastuzumab for patients, so the data regarding the use of trastuzumab affected by health insurance in Jiangsu is most representative.

Two studies have estimated that approximately 40.5% (10) and 29.8% (11) of patients with HER2-positive EBC received trastuzumab therapy in China. Jiangsu was one of the provinces with the highest rates of adjuvant trastuzumab therapy (11). Since both studies were conducted after 2012, we assumed that medical insurance coverage for trastuzumab in Jiangsu contributed to its widespread use. Therefore, the current study aims to investigate the current use of trastuzumab in patients with EBC, and to examine the changes caused by medical insurance coverage for trastuzumab in Jiangsu, China. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-3329).

Methods

Study design

This study was a retrospective, multicenter clinical study with follow-up data. It covered seven representative hospitals in seven cities in Jiangsu province. The study was based on data extracted from patients’ hospital records in 2010, 2011, and 2013 to avoid interference. The participating hospitals are listed in Table S1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Affiliated Hospital with Nanjing Medical University (Jiangsu Province Hospital, No.: 2018-SR-205). Informed consent form was signed by every patient.

Patients

This study included patients diagnosed with HER2-positive EBC. Patients had to meet the following criteria for enrollment: aged ≥18 and ≤85 years; were diagnosed with HER2-positive breast cancer on the basis of a pathological report after breast surgery or core needle biopsy; had undergone surgery for breast cancer and received related treatments; had been staged lower than T4N3M0. Patients who had inflammatory breast cancer, developed metastatic disease, or had pre-invasive carcinoma were excluded. All patients included in the study met the HER2-positive diagnostic standard (either HER2 gene amplified by fluorescent in situ hybridization or 3+ by immunohistochemistry) according to the American Society of Clinical Oncology/College of American Pathologists...
clinical practice guidelines (12). The eligible patients were divided into two groups: the trastuzumab group and the non-trastuzumab group. The different characteristics between the two groups were analyzed.

Data collection

Data were extracted from the medical records. Telephone conversations were permitted if necessary. Demographic and clinical data (patient identifier, date of birth, height, weight, medical insurance status, menstruation status, heart disease history), diagnosis data (diagnostic date, surgical method, pathological type, pathological stage, receptor status), treatment data (whether neoadjuvant or adjuvant chemotherapy was received, whether trastuzumab was administered, the duration of trastuzumab treatment, whether radiotherapy was received, whether endocrine therapy was received), and prognostic data (date of death) were recorded for each patient.

Overall survival analysis

Overall survival analysis was performed to compare between women in the trastuzumab group and women in the non-trastuzumab group. The last follow-up was 31 January, 2020. Patients without mortality information were excluded.

Stratified analysis

Several studies have indicated that medical insurance status affects the use of trastuzumab (11,13-15). Trastuzumab entered the medical insurance dictionary of Jiangsu Healthcare Security Administration in 2012. In the current study, we explored whether medical insurance cover affected the use of trastuzumab. To accurately assess this, patients diagnosed with breast cancer in 2012 were excluded from the study.

Statistical analysis

All continuous variables were presented as the mean ± standard deviation (SD). Levene’s test was used to test the homogeneity of variance. Categorical data and proportions were analyzed using the $\chi^2$ or Fisher’s exact test, whereas continuous variables were analyzed using the Student’s $t$-test (normally distributed) or the Mann-Whitney U test (non-normally distributed). The variables that attained a $P$ value of <0.10 by univariate analysis were entered into a multivariate logistic regression model. Multivariate logistic regression analysis was used to identify the factors influencing the use of targeted therapy, and the results were expressed as odds ratio (OR) and 95% confidence interval (CI). The Kaplan-Meier method was used to identify the differences in overall survival between the trastuzumab group and the non-trastuzumab group. All statistical tests were 2-sided, and $P<0.05$ was considered statistically significant. SPSS 23.0 (IBM Corp., Armonk, NY) was used for the analyses.

Results

Patients

A total of 641 patients (mean age 51.01±10.79 years) were enrolled in the study (Figure 1). All of them were diagnosed with HER2-positive EBC. Detailed baseline demographics for patients included in the analysis are presented in Table 1. Among all patients included, trastuzumab therapy was given to 214 (33.39%) patients. Only 8 patients received trastuzumab as a neoadjuvant therapy. A total of 412 (64.27%) patients had medical insurance.

