Triple-negative breast cancer outcomes: Does AJCC 8th staging improve chemotherapy decision-making

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A R T I C L E  I N F O

Article history:
Received 20 February 2021
Received in revised form 9 June 2021
Accepted 23 June 2021
Available online 28 June 2021

Keywords:
Triple-negative breast cancer
AJCC staging
Eighth edition
Chemotherapy
Prognosis

A B S T R A C T

Purpose: To investigate the effect of the 8th American Joint Committee on Cancer (AJCC) pathological prognostic staging on chemotherapy decision-making for triple-negative breast cancer (TNBC) patients with T1-2N0M0 disease.

Methods: Patients diagnosed with T1-2N0M0 TNBC were retrieved from the Surveillance, Epidemiology, and End Results program. Statistical methods including Kaplan-Meier survival curve, receiver operating characteristics curve, and Cox proportional hazard model.

Results: We identified 204,126 patients, including 93,711 (77.1%) patients who received chemotherapy. Overall, 57.4% of patients (n = 69,752) were upstaged after being reassigned by the 8th AJCC staging. However, the 8th staging of AJCC did not have a greater prognostic value compared to the 7th staging (P = 0.064). The receipt of chemotherapy significantly improved the breast cancer-specific survival for stage T1c and T2 tumors (P < 0.001), but not for stage T1a (P = 0.188) and T1b (P = 0.376) tumors. Using AJCC 8th staging, chemotherapy benefit was only found in stage IIA patients (P = 0.002), but not for stage IA (P = 0.653) and IB (P = 0.492) patients. There were 9564 patients with stage T1c and T2 diseases and 4979 patients with 8th AJCC stage IIA disease. Therefore, approximately half of patients (47.9%, n = 4585) may be safe to omit chemotherapy using the AJCC 8th staging compared to the current chemotherapy recommendation for T1-2N0M0 TNBC.

Conclusion: The 8th AJCC staging system did not demonstrate the superior discriminatory ability of prognostic stratification than the 7th AJCC staging system in T1-2N0M0 TNBC. However, this new AJCC staging could more accurately predict the chemotherapy benefit, thereby enabling more patients to avoid unnecessary chemotherapy.

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1. Introduction

Breast cancer (BC) is composed of different subtypes whose clinicopathological features, biological behaviors, response to therapies, and prognosis were of great heterogeneity [1]. Triple-negative breast cancer (TNBC) is defined as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) negative, which accounts for approximately 15–20% of all breast cancer subtypes [2]. Due to the invalidation of endocrine and target therapies, TNBC tends to be more aggressive and lethal than non-TNBC subtypes [3,4]. However, patients with small tumor size and nodal negative TNBC generally have a good prognosis [5].

Anatomic parameters of BC, including tumor size (T), regional lymph node involvement (N), and distant metastasis (M), have traditionally been the cornerstones for the American Joint Committee on Cancer (AJCC) staging [6]. In the recent decade, studies on
bakers have validated their outstanding role in the prognostic assessment and predict the treatment response, and these previous studies have demonstrated that specific biomarkers should be incorporated into the staging of BC [7–10]. Therefore, the AJCC 8th edition staging manual on BC incorporated the biomarkers including histologic grade, ER, PR, and HER2 status with the anatomic parameters to better distinguish the prognosis of patients [11]. Previous studies have demonstrated that the 8th prognostic staging of AJCC provided a more accurate prediction on the prognosis for BC patients than the 7th TNM staging [12–17]. Nevertheless, it is still controversial whether the new staging could predict the prognosis of TNBC patients more accurately [18–21]. There were conflict results regarding the discriminatory ability in predicting the prognosis of TNBC patients between these two AJCC staging systems [18–21]. In addition, it remains unclear whether making new AJCC staging changes can impact the current treatment decisions of TNBC. In light of this, we conducted the current study to assess the discriminatory ability of the new prognostic staging to predict the prognosis of T1-2N0M0 TNBC patients and whether the restaging will impact the chemotherapy decision-making in these early-stage patients with the TNBC subtype.