Univariate analysis of factors associated with trastuzumab use

Univariate analysis revealed that patients who received trastuzumab therapy and those who did not receive trastuzumab therapy differed significantly in regard to the following factors: age, menstrual status, medical insurance, lymph node stage, and radiotherapy (all $P<0.05$, Table 2). Patients who were younger, premenopausal, had medical insurance, had more lymph node involvement, and received radiotherapy were more likely to receive trastuzumab therapy. There was no significant difference between the two groups in body mass index (BMI), primary tumor stage, molecular subtype, or adjuvant endocrine therapy (Table 2).

Multivariate logistic regression analysis

Multivariate logistic regression analysis was performed to further identify the factors associated with the use of trastuzumab therapy. The factors that differed significantly in the univariate analysis were entered into the multivariate analysis. The details of the multivariate analysis are summarized in Table 3. The results showed that compared with patients who were older than 60 years,
patients who were younger than 35 years were more likely to receive trastuzumab therapy (OR: 3.095; 95% CI: 1.219–7.853). Medical insurance was strongly correlated with trastuzumab use (OR: 3.909; 95% CI: 2.505–6.101). Adjuvant radiotherapy was also associated with higher use of trastuzumab therapy (OR: 2.700; 95% CI: 1.630–4.472). Other factors, including lymph node stage and menopausal status, showed no significant association with trastuzumab therapy.

**Overall survival analysis**

A total of 161 patients without mortality information were excluded. The median follow-up time was 81.17 months in the non-trastuzumab group and 77.67 months in the trastuzumab group. The overall survival was significantly better in the trastuzumab group than in the non-trastuzumab group [hazard ratio (HR): 1.607; 95% CI: 1.046–2.469; P=0.404, Figure 2].

**Stratified analysis**

Trastuzumab entered the medical insurance dictionary of Jiangsu in 2012. Table 4 compares the demographic and clinical characteristics between patients who were diagnosed with HER2-positive EBC in 2010–2011 and those diagnosed in 2013. More patients received trastuzumab therapy in 2013 than in 2010–2011 (P<0.001). In addition, more patients diagnosed in 2013 were hormone receptor positive, and received adjuvant endocrine therapy and radiotherapy (all P<0.05, Table 4). It should be noted that more patients had medical insurance and more patients were
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Table 1 Baseline demographic and clinical characteristics of the patients included in the analysis

| Parameter                                | Value (N=641) |
|-------------------------------------------|---------------|
| Age, y                                     | 51.01±10.79   |
| <35, n (%)                                 | 47 (7.33)     |
| 35–60, n (%)                               | 474 (73.95)   |
| >60, n (%)                                 | 120 (18.72)   |
| Body mass index (BMI), kg/m²               | 23.19±2.46    |
| <18.5, n (%)                               | 14 (2.18)     |
| 18.5–23.9, n (%)                           | 418 (65.21)   |
| ≥24, n (%)                                 | 209 (32.61)   |
| Menstrual status, n (%)                    |               |
| Premenopausal                              | 317 (49.45)   |
| Postmenopausal                             | 324 (50.55)   |
| Primary tumor stage, n (%)                 |               |
| T1                                         | 320 (49.92)   |
| T2                                         | 284 (44.31)   |
| T3-4                                       | 37 (5.77)     |
| Lymph node stage, n (%)                    |               |
| N0                                         | 359 (56.01)   |
| N1                                         | 135 (21.06)   |
| N2                                         | 70 (10.92)    |
| N3                                         | 77 (12.01)    |
| Molecular subtype, n (%)                   |               |
| Hormone receptor positive                  | 296 (46.18)   |
| Hormone receptor negative                  | 296 (46.18)   |
| Missing                                    | 49 (7.64)     |
| Adjuvant endocrine therapy, n (%)          |               |
| Yes                                        | 267 (41.65)   |
| No                                         | 330 (51.48)   |
| Missing                                    | 44 (6.86)     |
| Radiotherapy, n (%)                        |               |
| Yes                                        | 201 (31.36)   |
| No                                         | 381 (59.44)   |
| Missing                                    | 59 (9.20)     |
| Trastuzumab therapy, n (%)                 |               |
| Yes                                        | 214 (33.39)   |
| No                                         | 427 (66.61)   |
| Medical insurance, n (%)                   |               |
| Yes                                        | 412 (64.27)   |
| No                                         | 229 (35.73)   |

diagnosed at an early tumor stage in 2013 than in 2010–2011, although this did not reach statistical significance.