2. Materials and methods

2.1. Patients

Women diagnosed with TNBC between 2010 and 2014 were identified using the Surveillance, Epidemiology, and End Results (SEER) database. SEER program provided anonymous cancer data on clinicopathological features, primary tumor location, stage, first-line treatments, and vital status. These data were collected from the SEER program’s registries that covered approximately 30% of the United States population [22]. Inclusion criteria for this study cohort included: 1) primary TNBC; 2) receiving breast-conservation surgery or mastectomy; 3) tumor size <5 cm and nodal negative disease (stage T1-2N0M0); 4) available data including race/ethnicity, age, histology, histologic grade, detailed T category, use of adjuvant radiotherapy, and use of chemotherapy. Patients aged <18 years or aged ≥70 years, without definite pathological diagnoses, or with unknown local treatments were excluded. This study did not need approval by the Ethics Committee of the First Affiliated Hospital of Xiamen University due to the anonymity of the SEER data.

2.2. Variables

The variables included were as follows: age, race/ethnicity, histology, histologic grade, T category, surgical procedures, use of adjuvant radiotherapy, and use of chemotherapy. The new stages were reassigned based on the 8th pathological prognostic staging of AJCC, and the T categories were allocated according to the 7th AJCC criteria. Tumor size >0.1 cm but ≤0.5 cm in greatest dimension was classified as T1a. Tumor size >0.5 cm but ≤1 cm was classified as T1b. Tumor size >1 cm but ≤2 cm was classified as T1c. Tumor ≥2 cm but ≤5 cm was classified as T2.

2.3. Statistical analysis

The receiver operating characteristics (ROC) curve was applied to compare the stratification abilities of the 7th and 8th staging manuals to predict breast cancer-specific survival (BCSS). The Harrell concordance index (C-index) was calculated to measure the model’s predictive performance between the two staging systems. The Akaike Information Criterion (AIC) was used for model comparison. A higher C-index correlates with a better predictive performance. In addition, a lower AIC value indicates superior model fit. Survival analyses were conducted by the Kaplan-Meier method and compared using the log-rank test. The multivariate Cox proportional hazards model was used to determine the independent prognostic factors correlated to BCSS. The current National Comprehensive Cancer Network (NCCN) breast cancer guideline recommended adjuvant chemotherapy for patients with tumor size >1 cm, but not for patients with tumor size ≤0.5 cm. Adjuvant chemotherapy should be also considered for patients with tumor size 0.6–1.0 cm according to the newly NCCN guideline [23]. Sensitivity analyses after stratification by tumor size (tumor size ≤0.5 cm, tumor size 0.6–1.0 cm, and tumor size >1.0 cm) and the 8th prognostic stages of AJCC (stage IA, IB, and IIA) were used to further identify the specific cohorts that were sensitive to chemotherapy. Statistical analyses in this study were performed by the MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium), R Version 3.4.3 (R Foundation for Statistical Computing, Vienna), and IBM SPSS 26.0 software package (IBM Corp., Armonk, NY). P values less than 0.05 were deemed as significant in statistics.

3. Results

3.1. Patient characteristics

A total of 12,156 TNBC patients were included. The detailed patient and tumor characteristics are shown in Table 1. The median age of the cohort was 45.5 years (range, 21–70 years). Most patients were with invasive ductal carcinoma (92.6%, n = 11,253) and poorly/undifferentiated disease (80.5%, n = 9,783). There were 743 (6.1%), 1849 (15.2%), 4585 (37.7%), and 4979 (41.0%) patients had stage T1a, T1b, T1c, and T2 diseases, respectively.

Regarding local and adjuvant treatments, 56.7% of the patients received chemotherapy. Table 1

| Variables | N (%) |
|-----------|-------|
| Age (years) |       |
| <50        | 3629 (29.9) |
| ≥50        | 8527 (70.1) |
| Race/ethnicity |       |
| Non-Hispanic White | 7524 (61.9) |
| Non-Hispanic Black | 2336 (19.2) |
| Hispanic (All Races) | 1394 (11.5) |
| Other      | 902 (7.4) |
| Histology  |       |
| IDC       | 11,253 (92.6) |
| ILC       | 100 (0.8) |
| Other      | 803 (6.6) |
| Histologic grade |       |
| Well differentiated | 248 (2.0) |
| Moderately differentiated | 2125 (17.5) |
| Poorly/undifferentiated | 9783 (80.5) |
| T category |       |
| T1a       | 743 (6.1) |
| T1b       | 1849 (15.2) |
| T1c       | 4585 (37.7) |
| T2        | 4979 (41.0) |
| Breast surgery |       |
| BCS       | 6895 (56.7) |
| MRM       | 5261 (43.3) |
| Adjuvant radiotherapy |     |
| No        | 6377 (52.5) |
| Yes       | 5779 (47.5) |
| Chemotherapy |       |
| No        | 2785 (22.9) |
| Yes       | 9371 (77.1) |

IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; T, tumor; BCS, breast conserving surgery; MRM, modified radical mastectomy.
underwent breast conservation surgery and the rest (43.3%) had a mastectomy. Of the breast conservation surgery cohort, 77.0% received adjuvant radiotherapy, whereas only 9.0% of the mastectomy cohort received adjuvant radiotherapy. A total of 9371 (77.1%) patients received adjuvant chemotherapy.

3.2. Restaging

In our study, T1-2N0M0 patients were staged as the IA (59.1%, \(n = 7177\)) and IIA (40.9%, \(n = 4979\)) diseases according to the 7th AJCC criteria. Based on the 8th AJCC staging, these patients were reclassified as stage IA (\(n = 202, 1.7\%\)), IB (\(n = 6975, 57.4\%\)), and IIA (\(n = 4979, 40.9\%\)) (Table 2). A total of 6975 (57.4%) patients had their stages changed and were upstaged from 7th TNM stage IA to the 8th stage IB using the 8th criteria of AJCC. All patients with the 7th TNM stage IIA diseases were unchanged and remained as stage IIA using the 8th criteria of AJCC. Stage change between these two AJCC staging systems is presented in detail in Table 2.

3.3. Survival

With the median follow-up of 41.5 months (range, 0–83 months), 807 breast-cancer related deaths occurred in the entire cohort. The BCSS rates at 5 years of the AJCC 7th edition stage IA and IIA patients were 94.5% and 88.0% (P < 0.001) (Fig. 1A). After restaged by the 8th criteria of AJCC, the 5-year BCSS of stage IA, IB, and IIA cohort was 98.5%, 94.4%, and 88.0%, respectively (P < 0.001) (Fig. 1B). However, in the ROC analysis, similar AUC values were found in these two staging systems in distinguishing the BCSS (AUC: 0.606 vs. 0.603, P = 0.064) (Fig. 2). In addition, similar C-index (0.606 vs. 0.609) and AIC (14501.85 vs. 14497.52) were found between 7th and 8th AJCC stagings. The findings reflected that the new staging model may not show superior discrimination ability to predict the BCSS compared to the 7th staging.

3.4. Prognostic analyses

The multivariate Cox proportional hazard model was used to determine the independent prognostic factors correlated to BCSS (Table 3). The results showed that the 8th prognostic staging of AJCC was independently associated with BCSS. Compared with stage IA, the 8th AJCC pathological prognostic stage IB (hazard ratio [HR] 3.448, 95% confidence interval [CI] 1.105–10.761, P = 0.033) and IIA (HR 7.673, 95%CI 2.459–23.945, P < 0.001) showed worse prognosis with gradually increased hazard ratios. In addition, the receipt of chemotherapy was independently associated with better BCSS compared to the non-chemotherapy cohort (HR 0.821, 95%CI 0.695–0.970, P = 0.021). Patients who received chemotherapy had a 17.9% reduction in breast cancer-specific mortality (BCSM) in comparison with those who did not receive chemotherapy. Furthermore, race/ethnicity and surgical procedure were also the independent prognostic factor for BCSS.