Discussion

The current study was implemented in seven general hospitals across different cities in Jiangsu province. Trastuzumab use in these hospitals was the highest in Jiangsu province. In 2010–2011 and 2013, trastuzumab therapy was given to 33.39% of patients with EBC. The percentage of patients who received trastuzumab in this study was similar to another study implemented in China in 2013–2014, in which 29.8% of patients with HER2-positive EBC received trastuzumab treatment (11). However, the data was much lower than developed countries. Several studies have shown that 66–78.1% of patients received trastuzumab treatment in developed countries between 2005 and 2013 (14–18), though data from other developing countries is insufficient. Furthermore, the overall survival in our study was consistent with 2 large prospective clinical studies (4,19).

In this study, several factors were found to be associated with trastuzumab therapy. The presence or absence of medical insurance was the strongest predictor of trastuzumab use. Patients who had medical insurance were 3.909 times more likely to use trastuzumab than those without medical insurance. Hospitals offered trastuzumab therapy to 42.96% of patients with medical insurance, whereas they provided trastuzumab to 16.16% of patients without medical insurance. There are two specific reasons behind this. On the one hand, medical insurance was limited to the urban population who had a higher income, so were more likely to afford trastuzumab. On the other hand, trastuzumab was covered by medical insurance from 2012, which greatly reduced the out-of-pocket costs of patients. Several studies also revealed that economic burden was the main barrier to the use of trastuzumab. In China, another study demonstrated that patients who resided in more prosperous provinces/cities (with higher incomes) or in provinces/cities which provided medical insurance for trastuzumab (Beijing, Jiangsu, and Ningxia) were more likely to be treated with trastuzumab (11). Other research has also shown that physicians can decide not to prescribe anti-HER2 therapies where such treatment has regulatory approval but is not funded or reimbursed. A survey of oncologists in the United States and emerging markets (Brazil, Mexico, Turkey, and Russia) showed that among the respondents who reported “not so often,” “rarely,” or
Table 2  Univariate analysis of the factors associated with the use of trastuzumab therapy

| Parameter                        | Trastuzumab (N=214) | Non-trastuzumab (N=427) | P value |
|----------------------------------|----------------------|--------------------------|---------|
| Age, y                           | 48.66±10.64          | 52.18±10.68              | <0.001  |
| <35, n (%)                       | 26 (12.15)           | 21 (4.92)                | 0.001   |
| 35–60, n (%)                     | 159 (74.30)          | 315 (73.77)              |         |
| >60, n (%)                       | 29 (13.55)           | 91 (21.31)               |         |
| Body mass index (BMI), kg/m²     | 23.10±2.58           | 23.24±2.40               | 0.498   |
| <18.5, n (%)                     | 3 (1.40)             | 11 (2.58)                | 0.578   |
| 18.5–23.9, n (%)                 | 143 (66.82)          | 275 (64.40)              |         |
| ≥24, n (%)                       | 68 (31.78)           | 141 (33.02)              |         |
| Menstrual status, n (%)          |                      |                          | 0.001   |
| Premenopausal                    | 125 (58.41)          | 192 (44.96)              |         |
| Postmenopausal                   | 89 (41.59)           | 235 (55.04)              |         |
| Primary tumor stage, n (%)       |                      |                          | 0.688   |
| T1                               | 107 (50.00)          | 213 (49.88)              |         |
| T2                               | 97 (45.33)           | 187 (43.79)              |         |
| T3-4                             | 10 (4.67)            | 27 (6.32)                |         |
| Lymph node stage, n (%)          |                      |                          | 0.017   |
| N0                               | 102 (47.66)          | 257 (60.19)              |         |
| N1                               | 50 (23.36)           | 85 (19.91)               |         |
| N2                               | 28 (13.08)           | 42 (9.84)                |         |
| N3                               | 34 (15.89)           | 43 (10.07)               |         |
| Molecular subtype, n (%)         |                      |                          | 0.487   |
| Hormone receptor positive        | 104 (52.00)          | 192 (48.98)              |         |
| Hormone receptor negative        | 96 (48.00)           | 200 (51.02)              |         |
| Adjuvant endocrine therapy, n (%)|                      |                          | 0.261   |
| Yes                              | 97 (48.26)           | 170 (42.93)              |         |
| No                               | 104 (51.74)          | 226 (57.07)              |         |
| Radiotherapy, n (%)              |                      |                          | <0.001  |
| Yes                              | 100 (51.28)          | 101 (26.10)              |         |
| No                               | 95 (48.72)           | 286 (73.90)              |         |
| Medical insurance, n (%)         |                      |                          | <0.001  |
| Yes                              | 177 (82.71)          | 235 (55.04)              |         |
| No                               | 37 (17.29)           | 192 (44.96)              |         |
“never” prescribing trastuzumab, between 37% and 49% considered the lack of drug funding a barrier to the use of trastuzumab (13). Of the 151 physicians participating in TEACH, an international survey conducted in 2011, 27% of respondents reported at least 1 instance within the previous year in which adjuvant trastuzumab was recommended to a patient who ultimately did not receive it, citing cost as the reason for withholding treatment. Furthermore, cost was more often taken into account by physicians in low- and middle-income countries (73%) than in high-income countries (7%, P<0.0001) as a reason for withholding adjuvant trastuzumab (20).