3.5. The value of chemotherapy in different tumor sizes

In the current NCCN clinical practice guidelines of breast cancer, the recommendation of chemotherapy in T1-2N0M0 TNBC was mainly based on the dimensions of the primary tumor [23]. No adjuvant chemotherapy was recommended in patients with tumor size ≤0.5 cm (T1a), but adjuvant chemotherapy should be considered in patients with tumor size 0.6–1.0 cm (T1b) and recommended in those with tumor size >1 cm (T1c and T2) (23). Therefore, we assessed the effect of chemotherapy on BCSS using this real-world data. The percentage of chemotherapy receipt was 30.3% (n = 225), 67.2% (n = 1243), 82.6% (n = 7903) in those with tumor size ≤0.5 cm, 0.6–1.0 cm, and >1 cm. The sensitivity analyses showed that the receipt of chemotherapy was associated with a significantly better BCSS in patients with tumor size >1 cm (HR 0.697, 95%CI 0.584–0.830, P < 0.001), but not for patients with tumor size ≤0.5 cm (HR 1.868, 95%CI 0.736–4.742, P = 0.188) or 0.6–1.0 cm (HR 1.315, 95%CI 0.717–2.413, P = 0.376) (Table 4). For patients with tumor size >1 cm, the 5-year BCSS was 91.0% and 88.2% in those with and without chemotherapy (P < 0.001), the receipt of chemotherapy could reduce BCSM by 30.3% in patients with tumor size >1 cm. Our study verified the rationality of the current recommendation of chemotherapy in T1-2N0M0 TNBC in the NCCN breast cancer practice guidelines. The survival curves between the two treatment arms according to the size of the primary tumor are listed in Fig. 3A–C.

3.6. The value of chemotherapy in different AJCC 8th pathological prognostic stages

The role of 8th AJCC staging on chemotherapy decision-making remains unclear. Thus, the effect of chemotherapy on the BCSS of the T1-2N0M0 TNBC patients was analyzed in this study on account of the 8th AJCC staging. There were 79 (39.1%), 5074 (72.7%), and 4218 (84.7%) patients with 8th AJCC stage IA, IB, and IIA diseases undergoing chemotherapy, respectively. The sensitivity analyses showed that the receipt of chemotherapy was associated with a significantly better BCSS only in stage IIA patients (HR 0.706, 95%CI 0.548–0.930, P < 0.001), but not for those with stage IA (HR 0.558, 95%CI 0.376–0.830, P = 0.002) or IB (HR 0.915, 95%CI 0.711–1.178, P = 0.492) diseases (Table 4). For stage IIA patients, the 5-year BCSS was 88.6% and 85.0% in those with and without chemotherapy (P < 0.001), the 5-year absolute BCSS gain was 3.6% for patients receiving chemotherapy, with a reduction of 29.4% in breast cancer-related death. The survival curves between the two treatment arms according to the 8th AJCC staging are list in Fig. 3D–F.

There were 9564 patients with tumor size >1 cm (stage T1c and T2) and 4979 patients with 8th AJCC stage IIA disease (Fig. 4). Therefore, approximately half of patients (47.9%, n = 4585) may be safe to omit chemotherapy using the 8th AJCC staging compared to the current chemotherapy recommendation for T1-2N0M0 TNBC.

4. Discussion

TNBC is a specific subtype of BC [24–26]. In this study, we

Table 2

| The 7th AJCC anatomic stage | The 8th AJCC pathological prognostic stage | Total |
|-----------------------------|------------------------------------------|-------|
| IA                          | IB                                       | IIA   |
| IA                          | 202 (2.8%)                               | 0     | 7177 (59.1%) |
| IIA                         | 0                                        | 0     | 4979 (40.9%) |
| Total                       | 202 (1.7%)                               | 6975 (57.4%) | 4979 (40.9%) | 12156 (100%) |
investigated the discriminatory ability in the prognostic assessment of the new AJCC prognostic staging and whether the restaging will influence the decision-making of chemotherapy for T1-2N0M0 TNBC. Our results revealed that although the new prognostic staging of AJCC did not show a better risk stratification ability for this patient subset, it might enable more patients to avoid unnecessary chemotherapy. Several studies have validated the prognostic ability of the 8th AJCC prognostic staging, and have reached similar conclusions that the prognostic staging is better than the traditional anatomic staging in predicting survival outcome in BC [12–17]. However, limited studies were focused on TNBC [18–21]. In all groups of BC, the overall upstaging rate and downstaging rate reported in those studies varied approximately from 5.5% to 41.0%, and from 15.2% to 42.1%, respectively [13–17]. In our study, the upstaging rate of TNBC patients were 57.4% (n = 6975), and the rate of stage unchanged was 42.6% (n = 5181), and no patient was downstaged. Other studies reported similar results [14,18]. A study conducted by Jang et al. found that 50.4% of the TNBC patients with stage I-IIIC diseases were upstaged, 49.6% of them were unchanged, and none of them were downstaged. However, in the subgroup analysis of hormone receptor-positive or HER2 positive BC, no patient was upstaged and all of them were downstaged or unchanged [15]. It was not surprising that the upstaging rate was greater and the downstaging rate was lower in the TNBC subtype than other breast cancer subtypes. In the contemporary studies, a higher proportion of downstaging was found in patients with hormone receptor