There was a significant difference in the percentage of patients who received trastuzumab between 2013 and 2010–2011 (44.59% in 2013 versus 16.21% in 2010–2011, P<0.001). It should be noted that in 2013, more patients had medical insurance (67.01% in 2013 versus 60.08% in 2010–2011), although this did not reach statistical significance (P=0.073). This trend was certainly due to the health-care reform in China. In April 2009, China unveiled a huge and complex health reform plan that pledged to provide all citizens with equal access to basic health care with reasonable quality and sufficient financial risk protection by 2020 (9). It emphasized insurance expansion in its first phase. Over the past 10 years, substantial progress

Table 3 Multivariate analysis of the factors associated with the use of trastuzumab therapy

| Parameter                  | Odds ratio (95% CI) | P value |
|----------------------------|---------------------|---------|
| Age, y                     |                     |         |
| >60                        | 1.000               |         |
| <35                        | 3.095 (1.219–7.853) | 0.017   |
| 35–60                      | 1.109 (0.622–1.979) | 0.726   |
| Lymph node stage           |                     |         |
| N0                         | 1.000               |         |
| N1                         | 1.064 (0.547–2.068) | 0.855   |
| N2                         | 0.925 (0.478–1.788) | 0.816   |
| N3                         | 0.870 (0.401–1.847) | 0.718   |
| Menstrual status           |                     |         |
| Premenopausal              | 1.000               |         |
| Postmenopausal             | 0.818 (0.530–1.261) | 0.363   |
| Radiotherapy               |                     |         |
| No                         | 1.000               |         |
| Yes                        | 2.700 (1.630–4.472) | <0.001  |
| Medical insurance          |                     |         |
| No                         | 1.000               |         |
| Yes                        | 3.909 (2.505–6.101) | <0.001  |

Figure 2 Overall survival between the trastuzumab group and the non-trastuzumab group calculated using the Kaplan-Meier method. HR: 1.607, 95% CI: 1.046–2.469, P=0.040.
Table 4 Comparison of trastuzumab use between patients who were diagnosed with early-stage breast cancer (EBC) in 2010–2011 and in 2013