Table 3

| Variables                        | HR (95% CI) | P    |
|----------------------------------|-------------|------|
| Age (years)                      |             |      |
| <50                              | 1           |      |
| ≥50                              | 1.037 (0.890–1.207) | 0.642|
| Race/ethnicity                   |             |      |
| Non-Hispanic White               | 1           |      |
| Non-Hispanic Black               | 1.265 (1.069–1.497) | 0.006|
| Hispanic (All Races)             | 0.996 (0.794–1.249) | 0.970|
| Other                            | 0.760 (0.561–1.028) | 0.075|
| Histology                        |             |      |
| IDC                              | 1           |      |
| ILC                              | 1.072 (0.508–2.260) | 0.856|
| Other                            | 0.926 (0.697–1.231) | 0.596|
| The 8th AJCC pathological stages |             |      |
| IA                               | 1           |      |
| IB                               | 3.448 (1.105–10.761) | 0.033|
| IIA                              | 7.673 (2.459–23.945) | 0.000|
| Breast surgery                   |             |      |
| BCS                              | 1           |      |
| MRM                              | 1.250 (1.088–1.437) | 0.002|
| Adjuvant radiotherapy            |             |      |
| No                               | 1           |      |
| Yes                              | 0.949 (0.784–1.148) | 0.590|
| Chemotherapy                     |             |      |
| No                               | 1           |      |
| Yes                              | 0.821 (0.695–0.970) | 0.021|

TNBC, triple-negative breast cancer; HR, hazard ratio; CI, confidence interval; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; BCS, breast-conserving surgery; MRM, modified radical mastectomy.
positivity or HER2 positivity that could benefit from endocrine therapy or anti-HER2 therapy. TNBC tends to have a higher rate of upstaging due to its aggressive behaviors. In terms of staging migration, the 8th AJCC prognostic staging seemed to have a better ability to predict the prognosis of TNBC patients than the traditional anatomic staging.

Currently, studies assessing the new AJCC prognostic staging for the TNBC cohort came to conflict results [18–21]. Li et al. [19] and Luo et al. [21] claimed that the new prognostic staging of AJCC could predict the prognosis of TNBC patients more accurately than the traditional anatomic staging. However, Li et al. [19] did not use the corresponding statistical analyses to further assess the prognostic abilities of the two staging systems. In addition, Luo et al. [21] also acknowledged that the two competing stage systems (the new AJCC prognostic staging vs. traditional TNM staging) did not have significant differences in AUC values. Same as the previous studies on TNBC, He et al. [18] derived the patient data from the SEER database and they further used the data from Sun Yat-sen University Cancer Center and Prince of Wales Hospital to verify the results from the SEER cohort. Their findings demonstrated that the new prognostic staging of AJCC did not demonstrate a superior ability of risk stratification than the traditional anatomic staging regarding TNBC. In our study, we further confirmed that in the T1-2N0M0 subgroup of TNBC patients, the discriminatory ability to predict prognosis of the 8th prognostic staging was no better than that of the 7th anatomic staging. These results suggested that in this special subgroup, tumor size may still be a determinant of survival, and histologic grade may not have significant prognostic value.

Lymph node-negative TNBC with tumor size <1.0 cm generally show a good prognosis without adjuvant chemotherapy [5,27]. However, the available evidence of recommendations on adjuvant chemotherapy to TNBC patients with small tumor burden and the negative lymph node is insufficient owing to the lack of prospective clinical trials. A multi-center study in France found that lymph node-negative TNBC patients with T1a-bN0M0 disease could not derive a significant survival benefit from adjuvant chemotherapy.