| Parameter                      | 2010–2011 (N=253) (%) | 2013 (N=388) (%) | P value |
|-------------------------------|-----------------------|-----------------|---------|
| Age, y                        |                       |                 | 0.291   |
| <35                           | 18 (7.11)             | 29 (7.47)       |         |
| 35–60                         | 195 (77.08)           | 279 (71.91)     |         |
| >60                           | 40 (15.81)            | 80 (20.62)      |         |
| Body mass index (BMI), kg/m²  |                       |                 | 0.496   |
| <18.5                         | 6 (2.37)              | 8 (2.06)        |         |
| 18.5–23.9                     | 158 (62.45)           | 260 (67.01)     |         |
| ≥24                           | 89 (35.18)            | 120 (30.93)     |         |
| Menstrual status              |                       |                 | 0.732   |
| Premenopausal                 | 123 (48.62)           | 194 (50.00)     |         |
| Postmenopausal                | 130 (51.38)           | 194 (50.00)     |         |
| Primary tumor stage           |                       |                 | 0.057   |
| T1                            | 112 (44.27)           | 208 (53.61)     |         |
| T2                            | 123 (48.62)           | 161 (41.49)     |         |
| T3–4                          | 18 (7.11)             | 19 (4.90)       |         |
| Lymph node stage              |                       |                 | 0.133   |
| N0                            | 148 (58.50)           | 211 (54.38)     |         |
| N1                            | 59 (23.32)            | 76 (19.59)      |         |
| N2                            | 22 (8.70)             | 48 (12.37)      |         |
| N3                            | 24 (9.49)             | 53 (13.66)      |         |
| Molecular subtype             |                       |                 | 0.041   |
| Hormone receptor positive     | 98 (44.55)            | 198 (53.23)     |         |
| Hormone receptor negative     | 122 (55.45)           | 174 (46.77)     |         |
| Adjuvant endocrine therapy    |                       |                 | 0.033   |
| Yes                           | 92 (39.32)            | 175 (48.21)     |         |
| No                            | 142 (60.68)           | 188 (51.79)     |         |
| Radiotherapy                  |                       |                 | 0.005   |
| Yes                           | 60 (27.40)            | 141 (38.84)     |         |
| No                            | 159 (72.60)           | 222 (61.16)     |         |
| Trastuzumab therapy           |                       |                 | <0.001  |
| Yes                           | 41 (16.21)            | 173 (44.59)     |         |
| No                            | 212 (83.79)           | 215 (55.41)     |         |
| Medical insurance             |                       |                 | 0.073   |
| Yes                           | 152 (60.08)           | 260 (67.01)     |         |
| No                            | 101 (39.92)           | 128 (32.99)     |         |
was made in improving equal access to care and enhancing financial protection (21). In Jiangsu province, the insurance expansion together with the medical insurance coverage for trastuzumab greatly improved the rate of adjuvant trastuzumab use.

We also observed a trend towards more patients diagnosed with an earlier tumor stage in 2013 (P=0.057). This may be the result of enhanced breast cancer screening. First attempted in 2005, a national screening program for breast cancer set a goal of screening 1,000,000 women with both mammography and ultrasound, but was terminated because of a lack of funding and concerns about false-positive diagnosis (22). In 2009–2011, a “two-cancer” (breast cancer and cervical cancer) screening program was implemented for women aged 35–59 years in rural China and in some urban areas (23). Therefore, more accessible health services were provided to Chinese women, and breast screening has been taken more seriously since then. The results in our study reflected this phenomenon, particularly that patients younger than 35 years old were more likely to use trastuzumab therapy. In fact, several studies have demonstrated that trastuzumab was withheld from patients because of advanced age (24,25).

The strength of this study is that it is based on real-world data. It is also the first study, to the best of our knowledge, to explore the significance of health insurance policy in China on clinical practice. However, as a retrospective study, the current research has some limitations. Data were missing for many of the variables analyzed in some of the patients, which may bring information bias. In addition, the characteristics of patients in the trastuzumab group and those in the non-trastuzumab group were not evenly distributed. The unevenly distributed characteristics does may make it unreliable to directly analysis factors associated with the use of trastuzumab therapy. However we also took all variables with P value <0.10, including these potential confounders, from univariate analysis into the multivariate logistic regression model to identify factors independent associated with the targeted therapy. And we finally used the outcomes of the multivariate analysis to identify influencing factors. Therefore, large prospective randomized clinical trials are warranted to further verify the results of our study.

In conclusion, this study analyzed the factors affecting the use of trastuzumab as an adjuvant therapy for HER2-positive breast cancer patients in China. The results showed that the percentage of patients who received trastuzumab in China was lower than developed countries. Patients who had medical insurance were more likely to use trastuzumab than those without medical insurance. With the development of health-care reform in China, more patients could afford the targeted therapy essential for tumor management. Considering all this evidence, the health insurance policy in China has made great progress towards improving access for breast cancer patients who require trastuzumab therapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).The study was approved by the ethics committee of the First Affiliated Hospital with Nanjing Medical University (Jiangsu Province Hospital, No.: 2018-SR-205). Informed consent form was signed by every patient.

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