Table 4

| Variables | Number (%) | HR (95% CI) | P |
|-----------|------------|-------------|---|
| T1a (tumor ≤0.5 cm) | | | |
| No chemotherapy | 518 (69.7) | 1 | |
| Chemotherapy | 225 (30.3) | 1.868 (0.736–4.742) | 0.188 |
| T1b (tumor 0.6cm–1.0 cm) | | | |
| No chemotherapy | 606 (32.8) | 1 | |
| Chemotherapy | 1243 (67.2) | 1.315 (0.717–2.413) | 0.376 |
| T1c and T2 (tumor >1.0 cm) | | | |
| No chemotherapy | 1661 (17.4) | 1 | |
| Chemotherapy | 7903 (82.6) | 0.697 (0.584–0.830) | 0.000 |
| 8th AJCC stage IA disease | | | |
| No chemotherapy | 123 (60.9) | 1 | |
| Chemotherapy | 79 (39.1) | 0.558 (0.044–7.091) | 0.653 |
| 8th AJCC stage IB disease | | | |
| No chemotherapy | 1901 (27.3) | 1 | |
| Chemotherapy | 5074 (72.7) | 0.915 (0.711–1.178) | 0.492 |
| 8th AJCC stage IIA disease | | | |
| No chemotherapy | 761 (15.3) | 1 | |
| Chemotherapy | 4218 (84.7) | 0.706 (0.563–0.884) | 0.002 |

BCSS, breast cancer-specific survival; HR, hazard ratio; CI, confidence interval; T, tumor.

a Indicates an adjustment of age, race/ethnicity, histology, histologic grade, surgery methods, adjuvant radiotherapy, and chemotherapy.

b Indicates an adjustment of age, race/ethnicity, histology, surgery methods, adjuvant radiotherapy, and chemotherapy.

Fig. 3. The effect of chemotherapy on breast cancer-specific survival according to tumor size (A, tumor size ≤0.5 cm; B, tumor size between 0.6 and 1.0 cm; C, tumor size >1 cm) and the AJCC 8th pathological prognostic stages (D, IA; E, IB; F, IIA).
diovascular function, and quality of life. Imposes non-negligible impairments on cognitive function, gastrointestinal reaction, and skin reaction to patients but also affects as hematological toxicity, hepatorenal toxicity, and skin reaction. To the best of our knowledge, no studies investigated AJCC stage IIIA disease but was not in those with stage IA, IB, and IIA diseases. To reveal that 8th AJCC staging could more accurately predict the chemotherapy benefit for patients with stage size >1 cm or 8th AJCC stage IIA disease. According to our findings, the utility of 8th AJCC staging for treatment decision of chemotherapy might decrease approximately half of the patients to omit unnecessary chemotherapy compared to the current chemotherapy recommendation using NCCN guidelines for T1-2N0M0 TNBC.

We acknowledged that this study still had several limitations. Firstly, selection bias inevitably appeared in this retrospective study. The reasons why patients received or did not receive chemotherapy are not captured in the SEER program, which can lead to potential bias. Secondly, the SEER database has no treatment information regarding the chemotherapy regimen and circles, the sequential use of chemotherapy and surgery, and the rate of chemotherapy completion. Thirdly, data on locoregional recurrence patterns and their treatment protocols are not embodied in the SEER database. Fourthly, the application of chemotherapy may be under-reported in the SEER database. However, the major superiority of this study was that the real-world data based on a large population was used to discriminate the prognostic abilities of the 7th and 8th AJCC staging in the T1-2N0M0 TNBC population. Furthermore, this study was the first to reveal that 8th AJCC staging may also have an important impact on chemotherapy decision-making of T1-2N0M0 TNBC patients.

5. Conclusion

Although the 8th edition of the AJCC pathological prognostic staging system did not demonstrate better risk stratification ability in T1-2N0M0 TNBC than the 7th AJCC TNM staging system, this new staging could more accurately predict the chemotherapy benefit for this patient subset, thereby enabling more patients to avoid unnecessary chemotherapy. Our study provides additional information for the clinical practice of breast cancer using the new AJCC staging. More prospective studies are urgently needed to validate the impact of 8th AJCC staging on treatment decision-making for BC patients.
Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

This work was partly supported by the Commission Young and Middle-aged Talents Training Project of Fujian Health Commission (No. 2019-ZQNBJ-25) and the Natural Science Foundation of Fujian Province (No. 2020J01240).

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